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ABSTRACTS COLLECTION

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Acute leukaemia

P001

Allogeneic Stem Cell Transplantation for AML Patients with Runx1 Mutation in First Complete Remission: A Study on behalf of the ALWP of the EBMT

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Background: Acute myeloid leukemia with RUNX1 gene mutation (RUNX1+ AML) has been proposed as a provisional entity in the 2016 WHO classification. Inferior response rates and outcome after conventional chemotherapy have been detected in patients with RUNX1 gene mutation and accordingly, RUNX1+ AML is allocated in the unfavorable prognostic category of the 2017 European Leukemia Net classification. Following allogeneic stem cell transplantation (alloSCT), RUNX1 mutation was an unfavorable factor in one study in MDS/secondary AML, while data in de novo AML are scarce. In this retrospective study by the EBMT Acute Leukemia Working Party, we elucidate the prognostic value of RUNX1 mutation in patients undergoing alloSCT for AML in first complete remission (CR1).

Methods: Adults undergoing alloSCT for AML in CR1 from matched related or unrelated donors between 2013 and 2018 with complete information on conventional cytogenetics and RUNX1 mutational status were selected from the EBMT registry. Variables of interest were overall and leukemia-free survival (OS/LFS), GvHD/relapse free survival (GRFS), cumulative relapse incidence (RI), non-relapse mortality (NRM) and GvHD. Log rank test, Gray test and Cox regression models were used for statistical analysis.

Results: A total of 516 patients were included, 128 RUNX+ and 388 RUNX-, with >80% of both subgroups presenting as de novo AML. As expected, RUNX1+ patients rarely had co-mutations in NPM1 (6% vs. 26%, $p=10^{-3}$), and showed a positive correlation with ASXL1 mutations (50% vs. 16%, $p=10^{-4}$). Cytogenetic categories and other mutations (FLT3-ITD, CEBPA) were equally

distributed between the two groups, as were age, donor and graft type, CMV, conditioning and T cell depletion (TCD).

Median follow-up was 16.4 (RUNX+) and 19.8 (RUNX-) months. 2y OS/LFS of the entire cohort were 64% [59-69]/57% [52-62], with no difference between RUNX1+ and RUNX1- patients either in univariate or multivariate analysis (2y OS: 67.9% [57.3-78.5] vs. 63.1%v [57.4-68.7]p=0.15; 2y LFS: 57.6% [46.4-68.7] vs. 57% [51.4-62.6], p=0.38]). RUNX1 mutation neither had any impact among patients with normal karyotype. Furthermore, no other outcome parameter was influenced by RUNX1 mutational status. Instead, multivariate analysis revealed age and donor type as risk factors for OS, LFS and NRM. Poor cytogenetic was associated with higher RI and inferior LFS/GRFS, in vivo TCD with a lower rate of aGvHD II-IV, cGvHD, and better GRFS. Among patients with available information, FLT3-ITD was an independent risk factor for relapse, LFS and GRFS. RUNX1 did not modify the role of FLT3-ITD.

Conclusions: Within the limits of a retrospective registry analysis, we could not find a negative influence of RUNX1 mutation on outcome after allogeneic SCT in CR1. Hence, transplantation in CR1 might overcome the unfavorable prognostic value of RUNX1 mutation and can be recommended as consolidation treatment in this entity.

Disclosure: Nothing to declare.

P002

Graft Failure after Unmanipulated haplo-hsct with pt-cy in Patients with Acute Myeloid Leukemia in Complete Remission, on behalf of the ALWP-EBMT

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Background: Graft failure (GF) is a life threatening complication following hematopoietic stem cell transplantation (HSCT). Its incidence depends on multiple parameters including type of donor, HLA disparity, stem cell source, graft composition and conditioning regimen. Incidence of GF in T-cell-depleted haploidentical-transplantations (Haplo-HSCT) can reach up to 10-20%. The use of Haplo-HSCT with post-transplant-cyclophosphamide (PTCy) as graft-versus-host-disease (GVHD) prophylaxis is a new standard in the treatment of hematological diseases. Paucity of data exists on GF in Haplo-HSCT with-PTCy.

Methods: To evaluate the incidence and risk factors of GF after Haplo-HSCT with-PT-Cy, we analyzed 1270 adults with acute myeloid leukemia (AML) reported to ALWP-EBMT who received a first Haplo-HSCT from 2010-2018. GF was defined as neutrophil count lower than 500 micro/L at day+45, competing risk was death without engraftment.

Results: Disease status was CR1 in 73% of patients and CR2 in the remaining. Secondary AML was reported in 13.7%. Median follow-up is 22 months and median age at Haplo-HSCT 54 years. Stem cell source was bone marrow (BM) in 41.4% and 44.6% of patents received a myeloablative conditioning regimen (MAC) with TBF(thiotepa, Bulsulfan and Fludarabine) in 59%. PT-Cy in association with calcineurin inhibitors and MMF was the most frequent GVHD-prophylaxis. Cumulative incidence of GF was 6.6 % (95%CI:5.3-8.1), median time to engraftment was 19 (1-45) days. Nine patients engrafted after day+45(47-79), 43 patients experienced primary GF and 41 died before day +45 with no sign of donor engraftment. Of the 43 patients with GF, 7 subsequently engrafted after day+45, 29 patients were rescued with a second HSCT. Overall 18 patients are alive at last fu, 2y OS being 32%. CI of engraftment was lower in patients transplanted for secondary AML (91% vs 94%, p=0.003) and was 95% in MAC versus 92.6% in RIC, p< 0.001. CI of day-100 grade II-IV and grade III-IV aGVHD was 29.1 % (95% CI: 26.5 - 31.6) and 10.4 % (95% CI: 8.7 - 12.2), respectively, and 2 years chronic and extensive GVHD was 31.6 % (95% CI: 28.6 - 34.6) and 11.5 % (95% CI: 9.5 - 13.7). At 2 years GRFS, LFS, and OS were 47.1 % (95% CI: 43.9 - 50.2), 55.8 % (95% CI: 52.7-59) and 61 % (95% CI: 57.9-64.1), respectively. Two-year CI of relapse and NRM were 21.2 % (95% CI: 18.7-23.8) and 23 % (95% CI: 20.4-25.6). Disease recurrence was the most common cause of death, with infections and GVHD being the most frequent transplant related causes. In multivariate analysis, factors independently associated with the risk of GF were: secondary-AML (HR 1.28, p=0.007), use of RIC (HR 1.32, p< 0.001), and use of BM (HR 1.21, p=0.002). RIC and adverse cytogenetic risk were associated with relapse and age, performance status and cytogenetic risk with OS.

Conclusions: Incidence of GF after haplo-HSCT with PT-Cy is lower than in T-cell depleted Haplo. Optimization of conditioning regimen and graft source should be

considered for reducing the risk GF in Haplo-HSCT recipients using PT-Cy. Comparison of GF in the different platforms of GVHD prevention (PT-Cy and ATG) is warranted.

Disclosure: Nothing to declare.

P003

Implications of Novel Risks Scores (AML-DRG and AML-HCT-CR) in Allogeneic CD34+ Selected Graft Transplant Outcomes

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Background: Several prognostic models to stratify allogeneic hematopoietic cell transplantation (allo-HCT) outcomes have been developed in recent years. Despite evidence that minimal residual disease (MRD) is an independent predictor of survival in patients with AML, MRD is excluded from most models. Two novel AML-specific disease scores that incorporate disease data, AML-specific disease risk group (AML-DRG) and AML-HCT-CR, have been shown to be predictive of survival in patients with AML who received an of unmodified HCT (Piyanuch et al. BBMT. 2019). T cell depletion (TCD) using ex vivo CD34 selection has been shown to decrease acute and chronic GVHD without increasing relapse in selected patients with AML, ALL and MDS, and results of a completed phase 3 trial are pending (NCT02345850). Our proposal is to validate both scoring systems in a cohort of patients who underwent ex vivo CD34 selected HCT.

Methods: We included 279 patients age > 18 years who underwent a first CD34+ selected allo-HCT for AML between 2008 and 2018 and calculated their AML-DRG and AML-HCT-CR scores. AML-DRG variables included: secondary AML, adverse European LeukemiaNet2017 genetic risk and MRD status. The AML-HCT-CR model also included HCT-CI score ≥ 3 and age ≥ 60 years. MRD was assessed pre HCT by flow cytometry and/or PCR or NGS as indicated. The primary outcome was survival (OS) and secondary outcomes were progression-free-survival (PFS), and incidences of non-relapsing mortality (NRM), and relapse.

Results: Median age was 55 years (range 19 to 73 years), 45.5% (n = 127) were females and median HTC-CI was 2. All patients received myeloablative conditioning. At time of HCT 20.8% patients had MRD+ status and 5.4% had active disease (Table 1). Median follow-up was 5.5 years (95% CI: 5.1-6.3). For the AML-DRG model, the 3-year OS in the low, intermediate, and high-risk groups were 65%, 52%, and 13%, respectively. PFS at 3 years were 63%, 43%, and 15% in the same groups. The OS predictive accuracy measured by c-statistic was 0.588. In the AML-HCT-CR model, patients in low, intermediate, high risk and very high risk had a 3 year OS of 72%, 58%, 39%, and 51%, respectively. The corresponding PFS at 3 years were 68%, 56%, 36% and 43%. The OS predictive accuracy measured by c-statistic was 0.615. Both scores significantly predicted relapse incidence (AML-DRG model p value= < 0.001; AML-HCT-CR model p value= 0.04), but AML-DRG model was not associated with NRM (p = 0.993).

Conclusions: The AML-DRG and AML-HCT-CR models are predictive of outcomes including OS, PFS, and relapse incidence in a large cohort of patients receiving TCD HCT with CD34+ selected allografts. These data should therefore lead to better patient selection for ex vivo CD34-selected allo-HCT. The predictive accuracy for both scoring systems is modest, however; and there remains a need for innovative models incorporating new clinical and genomic characteristics to achieve a scoring system with improved accuracy.

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P004

Downregulation of HLA-DR in Blasts of Patients with Acute Leukaemia Relapsing after Allogeneic Haematopoietic Stem Cell Transplantation

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Background: Relapse following allo-HSCT in patients with acute leukaemia remains to date a challenge in clinical practice and is associated with ominous prognosis. Identifying the mechanism leading to relapse will morph our therapeutic armamentarium in accordance with the underlying pathophysiology. Amongst recent studies, HLA Class II downregulation has emerged as a major mechanism of immune evasion after allo-HSCT in patients with AML. However, relapses of patients with ALL after allo-HSCT have not yet been studied in an identical manner. Our goal was to identify the downregulation of HLA-DR in blasts of patients with acute leukaemia after allo-HSCT using flow cytometry.

Methods: For this study, we retrospectively selected patients with a diagnosis of AML, ALL or MPAL who relapsed following allo-HCT for which raw flow cytometry data were available both at a pre-transplantation active disease and at relapse. Blast cells were gated, then analyzed based on their HLA-DR expression and a Mean Fluorescence Intensity was calculated for both timepoints (preMFI & relMFI). Analysis was performed using the FlowJo software (Version 10.5.3, FlowJo LLC). Normalisation of the MFI values was performed using the median HLA-DR MFI of blasts from 31 newly diagnosed acute leukaemias calculated as MFI/median. We defined HLA-DR Downregulation as the reduction of the normalized value at the time of relapse by at least 50% (preMFI-n/relMFI-n < = 0.5). Statistical analysis was performed using Graph Prism.

Results: We analyzed 16 patients (9 male, 7 female) median age of 44 years old (range 32-65) who underwent allo-HSCT for AML (n=12), ALL (n=3) and MPAL (n=1). Four patients received graft from a compatible sibling, 2 from an haploidentical donor and 10 from unrelated donors (7 from 7/8 HLA match, 3 from 8/8 HLA match). At the time of transplantation, 5 patients achieved CR1, 7 achieved CR2 and 4 had refractory disease. The median day of relapse was day 147 (60-405). Median preMFI and preMFI-n values were 10.035 (range 81-14818) and 1.01 (0.008-6.5) respectively, median relMFI and relMFI-n were 7.919 (69-62055) and 0.8 (0.007-6.2). In 8 out 16 paired samples we observed a reduction of the HLA-DR MFI and MFI-n by at least 50% at the time of relapse (median relMFI/preMFI 0.37, range 0.001-0.5). Moreover, HLA-DR downregulation was observed in 2 out of the 3 patients with ALL. There was no correlation between donor-recipient HLA incompatibility and HLA-DR downregulation (p=ns).

Conclusions: HLA-DR Downregulation represents a common mechanism of immune escape in acute leukaemias relapsing after allo-HSCT that accounts to 50% of our patients. We first describe this mechanism to be present in cases of ALL. Identifying this phenomenon in patients using flow cytometry provides valuable information

concerning their treatment choices as they will obviously not benefit from donor lymphocyte infusions.

Disclosure: no disclosures

P005

Establishment of a National Stem Cell Transplant Clinical Trials Network: The UK Impact Partnership for Accelerated Cellular Therapies

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Background: Stem cell transplantation (SCT) plays a central role in the management of haematological malignancies and is increasingly utilised in the management of non-malignant disorders. Treatment toxicity and disease relapse remain major causes of treatment failure after both autologous and allogeneic SCT. In contrast to other areas of haemato-oncology where clinical practice is informed by large prospective randomised trials, transplant practice is largely informed by retrospective registry studies and local practice. Very few patients undergoing stem cell transplantation enter prospective randomised trials aimed at improving transplant outcome. Reasoning that major barriers to transplant trial delivery was the twin absence of resource for trial development and research nurse capacity within a large networked population, a 4-year pilot was established in 2017 to create a national transplant trials network in the UK.

Methods: The IMPACT partnership was established in 2017 and £3.4 million was awarded for a 4-year pilot by NHSBT and the charities Anthony Nolan and Leukaemia UK. Funding was awarded with the aim of recruiting at least 500 patients to 9 prospective trials with embedded sequential collection of clinical samples. The IMPACT grant funded a central Hub within a well-established Clinical Trials Unit which was responsible for clinical trial design, set-up, management, and publication of trial results. The Hub was linked with a Trials Network consisting of 10 major transplant centres each staffed by a dedicated IMPACT research nurse chosen through an independent peer review process. 12 additional UK centres were awarded Affiliate status. This effectively created a funded trials network able to recruit to transplant trials in a cohesive manner across a 20 million patient population.

Results: In the 24 months since its establishment the IMPACT network has received 28 proposals for transplant trials - 12 of which have been developed with expert statistical and clinical input from the IMPACT team through national workshops. Rapid feasibility assessments were performed for 10 of these trials. To date 7 trials have been submitted for independent peer review and six have been approved. Key transplant questions addressed include defining the optimal conditioning regimen in acute myeloid leukaemia and acute lymphoblastic leukaemia, studying the role of post-transplant maintenance and donor lymphocyte infusion (DLI) and optimising graft-versus-host disease prophylaxis. 3 trials have been opened with a mean of 12 months to set-up (range 8-18). In its first two years, the IMPACT network has randomised 183 patients to 3 trials. Of note, one trial - Pro-DLI, a randomised trial of DLI administration post-transplant-has fully recruited within 24 months - 8 months ahead of its scheduled target.

Conclusions: Investment in the IMPACT trials hub and network has rapidly transformed set-up and recruitment to prospective randomised trials in SCT within the UK. Key to this success has been its ability to accelerate and coordinate both trials set up and recruitment across a 20 million population. Further investment in such accelerated trial models is required across Europe if patient outcomes after stem cell transplantation are to be improved.

Clinical Trial Registry: N/A

Disclosure: Nothing to declare.

P006

A region-wide Retrospective Analysis of Outcome for Patients with Newly Diagnosed Acute Lymphoblastic Leukemia

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Background: Recently, the prognosis for patients with acute lymphoblastic leukemia (ALL) has been improved by the introduction of tyrosine kinase inhibitors for Philadelphia chromosome-positive (Ph+) ALL patients and pediatric-inspired protocol for adolescent/young-adult (AYA) patients, and the indication of allogeneic stem cell transplantation (allo-SCT) at first complete remission (CR1) needs to be reassessed. We therefore retrospectively analyzed the impact of allo-SCT for patients with ALL in the era of TKIs and pediatric-inspired protocol for AYA.

Methods: Clinical data for 512 patients who were diagnosed as having ALL between 2007 and 2017 were collected from 21 centers in Hokkaido, Japan.

Results: The median age of the patients was 55 years (range: 15-84 years). Ninety-two of the patients were pediatric (0-14 years), 86 were AYA (15-35 years), 195 were adult (36-65 years) and 148 were elderly patients (66-years). Cytogenetic (G-banding) results were available in 486 patients. Three hundred forty-seven patients had abnormal karyotypes (AK), and 139 patients had normal karyotype (NK). The BCR-ABL fusion gene, including masked Ph+, was positive in 193 patients, and 181 (93.8%) of them were more than 36 years. Abnormalities of complex karyotype were seen in 94 of the patients. After a first remission induction therapy, 418 of 467 (89.5%) evaluable patients achieved complete remission (CR), and BCR-ABL positive patients showed better CR rate than those without BCR-ABL (93.7% vs. 87.4%, P=0.04). At the median follow-up of 1180 days (9-4049 days), overall survival (OS) was superior in patients with NK than those with AK (P=0.01), and BCR-ABL positive patients showed poorer OS than those without BCR-ABL (P=0.01). One hundred fifty-three patients received allo-SCT at CR1. The median age of those patients was 44, and BCR-ABL was positive in 53.9% of those patients. Allo-SCT did not improve overall survival (OS) for patients aged below 35 years. However, allo-SCT significantly improved OS in patients aged over 36 years with or without BCR-ABL (p< 0.01and p=0.03). In BCR-ABL positive patients, allo-SCT improved OS even for patients who achieved molecular remission after first course of chemotherapy (P=0.006). By subgroup analyses of the age groups (pediatric, AYA, adult and elderly), there were no difference of OS between NK and AK. In adult and elderly patients, OS was not different between BCR-ABL positive and negative patients, though in patients over 70 years, BCR-ABL positivity was associated with superior OS (Hazard ratio, 3.2; 95% confidence intervals, 1.04-4.78, P=0.02). In adult or elderly BCR-ABL negative patients, OS of patients with complex karyotype was inferior to those without complex karyotype. Among those patients who achieved CR1 after a first induction therapy, allo-SCT at CR1 was associated with superior OS [HR, 0.40; 95%CI, 0.39- 0.96, P=0.03].

Conclusions: Allo-SCT improved OS for patients with ALL aged over 36 years regardless of BCR-ABL positivity in the era of TKI. Allo-SCT at CR1 should be considered for adult BCR-ABL negative ALL patients, especially in patients who have received non-AYA chemotherapy regimen.

Disclosure: Shuichi Ota received the honoraria of lecture fee from Novartis.

P007

Pre-harvest Higher Donor Foxp3 Mrna and Lower CD4+ T Cell Concentration Predict Increased Risk of all Relapse after Myeloablative Hct with T-replete Bone Marrow Grafts

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Background: The curative effect of HCT for acute leukaemia is due in part to the donor T cell-mediated graft-versus-leukaemia reaction (GvL). Yet, post-HCT relapse remains a major cause of treatment failure. Donor regulatory T cells expressing the transcription factor Foxp3 (Tregs) have been found to reduce donor T cell-mediated GvHD without compromising GvL.

Methods: We have obtained contrasting results by assessment of the level of Foxp3 mRNA expression by qPCR in pre-harvest donor blood CD4+ T cells in a consecutive series of 45 children and adults, median age 16.7 years, with ALL in 1st or 2nd CR who received myeloablative HCT using T-replete bone marrow grafts and post-HCT cyclosporine GvHD prophylaxis. Donor was an HLA identical sibling (N = 11) or an alternative, unrelated (N = 33) or other family (N = 1) donor. Anti-thymocyte globulin (ATG) was given during the pre-HCT conditioning to 28 of 34 patients with an alternative donor.

Results: Post-HCT relapse, defined morphologically, occurred in 17 patients median 363 days post-HCT. By Cox multivariate proportional hazard regression, the effect of donor blood Foxp3 mRNA level on relapse did not meet the proportionality assumption. Proportionality was achieved after dichotomy at the median time of relapse. No effect of donor Foxp3 mRNA level was demonstrated within the first 363 days after HCT. However, after day 363 a higher donor Foxp3 mRNA level was associated with an increased risk of relapse. Thus, seven of eight late relapses occurred in recipients from donors with pre-harvest Foxp3 mRNA level above the median. In contrast, a higher pre-harvest donor CD4+ T cell concentration was associated with a reduced relapse risk. In the multivariate regression analysis, a significant interaction between the pre-harvest donor CD4 T cell concentration and the use of ATG in the conditioning regimen was observed, indicating that the effect associated with donor CD4 T cells was modified by ATG, compatible with the notion that the effect associated with donor CD4 T cell concentration was abrogated in recipients who received conditioning including ATG. However, due to the small sample size it is premature to draw definite conclusions regarding the effect of ATG. Cumulative relapse incidence curves supported the Cox univariate and multivariate regression analysis. Furthermore, we observed a reduction of the probability of surviving in continuous CR associated with higher pre-harvest donor Foxp3 mRNA level and decreased pre-harvest donor CD4 T cell concentration.

Conclusions: A higher Foxp3 mRNA level in CD4+ T cells isolated from pre-harvest donor blood was associated with an increased risk of late relapse in patients with ALL after myeloablative HCT with T-replete bone marrow graft, suggesting that donor Tregs may inhibit GvL. In contrast, a higher pre-transplant donor CD4+ T cell concentration was associated with a reduced relapse risk. The donor CD4 T cell effect was restricted to patients who did not receive ATG during pre-transplant conditioning.

Disclosure: Nothing to declare.

NJ and TF contributed equally to this work.

P008

Epidemiology, Management and Economic Impact of Acute Myeloid Leukaemia and Myelodysplastic Syndrome in Spain: A Claims Database Analysis

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Background: To review epidemiology, management, use of resources, and costs of acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) via the evaluation of patient records.

Methods: Data were extracted from the Ministry of Health records via the Spanish claims database Minimum Basic Data Set. The database contains patient records compiled in 192 private and 313 public hospitals, covering all Spanish regions, between 1997 and 2015 for AML and between 2008 and 2015 for MDS, according to data availability. All records corresponding to AML and MDS were identified using the International Statistical Classification of Diseases and Related Health Problems version 9 (ICD9) codes: 205.00, 205.01, 205.02, 238.72, 238.73, 238.74, and 238.75. The costs of healthcare usage were calculated based on the mean costs of medical procedures as determined by the Spanish Ministry of Health, which exclude prescription medication.

Results: Overall, records of 39,568 patients with AML and 33,091 with MDS were analysed. In most cases, the AML type was not registered; 9% of the patients were registered as in remission and 1% in relapse at first entry within the study period. When MDS was specified, 18% of the patients were registered with low-grade MDS lesions, 8% with high-grade lesions, and 1% with 5q deletion. Mean age at AML diagnosis was 59 years (SD=21), whereas for MDS it was 78 years (SD=13). Patients were mostly between 70 and 89 years of age and predominantly male. In terms of disease management, of the 102,783 and 64,556 admissions registered for AML and MDS, respectively, 79% and 48% were attributed to haematology services and 58% and 83% of admissions were not scheduled; the median length of hospital stay was 17 days (IQR=26) for AML and 7 days (IQR=9) for MDS. Chemotherapy was the most common procedure performed in patients with AML (44%), followed by platelets transfusion (31%). Transfusion of packed cells (41%) and chest x-ray (20%) were the most common procedures in patients with MDS. There was an

increase in bone marrow and hematopoietic stem cell transplants over time in Spain during the study period, from 171 in 1997 (1,494 patients) to 477 in 2015 (3,611 patients). Mean annual direct medical costs were measured throughout the study period and were €66,422,245 for AML and €42,635,313 for MDS; both displayed an increasing tendency over time, with the costs of AML increasing 3.7-fold between 1999 and 2011. Of these, €15,843,982 and €2,705,791 were directly linked to transplants. Mean annual costs per patient were €1,821and €1,288, respectively. In most admissions, (>96%) costs were financed by the Spanish social security system.

Conclusions: This retrospective study identifies patient characteristics, disease management, and health resource use related to AML and MDS treatment in Spain. AML and MDS represent a large burden for the National Spanish Healthcare System, with substantial costs incurred in secondary care settings. A large portion of these costs can be attributed to the increasing number of bone marrow and hematopoietic stem cell transplants.

Disclosure: Teresa Briones is an employee of and holds stock/stock options in Jazz Pharmaceuticals. The other authors have no conflicts of interest to declare.

P009

Pre-transplant Bone Marrow Cellularity and Blood Count Recovery are not Associated with Relapse or Survival Risk following Allogeneic Stem Cell Transplant for AML In Cr1

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Background: Allogeneic hematopoietic stem cell transplantation (HSCT) can be curative for acute myeloid leukemia (AML). Novel therapies may render patients' bone marrows profoundly hypocellular and be associated with prolonged post-therapy pancytopenia. In individual patients, bone marrow cellularity (BMC) at pre-transplant assessment (PTP) and post-treatment pancytopenia (leading to classification as CR-incomplete [CRi] as per ELN 2017 criteria) may be a manifestation of disease persistence, and this clinical response to chemotherapy is concerning for treating physicians.

Methods: In the present retrospective study, we examined the impact of BMC and post-treatment blood count recovery on a single-center cohort of 342 patients who underwent HSCT for AML in CR or CRi from January 2013 until December 2018. Data was updated as of November 2019. Median age was 57 years (range 18-73). Disease status at PTP was first complete remission (CR1) in 86% and CR2 or beyond in 56% of patients. Myeloablative conditioning was administered to 31% of patients while 69% received reduced-intensity conditioning. In vivo T-cell depletion was given to 75% of patients. Donors were matched-unrelated, matched-related and haplo-identical related (200, 108 and 34). The median follow-up of survivors was 31 months (10-81).

For BMC, patients were grouped as scoring aplastic (< 10%), hypocellular, normocellular and hypercellular for age (22, 89, 174 and 52 patients respectively; 5 patients had missing data); BMC was assessed by established pathology criteria. For ELN response (ELNr) at PTP, all patients had BM blasts fewer than 5%, and those having neutrophils ≥ 1 and platelets ≥ 100 at PTP were deemed as CR, otherwise CRi (190 and 152 patients respectively). MRC cytogenetic risk as per Grimwade, et al 2010 was favorable=21, intermediate=227, adverse=66 and unknown=28.

Cox proportional hazard model was used to analyze the effects of variables on overall survival (OS) and Fine and Gray's competing risk regression model was used to examine the effect of variables on cumulative incidence of relapse (CIR).

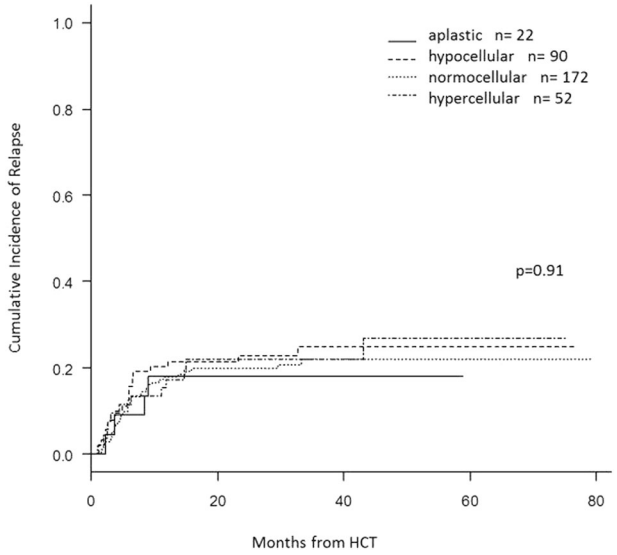
Results: OS of the whole cohort at 2y was 56.08%, while CIR was 20.31%. CIR for BMC groupings was aplastic 17.28%, hypocellular 22.60%, normocellular 19.63%, hypercellular 21.89%, p not significant (ns), see Figure 1; and for ELNr, CR 18.41%, CRi 22.69%, p ns. OS for BMC was aplastic 63.64%, hypocellular 49.39%, normocellular 56.34%, hypercellular 60.42%, p ns, and for ELNr, CR 56.97%, CRi 55.06%, p ns.

The distribution of MRC cytogenetic risk by BMC was not significantly different (p=0.26) nor was primary induction failure (p=0.759), HCT-CI (p=0.495) or usage of myeloablative conditioning vs reduced-intensity (p=0.988). ELNr CRi was more likely in BMC aplastic and hypocellular, than CR (p< 2.62e-8).

Multivariate analysis confirmed that neither BMC nor attainment of ELNr CR vs CRi had an impact on OS or relapse. Other factors such as age at transplant (p< 0.0001) and chronic GvHD (p=0.0003) influenced OS, while MRC cytogenetic risk (p=0.0009) and chronic GvHD (p=0.0011) affected relapse.

Conclusions: Neither ELN response status (CR vs CRi) nor bone marrow cellularity at pre-transplant assessment influence relapse post-transplant or OS. Hypocellularity and

CRi should not be considered negative prognostic factors for post-transplant outcomes of AML.



[Figure 1: Cumulative incidence of relapse of bone marrow cellularity groupings.]

Disclosure: Nothing to declare.

P010

Immunotherapy Salvage for b-precursor Acute Lymphoblastic Leukemia Relapsing after Allogeneic Stem Cell Transplantation: A Retrospective Analysis by the Alwp of the Ebmt

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Background: Blinatumomab (BLINA) and inotuzumab ozogamicin (INO) have been used for relapsed and refractory B precursor acute lymphoblastic leukemia (ALL) with or without prior allogeneic hematopoietic stem cell transplantation (HSCT). In an international phase II study of 64 patients relapsing after HSCT and treated with blinatumomab, 1-year OS was 36% (Stein AS et al., BBMT 2019), which compared favorably with historical cohorts treated with chemotherapy, donor lymphocyte infusions or a 2nd HSCT (Spiridonidis A et al., Leukemia 2012). Our retrospective analysis evaluates (i) the impact of BLINA and INO as salvage therapy post-HSCT on OS in a larger patient cohort, (ii) the safety of additional DLI and (iii) the outcome of patients undergoing a 2nd HSCT.

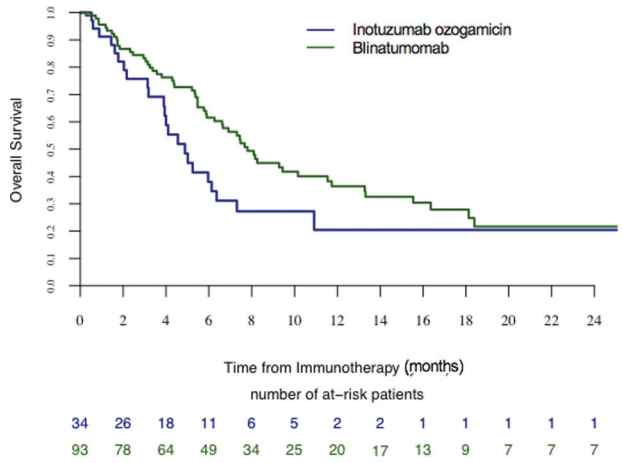
Methods: We identified 133 adult patients median age 36 (range, 18-68) years with Philadelphia-negative ALL who were treated with either BLINA (n=93, 70%), INO (n=34, 26%) or both (n=6, 4%) within 180 days after their first molecular or hematologic relapse following a first HSCT, performed 2012-2018. Patients were transplanted in CR1 (53%), CR2 (34%) or CR3 (13%) from a matched sibling (32%), matched unrelated donor (55%), other relative (11%) or umbilical cord blood (2%) using myeloablative or reduced-intensity conditioning (77% and 23%, resp.). OS was calculated by Kaplan-Meier analysis. In the multivariate Cox analysis, patient age, CR1 at HSCT, donor type as well as factors associated with a p value < 0.10 in the univariate analysis were included.

Results: Relapse occurred at a median of 7.1 (range, 0.8-80.6) months post-HSCT and immunotherapy was started a median of 15 (range, 0-172) days after relapse. With a median follow-up of 14.8 (range, 7.7-28.3) months after immunotherapy, 1-year OS in all patients was 30.9% (95% CI: 21.7-40.2). In patients treated with either INO or BLINA, probability of 1-year OS was 20.4% (95% CI: 3.6-37.2) and 36.4% (95% CI, 25.2-47.6), resp. (Figure 1, p=0.041). Immunotherapy was applied as monotherapy (n=81, 61%) or associated with chemotherapy (n=52, 39%). Additional cellular therapy included DLI prior to (n=6, 5%) or subsequent to immunotherapy (n=24, 18%) and probability of 2nd HSCT within one year was 26% (95% CI: 18.8-33.8); these 39 patients had a 1-year OS of 42.4% (95% CI: 23.8-61.1) after 2nd HSCT. However, neither additional chemotherapy nor DLI or 2nd HSCT (as time-dependent variable) had a statistically significant effect on OS.

A total of 85 patients died, mostly from leukemia (n=53, 63%) or infection (n=20, 24%). Out of all 40 patients treated with INO, two were reported as dead due to SOS

(both received a 2nd HSCT). In multivariate analysis, female gender (HR 0.45, p=0.001), sibling vs other donors (HR 0.52, p=0.009) and longer time to relapse (HR 0.96, p=0.012) proved to be independently associated with better OS.

Conclusions: In patients relapsing after an allogeneic HSCT, BLINA or INO immunotherapy was associated with 1-year OS rates of 20-36%. Additional DLI or subsequent HSCT seemed to be safe, but did not improve outcome.



[Fig. 1: Overall survival for patients receiving either INO or BLINA after relapse.]

Disclosure:

Gesine Bug: Pfizer: advisory board

Sebastian Giebel: Amgen: honoraria, advisory boards, travel grants; Pfizer: honoraria, advisory baords.

P011

Comparison of pre-transplant Comorbidity Indices in Acute Leukemia Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

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Background: In 2005, Sorror et al introduced a new prognostic scale for the candidates of allogeneic

hematopoietic stem cell transplantation (allo-HSCT). Since then, several methods were developed to predict the risk of transplant related mortality. This retrospective study was designed to evaluate and compare the efficacy of the conventional and novel prognostic tools including hematopoeitic cell transplant (HCT)-comorbidity index (HCT-CI), HCT-CI/Age and HCT-composite risk (HCT-CR) indices.

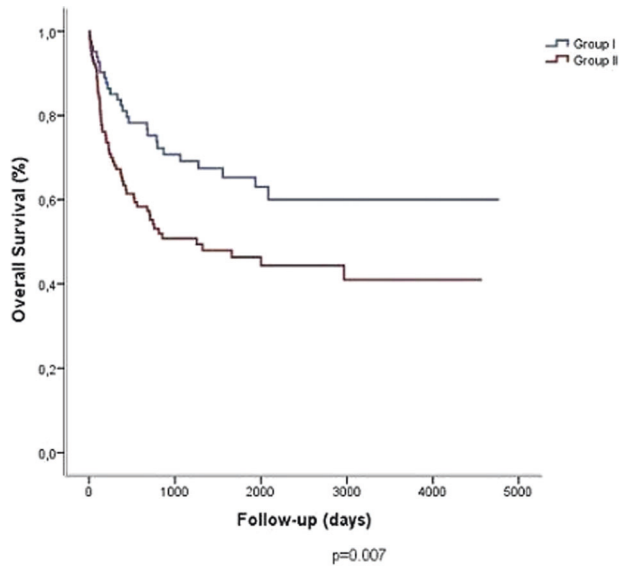
Methods: A total of 215 acute leukemia (acute myeloid leukemia / acute lymphoblastic leukemia:

129/86) patients [median age: 37(18-71) years; M/F: 135/80] were included in this study. Medical records of the patients were retrospectively reviewed. Besides European Society for Blood and Marrow Transplantation (EBMT) score, Eastern Cooperative Oncology Group (ECOG) and Karnofsky scales; pre-transplant risk evaluation was performed using HCT-CI, HCT-CI/Age and HCT-CR, as previously described. Disease risk stratification was based on European Leukemia Net guidelines.

Results: Pre-transplant risk scales including EBMT [median score: 3(0-7)], HCT-CI [median score: 1(0-6)], HCT-CI/Age [median score: 1(0-7)] and HCT-CR [Low: 84(39.1%); Intermediate: 11(5.1%); High: 112(52.1%); Very high: 8(3.7%)] were evaluated as well as ECOG [median score: 1(0-4)] and Karnofsky scales [median score: 40(40-100)]. Pre-transplant disease status was first complete remission (CR1) in 150 patients (69.8%), CR2 in 29 patients (13.5%), >CR2 in 1 patient (0.4 %), partial remission in 10 patients (4.7%) and progressive disease in 25 patients (11.6%). A total of 162 HSCTs (75.3%) were related, 44(20.5%) were unrelated and 9(4.2%) were haploidentical transplants. Graft source was peripheral blood in 208 (96.7%) and bone marrow in 7 transplants (3.3%). Conditioning regimen was myeloablative in 158 (73.5%) and reduced intensity in 57 patients (26.5%). Patients were divided into two subgroups based on HCT-CR. Group 1 represented low-risk patients, whereas Group 2 was composed of intermediate, high and very-high-risk patients. Sinusoidal obstruction syndrome was found to be more frequent in Group 2 (11.2% vs 2.8%; p=0.021). Prevalence of cytomegalovirus reactivation and acute/chronic graft versus host disease was similar in both groups. At a median 681(4-4774) days of follow-up, patients with low HCT-CR scores represented significantly higher probability of progression free survival (70% vs 53.5%; p=0.016) and overall survival (60% vs 41%;p=0.007) (Figure 1). In univariate analysis, HCT-CI (p=0.002), HCT-CI/Age (p=0.015), HCT-CR (p=0.009), EBMT (p=0.007), ECOG (p< 0.001), Karnofsky (p< 0.001) and C reactive protein levels had significant impact on survival. The significant impact of HCT-CI (p=0.018), HCT-CI/Age (p=0.008) and EBMT (p< 0.001) was confirmed in multivariate analysis.

Conclusions: To date, a variety of factors have been defined to determine allo-HSCT outcome. Both patient and disease related factors may have a role in predicting transplant related morbidity and mortality. This retrospective study underlines the importance of pre-transplant risk

evaluation, although more experience is required to identify the better approach in order to improve our foresight in allo-HSCT setting.



[Figure 1. Impact of Risk Groups on Overall Survival]

Disclosure: Nothing to declare.

P012

Salvage use of venetoclax-based Therapy for Relapsed AML Post Allogeneic Hematopoietic Stem Cell Transplant

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Background: Relapsed acute myeloid leukemia (AML) after allogeneic hematopoietic stem cell transplant (alloHCT) has a dismal prognosis. The efficacy of venetoclax (VEN) in post alloHCT relapse is understudied. Here we analyze the efficacy and application of VEN in this setting.

Methods: After IRB approval, retrospective analysis was performed for patients with de-novo or secondary AML who received alloHCT, and experienced relapse and were salvaged with VEN+ hypomethylating agent (HMA)/Cytarabine

Results: We identified 12 pts (50% female); median age 57 years (range 30 - 70). Five pts had de-novo AML (ELN adverse risk cytogenetics=2, intermediate risk cytogenetics =3) & 7 pts had secondary AML (ELN adverse risk=5, intermediate risk =2). The donor source was matched unrelated donor (n=7), matched related donors (n=2), haploidentical (n=2) and 1 umbilical cord transplant. 8 pts were in CR1, 3 pts were in CR2, and 1 with persistent residual disease at the time of transplant. Time from transplant to relapse was 196 days (range 77-1142). Time from alloHCT to VEN initiation was 378 days (range 104-1153). Median # of VEN cycles was 2 (1-5). Overall response rate (PR+CR) was 33% (n=4). Median time to CR was 82 days (range 38-125) with median duration of CR of 91 days (1 pt continuing in CR). The Grade 3 or 4 toxicities were infection (n=3) and neutropenia (n=5). Two pts had flare of GVHD on VEN requiring treatment: liver GVHD (n=1); skin, ocular GVHD (n=1). Full molecular information was available for 10 pts at diagnosis and in relapse post-alloHCT: 3 pts acquired TP53 mutations at relapse. Figure 1 outlines evolution of molecular abnormalities in the rest of the cohort, associated venetoclax doses and best responses. None of the pts experienced graft failure after salvage therapy. Estimated median overall survival after VEN was 73 days (Range 2- 403). Nine pts progressed on VEN, 2 pts received subsequent therapy [DLI (n=1), gemtuzumab ozogamicin (n=1)]; 8 of the 9 pts died. Median time from progression on VEN to death was 13 days (IQR 2-43). The most common molecular mutation among responders was TP53. Among 5 pts with TP53 mutation in our cohort; 3 achieved CR. Responders had a better survival compared to non-responders with a median OS 403 days vs 43 days respectively (Log-Rank p=0.011). Responders were naïve to HMA.

Conclusions: VEN-based therapy achieved an ORR of 33% in AML pts with post-transplant relapse, and prolonged survival in responders despite the presence of TP53 mutations. Our observations provides evidence that even in the context of post-transplant relapse with adverse mutations and limited treatment options, VEN- based therapy may be effective in inducing CR and possibly improves survival in responding patients.

Disclosure: Mark Litzow: Astellas: Research Funding; Amgen: Research Funding; Abbvie: Research Funding; Novartis: Research Funding; Sanofi: Consultancy; New-Link Genetics: Consultancy; Actinium: Research Funding; Pluristem: Research Funding; Servier: Consultancy

Mrinal Patnaik: Stem Line Pharmaceuticals.: Membership on an entity´s Board of Directors or advisory committees.

P013

Factors Predicting the Outcome of Allogeneic Stem Cell Transplantation in ph-negative Acute Lymphoblastic Leukemia

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Background: In modern practice, a significant proportion of adult patients with acute lymphoblastic leukemia (ALL) undergo allogeneic bone marrow transplantation (allo-HSCT). The technology of allo- HSCT is improving, therefore it is necessary to evaluate the results and factors affecting the outcome of allo- HSCT in patients with ALL.

Methods: In the study included 191 patients with Ph-negative ALL with median age of 25 years (range, 18-61) who received allo-HSCT undergoing allo-HSCT from HLA-matched sibling (n=38), unrelated (n=123) or haploidentical (n=30) donor in R.M.Gorbacheva Memorial Institute between 2007 and 2019. Median follow-up time was 30 months (range, 2-148 months). By the time of allo-HSCT 41 (21,5%) of patients were in first remission, 80 (41,9%) in second remission, 26 (13,6%) in third or more remission, 44 (23%) in active disease. Reduced intensity conditioning (RIC) was performed in 90 patients (47,1%), myeloablative - in 101 patients (52,9%). Conventional calcineurin-based graft-versus-host disease (GVHD) prophylaxis was used in 90 patients (47,1%). Posttransplant cyclophosphamide(Cy) GVHD prophylaxis was used in 101 patients (52,9%).

Results: 5-years OS and EFS were 44,5% and 37,7%, accordingly, whereas 5-year incidence of relapse was 28,8%. Disease status was the main factor determining the results of transplantation in Ph-negative ALL patients. 5-years OS, EFS and relapse rate (RR) were 73,1%, 56,2%, 34,6%, 2,3% (HR=1,772, 95%Cl 1,46-2,151, p< 0,001) and 68,3%, 45%, 26,9%,2,3% (HR=1,764, 95%Cl 1,469-2,119, p< 0,001), 17,1%, 21,2%, 38,4%,47,7% (HR=2,528, 95%Cl 1,37-4,735, p< 0,001) in 1st, 2nd, 3d and active disease, respectively. RIC was associated with worse survival and increased transplant-related mortality (TRM), 5-years OS, EFS and TRM were 35,3% vs 52% (HR=1,64, 95%Cl 1,113-2,417, p=0,01), 28,8% vs 45% (HR=1,538, 95%Cl 1,069-2,213, p=0,02), 43,4% vs 25% (HR=1,817, 95%Cl 1,073-3,129, p=0,01) for RIC and MAC, respectively. TRM was higher after haplo than after unrelated and HLA-matched sibling allo-HSCT (50% vs 32,5% vs 23,7%, p=0,04). Positive minimal residual disease (MRD) before allo-HSCT determined high RR: 57,1% vs 7,1% (HR=8.119, 95%Cl 2,809-23,21, p< 0,001) for MRD positive and MRD negative. GVHD prophylaxis with posttransplant Cy significantly improved relapse-free and GVHD-free survival (GFRS) and reduced TRM. GFRS in1st, 2nd remission was 45,9% vs 10,8% (p< 0,001) patients for Cy and standard GVHD prophylaxis, respectively.

Conclusions: Allo-HSCT in patients with Ph negative ALL is low efficacy. MAC and posttrsnsplant Cy can improve results of Allo-HSCT in patients with Ph negative ALL. Achievement of MRD-negative status is crucial for the outcome thus the studies of bridging strategies are warranted.

Disclosure: Nothing to declare.

P014

Role of Chimerism and flow-cytometric Monitoring of Measurable Residual Disease(MRD) after Allogeneic Hematopoietic Stem Cell Transplantation(Allo-HSCT) in Predicting Relapse in Acute Myeloid Leukemia(AML)

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Background: Allo-HSCT is a well-established postremission therapy in adults with AML with certain high-risk features. Two different techniques are currently available for posttransplantation surveillance of disease remission: characterization of posttransplantation chimerism and specific detection of MRD. In this retrospective single-center study, we have attempted to evaluate the impact of both chimerism and flow-cytometric MRD in relapse in a population of patients with AML who received an allo-HSCT.

Methods: A total of 65 patients with AML who achieved complete remission at day+100 after allo-HSCT were included. Chimerism and MRD analysis were performed routinely at 1, 3, 6, 9, 12 months after transplantation at our hematology laboratories. Flow cytometry analyses were done using the flow cytometry system FACSCalibur(BD Biosciences, San Jose, CA). Presence of donor chimerism was determined with microsatellite analysis of short tandem repeats(STR) by PCR (Qiagen Plex Plus Kit(100) PCR Assay, genemapper v3.2). We used our institutional database to evaluate details and characteristics of patients and transplant outcomes.

Results: A total of 194 consecutive patients with AML underwent allo-HSCT at our center between January 2010 and August 2019. For the present study, 65 patients (Female/male: 29/36; median age: 40.5 years(range: 18-67 years)) who had relapsed after Allo-HSCT were evaluated. Median follow up from allo-HSCT was 10.3 months(4-104 months). A total of 36(55.3%) patients underwent allo-HSCT from related donor while 29(44.7%) patients were transplanted from unrelated donors, respectively. The stem cell source was peripheral blood stem cells in 63 patients(96.9%). Fifty-patients received myeloablative conditioning, whereas 15 received a reduced intensity regimen. With regard to MRD status before transplantation,

37 of 65 patients were MRD-negative and 12 patients were MRD-positive and remaining 16 patients had active disease at the time of allo-SCT. After transplantation, 4 of the 37 patients who were initially MRD-negative changed to MRD-positive, whereas 9 of the 12 initially MRD-positive patients achieved at least temporary MRD negativity. Six of the patients with active disease achieved MRD negativity after Allo-HSCT. The relapse rate was 60% at 1 year and higher in the patients with mixed CD3 chimerism(n=20) compared with those with complete chimerism(n=45) at day+90. In addition, at time of relapse among study population only 33 patients had mixed CD3 chimerism. Patients with MRD positivity at day +28 after HCT had the highest incidence of relapse among all prognostic groups analyzed. The median time to hematologic relapse after detection of MRD relapse was median 62 days. Among all patients, 23 patients with MRD relapse and subsequent hematologic relapse also have been detected via a decrease in chimerism. Twenty-one patients had received DLI for MRD-positivity. During follow up 41 deaths were noted.

Conclusions: In light of recent advances in therapeutic options for post-transplantation relapse, improving our understanding of the available relapse prediction tools is becoming increasingly important. Our data presented here show the superiority of flow cytometric MRD over chimerism analysis to predict relapse after allogeneic stem cell transplantation. Therefore, further studies of larger randomized cohorts with high quality data management are required to clarify the role of post-transplantion MRD and chimerism in predicting relapsed in AML.

Disclosure: Nothing to declare.

P015

Sorafenib Prolonged Maintenance in flt3-mutated AML Post Transplantation

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Background: FLT3-mutated acute myeloid leukemia (AML) has high risk of relapse and still poor outcomes despite allogeneic stem cell transplantation (HSCT). Sorafenib is a multi-kinase inhibitor active in FLT3+ AML both in the pre- and post-HSCT setting.

Methods: from June 2017 to September 2019, 10 patients with advanced FLT3+ AML at transplantation received sorafenib as maintenance therapy after HSCT. Sorafenib was given off-label after provision of an informed signed consent and in the absence of alternative therapeutic options in all patients. Indications were both achievement of complete morphological remission (CR) and hematological engraftment. Exclusion criteria were active GvHD, infections and non-hematological toxicities. Sorafenib administration was prolonged until intolerance or disease progression.

Results: clinical-biological features at baseline and at sorafenib initiation are reported in Figure 1. Median time from HSCT to sorafenib initiation was 121 days (range 75-250). Nine out of 10 patients were still on GvHD prophylaxis. Sorafenib starting dosage ranged from 200 mg QD (6 patients) to 200 mg BID (4 patients) depending on clinical conditions and concomitant medications. Maximal dosage in our series was 200 mg BID in 6 patients and 200 mg QD in 4 patients.

Sorafenib was well tolerated: no hematological toxicity was observed. Most common grade I-IV adverse events (AE) were skin rash (20%), arterial hypertension (10%), sinus bradycardia (10%), diarrhea (10%), hyperbilirubinemia (10%) and peripheral neuropathy (10%). Most common grade III-IV AE was arterial hypertension (10%). Any patient died because of treatment. Four patients had dose reduction and 2 patients had temporary interruption of sorafenib because of AE.

Two patients developed acute GvHD grade 2 overall: no one had previous GvHD; one patient obtained complete remission with steroid treatment, the second completely resolved GvHD after second line therapy (infliximab). Three patients developed chronic GvHD: 2 classic and 1 overlap, maximal overall severity was moderate, 2/3 patients received ≥2 treatment lines.

After a median follow up of 15 months (range 6-36), all patients were alive. Nine patients were still on therapy while 1 patient finally stopped sorafenib after 4 days of administration due to a drug-related grade II sinus bradycardia.

Median duration of maintenance was 360 days (range 4-886). At last bone marrow evaluation, all patients were in CR and all evaluable patients (8/10) obtained MRD negativity.

Conclusions: post-transplantation maintenance with sorafenib proved feasible in FLT3+ AML: we did not reported major toxicity or adverse events. Sorafenib was effective both in preventing relapses and obtaining deep and durable remission.

Disclosure: Nothing to declare.

P016

Pulmonary Complications (PC) after Allogeneic Hematopoietic Stem Cell Transplantation (Allo-HSCT) in Children with high-risk Acute Leukemia (AL)

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Background: Despite advanced effective prophylaxes, PC occur in 40-60% of allo-HSCT recipients, accounting for considerable morbidity and mortality. Transplant procedure influence on development of PC, eg conditioning regimen, immunosuppresive therapy, status of diseases, but complex of these aspects didn't analyzed in children underwent allo-HSCT. Primary end point:to determine effect of PC in children with AL after allo-HSCT on overall survival (OS). Secondary end points:to describe causes, incidences rates PC and risk factors of such complications following allo-HSCT.

Methods: We included children (n=173) with ALL (n=99) and AML (n=74), median age 11(0-18)y.o. Remission of disease (CR) at allo-HCST was in 108 pts (62%). Related compatible donor-in 16(9%) patients, 80 (46%) haploidentical, and 77(45%) matched unrelated donor. Source of HSC was bone marrow (BM) n=138, peripheral blood stem cells (PBSC) n=35 cases. Myeloablative conditioning regimen (MAC) based on busulfan (Bu) (10-16 mg/b.w.) received 105(92%) patients on treosulfan-9(8%) pts., reduced intensity conditioning (RIC) based on melphalan-37(63%) pts, based on Bu(8 mg/b.w.)-22(37%) pts. GVHD prophylaxis was mono-PTCy in 25pts (15%), PTCy±CNI±m-TOR in 68 pts(39%), PTCy±CNI ±MMF in 80 pts(46%). Clinical data were analyzed to determine whether the incidence of PC was correlated with risk factors such as age, sex, underlying disease type, transplant type, conditioning regimen, prophylaxis of GVHD using SPSS 23. Kaplan-Meier curves were used to estimate the probability of OS. A p value of < 0.05 was considered statistically significant.

Results: Among 173 pts 121(69%) had PC. Early pulmonary complications (EPC) (before D+100) occurred in 81% (n=98) of pts. Infections EPC observed in 97% (n=95): bacterial complications in 23pts(24%), fungi in 13pts(14%), viruses in 15pts (16%), combined infections: viruses+bacteria in 19pts (20%), viruses+fungi in 7(7%), bacteria+fungi in 11(11%), and combination of viruses, bacteria and fungi in 7(7%) cases. Non-infectious EPC occurred in 39%(n=38)pts: engraftment syndrome 40% (n=15), pulmonary edema 39%(n=15), pulmonary bleeding 3%(n=1), respiratory distress syndrome 13%(n=5). Late pulmonary complications (LPC) (after D+100) occurred in 66%(n=80) pts., infectious LPC observed in 30% (n=24), non-infectious LPC observed in 26%(n=21) pts. According to our data pulmonary changes were seen in 80 pts. In 24(30%) cases were focal, in 17(21%) infiltrative, in 26(33%) interstitial, and 10(13%) cases fibrotic. Three pts developed hydrothorax. 41 pts had no complications. Development of EPC in underlying diseases significantly affects overall survival (p=0.001). 5-OS in patients with early mild complications is 55%vs92.1% without complications. The OS of pts with LPC is 72,7% compared 61.5% of patients who had EPC and LPC (p=0.001). Incidence of PC in remission after MAC is 67,5%(n=77)vs72,9% (n=43) after RIC(p>0,05). Incidence of PC in pts with active underlying disease after MAC-70%(n=31) vs 95% (n=20) after RIC. Type of allo-HSCT, source of transplant, sex, age at the moment of allo-HSCT in CR pts didn't affect on development of PC(p>0,05).

Conclusions: Incidence of PC was significantly lower in patients receiving allo-HSCT in CR. Intensity of conditioning regimen does not affect the incidence of PC in patients with CR. The use of RICs in relapse increases incidence of PC. Development of early PC in patients after allo-HSCT worsens the prognosis and reduces significantly OS.

Disclosure: Nothing to declare.

P017

More than two Cycles of Consolidation Therapy pre-transplantation Benefits AML Patients in Cr1 Who Underwent HLA-matched Sibling Allografts: A Multicenter Study

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Background: Although the need for consolidation chemotherapy after successful remission induction therapy is well established in patients acute myeloid leukemia (AML) in first complete remission (CR1), the value of consolidation chemotherapy before HSCT remains controversial.

Methods: Our study retrospectively compared the effect of the number of pre-transplant consolidation on outcome after HLA-matched sibling stem cell transplantation (MSDT) for AML patients in CR1 in multicenters across China. In addition, our multicenter study also compared the effect of the consolidation therapy pre-transplant between MRD negative patients and MRD positive patients with AML in CR1 who received MSDT.

Results: In our study, we analyzed data of 373 patients with AML in CR1 from three centers across China. All of these 373 patients received MSDT in different centers. With a median follow-up of 969 days, those patients with ≧ 3 cycles of consolidation chemotherapy had higher incidences of LFS (85.6% vs. 67.0%, p< 0.001) and OS (89.2% vs. 78.5%, p=0.007), and better cumulative incidences of relapse rate (10.5% vs. 19.6%, p=0.020) and NRM (4.2% vs. 14.9%, p=0.001). For pre-MRD (minimal residual disease) negative AML patients in CR1 receiving MSDT with ≧ 3 cycles of consolidation chemotherapy had better LFS (85.9% vs. 67.7%, p=0.003) and lower cumulative probabilities of relapse (9.6% vs. 23.3%, p=0.013) than those with ≦ 2 cycles, but the two groups had comparable probabilities of OS (90.0% vs. 80.3%, p=0.051) and NRM (4.9% vs. 10.9%, p=0.127).

Conclusions: In conclusion, our results indicated that AML patients in CR1 who received MSDT might benefit from pre-transplant consolidation chemotherapy.

Disclosure: All authors declare. no competing financial interests.

P018

What can Cnv Analysis add to the Routine Genetic Description of AML Cases?

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Background: Genetical description of AML cases belong now to the standard diagnostic procedure, however it includes mainly chromosome banding assay (CBA) or FISH. In the present study we added information from microarray CNV analysis.

Methods: 127 AML cases (age:21-84, median:59 yrs, 62F/65M) diagnosed in years 2008-2019 (FAB M0=11, M1=37, M2=25, M3=6, M4=27, M5=11, M6=2, secondary=20, primary=107), classified (ELN genetic guidelines) as favourable=17.3%, intermediate=51.2%, unfavourable=31.5%, received treatment according to the PALG guidelines. Genetic work in addition to the CBA, 83 cases or FISH analysis (33 cases) included the microarray analysis of copy number variations (CNV).

Results: 1. The observed survival pattern of the patients followed that seen in the ELN analysis on the dependence of CBA and FISH alterations with survival.

2. CNV number (Catalog Agilent Cancer CGH+SNP 180K (74 patients) or Roche-WG Catalog NimbleGene 12x270K (53 patients)) was worked out using the Partek program (segmentation algorithm with default settings). Numbers of CNVs deletions in the patients varied from 3-104 (median: 22), amplifications from 6-172 (median: 26). Only autosomes were analysed.

3. 197 CNVs> 5 Mbp found in 38 patients could be compared to the picture of CBA in 14 and that of FISH in 24 patients. It appeared that CNV detected were seen either in the CBA or in the FISH in 86 situations. 111 identified CNVs were missed in CBA or FISH among which in 73 instances because the FISH probes are not suited for detection of these particular CNV, the rest 38 CNV which might be seen either in CBA or FISH were missed likely due to the technical reasons. A majority of discrepant results between the FISH or CBA and microarray were likely due to difficulties in proper identification of a part of additional or deleted chromosome seen (6 patients). Altogether, the results of CNV and the standard techniques were the same in 25 cases.

4. In a univariate analysis of the survival risk factors, it was found that better overall survival enjoyed patients:

- under 48 years of age (39 vs 16%, p< 0.001),
- with primary AML (23% vs 15%, p=0.084) compared to secondary AML,
- lacking NPM1 gene mutation (25 vs 11%, p= 0.044),
- who received allogeneic hematopoietic stem cell transplantation (28 vs 19%, p< 0.001),
- having more CNV aberrations in the group with normal karyotype or FISH (50 vs 16%, p=0.008),
- having t(8:21) (RUNX1/RUNXT1, 67 vs 20%, p=0.004). 67% of patients with t(8:21) had an aberrant expression of CD19 (>22% in the blasts) compared to 5% incidence in the patients without translocation (p< 0.001). CNV amplification in the RUNX1 gene was associated with aberrant CD19 expression (40% vs 7%, p= 0.054). In opposite CNV amplifications in the KMT2A gene (9 cases), independently if seen in the FISH assay (3 cases) or not, inversely affected the survival (0 vs 43%, p= 0.032, at the 18 month time point).

Conclusions: CNV analysis offers some information which are clinically valid but missed by CBA or FISH due to the technical reasons.

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Clinical Trial Registry: no applicable

Disclosure: The authors declare. that they have no conflict ofinterest.

P019

Comparison of the Prognostic Ability of the HCT-CI the Modified EBMT and the EBMT-ADT Pre-transplant Risk Scores for Acute Leukemia

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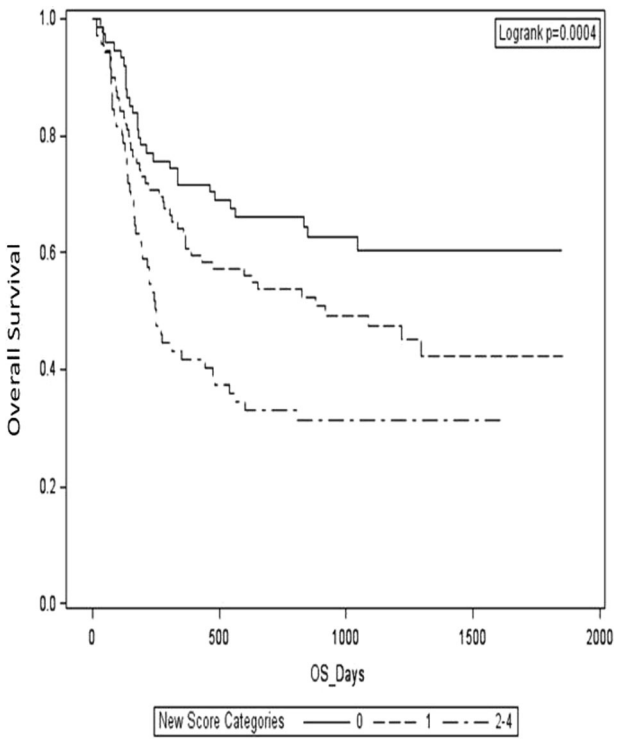
Background: Allogeneic hematopoietic cell transplantation (HCT) may provide cure for acute leukemia where indicated. However, its use is limited by transplant-related complications which lead to increased mortality. This has prompted the development of pre-transplant risk scores such as the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) and the modified European Group for Blood and Marrow Transplantation (mEBMT) score (that examines recipient age, remission status of leukemia, donor-recipient gender combination and donor match). In a large EBMT study Shouval et al (Journal of Clinical Oncology, 2015) developed a machine learning-based prediction model for mortality (EBMT-ADT) that can be used online.

Methods: In the present retrospective study, we examined the impact of the HCT-CI, mEBMT and EBMT-ADT on a single center cohort of 231 patients who underwent allogeneic HCT for acute leukemia from August 2014 until December 2017. Data was updated as of October 2019.

Results: Median age was 56 years (range 19-72). Acute myeloid leukemia (AML) was diagnosed in 200 patients, acute lymphoblastic leukemia (ALL) in 31 patients. Disease status at the time of HCT was first complete remission (CR1) in 81% and CR2 or beyond in 19% of patients. Myeloablative conditioning was administered to 31% of patients while 69% received reduced intensity conditioning. In vivo T-cell depletion was given to 76% of patients. Donors were HLA matched related in 33%, 10/10 matched unrelated in 44%, 9/10 unrelated in 12% and haploidentical in 11% of patients. The median follow up of survivors was 37 months (15-62 months).

For the HCT-CI, patients were grouped as score 0-1, 2-3 and >3 (116, 75 and 40 patients respectively). For the mEBMT score, patients were grouped as 0-2, 3 and 4-5 (76, 121 and 34 patients respectively), while for the EBMT-ADT the respective 100-day mortality was calculated for each patient (excluding haploidentical) and grouped as ≤4.1%, 4.1-11.5% and >11.5%. Patients with higher HCI-CI score demonstrated lower probability for OS (p=0.038, c-statistic 0.57), while neither mEBMT nor EBMT-ADT significantly stratified patients into prognostic groups (p=0.09, c-statistic 0.54 and p=0.28, c-statistic 0.53 respectively). Multivariable analysis for OS demonstrated that leukemia type (HR 1.82 for ALL, 95% CI 1.16-2.85, p=0.01), HLA matching (HR 0.61 for all fully matched donors, 95% CI 0.41-0.90, p=0.01) and HCT-CI (HR 0.50 for 0-1, 95% CI 0.31-0.81, p=0.004) had significant impact. Based on the HR, a new weighted score was developed for this cohort including leukemia type (AML=0, ALL=1), HLA matching (fully matched=0, mismatch unrelated or haploidentical=1) and HCT-CI (0-1=0, 2-3=1 and ≥4=2). The new score demonstrated improved prognostic capability compared to the other scores (p=0.0004, c-statistic 0.60) (Figure 1).

Conclusions: The mEBMT score and the EBMT-ADT do not adequately prognosticate OS in our cohort of acute leukemia patients undergoing allogeneic HCT. The HCT-CI performs better, however is not a powerful predictor. New approaches are required to develop a pre-transplant risk calculation tool that can be widely applicable to patients from various centers characterized by heterogeneous practices.



[Figure 1: stratification of OS by score based on leukemia subtype, mismatch and HCT-CI"]

Disclosure: Nothing to declare.

P020

GO-FLAG Regimen as a Bridge Therapy to Allogeneic Stem Cell Transplantation in Refractory/relapsed AML Patients

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Background: The patients (pts) with refractory or relapsed AML (r/rAML) have poor outcomes with 3-year overall survival (OS) no more than 10%. The main goal of therapy in pts with r/rAML is to achieve remission followed by allogeneic hematopoietic stem cell transplantation (alloHSCT). Introduction of targeted drugs is the most promising strategy in the modern therapy of hematological malignancies. Gemtuzumab ozogamicin (GO) is a recombinant, humanized anti-CD33 monoclonal antibody covalently attached to the cytotoxic antitumor antibiotic calicheamicin, which effectiveness depends on more than 75% expression of CD33-glycoprotein on leukemic blasts.

Methods: The study included 39 pts with median age 34 (18-61) years, 12/39, 31% pts were with primary refractory AML (RefAML), 27/39, 69% pts were with relapsed AML (RelAML). The first relapse (Rel1) had 19/27, 70% pts and two or more relapses (Rel≥2) - 8/27, 30%. The early relapse (eRel) was observed in 23/27, 85% and late relapse (lRel) were in 4/27, 15% of cases. Based on the ELN 2017 classification, the prognosis was favorable for 10 pts (26%), intermediate for 8 pts (20%), and adverse for 21 pts (54%). All pts treated by the combination of fractionated GO with regiment FLAG (GO-FLAG).

Results: The follow-up period was 27 month. The overall response rate (OR) was 69% (95% CI 54-81): complete remission was achieved in 63%, remission with incomplete hematologic recovery - 37%. The high OR was in pts with extramedullary disease - 85% (95% CI 58-96). AlloHSCT was performed after GO-FLAG in 17 (44%) pts (4- related, 4 - unrelated, 9 - haplo). In two cases alloHSCT was done in active disease. The median time from OR after GO-FLAG to HSCT was 61 (36-148) days. Overall survival and disease-free survival at 1 years (OS1 and DFS1) was 64% (95% CI 48-77) and 63% (95% CI 44-78), respectively. In the allogeneic group the median OS1 was 6 months and in the group without alloHSCT - 2 months. The median DFS1 in pts with and without alloHSCT after GO-FLAG was 4 and 3 months, respectively. The predictive factors associated with a higher response rate were: favorable ELN genetic group (favorable-90% vs intermediate-75% vs adverse-57%, p=0,05); RelAML (RefAML-42% vs RelAML-81%, p=0,02); blast level less than 60% (< 60% level -83% vs >60% level -50%, p=0,03). In all cases we observed neutropenia of 4 gr. and thrombocytopenia 4 gr. Severe hemorrhagic complications (subdural hematoma) was in 1 pts (2,6%). Sepsis was in 13% (95% CI 19-46); fungal infections were in 10% (95% CI 4-24). Hepatotoxicity was presented as a transient increase in ALT level (< 10ULN) in 10% (95% CI 4-24). Sinusoidal obstruction syndrome did not occur in any of the patients. Early mortality was 10% (95% CI 4-24), 4/39 pts. Causes of death were leukemia progression (1 pt), infectious complications (3 pts). No direct association with the GO and death was observed.

Conclusions: GO-FLAG demonstrated the efficacy and acceptable toxicity in pts with r/rAML and can be used as a bridge to alloHSCT.

Disclosure: Nothing to declare.

P021

The Impact of Allogeneic Transplantation in AML and Mds with Chromosome 3 Abnormalities

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Background: Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS) with chromosome 3 abnormalities are associated with adverse outcomes. The benefit of allogeneic stem cell transplantation (AlloHCT) in this setting is controversial. This study aims to assess outcomes in this group of patients undergoing AlloHCT.

Methods: This is a single-center retrospective study including 52 patients with AML and MDS with chromosome 3 abnormalities by conventional karyotyping, who received Allo-HCT from October 2000 to August 2019.

Results: The median age of patients was 50 years old (range 19-72). There were 38 patients with AML and 14 patients with MDS. Concurrent presence of monosomy 7

and complex cytogenetics was found in 15 (29%) and 36 (69%) patients respectively. Majority of patients with AML were in first complete remission (CR1) at the time of AlloHCT. Patients with MDS were Intermediate-2 (13%) or High risk (12%) by the International Prognostic Score System (IPSS). Patient and transplant characteristics are summarized in Table 1.

With a median follow up of 4 years, 2-year relapse free survival (RFS) was **33.65%** (95% CI, 20.75-47.03), overall survival (OS) was **32.46%** (95% CI, 19.63-45.95), cumulative incidence of relapse (CIR) was **48.08%** (95% CI, 35.39-65.31), non-relapse mortality (NRM) was **17.57%** (95% CI, 10.18-30.33) and graft vs host disease relapse free survival (GFRS) was **22.94%** (95% CI 12.17-35.75). Compared to other chromosome 3 abnormalities, patients with monosomy 3 showed the highest risk of relapse and death with 2 year RFS **11.53%** (95% CI, 0.86% - 37.51%) and OS **10.26%** (95% CI, 0.67% - 35.53%).

On univariate analysis, age greater than 50, monosomy 3, the presence of monosomy 7 and Allo-HCT in AML in CR2 or not in remission, were associated with increased risk of relapse and death. On multivariate analysis, AML in CR1 showed a trend towards improved RFS and OS, however, this was not statistically significant (HR 0.45 (0.20 - 1.04), P= 0.06 and HR 0.45 (0.20 - 1.02), P=0.056 respectively). The presence of monosomy 7 also showed a trend towards increased risk of relapse, however, this was also not statistically significant (HR 2.13 (0.96 - 4.7), p=0.06) (Table 2).

Conclusions: AlloHCT may improve outcomes in select patients with AML/MDS with chromosome 3 abnormalities. Further studies with a larger sample size and the inclusion of molecular mutations are recommended.

Disclosure: Nothing to declare.

P022

Allogeneic Hematopoietic Stem Cell Transplantation Versus chemotherapy-alone in the Treatment of Pediatric Acute Myeloid Leukemia Patients with Mixed Lineage Leukemia (Mll) Rearrangements: Single Center Experience

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Background: Acute myeloid leukemia (AML) represents 15%-20% of childhood leukemia. Despite substantial progress in the treatment of pediatric AML, approximately 40% of patients die from disease recurrence or treatment-related toxicities. Cytogenetic aberrations and response to the treatment are important prognostic factors in AML. MLL gene rearrangements in AML patients result in unique clinical and molecular genetic characteristics and generally indicate a poorer prognosis. At King Faisal Specialist Hospital and Research Centre (KFSH&RC), Riyadh, we examined the incidence and treatment outcome of MLL-rearranged AML pediatric patients.

Methods: We retrospectively reviewed the clinical data of pediatric patients (age at presentation ≤ 14 years) who were diagnosed and managed at KFSH&RC from January 2005 to December 2016. A total of 201 de novo AML patients´ profiles were reviewed, MLL-rearranged AML patients were identified based on the cytogenetic results. The median follow-up was 104±37.4 Months (95% CI: 30.5-177.6) Months.

Results: A total of 21 out of 201 (10.4%) AML patients found to have MLL gene rearrangements, 52%(11) were female, with a median age at diagnosis of 3.83 years (0.54-13.56). French-American-British (FAB) classification was M5 in17 patients(81%), M4 in 2(9.5%), M7 in 1(4.8%), and M1 in 1(4.8%). The commonest identified partner was t (9,11) in 8 patients(44.4%), followed by t(1,11) and t (11,19) in 4 patients (22.2%) each, t(11,18) and t(6,11) in 1 patient (5.6%) each. Three patients died early within 1 month from diagnosis. 14 out of 18 (77.8%) patients achieved complete remission 1 (CR1) after AML induction chemotherapy with cytarabine/daunorubicin/etoposide (ADE 10+3+5) and cytarabine/daunorubicin/etoposide (ADE 8+3+5).

Three out of 18 (16.6%) required second-line chemotherapy to achieve CR1. One patient failed to achieve CR despite second-line chemotherapy.

The 5-year Overall Survival (OS) for all MLL-rearranged AML patients was 42.9±10.8%. A total of 10 patients treated with chemotherapy alone without hematopoietic cell transplantation HSCT in complete CR1, 5 out of 10 patients have died with progressive disease (PD) /early relapse within an average of 6 months (1-9 months) from CR. 8 patients underwent HSCT in CR1, 4 died with relapse within an average of 13 months (6-18 months), 3 of them failed induction and got second-line chemotherapy before HSCT. All relapsed patients failed to achieve CR2 and died with PD.

Conclusions: Incidence of MLL gene rearrangements in our Centre was 10.4% and associated with poor outcomes. MLL-rearranged AML patients associated with increased risk of early relapse and re-induction failure. CR1 after first-line chemotherapy is an independent prognostic factor.

Disclosure: nothing to declare.

P023

Posttransplantation Bendamustine for GVHD Prophylaxis in Refractory Acute Leukemia Patients

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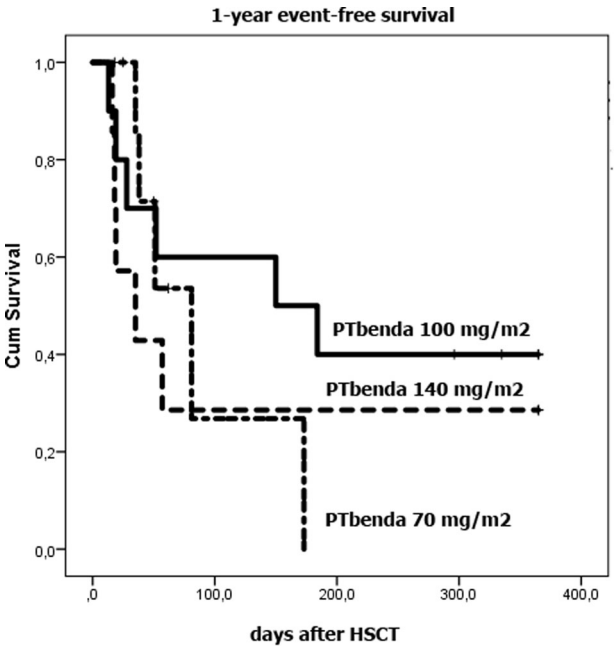
Background: Results of allogeneic stem cell transplantation (SCT) in primary or secondary refractory leukemia patients remain unfavorable despite the studies of new conditioning regimens. Preclinical studies by Stokes et al. (2016) indicate that substitution of posttransplantation cyclophosphamide with bendamustine (PTbenda) can possibly augment graft-versus-leukemia (GVL) effect in active leukemia mouse model. We conducted a study to evaluate the potential of PTbenda to prevent graft-versus-host disease (GVHD) and potentiate GVL.

Methods: The prospective (NCT02799147) Phase I de-escalation study evaluated 140-100-70 mg/m2 of PTbenda administered on days +3,+4 with or without additional immunosuppressive agents. All patients received myeloablative conditioning with fludarabine and busulfan. Inclusion criteria were diagnosis of acute lymphoblastic (ALL) or acute myeloblastic leukemia (AML), failure of at least to previous induction courses of chemotherapy or immunotherapy, more than 5% of clonal blasts in the bone marrow and good somatic status. The study enrolled 26 patients (pts), enrollment to the 140 mg/m2 group was halted due to stopping rules. Five pts had ALL and 21 - AML. Median blast count was 19% (6-97%). Four pts had matched sibling donor, 15 - matched unrelated donor and 7 - haploidentical, 10 pts had primary refractory and 16 secondary refractory disease. Half of patients received systemic antimicrobial therapy at the time of enrollment. Median age was 27 years (20-56).

Results: All patients but two with ALL disease progression engrafted and 89% had complete remission (CR) after engraftment, while 62% were MRD-negative. The evidence of augmented GVL was supported by the presence of cytokine-release syndrome in 73% of patients: 3 pts had grade 5 CRC, 5 pts - grade 4, 7 - patients grade 3 and 4 pts - grade 1-2. The pattern of CRC was distinct from BiTe and CAR-T one, with fever in all patients, skin vasculitis in 50%, liver function test elevation in 50%, polyserositis in 15% and neurotoxicity in 15%. CRC was associated with significant elevation of serum ferritin (mean 20188 vs 4915 ng/ml, p=0.005). 1-year overall survival was 29%, 40% and 70% in 140, 100 and 70 mg/m2 groups, respectively, but event-free-survival was 29%, 40% and 27% (Figure 1). None of ALL patients had long-lasting CR (0% vs 45%, p< 0.001). In the whole group relapse incidence was 19% and non-relapse mortality (NRM) - 43%. Grade III-IV acute GVHD was observed in 43%, 30% and 33% pts, with significantly higher incidence after haploidentical transplantation (75% vs 22%, p=0.046). Seventy percent of long-term survivors had chronic GVHD with higher incidence after single-agent PTbenda (100% vs 40%, p=0.038).

Conclusions: PTbenda is a promising strategy for refractory AML, but elucidation of the optimal immunosuppressive agent combination is required to control GVHD, CRC and reduce NRM.



[Figure 1. Event-free survival]

Clinical Trial Registry: NCT02799147, clinicaltrials.gov
Disclosure: The authors declare. no conflicts of interest.

P024

Immediate Allogeneic Hematopoietic Stem Cell Transplantation for NPM1-mutated AML in Molecular Relapse

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Background: NPM1-mutations can be identified in about 30% of adult AML patients (pts). According to ELN 2017 classification they are characterized as favorable or intermediate risk depending on the coexistence of FLT3 mutations. For pts with a favorable risk profile an allogeneic hematopoietic stem cell transplantation (HSCT) in first complete remission (CR) is not recommended, but can be an option for the intermediate risk group, depending on risk factors like comorbidity. Approximately 30% of NPM1-mutated AML pts will relapse after chemotherapy. Because NPM1 mutations are stable, and persisting or increasing levels are a strong predictor of relapse, monitoring of minimal residual disease (MRD) by quantitative PCR (qPCR) is recommended. With this strategy relapse can be detected earlier with lower leukemia burden. HSCT in molecular relapse could avoid possible complications of reinduction chemotherapy, but there are no data for this strategy. In 2014 we decided to start donor search immediately after molecular relapse and proceed to HSCT without reinduction chemotherapy. Here we report our experience with the first 6 pts treated with this strategy.

Methods: Between January 2014 and December 2018 28 patients under the age of 70 years, who were fit for intensive chemotherapy were diagnosed with NPM1-mutated AML. All pts received induction with DA 3+7 followed by consolidation with high-dose AraC in 15 pts. In 10 pts HSCT as consolidation treatment was performed. 3 pts had induction failure. MRD was monitored at least every 3 months (mos) after end of consolidation therapy by qPCR in bone marrow or peripheral blood in all pts in hematological CR. Relapse was defined as an increase of MRD over a cut-off of 1% NPM1/ABL1. The conditioning regimen consisted of Treosulfan (Treo, 30g/m^2) and Fludarabin (Flu, 120mg/m^2). In pts with hematological relapse at the time of HSCT Melphalan (Mel, 100mg/m^2) before Treo/Flu was added to induce aplasia. Immunosuppression consisted of ATG and Ciclosporin in combination with MTX or MMF.

Results: 25/28 pts achieved hematological CR after induction therapy, 24/25 pts showed molecular CR after the end of consolidation treatment. 10 pts (40%) relapsed. 4/10 pts developed an overt hematological relapse and are not part of this analysis. In 6 pts molecular relapse was detected. 5/6 pts relapsed after complete molecular remission, 1 pt relapsed after MRD positive remission. The median time to molecular relapse was 8 (7-42) mos after diagnosis. Median time from first positive MRD to HSCT was 2 (2-4) mo. 3/6 pts received conditioning with Treo/Flu only. 3/6 pts had hematological relapse at time of HSCT and received Treo/Flu after induction of aplasia with Mel. All pts reached complete hematological and molecular remission after HSCT. After a median follow-up of 15 (8-47) mos all pts are in ongoing CR. In all but one pt the remission free survival is longer than after primary treatment.

Conclusions: Although the number of pts is small and the follow-up short, this analysis shows the efficacy and feasibility of early allogeneic HSCT in molecular relapse for NPM positive AML pts and should be confirmed in a greater number of pts.

Disclosure: No disclosure

P025

Flat Regimen as Myeloablative Conditioning with Limited Toxicities for Autologous Stem Cell Transplantation in Patients with Acute Myeloid Leukemia: Results in 30 Patients

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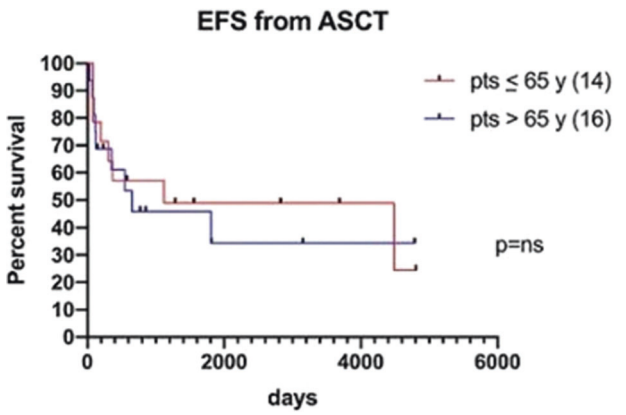
Background: consolidation of complete remission (CR) with autologous stem cell transplantation (ASCT) is an option for patients (pts) with acute myeloid leukemia (AML), in particular for those with a favourable genetic risk (ELN 2017). Most conditioning regimens for ASCT contain at least one alkylating agent, usually busulfan, cyclophosphamide or melphalan. Up to now, no regimen has proved preferable in terms of toxicities and improvement of event free survival (EFS). Treosulfan is an alkylating agent which demonstrated to achieve maximum disease control with minimal toxicity in combination with fludarabine prior to allogeneic SCT. We designed and tested a new treosulfan-based conditioning regimen (FLAT) prior to ASCT in AML pts in first complete remissione (CR1). Preliminary data on the feasibility and efficacy of the FLAT regimen are here presented.

Methods: period 7/2006-7/2019, 30 pts with AML in CR1, median age 68 y (18-76), 14 pts £ 65 y (group A: median 49 y, 19-65), 16 pts > 65 y (group B: median 73 y, 68-77). Cytogenetics: favourable 1, intermediate 26 (normal karytotype 25), complex 1, not evaluable 2. Molecular (21 pts): CBFB-MYH11 1, RUNX1-RUNX1T1 1, NPM1mut alone 5, CEBPAmut alone 4, FLT3ITD/NPM1mut 5 (FLT3ITD low ratio 3, unknown ratio 2), negative 5. Prognostic risk (ELN 2017): favourable 14, intermediate 7, adverse 1, not evaluable 8. At ASCT all pts were in CR1 after a median number of 2 chemo cycles (2-4). FLAT regimen: treosulfan 10 gr/sqm for 3 days, fludarabine 30 mg/sqm for 5 days, cytarabine 2 gr/sqm for 5 days, PEG

filgrastim 1 vial s.c. after autoSCT (27 pts). Graft: PBSC, median CD34+ 5x10^6/kg of BW (3.3-8.5). Time from CR1 to autoSCT: median 99 days (44-266).

Results: at day +100 after ASCT 29 pts were alive, 24 in CR, 5 relapsed. One 75-yo patient died for invasive fungal infection at day +31 (she was still in G4 pancytopenia). Median time to hematopoietic recovery: neutrophils (> 500/mcl) day +11 (8-38), platelets (> 20.000/mcl) day +20 (13-103). Neutrophils recovery in 3 pts who did not receive any growth factor was slower (day +26, 33, 38). Extra-hematologic toxicities (CTCAE v4.0): median grade 1 (0-4). Median EFS from ASCT was 1123 days (31-4808), for group A 1123 days (84-4808), for group B 653 days (31-4789); projected 3y EFS from ASCT was 51.2%, for group A 57.1%, and group B 47.8% (p=ns). At last update 15 pts (50%) are alive, 13 in CR1, 2 in second CR, with a median follow up of 1561 days (146-4810). Overall non-relapse mortality was 3%.

Conclusions: consolidation of AML in CR1 with the new myeloablative FLAT regimen and ASCT was feasibile and well tolerated, even in patients above 65 years of age. Around 50% of pts, regardless of age, mostly with favourable or intermediate genetic risk, obtained prolonged survival without relapse.



[EFS from ASCT]

Disclosure: nothihg to declare.

P026

Tyrosine Kinase Inhibitor Treatment after Allogeneic Hematopoietic Stem Cell Transplantation for Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia

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Background: Introduction of tyrosine kinase inhibitor (TKI) for the treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) has dramatically improved the survival outcomes. However, TKI therapy for Ph+ ALL has yielded controversial results evaluating the efficacy of post-hematopoietic stem cell transplantation (HSCT). The CIBMTR analyzed 197 patients with Ph+ ALL undergoing allo-HCT in first complete remission, 43 of whom received post-transplant therapy with TKIs. There was no difference in the 3-year cumulative incidence of relapse. In contrast, an EBMT study of 473 patients showed that post-transplant TKI was associated with a lower relapse rate and better overall survival. Recently, Akahoshi et al reported that TKI prophylaxis was not associated with a decreased risk of relapse or superior overall survival in the whole cohort. Therefore, we conducted a retrospective study of Ph+ ALL patients at our hospital to evaluate whether TKI prophylaxis after allogenic HSCT would reduce relapse and improve overall survival.

Methods: The Institutional Research Board approved the retrospective study. We identified 68 patients over 14 years of age with Ph+ ALL who received allo-HSCT from 1993 to 2001 (n=3) and from 2002 to 2019 (n=65) at National Taiwan University Hospital. Univariate and multivariate analysis was performed using Cox proportional hazard regression model.

Results: Before allo-HSCT, 8 of 68 patients (12%) didn't receive any TKI treatments, whereas the remaining 60 patients received imatinib (24%), dasatinib (54%), nilotinib (6%), and ponatinib (4%). After allo-HSCT, 28 patients (41%) didn't receive TKI treatments, and 40 patients (59%) received TKI treatment, including 2 patients (3%) with flank relapse, 17 patients (25%) with TKI prophylaxis and 21 patients (31%) with pre-emptive treatment because of positive-minimal residual disease (MRD) detected by quantitative PCR. The median time from HSCT to TKI treatment was 52 days (range, 21-542 days). Imatinib (15%), dasatinib (38%), nilotinib (4%), and ponatinib (2%) were given as TKI treatment. The median duration of TKI treatment of the patients was

453 days (range, 7-1775 days). Multivariate analysis identified advanced disease status before HSCT (primary induction failure, active disease) to be a risk factor for overall survival (OS) (HR=7.156; P=0.0002), disease-free survival (DFS) (HR=4.829; P=0.0113), and cumulative incidence of relapse (CIR) (HR=5.3; P=0.0188). Importantly, in the post-transplant period, the multivariate analysis identified TKI administration to be a significant factor for OS (HR=0.30; P=0.0014), DFS (HR=0.25; P<0.001), and CIR (HR=0.343; P=0.0039). Molecular relapse detected by quantitative PCR after HSCT was correlated with increased risk of hematological relapse (CIR, HR=8.158; P=0.005), but not associated with a worse DFS (HR=1.042; P=0.8827). This result could be explained by the fact that 21 of the 32 patients with molecular relapse received TKI treatment and 9 of them returned to negative MRD in a later follow-up assessment.

Conclusions: Despite the limitation of small sample size and the potential bias of patient selection by the physician, our study showed TKI treatment after allogeneic HSCT would reduce relapse and improve overall survival, indicating the potential benefit of TKI treatment in the post-transplant setting.

Disclosure: Nothing to declare.

P027

Outcomes of Allogeneic Transplantation for Cytogenetic intermediate-risk AML According to the Molecular Risk Based on ELN 2017 Risk Stratification System; Single Center Experience in Korea

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Background: Acute myeloid leukemia (AML) has been recognized as a clinically and genetically heterogeneous disease entity. Cytogenetic abnormalities that are associated with the prognosis of AML have been identified. However, as there are limitations for patients in the cytogenetic intermediate-risk group, more precise risk stratification systems based on genetic status have been proposed especially in nest-generation sequencing (NGS) era. In this study, we evaluated the usefulness of the European Leukemia Network (ELN) 2017 risk stratification system and transplant outcomes in the cytogenetic intermediate-risk group.

Methods: We performed a retrospective analysis of a total of 143 patients who diagnosed with cytogenetic intermediate-risk AML and received intensive standard '7+3' chemotherapy for remission induction from 2012 to 2018 at Yonsei university Severance hospital in Korea.

Results: According to the ELN 2017 risk stratification system, 30 (21.0%), 80 (55.9%), and 33 (23.1%) patients were allocated to the molecular favorable, intermediate, and adverse risk group. The 5-year overall survival (OS) rate was 78.5% in molecular favorable group, 51.2% in molecular intermediate group, and 33.1% in molecular adverse group (P = 0.010) The 3-year progression free survival (PFS) rate in molecular favorable group were also significantly higher than those in intermediate and adverse group (85.3% vs 56.0% and 49.1%, P = 0.021). The outcome of allogeneic hematopoietic stem cell transplantation (HSCT) was evaluated in 124 patients who achieved complete remission. Among them, 71 (57.3%) patients received allogeneic HSCT as post-remission therapy, and the remaining 53 (42.7%) patients received consolidation chemotherapies only. Despite the higher proportion of patients receiving more than 2 cycle of induction chemotherapy (21.1% vs 5.7%, P = 0.016), the 3-year PFS was significantly higher in the transplant group than non-transplant group (71.2% vs 50.3%, P = 0.013). In molecular risk subgroup analysis, molecular favorable-risk subgroup showed about 80% PFS in both groups and transplantation did not show superiority (P = 0.853). In molecular intermediate-risk group, allogeneic HSCT resulted a longer PFS (P = 0.003) than chemotherapy as a post-remission treatment. For patients with molecular adverse-risk, poor prognosis could not be overcome neither chemotherapy nor transplantation (P = 0.198).

Conclusions: The molecular risk stratification of the ELN 2017 successfully distinguished long term prognosis in cytogenetic intermediate-risk AML patients and validated in our center. Because molecular evaluation using NGS technique recently became one of standard pre-treatment evaluation for AML patients in Korea, clinical benefit of HSCT should be carefully and precisely evaluated for cytogenetic intermediate-risk patients according to the molecular risk stratification. Furthermore, more effective post-remission treatment strategy should be determined especially for cytogenetic intermediate- and molecular poor-risk AML patients.

Clinical Trial Registry: This study was approved by the institutional review board of Severance Hospital (4-2010-0669, NCT 02344953).

Disclosure: There is no funding to declare.

P028

The Prognostic Significance of Minimal Residual Disease Monitoring by Wt1 Gene Expression in Peripheral Blood Before and after Allogeneic Stem Cell Transplantation in AML Patients

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Background: The aim was to confirm our previous experience with prognostic relevance of WT1-MRD status before allo-SCT in AML patients in complete remission. Another aspect was to assess the significance of WT1-MRD monitoring in these patients after allo-SCT.

Methods: The expression of WT1 gene was measured by real-time polymerase chain reaction in peripheral blood according the European Leukemia Net recommendations. Between 2005-2019, we have analyzed 147 consecutive AML pts with high WT1 expression at diagnosis, transplanted in CR1 or CR2. Median age was 46 years (range; 21-66), 76 men, 21 good risk, intermediate risk 91, high risk 35. A total of 116 pts were transplanted in CR1 and 31 pts in CR2. In 128 pts PBPC were used, in 19 pts bone marrow. The donors were identical siblings in 30 pts, 9 haploidentical, matched unrelated donors in 73 pts and mismatched UDs in 35 pts. Conditioning was myeloablative in 117 pts, RIC in 30 pts. At the time of allo-SCT 107 pts were WT1-negative (WT1< 50 copies) and 40 pts were WT1-positive.

Results: Median follow-up was 21 months. Estimated 5-years OS and EFS was signifcantly better in WT1 neg cohort (65% and 57% vs 37% and 25% resp, p= 0,0003 and < 0,0001), as well as 5-years RI was significantly lower in WT1 neg group (25% vs 60%, p< 0,0001). 5-years NRM was not significantly different (24% and 27%). Multivariate analysis revealed WT1-MRD positivity and aGVHD grade 3-4 as a significantly negative prognostic factors for OS. Overall 50 pts developed WT1-MRD positivity in post-transplant period, in forty cases the therapeutical intervention was done. Haematological relapse occurred in 42 pts, in all relapsed patients where WT1-MRD was monitored (38 pts) we detected the positivity, in median of 28 days (0-485) before haematological relapse. 3-years OS in pts with molecular relapse only (12 pts) was 56% vs 74% in non-relapsed group (p=ns).

Conclusions: The results of the analysis confirmed our previous experience that WT1 status before allo-SCT is a strong prognostic factor for both OS and relapse risk. Our experience suggests that this marker is also useful for monitoring MRD after allo-SCT. Well-defined clinical studies will be needed to assess the importance of therapeutic intervention based on WT1-MRD positivity.

Disclosure: nothing to declare.

P029

Impact of Posttransplant Tyrosine Kinase Inhibitors Administration on Long Term Outcomes of Allogeneic Hematopoietic Stem Cell Transplantation in ph-positive Acute Lymphoblastic Leukemia Patients

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Background: Widespread use of targeted therapy with tyrosine kinase inhibitors (TKIs) in combination with allogeneic hematopoietic stem cell transplantation (allo-HSCT) has dramatically improved therapy results in the majority of Ph-positive acute lymphoblastic leukemia (ALL) patients, so nowadays their survival may be comparable with Ph-negative ALL patients in most cases. Nevertheless, relapses remain a major cause of treatment failure even after allo-HSCT that lead to dismal prognosis. One of the possible strategies to prevent relapse includes posttransplant TKIs maintenance, but the data about its application regimens is still controversial. The aim of our study was posttransplant TKIs impact evaluation on outcomes of alloHSCT in Ph-positive ALL recipients.

Methods: This study analyses the data in retrospective cohort of 96 Ph-positive ALL patients with median age of 30 years (range, 18-57) undergoing allo-HSCT from HLA-matched sibling (n=24), haploidentical (n=12) or unrelated donor (n=60) in R.M.Gorbacheva Memorial Institute between 2007 and 2019. Median follow-up time was 24,8 months (range, 1-98 months). At the time of allo-HSCT 54 (56%) of patients were in first remission, 16 (10%) in second remission, 10 (16%) in third or subsequent remission, 16 (10%) in active disease (relapse/resistance/progression). 88 (92%) patients received 1st, 2nd or 3rd generation TKI prior to allo-HSCT. 36 (38%) patients were MRD-negative before allo-HSCT, while 39 (40%) had MRD-positive status, measured by PCR analysis. In post-transplant period 60 (63%) patients received TKIs (imatinib or dasatinib). The goal of posttransplant TKIs administration was prophylactic in 43 (72%) patients, preemptive in 8 (13%) and relapse treatment in 9 (15%). Median time of

TKIs administration was 60 (range 30-125) days after allo-HSCT. Landmark analysis was used for comparison with patients without TKIs. Non-engrafted patients were excluded from analysis.

Results: 5-year OS and EFS were 59,4% and 45,8%, accordingly, whereas 5-year incidence of relapse was 35,4%. Comparing patients, who received posttransplant TKIs as prophylaxis with those, who did not receive prophylactic TKIs, we observed that 5-year EFS in 1st group was 63,3% vs 29% in 2nd (p< 0,001). 5-year incidence of relapse in 1st and 2nd groups were 51,6% vs.28,6%, accordingly (p< 0,001). We also estimated, that TKIs generation after allo-HSCT did not influence the results.

Conclusions: In our study 5-year EFS was twice better in patients, who received TKIs after allo-HSCT as prophylaxis, regardless the generation. Moreover, 5-year incidence of relapse was more than 20% lower in this group of patients. Thus, we can suggest that in order to reduce risk of relapse, it is preferable to prescribe TKIs no later than 60 days after allo-HSCT, before measurable residual disease appear, if there are no other factors that limit TKIs administration (toxicity of TKIs, poor graft function, etc.).

Disclosure: Nothing to declare.

P030

The Influence of anti-thymocyte Globulin(ATG) on the Outcomes of Patients with AML W/wo Measurable Residual Disease(MRD) at the time of Unrelated Donor Transplantation

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Background: Anti-thymocyte globulin(ATG) is a very effective form of in vivo T-cell depletion and has been extensively used for GVHD prevention. However, ATG can potentially eliminate alloreactive donor T cells and reduce the graft-versus-leukemia(GVL) effect and increased disease relapse and reduced overall survival(OS). Herein, we aimed to investigate the impact of ATG on the outcomes of patients with AML stratified by flow cytometric MRD status who underwent Allo-HSCT from unrelated donor (UD).

Methods: This was a retrospective single center analysis using the data set of our institutional database. Eligibility criteria for this analysis included 75 adult patients with AML who underwent allo-HSCT from either a HLA 10/10matched(n=34) or 9/10mismatched(n=41) UD, between October2012 and June2019. All recipients received peripheral blood stem cells grafts. Recipients of UD Allo-HSCT were routinely given rabbit Jurkat cell line-reactive ATG(ATG Fresenius®) in doses of 10mg/kg/day IV on days -3, -2, -1. Flow cytometry analyses were done using the flow cytometry system FACSCalibur(BD Biosciences, San Jose, CA) and sensitivity theresholds was 10^{-6}. All analyses were done separately in patients achieving or not MRD negativity before transplant.

Results: A total of 75 consecutive patients with AML who underwent allo-HSCT from an UD were evaluated. Median age was 48 years(range:19-71) and 40(53.3%) were females. Median follow up from allo-HSCT was 9.8 months (4-80.9 months). There were 43 $MRD^-$and 11 MRD^+patients and 21 patients who were transplanted in the setting of active disease also included in this analysis. Fifty-five(73.3%) patients received myeloablative conditioning (MAC) and 20(26.7%) reduced-intensity conditioning(RIC) regimens. The most common MAC and RIC regimens were busulfan/cyclophosphamide(BuCy,60%) and busulfan/fludarabine(BuFlu,25.3%), respectively. The common GVHD prophylaxis were cylosporinA(CSA) and methotrexate (Mtx) in 64(85.3%) of the patients. Eight patients out of 21 patients with active disease underwent to allo-HSCT after FLAMSA-based high-dose sequential conditioning regimen. The use of ATG was associated with a lower incidence of chronic GVHD(18.7%). We investigated the influence of ATG on transplant outcomes separately in MRD^-, $MRD^+$and active disease cohorts. As expected, lowest incidence of relapse was observed in MRD^- groups (MRD^-; 23.3%(10/43) vs MRD^+; 45.5%(5/11); p=0.168). MRD status at the time of allo-HSCT impact the leukemia free survival(LFS) significantly; MRD^-(not reached) or MRD^+(median 34.8(95% CI, 14.4-55.1)) or active disease (median 8.9 months(95% CI, 5.5-12.3))(p=0.021). In the group of MRD^+patients, the OS was 21.6 months(95 % CI, 0.60-31.5) with 1- and 3- year OS rates of 72.7 ± 0.8 % and 31.2 ± 1.7 %, respectively(p=0.117). For the MRD^-group, median OS after allo-HSCT was not reached versus 8 months in the active disease group(p=0.053). No outcome differences were found between MAC and RIC regimens. In addition, we did not find any association between type of HLA matched, relapse or GVHD incidences. Infection was the most common cause of death in the both groups.

Conclusions: Based on this single center study, the use of ATG was associated with a lower incidence of chronic GVHD. Most importantly, ATG could increase the risk of disease relapse or mortality in patients with pre-transplant $MRD^+$and active diseases. However, further prospective, randomized studies on a large number of patients are warranted to clarify these findings.

Disclosure: Nothing to declare.

P031

MLL-AF6 Fusion Gene Positive AML Treated by Allogeneic Hematopoietic Stem Cell Transplantation has Excellent Overall Survival

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Background: Acute leukemia with MLL-AF6 fusion gene positive is the adverse factor of prognosis. The purpose of this study is to evaluate the outcome of allo-HSCT in the treatment of MLL-AF6 fusion gene positive acute leukemia.

Methods: The clinical characteristics and prognosis of 32patients with MLL-AF6 fusion gene positive acute leukemia from May 2012 to September 2019 were retrospectively analyzed. Twenty four patients received allogeneic hematopoietic stem cell transplantation, including 21patients with AML and 3 patients with T-ALL. 13 were males and 11 were females. Median age was 22(4-48) years old. The disease status before transplantation was CR1 (n = 10) CR2 (n = 2), NR (n = 12). The median time from diagnosis to HSCT was 24(4-352) months.

Patients underwent matched sibling donors HSCT (MSD-HSCT)(n=4), haploidentical HSCT (Haplo-HSCT) (n=20). The conditioning regimens are based on BU/Cy (n=20) and TBI/Cy (n=4). GVHD prophylaxis consisted of ATG, CSA, MMF and MTX.

Results: The number of mononuclear, CD34+ and CD3 + cells was $(9.3\pm1.42)\times10^8$/kg, $(4.1\pm1.1)\times10^6$/kg, and $(1.6\pm0.5)\times10^8$/kg, respectively. White blood cells were successfully engraftment in 22 patients and the median time of ANC≥0.5×10^9/L was day 12(9-16). One patient failed to engraftment and one patient was not engraftment. Median time of platelet≥20×10^9/L was day 13(9-30) except 2 case. One patient failed to engraftment and one patient was not engraftment. DLI infusion was used to prevent recurrence in most patients after transplantation. The cumulative incidence of grade II - IV aGVHD was 41%, and the incidence of cGVHD was19%. Five-year overall survival(OS) rate and disease free survival(DFS) were 52.2% and 52% respectively. The five-year OS of allogeneic hematopoietic stem cell transplantation in CR1-2 and NR was 83.3% and 25%, respectively (P = 0.001). The mortality rate was 17% within 100 days. Transplant related mortality: 37%. Ten patients died, the causes of death were infection (n=2), IV aGVHD(n=3), and relapse(n=5). Eight patients received chemotherapy, all of them were AML patients, 5 males and 3 females, the median age was 26.5 (3-52) years old; eight AML patients were not relieved after the first chemotherapy, 3 patients only achieved remission after 2-4 chemotherapy, 5 patients were not relieved after multiple chemotherapy, 6 patients died, the cause of death: the primary disease was not relieved or relapsed; the overall survival was 2 cases. The OS rate was 52.2% in the transplantation group and 25% in the chemotherapy group (P = 0.237).

Conclusions: This study shows that MLL-AF6 acute leukemia has poor response to conventional chemotherapy and poorprognosis, so it is necessary to carry out allogeneic hematopoietic stem cell transplantation in remission state as early as possible.

Disclosure: Nothing to declare.

P032

Beneficial Outcome of Allogeneic Stem Cell Transplantation for Blastic Plasmacytoid Dendritic Cell Neoplasm

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Background: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare aggressive hematologic neoplasm which originates from the professional type I interferon-producing cells or plasmacytoid monocytes. The prerequisite for its diagnosis is the CD4+ and CD 56+ co-expression without common lymphoid or myeloid lineage markers. Recently, targeted therapy with Tagraxofusp (SL-401), an IL-3 fusion protein which binds to CD123, has proved its efficacy with an overall response rate (ORR) of 90% in 32 untreated and 67% in 15 previously treated BPDCN patients. Although several retrospective and small case series has been

published so far, there is few population-based study on BPDCN classified after 2008 WHO classification in Asian populati.

Methods: Data of 35 patients who were diagnosed with BPDCN from April, 2002 to February 2019 in 11 centers of South Korea were retrospectively collected and analyzed. Pathologic slides were reviewed in the central lab by the 2 pathologic experts and were finally confirmed for diagnosis. Overall survival was defined by the period from the date of the initial diagnosis to death by any cause or follow-up loss.

Results: The median age of the patients was 54.5 years (range, 17 - 84 years) with a male preponderance of 71.4% (25 of 35). 5 patients were preceded with hematologic malignancies. The most common initial presenting site was skin followed by lymph nodes, bone marrow, spleen, and liver. 32 of the included patients proceed to treatment with acute lymphoblastic leukemia (ALL)-like regimen (19 patients), acute myeloid leukemia (AML)-like regimen (5 patients) and lymphoma-like regimen (8 patients). Baseline characteristics of age ≥ 65 years, liver involvement and induction chemotherapy with lymphoma-like regimens expected worse prognosis in both univariate and multivariate analysis. Among the 32 patients who received induction chemotherapy, 11 cases proceeded to allogenic stem cell transplantation (SCT) and 3 received autologous SCT. With a median follow-up of 16.60 months (range, 0.53-79.73 months), patients who had been treated with leukemia-like induction regimen compared with lymphoma-like induction regimen (39.30 vs. 6.33 months, P=0.005) and allogeneic SCT compared with autologous SCT (54.13 vs. 7.70 months, P=0.015) showed markedly prolonged overall survival.

Conclusions: Induction treatment with leukemia-like regimen and proceeding to allogeneic stem cell transplantation can prolong overall survival in Asian patients with BPDCN.

Disclosure: There is nothing to declare.

P033

Nduction of Synergistic Apoptosis and Overcoming of Drug Resistance by Cotargeting of BCL-2 and Na/H Exchanger 1 Pathway in Acute Myeloid Leukemia Cells

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Background: Anti-apoptotic proteins like Bcl-2, Bcl-Xl, or Mcl-1 play an important role in tumor cell survival and has been considered attractive drug targets. Especially, Bcl-2 selective inhibitor, venetoclax, has been showing significant effects on hematologic malignancies, but lower sensitivity and resistance gain have to be overcome to achieve durable response in acute myeloid leukemia (AML). Because intracellular pH is one of important modulators for Bcl-2 or Bax via deamidation process, in this study, we examined whether the cotreatment of Na/H exchanger 1 (NHE1) inhibitor, HMA [5-(N, N-hexamethylene)-amiloride] can overcome the resistance to venetoclax in AML cell lines.

Methods: Based on the preliminary experiments, venetoclax were treated to both venetoclax sensitive cell lines (MOLM13, MV4-11, and RS4-11) and venetoclax resistant THP1 cell line (THP1 and U937) with various concentration, and HMA was co-treated with 10 uM. Apoptotic cells were measured after 24 hr treated with each agent or combination. Apoptosis was analyzed using Annexin-V assay.

Results: As expected, venetoclax monotherapy induced concentration-dependent apoptosis in venetoclax sensitive MOLM13, MV4-11, and RS4-11 cells. For these cell lines, cotreatment of HMA to venetoclax synergistically potentiated apoptosis, and relatively lower concentrations of both drugs could induce almost complete apoptosis. For venetoclax resistant THP-1 and U937 cells, venetoclax could not induce sufficient apoptosis even with higher concentration. However, the combination treatment of HMA overcome venetoclax resistance, and induced apoptosis with 80% of THP-1 cells and 90% of U937 cells.

Conclusions: Our study suggests that co-targeting of Bcl-2 and NHE1 pathways not only sensitized the AML cells to venetoclax but also suggests that it could be one way to overcome venetoclax resistance in AML.

Disclosure: Nothing to declare.

P034

Gemtuzumab-ozogamicin for Bridging to Transplant in Refractory/relapsed CD33 Positive Acute Leukemia - is it Worthwhile?

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Background: Outcome of allogeneic hematopoietic stem cell transplantation (alloHSCT) for acute leukemia (AL) is superior when performed in complete remission. Therefore, in refractory or relapsed patients not in remission after induction, consolidation or re-induction treatment, salvage strategies are being employed to reach at least marrow

aplasia without residual blast morphology. Gemtuzumab-ozogamicin (GO), a humanized anti CD33 monoclonal antibody linked to calicheamicin, with a twisted drug history of early approval, withdrawal from the market, and renewed licensing for AML induction, has been an interesting candidate for such a strategy of "bridging to transplant" in CD33 positive AL patients.

Methods: We retrospectively evaluated overall (OS) and disease-free survival (DFS) of all adult refractory/relapsed AL patients having received GO for bridging to transplant at Hannover Medical School between 10/2004 and 12/2018. They were compared to a matched cohort of AL patients not reaching complete remission, but transplanted without bridging, since off-label GO could not be obtained for all refractory/relapsed patients.

Results: 232 refractory/relapsed AL patients underwent alloHSCT between 10/2004 and 12/2018 at our institution. 133 patients among them were CD33 positive. GO could be obtained for bridging to transplant in 32 patients, whereas 101 patients had to be transplanted without bridging. Both cohorts of CD33 positive patients were comparable for age, gender, disease subgroups, donor source, HLA matching, and conditioning intensity. GO salvage successfully induced marrow aplasia without residual blasts in 63% of evaluable patients. However, survival of CD33 positive AL patients after GO bridging (OS 29% at 5 and 10 years; DFS 27% at 5 years, 21% at 10 years) was not different from CD33 positive AL patients without GO bridging (OS 38% at 5 years, 28% at 10 years; DFS 32% at 5 years, 24% at 10 years). Of the total cohort of 232 refractory AL patients, 39% survived for 5 years and 32% for 10 years.

Conclusions: In our single center retrospective analysis of CD33 positive AL patients, bridging to transplant with GO seemed to have limited impact on long-term OS and DFS. However, even in refractory/relapsed AL, alloHSCT was able to rescue about one third of patients.

Disclosure: No conflicts of interest.

P035

Azacytidine and Donor Lymphocytes Infusions in Relapsed AML after Allogeneic Hsct: Results in 40 Patients

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Background: azacytidine (AZA) alone or with donor lymphocytes infusions (DLI) is an option for the treatment of acute myeloid leukemia (AML) relapsing after allogeneic stem cell transplantation (HSCT).

Methods: according to institutional policy, from 2012 to 2019 we treated 40 patients with AML relapsed after HSCT with AZA +/- DLI. Indications were either minimal residual disease positivity (MRD+) (evaluated by qPCR, flow cytometry or cytogenetical analysis) or morphological relapse not eligible for intensive chemotherapy. AZA dosage ranged from 32 mg/mq G1-5 to 75 mg/mq G1-7 q28 days. DLI was given every 2 cycles of AZA at escalating dose as per institutional guidelines. Indication to DLI relied upon clinical-biological features of patient, disease and HSCT (active GvHD and HLA loss were contraindications).

Results: clinical-biological features at baseline and at relapse are reported in Figure 1. Median time from HSCT to relapse was 10 months (range 1-55). Fourteen patients had MRD+ (group 1) and 26 patients had morphological relapse (group 2). Nine patients (23%) received AZA 32 mg/mq while 31 patients (77%) received AZA 75 mg/mq. Median number of AZA cycles was 4 (range 1-28). Sixteen patients (40%) received AZA+DLI, median number of DLI was 2 (range 1-4), median amount of CD3+ cells/Kg per patient was 3,8 x10^6 (range 0,1-76).

Overall response rate was 55% (22 pts): 57% (8 pts) in group 1 vs 54% (14 pts) in group 2 (p=0.87). Complete response rate was 33% (13 pts): 43% (6 pts) in group 1 and 27% (7 pts) in group 2 (p=0.43).

Progression free survival (PFS) at 1-year was 32%: 57% in group 1 vs 19% in group 2. At 2-years PFS was 23%: 57% in group 1 vs 7% in group 2 (p=0.01). In group 1, 7 patients maintained CR (4/7 received DLI) after a median follow up of 22 months (range 11-64). In group 2, 1-year PFS in patients with < 20% blast at relapse was 22% vs 12% in patients with ≥20% (p=0.24).

Overall survival (OS) at 1 year was 60%, respectively 85% in group 1 vs 46% in group 2. At 2-years OS was 41%: 77% in group 1 vs 22% in group 2 (p=0.01).

Most common grade 3-4 adverse events were neutropenia (80%), thrombocytopenia (55%), anemia (45%) and febrile neutropenia (35%). Acute GvHD developed in 3 patients (no one had previous GvHD, 1 received DLI) while 5 patients had chronic GvHD (2 had previous acute GvHD, 2 had previous chronic GvHD, 1 received DLI). No patient died because of treatment.

Conclusions: AZA +/- DLI is a feasible salvage therapy in relapsed AML after HSCT. AZA +/- DLI was rarely curative in morphological relapse - independently by blast counts - while long-term remissions were achieved in patients treated for MRD+ after transplant.

Disclosure: Nothing to declare.

P036

The Results of AML Relapse after Allogeneic Transplantation Treatment, Single Centre Approach Evaluation

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Background: Although allogeneic transplantation brings a substantial survival benefit in AML, post-transplant relapse remains one of the major events leading to treatment failure. Together with non-existing definite approach guidelines it causes difficulties in further treatment decision.

Methods: A retrospective survival evaluation of relapsed AML (n=148) patients after allogeneic transplantation between the years 1990 and 2019 was done. The decision of relapse treatment was performed individually with the respect to biological parameters of the disease, patient´s physical status and will. For the evaluation purpose the whole cohort was divided to 3 groups -1) no chemotherapy treatment except of immunosuppression tapering and DLI administration (n=44), 2) "low intensity " treatment including low dose ARA-C, 5-azacytidine with immunosuppression modification and with or without DLI administration (n=36) and 3) "high intensity" treatment including intensive regimens with high dose ARA-C and anthracyclines preferentially with DLI or second transplant (n=68).

Results: The overall survival in 1, 2 and 5 years was 32%, 20% and 16%. There was an expected significant difference between not treated group (2%, 1%, and 1%) and treated group with no significant further difference between low intensity and high intensity groups (48%, 29% and 16% in high intensity group and 31%, 21% and 16% in low intensity group). Patients who relapsed earlier from transplant did worse in the first two years, but the difference disappeared in surviving patients after 24 months of relapse treatment. Not surprisingly patients who had achieved complete remission had significant OS advantage (71% vs 6% in 1 year and 52% vs 1% in 2 years). There was no survival advantage in treated patients without remission achievement to untreated patients at all, though among untreated patients there was one (1/36) fully responding to immunosuppression tapering. 34% of patients with remission achievement relapsed again. Treatment toxicity related death was in 21%. Another major contributor to death was GVHD.

Conclusions: The outcome of AML patients relapsing after allogeneic transplantation is very poor despite various treatment approaches. The survival benefit was seen in patients who achieved further remission, though the subsequent relapses were frequent. Treatment toxicity was rather high in this group of patients. The emphasis on prophylactic and preemptive treatment together with tight minimal residual disease monitoring should be carried out, and the introduction novel drugs (e.g. venetoclax, gilteritinib etc.) should be evaluated.

Disclosure: Nothing to declare.

P037

Allogeneic Hematopoietic Stem Cell Transplantation for Relapsed or Refractory Acute Myeloid Leukemia: A Single Center Analysis

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Background: Approximately 60-70% of adult patients with newly diagnosed acute myeloid leukemia (AML) will achieve a complete remission after induction regimen. However resistant disease or relapse (R/R) remain a significant cause of treatment failure and a major unfavorable prognostic factor. Role and timing of allogeneic hematopoietic stem cell transplantation (HSCT) remains a matter of debate for these patients with R/R AML, as well as their transplant outcome. For these reasons, we have retrospectively analyzed the outcome of adult patients who underwent HSCT for R/R AML in our center at Grenoble University Hospital from 2007 to 2017.

Methods: Adults who had received HSCT in our center between 01/01/2007 and 12/31/2017 for R/R AML, at time of transplantation, were included. Progression-free survival (PFS) was the primary end point, while secondary endpoints assessed overall survival (OS), graft-versus-host disease (GVHD) relapse-free survival (GRFS), and cumulative incidences of GVHD, relapse and non-relapse mortality (NRM).

Results: This retrospective study reports data from 56 patients receiving HSCT for de novo or secondary R/R AML. The median age at transplantation was 56 years (range, 20-69 years). Median of marrow blasts was 13% (range, 5,5-78%). Half of the cohort underwent a myeloablative conditioning regimen, while 29% of the patients received a sequential regimen approach. Median follow-up was 52 months for surviving patients (range, 24-132 months), and the PFS at 1 year was 21,4% (95% Confidence Interval [CI], 11,9-32,9%), with a median of 98 days (95% CI, 64-149 days). Overall survival was 25%

(95% CI, 14,6-36,8%) at 1 year, GRFS was 10,7% at 1 year (95% CI, 4,4-20,4%). Cumulative incidence of acute GVHD II-IV reached 47,8% including 13,6% of grade III-IV at 1 year, while 28,6% of patients were reported for chronic GVHD. Twenty four per cent of patients had a refractory disease at first assessment after HSCT. Relapse incidence was 62,7% (95% CI, 49,1-76,3%) at 1 year and progression of the disease was responsible for 53% of the whole cohort mortality. 88,5% of relapses occurred within the 6 first months following HSCT, and none appeared after the 8th month. NRM at 1 year was 32% (95% CI, 9,9-51,5%).

Conclusions: This study confirms the role of HSCT in R/R AML patients as the best curative approach available today, with similar outcome rates than previously published. No specific subgroup of patients was identified in terms of better outcome. However, the high incidence of early post-transplantation relapse reveals the persistent need to improve the procedure. The key points reported in larger trials are early donor identification, easier with the availability of haplo-donors, use of sequential conditioning regimen, early tapering of immunosuppression and post-transplantation maintenance, such as targeted therapies, hypomethylating agents, donor lymphocytes infusions or other forms of immunotherapies.

In **conclusion** allogeneic HSCT remains feasible in this poor prognosis subgroup of AML and a multicentric program is underway in Auvergne-Rhone-Alpes region, France, based on the harmonization of HSCT practices in this very high-risk AML patients.

Disclosure: No disclosure to declare.

P038

The Optimal Time for Allogeneic Hematopoietic Stem Cell Transplantation in Adult Patients with Acute Myeloid Leukemia

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Background: AML is the most common indication for alloHSCT. The EBMT manuscripts estimate the intermediate-risk ELN2017 patients as candidates for alloHSCT in CR1 from MSD. AlloHSCT from MUD is still a clinical option for this prognostic group. However, the outcome of relapsed AML remains poor, both due to low incidence of achieving a CR2 and higher NRM.

Methods: The study included 298pts for the period 2005-18, median(m) age was 36(18-70)years. The m follow-up was 24(13-168)months. Disease status: CR1 - 234(78%)pts, CR2 - 64(22%)pts. The favorable risk group (fav) included 50(17%)pts, the intermediate(int) - 200(67%) pts, and the unfavorable(unfav) - 48(16%)pts. AlloHSCT underwent 242pts, 178(74%)pts in CR1, according to ELN2017 fav - 21(12%)pts, int - 121(68%)pts and unfav - 36(20%)pts; in CR2 - 64(26%)pts, which were fav - 16 (25%)pts, int - 36(56%)pts and unfav - 12(19%)pts. In int group alloHSCT was performed from MSD in 36pts and from MUD - 85pts. Chemotherapy (CT) received 56pts in the CR1 - 13(23%)pts in fav and 43(77%)pts in int ELN2017. Since 2013 PTCy has been used for the prevention of GVHD in alloHSCT and, since 2016 MAC consisted of fludarabine and busulfan14mg/kg.

Results: OS and RFS in fav were: after CT - 78%(95% CI57-99) and 72%(95%CI53-99), after allotHSCT in CR1 - 76%(95%CI59-95) and 71%(95%CI51-91), in CR2 - 86% (95%CI73-99) and 71%(95%CI48-94), p=.7 and p=.9. Relapse rate(RR) and NRM were 28%(95%CI6-56) and 10%(95%CI1-39), 24%(95%CI8-44) and 5%(95%CI1-20), 22%(95%CI5-48) and 13%(95%CI2-35), p =.6.

In int OS and RFS were: after CT - 42%(95%CI17-67) and 34%(95%CI15-53), after alloHSCT in CR1 - 77%(95% CI70-84) and 72%(95%CI65-79), in CR2 - 46%(95%CI27-65) and 45%(95%CI31-59), p=.02 and p=.03. RR and NRM - 60%(95%CI38-77) and 6%(95%CI6-19), 16%(95% CI10-25) and 12%(95%CI7-18), 26%(95%CI11-43) and 29%(95%CI15-45), p=.09 and p=.06.

After alloHSCT in unfav OS and RFS in CR1 were 43% (95%CI26-60) and 34%(95%CI17-51), in CR2 - 31%(95% CI4-58) and 30%(95%CI3-57), p=.4. RR and NRM were 60%(95%CI40-75) and 6%(95%CI1-17), 52%(95%CI18-77) and 18%(95%CI2-47), p=.8 and p=.2.

In int the year of alloHSCT was evaluated 2005-12 vs 2013-18. In CR1 the OS, RFS, RR and NRM were 64% (95%CI51-77) vs 85%(95%CI78-92), p=.01, 62%(95% CI48-76) vs 76%(95%CI64-88), p=.05, 20%(95%CI10-33) vs 16%(95%CI7-29) and 18%(95%CI8-30) vs 8%(95% CI3-16). In CR2 OS, RFS, RR and NRM were 30%(95% CI8-52) vs 65%(95%CI44-86), p=.3, 29%(95%CI7-51) vs 64%(95%CI42-86), p=.2, 34%(95%CI13-57) vs 12%(95% CI2-32) and 33%(95%CI13-55) vs 23%(95%CI7-45). In case of MSD 2005-12 vs 2013-18 in CR1 OS, RFS, RR and NRM were 58%(95%CI32-83) vs 78%(95%CI60-96), p=.2, 54%(95%CI29-79) vs 59%(95%CI34-84), p=.5, 32%(95%CI11-55) vs 36%(95%CI12-61) and 14% (95% CI2-36) vs 5% (95%CI1-21). After MUD alloHSCT

2005-12 vs 2013-18 in CR1 OS, RFS, RR and NRM were 67%(95%CI51-83) vs 87%(95%CI79-95), p=.07, 67% (95%CI50-84) vs 81%(95%CI67-95), p=.07, 13%(95% CI4-28) vs 10%(95%CI2-26) and 20%(95%CI8-36) vs 9% (95%CI3-18).

Conclusions: AlloHSCT should be delayed to CR2 for patients in the favorable risk group. In the unfavorable group, alloHSCT is indicated in CR1. Given the improvement of transplantation methods for patients of the intermediate group, alloHSCT is recommended in CR1. The outcome of alloHSCT from matched unrelated donor comparable with matched sibling donor. Patients with intermediate ELN risk AML should perform alloHSCT in CR1 despite of donor type (MSD or MUD).

Disclosure: Nothing to declare.

P039

Impact of ABO Mismatch Allogeneic Transplant in Acute Myeloid Leukemia -A Single Centre Experience

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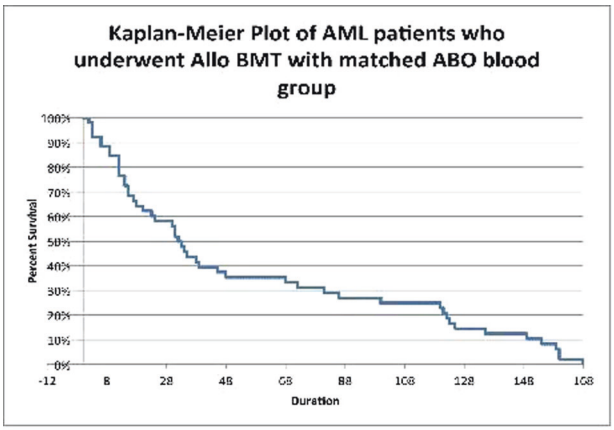
Background: Post remission therapy in patients with acute myeloid leukemia (AML) consist of giving maintenance chemotherapy or allogeneic hematopoietic stem cell transplantation (AlloHSCT) in high risk patients as a curative therapeutic option. Conflicting results have been reported on the impact of ABO mismatch on various transplant outcomes such as neutrophil and platelet engraftment, acute and chronic graft versus host disease (GvHD), non-relapse mortality and overall survival.

Methods: We analyzed data of 58 AML (Acute Myeloid Leukemia) patients who had undergone Allo HSCT, between 2005 to 2019, at our Centre. In this study, we evaluated the demographic and clinical characteristics of patients, the effect of ABO mismatch and graft source on HSCT outcomes, such as engraftment and graft versus host disease (GvHD)

Results: Out of 58 patients, 30 (51%) were males, 28 patients were female. The median age was 31 years (range 3- 60) years. PBSC was the major source of graft, and matched sibling were the predominant donor type (97.1%). There were 26 patients with gender mismatch (44.8%). Among the recipients, ABO group mismatch was seen in 15 patients (25.8%), of which 12 cases were major blood group mismatch. Majority of patients received Bu-Cy as conditioning regimen (65.5%). The mean time to neutrophil engraftment was 14.6 days (SD 3.08) and platelet engraftment was 15.8 days (SD 4.69), which were similar in all patients irrespective of ABO match/mismatch status. (p=0.04 and p=0.05 respectively). 75.5% patients developed febrile neutropenia, of which 15% had documented infection with an identifiable microorganism. 13 cases (22.4%) developed acute GvHD, while 4 cases had VOD. 3 patients had transplant related mortality. Patients with fully matched sibling donor had statistical significant association with improved survival outcome (p 0.017). Both major and minor blood group mismatch were associated with increased mortality (p=0.05). On comparing different variables in terms of standard deviation using unpaired t test, age at transplant was the only variable with significant association with survival outcome (p.0.003).

Conclusions: Our experience with ABO mismatch is encouraging with good tolerability and disease control even in the advanced stage heavily pre-treated patients. More aggressive strategies including second transplants and novel agents are needed in these patients on relapse.



[overall survival]

Disclosure: No conflict of interest. This study was not funded

P040

Donor Source Impacts on Long Term Survival following Reduced Intensity Allogeneic Stem Cell Transplant in AML Patients Aged 60 and Above

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Background: Outcomes in elderly AML remain poor due to high risk of relapse, higher incidence of adverse cytogenetics and of chemotherapy resistance. The advent of reduced intensity conditioning (RIC) regimens has led to increasing use of allogeneic transplant in patients over the age of 60. This can lead to durable disease free survival in this age group and improved outcomes compared to that achieved with chemotherapy alone

Methods: This retrospective study analysed outcomes of 100 consecutive patients over the age of 60 years old undergoing RIC SCT for AML between June 2006 and June 2018. Patients were conditioned with Fludarabine/Melphalan/Alemtuzumab (n=94) or Fludarabine/Cyclophosphamide/2GyTBI (n=6). Data was collected from Electronic patient records. Probability of Overall Survival (OS), Progression Free Survival (PFS) were calculated by Kaplan Meier method and log rank test performed. Cumulative Incidence (CI) of relapse risk (RR), non-relapse mortality (NRM) and GVHD was calculated using competing risk analysis

Results: 100 patients were included in the study with a median age of 65 years (range 60-1 - 71.8). 77% had De Novo AML, 13% had a preceding diagnosis of MDS or MPD, 10% had therapy related AML. 79% of the patients were transplanted in CR1 and 21% were transplanted in CR2. 34 patients relapsed at a median of 0.96 years post transplant (range 0.11-5.37). 53% of patients had a matched Unrelated Donor (MUD) SCT, 23% sibling donor, 18% Mismatched unrelated donor (MMUD) and 6% umbilical cord blood (UCB) donor. 39% of patients had adverse prognostic markers at diagnosis as per ELN 2017 guidelines.

2 year OS was 41% and 2 year PFS was 36%. RR at 2 years was 25% and 2 year NRM was 38%. CI of Grade 2-4 acute GVHD at Day 100 was 15% (9-23) and 2 year CI of chronic GVHD was 30%. 2 year OS for patients with sibling, MUD, MMUD and cord donors was 61%, 40%, 67% and 22% respectively and 2 year PFS for patients with sibling, MUD, MMUD and cord donors was 56%, 35%, 67% and 17% respectively. OS was significantly reduced in those with MMUD donors compared to sibling (p=0.009%) and MUD donors (p=0.04%) due to higher NRM. Age at transplant (< 65 years versus >/=65 years), transplant in CR1 versus CR2 and adverse versus non adverse risk group had no significant impact on OS or PFS.

Conclusions: T cell depleted RIC allogeneic HSCT can lead to durable disease free remissions in older patients with AML including patients with adverse risk disease or therapy related or secondary AML. Patients with MMUD had inferior OS and PFS compared to those with a sibling or MUD donor in this age group and the decision to perform a mismatched unrelated donor transplant in this age group should be carefully assessed. Whilst numbers of UCB were small, the of use of alternative donors rather than MMUD in this age group should be considered and warrants further evaluation in randomised setting

Disclosure: Nothing to declare.

P041

Extra-medullary Recurrence of Acute Myeloid Leukemia as Myeloid Sarcoma after Allogeneic Stem Cell Transplantation: A Case Series

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Background: Myeloid sarcoma (MS) as a solid extramedullary manifestation of acute myeloid leukemia (AML) is a rare presentation of relapse after allogeneic hematopoietic stem cell transplantation (HSCT). It may occur as an isolated extra-medullary relapse, multilocular or in association with a medullary relapse.

Methods: All patients aged 18 years or older who have received HSCT for AML at our center since 2002 (n = 327) were screened for onset of MS after HSCT. Of those, 12 patients (3.7%) suffered from MS as extra-medullary relapse after HSCT and were included in this study.

Results: We identified 12 patients (median age 53 years) with MS. They all received reduced intensity conditioning (RIC). 58.3% (7/12) received HSCT from a matched-unrelated, 33.3% (4/12) from a matched-related and 8.3% (1/12) from a mismatched-related donor. The median onset of MS was 490.5 days after HSCT (range: 134 and 1276 days). The regions and organs affected varied from very typical tissues such as skin, bone or lymph node up to extremely rare presentations of MS affecting the pituitary gland, breast tissue, the thoracic wall or the paranasal

sinuses. Eight (66.7%) patients developed MS despite a history of graft-versus host-disease (GvHD).

Concerning the treatment, various therapy options were considered. The most frequently applied treatment options were intrathecal triple therapy, cytarabine and azacytidine. None of the patients received another HSCT. Irradiation was implemented where possible. Although MS is associated with a poor prognosis, three patients (3/12) survived more than two years and one more than 11 years after diagnosis of MS. The median overall survival since diagnosis of MS was 255.5 days (Kaplan-Meier).

Conclusions: These observations demonstrate the limitations of graft-versus-tumor effects after HSCT, since extra-medullary relapse did occur in the presence of GvHD. The results may also indicate that reduced intensity conditioning protocols are associated with a higher rate of extra-medullary relapse.

Single isolated manifestations are more frequently treated successfully compared to multilocular manifestations of MS. This is in part due to fewer issues regarding accessibility by local therapies such as irradiation or intrathecal therapy (in cases of involvement of the central nervous system). Altogether occurrence of MS after HSCT is associated with a poor prognosis as curative concepts including intensive chemotherapy and another HSCT are often not viable.

Disclosure: The authors do not declare. any conflicts of interest.

P042

Allogeneic Stem Cell Transplants in Acute Myeloid Leukaemia; A Single Centre Experience

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Background: Allogeneic stem cell transplant remains the best consolidation therapy in intermediate and high-risk AML patients with a suitable donor. We conducted a retrospective analysis to identify those who may benefit from further intensification of therapy.

Methods: Eighty patients, aged 53.5 ± 12.6 years, diagnosed in period 2010-2016 were studied. All were treated with a curative approach with "3+7" induction therapy, followed by consolidation only of allogeneic stem cell transplantation. All living patients have been observed for at least two years. The FLT3 inhibitors were not used in this cohort.

Results: 55 patients (69%) achieved complete remission (CR) by induction therapy. 57 patients (71%) were allografted. Hematologic relapse ($P < 0.001$), high-risk cytogenetics ($P = 0.001$) and age ($P = 0.033$) influenced overall survival (OS). Patients relapse-free for at least two years (irrespective of consolidation by chemotherapy only or allografted) had low risk of relapse and longer OS ($P < 0.001$). Allografted patients were younger ($P = 0.009$) and had improved OS ($P = 0.010$). Patients aged ≥ 65 years had lower probability of prolonged remission and inferior outcome. Primary induction failure (PIF) in low- and intermediate risk AML (n = 8/47, 17%) was not associated with inferior OS. In high-risk AML and PIF (n = 14/33, 42%) the median OS was 6.7 months in the whole cohort, respectively 12 months in 8 allografted individuals.

Conclusions: In patients with low- and intermediate risk AML and PIF the allogeneic stem cell transplant may overcome the resistance to induction therapy. A substantial proportion of PIF patients have high-risk AML. The efficacy of allogeneic stem cell transplant is limited in this cohort and the overall survival is poor. These patients may most benefit from innovative treatment approaches.

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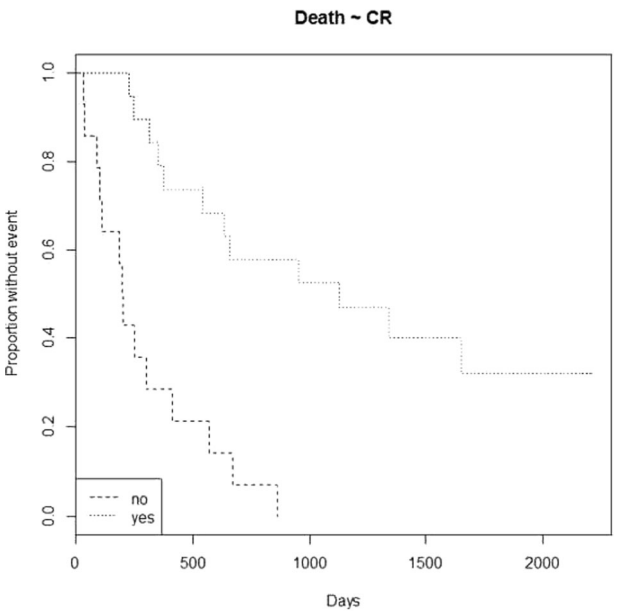

[PIF in high-risk AML]

Clinical Trial Registry: Not applicable.
Disclosure: Nothing to declare.

P043

Allogeneic Hematopoietic Cell Transplantation for Patients with Acute Myeloid Leukemia not Responding to First Induction Therapy

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Background: Patients with acute myeloid leukemia (AML) who did not achieve remission after first induction chemotherapy have a dismal prognosis. Prior reports have shown that these patients could be rescued with allogeneic hematopoietic cell transplantation (HCT). The aim of this retrospective study was to determine the clinical outcome of 34 AML patients who failed first induction chemotherapy and were treated with HCT (n=40) in our center between June 1995 and April 2019.

Methods: 34 patients with AML who did not achieve complete remission (CR) after first induction chemotherapy with "7+3" regimen (cytarabine associated to either daunorubicin or idarubicin) were enrolled in this study. As second induction chemotherapy, most patients received high dose cytarabine-based regimen. The median number of chemotherapy lines before transplantation was 2 (range, 2-3). The median time from diagnosis to first CR was 106 days (range, 63-225). At time of HCT, 30 patients were in CR1, 2 in CR2 and 2 in partial remission (marrow blasts 6-10%). Table 1 shows some characteristics of patient population at time of first transplant.

Results: Full engraftment of donor cells was evident in 31 evaluable patients (91%). 2 patients died before engraftment and 1 patient showed primary graft failure. The median time to reach >0.5 x10^9/L neutrophils was 23 days (range, 13-35). The CI of either acute (grade II-IV) or chronic (limited + extensive) GvHD was 32% and 21% respectively. Leukemia relapse occurred in 13 patients at a median of 411 days (range, 67-1824) after transplant for a CI of 42%. Of them, 5 died for leukemia, 6 underwent a second transplant after achieving second CR, 1 is waiting for second HCT and 1 is leukemia-free after sorafenib therapy. Among 6 patients who received a second transplant, 2 are living and cured, 2 died for infections, 1 died for VOD and 1 died for leukemia relapse. Nine patients died for transplant-related causes at a median of 53 days (range, 8-740) after transplant. Causes of death were infection in 5, acute GvHD in 2, and heart failure in 2. The 3-year-CI of transplant-related mortality was 27%. As of November 2019, 16 patients are living and doing well after a median follow-up of 116 months (range, 7-264). Of them, 15 (44%) are cured and 1 is waiting for second transplant. The 5-yr Kaplan-Meyer overall survival and disease-free survival were 47% and 29% respectively.

Conclusions: This study demonstrates that allogeneic HCT may produce durable remission and cure in patients with AML who failed first induction chemotherapy.

N. of patients/ transplants	34/40
Gender, male/ female	20/14
Median age, years (range)	44 (5-66)
2017 ELN risk: favorable/intermediate/adverse/not determined	2/17/6/9
Donors: HLA id sibling/unrelated/haploidentical	12/11/11
Stem cell source: BM/PBSC/CB	23/10/1
Conditioning: MAC/RIC	27/7
Conditioning: TBI/Busulfan/Melphalan/Treosulfan/ Thiotepa	3/27/2/1/ 1
GvHD prophylaxis: CSA/CSA+MTX/T-reg	2/31/1

[Table 1]

Disclosure: Nothing to declare.

Aplastic anaemia

P044

Salvage Allogeneic Hematopoietic Stem Cell Transplantation for Severe Aplastic Anemia Patients with Refractory Active Infection: A Prospective Multicenter Clinical Study in China

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Beijing, China, [9]Guangzhou First People's Hospital, Guangzhou, China, [10]Changhai Hospital, Naval Medical University, Shanghai, China, [11]Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [12]Ruijin Hospital, Shanghai Jiao Tong University, Shanghai, China, [13]Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China

Background: It is generally recognized that allogeneic hematopoietic stem cell transplantation (allo-HSCT) should not be managed to patients with active infection. However, in patients with severe aplastic anemia (SAA) especially very severe aplastic anemia (VSAA), it is usually difficult to control the infection without neutrophil. Rapid recovery of neutrophil by allo-HSCT might be a salvage treatment to control infection and rescue the patients. To evaluate the efficacy of allo-HSCT for SAA patients with refractory active infection, we designed this multicenter prospective clinical study in China.

Methods: Refractory active infection was defined as persistent fever without response to broad-spectrum antibacterial and antifungal treatment for more than three weeks with or without a definite infected site, or there was a definite infected site with fever less than 3 weeks. The probabilities of overall survival (OS) were calculated using the Kaplan-Meier estimator and compared between two groups using the log-rank test. The cumulative incidences were calculated using competing-risk models and analyzed by the Grey test between groups.

Results: Totally 75 patients were enrolled in this study from April 2014 to July 2018. All patients had persistent fever, including 52 (69.3%) with pneumonia (13 also accompanied with other site infection), 16 (21.3%) with other site infection and another 7 (9.3%) without a definite infected site. 51 (68.0%) patients received HSCT from a haploidentical family donor, 15 (20.0%) from an unrelated donor and only 9 (12.0%) from a sibling donor. For the prompt engraftment, peripheral blood stem cells (PBSCs) were given to all of our patients. Meanwhile, bone marrow was co-transplanted with PBSCs in 40 (53.3%) patients. The median age was 6.3 years (range, 1.0-38 years). Seven (9.3%) patients died of infection before engraftment. Two (2.7%) patients got primary mixed chimerism at day 28, and one developed secondary graft failure. The other patients sustained complete donor chimerism after HSCT. The median time for myeloid engraftment was 13 days (range, 9 to 32). The cumulative incidences (CI) of II-IV acute GVHD and chronic GVHD were 18.7±4.5% and 24.0±5.0% respectively. With a median follow-up of 730 days (range, 2 to 1568), the probability of OS was 77.2±4.9%. Because 68% of patients underwent haploindetical transplant, we compare the outcomes of patients receiving haploindetical transplant with active infection (n=51) to that of patients receiving haploindetical transplant without active infection (n=73) during the same period. There were no statistic differences in the CI of II-IV acute GVHD (17.6±5.4% vs 19.2 ±4.6%, p=0.771), CI of chronic GVHD (25.5±6.2% vs 20.5 ±4.8%, p=0.371), and the probability of OS (78.3±5.8% vs 89.0 ±3.7%, P=0.096) between the two groups. Compare to the other donor, the FFS II-IV, aGVHD and chronic GVHD with haploidental donor HSCT is simila to other donors.

Conclusions: Allo-HSCT is a feasible therapeutic option for SAA patients with refractory active infection. Haploidentical family donor is a good donor if without matched sibling donor. Peripheral blood stem cell may be the better graft source for this salvage HSCT owing to the rapidly engraftment.

Clinical Trial Registry: Clinical Trail registry number: ChiCTR-OCH-14005190

http://www.chictr.org.cn

Disclosure: Nothing to declare.

P045

Incidence and Management of Aplastic Anemia in Spain (IMAS). An Ambispective Study of Biodonostia / Pethema

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Background: Aplastic anemia (AA) is a rare, and life-threatening hematological disease. It is known that its incidence and prevalence might vary substantially among different geographic regions, and its presentation has been sometimes linked to environmental exposures. Montané et al reported an incidence of 2.34 per million inhabitants per year in the metropolitan area of Barcelona (Haematologica 2008). In the north of Spain, our group found 2.49 new cases/year (EBMT 2016). In Sweden, an incidence of 2.35 new cases/year has been recently reported (Vaht, Haematologica 2017). Our aim was to know the incidence and epidemiology of AA in a well-defined population.

Methods: In an ambispective study (IMAS), 7 general hospitals from 7 provinces situated in different geographical regions, that take care of a population of around 3.91 million inhabitants, participated in this study. All the patients diagnosed with AA were included. Data bases of the Hematology, Pathology, and Pharmacy Departments were used as a source of information.

Results: During the period 01/01/201031/07/2019, 103 new cases were identified (3-14 cases/year). The incidence of AA was 2.75 per million inhabitants per year. The median age at diagnosis was 56 years old (11-85), and gender was distributed almost equally between females and males. More than half of the cases were severe or very severe, and 9 out of 10 of the patients had transfusion needs. The most frequently employed approach at first line was immunosuppressive therapy with ATG/cyclosporine A (CsA). HSCT was a very infrequent 1st line therapy. At 1 year, two-thirds of the patients were in response (partial or complete). With a median follow-up of 6 years, three-quarters of the patients were alive. See table.

N = 103	
Period	01/01/2010-31/07/2019
Age (years) (median; range)	56 (11-85)
Gender (female/male)	52.8% / 47.3%
Severity of the disease (very severe and severe/moderate)	57.3% / 42.7%
Transfusion needs (yes/no)	90.3% / 9.7%
First line treatment	ATG/CsA: 52.4%; Allo-HSCT: 1.9%; Others: 45.7%
RR at day + 90	50.6% (45.4% PR / 5.2% CR)
RR at day + 180	53.3% (44.0% PR / 9.3% CR)
RR at day + 365	61.3% (46.8% PR / 14.5% CR)
Survival at last visit	75.3%
Follow-up (months) (median; range)	60 (5-115)

[Table. Description of the series]

Conclusions: 1) Worldwide, there are few studies focus on the epidemiology and management of AA patients. Particularly, this is the first national study of these characteristics ever performed in Spain; 2) We found an incidence of AA of 2.75 new cases/year; 3) No differences in gender were found; 4) ATG/CsA was the most frequently employed first-line therapy; 5) Long term response rate we found are similar to those shown in previous international reports of AA patients, and clearly show that there is an important room for improvement with new therapeutic approaches.

Disclosure: Nothing to declare.

P046

Allogeneic Stem Cell Transplantation from Alternative Donors for Children with Aplastic Anemia

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Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative treatment for children with severe aplastic anemia (AA). With the improvement in HLA typing resolution and advancement of supportive care for graft-versus-host disease (GVHD), various donor options are available for patients without HLA-matched sibling donors, such as unrelated donors, HLA-mismatched family (haploidentical) donors, and cord blood (CB). This retrospective study aimed to evaluate the HSCT outcomes from these donors.

Methods: Treatment outcomes of 65 children with AA (aged < 20 years) who underwent HSCT between 1991 and 2018 in our institute were analyzed. Unrelated donors were matched to patients at the allele level of HLA-A, HLA-B, HLA-C, and DRB1. Patients were divided into three groups: serologically matched or one-locus mismatched related donors (MRD/1MMRD, n = 37), 8/8-matched unrelated donors (MUD, n = 9), and alternative donors (AD, n = 19). AD was further divided into 7/8-matched unrelated donors (7/8MMUD, n = 9), serologically 2-3 mismatched related donors (Haplo, n = 6), and CB (n = 4). Treatment failure was defined as death from all causes, graft failure, and second malignancy.

Results: The median age at HSCT was 11.2 (range, 1.3-18.8) years. The median follow-up period was 69 (range, 1-196) months. Differences were found in the median follow-up according to the donor source, which was longer in MRD/1MMRD and AD, 93 and 45 months, respectively, and shorter in MUD, 18 months (P < 0.001). The median time from diagnosis to HSCT was 9 (range, 0-135), 11 (2-78), and 11 (0-69) months for MRD/1MMRD, MUD, and AD groups, respectively (P = 0.627). Neutrophil engraftment was achieved after HSCT in all patients. The median day of neutrophil recovery was day+18 (range, +11 to +36). Two patients experienced second graft failure, and all of them were in the AD group (Haplo, n = 1; 7/8MMUD, n = 1). Cumulative incidences of grade II-IV acute GVHD were 5% (95% confidence interval [CI], 0%-12%), 0%, and 21% (95% CI, 0%-37%) for MRD/1MMRD, MUD, and AD, respectively (P = 0.092). The 3-year cumulative incidences of chronic GVHD were 8% (95% CI, 0%-17%), 30% (95% CI, 0%-58%), and 16% (95% CI, 0%-32%) for MRD/1MMRD, MUD, and AD, respectively (P = 0.241). The 5-year overall survival was not significantly different among the three groups (MRD/1MMRD, 97% [95% CI, 82%-100%]; MUD, 88% [95% CI, 39%-98%]; AD, 100%; P = 0.266). The cause of death was infections without graft failure in two patients (MRD/1MMRD, n = 1; MUD, n =

1). Failure-free survival (FFS) was tended to be lower in the AD group (MRD/1MMRD, 97% [95% CI, 82%-100%]; MUD, 88% [95% CI, 39%-98%]; AD, 79% [95% CI, 53%-92%]; P = 0.082).

Conclusions: The overall survival rate of HSCT from both MUD and AD in children with AA is comparable to those from MRD/1MMRD. However, the algorithm for donor selection should be considered according to FFS. Further study with a larger number of patients is needed to determine the preferable AD.

Disclosure: The authors declare. no conflict of interest.

P047

Outcome of Pediatric Acquired Aplastic Anemia: Single Center Experience

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Background: Severe Aplastic Anemia (SAA) is a rare hematological disease characterized by pancytopenia and a hypo cellular bone marrow in the absence of abnormal infiltrates. Allogeneic hematopoietic stem cell transplantation (HSCT) is the current available curative treatment, however for patients who lack matched sibling donor (MSDs), immunosuppressive therapy (IST) is widely accepted as an alternative first-line treatment. Outcome data of children with acquired aplastic anemia (AA) are lacking from our region.

Methods: Laboratory and clinical information of all children < 18 years of age with acquired SAA diagnosed between January 2005 and December 2015 at KFSH&RC were retrospectively collected. Relevant details about treatment given i.e. IST and HSCT, treatment outcome, overall survival (OS) and event free survival (EFS) were also recoded. An events were defined as death, treatment failure, or rejection.

Results: Thirty children were included in the study. Fifteen (50.0%) patients were female and 18 (60.0%) patients underwent matched family donor (MFD) HSCT while the remaining patients received upfront IST. Three-year OS and EFS for children undergoing upfront MFD HSCT was 100%. Out of twelve children treated with IST, three were evaluable for response. Two children died before receiving a rescue transplant. Seven of the patients failed upfront IST and received rescue transplants, of these two children died with infection and rejection. The OS of the patients who received rescue after failed IST was 70% and there EFS was 71%. The overall response to IST was seen in three out of twelve (25%) patients with two patients achieving complete response while one patient had a partial response. The 3-year estimated OS and EFS for children treated with IST was 66.6% and 15% respectively.

Conclusions: We observed an inferior outcome in patients who received immunotherapy in our study comparison to published international literature. This could be explained by higher prevalence of consanguineous marriages in the Saudi population and their genetic background. Alternative transplant modalities should be considered for those who lack matched family donor.

Disclosure: no conflict of interest

P048

Impact of $CD34^+$-Stem Cell Boost on Outcome and Hematological Reconstitution in Patients with Severe Aplastic Anemia after Allogeneic Stem Cell Transplantation - A Retrospective Study

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Background: Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is still the standard treatment for acquired severe aplastic anemia (SAA) in patients younger than 40 years with sibling donors. Sufficient and durable reconstitution of haematopoietic donor stem cells is important for successful allo-HSCT. Poor graft function (PGF) after allo-HSCT is characterized by persistent pancytopenia, immunodeficiency and dependence on blood transfusions, despite of a complete donor chimerism. The probability of developing PGF seems to be increased in the absence of a regulatory bone marrow stromal microenvironment, even in cases where bone marrow is used as a source of stem cells.

Aim: To evaluate in a single-center retrospective analysis the long-term transplant outcome considering haematological recovery and overall survival (OS) in patients (pts) with SAA after allo-HSCT requiring $CD34^+$-selected stem cell boosts.

Methods: The analysis comprises data of 35 pts with aplastic anemia after allo-HSCT from HLA-matched sibling (n=14) or unrelated (n= 21) donors, who underwent allo-HSCT between 2006 and 2018. The median age of the 26 male and 9 female pts was 28 years (range, 17 to 66). A myeloablative conditioning regimen was used in 6 pts, while 29 pts were treated with a reduced intensity immunosuppressive conditioning regimen. Bone marrow (n=20) or peripheral blood stem cells (n=15) with a median of 3.89 x 10^6 $CD34^+$ cells/kg bodyweight (BW) (range, 1.4 to 14.6) were transplanted. PGF was diagnosed in 16 pts with a

median of 46 days (range, 40 to 106) after allo-HSCT by bone marrow biopsy. The stem cell boost was performed using immunomagnetically selected $CD34^+$ stem cells from original donors. The boost stem cell dose was 6.1 x 10^6 $CD34^+$ cells/kg BW (range, 0.95 to 13.25). Statistical analysis was performed on with SAS 9.4 using the method of Fine and Gray for competing risk cumulative incidences and Kaplan Meier estimates for overall survival.

Results: The rate of complete hematological engraftment was 94% (33 of 35 pts), including 16 pts with $CD34^+$-selected stem cell boosts infusion for poor graft function performed. The median time to recovery was 34 days (range, 16-100) for neutrophils and 62 days (range, 11-175) for platelets. The current 10-year survival rate is 80%. (without boost - 89.5%, with boost - 68,7%, p=0.03). No relapse of SAA developed. Seven (20%) pts died as a result of infectious complications (n=6), hemolytic uremic syndrome (n=1).

Hematological reconstitution in patients with or without CD34+ stem cell boosts - is presented in table 1.

Conclusions: The use of CD34+-selected peripheral blood stem cell boosts from the original donor allows a complete, albeit delayed regeneration of haematopoiesis in the majority of aplastic anemia patients with PGF after allo-HSCT. The leading causes of deaths were severe infectious complications due to prolonged cytopenia after allo-HSCT in this patient subset.

Cells	Recovery after allo-HSCT in pat. with SAA (median, days)		
	without boost	with boost	*P*
Leukocyte, more 1000/μL	22	37	*0.0037*
Neutrophils, more 500/μL	28	37	*0.0106*
Lymphocyte, more 500/μL	39	49.5	*0.0091*
Platelets, more 50 000/μL	27.5	71	*0.24*

[Table 1. Hematological reconstitution after allo-HSCT in patients with SAA]

Disclosure: Bogdanov: Neovii Biotech, Jazz Pharmaceuticals, MSD.: Other: Travel subsidies. Beelen: Medac GmbH Wedel Germany: Consultancy, Honoraria. Turki: Jazz Pharmaceuticals, CSL Behring, MSD.: Consultancy; Neovii Biotech, all outside the submitted work: Other: Travel subsidies.

P049

Hematopoietic Stem Cell Transplant in Adults with Acquired Severe Aplastic Anemia

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Background: Hematopoietic stem cell transplant (HSCT) provides curative therapy in almost 90% of patients with severe aplastic anemia (SAA). Older age, long duration of disease with consequent heavy exposures to transfusion and active infection at the time of HSCT have a negative influence on outcome, favouring graft failure (GF) and graft versus host disease (GVHD). This study aimed to evaluate outcome of all SAA patient who received hematopoietic stem cell transplantation at a tertiary centre in Malaysia.

Methods: Data was obtained from transplant database and patients' medical record at Ampang Hospital, Malaysia. Patients with acquired SAA who underwent HSCT between January 1999 until November 2019 were included. Demographics, clinical characteristics and treatment outcomes were collected and analyzed using descriptive statistics.

Results: A total of 84 cases were identified for this study with mean age of 23.7 ± 10.0 years. Fifty-eight percent of the cases were male (n=49). Malay ethnicity were the highest (51.8%) followed by Chinese (24.1%) and Native Sabah (14.4%). Majority were transplanted within 6 months of diagnosis (n=58, 69%) and out of this number, 20% received transplantation within six weeks. Forty-five cases (53.6%) used peripheral blood as stem cell source, 36 cases (42.%) used bone marrow and three cases (3.5%) used both. Most of the patients (60.7%) received non-Fludarabine based, Cy (cyclophosphamide)-ATG (anti thymocyte globulin) as their conditioning regime. Mean engraftment for neutrophil was 14.9 (range 6 - 29) days and 15.1 (range 8 - 35) days for platelet. Patients who underwent peripheral blood stem cell transplant had significant early engraftment for neutrophil ($p < 0.01$) in comparison to bone marrow. However, this finding is not observed with platelet engraftment. Twenty-nine cases (34.5%) died within 100 days of transplant from treatment-related complications (n=23), disease progression (n=4) and others (n=2). Four of the transplanted patients required second allogeneic transplant due to secondary graft failure, however only one survived.

Conclusions: This study shows that only small percentage of cases were transplanted less than six weeks from diagnosis. Early transplant strategy is necessary to improve outcome among patients with SAA. Further study is required to look into the factors leading to delay in diagnosis and treatment among them.

Disclosure: Nothing to declare.

P050

Hematopoetic Stem Cell Transplant in Fanconi Anemia using Matched Related and Haploidentical Donors- A Single Centre Experience

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Background: Hematopoetic stem cell transplant (HSCT) is the only curative option for progressive marrow failure in Fanconi Anemia (FA). There is paucity of data on HSCT for FA from India, especially using haploidentical donors. We report our experience of allogeneic transplants for FA.

Methods: We retrospectively analyzed the records of 13 children who underwent 15 HSCTs from 2014 to 2019.

Results: A total of 13 children underwent 15 HSCTs. The median age was 92 months (27-235). The donors were: Haploidentical donor (n=6), HLA matched siblings (n=5) and HLA matched related donor (n=2). Graft source: Bone Marrow (n=7); PBSC (Peripheral blood stem cells) (n=-8). Among haploidentical transplants, the graft source was T-cell depleted (TCD) PBSC in five and T-Cell replete (TCR) in one. The depletion method was TCR alpha/beta with CD19 + cell depletion using CliniMacs system. Conditioning regimen: Fludarabine/Cyclophosphamide (total dose of 40 mg/kg) and ATG in 14 (along with TBI in one), Treosulphan-Flu-Cy-ATG in one and Fludarabine-Busulfan-ATG in one. GvHD prophylaxis: Cyclosporine & Mycophenolate Mofetil in MSD/MRD HSCTs, Sirolimus in Haploidentical HSCTs with TCD grafts and Post-transplant cyclophosphamide (25mg per kg for 2 days), CSA and MMF in Haploidentical HSCT with TCR graft. The median infused CD34+ cell count was 7.8 × 10^6/kg (range 3.42-21.5× 10^6/kg). Of the 13 patients who underwent transplant, 10 engrafted with a median neutrophil and platelet engraftment at day 11 and 12 respectively. Three did not engraft (2-Haplo with TCD PBSC, 1-MRD with Marrow) -of which two engrafted after second transplant, one child had donor specific antibodies and expired secondary to infection. All the four who had acute GvHD received TCR stem cells (3-marrow, 1-TCR PBSC from haploidentical donor). Four patients had chronic GvHD (all were matched sibling/related, 3-Marrow, 1-PBSC) of whom one expired from severe bronchiolitis obliterans and the rest are alive with moderate skin GvHD. Interestingly, none of the patients who received TCD PBSC developed either acute/chronic GvHD. All alive patients developed full donor chimerism and are disease free. One achieved full donor chimerism after donor lymphocyte infusions for mixed chimerism. Day 100 survival rate was 76.9%. (10/13). OS: For entire cohort - 69.2 %, for haploidentical HSCT cohort -66.7% (4/6) at a median follow up of 211 days.

Mean follow up (days)	211 (30-570)
Neutrophil engraftment (in days)	11 (9-13)
Platelet engraftment (in days)	12 (8-18)
Acute GvHD Grade III-IV	4/13 (30.7%) 3/13
Chronic GvHD	4/10 (3-alive, 1-expired)
Primary graft failure	3/15 transplants, 2 underwent retransplant and alive, 1 expired
Expired	4
Cause of death	Rejection/Infection-2, GVHD-2
Chimerism	11/11 full donor chimerism, One achieved after four DLI
OS	69.2%

[Allogenic transplant outcomes in Fanconi Anemia (N=13, Number of transplants=15)]

Conclusions: HSCT for FA has good outcomes with reduced intensity conditioning regimens. Haploidentical donors are alternatives in the absence of matched donors with reasonably good outcomes and minimal GVHD rates using TCD stem cell source.

Disclosure: Nothing to declare.

P051

Hematopoietic Stem Cell Transplantation for Pediatric Severe Aplastic Anemia: Results of a Single Center

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Background: Aplastic anemia (AA) is a life-threatening form of bone marrow failure characterized by pancytopenia and hypo cellular marrow. The pathogenesis of the disease is thought to involve autoimmune process and it is associated with very high mortality if left untreated. Allogenic hematopoietic stem cell transplantation from a HLA-MRD is the preferred treatment in children and young adults. But when MRD is not available immunosuppressive therapy with CsA and ATGAM or transplantation from an alternative donor are the therapeutic options.

Methods: We retrospectively analyzed the data of AA patients who underwent HSCT at Pediatric Stem Cell

Transplantation Unit of Akdeniz University Hospital from January 2000 to December 2017.

Results: A total of 31 HSCT was conducted over 28 patients during this period. There were 19 boys and 9 girls with a median age of 10 years (range: 3.4-19.8) at transplantation. Eighteen patients have previously received immunosuppressive agents but were unresponsive to the treatment. Ten patients were receiving regular blood products before transplantation. The source of HSCT was PBSC in 16 and BM in the rest 15 transplantations. Patients received HSCT as graft from a matched unrelated donor (n:15), from a matched sibling donor (n:10), from a matched family donor (n:5), and from a haploidentical donor (n:1). All patients received FLU or CY based reduced intensity conditioning regimens and GVHD prophylaxis comprised a calcineurin inhibitor plus methotraxate in 90% of patients. The median infused CD34+ cell dose was 4.9 $\times 10^6$/kg (range:1.2-18.2$\times 10^6$/kg). Within a median follow up of 55 months (range: 2-206) after transplantation, 5-year overall survival was 78% in the total group and there was no statistical significant difference between the MRD and MUD groups (92% vs. 53% p=0.13). Grade III-IV aGVHD occurred after 3 of the transplantations (10%). Six patients died at a median of 9 months (range: 2-88) after transplantation.

Conclusions: Our results show that HSCT for AA patients has promising results and transplantation from unrelated donors are approaching those of MRD transplants. Application of immunosuppressive drugs, treatment rabbit ATG instead of ATGAM in previous years, and delay of transplantation waiting for appropriate donor might be the reasons for poor survival in MRD group.

Disclosure: Nothing to declare.

P052

Immunosupressive Therapy in Peadiatric Aplastic Anemia, Single Centre Experience

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Background: Aplastic anemia (AA) is life threatening disorder in pediatric age group with increasing incidence nowadays, with hematopoietic stem cell transplant being the 1st line therapy; immunosuppressive therapy (IST) is the alternative therapy and is the most commonly used modality of treatment especially. in the developing countries

Methods: We aimed to assess the outcome of IST in children with AA. Data for 25 children treated with IST from January 2014 to January 2019 (5 years) were retrieved from clinic records. IST included rabbit anti thymocyte globulin (ATG) along with cyclosporine A and another group were treated by sand immune alone

Results: Patient characteristics include median age (9) with 73 %male and 26.1 %female. with median interval between diagnosis and start of IST(0.5 -1) and around 30.4 % with hepatitis A associated aplastic anemia. Complete response, partial response and nonresponse was seen in 4 (37.5) (0%) and 1(12.5%) patients, respectively in patients received ATG and sandimune. while in patients received sandimune alone complete response and no response was seen in 7(46.7Z%) and 8 (53.3%) respectively. The median time to best response in the whole cohort was 12 months. There was no difference in outcome related to severity of AA, or higher ALC. There was a significantly better rate of response (p value: .03) in both groups of patients with higher Hb level, HCT, and PLT level before start of IST. An overall response rate in both groups around of 39.5% reported a 5-year OS of 50% with 16% of patients with complete response with HAAA. A delayed time to complete response with prolonged requirement of cyclosporine therapy was detected

Conclusions: In a developing country setting, IST with ATG and cyclosporine seems to be an alternative treatment for aplastic anemia in children lacking MRD.

Clinical Trial Registry: not applicable

Disclosure: Nothing to declare.

P053

Cyclosporine, Danazol and Romiplostim in Severe Aplastic Anemia in Prettansplant Period: Retrospective Analysis of Five Cases

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Background: Treatment of Aplastic anemia mainly consist of ATG+CSA or Hematopoietic stem cell transplantation. Due to financial constraints majority of patients cannot opt for these available treatment options. The patients who arrange the cost of HSCT, needs supportive care until the definitive treatment (transplant or ATG) is done. The cost of SDP and PCV and antibiotics for infection is a major hurdle to arrange the funds for BMT.

To reduce that, we have used combination of CSA, Danazol and Romiplastim as a bridge to BMT in our five patients of Aplastic anemia.

Methods: A retrospective study in a cohort of patients with AA. The study was conducted from January 2018 to December 2019. Romiplostim (5ug/kg) SC once a week was used for 4-8 weeks. Cyclosporine 5mg/kg per day was used to keep level between 150-200. Danazol was used 100 mg TDS, dose was increased upto 600 mg/day after monitoring liver function test.

Results: Five patients with a mean age of 47 (18-83) years were included in the study. Four patients achieved some form of remission (partial/complete), one patient died, one patient is in complete remission, and one underwent HSCT successfully. Two patients are in partial remission waiting for the HSCT.

Conclusions: Improved response rates with triple therapy was observed in patients with severe AA. The triple therapy can be used as a bridge for definitive treatment in Aplastic Anemia.

Disclosure: None

Autoimmune diseases

P054

The long-term Safety and Efficacy of Autologous Haematopoietic Stem Cell Transplantation for relapsing-remitting Multiple Sclerosis Indirectly Compared to Alemtuzumab: A Systematic Review

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Background: Multiple Sclerosis (MS) is a chronic, progressive, central neurological disease mediated by autoimmunity. Despite availability of anti-inflammatory drugs such as alemtuzumab, disease progression still occurs with minimal initial reversal of symptoms. Autologous haematopoietic stem cell transplantations (aHSCT) for treatment of MS has seen more dramatic reversal in symptoms but have not been previously directly compared to alemtuzumab.

Methods: Systemic review of cohort studies and randomised control trials (RCTs) of Relapsing Remitting MS (RRMS) patients treated with alemtuzumab or aHSCT.

Results: aHSCT.

A total of 144 studies met the search criteria. After application of eligibility criteria and removal of duplicate data, six studies including 277 patients with RRMS, who failed initial DMTs, were included in the review. All patients were initially alemtuzumab naïve. Mean baseline EDSS was 1.5-6.3. Three studies used myelo- and lympho-ablative BEAM-ATG conditioning; the others used lympho-ablative cyclophosphamide (50mg/kg/day for 3-5 days) with ATG (or alemtuzumab in a minority of patients). Both rabbit and horse ATG were used with dosing between 2.5-10mg/kg/day for 2 days or 0.5-1.5mg/kg/day for 5 days.

The available data showed a mean EDSS reduction from a baseline of 3.89 (3sf) to 2.96 at five-year follow-up.

Studies with lower pre-aHSCT EDSS experienced the greatest reduction in EDSS. Event-free survival (EFS) to five years was variable between studies ranging from 0% if high pre-aHSCT EDSS, to 85% if low EDSS pre-aHSCT. Studies with the lowest initial EDSS experienced higher progression-free survival (PFS) to five years, around 90%.

All-cause mortality across the studies was 2.6%; treatment related mortality (TRM) was 0.7%.

The percentage of patients retained in the studies after five years stood at only 28.9% compared to the alemtuzumab arm where retention stood at 83.0% ($p< 0.001$). Comparison of EDSS at five-year follow-up between the two study arms may therefore be misleading due to survivorship bias in the aHSCT arm.

Alemtuzumab.

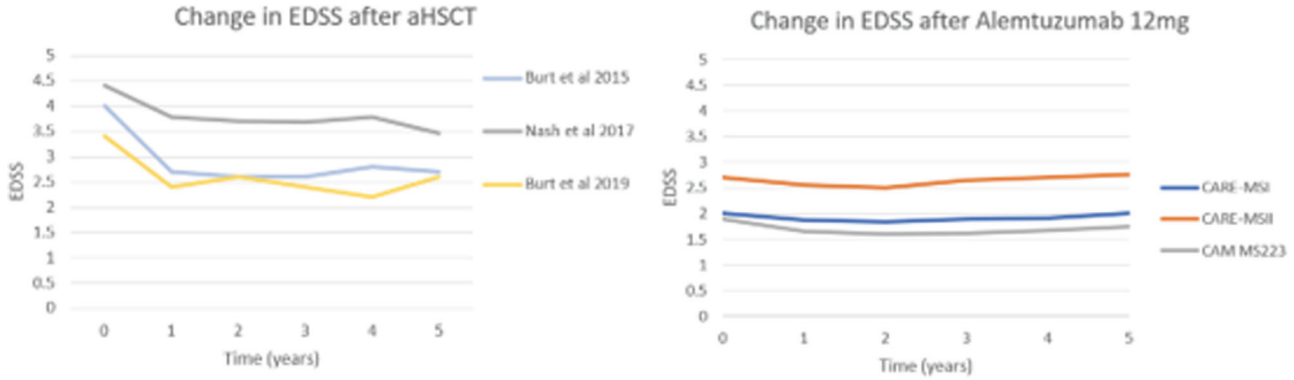
A total of 39 studies met the search criteria. After application of eligibility criteria and removal of duplicate data, three studies included 759 patients treated with alemtuzumab: CAM MS223, CARE-MSII, and CARE-MSI, were used in the study. Both CAM MS223 and CARE-MSI included treatment naïve patients; CARE-MSII (357 patients) included previously DMT exposed patients.

Mean EDSS pre-alemtuzumab was 1.9-2.7; only 6 patients had an EDSS >5.0. Peak post-alemtuzumab EDSS reduction occurred at 2 years with the CAM MS223 study; the best mean EDSS reduction was 0.3. The improvements at two years were negated by five years.

Mean EDSS across the studies progressed from a baseline of 2.31 (3sf) to 2.34 at five-year follow-up representing a mean increase of 0.03.

All-cause mortality across studies was 0.5%; TRM was 0.1%.

Conclusions: While it is imperfect to indirectly compare treatments from different studies, EDSS outcome patterns between aHSCT and alemtuzumab differed remarkably. aHSCT, in contrast to alemtuzumab, was associated with the largest magnitude of fall in EDSS that was sustained in the long-term to five years. A direct comparison of aHSCT with alemtuzumab in a RCT seems



[Mean change in EDSS post-HSCT or alemtuzumab]

warranted to confirm these observations of long-term benefit with aHSCT.

Disclosure: Nothing to declare.

P055

Reconstitution of Natural or vaccination-driven Immunity after aHSCT in Multiple Sclerosis

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Background: In the last 20 years, high dose chemotherapy with autologous hematopoietic stem cell transplantation (aHSCT) has emerged as an effective and safe treatment for aggressive forms of multiple sclerosis (MS). Nevertheless, no data have been published about reconstitution of either natural or vaccination-driven immunity after aHSCT and the consequent indication to re-vaccinate patients. We report an updated analysis of antigen-specific immune recovery in a series of MS patients after aHSCT, having increased the subset of patients included in the study.

Methods: Blood samples from 32 MS patients who underwent aHSCT in our Center between 2006 and 2017 were analyzed. Each patient underwent mobilization with cyclophosphamide (CTX) 4gr/sqm + GCS- F and was conditioned with BEAM/ATG regimen. Antibody titres for varicella-zoster, measles, rubella, and hepatitis B viruses were analysed before mobilization (baseline) and at 6 months, 1 year and then yearly after aHSCT. Chemiluminescent Microparticle Immunoassays (CMIA) were performed to determine Rubella and hepatitis B surface antigen antibodies (anti-HBsAg). Chemiluminescent Immunoassays (CLIA) were performed to assess Varicella Zoster and Measles. All patients received prophylaxis with acyclovir and Thrimethoprim-Sulphametoxazole for six months after aHSCT. Patients did not receive any re-vaccinations in the follow-up period.

Results: All patients showed a complete and sustained engraftment: median (range) time to PMN≥0.5x10^9/L and platelets≥20x10^9/L were 12(9-15) and 11(7-14) days, respectively. Patients showed also a complete return to a normal lymphocyte subset counts within two years from transplant. No case of measles, rubella, or chickenpox occurred after transplant, with a median follow-up of 40 (17-124) months. Table 1 reports the number of patients with positive or negative antibodies titres at baseline, 6 months and 2 years after aHSCT, respectively. A loss of serum protective immunity was observed in a variable rate of patients with all the tested agents: 14% in measles, 16% in rubella, 20% in hepatitis B, and 7% in Varicella Zoster.

Conclusions: Re-vaccination in patients who underwent an autologous HSCT for a severe autoimmune disease is a common practice in many centers and is also recommended in the EBMT guidelines. However, some concerns about this practice were raised for the putative role of vaccinations as an autoimmunity trigger. In the literature there is no study on the loss of protective antibody titer in either natural or vaccination-driven immunity with regards to patients transplanted for autoimmune diseases. In our series a high variability in antibodies titers at baseline was shown. The larger subset analysed confirms that most patients showing a protective titre against the tested agents, show a trend to maintaining it. A possible approach might be to revaccinate the patients with unprotective titre at 2 years after HSCT, taking into account the individual risk of being exposed to the infection; a larger series of data is necessary to provide conclusive evidences on this topic.

Disclosure: No disclosures

P056

High-dose Immunodepletion with Autologous Stem Cell Rescue for Treatment of Aggressive Multiple Sclerosis

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Background: Multiple sclerosis (MS) is the most common chronic inflammatory demyelinating disease of the CNS and the leading cause of non-traumatic neurological disability of young adults. Inflammatory forms of MS respond to immunomodulation with disease modifying treatments (DMTs), but some subgroups of patients continue to have clinical and/or MRI disease activity despite DMTs. There is increasing evidence, including randomized controlled trials, that demonstrates robust clinical efficacy of high-dose chemotherapy (HDCTx) with autologous stem cell rescue (ASCT) in patients with highly active MS.

Methods: In 07/2018 the Swiss Federal Office of Public Health approved the treatment of MS patients with HDCTx +ASCT at our single center (University Hospital Zurich). To be eligible for reimbursement (i) patients must have inflammatory breakthrough activity of MS despite highly effective DMT; (ii) the indication needs to be confirmed by our interdisciplinary hemato-neuroimmunological board; (iii) patients are required to participate in a registry study for 5 years post-ASCT. Patients are mobilized with 2 days of cyclophosphamide 2g/m^2 and Filgrastim. HDCTx comprises BEAM (BCNU, etoposide, cytarabine, melphalan) and ATG 3.75 mg/kg on d+1 and +2 post stem cell infusion.

Results: So far 20 patients (10 females, 10 males) with a mean age of 40.6 years ($\pm$7.5y) and disease duration of 8.4 years ($\pm$4.4y) were enrolled into the registry. On the "Expanded Disability Status Scale" (EDSS) patients had a mean score of 5.0 ($\pm$1.2). 6/20 (30%) patients had relapsing remitting MS (RRMS), 7/20 (35%) had secondary progressive (SPMS) and primary progressive (PPMS) disease, respectively. The indication for HDCTx+ASCT was clinical progression in 14/20 patients (70%), clinical disease activity in the form of relapses in 5 (25%), and/or radiological activity (new or contrast-enhancing lesions) in 7 patients (35%). Last treatments prior to ASCT were fingolimod (15%), rituximab (40%), ocrelizumab (30%), or natalizumab (15%).

Overall, treatment was tolerated well, although the majority of patients developed adverse events (AE). Most common AEs were oral mucositis/pharyngitis and/or enteritis in 18/20 patients. Upper airway and urinary tract infections were each observed in 4 patients, respectively. CMV reactivations occurred in 4/20 patients and were severe in 2 (including CMV enteritis and hospitalization for intravenous antiviral therapy). HSV reactivations (n=2) and BK cystitis (n=2) were also observed. A total of 9 serious AEs were recorded (CMV n=2; hemorrhagic cystitis, gastroenteritis with ileus, laryngitis, cervical abscess (post mobilization, prior to ASCT), pulmonary embolus (several months post ASCT), gastrointestinal bleeding, manic episode). Six patients experienced transient neurological deterioration. Other AEs were hypotension (n=3), cholecystolithiasis (n=1), and epistaxis (n=1). With the limitation of short follow-up, a substantial proportion of patients reported improvements of neurological functions and less fatigue, however, longer observation periods are needed to evaluate the potential benefits of this intensive treatment.

Conclusions: Here, we report on the establishment of a national registry program for MS patients undergoing ASCT. The fast recruitment indicates an unmet need for a subgroup of young patients with aggressive, conventional DMT-refractory MS. The safety profile is acceptable from a transplanter's perspective - however, bacterial and viral infections are common and require particular attention and prophylactic care.

Clinical Trial Registry: BASEC-number: 2018-01854 (Data and Biomaterial Collection for the Evaluation of Autologous Hematopoietic Stem Cell Transplantation in Relapsing Remitting and Progressive Multiple Sclerosis Patients (Registry))

Disclosure: Nothing to declare.

P057

Hematopoietic Stem Cell Transplantation does not Change the Expression of Endothelial Markers in Skin Biopsies of Systemic Sclerosis Patients

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Background: Systemic sclerosis (SSc) is an autoimmune disease characterized by vascular damage, deregulation of the immune system and fibrosis of the skin and internal organs. The injury and apoptosis of microvascular endothelial cells are indicated as initial events of the disease, leading to physiological changes in the endothelium and vasculopathy. Autologous Hematopoietic Stem Cell Transplantation (AHSCT) promotes resetting of the

immune system and has emerged as a treatment option for patients with severe and progressive SSc. Although AHSCT leads to clinical improvement, the mechanistic effects are still not completely understood. In this study, we aimed to investigate if AHSCT modifies the expression of endothelial markers in skin biopsies.

Methods: Samples of skin from the forearms of 27 SSc patients were evaluated by immunohistochemistry (IHC) before and at 6 and 12 months after AHSCT. Biopsies were marked with anti-CD31, -VEGF, -VEGFR2, -ANGIOPOIETIN 1, -ANGIOPOIETIN 2, -TIE, -ENDOTHELIN-1, -CD105 and -VE-CADHERIN antibodies and stained with Hematoxylin and Eosin (HE) and Picrosirius Red. The images were analyzed by ImageJ software

Results: Most participants were female (78%) with a mean (standard deviation, SD) age of 36 (9.4) years. The mean (SD) time between diagnosis of disease and transplantation was 3.2 (3.1) years. Clinical evaluation of fibrosis assessed by Rodnan´s score improved at 6 and 12 months compared to baseline ($p< 0.0001$). Histological analysis of fibrosis evaluated by HE and picrosirius red showed reduction of skin thickness ($p< 0.0001$) and collagen density ($p=0.0193$) after AHSCT.

The only endothelial marker that decreased after AHSCT was ANG1 ($p=0.0001$). All the other evaluated markers did not change ($p>0.05$) after AHSCT, when compared to baseline. Except for ANG1, our results indicate that ASHCT does not modify the expression of endothelial markers, anti-CD31, -VEGF, -VEGFR2, -ANGIOPOIETIN 1, -ANGIOPOIETIN 2, -TIE, -ENDOTHELIN-1, -CD105 and -VE-CADHERIN.

Conclusions: Our study shows that AHSCT therapy is able to improve fibrosis by reducing skin thickness and collagen fiber density, as assessed by Rodnan's score and by histopathological analysis, respectively. However, no changes in markers of endothelial damage were detected, except for ANG1, which is related to vessel stabilization. Our data suggest that AHSCT may affect disease pathogenesis differently, concerning fibrosis and vasculopathy. Our results suggest that AHSCT does not improve SSc-associated endothelial damage, indicating that additional therapies may be warranted to more effectively treat the endothelial injury. The decrease in Rodnan´s score may be more associated with improvement of fibrosis than to a beneficial effect on the microvascular compartment.

Disclosure: Nothing to declare.

P058

Autologous Stem Cell Transplantation for Non Hematological Diseases. The Dutch Experience of MS Patients going Abroad

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Background: In the Netherlands, an unknown number of patients go abroad to fee for service clinics for stem cell transplantation for non-hematological diseases. In this IRB approved study, we gather information about patients that went abroad and how it affected their health care.

Methods: Patients going abroad for stem cell transplantation on their own initiative for any kind of disease were recruited through (social) media like Facebook communities and newspapers.

Patients were invited to contact the research team. To participants giving informed consent, a questionnaire was sent.

The survey consisted of 3 parts: one set of questions regarding the stem cell transplantation abroad. Additionally, two validated patient-reported outcomes were included: the EORTC30 and NeuroQoL54.

Results: To date out of 51 participating patients, 30 finished the survey. 91,4% underwent a stem cell transplantation for multiple sclerosis (MS), 2,9% for Lyme's disease and 8,7% for other reasons

For the preliminary results presented here, we report on the first part of the questionnaire for 24 patients that had filled out the survey (before Dec. 2019) and received aHSCT treatment for MS.

A total of 24 people were included in this preliminary analysis (12 [50%] women; mean age, 46 [SD, 9.7]), 7 relapsing-remitting MS (RRMS, 7 secondary progressive MS (SPMS), 10 primary progressive MS (PPMS), (mean disease duration, 8 years [SD, 6.1], [Range 0-23]).

Most people were treated in Russia 10 [42%], Mexico 8 [33%], India 3 [13%]. The other three were treated elsewhere.

All except for one patient chose for their center based on "own research" or "success stories from other patients". None of the patients were referred by their physician. In three cases, the participants were advised in their decision for a specific clinic by their neurologist.

None of the participants was treated as part of an RCT.

Thirteen participants arranged for follow-up visits with a hematologist, three were advised so by their neurologist.

Five arranged these check-ups after their return. Six have not had any follow-up by GP or hematologist.

Sixteen participants did not feel supported by their treating physician in their decision.

The average cost was € 55000 [Range 27000-110000. Sixteen participants [67%] financed through crowdfunding. Others paid with their own means. In none of the cases, the health insurance contributed to financing the treatment. Aftercare was paid for by health insurance in 21 [87%] participants.

Conclusions: The decision to go abroad for HSCT for not supported indications is usually made by the patient, regardless of the advice of the treating physician. Many patients go abroad for SPMS and PPMS, whereas highly active RRMS is the only evidence-based indication. As a result, patients undergo high-risk treatment for non-evidence based indications (like progressive MS). Patients are easily lost to follow up, as they often arrange aftercare on their own. Central registration of people going abroad for this high-risk treatment could contribute to better safety with the ultimate goal to organize reimbursement for selected cases and attention to aftercare.

Clinical Trial Registry: Not applicable

Disclosure: nothing to declare.

P059

Analysis of Cost and Charges for non-myeloablative Hematopoietic Stem Cell Transplantation for Relapsing Remitting Multiple Sclerosis in the United States

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Background: Multiple sclerosis (MS) afflicts 2.5 million people worldwide (400,000 in the United States), and is a chronic disease, second only to congestive heart failure in cost of health care for a chronic illness. Lifetime direct costs per patients are greater than 4 million dollars and disease modifying therapy (DMT) is approximately 75% of the direct costs. DMT cost $80,000.00 per year (with a few costing more). We reported that after hematopoietic stem cell transplantation (HSCT) for frequently relapsing MS, only 16% relapsed and needed to restart DMT after 5 years. We now evaluated cost/ charges for HSCT on 42 consecutive patients treated with a non-myeloablative cyclophosphamide (200 mg /kg) and rabbit antithymocyte (ATG) (6.0 mg/kg) regimen.

Methods: Peripheral blood stem cells were collected 10 days after intravenous cyclophosphamide (2 g/m2) and 5 to 10 μg/kg per day of subcutaneous filgrastim beginning 5 days after cyclophosphamide. The immune ablative regimen was intravenous cyclophosphamide, 50 mg/kg per day on days −5 to day −2 before stem cell infusion (day 0) and rabbit antithymocyte globulin, 0.5 mg/kg on day −5, 1.0 mg/kg on day −4, and 1.5 mg/kg on days −3, −2, and −1. Methylprednisolone (1000 mg) was infused 30 minutes prior to rabbit antithymocyte globulin infusion.

Charges included all tests including blood draws, MRI imaging, echocardiograms, electrocardiograms, and chest radiograph, and all treatments and interventions including pre-HSCT evaluation, hematopoietic stem cell mobilization and cryopreservation, inpatient transplant admission charges, and all medications, nursing care, and room charges. The only charges not captured were physician history and physical and physician progress notes. Analysis was separated into direct costs (costs directly related to patient care (e.g. medications, laboratory tests, transfusions, nursing care), indirect costs (cost necessary to operate a hospital but not directly related to patient care e.g. managers, supervisors, medical records, accounting, information systems, marketing, legal, malpractice insurance, building maintenance and depreciation, house-keeping), total cost (sum of direct and indirect), net revenue collected, and net income (profit).

Results: Mean direct costs were $42,295 (range $33, 887 to $57,704), mean indirect costs were $42,888 (range $33,653 to $62,555), and mean total costs were $85,184 (range ($70,635 to $120,260). Mean revenue collected was $95,268 (range $16,544 to $173,204) and mean net income (profit) per patient was $10,084.

Conclusions: The mean costs and charges of HSCT using this non-myeloablative regimen are equivalent to DMT charges for one year (approximately $80,000) but comparable DMT charges do not include physician, laboratory, imaging, or hospitalization fees, if any. Since after a one-time treatment with a non-myeloablative HSCT regimen, the majority of patients remain treatment-free beyond 5 years, non-myeloablative HSCT with a cyclophosphamide ATG regimen appears to be cost effective.

Clinical Trial Registry: None

Disclosure: Nothing to declare.

P060

Autologous Stem Cell Transplantation in Behçet´s Disease: A Retrospective Study

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Background: Behcet´s disease (BD) is a rare autoimmune disease mostly presenting with recurrent oral and genital aphthous ulcers, and uveitis. Other common symptoms include gastrointestinal, vascular, neurological and articular manifestations[1]. Treatment is based on chronic immunosuppression with conventional disease modifying or targeted biologic drugs[2], although some refractory patients have been treated by autologous hematopoietic stem cell transplantation (AHSCT)[3]. This study aims to evaluate the outcome of AHSCT in adult patients with BD.

Methods: Adults who received AHSCT primarily for BD (according to International Classification Criteria) were identified retrospectively within the EBMT registry. Treating physicians were surveyed to produce a retrospective evaluation of outcomes. Complete Remission (CR) was defined as no evidence of disease activity and Partial Remission (PR) was defined as any documented clinical and/or laboratory response in patients that is less than CR.

Results: We retrospectively collected the data from 8 out of 9 cases reported to the EBMT registry and extracted data of 2 further patients from published literature[4]. Four were female, median age at onset of BD was 24 years (range 9-50). Median age at AHSCT was 32 years (27-51). Patients had received median 4 (2-12) prior lines of therapy: 89 % of the patients were treated with corticosteroids, and 50 % received either methotrexate, antiTNFa or cyclophosphamide. All had active disease before mobilization, which was performed with cyclophosphamide and G-CSF in 9 patients and G-CSF alone in 1 patient. Conditioning regimen was Melphalan 200mg/m² in 5 patients, BEAM in 3 patients, and Cyclophosphamide 200mg/kg plus antithymocyte-globulin (ATG) in 2 patients. Median follow-up was 48 months (range 6-120 months). No TRM was reported, three patients had infectious complications and a single patient had paroxysmal atrial fibrillation, line-associated deep venous thrombosis and depression. At 6 months, 6 patients were in PR with corticosteroid maintenance and 3 in CR without any further treatment. There was one relapse with pan-uveitis. One patient failed to respond to AHSCT and proceeded to rescue with allogeneic HSCT, but died five years post-transplant from chronic GvHD and CMV infection. Otherwise, no late complications in patients treated with AHSCT were reported.

Conclusions: AHSCT is feasible and safe in multi-refractory patients with BD. Although treatment-free CR was achieved in only 3 of 10 patients analyzed, AHSCT has the potential to stabilize BD in patients who fail to respond to conventional therapies. Further evidence, ideally from prospective studies, are warranted to determine whether AHSCT should be considered a standard of care in treatment-resistant BD.

Disclosure: No disclosure

P061

Safety and Tolerability of Autologous Hematopoietic Stem Cell Transplant in Multiple Sclerosis: A Single Center Experience

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Background: Multiple Sclerosis (MS) is an autoimmune disease in which there is both B and T cell mediated destruction of the nervous system. Historically it was observed that Autologous Hematopoietic Stem Cell Transplant (HSCT) is safe and effective in achieving long term Disease Modifying Therapy (DMT) free survival. Initially myeloablative conditioning with BEAM-ATG (BICNU, Etoposide, Ara-C, Melphalan - Anti Thymocyte Globulin) was used, but the mortality rates were high, so the non-myeloablative conditioning with Cyclophosphamide-ATG (Cy-ATG) was used, showing almost same outcome and with low mortality rates.

Methods: Seventy one consecutive patients of MS who underwent AHSCT were prospectively enrolled at a single center tertiary hospital.

Results: A total of 71 patients were of MS with median age 48 years (range 25-67 years) and a total of 65 patients underwent AHSCT out of which 36 (51%) males were included. Six patients were rejected due to various reasons. The diagnosis of MS was confirmed by clinical evaluation, MRI, VEP and BERA. Of these, 36(51%) were SPMS, 22 (31%) were RRMS and 13(18%) were PPMS with a median EDSS score of 5 (range 1 - 8.5). the median time from diagnosis to AHSCT was 11 years (range 0 - 37 years). In majority of these patients; 53(81%) stem cell mobilization

was done with G-CSF and in remaining either Cyclophosphamide + G-CSF 11(17%) or G-CSF + Plerixafor 2(3%) was used. Regimen related toxicity was seen in 9 patients in the form of anaphylaxis (5), hemorrhagic cystitis (3) and AKI (1). The median CD34 dose was 7.17 (range 2.82 - 13.84). The median time to neutrophil engraftment was 9 days (range 6 - 12 days) and platelet engraftment was 12 days (range 9 - 18 days). The median number of blood components transfused included RBC 2 units (range 0 - 7), RDPs [14 units (range 0 - 38) and SDPs 1 units (range 0 - 8). There was a significant improvement in the EDSS score [mean 5.07 SD 1.77 to mean 4.73 SD 2.09; p value < 0.001] till the discharge. There was only one death. Thirteen (20%) patients had transient worsening of MS related symptoms post-AHSCT which resolved completely before discharge. The most common type of infection was urinary (50%).

Conclusions: HSCT is a safe and effective treatment option in improving disability scores in patients of MS with refractoriness to DMTs. Our study showed that HSCT is well tolerated treatment option in MS with acceptable mortality of 1-2 %. However, long term follow up is needed to look for the response.

Disclosure: Nothing to declare.

P062

Outcome of Autologous Hematopoietic Stem Cell Transplantation for Refractory Takayasu Arteritis, A Retrospective Survey from the Autoimmune Diseases Working Party (ADWP) of the Ebmt

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Background: Takayasu arteritis (TAK) is a chronic granulomatous large-vessel vasculitis, commonly affecting young women, characterized by arterial thickening and fibrosis leading to stenosis and vascular occlusions. More than 10% of patients are refractory to conventional immunosuppressive disease-modifying drug (DMARD) therapy and are at high risk for vascular complications. Autologous hematopoietic stem cell transplantation (AHSCT) has emerged as a promising treatment option in severely affected and refractory patients with various autoimmune diseases. Several case-reports and small case series demonstrated the potential efficacy and safety of AHSCT for systemic vasculitis, particularly ANCA-positive vasculitis and Behçet's disease. This study, **approved by the ADWP**, aims to evaluate the use and outcome of AHSCT in adult TAK patients.

Methods: This is a retrospective survey of patients reported to the EBMT data management between 1998 and 2018, who received AHSCT primarily for TAK. A specifically designed questionnaire was sent to each referring transplant centre to obtain all relevant clinical and laboratory data. Remission was defined as no evidence of inflammation or worsening of vessel disease.

Results: Data from six adult patients treated with AHSCT between 2003 and 2018 for refractory Takayasu have been identified. Median (range) follow-up was 9.9 (1-14) years. Five patients were female (83%), median age was 25 (9-39) years at diagnosis and 28 (22-41) years at AHSCT. All patients were pretreated with a median of 6 (4-8) lines of therapy, including systemic corticosteroids (in 6 patients), methotrexate (5 patients), cyclophosphamide, mycophenolate mofetil or infliximab (4 patients), tocilizumab or etanercept (2 patients), and other biologic or conventional-synthetic DMARDs. Mobilization was performed with cyclophosphamide 2g/m^2 (4 patients) or 4g/m^2 (2 patients) in combination with granulocyte-colony stimulating factor (G-CSF). The graft was CD34 positive selected in 2 cases. Conditioning included cyclophosphamide 200 mg/kg in 5 patients, and cyclophosphamide 120 mg/kg plus fludarabine 90 mg/m2 in one patient. All patients received rabbit anti-thymocyte globulin. After AHSCT, 4 patients received G-CSF during a median of 5 (5-6) days. A median of 3.9 (2-4.20) x 10˟6 CD34+cells /per kilogram were reinfused. Engraftment, defined as neutrophils ³0.5 x10^9/L and platelet ³20 x10^9/L were detected at a median of 8 (5-13) and 8 (5-11) days, respectively. All patients had active disease before AHSCT. At six months post-transplantation, remission was obtained in all cases, which persisted at 12 months in 5 cases. Four patients reactivated TAK at a median time of 27 (7-52) months after AHSCT, and 3 resumed disease-modifying therapy. During follow-up none of the patients developed secondary malignancy and one patient had a miscarriage. At last follow-up, all patients were alive, 2 patients were in remission (off-therapy), 2 patients improved compared to

baseline, and 2 patients were in complete and partial remission, respectively, under immunosuppressive treatment.

Conclusions: This small retrospective series demonstrates that AHSCT has the potential to provide significant clinical responses in TAK patients who had been unresponsive to previous immunosuppressive therapy, with an acceptable safety profile. Therefore, AHSCT may be considered as a 'clinical option' for patients with severe, treatment-resistant and poor-prognosis TAK, ideally before the development of compromised vital organ function.

Clinical Trial Registry: na

Disclosure: JAS declare.s speaker fees at educational events supported by Sanofi, Janssen, Jazz, Mallinckrodt and Gilead

P063

The use of Autologous Haemopoetic Stem Cell Transplantation (aHSCT) in Multiple Sclerosis after Alemtuzumab Treatment Failure: A Case Series

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Background: Disease modifying therapies (DMT) for RRMS have been the mainstay of treatment for 20 years. Alemtuzumab is one of the most highly efficacious DMT for RRMS. However some patients continue to experience disease activity despite adequate Alemtuzumab therapy. AHSCT has been used with increasing frequency over the last decade to treat very active RRMS despite the use of DMTs. However efficacy and timing of delivering treatment in patients who failed Alemtuzumab remains unclear. Here we report a case series of patients with RRMS who received AHSCT after failing to respond to Alemtuzumab treatment.

Methods: A case series of all patients who received AHSCT for RRMS after failing to respond to a full course of Alemtuzumab was compiled. Details of 4 cases were collected from a national referral centre in the north of England. Clinical details, MRI changes, efficacy and safety data related to the use of Alemtuzumab and AHSCT were recorded. AHSCT was performed using a standard Cyclophosphamide / ATG mobilization and conditioning regime.

Results: All patients experienced clinical and radiological evidence of disease activity and progression whilst on Alemtuzumab. The mean treatment period with Alemtuzumab was 27 months (SD 23.2 months). Mean treatment courses was 2.5. Mean follow up after AHSCT was 48.5 months (SD 32.7). No patient experienced further relapses or MRI disease activity following AHSCT. EDSS scores improved in all patients following AHSCT (mean 1.12 points, SD 0.62). Patients experienced routine grade 1-3 complications during transplantation period. No autoimmune complications were recorded.

Conclusions: Our data suggests that AHSCT use is effective and safe in patients who failed to respond to Alemtuzumab.

Clinical Trial Registry: No Applicable

Disclosure: John Snowden declare.s speaker fees at educational events supported by Sanofi, Janssen, Jazz, Mallinckrodt and Gilead.

P064

Autologous Hematopoietic Stem Cell Transplantation for Treatment of Systemic Sclerosis, an Option for Refractory Patients

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Background: Autologous hematopoietic stem cell transplantation (aHSCT) is a promising therapeutic modality for severe autoimmune diseases, especially as a treatment option for systemic sclerosis (SS). The aim of this study was to describe clinical experience in the use of aHSCT for SS in three centers in Colombia.

Methods: We conducted an observational study of adult patients diagnosed with SS and treated with aHSCT at centers from three different cities of Colombia from 2010 to 2019. Patients with SS were autografted in the centers with peripheral blood stem cells. The autografts were performed after conditioning with cyclophosphamide and BEAM chemotherapy. Laboratory results and complications after aHSCT were evaluated. Patients were follow-up to 3 years.

Results: Information from 13 patients were collected from the three centers. Median age was 44 years (27-53). We included 11 females (85%) and 2 males (15%). As a first-line treatment, 11 patients (84,6%) were treated with steroids. Median dose for cyclophosphamide at mobilization was 2,3

mg/m2 (2-3,5 mg/m2). About conditioning treatment, cyclophosphamide was performed in 12 patients (92,3%), while BEAM chemotherapy was performed in 1 patient (7,7%). The total number of viable CD34+ infused cells ranged between 3,1-25,57x10^6 (average 8,1). Patients recovered ≥0.5x10^9/L absolute granulocytes by day 14 (8-43 days), and platelet values were also ≥20x10^9/L by day 14 (6-43 days). Febrile neutropenia presented in 4 patients (30,7%), mucositis in 2 patients (15,3%), Pneumocystis jiroveci Pneumonia in 4 patients (30,7%) and 1 patient presented cytomegalovirus reactivation (7,7%). Only 1 patient (7,7%) presented cardiovascular complications and another patient (7,7%) presented endocrine complications. To date, there have been no deaths attributable to the transplant, yielding a 3 years overall survival of 100% and progression-free survival was 92,3% for all the patients.

Conclusions: AHSCT reduces the risk of all-cause mortality and has properties of a disease-modifying antirheumatic treatment in SS patients, leading to a high overall survival time. AHSCT should be proposed for carefully selected patients with refractory SS, therefore, optimal patient selection, pre-transplantation workup and post-transplant management need to be stablished.

Disclosure: Nothing to declare.

P065

A Pilot Feasibility Study of non-myeloablative Allogeneic Hematopoietic Stem Cell Transplantation for Refractory Crohn Disease

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Background: Autologous hematopoietic stem cell transplantation (HSCT) induces remission of refractory Crohn disease (CD) but approximately 50% and 80% relapse and restart standard therapies at 3 and 5 years, respectively, post HSCT. We, therefore, undertook a pilot study of allogeneic HSCT using either matched sibling donor or umbilical cord blood (UCB), if a matched donor was not available.

Methods: Eligible patients were 18 to 45 years old, had an established diagnosis of Crohn disease, failed corticosteroids, 5-aminosalicylate, and at least two anti-TNF (infliximab, adalimumab, or certolizumab) drugs with a Crohn disease activity index (CDAI) between 250 to 400 or Craig Severity Score (CSS) $\geq$ 17. Donor preference was given for unmanipulated healthy adult HLA 6 / 6 matched sibling, followed by unrelated 6/6 matched UCB and then unrelated 5/6 matched UCB. When available two UCB units were infused. The conditioning regimen was dose escalated during the protocol's duration in an attempt to maximize donor engraftment. Conditioning drugs were: 1) cyclophosphamide 200 mg/kg divided as 50 mg /kg on days -5,-4,-3 and -2, 2) fludarabine (75 to 150 mg / m2) divided as 25- 30 mg /m^2 /day (between days -7 to -3), and alemtuzumab (60 mg to 90 mg) divided 30 mg day (between days -3 to -1). Cyclosporine (100 mg po bid) or tacrolimus (1.0 mg bid) was initiated on day -2 and continued for 9 months.

Results: Average time of hospital engraftment and hospital discharge was day 13 and 14, respectively, with no difference in mean day of engraftment or discharge between matched sibling versus UCB transplantation. The mean number of red blood cell and platelet transfusions were both 3.4. Neutropenic infections included one case each of diarrhea due to clostridium difficile, and blood cultures positive for Escherichia coli, Enterococcus faecalis, and extended broad spectrum beta-lactamase producing Escherichia coli. Late post discharge events were tacrolimus-induced chronic renal failure mandating renal transplantation in a patient with a history of pre-transplant tacrolimus induced acute renal failure, surgery for colonic stricture without evidence of active Crohn disease that was complicated by bowel perforation and pseudomonas sepsis, and one death 3 months post HSCT from disseminated adenovirus infection. Following the patient's death enrollment was terminated. There was no acute GVHD and one case of possible limited chronic GVHD.

Despite no evidence of donor engraftment, all patients entered and maintained without treatment a clinical remission (CDAI < 150), MRI imaging remission, endoscopic and histologic remission for the 5 years of study follow-up.

Conclusions: Complete treatment-free 5-year remissions without donor engraftment suggests that the conditioning regimen and nine months of maintenance tacrolimus, not the allogeneic hematopoietic stem cells, were responsible for remission. Alternatively, the infused donor graft may have provided a non-CD3+, non-CD33+ non-hematopoietic type of stem cell such as donor mesenchymal stem cells that in theory could facilitate a durable remission

Clinical Trial Registry: FDA IND 16908, www.clinicaltrials.gov NCT 01288053

Disclosure: Nothing to declare.

CAR-based Cellular Therapy – clinical

P066

National Implementation of the use of Tisagenlecleucel in Paediatric and Young Adult Patients with Acute

Lymphoblastic Leukaemia (ALL) in National Health Service England (NHSE)

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Background: Following European Medicines Agency (EMA) approval of Tisagenlecleucel (KYMRIAH®) for the treatment of relapsed/refractory acute lymphoblastic leukaemia (ALL) in children and young adults in 2018, England established a structured funding programme via the National Health Service England (NHSE) Cancer Drugs Fund.

Methods: NHSE established a national CAR-T clinical panel for ALL (NCCP ALL). The aim of the NCCP ALL was to review cases to confirm eligibility against published criteria in line with the ELIANA study inclusion criteria and ensure prompt national access to Tisagenlecleucel. All CAR-T centres (3 open at NCCP set up and 9 open at 1 year review) were accredited for the Immune Effector Cell Standards in the 7th edition of the JACIE Standards in line with EBMT/JACIE recommendations (Yakoub-Agha et al 2019). The NCCP ALL consisted of representatives from NHSE, CAR-T centres, patient representation and independent ALL clinical experts. We describe panel experience over a one year period.

Results: The NCCP met by weekly teleconference to review cases referred by individual CAR-T centre lead clinicians who endorsed eligibility. Approval for access to Tisagenlecleucel was granted through unanimous panel consensus agreement following review of eligibility criteria (according to disease and CD19+ status, absence of CNS disease, performance status and organ function). Allocation to centre was achieved by review of geography, slot availability and patient preference.

From 19.11.2018-18.11.2019 34 patients were approved (age range 9 months - 21 years, median age 10.5 years). 5 did not proceed to leukapheresis (2 incorrect diagnosis of relapse, 1 received alternative CAR-T clinical trial product, 2 unable to proceed due to disease progression/complications). At time of abstract submission 23/29 (79.3%) patients had undergone CAR-T infusion. 3 patients who underwent leukapheresis were unable to proceed to infusion (1 patient due to emergence of CD19 negative disease, 1 patient due to CNS disease progression, 1 patient received cranial radiotherapy to control CNS disease and suffered frank bone marrow relapse treated with Inotuzumab followed by a failed manufacture). 3 patients await infusion. Mean time from panel approval to leukapheresis was 15 days (range 0-47 days) and mean time from leukapheresis to CAR-T infusion for patients infused was 64 days (range 35 - 92 days) Of 15 patients evaluable beyond 100 days (8 patients yet to reach this time point), 11 have a documented status of 'alive in MRD negative remission'. This represents 73% patients infused (11/15). Brief toxicity and follow up data will be reported at EBMT 2020 with future planned efficacy analysis.

Conclusions: The establishment of a national panel in England for Tisagenlecleucel approval has allowed prompt, equitable and trackable access to this CAR-T product for ALL. From a worldwide perspective, NHSE is one of the first health services to introduce a national co-ordinated access programme of care and will utilise programme data to assess real world outcomes for patients treated with Tisagenlecleucel.

Disclosure: Nothing to declare.

P067

Real-world Clinical Features of Neurotoxicity Complicating CD19-targeted Chimeric Antigen Receptor (CAR) t-cell Therapy for High Grade Lymphoma and Management Including the off-label use of Anakinra

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Background: Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are the main toxicities complicating CAR T-cell therapy. High dose steroids are the current standard of care, though there remains a clinical need for patients that are refractory to front line treatment. Animal models have supported cytokine targeting therapies that can cross the blood brain barrier such as the IL-1 receptor antagonist anakinra. We report our experience with ICANS in a cohort of patients receiving CD19 CAR T-cells, including the first series of patients treated with anakinra for ICANS.

Methods: Patients with relapsed/refractory B cell non-Hodgkin lymphoma received axicabtagene ciloleucel (axicel) and tisagenlecleucel (tisagen) between Jan 2019 and September 2019. Eligibility was determined independently by a panel of clinical experts from NHS England and data collected prospectively. ICANS was graded according to ASTCT Consensus Grading.

Results: A total of 43 patients received treatment (14 transformed FL, 2 PMBCL and 27 DLBCL): 38 received axi-cel and 5 tisagen. 14 of 43 patients (33%) experienced any grade of neurotoxicity, with 7 of 43 (16%) grade 3 or 4, lower than the rate reported in previous trials and real-world data. The most common clinical features were disorientation or confusion, dyspraxia and expressive dysphasia (n=9). Intensive care admission was required for 8 patients, with 3 requiring intubation.

Neuroimaging was performed in 13 patients: five patients with CT brain, five with CT and MRI brain, and three MRI. The only clear acute change was bilateral hippocampal enhancement for one patient on MRI, subsequently attributed to viral encephalitis. Lumbar puncture was performed in six patients: glucose and cytology was normal, with a mild rise in CSF protein (mean 0.96g/L, range 0.25-0.45g/L). One patient was diagnosed with HHV6 encephalitis. EEG was performed in 12 patients, with almost all (92%) displaying encephalopathic features (generalised rhythmic delta activity) and 2 (17%) with epileptiform foci over the left fronto-temporal region. No periodic discharges or seizures were captured.

High dose steroids (dexamethasone up to 40mg daily) was started for 11 patients for treatment of ICANS; all patients had received tocilizumab for prior or concurrent CRS. Anakinra was administered to five patients concurrently with steroids for ICANS that was high grade or not responsive to initial therapy with dexamethasone. The ICANS grade for these five patients at time of treatment was grade 3 for two patients, and grade 4 for three patients. Anakinra was given as 200mg daily subcutaneously, started at a median of 3 days (range 1 to 5) after the commencement of dexamethasone for ICANS treatment, and median number of 5.4 doses given (range 3 to 8). ICANS resolved in all patients surviving to day 30 (n=13), with persistent neurological features in one patient likely sequelae of viral encephalitis and one treatment related death (sepsis).

Conclusions: We describe the clinical features of ICANS in our real-world cohort of patients receiving standard of care CD19 CAR T-cells, and demonstrate the feasibility of anakinra in combination with dexamethasone for treatment ICANS that is severe or not initially responsive to high dose steroids.

Disclosure: Nothing relevant to declare.

P068

Abstract already published.

P069

Abstract already published.

P070

Association of axi-cel CAR-T Cell Concentration with Treatment Response and Side Effects and Impact of Dexamethasone Treatment on Kinetics

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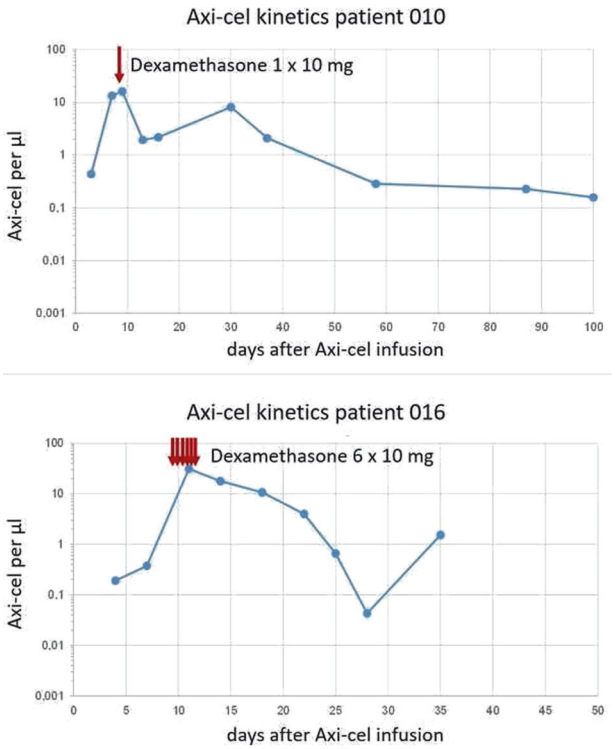
Background: Chimeric-antigen-receptor (CAR-) T cells have demonstrated remarkable efficacy in the treatment of B-cell hematological malignancies, leading to the recent approval of two CD19-CAR-T cell products (Tisagenlecleucel/Kymriah and Axicabtagene ciloleucel/Axi-cel/Yescarta) in the US and Europe. CAR-T cell engraftment and expansion represent crucial parameters for efficacy of treatment. Monitoring of CAR-T cell concentrations has however been limited by the lack of diagnostic assays.

Methods: We performed prospective serial measurements of CAR-T cell levels in blood and body fluids of 18 patients treated with Axi-cel. Informed consent was obtained from all patients and the study approved by the ethics committee. Per protocol, blood samples are collected on days 0, 3, 7, 10, 14, 21, 28, 35, 56, 84, 180 and 365 after CAR-T cell infusion. In case of ICANS and lumbar puncture, cerebrospinal fluid (CSF) is also analyzed for CAR-T cell numbers. Quantification of CAR-T cells was performed using a newly developed digital PCR assay (Fehse et al., EBMT 2020).

Results: We have treated 18 patients with diffuse large B cell lymphoma with Axi-Cel. Sixteen of these patients were evaluable for day 30 response at time of abstract submission. CAR-T cells could be detected in the blood of all 16 patients, expansion and contraction followed the expected kinetics with median peak value of 11.2 CAR-T cells on (median) day 11.5 after infusion. Clinically, we observed only 2 responses (1PR, 1 CR) in 7 patients who had poor expansion of CAR-T cells (defined as peak numbers below and peak time-points above median), while 9 out of 10 patients with comparatively good expansion showed response (5 CR, 4 PR) on day 30. Seven out of 10 patients with good expansion experienced CRS and/or ICANS whereas only 2 of 7 patients with poor expansion had CRS or ICANS. CSF was collected from 3 patients with ICANS. In all 3 cases, high concentrations of CAR-T cells were detected in CSF. Two patients received dexamethasone for the treatment of ICANS. In both cases, treatment with dexamethasone (1 dose and 6 doses of 10mg respectively) led to a drop in the concentration of CAR-T cells, followed by recovery after discontinuation of dexamethasone (Figure 1). Data on more patients and cytopenias will be presented at the meeting.

Conclusions: Despite the relatively small patient number, our data emphasize the importance of monitoring CAR-T concentrations after infusion and indicate an association with response and side effects. CAR-T cell proliferation appears to bounce back after treatment with dexamethasone.



[Figure 1]

Disclosure: FA has received honorarium from Kite/Gilead for advisory board. NK has received honorarium from Kite/Gilead for advisory board. The dPCR assay used in this work has been made available as an "Expert Design Assay" based on agreement with Bio-Rad. BF, AB, CB, and KR would profit from potential future commercialization of the assay.

P071

Nivolumab as Salvage Therapy in Patients who Failed to Achieve Complete Remission after anti-CD19 CAR T-cell Therapy for DLBCL

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Background: We report the efficacy and tolerance of nivolumab (Nivo) in patients who did not achieve a complete response (CR) at one month after Yescarta™ infusion.

Methods: Thirty-two patients with R/R DLBCL (13 male/19 female) were candidate for Yescarta™ and underwent leukapheresis between November 2018 and December 2019 in our center. As of December 15, 2019, 29 were infused, 2 patients are waiting to be infused and one patient never got infused because CAR T-cell production failed twice. Twenty-five patients are evaluable for response at one month post CAR T infusion since one patient died at day 21 of septic shock. Median follow-up was 152 days (range, 39-354 days).

Results: Response rates according to IWC 2014 (Cheson 2014) at one month after CAR T-cell infusion were CR (n=11; 42%), partial response (PR) (n=5, 19%), stable disease (SD) (n=3: 12%), progressive disease (PD) (n=6; 23%). One patient with PR converted to CR two months after CAR T-cell infusion without subsequent treatment. All patients who achieved CR are alive and received no further treatment. All but 4 of the 13 patients who did not achieve CR received salvage therapy with Nivo. The 9 patients (3 PR, 3 SD and 3 PD) received Nivo at the dose of 240 mg/2 weeks. All patients received prophylaxis with valaciclovir and cotrimoxazole. Median time of the onset of Nivo was 60 days (range, 37-144 days) after CAR T-cell infusion. Median number of Nivo injections was 5 (range, 2-9). Two out of the 3 patients

Patients #/sex/age in years	Response to CAR T-cell therapy at one month	Onset of Nivo after CAR T-cell infusion (days)	Number of injections	Main side effects	Response to Nivo	Current Nivo	Treatment after Nivo	Current status and survival after CAR T-cell therapy (days)
1/M/59	PR	86	5	psoriasis	CR	stopped	Allo-HCT	Alive 354
2/M/39	PR	133	4	-	PD	stopped	Allo-HCT	Died 306
3/F/63	SD	83	5	-	PD	stopped	Supportive care	Alive 275
4/F/69	PR	144	5	pneumonia	CR	ongoing	-	Alive 227
5/F/53	PD	37	5	-	PD	stopped	Ibrutinib lenalidomide	Alive 220
6/F/63	PD	51	9	pneumonia	PR	ongoing	-	Alive 179
7/M/55	SD	60	2	-	PD	stopped	Supportive care	Died 150
8/F/74	SD	46	4	pneumonia	PD	stopped	Supportive care	Alive 153
9/F/67	PD	39	3	-	ongoing	ongoing	-	Alive 76

[Table1. Patients' outcome after Nivo administration]

with PR achieved CR 60 days after initiation of Nivo. One of them subsequently received allogeneic hematopoietic cell transplantation and one is still receiving Nivo. In this latter patient, circulating CAR T-cells, mainly $CD8^+$, dramatically increased following Nivo administration. One out of the 3 patients with PD experienced PR 60 days after Nivo. The 6 remaining patients with PR, SD and PD progressed after Nivo, of whom 2 died at day 90 and 173 after initiation of Nivo. Table 1 depicts outcomes of all patients who received Nivo. Three patients developed grade 2 bacterial pneumonia and one patient who received subsequent allo-HCT developed grade 1 psoriasis that was probably linked to Nivo. Overall, response to Nivo was recorded as CR (n=2, 22%) and PR (n=1, 11%). Six patients (67%) progressed.

Conclusions: Nivo seemed to be effective and safe in a small number of patients who did not achieve CR after CAR T-cell therapy.

Disclosure: Nothing to declare.

P072

Surveillance of Minimal Residual Disease (MRD) in Diffuse Large B Cell Lymphoma (DLBCL) by Circulating Tumor Dna (CTDNA) Profiling after Chimeric Antigen Receptor T (CAR-T)

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Background: CAR-T therapy has become an ultimately effective solution for relapse or refractory (r/r) DLBCL. Therefore, after successful CAR-T therapy, patients are carefully monitored by positron emission tomography-computed tomography (PET-CT) instead of other treatment. Besides high cost, risk of ionizing radiation also limit the use of PET-CT in surveillance follow-up DLBCL. CtDNA derives from disrupted tumor cells preserving the characteristic of alteration in tumor genome. With the application of next generation sequencing (NGS), analysis large-scale sample of DNA become cheaper and faster showing great potential prospect in "liquid biopsy" avoiding the risk of failure of biopsy, surveillance of MRD in lymphoma, and observation of lymphoma subclone evolvement with early precise intervention.

Methods: We retrospectively collected clinical data, tumor sample preserved in formalin fixed paraffin-embedded tissue or liquid nitrogen storage and serum preserved in liquid nitrogen storage from the prospective clinical study aiming to evaluate the safety and efficacy of anti-CD19 CAR-T for r/r B cell lymphoma (ChiCTR-OCC-15007008). We profiled genome aberration with NGS in the baseline, relapsed, and progressive tumor sample after CAR-T therapy and ctDNA in baseline serum and reviewing serum in accordance with reviewing PET-CT scan. 8 DLBCL patients received CAR-T therapy between December 2016 and November 2017 were included in this analysis.

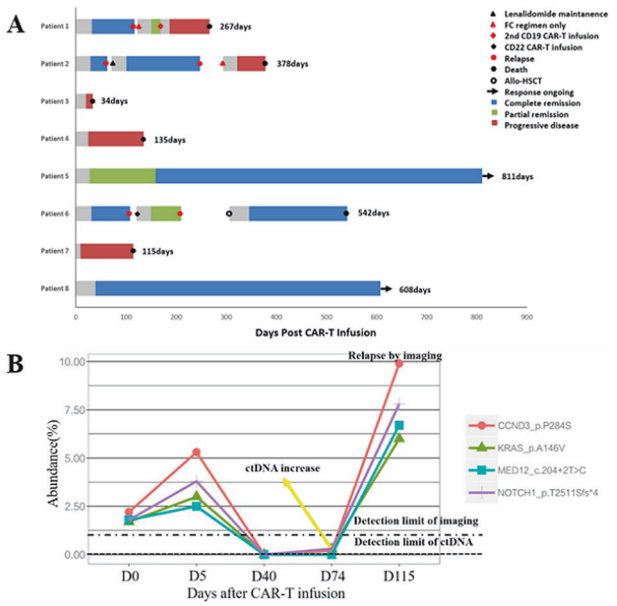
Results: The baseline characteristics are listed in table. The median follow-up is 322.5 days. 4 (50%) patients achieved complete response (CR), 1 (12.5%) patient achieved partial response and the rest of 3 (37.5%) patients showed no response 1 month after CAR-T therapy. 3 of 5

patients who achieved response relapsed within 4 months after CAR-T therapy while the rest of 2 patients remain CR for more than 20 and 27 months respectively.(Figure A) Grade 1, 2, and 3 cytokine release syndrome occurred in 2, 1, and 3 patients respectively. 89 and 446 hotspot genes NGS were performed in 1 and 7 patients respectively. Compared to PET-CT scan, the sensitivity and specificity of ctDNA profiling in detecting MRD is 94% and 64% respectively. Among 3 patients who relapsed from CAR-T, positive posttreatment ctDNA detection preceded PET-CT progression in patient 6 by 1.4 months (Figure B). The median number of abnormal genes in baseline tumor tissue is 4 and 15.5 (P=0.012) in the patients remained long-term CR and the patients failed from CAR-T therapy respectively. XPO1 E571K mutation was observed in 3 of 6 patients failed from CAR-T therapy.

Conclusions: CtDNA profiling is a promising new technique for surveillance of MRD in DLBCL after CAR-T therapy. In some cases, ctDNA can predict the disease progression earlier than PET-CT scan. A much number of abnormal genes in baseline particularly XPO1 E571K mutation may be a poor prognostic factor after CAR-T therapy in DLBCL.

Patient No.	1	2	3	4	5	6	7	8
Age	35	27	36	44	43	60	33	50
Disease stage	IVB	IVB	IVA	IVA	IIIA	IIISB	IVA	IIA
Prior lines of therapy	7	4	3	3	5	2	3	4
Prior ASCT	Yes	No	No	No	Yes	No	No	No

[Baseline characteristics]



[Figure 1A. | Figure 1B. Positive posttreatment ct]

Clinical Trial Registry: ChiCTR-OCC-15007008 http://www.chictr.org.cn/

Disclosure: Nothing to declare.

P073

A digital-pcr Assay for Precise in-vivo Quantification of Adoptively Transferred CD19-car T Cells after Treatment with Axicabtagene Ciloleucel (AXI-CEL)

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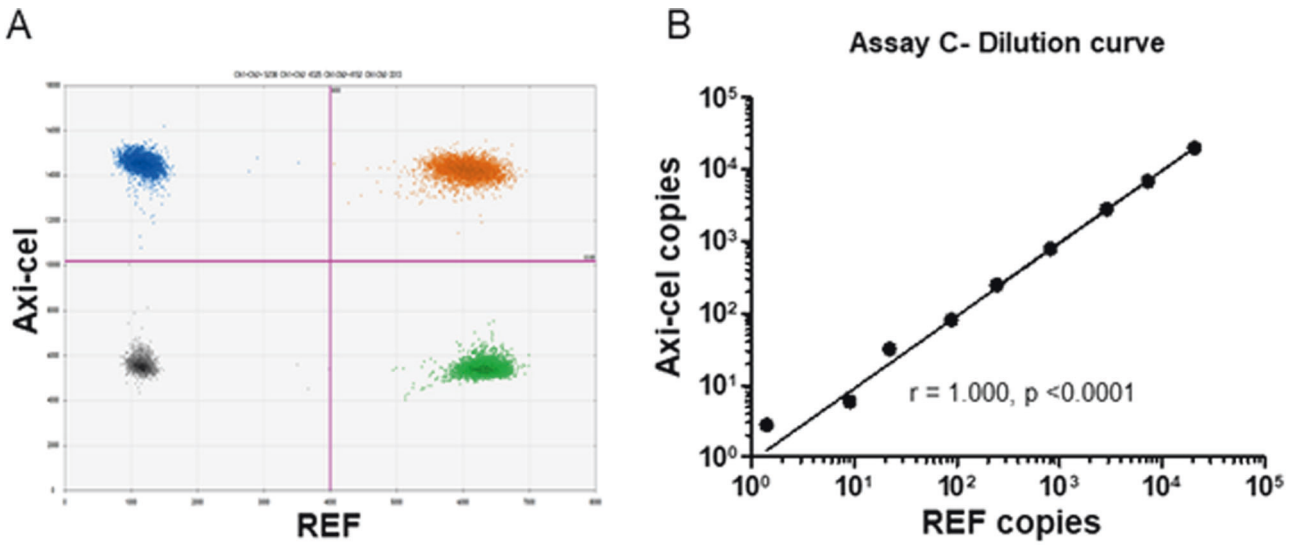
Background: Adoptive immunotherapy with CD19-specific CAR-T cells has shown excellent efficacy in late-stage relapsed/refractory B-cell cancers leading to the recent approval of two CD19-CAR-T cell products. Being 'living drugs', the in-vivo expansion, migration, contraction and persistence of CAR-T cells after infusion are important variables most probably impacting both disease response and treatment toxicity. Remarkably, widely available diagnostic tools to rapidly assess CAR-T-cell 'drug levels' in the clinical setting are largely missing. Digital PCR (dPCR) represents an advancement of quantitative PCR and is characterised by excellent sensitivity, specificity, and reproducibility making it an ideal tool for real-time diagnostics of rare events. Here we aimed at developing and evaluating a novel dPCR assay for detection and quantification of Axi-cel CAR-T cells in vivo.

Methods: To establish a CAR-specific dPCR assay, we first cloned and sequenced the complete cDNA of the Axi-cel vector construct. We designed different combinations of primers and dual-labelled hydrolysis probes, each amplicon spanning at least two different regions of the CAR vector. Three combinations of primers (A, B, C) were successfully tested on CAR-T cells, post-infusion PBMC, and negative controls in duplex reactions with the HCK reference (REF) gene; assay C was chosen for further application.

Results: For all three dPCR assays clear separation of negative and positive signals was observed (Fig. 1A) resulting in perfect specificity. Reproducibility tested on individual patient samples was excellent with neglectable intra- and inter-assay variations. Based on dilution curves (Fig. 1B) and the established negativity of non-transduced cells, the limit of detection was determined to be one single CAR copy. Considering Poisson distribution this translates into a limit of quantification of three copies, i.e. any sample



[Figure 1]

containing a mean of three target copies in the test volume could be expected to become positive with a likelihood >95%. In 100 ng genomic DNA (gDNA; approximately 30,000 haploid genome equivalents) this corresponds to a sensitivity of 0.01%. For male patients, a Y-chromosome located haploid reference gene was employed, which allows doubling the gDNA input and thus dPCR sensitivity. After thorough assay validation, we proceeded to monitor adoptively transferred Axi-cel T cells in 16 patients with advanced B-cell lymphoma treated at our centre (with informed consent) using assay C. Mean vector copy numbers were first assessed in the Axi-cel products, using leftovers from the infusion bags. CAR-T cells were reliably detectable in post-infusion samples of peripheral blood, bone marrow, and body fluids. Actual CAR-T numbers were calculated taking into account vector copy and PBMC numbers at the time point of analysis. We found robust CAR-T-cell expansion in 10 of our 16 patients with peak levels of up to 132 CAR-T cells/μL. The pattern of early CAR-T cell expansion and long-term persistence followed the kinetics previously described for Axi-cel patients.

Conclusions: We have established a novel dPCR assay for sensitive detection of Axi-cel CAR-T cells in vivo. Our assay is excellently suited as a diagnostic tool to monitor the infused cells in real-time in different body fluids.

Disclosure: The described dPCR assay is available as an 'Expert Design Assay from Bio-Rad. BF, CB, AB, and KR would profit from commercialisation of the Assay.

P074

Abstract already published.

P075

Axicabtagene Ciloleucel CD19 CAR T-Cells for Relapsed/refractory Large b-cell Lymphoma: real-world Outcomes, Toxicity and Predictors of Response from a Prospective UK Cohort

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Background: King's College Hospital was an early UK commissioned centre delivering licensed axicabtagene ciloleucel (axi-cel) for the treatment of relapsed/refractory high-grade lymphoma starting in January 2019. Eligibility was determined through both NHS England's National CAR Clinical panel and King's College Hospital CAR multi-disciplinary team meeting for NHS and private patients respectively. Real-world European data is required to validate trial data and look for predictors of response and toxicity.

Methods: Eligible patients were aged >18 with diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma (tFL) or primary mediastinal B-cell lymphoma (PMBCL), post 2 previous lines of treatment including anthracyclines. Adequate organ function was determined by King's College Hospital and data on outcomes were collected prospectively.

Results: As of December 2019, 42 patients have been infused with axi-cel with a median follow-up of 6 months. The median age was 55 (range 18-73), 63% were male and 19% were aged 65 or over at infusion. All patients had ECOG performance status of 0-1 at time of referral. 27 (64%) had DLBCL, 12 (29%) transformed follicular lymphoma and 3 (7%) PMBCL. 11 patients had previous transplants (26%), 3 allogeneic and 8 autologous.

Median time from leukapheresis to infusion was 36 days. Most patients received bridging therapy between leukapheresis and infusion, 20 (47%) with chemotherapy, 8 (19%) with radiotherapy and 10 (23%) with steroids only.

Toxicity was graded as per consensus ASTCT guidelines (Lee et al. BBMT 2019) with 41 patients evaluable. Grade 3 cytokine release syndrome (CRS) occurred in 5 patients (12%) with no grade 4 or 5 events. 40 patients (98%) had CRS of any grade, with 32 patients (78%) being treated with tocilizumab for CRS grade 2 or above. 7 patients (17%) had grades 3 or 4 immune effector cell associated neurotoxicity syndrome (ICANS) with 14 patients (34%) experiencing any grade. 41% of patients received steroids for CRS or ICANS management. There was one grade 5 event from pneumonia and sepsis. 16 patients were treated on intensive care (39%), however 8 of these patients only required observation.

38 patients had an evaluable response at 1 month, with 82% overall response rate (ORR) and 37% complete metabolic remission (CMR), at 3 months of 34 evaluable patients 44% ORR and 23% CMR. Overall survival of the infused cohort was 67% and 14 (33%) patients have moved to further therapies. Median progression free survival (PFS) was 3.6 months and was significantly inferior in patients with 3+ prior therapies, with extranodal disease and with DLBCL compared to tFL.

Conclusions: CD19 CAR T cells have been safely delivered in the NHS and our large single centre cohort demonstrates lower toxicity with axi-cel, particularly of ICANS then described in a recent large CIBMTR cohort (Pasquini et al. ASH 2019). Initial response rates are high although PFS is lower than expected. Interestingly, 3+ prior therapies were associated with inferior PFS, implying patients may benefit from earlier referral for consideration of CAR T cells. By EBMT further follow-up will allow 6-month outcomes and predictors of response to be presented.

Disclosure: Sanderson, Robin - Advisory boards/honoraria: Novartis, Kite/Gilead.

Benjamin, Reuben - Advisory boards/honoraria: Novartis, Kite, Celgene, Takeda, Jannsen, Amgen. Research funding: Servier, Allogene, Pfizer.

Kuhnl, Andrea - Honoraria: Kite. Research funding: Novartis.

P076

Abstract already published.

P077

Sinusoidal Obstruction Syndrome in Patients with Relapsed/Refractory (R/R) b-cell Acute Lymphoblastic Leukemia (B-all) Treated with ari-0001 Cells

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Background: Sinusoidal obstruction syndrome (SOS) is a life-threatening adverse event occurring mostly in the context of allogeneic hematopoietic stem cell transplant (alloHCT), with a mean incidence of approximately 14% (2-31%, depending on conditioning regimen and individual patient risk factors). Novel immunotherapy agents like inotuzumab-ozogamicin (IO) can also increase the risk of SOS in this setting. In the pivotal trial, the risk of SOS was 8.6% for patients who received standard of care therapy plus alloHCT and 24.6% for those who received IO plus alloHCT (Kantarjian HM, 2019). However, there is little data on the incidence of SOS after other novel agents like CAR-T cells.

Methods: The first academic pilot clinical trial (clinicaltrials.gov NCT03144583) using our fully academic (A3B1:CD8:4-1BB:CD3Z) CAR19 (ARI-0001 cells) finished recruitment in June/2019. Eligibility criteria included CD19+ R/R B-ALL (adult and pediatric), NHL and CLL who had failed standard available therapy. Lymphodepletion was with fludarabine (90 mg/m^2) and cyclophosphamide (900 mg/m^2), and the cell dose was 0.4-5 x10^6

ARI-0001 cells/kg, first as a single infusion (first 15 patients, cohort 1), and then in 2-3 fractions (last 23 patients, cohort 2). Here we report a descriptive analysis on the incidence of SOS in B-ALL patients included in this trial.

Results: We treated 38 R/R B-ALL patients with ARI-0001 cells. Median age was 24.5 years (3-68). All but 5 patients had relapsed after alloHCT (33/38 = 86.8%), and among patients with history of IO treatment (15/38 = 39.4%) only one had not previously undergone an alloHCT. We observed a total of 3 (7.9%) cases of SOS (see table 1) after ARI-0001 treatment, all occurring at cohort 2. The first 2 cases where 2 adult patients of 54 and 68 years diagnosed using the modified Seattle criteria in the context of weight gain, ascites, severe thrombocytopenia, increase in transhepatic gradient, and finally, confirmed by transjugular liver biopsy at day +31 and +49 after ARI-0001 cell infusion. Both patients had previous history of alloHCT and IO treatment with an inconclusive history of liver toxicity after IO treatment. They improved clinically from their SOS with support treatment and were eventually discharged from hospital. The third SOS case occurred in a post alloHCT young female patient (19 years) that after receiving ARI-0001 cell therapy was treated in another hospital with IO (day +161) and shortly after was diagnosed and treated as a SOS at day +171. This patient improved clinically after defibrotide treatment and was eventually discharged from hospital.

Conclusions: The incidence of SOS in patients with R/R B-ALL treated with ARI-0001 cells was 7.9%. However, it was 20% among those patients with both alloHCT and IO treatment. No SOS occurred in patients without prior alloHCT plus IO treatment. These results led us to incorporate liver imaging studies to our screening tests in patients with prior alloHCT/IO history who are referred for ARI-0001 cell therapy.

Clinical Trial Registry: Phase I, CART19-BE-01 clinical trial (EudraCT: 2016-002972-29, NCT03144583) for relapsed/refractory CD19+ leukemia and lymphoma at the Hospital Clínic de Barcelona and Hospital Sant Joan de Déu, Barcelona (Spain).

Disclosure: Source of funding: Proyecto ARI; Fundació Gloria Soler; ISCIII; CatSalut; FEHH; Generalitat de Catalunya

P078

Humoral Immune Response in Patients with CD19-positive Relapsed/refractory B-cell Malignancies Recruited into the CART19-be-01 Clinical Trial, an Academic CAR19

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Background: Chimeric Antigen Receptor (CAR)-T cells directed against CD19 have induced high rates of response in patients with relapsed/refractory (R/R) B-cell malignancies. Two CD19-targeting constructs have been approved by the FDA and EMA for B lymphoblastic leukemia (B-ALL) and aggressive lymphoma. Despite deep remissions, there are still major challenges and disparate data are reported about the immunogenicity induced by CART-cell therapy. The Spanish Agency of Medicine approved our first clinical trial with a fully academic CART-19 on May/2017.

Methods: Patients with R/R B-ALL (adult and pediatric), non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia(CLL) who failed standard therapy were included in the trial. The primary objective of the study was safety; secondary objectives were response rate and its duration. After lymphodepletion with fludarabine (90 mg/m2) and cyclophosphamide (900 mg/m2), a total dose of 0.5-5 x10^6 ARI-0001 cells/kg was infused (CAR-T with a single-chain variable fragment (scFv) with anti-CD19 specificity, conjugated with the co-stimulatory regions 4-1BB and CD3z; the scFv was originated from a mouse monoclonal antibody A3B1). The humoral anti-CART response was assessed by a cell-based fluorescence assay to detect human anti-murine antibodies (HAMA) in patients´ sera. Assessment was conducted at different time points: 1) at baseline (pre-dose), 2) on day 14 after the administration of ARI-0001 cells, 3) on day 28, 4) on day 100, and 5) every 3 months thereafter.

Results: Forty-seven patients (37 adults/10 pediatrics) received ARI-0001 cells. Thirty-eight patients had a diagnosis of R/R B-ALL (28 adults and 10 children); all but 5 had relapsed after allogeneic hematopoietic stem cell transplant (HCT). Seven patients had a diagnosis of NHL, four of them (57%) had relapsed after HCT, and 2 patients had a diagnosis of CLL. Median age was 27 years (3-68). Twenty-five per cent of the patients tested positive for the

presence of anti-CAR antibodies, all of them post-dose, in contrast to previous data reported on Kymriah ® with a significant presence of pre-dose anti-murine CAR19 antibody. Of these patients, 8 patients presented with a weak, and 4 patients with a strong presence of HAMA. The last had lost the effectiveness of the CART-therapy at that time point since a simultaneous B-cell recovery was observed in the periphery. Moreover, three of them received a second dose of CART-19, which did not revert the relapse.

Conclusions: These data suggest the importance of the immunogenicity induced by CART-cell therapies. Immune monitoring should include the assessment of humoral response, especially before considering a second dose after relapse.

Clinical Trial Registry: Identifier: NCT03144583 https://clinicaltrials.gov/ct2/show/NCT03144583

Disclosure: Nothing to declare.

P079

Real-world Data from Kings College Hospital: Infection Complications Post CAR-T Treatment in high-grade B Cell non-hodgkin Lymphoma

Shu Min Wong, Mili Shah, Shafqat Inam, Andrea Kuhnl, Robin Sanderson

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Background: Chimeric antigen receptor T (CAR-T) cells have shown promising results in treating patients with relapsed/refractory (R/R) B cell malignancies. With the recent approval of both axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisagen) for the treatment of R/R high-grade B non-Hodgkin lymphoma (NHL), we see more patients being referred for this novel therapy. There have been some published data looking at short- and long-term infection risks with this therapy and hypogammaglobulinaemia associated with B cell aplasia.[1,2]

We look at our cohort of patients being treated at Kings College Hospital with Axi-cel or Tisagen for R/R NHL to identify our incidence of short- and long-term infections and to identify risk factors that may contribute.

Methods: We collected our single centre's data on patients treated with CD19 CAR-T cells from Jan-Aug 2019. Eligibility is determined independently by a panel of clinical experts from NHS England and clinical data collected prospectively.

Results: A total of 31 patients were treated with axi-cel and 3 patients with tisagen during this period. All developed neutropenic fevers with at least Grade 1 cytokine release syndrome (CRS). A total of 26 patients required tocilizumab for CRS and 12 patients needed steroids for Grade 2 CRS unresponsive to tocilizumab. 3 patients had positive blood cultures within the first 28 days of CAR-T infusion and only 1 patient required treatment for proven fungal chest at D28. In regards to late infections, one patient had pneumocystis pneumonia at 6 months and another had line associated acinetobacter sepsis at 2 months in the setting of persistent neutropenia. 8 patients had positive respiratory viruses with 5 achieving lymphocyte recovery post CAR-T. 25 patients had B cell aplasia pre-CAR-T therapy and by 1 month nearly all patients had B cell aplasia. Pre-CAR-T 10 patients had IgG levels < 4g/L with 2 having regular immunoglobulin replacement prior and at 1-month post treatment 14 patients had levels < 4g/L. 2 patients required regular immunoglobulin replacement post CAR-T; one was for bronchiectasis. The other patient had significant infections within the first 100 days, this included HHV6 encephalitis, recurrent E. coli UTIs, Kliebsiella bacteraemia and pneumonia; he was treated with antibiotics as well as immunoglobulin replacement. One patient in remission died suddenly in their local hospital of sepsis at 7 months. All patients had routine prophylaxis with aciclovir, co-trimoxazole and fluconazole; patients were changed over to posaconazole as per hospital policy if evidence of prolonged neutropenia.

Conclusions: In our cohort most patients treated with CAR-T cells did not appear to have an increased risk of early or late infections and this is despite CRS and administration of tocilizumab and steroids. There was 1 patient who had significant infections post CAR-T likely due to persistent neutropenia and lymphopenia and another who died of late sepsis. Despite significant B cell aplasia pre and post CAR-T the immunoglobulin levels in most patients remained >4g/L which suggests that the humoral immune system can remain intact despite B cell aplasia. Immunoglobulin levels will be correlated with 6-month outcomes in final analysis.

Disclosure: Nothing to declare.

P080

Senescent/exhausted Phenotype of CD19-targeted CAR-T Cells and Immunoregulatory Environment Correlate with Reduced Response to car-t Cell Therapy in Relapsed/Refractory B Cell Malignancies

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Background: Chimeric antigen receptor (CAR) T cells have shown promising results in patients (pts) with B cell malignancies, yet up to 60% of the pts with diffuse large B cell lymphoma (DLBCL) will eventually relapse. Therefore, future efforts are needed to improve the outcomes of these pts.

Methods: A total of 22 pts with relapsed/refractory B cell malignancies, DLBCL (n=21) and ALL (n=1), were enrolled on a phase 1b/2 study (NCT02772198) of locally produced CD19 CAR T cells. All pts received a lymphodepleting preparative regimen with cyclophosphamide and fludarabine, followed by intravenous infusion of autologous CD19 CAR-T cells with a CD28 costimulatory domain. Clinical response was determined at 28 days following cell administration. Blood samples obtained prior to the lymphodepleting conditioning and at days 7, 14, 21, 30 and 60 after CAR T administration were collected. The manufactured CAR T products (n=11) were also subjected to immunophenotypic analysis.

Results: Clinically, 14 of 22 pts (63.7%) responded to CAR T therapy, 6 (27.3%) with complete response (CR), and 8 (36.4%) with partial response (PR). Analysis of the manufactured CAR T products revealed high CXCR3 expression (76% and 95% positive within the CD4+ and CD8+ subsets), indicating high migratory capacity of CAR T cells toward inflamed tissues. Furthermore, co-expression of CXCR4 (54% and 52% positive within the CD4+ and CD8+ cells) suggests increased homing ability of the manufactured CAR T toward CXCL12-rich bone marrow and lymph nodes. Interestingly, higher CCR7 expression (27.5% vs 8.5%) and lower CCR6 levels (14% vs 28%) were detected on CD8+ CAR T cells from responding pts who achieved CR and PR (n=8) versus non-responders (n=3), suggesting that less differentiated phenotype together with increased trafficking of CAR T to lymphoid tissue corresponds with improved clinical outcome.

Additionally, we assessed the immunoregulatory and senescent/exhausted phenotype in the CAR T products. Low percentage of CD4+CD25+CD127- Treg cells (13.5%, range 7-18%) was detected, with no correlation to clinical response. However, significantly higher frequency of exhausted CD57+CD39+CD28- cytotoxic CD8+ cells stand out as signature population in CAR T products of non-responders in comparison to CR pts (37% vs 9.5%, $p< 0.02$).

It is known that immunosuppressive environment affects CAR T cell activation. Notably, responding and non-responding pts presented distinct Treg patterns. Pts achieving CR demonstrated modest and delayed increase in Treg cells, reaching maximal frequency of 23% Treg out of CD4+ cells (range 17-30%) at day 21 post-CAR-T infusion, declining to basal low levels (12.5%) at day 30. In contrast, non-responders possessed rapidly increasing % of Treg cells (35%, range 25-50%, at day 14 post-infusion). In line with this finding, notable increase in proportion of immunosuppressive CD11b+CD14+CD163+CD206+ myeloid cells was detected in blood of non-responders, while pts achieving CR experienced transient increase in myeloid suppressor cells at day 7 that went back to normal levels at day 14.

Conclusions: Overall, these results elucidate in part the mechanisms of CAR T traffic, immunosuppressive responses as well as induction of T cell senescence/exhaustion that most probably downregulate CAR T effectiveness as observed in non-responding pts.

Clinical Trial Registry: NCT02772198

Disclosure: Nothing to disclose

P081

Characterisation of Early and Late Cytopenias in Lymphoma Patients following Treatment with anti-CD19 CAR-T Therapy

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Background: The anti-CD19 CAR-T therapies Axicabtagene ciloleucel and Tisagenlecleucel are now in use in the UK for patients with high grade lymphoma refractory to chemotherapy. As part of their treatment schedule patients receive lymphodepletion with Fludarabine and Cyclophosphamide prior to CAR-T infusion. However, as well as early haematological toxicity attributable to these agents, a second wave of cytopenias is observed in some patients after initial count recovery.

Methods: 39 patients were admitted to King's College Hospital between January and September 2019 and received anti-CD19 CAR-T therapy. Haemoglobin, neutrophil and platelet counts were interrogated from commencement of lymphodepletion until latest follow-up or myelosuppressive therapy for disease progression. Haematological toxicity was graded as per EORTC. Further clinical information was collected from electronic patient records.

Results: Of the 39 patients diagnoses totalled 28 DLBCL, 14 transformed FL and 1 PMBCL. 38 patients received Axi-cel, the remaining 5 received tisagen. Patients

had follow up duration of between 2 and 11 months post infusion, median follow-up 169 days. Maximal early haematological toxicity, as well as at the time of response monitoring at day+28, day+100 and 6 months post treatment is summarised in the table below.

Almost all patients (38 of 39) experienced grade 3/4 neutropenia during the first 28 days post infusion. No patients were given GCSF prior to D+14 due to concerns regarding exacerbation of CRS but 18 received it subsequently. Despite this, grade 3/4 neutropenia persisted in almost half of patients at D+28 (43%, 16/37). Grade 3/4 haematological toxicity persisting at D+28 occurred in 43% of patients (9/21) with < /=3 prior lines of treatment compared to 56% (9/16) of patients with >/=4 previous regimens. Incidence was also equivalent in patients with or without prior HSCT: 44% (12/27) without, 50% (5/10) with. 13 patients received bridging chemotherapy between apheresis and lymphodepletion, whereas 26 received no bridging, steroids or radiotherapy. Recent chemotherapy correlated with cytopenia at D+28: no bridging chemotherapy 36% (9/25), bridging chemotherapy 75% (9/12) (P=0.029).

Rates of grade 2 or worse CRS were similar in those with or without cytopenias at D+28: 61% (11/18) vs 47% (9/19) patients. ORR was 80% on D+28 PET imaging in patients without grade 3 or 4 cytopenias (16/20) and 94% in those with cytopenias (16/17) (p=0.22). Haematological toxicity at D+28 was also compared to D+100 outcomes. 47% (8/17) of patients without D+28 cytopenias had a maintained response, compared to 44% of those with progressive disease (7/16).

Conclusions: Many patients experience late cytopenias following CAR-T, therefore close monitoring of blood counts is required following discharge. Persistent cytopenias on discharge appear to correlate with prior bridging chemotherapy and are not associated with responses at 3 month follow up. Further work, including correlation with cytokine levels, is needed to determine the cause of late cytopenias. With maturation and expansion of the patient cohort we hope to determine whether cytopenias may be related to expansion and persistence of CAR-T and correlate with positive outcomes.

Clinical Trial Registry: n/a

Disclosure: Nothing to declare.

P082

Impact of Ethnicity in R/R DLBCL and B-cell all Patients Treated with Tisagenlecleucel

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Background: We assessed the impact of ethnicity on efficacy, safety, and cellular kinetics in Asian and non-Asian relapsed/refractory (r/r) DLBCL or B-cell ALL patients infused with tisagenlecleucel (anti-CD19 CAR-T cell therapy).

Methods: Data were obtained from r/r DLBCL (JULIET, NCT02445248) and B-cell ALL (ELIANA, NCT02435849; ENSIGN, NCT02228096) patients.

Results: Safety, efficacy, cellular kinetics, transduced dose range, and immunogenicity in the Asian and non-Asian subgroups are summarized in the Table. The assessed product attributes (eg, total cell count, % T cells, viability, and transduction efficiency) were comparable between Asian and non-Asian patients.

Conclusions: Asian and non-Asian patient populations in both indications were comparable with respect to safety, efficacy, dose-response, product attributes, and cellular kinetics of tisagenlecleucel.

	ELIANA and ENSIGN		JULIET	
	Asian (N=14)	Non-Asian (N=123)	Asian (N=10)	Non-Asian (N=105)
Tisagenlecleucel transduced cell dose, median (range)	1.00 x 10^8 cells (0.05 - 2.50 x 10^8)	1.08 x 10^8 cells (0.03 - 2.60 x 10^8)	2.10 x 10^8 cells (1.00 - 4.90 x 10^8)	3.00 x 10^8 cells (0.10 - 6.00 x10^8)
Within target dose range of cells transduced, n (%)	12 (85.7)	107 (87.0)	10 (100)	99 (94.3)
Efficacy				
ORR, % [95% CI]	64.3 [35.1-87.2]	78.3 (n=115) [69.6-85.4]	70.0 [34.8-93.3]	50.5 [40.5-60.4]
DOR at 18mo, % [95% CI]	70 [22.5-91.8]	63.6 (n=115) [51.0-73.7]	55.6 [7.3-87.6]	62.4 [47.5-74.2]

	ELIANA and ENSIGN		JULIET	
	Asian (N=14)	Non-Asian (N=123)	Asian (N=10)	Non-Asian (N=105)
OS at 18mo, % [95% CI]	66.8 [32.4-86.6]	64.4 [53.9-73.1]	51.4 [14.3-79.6]	43.1 [33.3-52.5]
Safety				
Any-grade CRS by Penn scale, n (%)	11 (78.6)	97 (78.9)	7 (70)	59 (56.2)
Any-grade neurologic event by CTCAE v4.03, n (%)	3 (21.4)	57 (46.3)	1 (10)	30 (28.6)
AUC 0-28d (copies/ug*days), geo-mean (CV%)	562000 (126.1)	303000 (179.2)	71800 (357.3)	63900 (223.0)
C_{max} (copies/ug), geo-mean (CV%)	59900 (78.3)	33300 (153.4)	4520 (464.5)	5740 (283.1)
Immunogenicity post infusion, positive n (%)	4 (28.6)	52 (42.3)	1 (10)	9 (8.6)

AUC 0-28d, area under the curve of CAR-T cell numbers between day 0 and 28; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; CV, coefficient of variation; DOR, duration of remission/response; ORR, overall remission/response rate; OS, overall survival.

[Table: Safety, efficacy, cellular kinetics, transduced dose range, and immunogenicity in the Asian and non-Asian subgroups]

Clinical Trial Registry: NCT02445248, NCT02435849, NCT02228096

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Katsutsugu Umeda: No relationship to disclose.

Souichi Adachi: No relationship to disclose.

Karen Thudium: Employment: Novartis.

Edward Waldron: Employment: Novartis.

Alessandra Forcina: Employment: Novartis.

Andrea Chassot Agostinho: Employment: Novartis.

Stephan Grupp: Grants and personal fees from Novartis Pharmaceuticals, during the conduct of the study; personal fees from Jazz Pharmaceuticals, personal fees from Adaptimmune, personal fees from TCR2 Therapeutics, personal fees from Eureka Therapeutics, personal fees from Cellectis/Servier, outside the submitted work; In addition, Dr. Grupp has a patent Toxicity management for anti-tumor activity of CARs (WO 2014011984 A1) issued.

Richard T. Maziarz: Honoraria, Membership on an entity's Board of Directors or advisory committees and Research Funding: Novartis; Consultancy and Honoraria: Incyte, Juno; Honoraria: Kite; Jazz Pharmaceuticals.

P083

Impact of different Chemotherapy Regimens and Duration of DLBCL on Lymphopheresis and car-t T-cell Immunophenotyping

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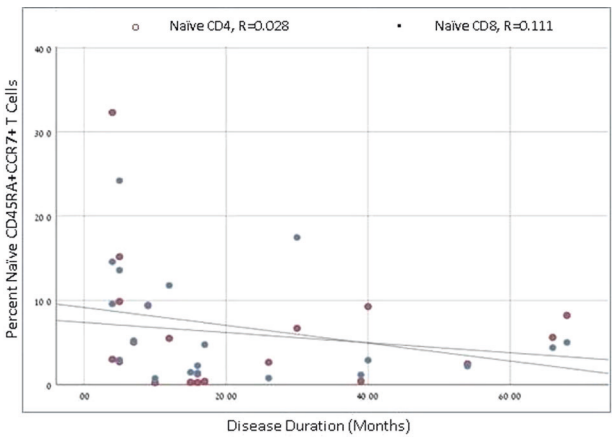
Background: CD19-directed CAR T-cell therapy becomes a standard of care treatment for relapse/refractory DLBCL. Production of CAR-T cells requires transduction and expansion of the collected lymphocytes. However, little is known about the impact of disease duration and specific treatment regimens on the harvested lymphocytes. Additionally, no sufficient data on the impact of the lymphopheresis product on treatment outcome.

Methods: Tisagenlecleucel (Kymriah™, Novartis) was commercially approved in Israel on May-2019. Since June-2019, we performed in all sequential patients flow-cytometry-based-T cell subsets (naïve-cell, central-memory (Tcm), effector-memory (Tem) and terminally-differentiated-CD45RA+ cells (Temra)) in the apheresis and in the CAR-T. In addition, activation marker HLA-DR and exhaustion marker PD-1 were also evaluated in the paired samples. All patients had a follow-up PET-CT scan one-month post infusion for response evaluation. We analyzed the effect of disease duration and the pre-apheresis treatment regimens being administered on the apheresis T-cell immunophenotyping, as well as the

correlation between immunophenotyping and treatment outcome.

Results: Between May and December 2019, 35 DLBCL patients were screened and considered for Tisagenlecleucel treatment. 29 (83%) patients underwent lymphopheresis and 21 patients received the product. The study cohort included 20 sequential patients for whom complete flow-based T cell immunophenotyping data were available. 30-day PET-CT was available in 12. Median age was 71 (range, 20-84) years and median duration of disease was 12 (range, 4-68) months. 38% received >3 lines of chemotherapy and 33% failed autologousHCT.

Of the different variables evaluated we observed statistically significant effect of bendamustine treatment(n=9) on apheresis T cell immunophenotyping resulting in lower percent of naïve CD4 T cells (CD45RA+CCR7+; 4.15 ±4.2% vs 10.4±7.5%, p=.05), higher percent of Tem CD4s (CD45RA-CCR7-; 71.3±15.9% vs 52.7±12.6%, p=.01), higher percent of PD1+ CD4 T cells (66.8±14.6% vs 41.5 ±17.9%, p=.27) and higher percent of activated HLA-DR+ CD4s and CD8s (68.2±17.5% vs 41.9±13.7%, p=.01 for CD4s, 63.7±20.8% vs 39.2±19.1%, p=.13 for CD8s). Prior autologous HCT was associated with a trend toward lower CD4 to CD8 ratio (0.459±0.146 vs 1.00±0.748, p=.076). Although immunophenotyping was not affected by the number of pre-pheresis treatment-lines, disease duration was correlated with lower percent of naïve CD4 (Spearman´s correlation coefficient=-.5, p=.02) and naïve CD8 T-cells (Spearman´s correlation coefficient=-.46, p=.04) (Figure 1).



[Figure 1: Scatter plot of correlation between duration of disease and naïve CD4 and CD8 count]

Among all analyzed T cell characteristics, only higher percent of pre-pheresis HLA-DR+ CD4s and CD8s were associated with higher incidence of CR (beta .78, p=.05 and .47, p=.09, respectively).

Conclusions: While there remains insufficient data to solidly confirm our hypothesis, it is reasonable to assume that pre-lymphopheresis disease duration and treatment history may affect pheresis product, which in-turn, determines the final CAR T-cell product and response to treatment. Preliminary data from our small cohort suggests that pre-pheresis bendamustine treatment is associated with more mature, activated and exhausted CD4 T-cell phenotype. Improved phenotyping to include additional exhaustion markers, as well as follow-up post CAR T-cell infusion (by evaluating peripheral blood CD19-Ig binding T cells) is ongoing.

Disclosure: Nothing to declare.

P084

Chimeric Antigen Receptor (CAR) T Cell Therapy Followed by Hematopoietic Stem Cell Transplantation May Improve Progression free Survival in Patients with Relapse/Refractory B-cell Non-hodgkin Lymphoma

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Background: Chimeric antigen receptor (CAR) T cells are emerging as a novel treatment modality that highly effective in the treatment of relapse/refractory B-cell lymphoma, providing alternative therapeutic options for patients who failed to respond to conventional treatment or relapse. Although highly remission rates have been reported with CAR-T cell therapy in relapse/refractory B-cell lymphoma, relapse or disease progression is common after CAR-T therapy. This current study is to better our understanding of whether consolidative hematopoietic stem cell transplantation(HSCT) confers superior survival outcomes to patients who got remission by CAR-T cells therapy.

Methods: Compare the efficacy and survival of CAR-T therapy followed by HSCT and CAR-T alone in patients with relapsed/refractory B-cell lymphoma. 30 cases with CR or PR disesse status after CAR-T cells therapy in the First Affiliated Hospital of Soochow University from 2017 to 2019 were included. 11 of these cases (36.7%) were treated with HSCT after CAR-T therapy, of which 7 cases were treated with autologous stem cell lymphoma(ASCT), and 4 cases were treated with allogeneic stem cell transplantation(Allo-SCT). 19 of these cases (63.3%) were treated with CAR-T only. Overall survival(OS) and progression-free survival(PFS) rates were estimated by the

Kaplan-Meier method, and Survival comparison was analyzed by using the log-rank test.

Results: Kaplan-Meier survival curve indicated that PFS of the HSCT following CAR-T group were higher than the CAR-T group, and log rank test showed that the difference of survival curve was statistically significant (P = 0.044). The estimated 1-year and 2-year progression-free survival (PFS)were 90.9%and 50% respectively in the CAR-T followed by HSCT group. The estimated 1-year and 2-year progression-free survival(PFS)were 71.6% and 27.8% respectively in the CAR-T group. Kaplan-Meier survival curve analysis indicated that OS of the HSCT following CAR-T group were higher than the CAR-T group, while log rank test showed that the difference of survival curve was no statistically significant (P = 0.250). The estimated1-year and 2-year overall survival(OS) were 90% and 89.4% respectively in the HSCT following CAR-T group, the estimated1-year and 2-year overall survival(OS) were90% and66.2% respectively in the CAR-T group.

Conclusions: Hematopoietic stem cell transplantation (HSCT) appear to improve progression-free survival (PFS) for the patients achieving remission following CAR-T therapy with relapse/refractory B-cell lymphoma. Future prospective studies needed to clearly define the role of consolidative HSCT in the relapse/refractory B-cell lymphoma patients who attained remission from CAR-T infusion and importantly, better identify this strategy whether exhibits superior overall survival outcomes.

Disclosure: there is no conflict of interest or source of funding

P085

Challenges in providing good Leukapheresis Products for the Production of Car T Cells for Patients with Relapsed/Refractory NHL or ALL

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Background: In patients with relapsed or refractory B-lineage acute lymphoblastic leukemia (ALL) or B-cell non-Hodgkin's lymphoma (NHL) therapy with chimeric antigen receptor T (CAR-T) cells has proven to be highly effective. As starting material for the production of CAR-T cells T lymphocytes from the patients are mandatory. To harvest sufficient lymphocytes, leukapheresis as first step in the production process has to be performed. This constitutes a challenge to the treating physicians with regard to timing of the apheresis in heavily pretreated patients suffering from rapid progressive disease and being treated by drugs with negative impact on T cells.

Methods: Data from 45 adult patients suffering from r/r DLBCL (68%), PMBCL (2%), MCL (4%), FL (2%), CLL (4%), ALL (13%) or multiple myeloma (5%) who received a leukapheresis for CAR-T cell production were analyzed. Apheresis procedures were effective using the Spectra Optia™ device. Peripheral blood counts pre- and post-apheresis, as well as leukapheresis product parameters were assessed. Further important tasks were the analysis of the medication used prior to apheresis and the optimization of the apheresis procedure. Fourteen leukapheresis products were produced for clinical trials including 11 patients in our in-house production HD-CAR-1 study.

Results: All patients qualified for leukapheresis due to the following criteria: hemoglobin > 8g/dl, platelets > 75/nl, ANC > 1/nl, ALC > 0.3/nl, negative PCR for HBV, HCV, HEV and HIV; no active GvHD, no florid infection, no severe impairment of cardiac or pulmonary function. Leukapheresis was feasible in all patients and could be performed through peripheral venous access using the Spectra Optia™ device without any serious side effects. In total we performed 48 leukaphereses. 45 patients received a single apheresis and in three patients a later second apheresis was required due to infectious complications or electrolyte disturbance leading to a manufacturing failure. CAR T cell production was feasible for 44 of 45 patients. A mean blood volume of 11.8 (range 5.8-15) L was processed over a time of 238 (120-326) minutes. The leukapheresis product contained a mean of 11.8 x 10^9 (0.9-34.1 x 10^9) total nucleated cells and 4.9 x 10^9 (0.4 - 23.2 x 10^9) CD3+ T cells with a viability of 99.9 (99.6 - 100) % in a mean volume of 235 (136 - 310) ml with a hematocrit of 3 (1.1 - 7.4) %.

Conclusions: Leukapheresis was feasible in all patients in an out-patient setting. To harvest a sufficient number of lymphocytes for CART cell production, a minimum of 12 -15 L total blood volume should be processed in patients with an ANC 1-3/nl and ALC 0.3-1/nl. We established therefore a standardized procedure for the apheresis handling and developed a recommendation list for the timing of the medication before apheresis.

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research grant. Co-PI of clinical trials on CAR-T cells. TolerogenixX: Co-Founder and shareholder.

AS: TolerogenixX: Co-Founder and shareholder, Mallinckrodt-Therakos: research grant, Jazz: travel grant.

PD: Advisory boards Novartis, Kite/Gilead

P086

NKG2D Car T Cells are not affected by Soluble NKG2D Ligands

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Background: NKG2D is an NK cell activating receptor that recognizes different stress-induced ligands (NKG2DL) that are overexpressed in different pediatric and adult tumors, while their expression in healthy tissues is rare. NKG2D-CAR T cells have shown potent antitumor effects against different types of cancer. However, tumor cells may develop immune escape strategies such as ligand release (sNKG2DL), whose effect on NKG2D-CAR has not been studied and could affect their clinical efficacy.

Methods: Clinical grade NKG2D-CAR memory ($CD45RA^-$) T cells were produced by lentiviral transduction (NKG2D-41BB-CD3z, MOI = 2) and expansion in CliniMACS Prodigy. NKG2D-CAR memory T cells were infused in two patients excluded from CD19 CART cell trial with refractory relapse after hematopoietic stem cell transplantation. Patient#1 suffered from r/r biphenotypic ALL. She received two cycles of CAR T cells infusions. In the first cycle, a total of $3x10^7$ cells/kg were infused into three weekly doses with no conditioning. In the second cycle, a total of $2x10^7$ cells/kg were administered weekly into two doses after lymphodepleting conditioning with Cy/Flu and low dose bortezomib. Patient#2 suffered from r/r B-ALL and bronchopulmonary aspergillosis. She received a single dose of $1x10^7$ cells/kg after lymphodepleting conditioning Cy/Flu and low dose bortezomib. sNKG2DL concentration was monitored in the patient´s sera by ELISA. The effects of sNKG2DL on NKG2D-CAR T cells (NKG2D expression, proliferation, cytokine release and cytotoxicity) were explored after exposition to different concentrations of sNKG2DL for 7 days, by flow cytometry, ELISA or LUMINEX, and a 2 hour-degranulation assay using K562 cells as target, respectively.

Results: NKG2D-CAR memory T cells were infused without severe side effects. Patient #1 showed no cytokine release syndrome (CRS), hypotension, pain or neurological events. At day +28 after the first infusion and one week after the first dose of the second cycle she developed pruriginous skin rash. Biopsy described toxicodermia versus grade I skin GvHD. Bone marrow evaluation described leukemia progression. Only 24 hours after infusion, patient #2 presented a respiratory impairment without fever and other CRS symptoms and required intensive care. Ten days after the CAR-T cell infusion, bone marrow aspiration revealed blast persistence and the family suggested to limit the therapeutic effort. Patient#2 showed an increase on sULBP2 compared to control. After NKG2D CAR T cells infusions, sNKG2DL trended to decrease in both patients. In vitro, physiological concentrations of sNKG2DL increased NKG2D-CAR expression. However, supra-physiological levels of sNKG2DL reduced NKG2D-CAR expression, increased cell proliferation, and stimulated TNF-a and IFN-g production, which was further increased in the presence of IL-2. High doses of sMICA decreased degranulation of NKG2D-CAR T cells, which was associated with receptor down-regulation. The effects of sNKG2DL were dose-dependent and slightly attenuated by IL-2.

Conclusions: NKG2D CAR memory T cells are essentially safe. Only supraphysiological levels of sNKG2DL caused NKG2D-CAR downmodulation, while normal levels induce cell proliferation and production of pro-inflammatory cytokines. Altogether these data suggest NKG2D CAR could be more resistant to the negative effects of sNKG2DL than endogenous NKG2D receptor. However, we did not observe a beneficial clinical effect in this advance situation.

Disclosure: The authors have nothing to disclose.

P087

Emerging Cytokine Release Syndrome is associated with Reduction of CD4+CD25high127dim T Regulatory Cells in Patients after Car T Cell Therapy

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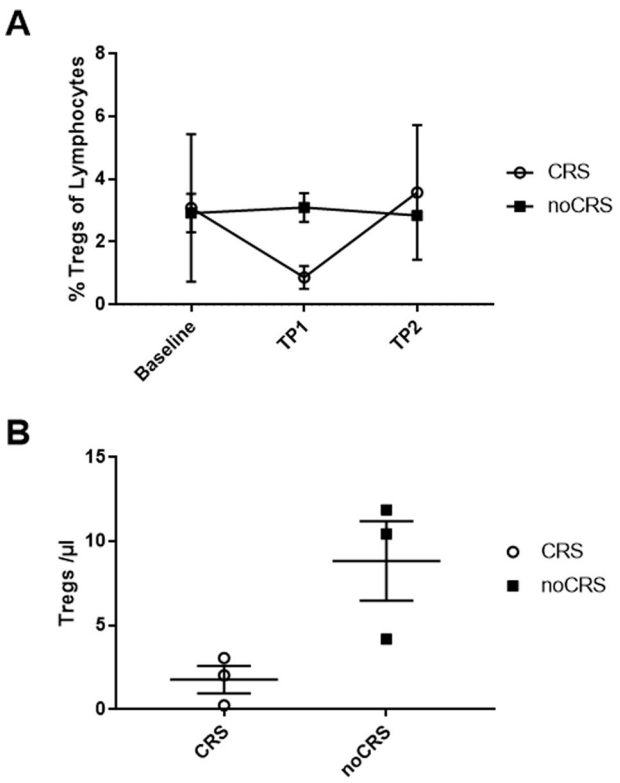
Background: Chimeric antigen receptor (CAR) T cell therapy is often accompanied by potentially life-threatening cytokine release syndrome (CRS). The role of T regulatory cells (Tregs) during CRS remains to be elucidated. Here we prospectively investigated the Tregs population in patients with and without CRS after anti-CD19-CAR T Infusion.

Methods: The cohort consisted of 11 patients with relapsed or refractory transformed follicular lymphoma and diffuse large B cell lymphoma (DLBCL). All received anti-CD19-CAR T infusion (Tisagenlecleucel) after lymphodepletion with fludarabine and cyclophosphamide. All patients gave written informed consent to participate in the study. Patients were grouped based on emergence of CRS. Tregs were detected from peripheral blood via flow cytometry by staining for CD4+CD25+CD127dim- lymphocytes. To determine the absolute frequencies BD Trucount™ tubes were employed. Three time points were selected for analysis: baseline (d-1 - d+2 from Tisagenlecleucel infusion); 1 day prior or at the day of CRS diagnosis before start of CRS treatment (TP1, d+1 - d+6); after CRS clearance (TP2, d+3 - d+10). As control group served patients without CRS using comparable time points.



[Figure 1: Tregs frequencies in CRS vs no CRS patients.]

Results: Four patients met CRS criteria (Grade 1-4). On 3/4 CRS patients blood samples were available at all three time points and these were thus selected for analysis. Upon emergence of CRS (TP1) Tregs (measured in frequency of lymphocytes) showed a mean reduction of -46.91% compared to the baseline time point while the no-CRS controls increased their frequency by on average +10.57% (Figure 1A). Intergroup comparison at TP1 revealed differences of Tregs levels (0.87 vs. 3.10 % of lymphocytes) as well as in absolute Tregs count (1.79 Tregs/µl vs. 8.84 Tregs/µl, Figure 1B). Tregs frequencies in patients after CRS clearance (TP2) increased on average by 3.05-fold compared to TP1 while Tregs frequencies stayed stable in controls (Figure 1A). Based on this increase, Tregs frequencies at TP2 were similar to values of no-CRS patients. These findings are limited by the small patient number and in general low frequencies of Tregs early after CAR T infusion. Therefore, these pilot data need validation in a larger cohort.

Conclusions: In this prospective single center pilot study, blood samples of emerging CRS showed a reduction of Tregs frequencies and absolute numbers compared to no-CRS patients. After clearance of CRS, Tregs frequencies increased to values of no-CRS patients. Therefore, investigation of Treg frequencies as a predictive marker for CRS should be further investigated. However, future studies are needed to validate these findings in a larger cohort.

Disclosure: Nothing to declare.

P088

Excellent Proliferation and Persistence of Allogeneic CAR-T Cells Despite Immunosuppression with Cyclosporine A

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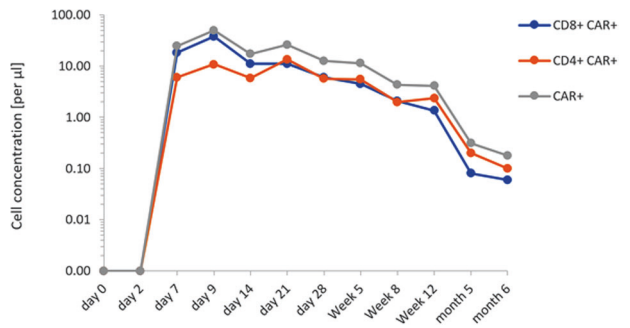
Background: Allogeneic CAR-T cell therapy bears the potential to combine graft-versus-malignancy effects and CAR-directed target killing, but comes with a considerable risk of graft-versus-host disease (GVHD). Animal studies indicate that the risk of GVHD after CAR-T infusion from an allogeneic donor may in part depend on the costimulatory domain used, first generation and 4-1BB-based CAR-T cells bearing an increased risk of GVHD [Gosh et al., 2017]. Interestingly, in the only report on donor-derived CAR-T cells with a 4-1BB costimulatory domain, both patients developed acute GVHD [Dai et al., 2015]. Use of immunosuppression to prevent GVHD after CAR-T cell infusion may prevent their expansion and efficacy. Here we present for the first time data on expansion and persistence of 4-1BB based CAR-T cells under immunosuppression with clinically relevant concentrations of cyclosporine A.

Methods: A 64-year old female with early relapse of follicular lymphoma grade 3A (day 65 after allogeneic hematopoietic stem cell transplantation, allo-HSCT) consented for compassionate-use treatment with CAR-T cells. CD19-CAR-T cells were manufactured from freshly collected allogeneic donor leukocytes using the CliniMACS Prodigy system and a lentiviral vector encoding the CD19-CAR containing a 4-1BB costimulatory domain.

The patient received lymphodepleting chemotherapy with cyclophosphamide and fludarabine and 1 x 10^6 /kg BW CAR-expressing cells on day 0 (3 months after allo-HSCT). Because the patient had history of acute GVHD, we maintained her on GVHD prophylaxis with cyclosporine A at a mean cyclosporine A trough level of 170 µg/l (range 122-206 µg/l) until day 21 after CAR-T cell infusion. With no evidence of active GVHD, cyclosporine A was tapered off from day +21 and stopped on day +56 after CAR-T cell infusion.



[Figure 1: CAR-T cell expansion and persistence]

Results: No CRS or ICANS were observed. Haematopoietic recovery was expectedly slow despite use of G-CSF as from day +21. Stable neutrophil counts > 1000/µl without further G-CSF support was attained on day 32, platelet count > 50.000/µl on day 150 after CAR-T cell infusion.

FDG-PET scan on day +30 revealed complete resolution of most of the lymphoma manifestations seen in the CT scan, but also showed new bone lesions in both sacrum and femur. A follow-up FDG-PET scan on day 120 showed regression of all lymphoma manifestations with only residual manifestations in the left sacrum.

Highest CAR-T cell numbers were measured on day +9 (50 CAR-T cells/µl) with continuous persistence of CAR-T cells up to the last examination 6 months after infusion (figure 1). While overall T cell reconstitution was well evident, B cell aplasia is persistent. Interestingly, the analysis of the CAR-T cells for activation and exhaustion markers revealed a decline in the fraction of effector and effector memory and a relative increase in central memory CD4+ CAR-T cells.

Conclusions: In conclusion, we for the first time present data on proliferation and persistence of allogeneic donor-derived 4-1BB based CAR-T cells under therapeutic levels of cyclosporine A. This indicates that for patients with early relapse after allo-HSCT with ongoing immunosuppression donor CAR-T cell therapy may be a feasible Treatment.

Disclosure: Nothing to declare.

P089

A French Biobanking Network to Create a Unique Collection of Samples of Patients Treated with car-t Cells

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Background: Even if Chimeric Antigen Receptor (CAR)-T cells therapies are a promising way to treat relapsed/refractory hematologic cancers, authorities face major issues regarding their economic impact, the evaluation of their efficiency and adverse effects. Since their launch the number of patients with CAR-T cells indication is increasing, as well as the number of hematological cancers likely to be treated. Nationwide collections of biological resources are warranted to develop scientific projects to monitor CAR-T cells treatments and improve our understanding of the underlying biological mechanisms.

In this context, a biobanking initiative resulted from the collaboration of two French consortia : CALYM, gathering together the LYSA (Lymphoma Study Association), LYSARC (Lymphoma Academic Research Organization)

and 18 academic laboratories in the field of lymphoma, and CRYOSTEM, a collaborative biobanking network. After demonstrating respectively their ability to set up the first collection of viable cells from lymphoma patients (CeVi_-collection) and the first European collection of biological resources dedicated to Hematopoietic Stem Cell Transplantation, CRYOSTEM and CALYM joined their expertise to constitute a biocollection from lymphoma patients receiving CAR-T cells.

Methods: The collaboration between CRYOSTEM and CALYM networks brings together hematological clinical units and biological resources centers (BRCs) to include patients, collect and process samples. Any patient suffering from lymphoma, justifying a CAR-T cells treatment is eligible for inclusion. Several types of samples are collected and derived pre- and post-CAR-T cells administration following a specific timeline. CALYM BRCs are in charge of the treatment and storage of lymph nodes and bone marrow samples in viable cells whereas CRYOSTEM BRCs enrich this collection by processing blood samples in viable cells and plasma, and also stools and urines. Annotated biological samples are centralized in CALYM database.

Results: In less than one year, CRYOSTEM and CALYM set up the organizational and regulatory framework of the first collection of samples and associated data dedicated to CAR-T cells treated patients:

- Constitution of governing bodies including representatives from both organizations;
- Identification of the 9 clinical units and BRCs involved in the protocol;
- Practices harmonization and standardization regarding samples and protocols;
- Establishment of sampling kinetics integrated to patients' care. Paired with lymph nodes, 8 blood sampling points are planned from apheresis to 6 months post-injection and/or at relapse;
- Estimation of the collecting rate of each sampling point according treatment failure and mortality rate;
- Evaluation of the annual number of inclusions.

First inclusions are planned in January 2020.

Conclusions: With the creation of the first biobank focused on CAR-T cells treated patients, the CALYM-CRYOSTEM collaboration opens new research perspectives by providing access to raw material. This approach would impact CAR-T cells treatments by providing a large amount of post-infusion data, contributing to consolidating knowledge on this recent cell-based therapeutic approach.

This initiative, focused on lymphoma, sets up the bases of the constitution of new type of collection integrating complementary expertise and actors in CAR-T care and research. It will constitute a proof of concept for other initiatives in this field, independently of the initial hematological disease.

Clinical Trial Registry: Non applicable

Disclosure: Any conflict of interest

P090

CAR T Cell Therapy Directed against CD19 in Patients with B-cell Lymphoma after an Allogeneic Hematopoietic Stem Cell Transplantation (AlloHCT) is Feasible and Safe

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Background: CD19-directed chimeric antigen receptor T cells (CARTs) have been successfully used in patients with acute lymphoblastic leukaemia (ALL) after a preceding allogeneic stem cell transplantation (alloHCT). However, data on feasibility and outcome of CARTs in patients previously allotransplanted for B-cell lymphoma are lacking. Here, we report our institutional experience in this setting.

Methods: Course and outcome of allo-grafted patients treated with CD19 CARTs for B-cell lymphoma between October 2018 and November 2019 were studied in a single-center retrospective analysis. CARTs were administered either as third-generation CARTs within the Heidelberg CART 1 (HD-CAR-1) clinical trial (Eudra-CT No. 2016-0048; NCT03676504), or with commercially manufactured second-generation CARTs Axicabtagene Ciloleucel (Axi-cel, Gilead). Number of infused CARTs ranged from $1x10^6$-$2x10^7/m^2$ (HD-CAR-1) or were within the label-specified range (Axi-cel).

Results: 10 CART dosings using recipient leukapheresis products have been administered to 8 patients: 4 patients (2 mantle cell lymphoma (MCL), 2 CLL) received 6 infusions with HD-CAR-1 CARTs. 4 patients (all with DLBCL) received 4 infusions with Axi-cel. Lymphodepleting chemotherapy with flu/cy (30/500 $mg/m^2/d$ for 3 days) was administered to all patients prior to CART infusion. All 8 patients were male with a median age of 57 (27-70) years. A median of 4 (3-11) treatment lines had been administered

during 5.8 (1.5-12.5) years from diagnosis. Median time from alloHCT to CART treatment was 2.4 (1.0-8.2) years. AlloHCT had been performed from matched related (MRD) (3), matched unrelated (MUD) (4), or haplo (1) donors after myeloablative conditioning. Acute and chronic GvHD after alloHCT had been observed in 2 and 6 patients, respectively. No patient had active GvHD or was under immune suppression at the time of leukapheresis and all patients had active disease. CART treatment was well tolerated with higher grade CRS and ICANS each being observed after 1 of 10 evaluable dosings. Patients had complete resolution of CRS and ICANS following administration of tocilizumab and steroids, respectively. A single patient had cutaneous and hepatic reactions suspicious of chronic GVHD early after dosing, whereas all other dosings were not accompanied by GVHD. CARTs were detectable in the peripheral blood (PB) in all but one patient. The patient developing ICANS displayed the highest CART frequency in the PB. With a median follow-up of 108 (18-314) days, all patients are alive with an overall best response rate of 88%. 3 of 7 evaluable patients achieved ongoing CRs. B cell aplasia and cytopenia were observed in all patients following CART dosings. B cell aplasia is ongoing in 8 instances and long-term (>1 month) leukopenia and thrombocytopenia were observed following 8 and 7 dosings, respectively.

Conclusions: Therapy with CARTs manufactured from recipient-derived leukapheresis products after prior alloHCT was feasible, safe and efficient. Therefore, CARTs as salvage treatment for patients with B-cell lymphoma relapsing after alloHCT constitute a justifiable treatment option. Cytopenia as a result of multiple myelotoxic treatments needs to be carefully monitored.

Disclosure: Dreger: AbbVie, AstraZeneca, Gilead, Janssen, Novartis, Riemser, Roche: Consultancy; AbbVie, Gilead, Novartis, Riemser, Roche: Speakers Bureau; Neovii, Riemser: Research Funding; MSD: Membership on an entity´s Board of Directors or advisory committees, Other: Sponsoring of Symposia. **Schmitt:** Therakos Mallinckrodt: Other: Financial Support. **Sellner:** Takeda: Employment. **Müller-Tidow:** MSD: Membership on an entity´s Board of Directors or advisory committees. **Schmitt:**Therakos Mallinckrodt: Other: Financial Support; MSD: Membership on an entity´s Board of Directors or advisory committees, Other: Sponsoring of Symposia. **Stilgenbauer:** Pharmacyclics: Other: Travel support; Gilead, Celgene, Amgen, AbbVie, Novartis, AstraZeneca, Hoffmann La-Roche: Consultancy, Honoraria, Research Funding, Speakers Bureau.

P091

Lymphocyte Collection for Generation of CAR T-cells in Pediatric Patients: A Single Center Experience

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Background: Chimeric antigen receptor (CAR) T-cell therapy is a novel anti-tumor strategy in which autologous T-cells are engineered to express a CAR construct targeting an antigen expressed on membrane malignant cells. The CAR T-cell manufacturing process consists of different steps performed by different units, namely apheresis, cell therapy laboratory and the clinical unit. The collection of patient's T-cells by the apheresis unit is the first step, followed by the characterization and manipulation of the cell product.

Herein, we report on 70 apheresis procedures performed on children and young adults with hematological and non-hematological diseases who underwent PBMC purification and cryopreservation for subsequent CAR T-cell production for academic trials at our institution.

Methods: Seventy collections were performed between January 2017 and November 2019; 51 patients were males, 19 females, median age being 9 years (range, 3-25) and median body weight (BW) 24 kg (range, 11-106). Indication for CAR T-cell production was refractory/relapsed Acute Lymphoblastic Leukemia (ALL, n=27), non-Hodgkin's lymphoma (NHL, n=6) or Neuroblastoma (NBL, n=37). Leukapheresis was performed by Spectra Optia using continuous and discontinuous mononuclear cell protocol (CMNC vs MNC), with a collection target >4x10*9 mononuclear cells (MC). In 37/70 (53%) cases, patients had a central venous double lumen catheter (CVC), 17/70 (24%) were collected through peripheral venous accesses (VP) and 16/70 (23%) using both approaches (CVC+VP). Sodium heparin and Acid Citrate Dextrose Solution-A (ACD-A) were used in combination as anticoagulants. After apheresis, a density gradient PBMC purification using the Sepax 2 device was performed and the MCs were eventually cryopreserved.

Results: The median lymphocyte counts before apheresis were 1080/ul (200-4070). Out of 70 collections, 34/70 were performed using MNC (49%) and 36/70 using CMNC (51%). For all patients, the median total blood volume (TBV) processed was 2.1L (0.59-4.3), while for patients < 15kg (11/70, 16%) the processed TBV was 2.7L (1.6-4.3). Apheresis bags contained a median of 5.2x10*9 nucleated cells (1.5-15.4). Lymphocyte collection efficiency (lympho-

CE) had a median value of 68% (range, 24-100). 27 products from ALL patients, 6 products from NHL patients and 37 products from NBL patients underwent a density gradient purification for PBMC enrichment. For ALL and NHL patients, median recovery for MNC was 76% (61-93) and median red blood (RBC) depletion was 81% (45-94). Total MNC and CD3 cells were 2.75x10*9 (0.84-8.26) and 1.33x10*9 (0.58-2.74) respectively. For NBL patients, median recovery for MNC was 73% (54-89) and RBC depletion was 79% (64-96). Total MNC and CD3 cells were 2.7x10*9 (1.0-6.0) and 1.0 (0.4-8.0).

Conclusions: Sufficient numbers of cells can be obtained from pediatric patients with BW < 15 kg, with a median value of processed TBV of 2.7L (1.6-4.3), provided that their lymphocyte counts are >900/ul. All patients reached the target cells in a single apheresis, including 2 patients with lympho-CE < 30%. In 56/70 (80%) of collections, lympho-CE was ≥50%.

Density gradient purification with the Sepax device is helpful to remove a fraction of RBC, allowing subsequent cryopreservation of pure products in which CD3+ cell concentration is higher with respect to other cellular components.

Disclosure: Nothing to declare.

P092

Baseline Hypoalbuminemia does not appear to be an Adverse Prognostic Factor in Patients with Relapse/Refractory B-cell Lymphomas Treated with Axicabtagene Ciloleucel (Axi-cel)

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Background: Axi-cel is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy that is approved for treatment of relapsed/refractory (R/R) large B-cell lymphoma and is associated with high response rates and durable remissions. Recent data show that axi-cel is effective across various adverse prognostic features, namely cell of origin, disease bulkiness, and extranodal disease, among others. Hypoalbuminemia is a known adverse prognostic factor in lymphomas. Yet, it is unknown if axi-cel overcomes the adverse prognostic feature of hypoalbuminemia in R/R large B-cell or transformed follicular lymphoma.

Methods: We conducted a retrospective analysis of patients treated with axi-cel across three Mayo Clinic campuses (Rochester, Jacksonville, and Phoenix) from 06/01/2016 until 12/01/2019. The primary objective of this analysis was to assess the correlation of hypoalbuminemia defined as a serum albumin levels ≤ 3.5 g/dL on day 0, prior to infusion on outcomes after axi-cel therapy.

Results: A total of 69 (male=48, 70%) patients (pts), median age of 53 (24-74) years received axi-cel. The median number of prior lines of therapy was 3 (2-8) (Table 1). Two pts had no available serum albumin levels at time of axi-cel infusion. Thirteen (19%) of 67 pts had hypoalbuminemia (median= 3.3 g/dL (range 2.5-3.5)) and the median follow-up of survivors in this group was 6.7 (1.7-17.8) months. The best overall response rate (ORR) and complete remission (CR) rates in these pts were 62% and 46%, respectively. One (8%) patient had stable disease and 4 (31%) had disease progression. On the other hand, 54 (81%) pts had a normal serum albumin (defined as > 3.5 g/dL) level (median=4.1 (range 3.6-5.1) g/dL) and the median follow up for survivors in this group was 5.4 (1.0-30.9) months. The best objective response rate (ORR) and complete remission (CR) rates in these pts were 81% and 41%, respectively. There was no difference in 1-year OS between the group with hypoalbuminemia (64% (95%CI=30-99%)) and the group with normal serum albumin level (57% (95% CI=34-79%), p=0.88. All grades cytokine release syndrome (CRS) was diagnosed in all 13 pts with hypoalbuminemia (100%) and in 48 of 54 (89%) pts without hypoalbuminemia. There was no difference in the median duration of CRS between pts with or without hypoalbuminemia [5 (1-11) days vs 5 (1-19) days, p=0.84]. Neurotoxicity (all grades) was observed in 8 (62%) pts with hypoalbuminemia compared 27 (50%) with normal albumin levels. There was no statistically significant difference in median duration of neurotoxicity between pts with hypoalbuminemia and those with normal baseline albumin levels [9 (range 1-56) days vs. 3 (range 0-25) days, p= 0.07].

Conclusions: Hypoalbuminemia does not have a significant impact on the outcomes of axi-cel therapy, including OS or the incidence of CRS or neurotoxicity. Large multicenter clinical trials are needed to validate these findings.

Clinical Trial Registry: None

Disclosure: Lin, Yi: Research funding: Janssen, Merck, Kite/Gilead, Celgene, BlueBird Bio, Takeda

Consulting: Janssen, Legend BioTech, JUNO, Celgene, BlueBird Bio, Kite/Gilead, Novartis, Gamida Cells, AlloGene.

DSMB: Sorrento

Steering committee: Celgene, Janssen, Legend Biotech

P093

Factors Predicting CD3+ Collection for the Production of Chimeric Antigen Receptor (CAR) T Cells

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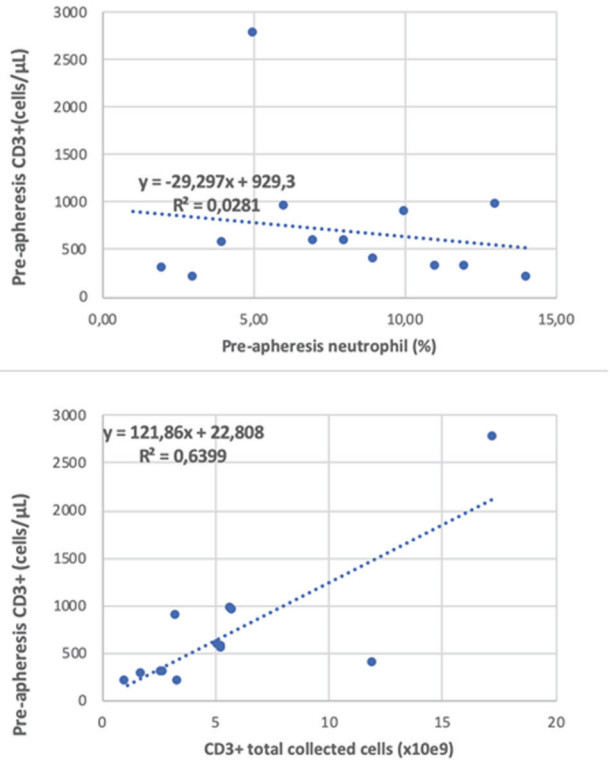
Background: Chimeric antigen receptor (CAR) T cells are a promising new immunotherapy. However, the challenges of collecting CD3+ lymphocytes in this population of patients have not been well-characterized. The aims of the study were to evaluate the feasibility of collection adequate numbers of CD3+ cells, analyze the rate of adverse events and to identify the variables that can predict inadequate collections.

Methods: We prospectively study the apheresis for lymphocyte collections (ALC) from patients in real live for CARs from May-19 to November-19. Collections were performed on the same Cobe Optia device, at hematocrit of 1 to 2% and collection flow rate of 0.8 mL/min. All patients had Hickman central venous catheters placed before the procedure, and received intravenous calcium gluconate as per SOP. The product goal was a target of 1 x 10^9 CD3 + cells.

Results: 14 ALC were performed. Median age 59.5 years (28-69). 57%(n=8) were male. 57%(n=8) were sent for the production of axicabtagene ciloleucel, 43% for tisagenlecleucel. Diagnosis was 100% lymphoma, median of 16.4 months from the diagnosis to ALC (6-48.8). Ann arbor stage was 3 in 2 patients(14%), 4 in 11 patients(79%). 50%(n=7) received 3 or more prior lines of treatment. Potential treatment affecting the collection prior apheresis: 36%(n=5) purine nucleoside antimetabolites, 21% (n=3) received IMiDs, 50%(n=7) Autologous Stem cell transplant and 36% (n=5) radiotherapy. Last treatment before ALC was systemic chemotherapy in 7 patients (57%), radiotherapy 4 patients (29%), immunotherapy 2 patients (14%). Median of 45 days from the treatment to ALC (15-1000).



[Correlation between pre-apheresis CD3+ (cells/µL) neutrophils and CD3+ yield]

Pre-apheresis laboratory testing were : median leucocyte (x 10^6/mL) of 4 (1-14.4), median hematocrit (%) 30.2 (25-41), median platelets (x10^6/mL) 112 (25-345), median neutrophils (%) 63.5 (34.3-86), median lymphocyte (%) 20.2 (30.8-50), median NK (%) 3.2 (0.3-8.7), median (%) CD19+ 0(0-4.8), median CD3+ (cells/µL) 460 (147-2770), median CD3+(%) 12.2(4-38) of which median CD4+(%) 37.25(10-72) and CD8+(%) 55.9 (24.5-85)

Apheresis parameters were: median of 12 liters processed (5-15), collection efficiency median (%) 52.9 (40.9-75.5). One patient developed symptomatic hypotension during the procedure, other complications related to hypocalcemia including paresthesias were managed in the apheresis unit.

Apheresis collection yields from 13 products were: median volume of 199 mL (86-240), median hematocrit(%) 3.2 (1.8-17.7), median platelets(x10^6/mL) 811(255-3784), median volume ACD-A(mL) 22(10-31), cell concentration (cellsx10^6/mL) 58.9 (12.7-247.7), median total nucleated cells (x10^9) 9.9 (2.8-52.5), median mononuclear cells(x10^6/mL) 51.3(12.6-242.7). Median(%) CD3+ of CD45+ was 53(23-83.5) with a median total number of CD3+ (x10^9) of 5.2 (1.1-17.3).

Univariate analysis showed that higher pre-apheresis CD3+ (cells/µL) was significantly correlated with CD3+ total collected cells in the apheresis product. Thus, there is an association with higher proportion of neutrophils in

peripheral blood with lower pre-apheresis CD3+ counts (figure1).

Conclusions: In most patients undergoing CART cell therapy, leukapheresis is well-tolerated and adequate numbers of CD3+ lymphocytes are collected. A personalized approach to the collection process is the essential first step for CART cell immunotherapy. However, further studies of larger cohorts of patients including new variables are necessary to confirm this findings to ensure that all patients can have sufficient cells for manufacturing.

Disclosure: Nothing to declare.

P094

Cytopenias after Tisagenlecleucel in Paediatric/young Adult Patients with Refractory/relapse b-cell Acute Lymphoblastic Leukaemia (R/R B-all): A real-life Single-centre Experience

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Background: Tisagenlecleucel (Kymriah™) is a CD19-targeted CAR-T cell therapy approved for r/r B-ALL in paediatric/young-adult patients. Cytopenias following CAR-T cells are relatively common across multiple studies[1] including those targeting CD19 and CD22 and are therefore not antigen-specific. The incidence and clinical impact of persistent or recurrent cytopenias has been under-recognized in clinical studies to date and the aetiology is as yet unclear. The objective of this study is to describe cytopenias and related complications in paediatric/young-adult patients with r/r B-ALL treated with Tisagenlecleucel.

[1] Jacoby et al. https://doi.org/10.1038/s41409-019-0487-3

Methods: We retrospectively analyzed 12 consecutive patients with r/r B-ALL treated with Tisagenlecleucel between January 2019 and November 2019 in a single centre. Patients received lymphodepletion with fludarabine (120 mg/m2) and cyclophosphamide (1000 mg/m2). Cytopenias were graded according to CTCAE V-5.0. Persistent cytopenias were defined as grade 2-4 cytopenias after day-28. Recurrent cytopenias were defined as new-onset grade 3-4 cytopenias after day-28 when and after achieving normal counts on day-28. Cytopenias were considered resolved when grade 1 or normal counts were achieved.

Results: Patient characteristics are summarised in Table 1. Nine patients were diagnosed with relapsed B-ALL after HSCT, 2 had relapsed B-ALL with a contraindication for HSCT and 1 had primary refractory disease. With a median follow-up of 4 months (range 1-10) after CAR-T cell infusion, MRD was negative in 11 patients (92%), B cell aplasia was persistent in 10 (83%) and 1 (8%) had a relapse and died.

Eight patients (67%) presented with grade 2-4 cytopenias before lymphodepletion.

Before day-28, all patients developed grade 2-4 anaemia (9=75% grade 3-4), 8 patients (67%) developed grade 2-4 thrombocytopenia (6=50% grade 3-4), and all patients developed grade 3-4 neutropenia.

Four patients (33%) had persistent grade 2-4 anaemia, 2 (17%) grade 3-4. Five (42%) had persistent thrombocytopenia, all grade 3-4. Seven (58%) had persistent neutropenia, all grade 3-4. Two patients (17%) with normal counts on day-28, developed recurrent grade 3-4 neutropenia after day-28.

Secondary causes of cytopenias were excluded. Among patients with persistent cytopenias, 4 (50%) had a hypocellular marrow on histology of the BM trephine.

Eight patients (67%) received at least one RBC transfusion before day-28, and 2 (17%) after day-28. Three patients (25%) received at least one platelet transfusion before day-28, and 4 (33%) after day-28. Seven patients (58%) received at least one Filgrastim dose after day-28. Eight documented infections were diagnosed, 3 of them after day-28, with 0% of infection-related mortality.

At last follow-up, anaemia was resolved in all patients, 2 (17%) had ongoing thrombocytopenia, (1 with platelet transfusion dependence), and 3 (25%) ongoing neutropenia (1 with Filgrastim dependence).

Conclusions: Cytopenias were frequent in patients treated with Tisagenlecleucel. Whilst early cytopenias are expected due to lymphodepletion, mechanisms of persistent and recurrent cytopenias are unclear and might be related to CAR-T cells persistence. More studies are needed to determine etiology and risk factors for persistent cytopenias. Cytopenias are of relevance in terms of increased requirement for supportive care, however, in our cohort, were not associated with significant or persisting complications.

Disclosure: Nothing to declare.

P095

The risk of Hepatitis B Reactivation is controllable in B-cell Malignancies Patients with Concomitant Hepatitis B Virus Infection after Chimeric Antigen Receptor T Cell Therapy

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Background: Chimeric antigen receptor- modified (CAR) T-cell immunotherapy is a novel promising therapy for relapsed/refractory B cell malignancies. Prolonged B- cell aplasia is a common and expected toxicity after receiving CAR-T cell treatment. However, the risk of HBV reactivation after CAR-T cell therapy is still unknown. We summarized the risk of HBV reactivation in R/R B-cell Malignancies patients with Concomitant Hepatitis B Virus infection after Chimeric Antigen Receptor T Cell Therapy at our hospital.

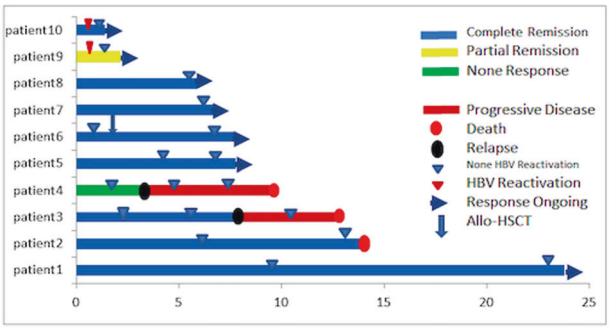
Methods: Patients with R/R B-cell lymphoma, B-ALL and Multiple Myeloma who received CAR-T cell treatment in four clinical trials (ChiCTR-ORN-16008948, ChiCTR-OIC-17011310, ChiCTR1800015575, ChiCTR1800017404) in our center were retrospectively analyzed. All patients were screened for hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), antigen antibody to hepatitis B core antigen (anti-HBc) and HBV DNA copy numbers before and after CAR-T cell treatment. Those with positive HBsAg were eligible for this retrospective study.

Results: Between December 2017 and October 2019, 10 patients with relapsed or refractory B cell malignancies and concomitant HBV infection who were treated with CAR-T cells were included in this study. The median age was 50 years (range: 39-67 years), with 60% were male. Details are summarized in table I. All of the 10 patients with chronic HBV infection received prophylactic entecavir treatment. And at the time of CAR-T cell infusion, HBV DNA levels of all patients were lower than the normal limit. With median follow-up 7.77 months (range:1.43-23.8 months) from CAR-T cell infusion, 2patients (patient 9 and patient 10) had transient HBV reactivation. However, the HBV DNA copy numbers came back to lower than the normal limit with the entecavir and Adefovir treatment. All patients reminded on prophylactic NAT by the time of last follow-up. Figure1 showed the Time points of HBV detection and response after CAR-T cell treatment.

Conclusions: our results showed that CAR-T cell treatment could be safely administered in patients with Concomitant Hepatitis B Virus infection. Considering the small group sample size and retrospectively analysis, the risk of HBV reactivation with prophylactic entecavir treatment after CAR-T cell treatment should be further evaluated in large and prospective studies.

Patient1	39 y	Male	24 cycles treatment before CAR-T therapy	DLBCL	CD19-CD22	6.44*10^6/kg	No HBV reactivation
Patient2	60 y	Female	6	DLBCL	CD22	5.85*10^6/kg	No HBV reactivation
Patient3	55 y	Male	12	MM	BCMA	2.64*10^6/kg	No HBV reactivation
Patient4	49 y	Male	6	Aggressive B cell lymphoma	CD19-CD22	10.28*10^6/kg	No HBV reactivation
Patient5	43 y	Female	18	DLBCL	CD19-CD22	5.72*10^6/kg	No HBV reactivation
Patient6	47y	Male	5	B-ALL	CD19	5.6*10^6/kg	No HBV reactivation
Patient7	67 y	Male	7	MM	BCMA	3.49*10^6/kg	No HBV reactivation
Patient8	50 y	Female	9	MM	BCMA	5.59*10^6/kg	No HBV reactivation
Patient9	50 y	Female	6	Lymphoblast lymphoma	CD19-CD22	8.04*10^6/kg	Yes, and recovered after entecavir treatment
Patient10	53 y	Male	6	MM	BCMA	5.1*10^6/kg	Yes, and recovered after entecavir treatment

[Patient clinical characteristics before and after chimeric antigen receptor T cell therapy]



[Figure1. Time points of HBV detection and response after CAR-T cell treatment]

Clinical Trial Registry:
ChiCTR-ORN-16008948
ChiCTR-OIC-17011310
ChiCTR1800015575
ChiCTR1800017404
The website is http://www.chictr.org.cn

Disclosure:
Nothing to declare.

P096

Cumulative Rituximab Exposure Prior to Axicabtagene Ciloleucel is not associated with Persistent Leukopenia and Thrombocytopenia at Day +90 Post Infusion

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Background: Cytopenias occur frequently after axicabtagene ciloleucel (axi-cel), a recently approved anti-CD19 CAR-T cell therapy. The direct cause(s) of cytopenia (s) remains elusive. Rituximab has been associated with delayed onsent cytopenia in patients with non-Hodgkin lymphoma. Here, we investigate the impact of various patient- and pre-CAR-T treatment related factors including cumulative rituximab exposure, prior lines of treatment and prior auto-HCT on the persistence of cytopenia (s) in the setting of axi-cel.

Methods: We conducted a retrospective analysis of patients treated with axi-cel across three Mayo Clinic campuses (Rochester, Jacksonville, and Phoenix) from June 2016 until October 2019. Five patients received axi-cel in a clinical trial. The primary objective of this analysis was to identify factors associated with persistent cytopenias (leukopenia and thrombocytopenia) at day +90 in axi-cel recipients. Leukopenia was defined as less than 3 $x10^9$/L and thrombocytopenia as a less than 100 $x10^9$/L. Univariate analysis was used to analyze predictors and outcomes.

Results: A total of 57 patients, males (n=41, 72%), who had received a median of 3 (2-8) prior lines of therapy received axi-cel. Seventy three percent of patients (33/45, 12 patients had missing data) experienced at least a grade 1 cytopenia per CTCAE v5.0 at day+90. Twenty-four patients had failed a prior autologous transplant. The median number of prior rituximab doses was 8 (2-19). Pertaining to day +90 persistent leukopenia, age (≤ 52 vs. > 52 years, p=0.75), gender (p=0.72), number of prior therapies (p=0.80), a prior auto-HCT (p=0.66), and cumulative doses of rituximab (p=0.51) were not significant variables. None of these factors was predictive of persistent neutropenia (defined as less than 1.5 $x10^9$/L) by day +90 post axi-cel. Pertaining to day +90 persistent thrombocytopenia, age (≤ 52 vs. > 52 years, p=0.3), gender (p=0.1), number of prior therapies (p=0.06), a prior auto-HCT (p=0.54), and cumulative doses of rituximab (p=0.06) were not significant variables.

Conclusions: Our analysis did not identify rituximab or any other patient- or pre-CAR-treatment related factors to be associated with persistence of leukopenia and thrombocytopenia at day +90 post axi-cel.

Characteristic	Total number of patients = 57
Age (years-range)	52 (25-68)
Gender (male)	41 (72%)
Histology	DLBCL:32(56%);PMBCL:6(11%); TFL: 11(19%);HGBCL:8(14%)
Prior lines of treatment (Median, range)	3 (2-8)
Autologous Stem Cell Transplant	24 (42%)
Number of Rituximab Doses (Median, range)	8 (2-19)
Time from initial diagnosis to CAR-T (Median, range)	13.7 months (3.2-193.6)

[Table 1]

Disclosure: YL declare.d the following conflicts of interest:

Research funding: Janssen, Merck, Kite/Gilead, Celgene, BlueBird Bio, Takeda

Consulting: Janssen, Legend BioTech, JUNO, Celgene, BlueBird Bio, Kite/Gilead, Novartis, Gamida Cells, AlloGene.

DSMB: Sorrento

Steering committee: Celgene, Janssen, Legend Biotech

MAK-D: consultancy for Daiichi Sankyo

Remaining authors disclose no relevant conflicts of interest.

P097

Comprehensive Immune Cell Monitoring Reveals an Altered Lymphocyte Subset Phenotype in Patients not Responding to Tisagenlecleucel One Month Post Infusion

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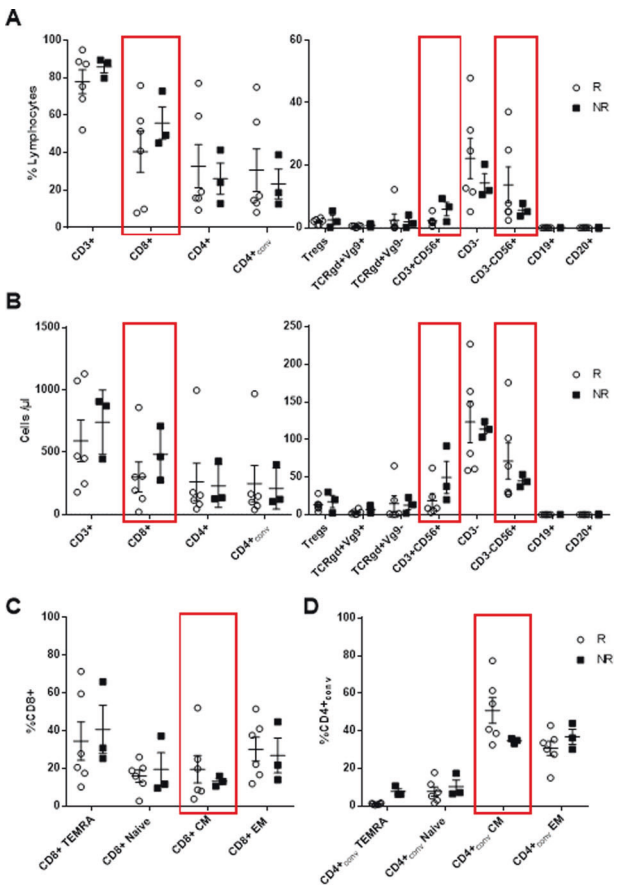
Background: Reconstitution of lymphocyte subsets following lymphodepletion and chimeric antigen receptor (CAR) T cell infusion is pivotal for pathogen control. Moreover, lymphocyte subsets are thought to support CAR T antitumor activity. In this prospective single center pilot study we aim to investigate whether failure of anti-CD19-CAR T cell (Tisagenlecleucel) response one month post infusion is associated with a specific lymphocyte subset phenotype.

Methods: Blood samples of eleven patients with relapsed or refractory transformed follicular lymphoma and diffuse large B cell lymphoma (DLBCL) were examined by multi-color flow cytometry. Following lymphodepletion with fludarabine and cyclophosphamide, all patients received Tisagenlecleucel. The institutional review board approved the study and all patients gave written informed consent for prospective immune cell monitoring. Lymphocyte subsets were detected from peripheral blood using a 10-color antibody mix for T, B, and NK cell subsets as well as activation markers via flow cytometry. For determination of absolute frequencies BD Trucount™ tubes were used. Treatment response to anti-CD19-CAR T therapy was assessed via PET-CT one month post infusion.



[Figure 1: Analysis of lymphocyte subsets in responders (R) vs. non-responders (NR) at day +28.]

Results: Blood samples and PET-CT data were available on 9 out of 11 patients one month post infusion of Tisagenlecluce l. Disease progression or no response to therapy was observed in 3 patients, termed non-responders (NR). The remaining 6 patients, termed responders (R), all showed reduced PET activity, with two (33%) achieving complete metabolic remission and four (66%) achieving partial metabolic remission. We compared different lymphocyte subsets in non-resonders vs. responders on day +28 (range 11-34). Interestingly, non-responders displayed higher relative frequencies and absolute numbers of CD8+ and CD3+CD56+ cells and fewer CD3-CD56+ cells compared to responders, albeit lacking statistical significance, likely due to the small sample size (Figure 1A and B). Moreover, CD4:CD8 ratio was markedly lower in non-responders (0.53 vs. 2.73), implying a shift in immune response. Further analysis of activation markers in conventional CD4+ ($CD4_{conv}$) and CD8+ cells revealed a trend towards decreased central memory populations in non-responders (Figure 1C and D).

Conclusions: Immune cell monitoring of lymphocyte subsets in CAR T cell patients may provide important insights in immune function supporting CAR T cell activity. In this prospective single center pilot study we describe an altered lymphocyte subset phenotype in patients failing to respond to Tisagenlecleucel. The phenotype consisted of a reduced CD4:CD8 ratio, lower CD3-CD56+ frequencies and central memory populations together with higher CD8+ and CD3+CD56+ populations. However, these data are limited by the small cohort size and warrant further validation in a larger cohort.

Disclosure: Nothing to declare.

P098

Neurotoxicity associated with CAR T Cell Therapy: Neurological Management and work-up of 11 Adult Patients

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Background: Treatment with CD19 chimeric antigen receptor (CAR) T cells represents a novel treatment approach for patients with relapsed or refractory diffuse large B cell lymphoma (r/rDLBCL) or B-lineage acute lymphoblastic leukemia (ALL). However, impressive therapeutic response rates are often accompanied by specific and severe toxicities. Besides the common cytokine release syndrome (CRS) which is characterized by fever, hypotension, hypoxia, and in more severe cases multisystem organ dysfunction, specific neurotoxicity termed immune effector cell-associated neurotoxicity syndrome (ICANS)

has been observed as well and is treated as a separate entity with distinct timing and treatment requirements. Although symptoms can be more diverse than those of CRS, many patients with neurotoxicity show specific clinical features with expressive aphasia being one of the most characteristic ones.

Methods: Eleven r/rDLBCL patients have been treated with Tisagenlecleucel at Hannover Medical School between April 2019 and November 2019. All patients received an extensive neurological examination prior to CAR T cell infusion. This included clinical examination, handwriting sample, cognitive testing (Montreal-Cognitive-Assessment (MoCA)), brain magnetic resonance imaging (MRI), electroencephalogram (EEG), electroneurography (ENG), and analysis of cerebrospinal fluid (CSF) in 8/11 patients. After CAR T cell infusion, patients were neurologically examined for 10 consecutive days. Up to 4 weeks following infusion, we assessed all patients at least once a week.

Results: Baseline clinical neurological examination and ENG showed signs of axonal polyneuropathy in 10 of 11 patients before CAR T cell therapy indicating damage due to prior chemotherapy. Two patients presented with slightly impaired MoCA-results (25/30 points) and 1 patient achieved only 23/30 points prior to CAR T cell treatment. Brain MRI was unremarkable in all cases. CSF did not show signs of inflammation in all 8 patients (cell count 1-3/µl, oligoclonal bands negative) and no relevant disturbance of the blood-CSF-barrier (Qalbumin 4.7-8.5). No one exhibited antineuronal or autoimmune encephalitis antibodies. During the four-week follow-up period one patient developed a severe CRS at day 5 accompanied by mild signs of cognitive impairment (MoCA minimum 23/30), but without abnormalities in brain MRI. He died on day 23 following CAR T cell therapy due to infection. Two patients exhibited signs of cognitive impairment at day 4 and 5, respectively. Both patients showed very similar symptoms including apraxia, expressive aphasia, disorientation, and hallucinations. Symptoms developed very quickly, while brain MRI was inconspicuous in either case. Grade 2 ICANS was assumed in both patients and both were treated with dexamethasone 40 mg/d. As symptoms rapidly resolved steroid treatment was quickly tapered and stopped after 5 days. Both patients showed neither signs of cognitive nor neurological impairment afterwards.

Conclusions: Neurotoxicity is a feared complication of CD19 CAR T cell therapy and initial symptoms can be very subtle. Our longitudinal examinations in 11 patients revealed specific clinical symptoms of ICANS in 2 patients without relevant radiological abnormalities. Further studies with higher numbers of patients including a structured and detailed neurological examination are required to uncover CD19 CAR T cell-related neurotoxicity and its especially pathogenesis.

Disclosure: Nothing to declare.

P099

Nutritional Assessment of Patients undergoing CD19-targeted CAR-T Therapy for Non-hodgkin's Lymphoma and the Short Term Effect of Treatment on Nutritional Status

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Background: Chimeric antigen receptor (CAR) T-cell therapy targeting CD19 has demonstrated efficacy in the treatment of relapsed and refractory B cell non-Hodgkin lymphoma. In haematological cancers, nutrition is a concern, particularly in patients undergoing high dose therapies and haemopoietic stem cell transplantation (HSCT). The high-dose radiotherapy/chemotherapy associated with treatment and its typical spectrum of side effects, including nausea, vomiting, mucositis, diarrhoea and infections, further impacts oral food tolerance. This contributes significantly to weight loss (WL), particularly in the first 40 days of admission. As of yet, there have been no reports on the effects of CAR T-cell therapy on nutritional status.

The aim of this study is to report on the nutritional status of patients undergoing CAR T-cell therapy for CD19 positive non Hodgkin lymphoma, both prior to, and during their approximate 3-4 week inpatient admission for treatment.

Methods: 40 patients who underwent treatment between January and October 2019 had a comprehensive nutritional assessment prior to receiving CAR T-cell therapy. Of these patients, 39 had diffuse large B cell lymphoma and one patient mediastinal B cell lymphoma. They were reviewed during their inpatient admission stay and symptoms which impair nutritional intake (e.g. diarrhoea, poor appetite) were monitored, as well as WL and their requirement for oral, enteral and parenteral nutritional interventions.

Results: 25% of patients were identified as malnourished prior to treatment with poor nutritional status typically being related to pre-existing chronic illness e.g. inflammatory bowel disease or disease involving the GI tract. 38 patients were nutritionally assessed as inpatients in the 3-4 weeks after infusion of CAR T-cells. During this period, no

significant impact on body weight (5% or more WL) was observed in 66% of patients who underwent therapy. This is hypothesised to be due to the reduced observation of side effects such as vomiting, diarrhoea and mucositis, which are frequently observed with other treatments for haematological cancers, in particular HSCT. Significant WL during this period (>10% of body weight) was observed in 8% (n=3) of patients.

50% of patient's required nutritional supplements to meet their requirements and prevent unintentional WL during their admission. 18% (n=7), including all patients who suffered neurotoxicity required a period of enteral feeding via nasogastric tube. In the other 3 cases, nasogastric tube feeding was indicated due to severe anorexia/malnutrition or dysphagia due to disease being localised to the neck region.

Conclusions: CAR T-cell therapy appears to have a less significant impact on nutritional status than other similar treatments for haematological malignancies, primarily due to a lower incidence in adverse effects. However, all patients undergoing treatment should be nutritionally screened prior to treatment due to the high incidence of malnutrition in this population group. Patients who experience neurotoxicity are also at high risk of malnutrition and are likely to require nasogastric enteral feeding for a period to prevent significant WL. Further research on the impact of neurotoxicity on nutritional status, and longer term follow up on the nutritional impact of CAR T-cell therapy is required to influence future dietetic practice in this field.

Disclosure: Nothing to declare.

P100

Effectiveness of Autologous Leukapheresis Collections for CAR T-cell Manufacturing in Patients with B-cell Malignancies

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Background: Chimeric antigen receptor (CAR) T-cell therapy is a novel and promising cellular treatment modality for a variety of malignancies. So far, it is mainly being used in haematological malignancies including relapsed or refractory high-grade lymphoma, acute lymphoblastic leukemia (ALL) and multiple myeloma. An autologous leukapheresis product is collected as source material for the CAR T-cell manufacturing process. This cohort of patients is typically heavily pretreated, cytopenic and presenting significant disease- or treatment related complications. The effectiveness and feasibility of leukapheresis procedures in this setting was analysed.

Methods: In this retrospective analysis, 66 leukapheresis collections from patients participating in CAR T-cell clinical trials or from patients in preparation for CAR T-cell treatment with tisagenlecleucel in the commercial setting were reviewed. Collections were performed on the COBE Spectra apheresis device by experienced nurses. Pre-apheresis peripheral blood counts, apheresis parameters, and product cell counts were analysed.

Results: Patients with relapsed or refractory diffuse large B-cell lymphoma including Richter's transformation (n=57), ALL (n=1), mantle cell lymphoma (n=3), follicular lymphoma (n=1) underwent leukapheresis collection for CAR T-cell production. Median age of the patients was 60 years (range 20-83). The median body weight of the patients was 73kg (range 39-137). Median pre-collection CD3 and lymphocyte counts were 540/µl (range 30-3400) and 620/µl (range 90-4960), respectively. The median pre-collection leukocyte count was 5240/µl (range 700-52650) and the median hematocrit was 30% (range 18-44). A median number of 3,92 x10e9 CD3+ T-cells was collected (range 0,2-18,23 x10e9) by processing a median number of 2,1 total blood volumes (range 0,4-3,8). This corresponds to a collection of 0,37x10e9 CD3+ T-cells per liter blood processed. The collection efficiency was 60% (CE2). Only one patient failed to collect sufficient T-cells, in this case in the context of massive tumor progression and infection. Two patients had to be collected twice on consecutive days. Vascular access was a central line in 32 and a peripheral vein in 34 procedures. Leukapheresis was well tolerated in all cases.

Conclusions: Our data demonstrates that a standard leukapheresis is effective to collect sufficient CD3 T-cells for CAR T-cell production. Patients can be safely and successfully collected with CD3 counts down to 50-100 CD3 T-cells/ µl peripheral blood. Follow-up of completed infusion rates and reasons for infusion failure are currently under investigation and will be presented.

Disclosure: The authors have no conflict of interest to disclose.

P101

Definition and Implementation of Clinical and Quality Endpoints in Centers Administering a Commercial CAR-T Product

CARTangle Model						
Domain	Patient		Disease		Logistics	
Subprocess	Course	Clinical/ Quality parameters	Course	Clinical/ Quality parameters	Course	Clinical/ Quality parameters
Referral of a patient and eligibility criteria for the CAR-T program	Primary physician refers a patient via specific form, patient is screened by a multidisciplinary team. Assessment of inclusion and exclusion criteria.	1. % patients fulfilling predefined eligibility criteria. 2. % patients excluded. 3. % patients with screening failure.	Assessing inclusion and exclusion criteria.		Patient is enrolled into the system. Tentative plan is discussed with the referring physician.	N Days from referring a patient to enrolment.
Bridging to apheresis, collection and processing	Patient is scheduled to undergo apheresis. Product is collected and processed.	1. Collection coefficiency. 2. Deviations in the labelling of the product. 3. Central line complications.	Assessing potential compromised organ function. If none, avoid therapy Schedule apheresis based on the ASTCT recommendations.	1. % patients who were not apheresed d/t disease progression. 2. % violation of ASTCT recommendations.	Product is processed, (±cryopreserved), and shipped.	1. N Days from enrolment to apheresis. 2. N days from apheresis to pickup.
Bridging to infusion	Patient is scheduled for infusion. Patient usually is discharged back to the referral physician.	% patients that were given the CART	Disease should be controlled with additional chemotherapy.	Bridging therapy results.	Patient is being monitored by referral physician with a close communication with the CAR-T center.	N days from pick up to infusion.
Infusion of the product and short-term follow-up	Patient is admitted for preparative regimen and CAR-T infusion. Early toxicities are monitored and treated. Patient is discharged after all toxicities have resolved and counts have recovered.	1. % Infusion reactions. 2. CRS/ICANS incidence and grading. 3. N doses of tocilizumab. 4. Length of neutropenia. 5. Incidence of MDI/IFI. 6. Persistence of CAR-T. 7. NRM at 30 days. 8. QUAL questioners.	Disease may be further controlled with additional chemotherapy/ radiotherapy.	1. % of patients that need early salvage treatment. 2. Results of early salvage treatment.	Patient is hospitalized in the CAR-T center.	Length of hospitalization.
Long-term follow-up	Patient continues follow-up at the referral center that provides surveillance data to the CAR-T center.	1. NRM at 100 days. 2. Incidence of CMV. 3. QUAL questioners.	Disease should be monitored at 1 month and at 3 months and then, per physician discretion.	1. Status of disease at 1 month. 2. DFS, OS. 3. Additional treatment after progression.	Data is retrieved, analyzed and reported to the EBMT database	1. % patients reported within 6 months from infusion. 2. Accurate of 5 points domains.

[Clinical and quality management parameters for patients undergoing CAR-T cell therapy]

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Background: CAR-T (Chimeric Antigen Receptor Therapy) has become an acceptable therapy option in patients with chemo-refractory DLBCL. Patients in most cases have a rapidly progressive disease hence the CAR-T process should follow a very strict time course to ensure high percentage of patients receiving the final product, while maintaining patents' safety and product integrity. We aim to develop a clinical and quality management system to ensure the overall success of the procedure.

Methods: We established a system to allow a CAR-T team to self-assess against a group of standard guidelines/ procedures. This system will serve as a control process to review, analyse, implement and improve suboptimal results. All subprocesses of the CAR-T were identified

and individually dissected into different parameters based on the **CARTangle** - our unique centre model based on 3 domains - patient, disease and logistics. Subprocesses and domains are prospectively monitored for defined end-points, flaws, deviations and events, corrective actions and change control procedures are then implemented, when indicated.

Results: The following subprocesses were defined - 1. Referral of a patient and eligibility criteria for the CAR-T program, 2. Bridging to apheresis, 3. Bridging to infusion, 5. infusion of the product and short-term follow-up, and 6. Long-term follow-up. The correspondence clinical and quality management parameters are defined below (**Table**). Data of enrolled patients with the corresponding quality management parameters will be presented at the meeting.

Conclusions: This pivotal clinical and quality management system is an ongoing process and is obliged to maximize patients and products´ safety and performance.

Disclosure: Nothing to declare.

P102

CAR-T in Breast and other extra-medullary Relapsed/ refractory All

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Background: Extra-medullary ALL develops in sanctuaries including, CNS, genitourinary and "sequestered sites" (gut, breast, skin). Data regarding complete remission (CR) rates and durability of response among patients receiving CART with relapsed/refractory (r/r) ALL and extra-medullary disease is still emerging.

Methods: We report two AYA patients with r/r ALL and extra-medullary involvement who achieved CR after tisagenlecleucel.

Results: Patient 1 was refractory to 7 prior lines of therapy and developed CNS, liver, spleen and bilateral kidney involvement; He experienced CD19 negative relapse approximately 8 weeks later. He subsequently achieved CR following two doses of inotuzumab and then received a reduced intensity (RIC) related haplo-identical SCT. He experienced a CNS relapse approximately 2 months later and died shortly after. Patient 2 had isolated bilateral breast involvement following allogeneic stem cell transplantation (SCT). She experienced swelling and erythema of the breast tissue following CART and achieved MRD negative CR in the bone marrow with partial response in the breast. She subsequently received XRT to the breast and was consolidated with a RIC SCT. She died approximately 100 days post-SCT from sepsis.

Conclusions: The majority of 53 reported patients with ALL and extra-medullary breast involvement (22 occurred post-SCT) received combined radiation and chemotherapy; 4 received DLI and achieved CR but 2 died of severe GvHD. CAR-T cells, may likewise circulate and act in sequestered sites but without GvHD. Lympho-depletion preceding CAR-T may also eliminate regulatory T lymphocytes and potentially enhance the immune response. Combined treatment with CAR-T and radiation may help eradicate extra-medullary disease, taking advantage of the local death of dividing cells with radiation with potential enhancement of the micro-environment to facilitate CAR-T function and enhance anti-tumor immune response of resident T cells. Future studies will elucidate the optimal timing of CART among patients with extra-medullary disease, which may improve durability of response and long-term outcomes.

Disclosure: Nothing to declare.

P103

Predicting CAR T-cell Infusion after Successful Manufacturing: real-world Data

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Background: CAR T-cells directed against CD19 are a newly approved cellular therapy for treating patients (pts) with relapsed or refractory (r/r) pediatric and adolescent acute lymphoblastic leukemia or diffuse large B-cell lymphomas (DLBCL). Given the aggressive nature of the underlying diseases bridging pts from lymphapheresis (LA) to CAR T-cell infusion remains a challenging task. Very little is known on factors predicting successful bridging pts during this period in the real world population.

Methods: We evaluated clinical variables potentially affecting successful re-infusion of CAR T-cells in pts receiving CD19 CAR tisagenlecleucel at our CAR T-cell center.

Results: Ten pts were assigned to CAR T-cell therapy and underwent LA between May to August 2019 for r/r

DLBCL. 3 pts died prior to infusion. 7 pts received CAR T-cells after a median time of 49 days after LA. Pts receiving the CAR T-cells presented with lower lactate dehydrogenase (LDH) and C-reactive protein (CrP), better ECOG performance score (PS) at the time of LA and had received fewer lines of therapy than patients not receiving CAR T-cells. We developed a scoring system, which included the mean LDH (>8.3 μkat/l) and CrP (>90 mg/l) at the time of LA forpatients that did not receive the CAR T-cells (2 points each), ECOG PS (1 point per ECOG PS), lines of therapy after 1st salvage (1 point per line) and referral from an external hospital (1 point) in order to predict outcome. All but one patient receiving the CAR T-cells had a score of < 5.

Conclusions: Bridging eligible patients from LA to CD19 CAR T-cell infusion remains a challenge. Patients with a CAR T score >4 should be considered to be at higher risk for complications. The proposed score has to be evaluated in a larger cohort.

Disclosure: Franke: Novartis, Pfizer, Jazz, MSD, Takeda: Honorary. Gilead: travel support

Vucinic: Novartis, Gilead, Takeda, Abbvie: Honorary

P104

Evaluation of the Interest of a Drug Reconciliation Activity in Patients Treated with Car T-cells: A Descriptive Study

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Background: CAR T-cells (CARTc) are patient T-cells that express artificial chimeric antigenic receptors (CAR) capable of recognizing tumor cells antigen. Axicabtagene ciloleucel is indicated in patients with relapsed diffuse large B-cell lymphoma or those who are refractory to other treatments. A medication reconciliation activity has been carried out since the beginning of 2019. The objective is to assess the value of medication reconciliation at admission of patients receiving CARTc.

Methods: A medication reconciliation have been conducted by pharmacy students under the supervision of pharmacists for patients receiving CARTc. A medication history, including self-medication treatments, has been established according to at least 3 information sources. Intentional or unintentional discrepancies were underlined for each difference between the medication history and the first medical prescription at admission. Pharmaceutical interventions (PI) resulted from a discrepancy. Medication adherence was assessed according to the medication adherence scale of our national insurance system. Patients were considered: good, minimal or not adherent. In parallel, allergies and medication difficulties were reported. Data were prospectively recorded anonymously on an Excel® datasheet.

Results: Between January 3rd and October 30th, 2019, 30 patients received CARTc. The age was 60±10 years and gender ratio was 0.7. Patients received 4±2 previous lines of treatment. Reconciliation could have been performed in 18 patients. They took an average of 6 medications ([1; 19]), notably anti-infectious prophylaxis: valaciclovir (N=12/18) and co-trimoxazole (N=9/18). Intentional discrepancies (N=93) and unintentional discrepancies (N=8) were found. Six PI were formulated, and 5 accepted: 1 discontinuation of lansoprazole (no indication found), 1 dose adjustment for irbesartan, 1 dosage error for morphine, 2 missed treatment continuations (pravastatin and isradipine). Patients were considered good adherent (N=4/18), minimal adherent (N=12/18) and not adherent (N=2/18). The main reasons for low adherence were notably: too many tablets to take, forgetfulness, and delays. No patients had any trouble for drug intake. Acetaminophen was the main self-medicating drug.

Conclusions: During the study period, some patients were not reconciled due to a lack of staff in the department, particularly at the beginning of the year. Usually, the studied population takes few drugs. Therefore, some patients took more than 10 drugs. In this study, drug adherence was often minimal as shown in a literature review that evaluates drug adherence in patients receiving hematopoietic stem cell transplantation[1]. This shows that reconciliation activity for these patients appears essential in order to review treatments, insist on medication adherence and to prevent the risks of drug-drug interaction, especially with the conditioning regimen. The data from this preliminary study need to be confirmed on a larger population.

[1] Morrison CF, Martsolf DM, Wehrkamp N, Tehan R, Pai ALH. Medication Adherence in Hematopoietic Stem Cell Transplantation: A Review of the Literature. Biology of Blood and Marrow Transplantation. avr 2017;23(4):562-8.

Clinical Trial Registry: /

Disclosure: /

CAR-based Cellular Therapy – preclinical

P105

Breaking PD-l1-mediated Resistance in anti-CD19 and anti-CD22 Car T Cells with PD-1/CD28 Fusion Receptors

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Background: Therapy with autologous T cells expressing an anti-CD19 chimeric antigen receptor (CAR) has been recently approved for patients with B-cell lymphoma and B-cell precursor acute lymphoblastic leukemia (BCP-ALL). Despite tremendous success in pediatric BCP-ALL, 40 to 50% of the patients do not experience long-term relapse-free survival after CAR T-cell treatment. Allogeneic stem cell transplantation (allo-SCT) is offered to selected patients after CAR treatment to prevent relapse.

Methods: To increase functionality of conventional anti-CD19 and anti-CD22 CAR T cells pre allo-SCT and protect the T cell from leukemia-mediated inhibition, a PD-1/CD28 fusion receptor was designed. Fusion receptors convert an inhibitory signal into an intracellular activation cascade. PD-1/CD28 anti-CD19 and anti-CD22 CAR T cells were functionally characterized and compared to conventional CAR T cells in terms of cytotoxic capacity, proliferation, activation and cytokine release after single and multiple contact with leukemic cells.

Results: The impact of prominent co-inhibitory immune checkpoint axes (such as PD-1/PD-L1) for relapse or non-response to CAR T-cell therapy is not yet fully understood. Bone marrow analyses of >100 BCP-ALL patient samples pre allo-SCT showed substantial heterogeneity in initial PD-L1 expression levels of leukemic blasts and the ability to up-regulate PD-L1 upon T-cell attack. Cytokine release of conventional 2nd generation anti-CD19 CAR T cells was significantly reduced after contact with a PD-L1 over-expressing ALL. We hypothesized that a PD-1/CD28 fusion receptor can increase functionality of conventional CAR T cells while protecting the T cell from leukemia-mediated inhibition. Anti-CD19 CAR T cells with PD-1/CD28 fusion receptors were generated and showed strong CD19-dependent cytotoxicity, proliferation, activation and cytokine release. No unspecific cytokine release mediated by the fusion receptor in absence of CD19 was detected. In presence of PD-L1, fusion receptor CAR T cells out-competed conventional 1st and 2nd generation anti-CD19 CAR T cells and released significantly higher levels of Th1 cytokines IFN-γ, IL-2 and TNF-α. PD-1/CD28 anti-CD19 CAR T cells were able to persist after >4-fold stimulation with leukemic cells and showed significantly increased long-term killing capacity and cytokine release compared to conventional CAR T cells after multiple stimulations. Superiority of CAR T cells with PD-1/CD28 fusion receptor was confirmed in an anti-CD22 CAR T cell model.

Conclusions: Anti-CD19 and anti-CD22 CAR T cells with PD-1/CD28 fusion receptor can increase functionality of conventional CAR T cells by circumventing leukemia-induced T-cell inhibition pre allo-SCT.

Disclosure: Nothing to declare.

P106

Allogeneic Chimeric Antigen receptor-invariant Natural Killer T Cells Exert Both Direct and Indirect Antitumor Effects through Host Cd8 T Cell cross-priming

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Background: Chimeric antigen receptor (CAR) T cells have shown impressive results in B-cell malignancies but, unfortunately, their widespread use is still limited by the logistical and financial burdens related to the need of generating autologous cell products. The development of universal allogeneic CAR T cells to be used off-the-shelf has faced major limitations, namely the risk of Graft-versus-Host-Disease (GvHD) induction and the rejection of the cells by the host immune system. Invariant Natural Killer-T (iNKT) cells are innate lymphocytes deprived of GvHD induction potential and displaying antitumor effects, both directly and indirectly, through enhancement of CD8 T cell responses. Preclinical studies in xenogeneic mouse models demonstrated the feasibility of using iNKT cells as a platform for CAR-based therapies, and two clinical trials are currently ongoing. In this work, we assessed the immunoadjuvant effect of allogeneic CD19-specific iNKT CAR on the host immune system.

Methods: We transduced murine iNKT cells from FVB/N (H-2K^q) mice with a CD19-specific CD28/CD3ζ CAR and assessed their antitumor effect in vitro and in vivo.

Results: CD19-iNKT CAR had a direct cytotoxic effect in vitro against the CD19+ A20 lymphoma cells and significantly improved survival of mice after administration to major histocompatibility complex (MHC)-mismatched, immunodeficient BALB/c (H-2K^d) Rag2$^{-/-}$ gamma-chain$^{-/-}$ mice receiving A20 lymphoma cells (2x10e4; Figure 1A) without inducing any signs of GvHD. To test the efficacy of iNKT CAR cells in the presence of host immune cells, we employed BALB/c mice receiving sublethal irradiation (4.4 Gy), resulting in only a partial and transient lymphopenia. The antitumor effect of allogeneic iNKT CAR cells was greatly enhanced suggesting the participation of host cells in the antitumor effect. Interestingly, the iNKT CAR effect was partially abrogated when we employed as recipients BALB/c BATF3$^{-/-}$ mice, in which CD8 T cell cross-priming is impaired as a result of the absence of BATF3-dependent CD103+ CD8a+ dendritic cells known to play a role in iNKT cell interactions with other immune effector cells. Moreover, co-administration of allogeneic FVB/N iNKT CAR with autologous BALB/c CD8 T cells at the time of transfer of T-cell-depleted autologous bone marrow cells and A20 cells into lethally irradiated BALB/c recipients resulted in a synergistic effect. To prove the induction of tumor specific CD8 T cell responses, host CD8 T cells were isolated at day 60 from sublethally irradiated BALB/c mice receiveing A20 cells and treated with iNKT CAR. CD8 T cells primed in the presence of iNKT CAR transferred into new lethally irradiated recipients receiving A20 cells and BM from syngeneic Rag2$^{-/-}$ gamma-chain$^{-/-}$ mice significantly increased survival. Due to their immuno-adjuvant effect on host CD8 T cells, low numbers of allogeneic iNKT CAR outperformed allogeneic conventional CAR T (Tcon CAR) when administered to sublethally irradiated BALB/c mice receiving A20 cells.

Conclusions: Collectively, these results demonstrate the potent immunoadjuvant effect exerted by allogeneic iNKT CAR cells toward the host immune system suggesting that iNKT CAR cells are an attractive off the shelf product for adoptive immunotherapy.

Clinical Trial Registry: N/A

Disclosure: Nothing to disclose

P107

NKG2D Chimeric Antigen receptor-expressing Lymphocytes Target Acute Myeloid Leukemia Cells

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Background: Chimeric antigen receptor (CAR) therapy is showing promising results in hematological malignancies. Since AML exhibits high heterogeneity and does not have specific differential antigens of the hematopoietic stem cell, using NKG2D-CAR cells could be an appropriate therapeutic strategy against AML. NKG2D receptor has a wide range of specific tumor cell ligands expressed in more than 80% of all tumors. Here we evaluate the anti-tumor activity of activated and expanded natural killer cells (NKAE) and T cells expressing an NKG2D CAR.

Methods: T cells and NK cells were isolated from the healthy donor´s PBMCs (n=5). NKAE cells were obtained by co-culture with subletally irradiated CSTX002 cells. Then, NKAEs and T cells were transduced with an NKG2D CAR. The efficiency of transduction was evaluated by flow cytometry. The cytotoxicity and toxicity on healthy tissues was evaluated by 4 hour europium release assay. The safety of NKG2D-CAR transduced cells was evaluated using CGH arrays.

Results: Both the AML cell lines and primary blasts from AML patients showed expression of the MICA/B and ULBPs-1 to 3 ligands (high expression of at least 3 of the 5 analyzed ligands). Four hour europium release assays revealed that untransduced T cells had higher cytotoxicity than untransduced NKAE cells at the same ratio (32:1) against both OCI-AML-3 cytarabine-resistant cell line (52.7% ± 14.2% vs. 32.5% ± 7.2%) as to the cytarabine-sensitive cell line (56.42% ± 5.6% vs. 50.14 % ± 5.9%). T cells showed a better transduction efficiency than NKAE cells at a multiplicity of infection (MOI) of 5. It was observed that both the CAR-NKAE cells and the CAR-T cells had higher cytotoxicity against these two lines (OCI-AML-3R and OCI-AML-3S) after being transduced with our NKG2D-CAR. However, the antitumor activity of CAR-T cells always remained superior to that of the CAR-NKAE for both OCI-AML-3R (54.26% ± 3.8% vs. 35.3% ± 6.7%) and for OCI-AML-3S (63.36% ± 3.5% vs. 54.3% ± 3.7%) cell lines, with a greater difference compared to drug resistant cells. The antitumor activity of CAR-T cells and

CAR-NKAE cells was always superior on the sensitive cell line. The antitumor activity of NKG2D CAR-T cells was evaluated against primary blasts from AML patients (n = 4), observing a nearly complete destruction of the blasts after 24 hours, at low target: effector ratio (4:1). CAR-T cells were highly positive to CD45RO and showed reduced expression of CD45RA. They showed high IL-2 production exhibiting a central memory phenotype. CAR-T cells exhibited some toxicity on third party PBMCs being null in the case of CAR-NKAE. CGH arrays studies showed no variation in the copy number, resulting from the introduction of the CAR. In vivo studies are ongoing.

Conclusions: AML cells could be target with an NKG2D-CAR. Primary NKAE cells and T cells can be transduced with an NKG2D-CAR at a very low MOI to enhance their antileukemic activity. CAR-T cells were able to completely destroy AML blasts. Although further studies are needed, these results show the potential of NKG2D-CAR T and NK cell therapy in AML.

Disclosure: Dean A. Lee declare.s an equity interest, advisory role, and intellectual property licensing to CytoSen Therapeutics and Kiadis Pharma, and advisory role with Caribou BioSciences and Courier Biosciences. Daniel J. Powell Jr. hold patents in the area of CAR T cell therapy. Rest of the authors have nothing to declare.

P108

Clinical-grade Manufacturing of ROR1 CAR T-cells using a Novel virus-free Protocol

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Background: Immunotherapy with T-cells that were modified to express a ROR1-specific chimeric antigen receptor (ROR1 CAR-T) has therapeutic potential in ROR1$^+$ malignancies in hematology and oncology. In toxicology studies in non-human primates, the adoptive transfer of ROR1 CAR-T did not disclose relevant clinical toxicity, encouraging the initiation of clinical trials to assess the safety and efficacy of ROR1 CAR-T therapy in patients with advanced ROR1$^+$ malignancies. In this study, we sought to establish and validate clinical-grade manufacturing of ROR1 CAR-T to enable a Phase I/IIa clinical trial. In particular, we sought to integrate virus-free gene-transfer based on Sleeping Beauty transposition into this manufacturing protocol to easily permit scale-up, and to reduce the regulatory burden associated with conventional viral gene-transfer.

Methods: Buffy coats or leukaphereses were obtained from healthy donors to perform protocol optimization (n=7) and scale-up runs (n=1). CD4$^+$ and CD8$^+$ T cells were isolated separately and stimulated with CD3/CD28 TransACT reagent (Miltenyi). T cells were transfected with mRNA encoding hyperactive Sleeping Beauty transposase (SB100X) and minicircle DNA encoding a pT2 transposon comprising the ROR1 CAR and an EGFRt marker gene using the MaxCyte GTx electroporation platform. Following transfection, T cells were expanded for 10-13 days in G-REX bioreactors and then harvested and formulated into the drug product at a 1:1 ratio of CAR-expressing CD4: CD8 T-cells. The drug product underwent comprehensive phenotypic, functional and genomic analyses as part of product qualification.

Results: The set of protocol optimization runs provided insights into the optimal timing between T-cell activation and transfection, as well as the amount of SB100X mRNA and ROR1 CAR minicircle DNA for transfection into the T-cells. On average, the stable gene-transfer rate at the end of the manufacturing process was 71% in CD4$^+$ (n=5) and 54% in CD8$^+$ T-cells (n=7). The average yield of CAR-expressing T-cells relative to the number of input T-cells was 12.6-fold for CD4$^+$ and 9.4-fold for CD8$^+$ after 12-15 days of expansion, with an average viability of 84% for CD4$^+$ and 82% of CD8$^+$ T-cells. The set of scale-up runs was performed with leukapheresis product from which 70x10^6 CD4$^+$ T-cells and 130x10^6 CD8$^+$ T-cells were further processed. At the end of the manufacturing process on day 12, there were 844x10^6 CAR-expressing CD4$^+$ and 857x10^6 CAR-expressing CD8$^+$ T-cells, which equals a 16-fold and 7.9 fold expansion relative to the input T-cell number, respectively. Overall, ROR1 CAR-T showed specific recognition and potent elimination of ROR1$^+$ target cells, as well as antigen-dependent cytokine production and productive proliferation. Experiments to determine the antitumor potency of the drug product in vivo and detailed genomic analyses are ongoing.

Conclusions: With this novel protocol, we aim to obtain the first manufacturing license for CAR-T in Europe that integrates our optimized approach with SB100X mRNA and transposon minicircle DNA for CAR gene-transfer on the MaxCyte transfection platform. The quality and yield of the drug product support the design and dose escalation of the proposed clinical trial with ROR1 CAR-T, and will serve as a blueprint for other CAR-T products from our pipeline.

Disclosure: Nothing to declare.

P109

Lentivirally and Alpharetrovirally Engineered CD19-specific Chimeric Antigen Receptor Natural Killer Cells are Highly Cytotoxic against Acute Lymphoblastic Leukemia

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Background: Autologous chimeric antigen receptor-modified (CAR) T cells with specificity for CD19 showed potent antitumor efficacy in clinical trials regarding relapsed and refractory acute lymphoblastic leukemia (ALL). Natural killer (NK) cells are cytotoxic lymphocytes that are capable to kill their targets in a non-specific manner and additionally do not cause GvHD. Therefore, using CD19-CAR-NK cells exhibits several advantages, such as safety in clinical use, possible allogenic settings and the potential to also attack heterologous leukemia cells which lost CD19. Here, we focused on the optimization of generating CD19-CAR-NK cells by viral transduction under feeder-cell free conditions.

Methods: Human NK cells were isolated from healthy donor peripheral blood mononuclear cells via CD56 negative selection. After a feeder-cell free expansion phase with interleukin 15 (IL-15), transductions were performed with a CD19-CAR encoding vector at different multiplicities of infection (MOI). To optimize gene modification different viral vector systems were compared using lentivirus and alpharetrovirus, pseudotyped with either VSV-G or RD114-TR. Finally, generated CD19-CAR-NK cells were tested in their ability to kill CD19-positive and CD19-negative cell lines.

Results: Transduction efficiencies of NK cells transduced with the RD114-TR pseudotyped alpharetroviral or lentiviral CD19-CAR vectors outperformed transduction with VSV-G pseudotyped lentiviral vector (lentiviral/RD114-TR: MOI 1: 10,9%, MOI 5: 24.0%, MOI 10: 27.3%; alpharetroviral/RD114-TR: MOI 1: 14.7%, MOI 5: 28.5%, MOI 10: 37.4%; lentiviral/VSV-G: MOI 1: 0.9%, MOI 5: 4.4%, MOI 10: 8.2%). As possible mechanism, dependent on IL-15, we observed a significant upregulation of the surface expression of ASCT-2 on the primary NK cells that is an entry receptor for RD114-pseudotyped vectors.

Remarkably, CD19-CAR-NK cells generated by RD114-TR pseudotyped retroviral vectors showed stable transgene expression and were able to expand almost as good as non-transduced (NT) NK cells over a time period of 14 days.

Independent of the transduction method, engineered CD19-CAR-NK cells showed an impressively high cytotoxic capacity against CD19-positive ALL cells compared to NT-NK cells; alpharetroviral/RD114-TR CD19-CAR-NK inducing 73.1% vs. lentiviral/RD114-TR CD19-CAR-NK cells inducing 74.7% vs NT- NK cells inducing 35.9% of cell death; E:T ratio 1:1 in 4 hours).

Conclusions: CD19-CAR-NK cells can be successfully generated under feeder-cell free conditions using different transduction enhancers and viral vector systems. Our data suggest the usage of Vectofusin-1 in combination with RD114-TR pseudotyped retroviral vectors to genetically modify NK cells to achieve sufficient amounts of highly cytotoxic transduced cells. These CD19-CAR-NK cells mediate high cytotoxicity and therefore may offer a new therapeutic option in the treatment of ALL. These insights will be transferable in CAR-NK-cell engineering to target different other malignancies.

Disclosure: Axel Schambach is an inventor on a patent describing alpharetroviral SIN vectors. Winfried S. Wels is an inventor on a patent describing chimeric antigen receptors with an optimized hinge region. The remaining authors have nothing to disclose.

P110

Novel Strategies to Enhance the safety of CAR T-cell Immunotherapy: The Imsavar Project

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Background: Adoptive immunotherapy with gene-engineered CAR-T-cells is a transformative treatment in hematology but can be associated with significant toxicity from e.g. cytokine release syndrome (CRS). Preclinical testing to assess CRS is not standardized and there is a strong medical need and desire to establish algorithms to assess the propensity of novel CAR-T-cell products and technologies to induce CRS and other toxicity. imSAVAR - immune safety avatar - is an EU Innovative Medicines Initiative (IMI) project that tackles this challenge in a joint academia-industry consortium and seeks to establish a framework and platform for assessing the utility of innovative non-clinical models and endpoints for enhancing the safety assessment of e.g. CAR-T cells.

Methods: imSAVAR is pursuing a 4-step approach: Step 1 comprises a systematic literature review on pathophysiology and clinical occurrence of CRS after CAR-T-cell therapy. Step 2 comprises a survey amongst academia and industry stakeholders to identify current gaps of existing and emerging preclinical test systems that are used to assess CRS. Step 3 is an open multi-stakeholder workshop that also engages EU and US regulators and patients to determine a roadmap for studies that establish a new set of non-clinical assays and endpoints that will subsequently be validated for their ability to enhance hazard identification, provide mechanistic insight, and help mitigate clinical safety concerns in Step 4.

Results: In Step 1 imSAVAR established a new conceptual map of CRS pathogenesis as an immune-related adverse outcome pathway (irAOP) comprising key molecular events (CAR target antigen engagement, signaling and T-cell activation) and cellular events (CAR-T-cell migration to tumor site, engagement with tumor cells in an immune synapse, secretion of pro-inflammatory mediators, activation of tissue resident and endothelial cells, and systemic inflammation). To each of these events, existing and emerging pre-clinical assays were allocated. In Step 2, a pilot survey was conducted with n=3 CAR-T-cell products from within the consortium. Encouragingly, the repertoire of novel test systems available in imSAVAR for evaluating CAR-T mediated cytokine release include in vitro co-culture assays of CAR-T with tumor cells, single-cell resolution molecular endpoints, in vivo humanized mouse models (e.g. NSG-3G) as well as microphysiologic organ-on-a-chip models. imSAVAR is preparing an open survey to collect data from n≥10 CAR-T and n≥10 other immune-oncology products to inform the research roadmap. All data will then be normalized and correlated with clinical data to identify optimal pre-clinical assays for enhancing the assessment and prediction of CRS.

Conclusions: imSAVAR has established an irAOP that will enable the development and validation of novel non-clinical assays that aim to enhance the characterization of CAR-T-cell associated cytokine release during pre-clinical development. This effort is ultimately anticipated to enhance the safety assessment of therapeutic CAR-T products, thus potentially accelerating patient access to CAR-T products with an enhanced therapeutic index. This CAR-T irAOP strategy forms part of imSAVAR's broader efforts to enhanced non-clinical safety assessment algorithms for additional immunomodulatory therapeutic modes-of-action (e.g. TCR-transgeneic T cells, bi-specific T-cell engaging antibodies; checkpoint inhibitor antibody combinations; Treg modulators), and a range of immune system-related toxicities (e.g. ICANS, infections).

Disclosure: Nothing to declare. This project receives funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 853988.

P111

Adult Peripheral Blood and Umbilical Cord Blood NK Cells Are Good Sources for Effective Car Therapy Against CD19 Positive Leukemic Cells

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Background: Among hematological cancers, Acute Lymphoblastic Leukemia (ALL) and Chronic Lymphocytic Leukemia (CLL) are the most common leukemia in children and elderly people respectively. Chimeric antigen receptor (CAR) therapy is one of the newest and more effective treatments against these cancers. CAR T cell therapy presents still some risks for the patients, including cytokine release syndrome (CRS) and neurotoxicity. We proposed NK cells from different cell sources for allogeneic CAR therapy.

Methods: 1. Enrichment and culture of NK cells from AB and CB. NK cells were isolated from AB or CB PBMCs by negative selection after magnetic cell isolation. Then, the NK cells were cultured with IL-2 and IL-15 for 8 days.

2. CD19-CAR lentiviral transduction to AB and CB NK cells

3. Functional assays facing CD19-CAR transduced and non-transduced AB and CB NK cells against CD19 expressing target cells. We measure CD107a marker in degranulation assays; and Calcein-AM released by target cells in cytotoxicity assays.

Results: 1. Percentage of the purity of the CD56+ NK cell population was 92.68±2.90 in AB and 91.46±5.14 in CB. NKp46 levels during the culture increase significantly from day 0 to day 7 in both cell sources. In fact, CB NK cells were significantly more stimulated than AB NK cells. We obtained more cells from the isolation from CB than from AB. During the first week, both sources expanded similarly; however, slightly higher fold expansion was observed after two weeks in CB NK cells

2. The mean AB CAR-NK transduction efficiency was 47.46 (range 62.6-20.2%; n=12) while CB CAR-NK transduction efficiency was 46.8 (range 79.7-18.1%; n=12). Seven days post-transduction the viability of AB and CB NK cells remained at 78.85% ± 10.18% and 76.2% ± 5.3%, respectively. In both cases, viability decreased over time until day 28. CAR expression shows a stable decrease of transduction from 40% to 20% with time as determined by flow cytometry every 7 days.

3. On one hand, when exposed to CD19 positive cells, AB CD19-CAR NK cells showed a significantly higher degranulation than non-transduced AB NK cells. On the other hand, when exposed to CD19 positive cells, CB CD19-CAR NK cells showed a significantly higher degranulation than non-transduced CB NK cells. We observed the same results when performing a cytotoxicity assay. AB CD19-CAR NK cells kill slightly better than CB CD19-CAR NK cells.

Conclusions: - CB NK cells present a more stable number of cells per unit than AB NK cells, and they can be stimulated with different interleukins in order to enhance the in vitro expansion, their killing activity and survival.

- Despite the difficulty of infecting NK cells, in our hands we obtain around 40-50% of infection with AB and CB NK cells with CD19-CAR.

- CD19 expressing target cells are killed more efficiently by AB and CB NK cells transduced with CD19-CAR than by non-transduced AB and CB NK cells.

CD19-CAR infected NK cells from AB and CB kill similarly CD19 expressing target cells. However, we observe a higher degranulation of the AB NK cells.

Disclosure: Nothing to declare.

P112

Tyrosine Kinase Inhibitor Followed by Cart Therapy for the Treatment of Relapsed Philadelphia chromosome-positive B-cell Acute Lymphoblastic Leukemia after Allogeneic Hematopoietic Stem Cell Transplantation

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Background:

Philadephia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) is a distinct type of ALL, which has a high incidence of adult patients and a dismal poor prognosis. Resistance/relapse(r/r) after allogeneic hematopoietic stem cell transplantation (allo-HSCT) remain a significant challenge. Once relapsed, almost patients are resistant to the TKI because T315I mutation of ABL-kinase domain mution (AKDM).

Chimeric antigen receptor T-cells (CART) has shown a higher complete remission(CR)rate in r/r B-ALL patients and has a good security.

So we sequentially applied CART and TKI therapy to treat the Ph+ALL patients relapsed after allo-HSCT and observed the effect.

Methods: From January 1,2018 to June 31,2019, fourteen adult Ph+ALL patients relapsed after allo-HSCT were enrolled. CD19 and/or CD22 expression on blasts and AKDM were detected by flow cytometry(FCM) and polymerase chain reaction(PCR), respectively.

Recipient-derived donor T cells were collected and cultured CART cells, which were transfected by lentiviral vectors encoding the CAR composed of CD3zeta-4-1BB.

ALL patients received fludarabine with or without cyclophosphamide before CART cell infusion, some patients received othder chemotherapy or TKI based on the precondition because high disease burden or extramedullary disease (EMD). CART cell dose was 0.5-2×105/kg (CD19-CART) and 1-2.8×105/kg (CD22-CART). After CART cell infusion, CART cell, cytokines were measured on D7, D9, D11 etc. and other days depending on the patient's condition. We evaluated Bone marrow(BM) and cerebrospinal fluid (CSF)morphology, minimal residual disease (MRD)by FCM and BM BCR-ABL1fusion transcripts by real-time quantitative PCR(QPCR) on D30, EMD was examined by imaging examination and once every month later.

Once these patients acquired CR, TKI treatment was followed according to the AKDM and followed up to November 26,2019(6-22 months).

Results: Fourteen patients were aged 17 to 55 years (medium 29), including ten P190, three P210, one special BCR-ABL1 and nine hematological relapse, two FCM-MRD+, two BCR-ABL1+:one with multiple EMD, one only central nervous system leukemia(CNSL). After HSCT, twelve patients relapsed within 12 months(1.5-12 months), two patients relapsed in the 28th and 48th month. Twelve patients had received chemotherapy, TKI, donor lymphocyte infusion (DLI), murinized CD19-CART, radiotherapy before, but all failed;Two patients didn't received any therapy.

Thirteen patients were detected AKDM:five T315I, one T315I and Y253H, one T315L, one Y317L, five no mutation(one T315I before HSCT). One patient didn't detect AKDM because blast cells was not enough.

After first CART therapy, two patients had no effect and died, one patient gave up and died. Another 11(100%) patients all achieved CR and MRD negative(CRMRD-) with incomplete blood count recovery(CRiMRD-), and 10/11(90.91%)patients achieved molecular complete response (CRmi) and all of them hadn't CNSL. ALL these patients received other therapies:three patients received second CART and one then received DLI, TKI was used in eleven patiets based on their AKDM results. To the present, eleven patients remained CRm:two patients stoped use TKI in February and July 2019, one patient received second HSCT in May 2019.

Cytokine release syndrome(CRS) occurred 9/14(64.29%) patients after the first CART:8 grade I, 1 grade III. Only one patient exhibited CAR T-cell-related encephalopathy syndrome (CRES) who had CNSL before CART, and no fetal graft-versus-host disease(GVHD)occurred.

Conclusions: CART therapy for Ph+ALL patients relapsed after HSCT is efficacy

and secure, once they achieved CR after CART therapy, sequencial TKI therapy may prolong the overall survival, leukemia free survival.

Disclosure: Nothing to declare.

Cellular Therapies other than CARs

P113

Abstract already published.

P114

Adoptive Immunotherapy of Refractory Viral Infections after Allogeneic HSCT: An Academic Network Framing the use of an Atmp under Hospital Exemption

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Background: Viral infections are major complications of Hematopoietic Stem Cell Transplantation (HSCT). As efficacy of anti-viral drugs is limited in absence of immune reconstitution and often associated with severe side effects, infusion of Virus-Specific T cells (VSTs) becomes a promising alternative treatment for viral infections and diseases after HSCT. We previously performed a successful phase I/II clinical trial and secondarily obtained an ATMP under hospital exemption authorization from the French regulatory agency for the preparation of VSTs (especially ADV-STs) for all the clinical centers in need. A national group was created under the aegis of the Francophone Society of Bone Marrow transplantation and Cell Therapy (SFGM-TC) to analyze, validate and follow the different requests. We present here the results that have been collected until 2016.

Methods: We previously demonstrated the feasibility of isolating ADV-STs from donors using the IFNg-capture system from Miltenyi biotec followed by immunomagnetic selection on the CliniMACS device (Aissi-Rothé et al, 2010; Qian et al, 2017). Since we obtained the ATMP authorization, we have treated patients with an infusion of polyclonal ADV-STs (n=8) or CMV-STs (n=4) or EBV-STs (n=2) generated by a 6-hour ex vivo stimulation with an appropriate peptide pool (PepT-ADV5 Hexon, PepT-CMV pp65, PepT EBV Select, respectively, Miltenyi Biotec) of leukapheresis collected from their original stem cell donor or more often from third party haploidentical donors, followed by isolation of IFNg producing cells.

Results: We report more than 40 requests to the group, 75% of them in 2019, from different French and Belgium centers followed by 8 refusals, the generation of 14 VST preparations and the infusion of patients (4 months-65 years) with viral infection disease. They received a mean of 0.96 10^4 CD3-IFNg+ cells/kg (range: 0,042 to 1.436 10^4). In vivo expansion of transferred VSTs was observed from day 15 to 60 following adoptive transfer infusion associated with viral

load decrease or clearance in more than half of the patients. During the 3 month-follow-up, 4 patients experienced failure of the treatment with a persistent increase of viral load. Neither de novo GVHD, nor side effects were observed. Reactivation of grade I aGVHD occurred in 2 patients in the month following infusion and in 3 patients after D45 (grade II and IV). Unfortunately, eight patients died, 4 related to persistent viral infection or disease. However, none of the responders experienced a viral-associated mortality.

Conclusions: Adoptive transfer of VSTs is a feasible and well-tolerated therapeutic option, representing a fast and efficient procedure to achieve reconstitution of antiviral T-cell and decrease or clearance of viral load. However, today this is a last chance therapy and viral load is often over 6.5 log (4 patients) when infusion is performed, not giving VST time to expand and be efficient. The French organization, under the aegis of SFGM-TC, is very secure and reactive and contributes to encourage clinical centers to initiate their request earlier.

Disclosure: Danièle Bensoussan, start up StemInov, CSO

P115

How to Benefit from Exhaustion: patient-derived Inhibited T Cells as a Novel Source of tumor-reactive T Cell Clones

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Background: A notable percentage of blood cancer patients who undergo Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT) still suffers a dismal prognosis; this therapeutic gap could be filled by Adoptive T cell therapy, but its exploitation is still limited by the incomplete knowledge of tumor-specific T cells dynamics in vivo and by the difficulty to isolate such T cell specificities for therapeutic purposes.

Methods: To visualise and purify tumor-specific T cells ex vivo, we screened circulating cells at 30,60,90,120,180 and 365 days after alloHSCT in N=35 patients affected by blood malignancies with a 18-colour Flow Cytometry panel including fluorescent MHC-I complexes loaded with Tumor-Associated Antigen (TAA) peptides or with a viral peptide. Together, we followed T-Cell Receptor (TCR) clonal dynamics by cell sorting and sequencing.

Results: TAA-Specific T cells were found circulating in the patients' peripheral blood, as soon as 30 days after alloHSCT. By exploiting high-dimensionality un-biased analytical tools we dissected their phenotype, showing that they express multiple inhibitory receptors at higher levels if compared with either the total CD8 T cell population or viral-specific T cells, independently from major clinical variables (disease status at transplant, disease type, GvHD incidence). The inhibitory signature was the most pronounced 4 months after alloHSCT, and was followed by a substantial contraction of the pool of TAA-specific memory T cells.

We also took advantage of cell sorting to isolate and expand TAA-specific T cells. We established a rapid, highly specific protocol that isolated 24 tumor-specific T cell colonies from n=13/20 screened patients, each one enriched for a single TCR clonotype identified by RNA sequencing. When challenged with peptide-pulsed targets, such ex vivo clones were poorly responsive but when the TCR sequences were cloned into lentiviral vectors and transferred in T cells after Crispr/Cas9 disruption of the endogenous TCR (TCR-edited lymphocytes), cells proved highly efficient and specific in lysing matched pulsed targets (fig.1A). This observation, linked with the previous phenotypic analysis, suggests that TAA-specific T cells are circulating in vivo but are exhausted. We thus tried to broaden the search of Tumor-reactive T cell clones by exploiting the exhaustion signature to purify a T cell subset enriched with anti-tumour reactivities. We sorted T cells from 3 patients affected by Acute Myeloid Leukemia (AML) on the basis of the inhibitory receptors (IR) expression and stimulated both IR+ and IR- cells with matched Leukemic Dendritic Cells (LDC). Serial LDC stimulations promoted the expansion of dominant clones over time in the IR+ but not in the IR- fraction and IR+ T cells proved superior in killing autologous AML blasts in vitro. Again, dominant TCRs were identified in IR+ cultures from the first patient, and TCR-edited lymphocytes efficiently and selectively recognized autologous blasts (fig.1B).

Conclusions: Our findings shed some light on the in vivo dynamics of tumor-specific T cells and introduce two models for the isolation of tumor-specific TCRs, one requiring the knowledge of the target peptide, the other exploiting the IR signature to discover novel tumor specificities.

Disclosure:

Chiara Bonini recieves Resarch funds from Intellia Therapeutics and Immudex, and she´s consultant for Intella Therapeutics, Novartis and Molmed.

The other authors declare. no relevant conflict of interest

P116

Efficient Crispr/Cas9-mediated Inactivation of the

Glucocorticoid Receptor for antigen-specific T-cell Immunotherapy

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Background: Adoptive immunotherapy (AI) with pathogen-specific T cells (pSTs) is a promising alternative to pharmacotherapy for the treatment of opportunistic infections after allogeneic hematopoietic stem cell (allo-HSCT) or solid organ transplantation. However, clinical implementation of AI is limited to patients receiving either low dose or no steroids, a prerequisite for optimal T-cell function, practically excluding the most susceptible to infections patients from the benefits of AI. **Aims**. We evaluated the impact of dexamethasone (DEX) on primary T cells and developed a CRISPR/Cas9 system to genetically disrupt the glucocorticoid receptor (GR) in lymphocytes and confer resistance to steroids, in order to ultimately develop steroid-resistant pSTs.

Methods: The impact of DEX on T cell proliferation, phenotype and apoptosis was evaluated in human OKT3 blasts generated by stimulating peripheral blood mononuclear cells through CD3 and CD80 ligation. To inactivate the GR gene, 10 guide RNAs (gRNAs) were prepared to target different genomic sequences corresponding to various domains of the GR (a transcription start site, and exons 2, 3, 4 and 5) and delivered separately into the T2 lymphoblastic cell line using lentiviral vectors. Cells transduced with an "empty" viral vector expressing Cas9 but no gRNA were used as negative control. The resistance of T2 cell line to glucocorticoids was assessed as cell viability by trypan blue exclusion. The on-target inactivation of the GR in T2 cell line was measured by western blot and T7 assay.

Results: A 3-day exposure of OKT3 blasts to DEX negatively impaired the proliferation of stimulated primary T cells and induced early apoptosis over the "no DEX" condition ($p=0.001$, $p=0.01$ respectively). These effects correlated with a DEX-induced upregulation of T regulatory cells ($p=0.0002$). DEX also upregulated PD-1 and CTLA-4, the major coinhibitory molecules in antigen-specific immune responses, over the "no DEX" condition ($p< 0.05$). Then, in order to render cells steroid-resistant, T2 cells were transduced with lentiviral vectors encoding Cas9 and 10 different gRNAs targeting GR and subsequently incubated in the presence or absence of DEX. T2 cells edited with 7/10 single gRNAs, presented normal proliferation on DEX treatment as contrasted to their untreated counterparts and the empty vector-transduced cells, suggesting functional DEX-resistance. The on-target GR inactivation in T2 cells was confirmed by both western blot and T7 assay. Among tested functional gRNAs, the optimal gRNA was selected for further studies, on the basis of high GR disruption efficiency and low off-target activity.

Conclusions: Overall, we provide a series of gRNAs to CRISPR/Cas9-disrupt the GR and ultimately generate steroid-resistant pSTs in order to offer the benefits of AI to the most vulnerable to infections patients, as those with graft-versus-host-disease receiving high-dose steroids post allo-HSCT.

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P117

Comparison of Outcome post-second Allogeneic Hematopoietic Cell Transplantation Versus Donor Lymphocyte Infusion in Allogeneic Hematopoietic Cell Transplant Patients

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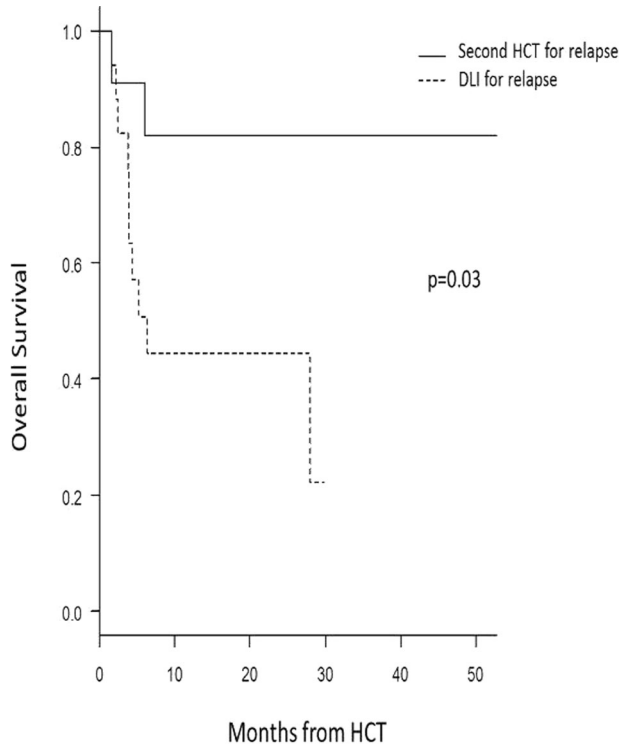
Background: Allogeneic hematopoietic cell transplantation (HCT) is potentially curative for a variety of benign and malignant hematological disease, however may be complicated by disease relapse or graft loss/poor graft function. Both second allogeneic HCT and donor lymphocyte infusions are utilized in the management of both complications. The purpose of the present study is to compare outcomes following both interventions in a single center cohort of patients transplanted over the last five years.

Methods: We retrospectively investigated 65 patients in total, 34 (52%) underwent second allogeneic HCT and 31 (48%) received donor lymphocyte infusions (DLI), from June 2011 to November 2018.

Results: Median patient age at the time of the post-transplant intervention was 51 years (range 19-72). Second HCT was performed for disease relapse in 11 patients (5 of which were transplanted for AML) and for graft failure (GF) in 23 patients (primary in 6 and secondary in 17 patients). Donors for second HCT were related (n=10), unrelated (n=18) and haploidentical (n=6), the same donor was used in 20 (59%) patients. At second HCT, the HCT-CI was 0-2 for 22 patients (65%) and ≥3 for 12 patients (35%). Concerning DLI patients, this was performed for relapse for 17 patients (8 of which were transplanted for AML) and for secondary GF or chimerism loss in 14 patients. Donors for DLI were related for 13 patients, unrelated for 16 patients and haploidentical for 2 patients. KPS at first DLI was 90-100% for 20 patients (65%) and 70-80% for 11 patients (35%). Median number of DLI administered was 2 (range 1-11).



[Figure 1: Overall survival with second transplant vs donor lymphocyte infusion for relapsed patients]

Median follow-up of survivors following intervention was 18 months (range 3-66 months). Univariate analysis demonstrated 2-year overall survival (OS) of 50% (95%CI 37-62%) for the entire cohort, while 2 year OS was identical between all second transplant patients and DLI patients (50% for both groups, p=0.9%). For second HCT patients, 2-year OS was 82% (95%CI 45-95%) and 35% (95%CI 17-54%) for relapse as an indication versus GF respectively (p=0.01). For the DLI patients, 2-year OS was 44% (95% CI 20-66%) and 56% (95%CI 27-78%) for relapse as an indication versus GF/loss of chimerism respectively (p=0.64). For disease relapse as an indication, second HCT was significantly superior to DLI (p=0.03, Figure 1). Multivariable analysis for second HCT patients demonstrated age (HR 1.04, 95%CI 1.00-1.07, p= 0.03) and donor type (HR 0.17 for related donor, 95%CI 0.04-0.75, p=0.02) to independently predict OS. For DLI, multivariable analysis demonstrates KPS at the time of the first dose of DLI as the predominant predictor of survival (HR 0.89, 95%CI 0.82-0.96, p=0.002).

Conclusions: Second allogeneic HCT demonstrates superior survival when performed for disease relapse post-transplant compared to DLI. In contrast, second HCT for graft failure results in poor long-term survival. Second allogeneic HCT should be preferred as a reasonable treatment option for patients that relapse post-transplant and achieve pre-second HCT remission.

Disclosure: Nothing to declare.

P118

Automated Application for Depletion of Tcrab$^+$, CD19$^+$ and CD45RA$^+$ Cells from Apheresis Products using the Clinimacs Prodigy®

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Background: Major complications of allogeneic stem cell transplantation are GvHD and infections. Ex-vivo T cell depletion (TCD) can effectively prevent GvHD, however it may prolong immune reconstitution and increase the risk of infections. Depletion of TCRab$^+$ T cells combined with the transfer of CD45RA$^-$ donor memory T cells may ameliorate the infection risk and simultaneously decrease the risk of GvHD. Here, we report the development of a single, automated manufacturing process on the CliniMACS Prodigy® to generate personalized grafts providing a TCRab-depleted stem cell product and a memory T cell product.

Methods: Currently, the combined depletion of TCRab$^+$/CD19$^+$ cells and the depletion of CD45RA$^+$ cells exist as two separate applications on the CliniMACS Prodigy. The novel integrated CliniMACS Prodigy LP-TCRab-19-45RA depletion process merges these two strategies in one application

performed in one tubing set, namely CliniMACS Prodigy TS 320. Depending on the desired cell composition of the graft, the user can choose to perform either:

· sequential depletion of $CD45RA^+$ and $TCRab^+$ cells with or without simultaneous depletion of $CD19^+$ cells,

· a depletion of $TCRab^+$ cells with or without simultaneous $CD19^+$ cells or

· a $CD45RA^+$ cell depletion only.

All TCRab depletion cases (with or without simultaneous depletion of $CD19^+$ cells) can be performed in normal or large scale, depending on the number of total WBC, $TCRab^+$ and $CD19^+$ cells. The memory T cell product and the stem cell product are collected in separate bags and can be combined to a single cell product, according to each patient's need (personalized graft).

The new application software effectively depletes $2.4x10^9$ $CD45RA^+$ cells from up to $6x10^9$ total WBC, and $48x10^9$ total $TCRab^+$ cells plus $15x10^9$ total $CD19^+$ cells from up to $120x10^9$ total WBC.

Results: In-house evaluation runs (total n = 41, 10 mobilized and 31 non-mobilized apheresis products) resulted in comparable values for depletion, yield, recovery, and WBC viability of the target products regardless of the application case performed. The mean log depletion achieved for the TCRab±CD19-depleted products (n = 41) was 4.5 (range 3.5-5.2) for $TCRab^+$/$CD45RA^+$ cells and 3.4 (range 2.6-4.3) for $CD19^+$ cells with a stem cell viability over 90% and mean yield of 81%. In the CD45RA-depleted products (n=31) a mean log depletion of 5.4 (range 3.8-6.4) for $TCRab^+$/$CD45RA^+$ cells was obtained.

The duration of CD45RA depletion takes between 1.5-1.7 hours, while the duration of TCRab±CD19 depletion ranges between 5.1-8.3 hours. Finally, the combined TCRab ±CD19/45RA depletion needs 6.7-10.3 hours to complete, depending on total cell numbers. Importantly, input of a defined process end time is possible.

Effective quality control panels and express modes for MACSQuant® Flow Cytometers enable easy and accurate monitoring of the entire cell manufacturing process.

Conclusions: In summary, the novel automated CliniMACS Prodigy LP-TCRαβ-19-45RA depletion process is capable to deplete $CD45RA^+$, $TCRab^+$ and $CD19^+$ cells efficiently from apheresis products with a mean yield of 81% for $CD34^+$ cells. The performance verification and submission to an European notified body for CE marking as medical device application are the important next steps.

Clinical Trial Registry: n/a

Disclosure: n/a

P119

Abstract already published.

P120

Good Response Rates of WJ-MSC, Comparable to BM-MSC, in the Treatment of Refractory GVHD

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Background: Acute graft-versus-host-disease (aGVHD) is one of the main complications derived from an allogeneic hematopoietic progenitor cell transplant (HPCT). First line therapy is based on the use of steroids but many patients are refractory. Due to the immunomodulatory characteristics of multipotent mesenchymal stromal cells (MSC) this cell type have been used with success in the treatment of refractory aGVHD. Wharton Jelly's (WJ) is a new source of MSC with advantages for large-scale production and standardization. The aim of this study is to evaluate the ability of WJ MSC's to improve refractory aGVHD compared to MSC's obtained from Bone Marrow (BM).

Methods: Retrospective study of patients with refractory aGVHD treated with MSC produced at Banc de Sang I Teixits between (2017-2019). All patients received at least two doses of MSC (1E6 MSC/kg of patient body weight per dose). To obtain and process the cells, an approved IND was followed in our production facilities using BM-MSC's (PEI 13-081) or WJ-MSC's (PEI 16-017). Patients were treated in 4 hospitals of Barcelona area, after receiving corticosteroids and second or further lines of alternative drugs. Upon request by transplant center, MSC samples were released for a therapy scheduled for infusion on days 1, 4, 11 and 18 using a compassionate schema.

Results: Eighteen patients (12 pediatric and 6 adults) have been treated during this period. Table 1 shows diagnosis, graft source, GVHD grade and organ involvement and MSC source. The first MSC infusion was performed on median 5 months after the onset of the GVHD (range 0.6 to 46). There were no adverse reactions related to the MSC infusions. Two patients died before day 7 due to sepsis and viral infection not related to the procedure. They received only 2 doses of therapy and were not included in the survival analysis. Over 16 patients, five

patients died due to GVHD progression, relapse or infection. Remarkably, ten patients (63%) have responded to treatment, and five (31%) achieved complete response. Responders achieved high overall survival. The median response time was 14 days after the first MSC infusion (range, 7-28 days). Evaluating performance status (Karnofsky/Lansky scale) median improvement was in day 21 (range, 7-49 days). One responder died later on time, due to sepsis after achieving CR. According to the source of MSC, 7 of 12 evaluable patients that were treated with WJ-MSC responded to treatment (58%), comparable to 3 of 4 from BM-MSC (75%).

Conclusions:

MSC treatment resulted in a safe procedure with a response rate of 63% of heavily pretreated patients. WJ-MSC showed similar results than BM-MSC. These results show the feasibility and support the proposal of a prospective trial in order to demonstrate efficacy in this setting.

Diagnosis	Acute leukaemia (12) Non malignant diseases (6)
Graft source	Related (5) Unrelated (9) Cord blood (4)
GVHD grade	I (2) II (1) III (8) IV (7)
Organs Involved	Skin (9) Gut (15) Liver (7)
MSC source	Wharton Jelly (12) Bone Marrow (6)

[Table 1]

Disclosure: Nothing to declare.

P121

An "all in one" T-cell Product from non-transplantable Cord Blood Units for Virus- and leukemia-specific T-cell Immunotherapy

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Background: Leukemic relapse and opportunistic viral infections represent the major causes of morbidity and mortality post allogeneic hematopoietic cell transplantation (allo-HCT). T-cell immunotherapy with chimeric antigen receptor T-cells (CAR-Ts) is currently the spearhead of research in refractory hematological malignancies, however, CAR-Ts for myeloid leukemias lag well behind CAR-Ts for B-cell lymphoid malignancies, mainly due to the lack of an appropriate, targetable antigen. On the other hand, while immunotherapy with non-genetically engineered virus-specific T cells has been shown to successfully control viral infections post-allo-HCT, single-epitope leukemia-specific T-cells (Leuk-STs) targeting the less immunogenic leukemia-associated antigens (LAAs) have met limited clinical success. **Aim**. By adapting our previously developed protocol of generating multivalent Leuk-STs, targeting multiple epitopes of various leukemic antigens by stimulation with overlapping peptides spanning the whole proteins, we here aimed to generate a non-engineered, "all-in-one", T-cell product from Non-Transplantable Umbilical Cord Blood Units (NT-UCBUs), called LEukemia-VIrus-specific T-cells (LEVIS), which simultaneously targets four viruses and two common LAAs.

Methods: Matured CD34+-derived dendritic cells from NT-UCBUs were stimulated with both leukemic [Wilms tumor protein (WT1) and Preferentially Expressed Antigen in Melanoma (PRAME)] and viral [EBNA1, LMP2 and BZLF1 (EBV); IE1 and pp65 (CMV); Hexon and Penton (AdV) and Large-T and VP1 (BKV)] pepmixes and used to "educate" autologous, naive T-cells.

Results: By reclaiming disqualified for allo-HCT NT-UCBUs and using our approach, we have been consistently obtaining clinical doses of LEVIS (CD3+ cells: 1.01 ±0.2x10^8). The resultant T-cell products are polyclonal, containing both CD4+ and CD8+ T-cell subsets (39±2% and 50 ±2%, respectively), expressing effector memory (CD45RA-/CD62L-: 47.36±5%) and effector memory RA markers (CD45RA+/CD62L-: 48.50±4%), while containing insignificant amount of naïve and regulatory ($CD4^+/CD25^{high}$) T cells. LEVIS demonstrated high specificity against all targeted antigens [spot-forming units (SFC)/2x10^5 cells: CMV: 311±149, EBV: 319±111, BKV: 245±122, AdV: 432±32, Leuk: 553±257], similar to that conferred by Leuk-STs alone, suggesting successful "training" of naïve T cells and lack of antigen competition by the addition of immunodominant viral antigens. Importantly, LEVIS demonstrated low expression levels of Programmed cell Death protein-1 (PD-1) and barely detectable Cytotoxic T-Lymphocyte Associated Protein-4+ (CTLA-4), which remained stable throughout the culture, suggesting that persistent antigen exposure did not impair their Th-1-polarized function in vitro, an effect that could be translated into anti-leukemic and antiviral response after infusion.

Conclusions: Overall, by "recycling" NT-UCBUs, we provide the potential for future banking of LEVIS, to serve as third-party, "off-the-shelf", multipotent T-cell products, thus further optimizing adoptive immunotherapy and improving the outcome of allo-HCT.

Disclosure: Nothing to declare.

P122

Clinical Success of Granulocyte Transfusions in Adult Neutropenic Patients after Chemotherapy and/or Allogeneic Transplantation - Time Matters!

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Background: For decades, granulocyte transfusions (GTX) have been performed to treat neutropenic haematological patients with infectious complications. Nevertheless, the clinical efficacy of this cellular therapy is remaining controversial.

Methods: We performed a risk factor analysis in a large cohort of patients who received GTX between 2004 and 2014 at the University Hospital Dresden. Demographical data, diagnosis and outcome of the patients were registered. Among other parameters, type and state of the infection, dosage of the transfused granulocyte concentrates, and adverse effects had been recorded during each GTX cycle. GTX during an active infection were considered as "therapeutically" and GTX in patients who previously had survived life-threatening infections were considered as "prophylactically". We evaluated overall survival and day-30-mortality from infection according to several risk factors. Treatment-cycle- or product-related variables were modeled as time-dependent variables and analyzed with Cox regression with time-dependent covariate. Cumulative incidences of infection related deaths were estimated according to the methodology of Gray. Competing risk was death from other causes than infection. The cause specific hazard for death due to infection was estimated with Cox regression.

Results: A total of 187 patients received 886 transfusions within 232 treatment cycles. The mean dose was $8.05 \cdot 10^{10}$ neutrophil cells (SD =2.5) per transfusion. In 194 of 232 cycles (84 %) granulocytes were transfused therapeutically, in 37 cycles (16 %) prophylactically.

Patient-related factors had impact on clinical outcome. State of the infection appeared to be the most important factor: Patients with septicemia had significantly lower treatment success than patients with localized infections with a significantly lower Overall survival (HR 2.4; CI: 1.68 - 3.52; $p < .001$) and a 4.8-fold higher cause specific hazard for infection-related death within 30 days after the first GTX (CI: 2.48 - 9.32; $p < .001$). Analysis of surrogate parameters for the severity of infections supported these findings (e.g. patients in ICU, patients requiring ventilation support, bacterial versus mycotic infections or a combination of both).

Among transfusion-related factors, early administration of GTX was favorable for therapeutic success. Patients with prophylactic GTX had a significantly lower 30-day-infection-mortality than patients with therapeutic GTX (HR 0.14; CI: 0.02 - 0.94; $p = .044$) and a slightly better overall survival (HR 0.71; CI: 0.38 - 1.27; $p = .238$). Patients who received $\geq 4 \cdot 10^{10}$ granulocytes per transfusion had a significant lower 30-days-infection-related mortality (HR 0.76; CI: 0.63 - 0.92; $p = .005$). Transfusion reactions were seen in 60 out of 886 (7 %) transfusions. Our analysis revealed no difference in the frequency of side effects with respect to the amount of granulocytes per transfusion (HR 0.95; CI: 0.67 - 1.34; $p = .756$).

Conclusions: Our data indicate that patients receiving GTX at an early stage of their infection seem to particularly benefit from this treatment. High dose GTX seem to be advantageous, In our cohort, GTX proved to be a safe approach without any severe side effects.

Nevertheless, these retrospective data are limited and should be validated in further prospective controlled studies.

Disclosure: Nothing to declare.

P123

Impact of long-term Cryopreservation of Autologous Hematopoietic Stem Cells Products

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Background: Freezing and storage of hematopoietic stem cells (HSC) graft are keys steps of therapeutic intensification process by autograft. No maximum storage period is defined in literature and less data are available concerning the quality of graft cryoconserved for a long duration. Now a day, only the notion that storage duration more than 15 years may be potentially harmful was advanced by 2014 SFGM-TC guidelines. (Calmels and al, Pathologie biologie 2014; 62: 221-225)

Methods: Fifty seven autologous grafts with long term storage (more than 5 years) were thawing in our study and were:

- evaluated by a quality control using Stem-Kit (Beckman Coulter, France) by flow cytometer including: viability/total nucleated cells count (TNC), viability/number of CD34+ cells, hematopoietic reconstitution evaluation (CFU-GM)
- compared with 60 short-term storage autologous grafts (less than 2 years) thawing routinely in laboratory.

Results: By comparison with routinely thawing graft quality criteria, we observed that CD34+ yield ($p< 0.0001$),

TNC yield (p = 0.037) and number of CFU-GM/kg (p< 0.0001) were negatively impacted, based on lengthening of storage period. Moreover, we highlighted a significatively decreased of clonogenicity linked with increase graft storage duration (p=0.02).

Conclusions: Autologous graft long-term cryopreservation has a clear impact on product quality, in view of decreased CD34+ cells as well as CSH functionality in vitro. No national consensus defining cryopreservation modality and grafts storage, capable of influencing positively or negatively grafts quality, notably during long term conservation.

Disclosure: Nothing to declare.

P124

Optimizing Lentiviral Vector Transduction to Gene Modify Cord Blood CD8$^+$ T Cells for off-the-shelf Adoptive Cell Therapy to Treat Cancer

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Background: Adoptive T cell therapy utilizing autologous T cells has shown promising results for cancer treatment. However, the limited numbers of tumor associated antigen (TAA)-specific T cells and the functional aberrancies due to disease progression or treatment remain factors that may significantly limit the success of the therapy. The use of allogeneic T cells as an off-the-shelf therapy overcomes these issues, but requires gene-modification to induce a robust and specific anti-tumor effect. Umbilical cord blood (CB) might be particularly suited for this purpose; CB T cells are readily available in cord blood banks, show low toxicity, high proliferation rates and increased anti-leukemic effect upon transfer. Moreover, CB T cells can be used as combinational therapy in the hematopoietic cell transplantation setting to prevent minimal residual disease, relapses, and completely eradicate all tumor cells. However, combining anti-tumor gene modification and preserving advantageous immunological traits of CB T cells represents a major challenge for the harmonized production of T cell therapy products.

Methods: CB CD8$^+$ T cells were isolated from fresh CB donors, subsequently expanded and activated. CB CD8$^+$ T cells were transduced with lentiviral vectors (LV) expressing GFP and WT1-TCR, in order to compare methods, culture media, promoter strength and use of transduction enhancers. Analysis of immune-phenotype was performed in CB CD8$^+$ T cells and PB CD8$^+$ cells after isolation, expansion and transduction.

Results: In this manuscript we describe an efficient protocol to expand and transduce CB CD8$^+$ T cells using LV, achieving an efficiency up to 83% of transduced cells. The protocol was established by optimizing the timing of LV treatment, selection of culture media, and application of different promoters. We confirmed LentiBOOST as a non-toxic transduction enhancer, however its use decreased the proliferation capacity of the T cells. Finally, we show that CB CD8$^+$ T cells were more amenable to LV transduction than PB CD8$^+$ T cells, and that the immune phenotype of the two cell sources were remarkably different with respect to the expression of inhibitory receptors and maturation markers.

Conclusions: We show an efficient method of gene modification of CB CD8$^+$ T cells using LV, which is especially useful for off-the-shelf adoptive cell therapy products for cancer treatment, especially in post hematopoietic cell transplantation setting.

Disclosure: Nothing to declare.

P125

Donor Lymphocyte Infusion after Allogeneic Hematopoietic Stem Cell Transplantation. Single Centre Experience

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Background: Donor Lymphocyte Infusion (DLI) is often used to treat relapsed haematological malignancies after allogeneic stem cell transplantation. DLI is an immune-mediated therapy, mainly driven by the antitumor effect of donor T cells which can, in part, augment the graft-versus-tumor effect. However it can sometimes induce fatal adverse events such as severe graft-versus-host-disease (GVHD) and infectious complications.

Methods: We retrospectively analyzed 72 patients who received DLI for treatment of relapsed haematological malignancies, who had been allotransplantated in our centre between 1994 and 2018. Median age of 43 years old (range 16-70) at the time of DLI. Underlying diseases treated with DLI included chronic myeloid leukemia (CML) (n=20), acute myeloid leukemia (AML) (n=20), acute lymphocytic leukemia (ALL) (n=11), Hodgkin lymphoma (HL) (n=8), non Hodgkin lymphoma (NHL) (n=7), myelodysplastic syndrome (MDS) (n=5) and multiple myeloma (MM)

(n=1). Fifty-nine patients received HLA-matched sibling donor, 2 haploidentical related donor and 11 matched unrelated donor transplant. Conditioning regimen was mieloablative in fifty-three patients, and reduced intensity conditioning in nineteen patients. All patients received DLI as treatment for relapsed disease after allogenic transplantation. In the present study we analyse response rate, graft-versus-host-disease (GVHD), progression free survival (PFS) and overall survival (OS).

Results: Our patients received a median of 3 infusions (range 1-5). The median number of infused CD3+ cells was $0.5x10^8$/kg (range $0.1x10^8$/kg to $2.84x10^8$/kg). Sixty-eight percent of patients received dose-escalation DLI. Patients with low disease burden only received DLI. Thirty-nine percent received DLI-associated therapy (chemotherapy, radiotherapy, tyrosine-kinase inhibitors).

From the sixty-three patients eligible for evaluation, 35 (56%) got clinical benefit (CML n=14, ALL n=6, AML n=6, HL n=5, MDS n=2 NHL n=2). Progression free survival was higher in CML, with a median of 132 months, followed by NHL (84 months). Acute graft-versus-host-disease developed in 15% of the patients (5 patients grades I-II, the other 5 grades III-IV). Two patients died from acute hepatic GVHD. Chronic GVHD developed in 22% (6 cases limited, 9 extend). One patient died from chronic pulmonary GVHD.

With a median follow up of 16 years, median progression-free survival was 120 months [IC 95% 84.51-155.49] for the whole series. There are substantial survival differences according to underlying diseases, with a better survival rates for CML and LH.

Conclusions: Inmunotherapy with DLI is an attractive strategy for relapsed patients after allogeneic transplantation. In our experience, patients with CML have more clinical benefit, with a response rate of 70%, similar to published. DLI response in other pathologies is lower, although it can be useful in association with other therapies. However, further studies are needed to develop strategies to reduce toxicity and enhance anti-tumor activity.

Disclosure: Nothing to declare.

P126

Case Report: Chronic Active epstein-barr Virus Infection (CAEBV) Controlled by Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT) and Transfusion of EBV-specific T-cells

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Background: Chronic active Epstein-Barr virus infection (CAEBV) is one of the Epstein-Barr virus (EBV)-positive lymphoproliferative diseases. It is a rare and often fatal complication of EBV infection. In CAEBV, EBV-infected B-, T- or NK-cells clonally proliferate and infiltrate multiple organs, leading to their failure. At present, allogeneic hematopoietic stem cell transplantation (alloHSCT) is the only curative therapy. Other treatments such as high-dose systemic corticosteroids or ganciclovir combined with either histone deacetylase inhibitors or proteasome inhibitors (e. g. bortezomib) may temporarily reduce systemic toxicity and allow the patient time to receive a transplant.

Methods: We report a case of T-cell-type CAEBV in a 27-year-old female caucasian patient with severe skin, neurological, hepatic and pulmonary involvement.

Results: After several therapeutic approaches including high-dose systemic steroids, ganciclovir combined with bortezomib and rituximab had failed with EBV encephalitis requiring mechanical ventilation, third-party EBV-specific T-cells were administered and clinical symptoms resolved, while EBV viremia persisted. Subsequently, alloHSCT was performed from an HLA-matched unrelated donor after conditioning with antithymocyte globulin (ATG), fludarabine and treosulfan followed by an alpha-beta T-cell depleted and EBV-specifc T-cell enriched peripheral stem cell graft and GvHD prophylaxis with everolimus. Intriguingly, the viremia cleared after administration of ATG in alloHSCT setting. When the virus reactivated again in persisting host T-cells everolimus was tapered and viremia could again be controlled by transfusion of donor derived EBV-specific T-cells. Until now, no underlying immunodeficiency was found in the patient while complete host genome DNA and EBV genome sequencing is pending.

Conclusions: Treatment with EBV-specific T-cells from a third party donor followed by alloHSCT from an EBV seropositive donor is an effective therapeutic approach in CAEBV. As EBV-viremia was cleared after the administration of ATG in the alloHSCT setting for the first time in the patient, ATG might be further analysed as a potential treatment option in T-cell-type CAEBV due to its depletive activity on T-cells.

Disclosure: Nothing to declare.

Chronic leukaemia and other myeloproliferative disorders

P127

Incidence of late Relapse after Allogeneic Stem Cell Transplantation for Myelofibrosis

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Background: Despite advances in transplantation procedures and significant prolongation in survival, relapse following allogeneic hematopoietic stem cell transplantation (SCT) for myelofibrosis (MF) remains a significant issue. Most relapse occurs during the early period of allogeneic SCT. We aimed to analyze the clinical characteristics of the patients with late relapse following allogeneic SCT.

Methods: In this cross-sectional study we retrospectively evaluated the files of 259 patients with myelofibrosis transplanted between 1994 and 2015 for late relapses. Late relapse was defined as the relapses later than first five years of stem cell transplantation (SCT). Study patients were grouped according to their relapse status under follow-up after five years. Group A consisted of patients with a late relapse. Patients under long term follow-up after five years with no relapse consisted Group B. Clinical and laboratory parameters of late relapse were investigated.

Results: A total of 94 patients (M/F=55/39, 58.5 vs. 41.4%, respectively) out of 259 MF transplant patients were identified with a median follow-up of 9.15 years (range, 5.12-19.61). Median age at transplantation of the whole study population was 56 (range;29-75). Sixty two patients (66%) had primary MF (PMF), 18 (19.1%) had post polycythemia vera (PV) and 14 (%14.9) had post essential thrombocythemia (ET) myelofibrosis. Thirteen patients (M/F=7/6) experienced (12%) late molecular (n=6) or hematological (n=6) relapses at a median of 7.1 years (range, 5.02-10.20). Eighty- one patients (M/F=48/33) with a median follow-up of 8.76 years (5.02-19.61) did not experienced relapse. Median age at transplant was similar in both groups (Group A vs Group B: 55 (36-73) vs. 57 (29-75)). Although, numerically smaller, median time from diagnosis to transplantation, 20 months (3-100) in Group A and 13 months (1-353) in Group B, had no effect on relapses. Other clinical and laboratory parameters analyzed were not associated with a significantly higher risk of late relapse. Relapse patients received either DLI (n=9) and/or second transplantation (n=4). Of those 61.5 % achieved again full donor cell chimerism and/or molecular remission. After a median follow up of 105 months (range,4-236) of the relapsed patients the 2 years PFS and overall survival is 92.3% and 84.6%, respectively.

Conclusions: In this large MF group we observed late molecular or hematological relapses. DLI and second SCT are effective to induce remission. Early detection of minimal residual disease (MRD) and therapy adjustment resulted in full chimerism and negative MRD status. Our results implicate the importance of close monitoring of MF patients even after 5 years post allograft.

Disclosure: Nothing to declare.

P128

Hematopoietic Stem Cell Transplantation in Myelofibrosis: The Experience of Three University Transplant Centres in Rome

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Background: Myelofibrosis (MF) is a rare BCR-ABL negative myeloproliferative neoplasm, which can only be cured by Hematopoietic Stem Cell Transplantation (HSCT). Because of transplant related mortality (TRM) and morbidity, HSCT is reserved only to patients aged < 70 years with intermediate-2 or high risk MF, according to IPSS or DIPSS, or intermediate-1 with biological high-risk characteristics. Recently, Myelofibrosis Transplant Scoring System (MTSS) has been proposed in order to estimate the transplant risk. The aim of this analysis was to evaluate the outcomes of patients transplanted for MF in three University Transplant Centres in Rome and to verify the accuracy of MTSS in this population.

Methods: We retrospectively analysed 83 MF patients transplanted in Rome at Policlinico Umberto I (25 pts), Policlinico Tor Vergata (23 pts) and Policlinico Agostino Gemelli (35 pts), between 1986 and 2019 (75% of HSCT performed after 2012). Overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan-Meier

method. The log-rank test was used to compare risk factors categories. Cumulative incidence (CI) was used to calculate TRM, Relapse Risk (RR), graft failure (GF) and GVHD. A modified MTSS not including ASXL1 mutation was used (ASXL1 mutation data available for only 2 patients).

Results: Median age was 54 years (range 21 - 72). 44%, 28% and 28% of patients received transplant from HLA-identical related, unrelated and haploidentical donors, respectively. Peripheral hematopoietic stem cells were used in 59% of patients. RIC regimens (mainly Thiotepa, Busulphan and Fludarabine-based) were employed in 70%. Forty patients had been previously treated with Ruxolitinib: 27 patients responded or showed disease stability; 13 patients progressed during treatment. Modified MTSS was evaluated in 47 patients, for whom driver mutation data was available. The risk was low in 12 (25%), intermediate in 21 (45%) and high in 14 (30%) patients. Five-year OS was 60%. Features associated to a better OS were: Karnofsky ≥90% (p=0.04), spleen< 22 cm (p=0.04) and cGVHD (p=0.013). A trend to a worse OS was observed in patients who had progressed while in treatment with Ruxolitinib. At 5 years, DFS and RR were 56% and 22%, respectively. CMV and EBV reactivations were associated to an increased RR. TRM was 12% at 100 days, 20% at 1 year and 28% at 5 years. CI of GF at 100 days was 6.5%, with a higher risk trend for HSCT performed before 2012 and donor/recipient sex mismatch (F/M). Acute GVHD CI was 38% (III-IV grade 11% of patients). Two-year CI of cGVHD was 45%; mild and moderate cGVHD was observed in 82% of cases. Transplant from sibling donor and MAC regimen were associated to an increased risk of cGVHD. The 2-year OS according to modified MTSS was: 100% for low, 85% for intermediate and 50% for high risk (p=0.01).

Conclusions: In our experience, better outcome was observed for patient < 57-year-old, with higher PS, not progressing during Ruxolitinib treatment before HSCT. Modified MTSS was a robust tool for the evaluation of transplant risk.

Disclosure: Nothing to declare.

P129

Abstract already published.

P130

CML Relapse after Allogeneic HSCT: Survival, Treatment Efficacy and Prognostic Factors for Outcome

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Background: Tyrosine kinase inhibitors (TKI) have fundamentally changed the therapeutic concept in CML leading to excellent outcome. Although allogeneic stem cell transplantation (HSCT) is currently only required for a limited number of patients (pts) post-transplant relapse remains a major challenge.

Methods: Retrospective single center long-term evaluation of overall survival (OS), relapse-free survival (RFS) and the incidence of CML relapse after allo-HSCT. Analysis of OS and leukemia-free survival (LFS) among relapsed transplant recipients compared to non-relapse pts, review for prognostic factors and evaluation of response to relapse treatment. Data on 488 eligible CML pts transplanted between January 1996 and September 2015 were analyzed. At time of transplant 80% of all pts were in chronic, 12% in accelerated and 8% in blast phase. For the comparison between OS in pts with and w/o relapse after HSCT only survival longer than 15 months post-transplant (n=352) was considered to minimize lead-time-bias by landmark analysis. Cox regression was used to ascertain influencing factors for RFS.

Results: Median follow-up in the cohort was 129 months, 25% (n=120) of all transplant recipients sustained relapse with a median onset of 15 months after HSCT. Cumulative incidences (CI) of relapse were 13%, 23%, 26%, 28% and 30% after 1, 3, 5, 10 and 15 years post-transplant. RFS was assessed 67%, 53% and 47% after 1, 5 and 10 years post-transplant. Multivariate analysis of RFS proved advanced disease stages (> 1. chronic phase) at time of HSCT to be an independent adverse prognostic factor (p=0,005) whereas chronic GvHD showed only significant impact in univariate analysis. Based on landmark analysis, OS could be demonstrated to be significantly higher in transplant recipients w/o relapse (p=0,042). Among relapsed pts OS was significantly worse in hematologic compared to molecular or cytogenetic relapse (p=0,018; p=0,012). In 72% of pts with CML-relapse long-term remission could be induced resulting in a median progression-free survival of 98 months. For molecular relapse 15-year OS was 92% after discontinuation of immunosuppression, 100%, 89% and 80% after treatment with DLI, IFN or TKI. For cytogenetic relapse 15-year OS was 56% after discontinuation of immunosuppression and 100% after treatment with DLI, IFN or TKI. Hematologic relapse resulted in a 10-year OS of 100% after treatment with IFN and 67% after TKI therapy.

Conclusions: To achieve favorable RFS in CML, allo-HSCT should be applied in non-advanced disease stages. However, even in case of relapse after HSCT remissions with favorable long-term survival can be induced in particular when relapse is diagnosed as molecular or cytogenetic CML recurrence.

Disclosure: Nothing to declare.

P131

Chronic Myeloid Leukemia: Allogeneic Hemopoietic Stem Cells Transplantation in the Era of Tyrosine Kinase Inhibitors

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Background: The overall therapeutic tactics strategy in CML patients has changed drastically after tyrosine kinase inhibitors (TKIs) were introduced. There is, however, a subgroup of advanced disease phase patients or patients with TKIs intolerance/ loss of response, in which the overall prognosis is dismal and allo-HSCT is the only curative option. As a large transplant center we have observed the overall treatment landscape change with new TKIs generations being introduced. This retrospective study summarizes our experiences in pre- and post-TKIs era.

Methods: Our retrospective cohort study includes allo-HSCT recipients with CML treated between 1995 and 2019 (n=114). The diagnosis was based on clinical and laboratory criteria. In all patients either Philadelphia (Ph) chromosome or chimeric BCR-ABL gene were found. Disease stage was determined according to WHO criteria. The chronic phase 1 (CP1) was confirmed in patients with no history of accelerated phase (AC) or blast crisis (BC), otherwise CP≥2 was confirmed. Pre allo-HSCT hematological, cytogenetic or molecular response was evaluated according to ELN criteria. The myeloablative conditioning regimen used consisted of 16 mg/kg of busulfan and 120 mg/kg of cyclophosphamide. However, 96% of patients received reduced intensity conditioning regimen with 180 mg/m^2 of fludarabine and 8-14 mg/kg of busulfan or 140 mg/m^2 of melphalan.

Results: The number of transplant-eligible CP1 patients decreased dramatically after TKIs introduction. While in 1995-2004 as much as 75% transplant recipients were in CP1 there were only 12% in 2017-2019. In recent years most CP1 patients scheduled for allo-HSCT (93%) have history of TKIs resistance, some also are transplanted after T315I mutation is found or due to treatment intolerance (7%). From 2008 on, there is also a concurrent trend for less CML patients receiving allo-HSCT in AP or BC (50% in 2008 and 21% in 2017-2019). Most of these patients reached CP≥2 on 1st and 2nd generation TKIs. Since 2004-2005 the CP≥2 patients' proportion is consistently raising reaching as much as 65.6% in 2017-2019. Due to the targeted therapy improvement we are now able to achieve response even in BC patients. Therefore, the proportion of patients with BC history increased from 12% in 2004 to 60% in 2019, 20% of current allo-HSCT recipients having history of several BCs. The latter may point at a failure to refer a patient to allo-HSCT in time. Some recent years are marked by increase of 5-year overall survival (OS) from 25% to 58%, which may be explained by the fact that much less patients are now receiving allo-HSCT in AC or BC. A total of 46 patients in our cohort died, 29% of them (n=13) due to GVHD, 24% (n=11) of infectious complications, 39% (n=18) after disease relapse, 4% (n=2) due to heart attack, 4% (n=2) due to VOD.

Conclusions: The allo-HSCT belongs currently to 3rd or 4th line therapy for CP1 CML patients. It is also still a modality of choice if there is history of AC or BC. New generation TKIs are used to prepare patients for allo-HSCT thus raising significantly the CP≥2 allo-HSCT recipients proportion.

Clinical Trial Registry: NA

Disclosure: Nothing to declare.

P132

Reduced Intensity Allogeneic Stem Cell Transplant with Campath T-cell Depletion for Myelofibrosis in the Era of Jak Inhibitors- A Single Centre Experience

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Background: Despite recent advances in understanding the pathogenesis and molecular landscape of myelofibrosis over recent years, the condition continues to pose a number of challenges for the treating clinician. Allogeneic stem cell

transplant remains the only potentially curative option, however, the heterogeneity in both clinical course and therapeutic response, as well as patients' comorbidities, can make it difficult to weigh up the risks and benefits for individual patients. The advent of JAK inhibitors has revolutionized the treatment paradigm over the last decade with preliminary data suggesting positive impact on transplant outcomes. We conducted a retrospective review of patients undergoing a reduced-intensity Alemtuzumab-conditioned allogeneic stem cell transplant for myelofibrosis over a 9-year period, at Birmingham Heartlands Hospital, in order to provide real world data and identify any significant correlation between patient characteristics, JAK-2 inhibitor use, and outcomes.

Methods: We identified 27 patients (16 Male vs 11 Female, 8 sibling donor vs 15 matched-unrelated donor vs 4 mismatched-unrelated donor) who had undergone an allogeneic stem cell transplant for myelofibrosis at Heartlands Hospital between 16th April 2010 and 7th August 2019. 9 patients had received Ruxolitinib prior to allogeneic stem cell transplant. All patients were DIPS score intermediate 2/high. Data was obtained from transplant protocols, discharge letters and clinic letters accessed via the hospital online record system. The information was inputted onto an excel spreadsheet and statistical analysis was carried out using SPSS.

Results: Patients had a median age of 64.6 years and were followed up for a median of 23 months. Median overall survival for the cohort was 65.9%. (see figure 1)

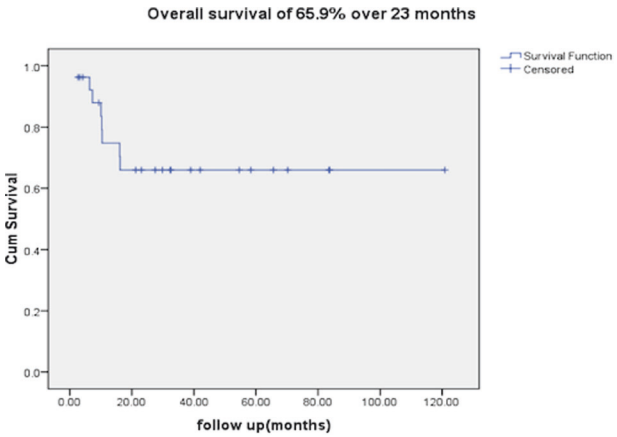
25% patients developed acute graft versus host disease (GVHD) grade 3/4, including 2 patients who died of GVHD, and 14% patients developed chronic GVHD. Only 1 patient died of disease progression post transplant, a 2nd patient progressed but regained remission with donor lymphocyte infusion (DLI) and ruxolitinib. Progression free survival was 62% at 23 months.

37% patients in total received DLI and 1 patient received a stem cell top up for secondary graft failure. 7.4% patients had a prior diagnosis of essential thrombocythemia, and 81% patients had neutrophil engrafted by day +28.

Sibling donors were associated with significantly better survival than matched unrelated donors (p=0.033). There was also a statistically significant improvement in survival in those patients who received DLI (p=0.037).

In our cohort, we did not identify any statistically significant correlation between prior ruxolitinib use and risk of death, progression, or acute and chronic GVHD.

Conclusions: Although patient numbers were small, our results highlight the curative potential of allogeneic stem cell transplantation in myelofibrosis using a reduced intensity approach with Alemtuzumab-based T-cell depletion. This approach is both safe and effective, even in a relatively older population, and the suggestion that post -transplant DLI may confer a survival benefit will need further evaluation in larger multicentre cohorts.



[Figure 1- overall survival]

Disclosure: Nothing to declare.

P133

Allogenic Stem Cell Transplantation in advanced Systemic Mastocytosis after Cytoreductive Treatment with Cladribine - A Single Center Experience on Two Patients

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Background: Systemic mastocytosis (SM) is characterized by proliferation and accumulation of clonal mast cells in bone marrow, skin and visceral organs. Bone marrow mast cell infiltration, elevated serum tryptase and a KIT D816V mutation (>90% of patients) are diagnostic hallmarks. The various subtypes of this rare haematological neoplasm are characterized by a more or less aggressive course. Targeted therapy against mutant-KIT with midostaurin has been approved, however, complete responses have not yet been reported and durable major response may only occur in 50-60% of patients. Cladribine has demonstrated efficacy in treatment of indolent SM and advanced SM (AdvSM) while allogeneic stem cell transplantation (ASCT) is a treatment option for eligible AdvSM patients with refractory or aggressive clinical course. In a retrospective study, response

rates of 70% have been reported at day +100, followed by long term survival in 50-60% of patients.

Methods: We here report on ASCT in two patients (female, 70 years old; male, 50 years old) with aggressive SM and associated myelodysplastic/myeloproliferative neoplasm (ASM-MDS/MPN). The first patient presented with a bone marrow infiltration of 5%, a serum tryptase of 320 μg/l (normal value < 11.4), massive splenomegaly and multiple additional somatic mutations in ASXL1, SETBP1 and CSF3R in addition to KIT D816V. The second patient presented with a bone marrow mast cell infiltration of 80%, a serum tryptase of 540μg/l and only mild splenomegaly. Somatic mutations were identified in KIT D816V, NRAS and TET2. Both patients were resistant to midostaurin but achieved a stable partial remission on one and seven cycles cladribine, respectively. Bone marrow biopsy revealed residual mast cells of < 5% and serum tryptase was decreased to 52μg/l and 102μg/l when conditioning therapy with fludarabine (150mg/m2), treosulfan (36g/m2) and ATG Neovii® (45mg/kgBW) was initiated. Peripheral stem cells from unrelated 10/10 donors were used as stem cell source. While one patient had negligible skin reactions associated to the central line, the second patient presented with high fever and rash one week after transplantation mimicking hyperacute GvHD, which was, however, most likely an associated with mediator release/allergic reaction upon antimycotic treatment with an echinocandin.

Results: Both patients show complete chimerism on day +100, tryptase is normal in the first patient and near normal (35μg/l) in the second patient. The first patient shows mild mucocutaneous chronic GvHD.

Conclusions: Our experience shows feasibility and short-term efficacy of ASCT in ASM-AHN after induction of best possible remission with several cycles of cladribine and treosulfan-based conditioning. Mediator release may remain an important issue during and after transplantation and its differentiation from GvHD may be difficult.

Disclosure: Nothing to declare.

P134

Allogeneic Stem Cell Transplantation for Idiopatic Myelofibrosis: A Single Centre Experience

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Background: Allogeneic Stem Cell Transplantation (ASCT) is the only curative option for Myelofibrosis (MF). Development of reduced intensity conditioning (RIC) regimens and introduction of Ruxolitinib (Rux) have improved the outcome of ASCT. However, this procedure is still burdened by substantial morbidity and high transplant-related mortality (TRM). Here we report our experience with ASCT in MF setting, in order to evaluate the factors influencing post-transplant outcome, in term of overall survival (OS) and Progression-free survival (PFS).

Methods: In the last 10 years we performed 30 ASCT on 27 MF patients (pts); 3 pts of them received a second ASCT for MF relapse. The median age was 51 (range: 25-68) years. Driver mutations were found in 23 pts and were: JAK2V617F in 16 (59%), MPL in 3(11%) and CALR mutations in 4 (15%) pts; 4 (15%) pts were defined as "triple-negative". According to Dynamic International Prognostic Scoring System (DIPSS) at transplant, pts were stratified into high, intermediate-2 and intermediate-1 risk in 11 (41%), 12 (44%) and 4 (15%) cases, respectively. Considering the first ASCT, donors were matched related (MRD), matched unrelated (MUD) and haploidentical in 18 (67%), 7 (26%), and 2 (7%) of cases, respectively. Conditioning regimen (CR) was RIC in 11 pts (41%) or myeloablative in 16 pts (59%); all CR were Busulfan and Fludarabine-based, in 48% of cases (n=13) associated with Tiothepa. Conventional GVHD prophylaxis regimens were used according to type of ASCT. Splenectomy or spleen irradiation were performed before ASCT in 2 and 6 pts in pre-Rux era; 16 pts (59%) received Rux before ASCT. Source of stem cells were bone marrow in 15 (56%) or peripheral blood stem cells in 12 (44%) pts. OS and PFS have been evaluated by Kaplan-Meier analysis.

Results: Aafter a median follow-up of 18.5 (range: 0.5 - 175) months from first ASCT, 4/27 pts (15%) died for early TRM, 6 (22%) pts for MF relapse (4) or leukemic evolution (2). 17 (63%) pts were alive, 15 of them with full chimerism and complete remission (one after the second ASCT); 2 pts were alive in MF relapse. Chronic GVHD occurred in 6 (22%) pts.

The probability of OS for the entire cohort at 2 and 5 years was respectively 75% and 60% and the 2 and 5 year PFS was 75% and 55% respectively. In statistical analysis, significant predictive factors of good outcome were: intermediate-1 DIPSS score at transplant, Rux-exposition pre-transplant and development of chronic GVHD. There was no correlation between clinical outcome and type of driver mutations, age at transplant, donor type, CR, source of stem cells.

Conclusions: ASCT in MF is actually a valid therapeutic option for pts eligible to the procedure also in the Rux era. In our experience, earlier stage of MF at time of transplant and Rux exposition before transplant seem to have a

favourable impact on the outcome post-ASCT; also a chronic GVHD seems to play a protective role for reducing relapse risk post-ASCT.

Disclosure: Nothing to disclose

P135

A case of Successful Second Haploidentical Bone Marrow Transplantation after Secondary Graft Failure in a Patient with Refractory Chronic Myeloid Leukemia

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Background: Allogeneic hematopoietic stem cell transplantation (alloHSCT) is currently considered a mandatory therapy option in patients with refractory to at least two of tyrosine kinase inhibitors (TKI). Haploidentical alloHST are becoming increasingly important in this cohort of patients.

Methods: 33 years old, male. History of CML: blast crisis as a debut; the disease was characterized by primary cytogenetic resistance to imatinib and bozutinib. In the study of BCR-ABL mutations during bozutinib therapy, the T315I mutation was detected. The loss of complete hematological response (CHR) was stated with the preservation of the chronic phase (CP) of CML; cytoreductive therapy with hydroxyurea 3000 mg/day was added to bozutinib. Patient only had one haploidentical donor (mother).

When CHR was achieved, alloHSCT was performed (period from disease debut to alloHSCT is 58 months). Conditioning regimen (CR):fludarabine 150 mg/m2, busulfan 8 mg/ kg; prophylaxis of the graft-versus-host disease (GVHD): high-dose (50 mg/kg DD3,4) cyclophosphamide was administered, tacrolimus and mycophenolate mofetil therapy was initiated at D5. To D+30 the patient had 100% donor chimerism, Ph-chromosome in cytogenetic studies of bone marrow was not determined, but minimal residual disease (MRD) remained-0,210% BCR-ABL p210 (15349 ABL copies). Prophylactic therapy with TKI-dasatinib 50 mg/day was initiated at D+58. From D+62, there was a decrease in donor chimerism: 93.8% (D+62) => 91.5% (D+82) => 91.6% (D+118), MRD by these terms decreased by 1 log. By D+128 immunosuppressive therapy (IST) was withdrawn. From D+148: deepening profundity of persistent cytopenia, decreasing of donor chimerism to 82%. Infusion of donor lymphocytes (DLI) - 1*10^6 CD3+CD45+/kg was performed on D+152. Total bone marrow hypoplasia, decreasing of donor chimerism to 33.5% were detected on D+158. The secondary graft failure was stated.

Results: Second alloHSCT from the same donor was performed within 7 days after the diagnosis of secondary graft failure. CR: fludarabine 150 mg/m2, melphalan 140 mg/m2; prophylaxis of GVHD was the same. On D+29 100% donor chimerism was detected, BCR-ABL p210-0% (11212 ABL copies). By D+63 decreasing of donor chimerism to 93,3% was stated, on D+63 IST was completely withdrawn. On D+78, donor chimerism increased up to 98%. On D+83, due to high risk of secondary graft failure, DLI was performed (5*10^5 CD3+CD45+/kg). On DD +110, +137 full donor chimerism was defined. MRD was not detected during the entire post-transplant period, and therefore prophylactic administration of TKI was not resumed. To date, chronic multilocus GVHD (skin, mucosa, liver) has occurred, which was successfully treated with ruxolitinib and extracorporeal photopheresis.

Conclusions: Allogeneic (haploidentical) HSCT in patients with refractory CML may be a successful alternative to a fully HLA-compatible SCT. Second allogenic (haploidentical) HSCT from the same donor with the change of CR in our patient was effective. As a stimulation of the graft-versus-leukemia (GVL) effect, "earlier" withdrawal of IST and DLI may be successfully performed. “Deep molecular response” in post-transplant period can be achieved without administration of TKI due to satisfactory graft function. Ruxolitinib is actively used in GVHD treatment, and can also stimulate an antitumor response.

Earlier alloHSCT can contribute to reduce incidence of complications.

Disclosure: Nothing to declare.

Conditioning regimens

P136

Combining Clofarabine and Fludarabine with Exposure Targeted Busulfan for Pediatric Leukemia: An Effective, Low Toxic, TBI-free Conditioning Regimen

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Background: The combination of Clofarabine + Fludarabine + Busulfan (CloFluBu) was found to have synergistic anti-leukemic activity against ALL and AML blasts in vitro (Andersson et al: BBMT 2011). As TBI induces significant late effects in childhood ALL, and AML patients have high relapse rates, we hypothesized that CloFluBu may be a potential alternative to TBI in ALL, and could add anti-leukemic activity in AML. Within the "Dutch COG HCT Working Group" we prospectively studied the outcomes of a CloFluBu-conditioning regimen for lymphoblastic and myeloid malignancies.

Methods: Patients from the 2 pediatric HCT programs (LUMC and UMC Utrecht/Princess Máxima Center for Pediatric Oncology) in the Netherlands with a lymphoblastic or myeloid malignancy receiving their first HCT, between August 2011 and April 2019, were included. Over 4 days, Clofarabine 30mg/m2 was given in 1 hour, followed by Fludarabine 10mg/m2 in 1 hour, followed by a 3-hour infusion of once-daily targeted Busulfan (weight-based dosing + therapeutic drug monitoring to a total Bu-exposure of 90mg*h/L). Thymoglobulin was added in unrelated donors (except in AML patients receiving cord blood). GvHD-prophylaxis was according to standard protocols. Minimal Residual Disease (MRD) negative was defined as < 10e-4. Primary endpoints were Overall Survival (OS) and Leukemia Free Survival (LFS). Secondary endpoints were Non Relapse Mortality (NRM), Relapse, acute and chronic Graft-versus-Host Disease (GvHD), and VOD/SOS. Cox Proportional Hazard and fine and gray competing risk models were used for data analysis.

Results: 155 children were included; 66 ALL (38 in CR1, 28 ³ CR2), 69 AML (28 in CR1, 40 in CR2, 1 in active disease) and 20 other malignancies (mostly MDS-EB). Median age was 9.7 (0.5-18.6) years. Most donors were unrelated (119 vs 36 related); 79 Bone Marrow (BM), 66 Cord Blood (CB) and 10 Peripheral Blood Stem Cells. Median follow up was 964 (19-2994) days. Overall the 3-yr estimated OS and LFS was 72 ± 4.5% and 65 ± 5% respectively. Estimated 3-yr LFS for MRD-neg ALL, MRD-pos ALL, AML CR1 and AML CR2 was 74 ± 7%, 40 ± 12%, 64 ± 10%, 65 ± 9% respectively). NRM in whole cohort was 10.3 ± 3.0% (with 25 ± 4.3% for AML CR1 (n=28), and 5.8 ± 2.3% in the rest). Other endpoints: only 2 graft-failures were noted, incidence of aGvHD III-IV at 6 months was 11 ± 3%, extensive chronic GvHD at 3-yr was 5.2 ± 2.2%. Relapse at 3-yr was 25 ± 4.3% (MRD-neg ALL 16.2 ± 3.7%, versus 60 ± 4.9% in MRD-pos ALL, in AML 22.5 ± 4.2%) and no VOD/SOS was noted.

Conclusions: CloFluBu in myeloid- and lymphoblastic malignancies, showed very limited toxicity and encouraging LFS in all groups, in particular for MRD negative ALL. More studies, preferably in randomized controlled clinical trials, are needed to draw firm conclusion with regards to the anti-leukemic effect and late effects.

Clinical Trial Registry: N/A

Disclosure: nothing to disclose

P137

Benda-beam High-dose Therapy Prior to auto-sct is Effective in Resistant/relapsed DLBCL: A Phase II Study

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Background: A major drawback affecting clinical trials of high-dose therapy (HDT) followed by autologous stem cell transplant (ASCT) in lymphomas is the high heterogeneity of histological entities. As a consequence, the statistical power is reduced when we focus on a specific histological subset, and data are often not conclusive. We designed a phase II study to evaluate the efficacy of the BeEAM conditioning (bendamustine 200 mg/m2 on days -7,6, cytarabine 400 mg/m2 days -5-4-3-2, etoposide 200 mg/m2 days -5-4-3-2, melphalan 140 mg/m2 day-1) in resistant/relapsed diffuse large B-cell non-Hodgkin lymphoma (DLBCL) patients.

Methods: The study was registered at European Union Drug Regulating Authorities Clinical Trials (EudraCT) N. 2011-001246-14. 64 patients (median age 54.5 years, range 19-70) with resistant/relapsed DLBCL or transformed follicular lymphoma were enrolled. The primary

end-point of the study is to evaluate the 1-year complete remission rate.

Results: Briefly, 47/64 patients had advanced stage disease (III-IV); 21 were primary refractory and 43 had relapsed. 33/64 were in II or subsequent CR after salvage therapy, whereas 24 were in PR and 7 in progressive disease. A median number of $5.55x10^6$ CD34+/Kg cells (range 2.07-12.20) collected from peripheral blood was reinfused to patients. All patients engrafted, with a median time to ANC>$0.5x10^9$/l of 10 days. Median times to achieve a platelet count >$20x10^9$/l and >$50x10^9$/l were 13 and 18 days respectively. Twenty-four out of 64 patients presented a FUO (37.5%). One patient died due to an incomplete hematological recovery after transplant and one patient died due to acute liver failure, producing an overall transplant related mortality of 3.1%. Sixty-two patients are evaluable for response: 51/62 (82%) obtained a CR, 4/62 (6%) a PR, whereas 7/62 (11%) did not respond to therapy. The median follow-up after transplant was 34 months (range 1-90).

Conclusions: The stringent inclusion criteria at enrollment allow to precisely evaluate the impact of HDT with Bendamustine followed by ASCT in a highly selected population of patients with DLBCL. The 1 year remission rate was superior to 55%, thus reaching the primary endpoint. Accordingly, our data provide the evidence that the Benda-BEAM regimen is safe and has promising high efficacy in resistant-relapsed aggressive diffuse large B cell lymphoma.

Disclosure: Nothing to declare.

P138

Reduced-toxicity Conditioning with Fludarabine, Thiotepa and Melphalan in Allogeneic Hematopoietic Cell Transplantation for Patients with Impaired Lung Function

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Background: The age of patients undergoing allogeneic hematopoietic cell transplantation (allo-HCT) has increased during the last decades, mainly due to improved reduced intensity/toxicity conditioning protocols. A reduced-intensity conditioning based on fludarabin, carmustin/BCNU and melphalan (FBM) has been previously developed at our institution. Since we observed detrimental effects in patients with compromised lung function prior allo-HCT and conditioned with FBM, efforts have been made in order to replace BCNU by thiotepa (FTM) to reduce toxicity.

Methods: In this study, we retrospectively analyzed the outcome, Graft-versus-Host (GvHD) incidence, lung function and organ toxicity of patients transplanted at our institution after conditioning with the reduced intensity/toxicity protocols FBM (n=122) and FTM (n=73) between January 1st 2013 and December 31st 2017. Patients were stratified by caring physicians to receive conditioning according to FBM protocol (fludarabine 4x30mg/m², BCNU/carmustine 2x150mg/m² and melphalan by patients >55 years:1x110mg/m² or < 55 years:1x140mg/m²) or FTM (fludarabine 4x30mg/m², thiotepa 2x5 mg/kg and melphalan for patients >55 years:1x110mg/m² or < 55 years:1x140mg/m²). We included in the analysis all patients at first allo-HCT and surviving at least 100 days after allo-HCT. During the observation period, continuously increasing number of patients were treated with FTM. Therefore, patients treated with FBM had a longer median follow-up of 957 (range 104 -2337) vs. 801 days (range 124 -1667) of FTM-treated patients.

The Cox proportional hazards regression model was used to estimate hazard ratios (HR) and confidence intervals (CI) for overall survival and progression-free survival. We applied the Fine and Gray model to compare cumulative incidence rates in the presence of competing risks and presented as subdistribution hazard ratios for relapse incidence, non-relapse mortality, aGvHD and cGvHD incidence. Pearson's chi-square and Fisher's exact tests were used to compare categorical variables as appropriate and Student's T-test to compare continuous variables.

Results: Compared to patients conditioned with FBM, FTM-treated patients were younger and received less frequently GvHD prophylaxis with alemtuzumab. Patients treated with FTM suffered more frequently lymphoid malignancies and received more chemotherapy cycles. As expected, there were more patients with a HCT-CI score ≥ 4 and with impaired lung function allocated in the FTM group, due to the patient selection by caring physicians to the presumably less pulmonary toxic protocol.

Despite a higher comorbidity-index prior allo-HCT, patients conditioned with the FTM protocol show similar overall survival and relapse incidence. Hence, patients with impaired lung function prior allo-HCT, as defined by FEV1< 80% of predicted or DLCOcSB< 80% of predicted, and conditioned with FTM had a 2-year overall survival of 83.0% compared to 71.1% of FBM-treated patients (p=0.11). FTM-treated patients had less pulmonary cause of death compared to patients treated with FBM. In contrast, gastrointestinal complications were more frequently

observed in patients conditioned with FTM. No differences were observed in incidence and severity of acute and chronic GvHD. Lung function was reduced in FTM-treated patients prior allo-HCT and 1 year after allo-HCT compared to FBM-treated patients.

Conclusions: In summary, the FTM protocol has reduced toxicity but sufficient anti-neoplastic effect and is suitable for patients with impaired lung function prior allo-HCT.

Disclosure: Nothing to declare.

P139

Allogeneic Stem Cell Transplant with minimal-intensity Conditioning in Patients with Cutaneous T-cell Lymphoma. A Single Centre Retrospective Review

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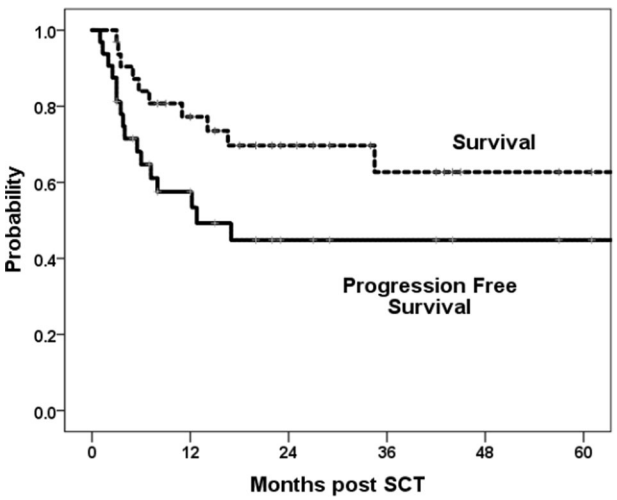
Background: Haematopoietic stem cell transplantation (HSCT) in advanced cutaneous T-cell lymphomas (CTCL), of which mycosis fungoides (MF) and Sezary syndrome (SS) are the most common subtypes, is increasingly practiced as a curative therapy. Minimal-intensity conditioning, using a protocol established in Stanford using anti-thymocyte globulin (ATG) and total nodal lymphoid irradiation (TNLI), is an option for CTCL patients, particularly those of older age, and those with chronic colonisation of skin lesions by potentially multi-resistant organisms which would render myeloablative conditioning regimens higher risk. The conditioning protocol comprises initial total skin electron beam therapy (TSEB) (4-8 week course) pre-transplant, followed by TNLI (day -11 to day 0), 10 x in 80cGy fractions of 4 radiation fields (2 anterior and 2 posterior including all major lymphoid areas) and ATG (day -11 through day -7, 1.5mg/kg/day). Ciclosporin was given from day -3 onwards, MMF was given from day +1 onwards. The benefits of this protocol include reduced incidence of acute GvHD and prompt multi-lineage engraftment, with evident graft vs tumour effect.

Methods: This is retrospective case series of 32 CTCL patients who underwent allogeneic transplant for advanced CTCL using the TSEB/ATG/TNLI protocol at a single centre after failure of standard therapy between 2012 and 2019. Of the 32 patients, 3 had SS and 29 of had MF. The number of prior treatments ranged from 3-8. 11 patients had matched sibling allografts, 2 patients had haploidentical sibling allografts and 19 patients had grafts from matched unrelated donors. We used the patients' transplant protocols and hospital electronic records to retrieve information. We collected data for DFS and OS analyses as well as transplant-related mortality, and the doses and responses to donor lymphocyte infusions (DLI).

Results: We used the Kaplan Meier method to generate survival curves looking at time to two events; disease-free survival (DFS) and overall survival (OS). Of the 32 patients who were transplanted, 14 patients relapsed, of which 4 then died due to the disease progression. 7 patients received at least one DLI post-transplant, either for relapsed disease or falling chimerism, and 4 were successfully salvaged with DLI and chemotherapy/radiotherapy. An additional 5 patients died due to sepsis/GvHD. 13 patients remain in remission. The Kaplan Meier estimates of 5-year OS and 5-year DFS in this study were 63% and 45%, respectively.

Conclusions: Use of this minimally intensive protocol resulted in a predicted OS of 2/3 of patients at 5 years with approximately half of the patients being disease free, suggesting promising long-term outcomes in a disease with otherwise poor overall survival. This study has shown successful engraftment can be achieved with this minimally-invasive protocol and suggests reducing the risk of non-relapse related mortality can be achieved without increasing risk of relapse or progression. For those who relapse DLI may be of benefit and further study of its use in this setting is recommended.



[Kaplan Meier Survival Curves]

Disclosure: Nothing to declare.

P140

Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Acute Lymphoblastic Leukemia and Karnofsky Performance Status Score Equal or Lower Than 80%. A Study from the ALWP-EBMT

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Background: We report here the results of a retrospective study designed to evaluate outcome of ALL patients undergoing allo-HCT with KPS score ≤80%.

Methods: The analysis included ALL patients aged ≥18 years, undergoing allo-HCT in first remission between 2000 and 2018, with a KPS score of 50% to 80% at the time of transplant. Patients who received manipulated grafts or had incomplete data about cytogenetics were excluded. Conditioning intensity was defined according to EBMT definitions (Aoudjhane M. et al, Leukemia 2005; 19: pp. 2304-2312).

Results: A total of 1,010 patients were identified. Median age at transplant was 43 years (18-76 years). Median year of transplant was 2011. The KPS score was =80% in 83% of the patients and < 80% in 17% of the patients. Diagnosis was Philadelphia chromosome (Ph) negative B-ALL, Ph positive B-ALL or T-ALL in 34%, 44% and 22% of the patients, respectively. Donor type was MSD or 10/10 UD in 60% and 40% of the patients, respectively. Conditioning was myeloablative (MAC) or reduced-intensity (RIC) in 78% and 22% of the patients, respectively, and it was TBI-based in 79% of the patients. Stem cell source was PBSC in 76% and BM in 24% of the patients, respectively. Anti-thymocyte globulin (ATG) was administered to 21% of the patients receiving MSD and 68% of the patients receiving 10/10 UD as donor type. Cumulative incidence of grade II-IV and III-IV aGVHD was 32% and 9%, respectively. The 2-year cumulative incidence of chronic GVHD (cGvHD) and severe cGVHD was 43% and 18%, respectively. Non relapse mortality (NRM) and relapse incidence (RI) at 2 years were 18% and 28%, respectively. At 2 years, leukemia-free survival (LFS), overall survival (OS) and GVHD-free, relapse-free survival (GRFS) rates were 54%, 64% and 41%, respectively.

On multivariate analysis, transplant from 10/10 UD was associated with higher incidence of aGVHD (HR 1.8, p< 0.0001) and higher risk of NRM (HR 1.7, p< 0.01) as compared to MSD. RIC conditioning was associated with higher risk of relapse (HR 1.2, p=0.02), lower LFS (HR 1.3, p=0.03) and lower GRFS (HR 1.3 p=0.02) as compared to MAC. NRM was not significantly different between MAC and RIC. Factors independently associated with improved OS were younger age at transplant, female sex, more recent year of transplant and Ph+ B ALL phenotype. Administration of ATG was associated with reduced risk of developing grade II-IV aGVHD (HR 0.6, p< 0.001), cGVHD (HR 0.5, p< 10^{-4}) and severe cGVHD (HR 0.4, p< 10^{-4}).

Conclusions: In conclusion, allo-HCT is feasible in patients with acute lymphoblastic leukemia in first remission and KPS score ≤80%, with acceptable NRM and survival rates. Transplant from a sibling donor was associated with reduced risk of NRM and aGVHD as compared to matched unrelated donor. Interestingly, despite the poor KPS score of the patients included in the analysis, a MAC protocol was associated with similar NRM, lower relapse and better LFS and GRFS as compared to RIC in the selected population. Finally, administration of ATG was associated with reduced acute and chronic GVHD rates.

Disclosure: Nothing to declare.

P141

A Prospective Cohort Study Comparing long-term Outcomes with and without Palifermin in Patients Receiving Hematopoietic Cell Transplantation for Hematologic Malignancies

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Karen Ballen[5], Patrick Stiff[6], Miguel-Angel Perales[7], Stephen Forman[8], Richard Champlin[9], Amelia Langston[10], Torbjörn Kullenberg[11], Mattias Rudebeck[11], Mary Horowitz[1]

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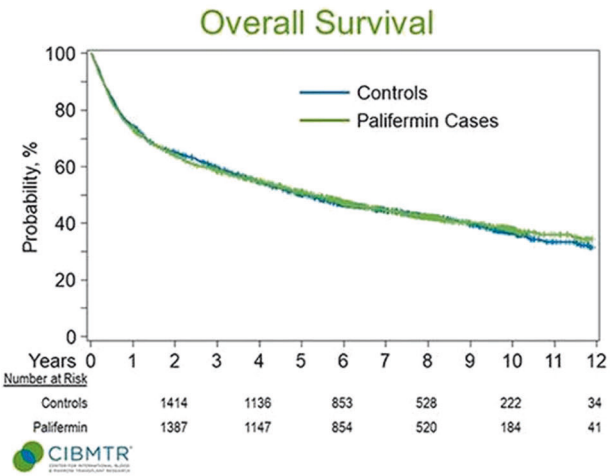
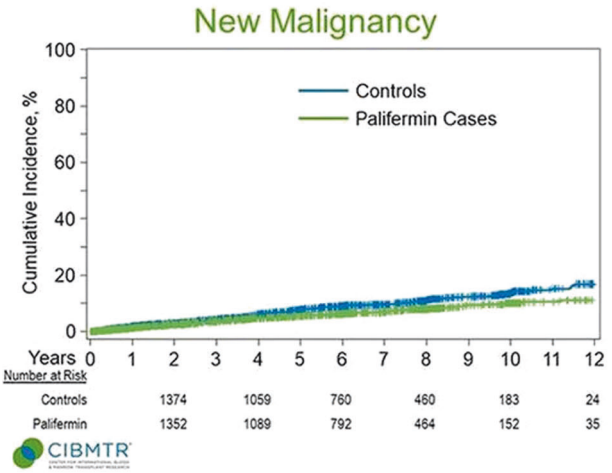
Background: Incidence of debilitating oral mucositis (OM) can be as high as 99% after myeloablative conditioning regimens preparing patients with hematologic malignancies for hematopoietic cell transplant (HCT). Palifermin is a recombinant human keratinocyte growth factor that stimulates proliferation and differentiation of epithelial cells. In randomized controlled trials, palifermin reduced incidence and duration of severe OM in patients with hematologic malignancies receiving myelotoxic therapy in the setting of autologous hematopoietic cell support. Long-term safety of palifermin or the potential risk of stimulation of new malignancies (NM), however, has not been well established.

Methods: In this long-term, prospective, matched cohort study, patients who received palifermin and underwent autologous or allogeneic HCT for hematologic malignancies from 2006-2013 were 1:1 matched to patients who did not receive palifermin. Subjects were matched on age, HCT type, donor type, HCT date, disease type, disease status, region, and whether TBI was included in the conditioning regimen. Primary outcomes were overall survival (OS), relapse, and NM.

We adjusted for imbalances with a propensity score, modeled by logistic regression. The following covariates were used to identify factors associated with treatment assignment: age, race, disease, disease status, time from diagnosis to HCT, prior radiotherapy, type of HCT, growth factors use, graft source, donor age, donor-recipient sex and cytomegalovirus (CMV) serostatus match, conditioning regimen, graft-vs-host disease (GVHD) prophylaxis, year of HCT, and region. Equal propensity scores in both groups predicted they were equally likely to be treated with palifermin. Relative risks were estimated using Cox proportional hazards regression analysis, stratifying on the matched pair and considering the propensity score as a continuous covariate.





[Figure 1 overall survival; Figure2 New Malignancy]

Results: The analysis population consisted of 2191 matched pairs. The median follow-up was 8 years (range, 1-12.5 y), with excellent completeness of data across both arms (93% at 8 y). Overall, the median age was 51 y (range, < 1-80 y). HCT for acute leukemia was the most common indication (40%), followed by plasma cell disorder (28%), and non-Hodgkin lymphoma (13%). TBI was used in 41% of conditioning regimens. Fifty percent of the matched pairs underwent allogeneic HCT, and the two most common donor types were identical siblings (37%) and well-matched unrelated donors (35%). Among allogeneic HCT recipients, the majority (88.5%) received

myeloablative regimens. In multivariate analyses, the relative risks of OS, relapse, and NM were not statistically significantly different between those who received palifermin and those who did not (relative risk [RR] for OS 1.01 (95% confidence intervals [CI] 0.91-1.12); RR for relapse 1.06 (95% CI 0.94-1.18); RR for NM 0.89 (95% CI 0.67-1.18)) (Figures 1, 2). The potential interactions between receiving palifermin and propensity score were tested, and no interactions were detected.

Conclusions: Long-term safety of palifermin was confirmed with no increased risk of overall mortality, relapse or NM.

Clinical Trial Registry: Not applicable

Disclosure: Swedish Orphan Biovitrum (Sobi) contracted with CIBMTR for services associated with fulfillment of the LTFU study. CIBMTR aligns all activities through the lens of its research mission and utilizes funding sources only to expand research infrastructure and to facilitate a broad research portfolio. It contractually maintains independent review and publication rights and, as such, does not consider the services provided to be a conflict of interest.

Kullenberg and Rudebeck are employees and shareholders of Sobi.

Dr. Perales reports honoraria from Abbvie, Bellicum, Celgene, Bristol-Myers Squibb, Incyte, Merck, Novartis, Nektar Therapeutics, Omeros, and Takeda. He serves on DSMBs for Cidara Therapeutics, Servier and Medigene, and the scientific advisory boards of MolMed and NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead and Miltenyi Biotec. He serves in a volunteer capacity as a member of the Board of Directors of American Society for Transplantation and Cellular Therapy (ASTCT) and Be The Match (National Marrow Donor Program, NMDP), as well as on the CIBMTR Cellular Immunotherapy Data Resource (CIDR) Committee.

P142

Pharmacokinetics of Melphalan in Lymphoma Patients undergoing Beam and Autologous Hematopoietic Stem Cell Transplant

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Background: High dose chemotherapy with BEAM (Carmustine, etoposide, cytarabine and melphalan) is a standard regimen for autologous hematopoietic cell transplantation (AHCT) in lymphoma patients. Multiple myeloma studies have shown that dosing melphalan as a fixed dose based on body surface area leads to inter-patient differences with a 5-fold variability in area under the curve (AUC), with higher AUCs associated with improved outcomes but increased toxicity. In this study, the pharmacokinetics (PK) of Evomela® (propylene glycol free melphalan, PGF-MEL) in BEAM, and its associations with outcome and toxicity were evaluated.

Methods: On D-1 prior to AHCT, 140 mg/m2 of PGF-MEL was given over 30 minutes and serum sample were drawn serially at 5, 15, 30, 40, 75, and 150 minutes after the dose. AUC PK modeling was done with Cetara Phoenix WinNonlin, Princeton, NJ. Toxicity collection is ongoing using CTCAE v4 through D+100 after AHCT.

Results: Eighty-seven patients that received BEAM conditioning between 08/2016 and 09/2019 had melphalan PK analysis. The median age was 51 (range, 19-74), 62% were male, and 53% had aggressive B-cell lymphoma. The median PK parameters were as follows: AUC 8.1 mg*h/L (range, 3.8-18.8); clearance 31.8 L/h (range 16.4-79.1); volume of distribution 33.2 L (range, 19.7-70.1); and half-life of elimination 0.7 hours (range, 0.5-1.7). The median dose of melphalan given was similar between patients ≤ median AUC and those above (260 mg [range, 200-340 mg) and 270 mg [range, 210-340 mg], respectively.) With a median follow up of 8.94 months (range 0.72-32.91) in survivors, univariate analysis showed no difference in 1-year overall survival (OS) (95.5% [84-100%] vs. 87.4% [76.5-100%], p=0.2) or progression-free survival (PFS) (78.4% [63.6-96.6%] vs. 78% [63.7-95.5%], p>0.99) when evaluating patients ≤ or above median melphalan AUC, respectively. Patients with a melphalan AUC ≤ the median had an average length of stay of 19 days (range, 5-27) vs. 21 days (range, 7-38) for those above the median exposure (OR 1.19 [1.05-1.38], p = 0.004). Toxicity data collection is ongoing.

Conclusions: Melphalan exposure ≤ 8.1 mg*h/L resulted in a shorter length of hospitalization likely driven by less toxicities, that will be reported upon completion of toxicity collection. Despite early results showing no difference in OS and PFS, the 5-fold variability seen with PGF-MEL AUC suggests that a sweet spot to optimize outcomes and minimize toxicities is needed.7

Characteristic	≤ Median AUC (N = 45)	> Median AUC (N = 42)	OR (95% CI)	P-value
Age - yr (median, range)	40 (19-74)	62 (30-74)	1.09 (1.05-1.14)	< 0.001
Sex - N (%) Male	28 (62)	26 (62)	1.02 (0.43-2.45)	> 0.9
Disease- N (%)				< 0.001
B-cell lymphoma (aggressive)	15 (33)	31 (74)	-	
B-cell lymphoma (indolent)	3 (7)	3 (7)	0.73 (0.11-5.95)	
Hodgkin lymphoma	16 (36)	3 (7)	3 (7)	
T-cell lymphoma	11 (24)	5 (12)	0.22 (0.06-0.72)	
Length of stay - days (median, range)	19 (5-27)	21 (7-38)	1.19 (1.05-1.38)	0.004

[Table 1. Baseline Characteristics]

Clinical Trial Registry: n/a

Disclosure: Valkal Bhatt (Incyte)

Miguel Perales (MolMed, NexImmune, Abbvie, Bellicum, Bristol-Myers Squibb, Incyte, Nektar Therapeutics, Novartis, Omeros, Takeda, Kite, Merck, Servier, Medigene)

Craig S. Sauter (Juno Therapuetics, Sanofi-Genzyme, Celgene, Spectrum Pharmaceuticals, Novartis, Genmab, Precision Biosciences, Kite, a Gilead Company, Gamida Cell, Pfizer, GSK)

Gunjan L. Shah (Janssen, Amgen)

P143

Comparison of Total Body Irradiation- vs chemotherapy-based Conditionings for Early Complications of Allogeneic Hematopoietic Stem Cell Transplantation in Children with All

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Background: Pediatric patients with acute lymphoid leukemia (ALL) mainly receive myeloablative conditioning regimens based on total body irradiation (TBI) or chemotherapy (CHT) including busulfan before allogeneic hematopoietic cell transplantation (allo-HSCT). Due to severe long term complications of TBI, CHT-based conditioning has been preferred in many centers for pediatric patients. But there is lack of data about the early complications of allo-HSCT comparing TBI vs CHT.

Methods: To compare early complications of TBI and CHT consisting of busulfan, fludarabine and thiotepa conditioning regimens, we performed a retrospective analysis of single center registry data collected between 1st of January, 2015 and 30th of June, 2019 to assess the outcomes of patients receiving these regimens before an allo-HSCT. Variables associated with early complications of allo-HSCT (only in the first 100 days after transplant) and hence included into the analysis were: engraftment time, engraftment syndrome, acute graft versus host disease (aGVHD) grade 2-4, veno-occlusive disease (VOD), capillary leakage syndrome (CLS), thrombotic microangiopathy (TMA), cytomegalovirus (CMV) reactivation, bloodstream infection (BSI), hemorrhagic cystitis and posterior reversible encephalopathy syndrome (PRES).

Results: The characteristics of 72 patients was revealed in Table 1. These two conditioning regimens (CHT, n: 50; TBI, n: 22) were compared in pediatric ALL patients aged 18 years or younger at the time of transplantation in complete morphological remission (CR) (CR1, n: 40/CR2, n: 30/>CR2, n: 2). The incidences of aGVHD grade 2-4, VOD, CLS, TMA, BSI, hemorrhagic cystitis and PRES before day 100 were similar for both conditioning regimens; however, patients received TBI-based conditioning had significantly longer neutrophil engraftment time (17.5 vs 13 days, p: 0.001) and tended to have more engraftment syndrome (45.5% for TBI vs 24.0% for CHT, p: 0.069). Multivariate analysis showed that TBI-based conditioning was associated with a longer neutrophil engraftment time (HR: 1.20, p: 0.006), more CMV reactivation (HR: 3.65, p: 0.038) and more engraftment syndrome (HR: 3.18, p: 0.078). At the time of last follow-up, 59 patients were alive. Four patients died of disease progression and infection (n: 4) was the most common cause of non-relapse mortality (NRM). With a median follow-up of 25 months (2-45 months), 3 year-overall survival (OS) and -event-free survival (EFS) were 79.1% (95% CI 68.9-89.4). There was no survival advantage between two conditioning regimens [84.2% (95% CI 67.7-100.0) for TBI and 77.0% (95% CI 64.2-89.7) for CHT, p: 0.538]. Cumulative incidence of relapse (CIR) and NRM were 11.9% (95% CI 6.2-22.4) and 14.0% (95% CI 7.6-26.0), respectively, for all patients. Both groups showed a similar CIR and NRM [CIR, 5.0% (95% CI 0.7-37.1) for TBI and 6.6% (95% CI 2.2-19.7) for CHT, p: 0.844; NRM, 10.2% (95% CI 2.7-38.3) and 15.7% (95% I 7.9-31.5), respectively, p: 0.588].

Conclusions: Although this retrospective registry-based analysis has several limitations, both conditioning regimens showed a similar early complications profile. Conditioning by TBI demonstrated longer neutrophil engrafment time and more CMV reactivation in comparison to CHT and also there

is a tendency for engraftment syndrome with TBI based conditioning. Comparison of these conditioning regimens warrant further evaluation in a prospective manner.

Disclosure: Nothing to declare.

P144

Differential Alemtuzumab Dosages in T-cell Deplete Allogeneic Haematopoietic Stem Cell Transplants for Myeloid Malignancies

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Background: Alemtuzumab is a monoclonal anti-CD52 antibody, a pan-lymphodepleting immunosuppressive agent in common use as part of conditioning for allogeneic stem cell transplantation (Allo-HSCT) in United Kingdom and many other centres across the globe, with benefits related to reduced graft versus Host disease (GVHD) and lower non-relapse mortality (NRM). However, evidence for effective dose schedule in Allo-HSCT remains debatable with some concerns related to delayed immune reconstitution, increased relapses with higher doses; but increased risk of acute and chronic GVHD with lower doses.

Methods: We retrospectively evaluated 391 patients undergoing Allo-HSCTs for myeloid malignancies(AML/MDS/MPNs) during 12-year period (Jan 2008 to April 2019) at Kings College Hospital, London. Two dosage schedules of Alemtuzumab based T-cell deplete conditioning with FluBu and Bu-Cy regimens using standard 100mg dose (n-158; 40.4%) were compared to those (n-233; 59.6%) receiving a lower < 100mg dose, with respect to HSCT outcomes. Close monitoring for infections, GVHD, chimerism (included fractionated lymphoid/myeloid) and disease assessments post HSCT were undertaken as per institutional policy.

Results: Baseline characteristics were broadly similar between the 2 groups in terms of conditioning intensity, patient age, underlying disease, disease risk index and donor HLA matching. Median follow up of survivors was 38 months (range 01-136months) with significantly longer follow up available for 100mg group (median 102 months vs 28 months;p< 0.001). Standard Alemtuzumab dose (100mg) was associated with a significant improvement in composite GRFS (54% vs 24% at 60 months; p< 0.001; Fig 1a) and significantly lower incidence of both grade 3-4 acute (18% vs 42% at D100; p-< 0.003; Fig 1b) and chronic GVHD (all grades)(19% vs 42% at 12 months; p< 0.001; Fig 1c) compared to < 100mg dose. No differences in OS (45% vs 45% at 60 months; p-0.55; Fig 1d), NRM (28% vs 23% at 60 months; p-0.32; Fig 1e) and relapse incidences (29% vs 30% at 60 months; p-0.75; Fig 1f) were observed along with no impact on rates of CMV, Adenoviraemia or invasive fungal disease(IFD) between the 2 cohorts, except lower EBV viraemia incidence was noted in 100mg dose group(49% vs 66%; p< 0.001).

Multivariate adjusted cox analysis (MVA) confirmed older age>60 years, mismatched unrelated donor, absence of chronic GVHD, disease relapse, ITU admission event, CMV reactivation and absence of any EBV reactivation post HSCT as significant predictive factors for poor OS, but this not affected by different Alemtuzumab doses, disease risk index or type of disease. Similarly NRM was not affected by differential alemtuzumab doses, while GRFS was positively influenced by standard 100mg dose on MVA

Conclusions: Despite concerns of relapses and delayed immune reconstitution, this report on a homogenous cohort of allo-HSCTs in myeloid malignancies confirms the contrary with no impact on OS, NRM or relapses and no significant increase in opportunistic infections with 100mg dose. With improved supportive care, effective infection management and pre-emptive cellular therapy approaches available in current era, standard dose (100mg) of alemtuzumab can be considered safe and effective in both RIC and myeloablative allo-HSCTs for myeloid malignancies, with significantly lower GVHD related morbidity and overall better GFRS.

Disclosure: No disclosures or conflict of interest to declare.

P145

Novel Reduced Intensity Conditioning (RIC) Approach to Allogeneic Hematopoietic Cell Transplantation (HCT) in Patients with Benign and Malignant Disorders of T Cell Proliferation or Dysregulation

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Background: HCT has been used for decades as a definitive therapy in both primary immunodeficiency (PID) and hematological malignancy. A subset of these patients have a dysregulated T cell compartment either due to underlying PID or peripheral T cell lymphoma (PTCL) and are at particularly high risk of graft failure and/or relapse but may also enter HCT with significant comorbidities necessitating a low toxicity approach.

Methods: Twelve patients with PID (n=7) or PTCL (n=5; relapsed, n=3 and primary refractory, n=2), median age 22 years (range 7-64) received a serotherapy-based, radiation-free RIC platform designed with the goals of enhancing host T cell depletion pre-HCT to reduce graft failure risk and provide disease control, while also optimizing immune reconstitution, minimizing toxicities and complications such as graft-versus-host disease (GVHD), and permitting use of alternative donors via a post-transplantation cyclophosphamide-based approach. This was a high-risk cohort with median HCT comorbidity index score of 3 (range 0-7), and active disease in 2 PTCL patients at time of HCT. Alternative donors were commonly used: 5 patients received mismatched grafts (4 haploidentical, 1 mismatched unrelated) and 5 matched unrelated grafts. Patient and donor characteristics are detailed in Figure 1b.

Results: Neutrophil recovery occurred at median day +16 (range 13-25). With median follow up of 6 months (range 2-14), graft-failure-free survival was estimated at 81% at 6 months, with no deaths. There were 2 graft failures (1 primary, in context of rising donor-specific HLA antibodies despite desensitization, and 1 secondary), both now with full donor chimerism after retransplantation. GVHD rates have been low, with grade 1 skin only acute GVHD, not requiring systemic therapy (n=1), grade 2 steroid-responsive acute GVHD of the skin and gut (n=1), and mild chronic GVHD (n=1). Bacterial infectious complications included sepsis/pneumonia (n=2), bacteremia (n=2), and furunculosis (n=1). While BK virus-associated hemorrhagic cystitis occurred at high rates (58%), severe viral complications were infrequent. CMV reactivation occurred in 29% of known at-risk patients (n=2 of 7), with no CMV disease. RSV, asymptomatic adenoviruria, and anemia due to parvovirus B19 occurred in 1 patient each, none requiring inpatient management. At last follow up, some degree of phenotype reversal is evident in all PID patients, and all PTCL patients are either in confirmed complete remission (n=2) or show no clinical signs of disease (n=3).

Conclusions: Based on promising early outcomes, this novel platform offers a safe and effective HCT approach to diseases with historically poor survival or high risk of graft failure, while enabling use of alternative donors. Longer term follow up is needed to better characterize phenotype reversal in PID patients, incidence of relapse in PTCL patients, graft durability, immune reconstitution and late toxicities of the platform.

Clinical Trial Registry: NCT03663933
NCT03922724

Disclosure: None

P146

Profound Lymphopenia at the time of anti-thymocyte Globulin Administration is not Predictive of Survivals after allo-transplantation

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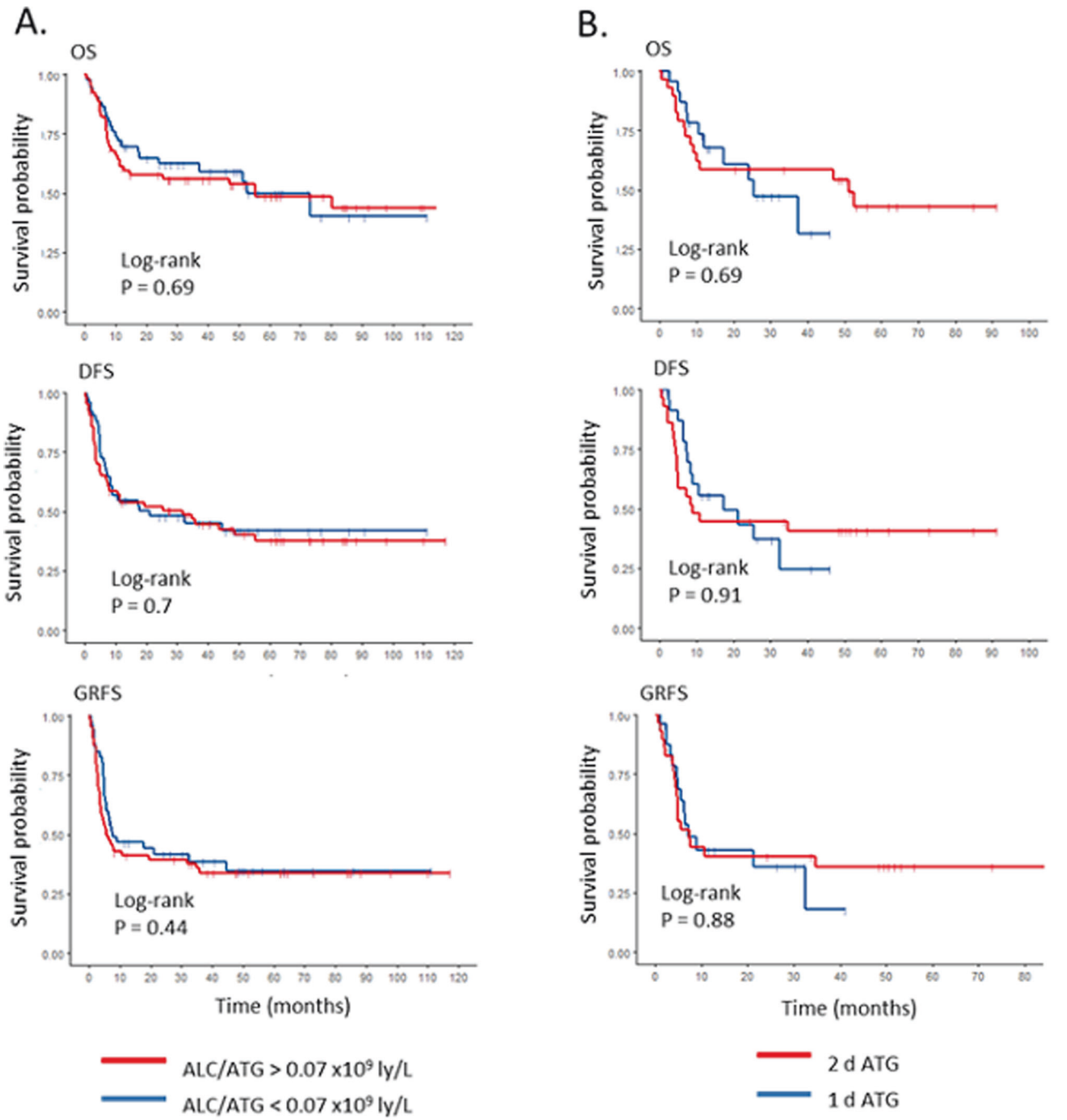
Background: Prophylactic T cell depletion via anti-thymocyte globulin (ATG) during ASCT conditioning is a standard of care for GVHD prophylaxis, although the optimal dosing strategy is still unknown. Recent studies have reported that absolute lymphocyte counts at the time of ATG administration (ALC/ATG) may predict survivals in ASCT with unrelated donors, suggesting that the dose (especially at the cut-off of $< 0.1x10^9$/L) and timing of ATG administration must be taken into account (Soiffer et al, JCO 2017; Kennedy et al, BBMT 2018).

Methods: To examine this issue, the outcome of ASCT was evaluated in all consecutive patients transplanted between 2009 and 2019 for a hematologic malignancy in our department. Conditioning regimen were purine analogue/busulfan/ATG-based. The reduced-intensity conditioning (RIC) regimen consisted of fludarabine 30mg/m²/day (d) from d-6 to d-2, busulfan 3,4 mg/kg/d from d-4 to d-3 and ATG (Thymoglobuline, Sanofi, Lyon, France) 2,5 mg/kg/d, d-2 and d-1 (FB2A2) or the same but with clofarabine 30mg/m²/d in replacement of fludarabine with 1 or 2 d of ATG (CloB2A2/CloB2A1). Reduced-toxicity myeloablative conditioning regimens (RTMAC) consisted of the same as FB2A2 but with 3 or 4 d of busulfan instead of 2



[Survivals according to (A) ALC/ATG (B) number of ATG administration in lymphopenic patients]

(FB3A2/FB4A2). Peripheral blood stem cells were used as source of graft from matched or 9/10 mismatched unrelated donors or siblings. We exhaustively looked at patients for whom a blood differential was available in order to evaluate the impact of lymphocyte counts at the time of ATG administration (ALC/ATG) in terms of overall, disease-free and GVHD-free/relapse-free survival.

Results: Of 395 eligible patients, 116 had a documented differential on the day of ATG administration. The median follow-up for alive patients was 49 months. RIC was administered in 80 (69%) of the patients as follows: 39 FB2A2, 12 CLOB2A2 and 29 CLOB2A1. The 36 other patients received RT-MAC: FB3A2 for 27 and FB4A2 for 9 respectively. Four-year OS, DFS and GRFS were 56.2%

(47-66), 40.9% (32-51) and 34.5% (26-45), respectively for the whole cohort.

ROC curve analysis failed to identify a cut-off allowing to predict better survivals according to ALC/ATG. The median ALC/ATG was $0.070x10^9$/L (range: 0-2.300). No difference in terms of survivals was observed when considering patients under this threshold vs others (Fig A). The same was true when considering $0.100x10^9$/L as ALC/ATG cut-off. Regarding MAC, the median ALC/ATG was $0.100x10^9$/L with no difference in survivals between patients under or above this value. The same was true for RIC with ALC/ATG cut-offs below the median ($0.055x10^9$/L) or below $0.100\ x10^9$/L. Interestingly, considering patients with ALC/ATG below $0.100\ x10^9$/L within the RIC setting, survivals were similar between patients who received 1d (n=25) or 2d (n=29) of ATG (Fig B).

Conclusions: This study indicates that ATG can be administered to ASCT recipients whatever the conditioning regimen and the lymphocyte count.

Clinical Trial Registry: Non applicable

Disclosure: Nothing to declare.

P147

Lipid Core Nanoparticles as Vehicle for Etoposide in the Conditioning Regimen of Marrow Transplantation in Acute Myeloid Leukemia not Responding to Induction Therapy: Pilot Study

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Background: Myeloablative conditioning regimens for HSCT elicits high toxicity

Maranhao (1994, 2003) have already showed that lipid core nanoparticles (LDE), as carrier of anti-cancer drugs reduces drug toxicity. We tested LDE-etoposide in the myeloablative conditioning regimen of HSCT of AML patients not responding to induction therapy.

Methods: A prospective pilot study with 15 patients from 2 academic hospitals in São Paulo, Brazil

Inclusion criteria: primary AML not responding to the induction therapy, 18 - 70yr, HLA-matched related or unrelated donor, ECOG ≤ 2, Karnofsky ≥ 80, and comorbidity score ≤ 2. Exclusion criteria: haploidentical donor or umbilical cord blood.

Conditioning regimen: LDE-etoposide from 20mg/kg/BW until 60mg/kg/BW on D-7 and D- 6 and TBI 1200cGy on D-3, D-2 and D-1. D0: day of stem cells infusion. For unrelated donors, thymoglobulin was added. Graft-vs-host disease (GVHD) prophylaxis: cyclosporine and methotrexate.

Results: 15 AML patients (8 males, 7 females), aged 22-66 yrs (median 47 yrs), 10 x 10 HLA-matched stem cells (9 related, 6 unrelated donors) were enrolled. Peripheral stem cell donors were mobilized with GCSF. CD34+ average infused cells were $7.6\pm1.6 \times 10^6$ /kg/BW. Two patients received peripheral and marrow stem cells: CD34+ ($9.0\pm1.0 \times 10^6$ cells/kg/BW) and TNC ($3.5\pm0.5 \times 10^8$ cells/kg/ BW). Neutrophil engraftment occurred on day 20 ± 5 and platelet 16 ± 4. All patients engrafted. There were no episodes of hypotension, anaphylaxis, or other adverse effects during LDE-etoposide infusion. There was no grade 4 or higher toxicities. Grade 3 toxicity: mucositis (6 patients), diarrhea (3) and elevation of total bilirubin (1), all before D+30. SOS was observed in 1 patient based on the Seattle criteria, which did not fulfill the Baltimore criteria.

Acute GVHD: skin grade 1 in 4 patients and grade 2 in 1. One patient had skin and GI grade 1 aGVHD. The rate of systemic aGVHD was 33,7% (26.7% grade 1, 6.7% grade 2). Chronic GVHD: 8 patients (57,1%): 4 moderate global cGVHD (28.6%) and 4 severe global cGVHD (28.6%). No fatal GVHD events occurred.

CMV reactivation: 5 patients before D+100 and 1 patient after D+100. Bacterial infection: 7 patients before D + 100 (3 by multiresistant bacteria) and in 7 patients after D +100 (2 by multiresistant bacteria). One patient had disruption of the pulmonary aspergilloma on D+41 after engraftment and one reactivated Aspergilosis sp infection after D+60.

Five patients died, one before D+100 (aspegilloma disruption), 3 patients of refractory relapse on D+174; D +207, and D+285; and 1 patient during re-induction therapy on D+181. Seven patients are in complete response with 100% chimerism.

The median follow-up time of patients was 17.4 months (41 - 836days). Cumulative incidences of overall survival, event-free survival, relapse and non-relapse mortality at 27 months were 66.7%, 46.7%, 46.7% and 6.7% respectively.

Conclusions: LDE-etoposide based conditioning regimen of HSCT for AML has a clear-cut potential for being advantageously introduced in the clinical practice.

Disclosure: Nothing to declare.

P148

A Phase II Study to Investigate the Efficacy of short-term Everolimus in Addition to post-transplant

Cyclophosphamide as graft-versus-host-prophylaxis after Allogeneic Stem Cell Transplantation (Octet-ever)

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Background: Conditioning regimens and the choice of immunosuppression have substantial impact on immune reconstitution after allogeneic hematopoietic stem cell transplantation (aHSCT). The pivotal mechanism to achieve and maintain remission in patients undergoing allogeneic transplantation is the induction of the graft-versus-tumor effect (GvT). Such GvT effects are not achieved in all patients transplanted and relapse is a common event. Moreover, graft versus host disease (GvHD) attacking the recipients' healthy tissues often preceeds the development of the GvT effect and requires prolonged immunosuppressive therapy hereby abolishing the desired GvT effect. Classic immunosuppressive strategies implementing calcineurin inhibitors (CNI) hamper the immune recovery and built-up of the anti-cancer immune response.

Methods: We designed a phase II clinical study for patients with high-risk hematological malignancies using a CNI-free approach consisting of post-transplant cyclophosphamide and short-term everolimus, an immunosuppressant with anti-proliferative properties given from d+5 to d+100, after reduced-intensity conditioning and matched peripheral blood stem cell transplantation. Results after recruitment of all 19 patients planned will be presented.

Results: Nineteen patients with relapsed or refractory lymphoma and myeloma at high-risk for relapse underwent allogeneic peripheral blood stem cell transplantation with a matched related or unrelated donor after conditioning with fludarabine and busulfan. After application of post-transplant cyclophosphamide on d+3 and +4 after transplant, short-term everolimus was given from d+5 to d+100. Primary endpoint is the cumulative incidence and severity of acute GvHD. All patients presented a complete donor chimerism by d+30 and d+100. Engraftment was delayed with 17, 29 and 27 days for neutrophils, hemoglobin and platelets, respectively. The overall incidence of acute GvHD was 53%. Grade II aGvHD was found in 36% while none of the patients experienced grade III or IV aGvHD. In most cases aGvHD presented as cutaneous manifestation shortly after engraftment. The overall incidence of chronic GvHD was 21%, which was mild in all cases. Two patients died due to sepsis 18 and 20 days after transplant. One patient died due to secondary AML/ MDS three years after transplant. The cumulative incidence of non-relapse mortality on d+100 and d+365 was 11% with a median follow-up of 628 days (18-1152 days). There was one secondary graft failure. The cumulative incidence of relapse was 32% and 37% at one and two years after transplant, respectively. Relapse-free survival was 58% and 52% after one and two years. The overall survival was 73% and 64% after one and two years. All surviving patients are currently without cGvHD and immunsuppressive medication.

Conclusions: The use of post-transplant cyclophosphamide and short-term everolimus is safe with low rates of aGvHD, no severe aGvHD and a low incidence of mild cGvHD translating into a low rate of early non-relapse mortality. The relapse rates in this difficult to treat patient population are encouraging and warrant further studies using the combination of post-transplant cyclophosphamide and everolimus.

Clinical Trial Registry: Study protocol code: Uni-Koeln-1717 EudraCT number: 2013-005507-14

Disclosure: The study was supported by a research grant from Novartis to CS/UH. The other authors have no conflicts of interest to disclose.

P149

Allogeneic Stem Cell Transplantation in Patients ≥ 65 Years with Hematological Malignancies after Myeloablative treosulfan-based Conditioning: Results in 118 Patients

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Background: Allogeneic hematopoietic stem cell transplantation (allo-SCT) remains the only potentially curative treatment for many hematological malignancies. For most of these, median age of occurrence is 60 years and even more. Nevertheless, the use of allo-SCT had been usually limited to a younger population because of concern related to non-relapse mortality (NRM) of older patients. We here report our large experience in allo-HSCT in patients diagnosed with hematological malignancies and older than 64 yrs.

Methods: From 2005 to 2019, 118pts older than 64yrs received a T-replete allo-SCT for acute leukemias (88pts, 75%), myelodysplastic syndromes (21pts, 18%) or others hematological malignancies (9pts, 7%) at our center. Donors were matched siblings in 19pts (16%), unrelated in 39pts (33%), haploidentical in 57pts (48%) and single cord blood unit in 3pts (3%). Median age at transplant was 67y (65-76). Seventy-seven patients (65%) were transplanted in early disease status (complete remission, CR, or upfront) while 41pts in active disease (35%). One-hundred and six patients out of 118 (90%) received a myeloablative treosulfan-fludarabine based conditioning regimen. Graft-versus-host-disease prophylaxis was sirolimus-based in 91 out of 118 pts (77%), cyclosporine-based in 27pts (23%). Post-transplant Cyclophosphamide was used in 68pts (58%), antithymocyte globulin in 41pts (35%).

Results: Median follow-up among survivors (63pts) was 35 months (3-104). All but two patients engrafted. Median time from transplant to engraftment was 21 days for neutrophils (11-50) and 24 days for platelets (9-632).

Overall survival (OS) at 1 and 3 years was 67+/-4% and 56+/-5%, respectively. Disease free survival (DFS) at 1 and 3 years was 62+/-5% and 46+/-5%, respectively. Day-100 NRM was 18+/-4%. The 1 and 3-year NRM was 26+/-4% and 36+/-5%, respectively. The 1 and 3-year cumulative incidence (CI) of relapse was 16+/-4% and 27+/-5%. Day-100 CI of acute GvHD grade II-IV was 41+/-5%, of grade III-IV was 15+/-3%. CI of overall cGvHD at 1 year was 30+/-5%, of extensive cGvHD was 19+/-4%. No differences in transplant outcomes were found in patients younger or older than 70yrs.

In multivariate analysis early disease status at transplant was the only risk factor associated to OS (HR 0.478; p=0.007. CI: 0.279-0.818), DFS (HR 0.435; p=0.001. CI: 0.262-0.722) and NRM (HR 0.433; p=0.011. CI: 0.227-0.823). The 3-year OS, DFS and NRM for patients transplanted in early disease status were as follows: 70+/-5%, 58 +/-6% and 13+/-4%, respectively. Matched sibling donors were associated to lower CI of day-100 aGvHD in multivariate analysis (HR 0.538; p=0.023. CI: 0.316-0.918). Diagnosis of acute leukemia was the only risk factor associated to lower CI of cGvHD (HR 0.311; p=0.00044. CI: 0.162-0.597).

Conclusions: Based on our results we can conclude that age alone should not limit allo-SCT eligibility of patients with hematological malignancies, above all in early disease status. The use in the majority of our patients of treosulfan, an alkylating agent with a low toxic profile, could have contributed to the low incidence of NRM without negatively affecting long-term disease control.

Disclosure: Nothing to declare.

P150

Abstract already published.

P151

Fludarabine-melphalan Conditioning Results in Favorable leukemia-free Survival after Allogeneic Transplantation in Patients with Active or Measurable Residual AML

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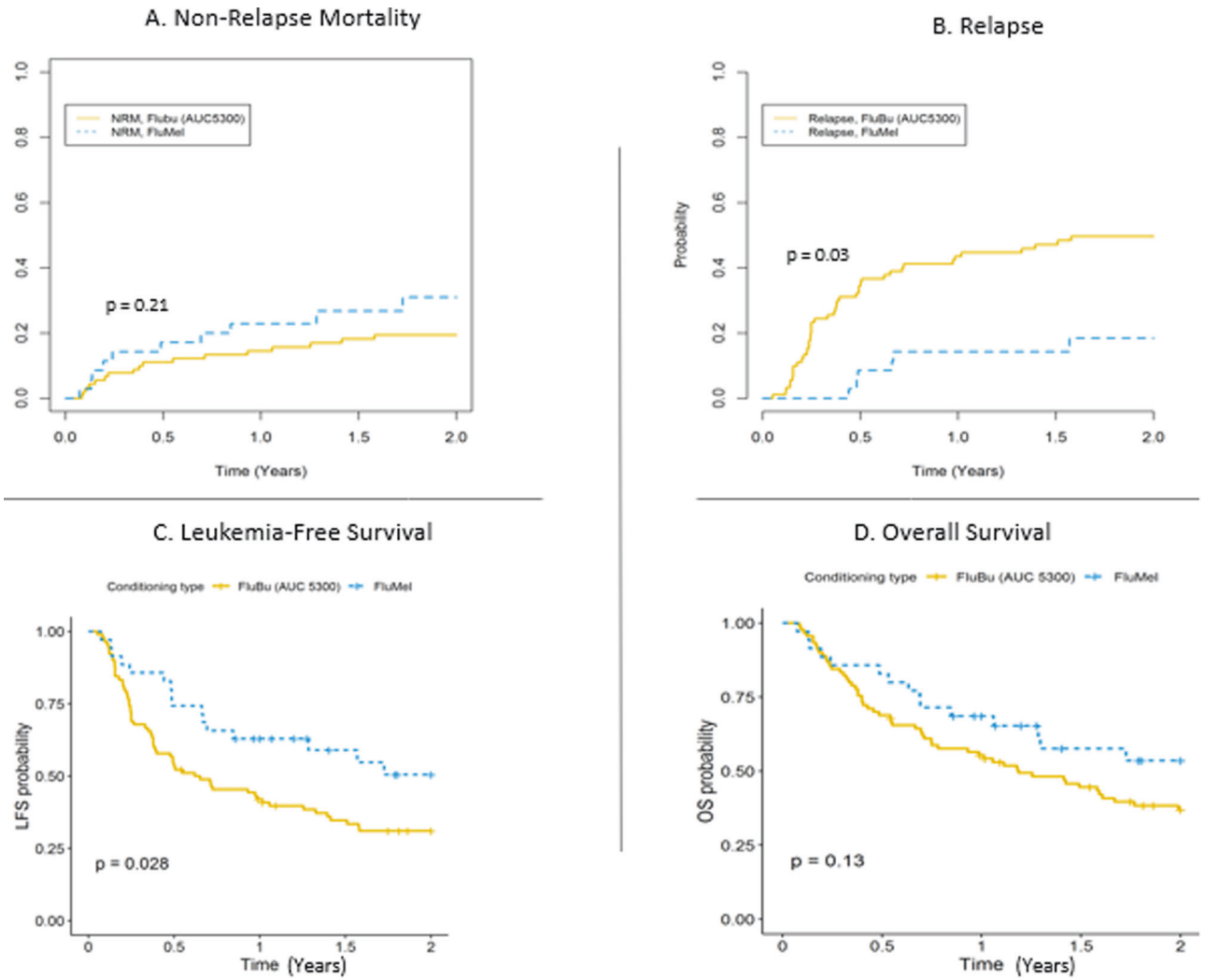
Background: A recent large CIBMTR study demonstrated no survival benefit with use of myeloablative (MAC) compared to reduced-intensity conditioning (RIC) in patients receiving allogeneic hematopoietic cell transplant (alloHCT) for acute myeloid leukemia (AML) or myelodysplastic syndrome with high-risk disease risk index (DRI) (Bejanyan, ASH 2019). While commonly used MAC fludarabine-busulfan (FluBu) and RIC fludarabine-melphalan (FluMel) result in similar outcomes after alloHCT for AML in remission (Eapen, Blood Adv 2018), the preferred conditioning regimen for active or detectable residual (MRD+) AML at alloHCT remains unknown.

Methods: We analyzed outcomes of 125 patients with active (n=62) or MRD+ (n=63) AML who received alloHCT (2005-2017) with either MAC FluBu4 (72%) with PK-targeted IV daily average Bu AUC of 5300 or RIC FluMel (28%) with total Mel dose of 140 mg/m2.

Results: The group receiving FluMel had a higher proportion of >60-year-old patients (74% vs 21%, p< 0.001), adverse genetic risk AML by ELN 2017 (63 % vs. 51%, p=0.015), alloHCT performed from 2015-2017 (83% vs. 33%, p< 0.001) and Tacrolimus/ Sirolimus-based GVHD prophylaxis (86% vs. 50%, p=0.001). The rest of the characteristics were similar between FluBu and FluMel recipients, including the disease status at HCT (active AML, 54% vs. 37%, p=0.14). Probabilities of 2-year non-relapse mortality (NRM), relapse, leukemia-free survival (LFS) and



[Clinical outcomes of active or MRD+ AML patients by conditioning regimen]

overall survival (OS) are shown in the Figure. In multiple regression analysis after adjusting for disease status at alloHCT (active vs. MRD+) and DRI, the FluMel regimen compared to FluBu resulted in significantly lower risk of relapse (HR=0.26, 95% CI 0.11-0.63; p=0.003) and higher LFS (HR=0.49, 95% CI 0.28-0.86; p=0.014), but there was only a statistically non-significant trend of better OS (HR=0.57, 95% CI 0.32-1.02; p=0.06) (Table). NRM was similar between the two conditioning groups.

Conclusions: In conclusion, our data support the use of the RIC FluMel regimen for alloHCT in patients with MRD + or active AML as it results in lower risk of relapse and better LFS compared to MAC FluBu. This study´s findings require confirmation in a larger cohort of patients with MRD+ and active AML.

Variables	NRM		Relapse		LFS		OS	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
FluMel vs FluBu	1.50 (0.71-3.17)	0.29	0.26 (0.11-0.63)	0.003	0.49 (0.28-0.86)	0.014	0.57 (0.32-1.02)	0.06
Active Disease vs MRD+	2.18 (0.81-5.92)	0.12	1.07 (0.44-2.60)	0.89	1.40 (0.69-2.84)	0.35	1.72 (0.84-3.52)	0.14
High/Very High DRI vs Low/Intermediate DRI	1.79 (0.68-4.71)	0.24	3.11 (1.11-8.68)	0.03	3.01 (1.40-6.51)	0.005	3.61 (1.64-7.95)	0.0015

[Multivariate Analysis of Clinical Outcomes]

Disclosure: Aleksandr Lazaryan- Eusa Pharma LLC scientific advisory board

The rest of the authors have nothing to declare.

P152

Sequential Conditioning: Flamsa-TBI versus flamsa-treo in High Risk Acute Myeloid Leukemia (AML) in First Complete Remission and High Risk Myelodysplastic Syndrome (MDS)

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Background: Reduced Intensity Conditioning (RIC) regimens allowed allogeneic stem cell transplantation (allo-SCT) for patients with high risk hematological malignancies at advanced age and/or with comorbidities. In aggressive leukemia, RIC regimens may not be sufficient to control the disease, resulting in high relapse rates. The FLAMSA RIC regimen, that associates a short course of chemotherapy with a RIC backbone including TBI 4Gy, reported encouraging results in the treatment of high risk AML and MDS. Still the original protocol is associated with acute toxicity, mainly due to TBI. In this context Treosulfan is being investigated at different dosages as an attractive alternative in order to ameliorate the toxicity profile, preserving the anti-leukemic activity in a high risk population.

Methods: We substituted in the FLAMSA protocol (Schmid, JCO 2005) the TBI with Treosulfan 12g/m2/d from day -6 to -4 (FLAMSA-Treo). A retrospective comparison was then performed between FLAMSA-TBI and FLAMSA-Treo considering patients with high risk AML in first Complete Remission (CR1) and high-risk MDS. The high risk status was defined according to molecular markers, karyotype, delayed response to induction chemotherapy, and AML secondary to MDS or previous chemotherapy. Standard risk AML patients in molecular relapse after standard treatment were also considered "high risk". The decision to treat patients with FLAMSA-Treo instead of FLAMSA-TBI conditioning was at the physician's board discretion according to TBI availability, patient age and/or presence of comorbidities.

Results: Between 01/2006 and 06/2019 a total of 59 patients with high risk AML in CR1 (n=53) and high risk MDS (n=6) received allo-SCT after a FLAMSA conditioning. Out of 59 patients, in 45 (76%) a FLAMSA-TBI protocol was administered, while in the remaining 14 (24%) Treosulfan replaced TBI. All the patients, except three, received PBSC as source of transplantation. The GvHD Prophylaxis was based on a combination between CyclosporinA and Mycophenolate Mofetil. Further Patients' characteristics are listed in **Figure 1a**. Comparing the outcome of the two subpopulations (TBI vs Treo), no significant differences were observed in terms of OS (1yOS 73% vs 90% respectively, p=0.15), TRM (1yTRM, 45% vs 7%, p=0.3) and relapse incidence (1yRI 22% vs 20%, p=0.4). Considering that we introduced the FLAMSA-Treo platform mostly in the last two years (13/14 pts) and in order to minimize potential biases related to the year of transplantation, we performed a time driven sub-analysis, including only patients transplanted since 01/2017 in both cohorts (n=23, TBI n=10, Treo n=13). In this context, Treosulfan proved to confer a survival advantage to TBI-based conditioning (1yOS 92% vs 50%, p=0.05), manly due to a reduction in the transplant related mortality (1yTRM 8% vs 40%, p=0.09).

Conclusions: In our analysis the Treosulfan-based FLAMSA protocol demonstrated a favorable toxicity profile, at least not inferior to the standard platform including TBI, for the treatment of high risk AML/MDS older patients and/or with comorbidities. The reduced toxicity profile of Treosulfan could favor especially AML patients in first complete remission. A larger prospective series of patients is needed in order to confirm these promising preliminary findings.

Disclosure: Sala E: Honoraria with Gilead.

P153

Increased non-relapse Mortality and Poor Overall Survival in Elderly Patients Treated with Fludarabine and Myeloablative Dose of Busulfan: Transplant Complications Working Group of the JSHCT

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Background: Fludarabine and a myeloablative dose of intravenous busulfan (Flu/Bu4) are widely used together in

allogeneic hematopoietic stem cell transplantation (alloHSCT) as a reduced-toxicity conditioning regimen. Although Flu/Bu4 has been applied to a wide range of age groups, the increasing number of transplant-related complications observed among elderly patients remains a major concern.

Methods: We conducted a retrospective survey of alloHSCT in Japan, using the transplant outcomes registry database maintained by the Transplant Registry Unified Management Program. The following inclusion criteria were applied: patients >15 years old with hematological malignancies who had received their first alloHSCT between 2006 and 2017, and who were treated with Flu/Bu4 (total intravenous busulfan dose of 11.2-16 mg/kg or equivalent). Patients who received total body irradiation (TBI) or other chemotherapeutic drugs were also included. Patients who received alloHSCT from cord-blood donors were excluded.

Results: The median age of patients was 58 years (range 16-80), and 43.4% of patients were 60 years or older. Of 1,443 patients, 62.6% were male. Patients were diagnosed with myeloid malignancies (87.1%), lymphoid malignancies (9.1%), and other malignancies (3.0%). Approximately two-third of the patients (66.4%) received bone marrow transplantation, and 584 (25.5%) and 830 (36.3%) patients received alloHSCT from matched related donors and 8/8 matched unrelated donors. The 5-year overall survival (OS) rate after alloHSCT was 45.5% (95% confidence interval [CI]: 42.3.5%-48.6%) for the young group (< 60 years) and 34.8% (95% CI: 31.2%-38.5%) for the elderly group (≥60 years). Although the 5-year cumulative incidence of relapse was equivalent between the two groups ($P = 0.67$, 32.7% and 33.8%, respectively), the 5-year non-relapse mortality (NRM) was significantly higher for the elderly group (34.0%) than for the young group (25.0%) ($P < 0.01$). According to the multivariate analysis, increased patient age (≥60 years) was associated with an increased risk of poor OS (hazard ratio [HR] 1.33, 95% CI: 1.19-1.49, $P < 0.01$) and poor NRM (HR 1.40, 95% CI: 1.19-1.65, $P < 0.01$). In the subgroup analysis of the elderly group, advanced diseases, administration of chemotherapeutic drugs in addition to Flu/Bu4, and poor performance status (>0) were significant risk factors for poor OS. Those patients who received chemotherapeutic drugs in addition to Flu/Bu4 experienced thrombotic microangiopathy and bleeding complications more frequently than those who did not ($P < 0.01$ for both comparisons); however, no significant differences were observed for primary causes of death. Nearly half of the elderly patients received TBI with Flu/Bu4. No significant difference in the OS was observed between patients treated with and without TBI; however, TBI resulted in significantly increased NRM ($P < 0.01$). Elderly patients treated with TBI experienced sinusoidal obstruction syndrome ($P < 0.01$) and bleeding complications ($P = 0.04$) more frequently than those treated without TBI.

Conclusions: Flu/Bu4 for elderly patients was associated with increased NRM, resulting in poor OS. In particular, the administration of additional chemotherapeutic drugs or TBI in combination with Flu/Bu4 in elderly patients increased the incidence of certain complications, which might be associated with poor NRM. Therefore, Flu/Bu4 should be used with caution in elderly patients.

Clinical Trial Registry: Not applicable

Disclosure: The authors declare. no conflict of interest. This work was supported in part by the Practical Research Project for Allergic Diseases and Immunology (Research Technology of Medical Transplantation) from Japan Agency for Medical Research and Development, AMED.

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Total Marrow and Lymphoid Irradiation (TMLI) in Combination with Cyclophosphamide and Etoposide improves the Outcome of Patients with poor-risk Acute Leukemia

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Background: Total marrow and lymphoid irradiation (TMLI) delivers augmented doses of radiation to the bone marrow while maintaining low doses to vital organs. We have conducted a phase II study in which we combined TMLI with cyclophosphamide (Cy) and etoposide (VP16) as a conditioning regimen to evaluate its anti-leukemia activity and safety/tolerability in patients with relapsed/refractory acute leukemia. We report here on 57 patients with a median of more than one year of follow-up.

Methods: TMLI (2000cGy to targets, 1200cGy to liver/brain) was administered on days -9 to -5, VP16 60mg/kg (adjusted body weight) on day -4, and Cy 100mg/kg (ideal body weight) on day -2. Bone marrow (n=6) or peripheral blood stem cells (n=51) were given on day 0. Graft versus host disease (GVHD) prophylaxis used was tacrolimus and sirolimus. The primary endpoint was progression free survival (PFS), and secondary endpoints included overall survival (OS), non-relapse mortality (NRM), and toxicity.

Results: Of the 57 patients (Table) with a median of at least 1 year of follow up, the median follow up was 12.5 months (range 1.1-48.3). Engraftment was noted for all patients. The CR/CRi rate at day +30 was 100% for the 56 patients with available data. Disease relapse/progression at 1 year was 47% (95%CI: 35-62). The estimates of NRM at 100 days and 1 year were 4% (95%CI: 1-14) and 6% (95% CI: 2-17), respectively. Relapsed disease after transplant occurred in 34 patients (60%). Four patients died in remission because of infections (n=2), West Nile encephalitis, and cGVHD.

One-year estimates of OS and PFS were 67% (95%CI: 53-78) and 48% (95%CI: 34-60), respectively. The OS/PFS of patients with a Duval score of ≥2 (i.e., high risk) was not statistically significantly different than those associated with a score < 2.

Grade ≥2 Bearman toxicities were bladder (Gr2 n=2), central nervous system (Gr2 n=1), gastrointestinal (Gr2 n=4), hepatic (Gr2 n=1, Gr3 n=1), pulmonary (Gr2 n=1), and renal (Gr2 n=2, Gr3 n=2). Grade 2 and 3 stomatitis occurred in 12 and 2 patients, respectively. There were no grade 4 toxicities or toxicity-related deaths. Acute GVHD was manageable and consistent with previous experience with the regimen.

Conclusions: 1) TMLI can be safely delivered in combination with VP16 and Cy, with NRM rates < 10%; 2) The regimen is effective for patients with relapsed/refractory acute leukemia; 3) Patient outcomes are superior over traditional rates as reported by Duval et al (Duval et al., J Clin Oncol 2010, pp.3730-9).

Variable	Median(range) or N(%)
Age at transplant (yrs)	40(16-59)
Prior regimens	3(1-7)
Disease diagnosis: AML, ALL	43(75), 14(25)
Disease status at alloHCT: 1RL, 2RL, IF	18(32), 4(7), 35(61)
Donor source: Sibling	26(46)
Matched unrelated, mismatched (9/10) unrelated	5(9), 26(45)
% Blasts in bone marrow, blood* at baseline	25(0**-95), 17.5(1-83)
Cytogenetics at baseline: ALL: Intermediate, Adverse, Unknown	7(12), 6(11), 1(2)
AML: Favorable, Intermediate, Adverse	1(2), 16(28), 26(45)

*[Patient characteristics. *28 patients had 0% and were excluded. **5 patients had extramedullary disease.]*

Clinical Trial Registry: NCT02094794

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Joycelynne Palmer: Gilead Sciences: Consultancy.

Haris Ali: Incyte: Consultancy, Speakers Bureau.

Ibrahim Aldoss: Jazz Pharmaceuticals: Honoraria, Other: travel/accommodation/expenses, Speakers Bureau; Agios: Consultancy, Honoraria; Helocyte: Consultancy, Honoraria, Other: travel/accommodation/expenses; AUTO1: Consultancy.

Ryotaro Nakamura: Kirin Kyowa: Other: support for an academic seminar in a university in Japan; Merck: Membership on an entity´s Board of Directors or advisory committees; Celgene: Other: support for an academic seminar in a university in Japan; Alexion: Other: support to a lecture at a Japan Society of Transfusion/Cellular Therapy meeting

Amandeep Salhotra: Celgene: Other: Research Support; Kadmon Corporation: Other: Non paid consultant. Ali: Incyte: Consultancy, Speakers Bureau.

P155

A CD45-targeted Antibody Drug Conjugate Enables Allogeneic Hematopoietic Stem Cell Transplantation as a Single Agent in Mice

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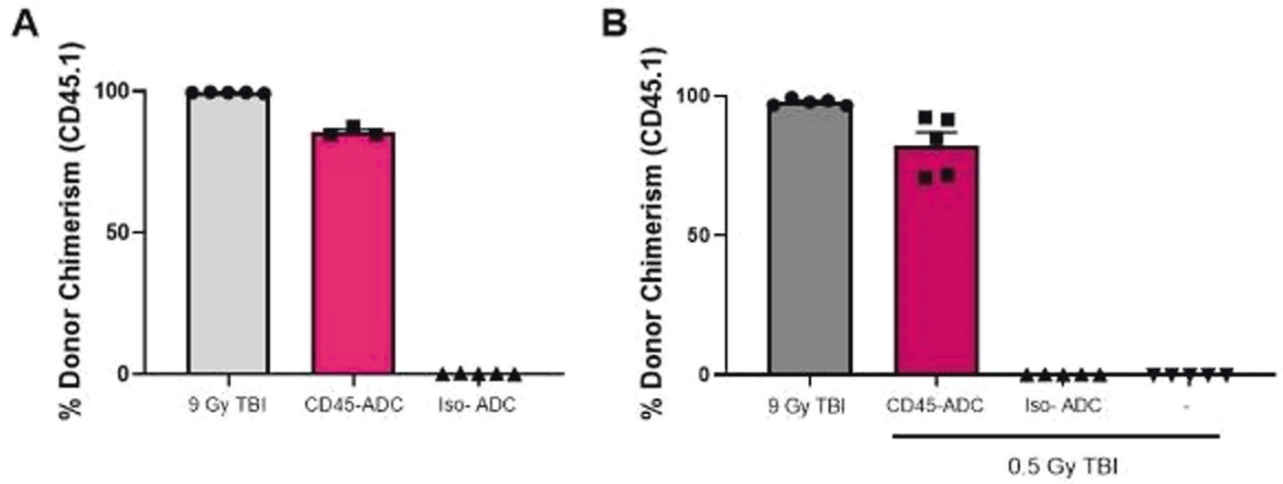
Background: Allogeneic hematopoietic stem cell transplant (Allo-HSCT) is a potentially curative treatment for malignant and non-malignant blood disorders. However, current conditioning regimens limit the use of this curative procedure due to conditioning-related mortality and morbidities. As a result, many patients are not able do not undergo this potentially curative therapy. We developed a novel antibody drug conjugate (ADCs) to provide a readily translatable approach that is fully myeloablative as a single agent while reducing the toxicity associated with current conditioning agents. We have generated an anti-mouse CD45 ADC to model this approach for conditioning recipients for minor mismatch and fully allogeneic HSCT.

Methods: Our tool CD45 ADC is engineered for rapid clearance (T1/2=1.7hr) to enable HSCT after conditioning, and a single dose of 3 mg/kg is fully myeloablative. To determine if the tool CD45-ADC could successfully condition recipients for minor histocompatibility antigen mismatched allo-HSCT, we used a single dose of the tool CD45-ADC to condition DBA/2 hosts (H-2d, CD45.2+) for transplant with CByJ.SJL(B6) mice (H-2d, CD45.1+).



[Figure 1]

A matched dose of non-targeted isotype ADC (Iso-ADC) was used as a negative control, while 9 Gy TBI was used as the conventional conditioning positive control. To determine if the tool CD45 CD45-ADC could successfully condition recipients for fully mismatched allo-HSCT, we compared the ability of a single dose of the tool CD45-ADC, alone or supplemented with various levels of TBI, to condition C57BL/6 hosts (H-2b, CD45.2+) for transplant with cells from CByJ.SJL(B6) mice. We used matched doses of Iso-ADC with and without supplemental TBI and 9 Gy TBI as controls. In both studies, conditioned mice were transplanted with 2x107 whole BM cells, and peripheral chimerism was monitored over 16 weeks.

Results: In the minor mismatch (Balb/c CD45.1+→DBA/2 CD45.2+) model of allogeneic HSCT, a single dose of the tool CD45-ADC enabled full donor chimerism through 12 weeks as a single agent (Figure 1A); >90% donor chimerism was observed in T-, B-, and myeloid lineages, comparable to 9 Gy TBI conditioning. Treatment with a matched dose Iso-ADC was not effective. In the fully mismatched Balb/c → C57Bl/6 allo-HSCT model, CD45-ADC as a single agent enabled partial, transient chimerism at 3 weeks post-transplant; an iso-ADC did not. With CD45-ADC as the primary agent, supplementation with TBI doses as low as 0.5 Gy enabled durable full donor chimerism (Figure 1B), comparable to 9 Gy TBI alone. Iso-ADC required a minimum supplementation of 4 Gy TBI to enable donor chimerism.

Conclusions: Conditioning with CD45-ADC is fully myeloablative and enables complete chimerism in a minor mismatch allo-HSCT model as a single agent and enables complete chimerism in the full mismatch allo-HSCT model when supplemented with low dose (0.5 Gy) TBI. This targeted, readily translatable approach for safer conditioning could improve the risk-benefit profile for allogenic and haploidentical HSCT and may extend the curative potential of HSCT to more patients suffering from blood cancers and other diseases that may benefit from HSCT.

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Rahul Palchaudhuri- Ownership Interest and Salary, Magenta Therapeutics

Jennifer Proctor- Ownership Interest and Salary, Magenta Therapeutics

Bradley Pearse- Ownership Interest and Salary, Magenta Therapeutics

Ganapathy Sarma- Ownership Interest and Salary, Magenta Therapeutics

Geoff Gillard- Ownership Interest and Salary, Magenta Therapeutics

Asim Saha- Nothing to declare.

Tahirih Lamothe- Ownership Interest and Salary, Magenta Therapeutics

Melissa Brooks- Ownership Interest and Salary, Magenta Therapeutics

Katelyn Hammond- Ownership Interest and Salary, Magenta Therapeutics

Anjali Bhat- Ownership Interest and Salary, Magenta Therapeutics

Nicholas Clark- Ownership Interest and Salary, Magenta Therapeutics

Charlotte McDonagh-- Ownership Interest and Salary, Magenta Therapeutics

Hans-Peter Kiem- Nothing to declare.

John Wagner- Consultant, PI (Magenta Therapeutics); Board Member (Gadeta); PI (BlueRock); Consultant (Rocket Pharma); PI (Novartis)

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Anthony Boitano- Ownership Interest, Royalty and Salary (Magenta Therapeutics)

Michael Cooke- Ownership Interest and Salary (Magenta Therapeutics)

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Final Results of a Prospective, Multicenter, non-interventional Study on thiotepa-based Autologous Hematopoietic Cell Transplantation (ASCT) for CNS or non-CNS Lymphoma

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Background: Thiotepa-containing high-dose chemotherapy (HDCT) followed by ASCT is considered as standard of care in the treatment of primary or secondary central nervous system lymphoma (PCNSL/SCNSL) based on its capacity to penetrate the blood-brain barrier. In order to collect data in daily practice, this prospective, multicenter, non-interventional study was initiated to evaluate thiotepa-based HDCT prior to ASCT in patients with PCNSL or SCNSL, or non-CNS lymphoma: non-Hodgkin or Hodgkin lymphoma (NHL, HL). Primary aims of this study were assessment of safety and efficacy of thiotepa-based high-dose regimens in ASCT for lymphoma.

Methods: Eligible patients were 18 years of age or older and were assigned to undergo ASCT after HDCT either with thiotepa 20 mg/kg, BCNU 400 mg/m² +/- etoposide 450 mg/m² (TT+BCNU) for PCNSL/SCNSL; or thiotepa 10 mg/kg, etoposide 800 mg/m², araC 1600 mg/m², melphalan 140 mg/m² (TEAM) for non-CNS lymphoma (B-/T-NHL, HL). Primary endpoints were toxicity and efficacy. Data were documented at 4 time-points: before therapy, at day 30, day 100 and 1 year post ASCT.

Results: From Oct 2013 to Apr 2017, 83 patients were registered by 16 centers, of whom 80 [51 male,] had a complete dataset available and were included in this analysis. Median age was 59 years (range: 22-78), with 12 patients being older than 65 years. T+BCNU and TEAM were used in 44 (55%) and 33 (41%) patients, respectively, and other combinations in the 3 remaining patients. Diagnosis was PCNSL in 32 (40%) patients, SCNSL in 13 (16%) patients, and NHL/HL) without CNS involvement in 35 (44%) patients. Main non-hematological grade 3-4 organ toxicities up to day +30 were mucositis, diarrhea, infection, and fever, occurring in 67%, 21%, 47%, and 16%, respectively, of all 80 patients. Neutrophil recovery (>500/µl) occurred at a median of 10 days (4-21), and platelet recovery (>20.000/µl) at a median of 13 days after transplantation. Non-relapse mortality at day +100 and 1 year was 8.8% corresponding to non-adjusted 7 fatalities, all infection related with no impact of underlying disease, thiotepa regimen used, and age. On day 100, 72 patients were evaluable for response, here 42 (53%) achieved complete response, 20 (25%) partial response and 3 (4%) patients stable disease. Nineteen (24%) patients experienced relapse/progression, translating into a progression-free survival at one year of 68% (PCNSL: 78%; SCNSL: 54%; B-/T-NHL, HL: 63%), and an overall survival of 78% (PCNSL: 81%; SCNSL: 69% and B-/T-NHL, HL: 77%). No difference of therapy outcome could be detected in patients being < or > 60 years, but a worse PFS and OS for patients older than 65 years.

Conclusions: The results of this prospective study suggest that thiotepa-based high-dose chemotherapy for ASCT for both CNS and non-CNS lymphoma is effective and does not raise safety concerns compared to other HDCT regimens commonly used for ASCT of lymphoma across all age groups.

Clinical Trial Registry: CTU82G

Disclosure: Herbert G. Sayer: Honoria from RIEMSER Pharma GmbH

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Post-Transplant Cyclophosphamide (PT-CY), Cyclosporin (CSA) and Mycophenolate (MMF) for Patients Grafted from HLA Identical Siblings or Matched Unrelated Donors

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Background: GvHD remain a significant complication in HLA matched grafts, receiving prophylaxis with cyclosporin (CSA), methotrexate (MTX), also when combined with anti-thymocyte globulin (ATG). In a prospective study the triple combination of post-transplant cyclophosphamide (PT-CY), CSA and mycophenolate (MMF), has shown to provide the best protection against GvHD in HLA matched transplants (Bolanos, Lancet Haematol, 2019)

Methods: To assess the outcome of HLA matched grafts receiving GvHD prophylaxis with PTCY+CSA+MMF or ATG+CSA+MTX, we retrospectively analyzed the outcome of 113 HLA identical transplants grafted from identical siblings (SIBS) (n=58) or 8/8 allelic matched unrelated donors (MUD) (n=55). GvHD prophylaxis was PTCY based in 28 and ATG based in 85.

The median age was borderline lower in the PTCY arm (48 vs 53 years, p=0.08). The conditioning regimen for 82% of patients in both arms, was thiotepa (10 mg/kg), busulfan 9.6 mg/kg and fludarabine 150 mg/m^2 (TBF); full dose TBI (12 Gy) was given to 4% of the ATG based patients and 14% of the PTCY based patients (p=ns). The disease phase was equally distributed in the two groups. Acute leukemia was the most frequent diagnosis in 48% and 46% of patients respectively, followed by MDS in 19% and 16% and myelofibrosis in 14% and 17%. Peripheral blood was the graft source for all patients.

Results: Median time to neutrophils 0.5x10^9/l was day 16 vs 18 days in the ATG vs PTCY patients (p=0.01). The proportion of patients with grade 0 acute GvHD was 25% for ATG and 94% for PTCY (p=0.00001); GvHD grade II developed in 19% vs 5% respectively an grade III-IV in 2% vs 0% (p=0.002). Chronic GvHD was absent in 54% vs 96% of ATG vs PTCY patients, and moderate severe cGvHD was diagnosed in 27% vs 0% (p=0.0008). TRM was documented in 22% vs 7% of ATG vs PTCY patients (p=0.07). Follow up is too short to analyzed relapse and survival. We compared matched grafts receiving the triple PTCY based GvHD prophylaxis, with a large concurrent group of HAPLO mismatched family grafts receiving the same prophylaxis (n=105): the incidence of GvHD grade II-IV was 21% in the HAPLO grafts and 3% in the matched grafts (p=0.01), given the same GvHD prophylaxis. Similarly cGvHD (moderate severe) was diagnosed in 19% of HAPLO grafts vs 0% of matched grafts (p=0.0009).

Conclusions: Data suggest that for HLA matched transplants, a triple PTCY based -GvHD prophylaxis is significantly superior to a triple ATG based -GvHD prophylaxis, in protecting patients from acute and chronic GvHD and results in a low TRM. It also suggests that, given the same PTCY based prophylaxis, GvHD is less frequent in matched related and unrelated grafts as compared to HAPLO mismatched grafts, reassessing the role of HLA matching in allogeneic transplants. We need to determine whether relapse is not increased given the extremely low incidence of GvHD, with the triple PTCY based GvHD prophylaxis in matched grafts. However, if these results can be reproduced, we may find out that HLA matching returns as a major predictor of GvHD.

Disclosure: No disclosures

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Conditioning Regimen Comparison for Allogeneic Stem Cell Transplantation in non-hodgkin Lymphoma

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Background: Allogeneic hematopoietic cell transplantation (allo-HCT) allows for the possibility of cure for patients (pts) with non-Hodgkin Lymphoma (NHL) as it provides an immunologic graft-versus-lymphoma effect. Non-relapse mortality (NRM) was felt to be prohibitive with myeloablative regimens, but technical advances with the advent of reduced-intensity conditioning (RIC) or nonmyeloablative (NMA) regimens have decreased these rates. RIC regimens are generally associated with more toxicity and higher NRM than NMA regimens. Though studies showed both approaches are safe and effective, there is lack of direct comparison between these different intensities of in NHL.

Methods: This retrospective study identified patients aged ≥ 18 years who underwent allo-HCT for relapsed/refractory NHL between 3/2008-6/2017 at our center. Outcomes were compared between pts who received NMA and RIC conditioning, with intensity delineated per CIBMTR definitions. Progression-free survival (PFS) was the primary outcome. Secondary outcomes included overall survival (OS) and non-relapse mortality (NRM). Additional outcomes included rates of acute GVHD at Day 100, chronic GVHD, and CMV reactivation at Day 100. Regimen intensity and other variables significant by univariate analysis were included in the multivariate analysis.

Results: For the 144 patients identified, the median age was 56 years (range, 19-79). More pts received NMA regimens (n=80, 56%) and most did not undergo prior autologous HCT (n=103, 72%). NMA regimens were given more frequently to pts with indolent B-cell lymphoma and were more likely to receive ATG and/or rituximab ($p = 0.008$, $p < 0.001$, and $p < 0.001$, respectively). At a median overall follow-up of 57.8 months (range 49 - 75.1) neither median PFS or OS were reached. In univariate analysis, NMA conditioning was associated with a longer PFS than RIC [HR 1.9 (1.11-3.24), $p = 0.019$). No difference in OS when comparing NMA and RIC regimens [HR 1.56 (0.85-2.85), $p = 0.15$). There was an increase in all grades of aGVHD [HR 3.68 (2.16, 6.28), $p < 0.001$)] with RIC regimens, but only 12 events of grade III/IV aGVHD overall.

In multivariate analyses (with histology and ATG as covariates) NMA with rituximab had improved PFS compared to RIC without rituximab [HR 0.43 (95% CI 0.22, 0.81; p=0.009)]. However, PFS was similar comparing NMA and RIC groups [HR 0.72 (95% CI 0.37, 1.41; p=0.3)]. Similarly, aGVHD (any grade) risk was lower in NMA pts receiving rituximab compared to RIC pts who did not [HR 0.15 (0.07-0.32), $p < 0.001$). No significant differences were noted in NRM or CMV reactivation between groups.

Conclusions: Our study suggests that there are comparable and favorable outcomes between RIC and NMA conditioned allo-HCT for NHL with careful patient and regimen selection. Further studies are needed to better define specific criteria in choosing between NMA and RIC allo-HCT conditioning regimens for pts with NHL.

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Sergio Giralt - Amgen: Consultant and Investigator, Research Funding + Actinium: Consultant and Investigator, Research Funding + Celgene: Consultant and Investigator, Research Funding + Johnson & Johnson: Consultant and Investigator, Research Funding + Miltenyi: Investigator, Research Funding + Takeda: Consultant and Investigator, Research Funding + Consultant for Kite + Spectrum Pharmaceuticals + Jazz Pharmaceuticals + Novartis

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A Thiotepa Based Intensified Reduced Intensity Conditioning Regime in Adult Cord Blood Transplant is a Promising Alternative in Patients Unable to Receive Myeloablative Conditioning

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Background: High relapse and graft failure rates have been seen with the Minnesota reduced-intensity conditioning (RIC) for umbilical cord blood transplantation (UCBT) regimen consisting of fludarabine (Flu) 200mg/m^2, cyclophosphamide (Cy) 50mg/kg and 2 Gy of total body irradiation (TBI). We evaluated a new thiotepa-based intensified RIC regimen consisting of Flu 150mg/m2, Cy 50mg/kg, thiotepa 10mg/kg, and 4Gy TBI, which has shown promising results with sustained engraftment and acceptable toxicity.

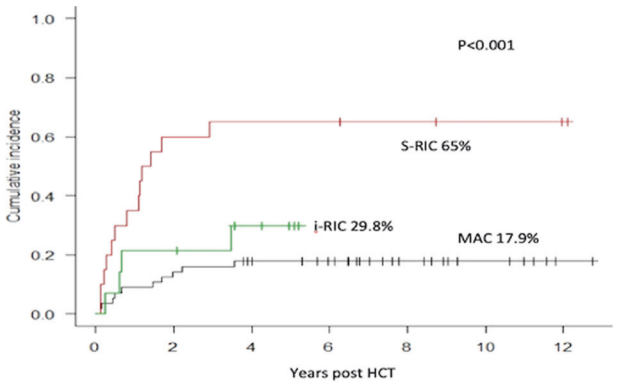
Methods: We performed a retrospective analysis of 90 adult patients in 2 institutions in Singapore receiving 4/6-6/6 HLA matched UCBT for various haematological malignancies between Aug 2006 and May 2019. Patients received 1 of 3 conditioning regimens - myeloablative Conditioning (MAC, n=56) regimen of Flu 90mg/m^2, Cy 120mg/kg and 12 Gy TBI, standard reduced intensity conditioning (s-RIC, n=20) and thiotepa-based intensified reduced intensity conditioning (i-RIC, N=14) regimen.

Results: There was no significant difference in the median day to neutrophil engraftment among the 3 groups (p=0.18). The cumulative incidence (CI) of relapse-related mortality (RRM) was the highest in patients receiving s-RIC (HR 5.35, 95% CI 2.35-12.18; p=0.003) compared to the MAC and i-RIC (Figure 1). This difference remained statistically significant in multivariate analysis (p=0.004).

5-year overall survival was lowest amongst patients receiving s-RIC (MAC 46%; s-RIC 20 %; i-RIC 43%; p=0.165). CI of transplant related mortality (TRM) was comparable among the 3 groups (MAC 36%; s-RIC 15 %; i-

RIC 29%; p=0.245). There was no statistically significant difference in CI of grade 2-4 acute graft-vs-host disease (GVHD) or chronic GVHD among the 3 groups.

Conclusions: The results of this retrospective analysis show improvements in OS and decrease in RRM without an increase in TRM in patients receiving thiotepa-based intensified RIC as compared with standard RIC. CI of RRM was comparable between patients receiving MAC and i-RIC, which were both significantly lower compared with patients receiving s-RIC. A thiotepa based intensified reduced intensity conditioning regimen provides an alternative option that may improve outcomes in patients not fit to receive MAC for UCB transplantation.



[Figure 1: Cumulative Incidence of Relapse Related Mortality MAC, S-RIC and I-RIC]

Disclosure: Nothing to declare.

P160

Haploidentical Stem Cell Transplantation with post-transplant Cyclophosphamide using as Conditioning Fludarabine Melphalan plus low Doses of Total Body Irradiation. Long term follow-up of 60 Patients

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Background: The use of Haploidentical Transplantation (haploSCT) with pos-transplantation cyclophosphamide (PTCy) is a valid alternative for patients without a matched donor, however it is not clear what is the "best" conditioning regimen in this setting. With the scope of increasing the anti tumor effect and also improve the engraftment rate, we added to, the well- known fludarabine-melphalan conditioning, a dose of 200-400 cGy of total body irradiation (TBI). We present the long-term results obtained with the use of this combination in a group of 60 patients with leukemia and lymphoma

Methods: The cellular source in all cases was PBSC. The conditioning consisted of melphalan 100-120 mgs/m2, on day -7, fludarabine 40 mgs/m2 from day -6 to -3 and TBI 200-400 cGy on day -2. PTCy 50 mg/kg/day was administered on D+3 and D+4, the cyclosporine and mycophenolate were initiated on day + 5 in 28 patients and, after an amendment, on days 0 and + 1, in 32

After a signed informed consent, 60 patients underwent to transplant; median age was 35 years (19-65), the diagnoses were: acute lymphoblastic leukemia 27, acute myeloid leukemia or myelodysplasia 21, lymphoma 6, and 3 with other diseases. 44% of the patients were beyond CR1, the disease risk index (DRI) was low in 28%, intermediate in 37% and high in 30%, three cases were not classified.

Results: 80% of patients received flu-mel +TBI 200-300 cGy, while in 20% the dose was 400 cGy. A mean of 10 million of PBSC/kg was infused. The neutrophil engraftment rate was 98%, median time to achieve 500 or more was 15 days (range 13-29), 4 patients died before d+ 100 without platelet recovery, the remaining had a self- sustained platelet count of 20.000 or more at an average of 16 days (range 12-50). Chimerism was done in all cases that survived beyond day + 100 and all of them had full donor hematopoiesis.

The main toxicity was gastrointestinal; diarrhea 70%, mucositis G II-III 30%. With a median follow-up for surviving patients of 22 months, the incidence of GVHD acute (GII-IV) and chronic extensive was 41 and 16% respectively. The transplantation related mortality was 21% while the rate of relapse was 15%. Causes of non-relapse mortality were infections associated to GVHD 11.5%, without GVHD 8.3%, and hemorrhagic cystitis one case

Event was defined as death for any cause or relapse, the event free survival (Kaplan Meier) at 36 months for the whole group was 55% (CI 0.37-0.69), and 70%, 55% and 44% for patients with DRI low, intermediate and high (fig 1)

Conclusions: The long-term follow-up of 60 patients transplanted using flu-mel-low TBI as a preparative regimen in the haplo PBSC setting showed a fast and almost universal engraftment, acceptable toxicity and favourable disease free survival. A good balance between tolerance and anti tumor activity. The incidence of aGVHD was high, with the scope to decrease it, we are working in a modification of the time of starting the immunosuppression and in decreasing the number of CD34 and CD3 infused

Disclosure: Nothing to declare.

P161

Comparison of Beam and Team as Conditioning Regimen for Lymphoma Patients undergoing Autologous Stem Cell Transplantation

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Background: Autologous stem cell transplantation with high-dose therapy is frequently used in lymphoma patients for consolidation of first complete response or after salvage chemotherapy after relapse. BEAM (carmustine-etoposide-cytosine arabinoside-melphalan) is the most commonly used conditioning regimen. TEAM (thiotepa- etoposide-cytosine arabinoside-melphalan) is becoming a more frequently used regimen in recent years. In this study, we aimed to compare the results of these two regimens.

Methods: We retrospectively analysed the results of 225 lymphoma patients from 2 different centers who had been transplanted with conditioning regimens BEAM and TEAM between January 2015 and July 2019.

Results: There were 167 lymphoma patients who had received BEAM conditioning regimen and 58 lymphoma patients who had received TEAM conditioning regimen. Patients with primary central nervous system lymphoma were excluded from the analysis. 34,2 % of the patients had Hodgkin Lymphoma, 31,6% of the patients had Diffuse Large B cell Lymphoma, 12,9% of the patients had Mantle Cell Lymphoma, 10,7% of the patients had Peripheral T cell Lymphoma and the rest 10,6% had varying types of Non-Hodgkin Lymphoma. Neutrophil engraftment time and thrombocyte engraftment time did not differ between 2 groups. Hospitalization duration was statistically shorter in patients who received BEAM conditioning regimen (p=0,04). Although the differences were not statistically different, rates of documented bacterial, viral and fungal infections were higher in patients who received TEAM conditioning regimen. Clinical results of patients receiving BEAM or TEAM conditioning regimen are shown in Table 1. The PFS and OS were not different between groups (p=0,37, p=0,61, respectively).

Conclusions: According to our results BEAM and TEAM conditioning regimens seem equally effective in terms of survival end-points. But hospitalization period of patients who received TEAM was longer than patients who received BEAM conditioning regimen. This can be explained by higher infection rates observed in patients who received TEAM, even though statistically significant difference could not be demonstrated.

	BEAM	TEAM	p
Neutrophil engraftment time	9,5(8-16)	10(8-23)	0,89
Thrombocyte engraftment time	11(8-23)	12(7-28)	0,06
Hospitalization duration	22(12-35)	23(14-57)	0,04
Documented bacterial infection	26,3%	37,9%	0,09
Documented viral infection	4,2%	8,6%	0,19
Documented fungal infection	1,8%	3,4%	0,6

[Table 1: Clinical results of lymphoma patients who had received BEAM or TEAM conditioning regimen for autologous stem cell transplantation]

Disclosure: Nothing to declare.

P162

Assessment of the Safety and Efficacy of the Conditioning Regimen Beeac before auto-hsct for the Treatment of primary-refractory and Relapsed forms of Malignant Lymphomas

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Background: There are several most commonly used conditioning regimens for high-dose chemotherapy (HDCT) followed by autologous transplantation of hematopoietic stem cells(auto-HSCT)to patients with malignant lymphomas(ML). However, there are currently no data on the conduct of randomized studies that would compare the effectiveness of different regimens and their toxicity.

Methods: Assessment of the safety and efficacy of the BeEAC regimen as a conditioning regimen before auto-HSCT for the treatment of primary-refractory and relapsed ML

Materials and Methods From January 2016 to June 2018 the study included 113 patients:72 with Hodgkins lymphoma,41 with non-Hodgkins lymphomas;55 women and 58 men. The median age was 33 years. Tumor status before auto-HSCT:complete remission - 58 patients, partial remission and stabilization - 52 and 3 patients, respectively. Median follow-up was 26 months. BeEAC conditioning regimen: increasing doses of bendamustine 160-200 mg/m^2, administered on D-6 and D-5, combined with fixed doses: cytarabine 200 mg/m^2 every 12 hours on D-4 - D -1,

etoposide 200 mg/m^2 on D-4 - D-1, cyclophosphamide 140 mg/kg on D-4 - D-1.

Results: In Phase I of the study(3 cohorts of 3 patients each), when the dose of bendamustine was increasing from 160 to 200 mg/m^2, **no manifestations of dose-limiting toxicity were identified**. Subsequently, patients received bendamustine at a dose of 200 mg/m^2.

Hematologic toxicity of BeEAC presented in table 1.

Characteristic	Result (Median)
Day (after transplantation) of maximum neutrophil reduction	D+5
Duration of agranulocytosis (days)	8
Maximum platelet reduction	5x10 9/L
Duration of thrombocytopenia (days)	11
Day of maximum hemoglobin reduction	D+9
Maximum decrease in hemoglobin	82 g/l

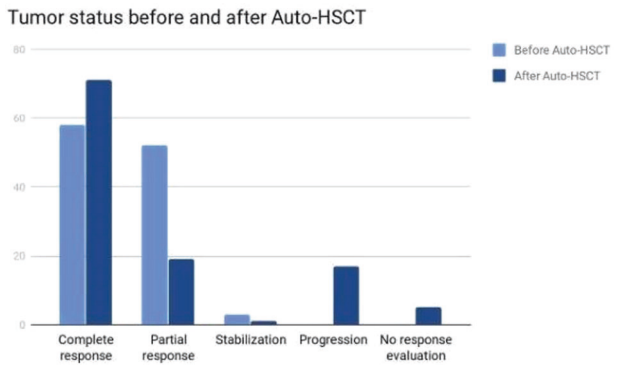
[Table 1. Hematologic toxicity of BeEAC]

According to WHO criteria for **oral mucositis**, grade II mucositis was diagnosed in 27 patients(42.2%), grade III and IV - in 14 patients(21.9%).

According to NCI-CTC criteria, grade III and IV **enteropathy** was diagnosed in 17 patients (37.0%).

Cardiotoxic effects were detected in 10 patients(8.9%) and manifested as hydropericardium, dry pericarditis, paroxysmal atrial flutter, acute biventricular insufficiency and acute post-cytostatic cardiomyopathy.

Pulmonary toxicity occurred in 2 patients(1.8%)-post-cytostatic pulmonitis.



[Table 2. Comparison of tumor status before and after auto-HSCT]

Hepatic toxicity occurred in 34 patients (30.1%), mainly grade I.

Assessing the tumor status after auto-HSCT (after 2-3 months), the following results were obtained:complete remission - 62,9%(71 patients), partial remission - 16,8% (19 patients), stabilization - 0,9%(1 patient), progression - 15,0%(17 patients). In 5 patients, the effect was not evaluated (Table 2.)

Transplant-related mortality(until D + 30)was 3,6%(4 patients;causes:2-complications of sepsis,2-acute cardiotoxicity). The total mortality over the observation period (median-26months)was 23%(26 patients).

The overall survival rates(OS)for the entire cohort of patients at 12,18,24 and 36 months were 88%,82%,78% and 64%, respectively, and the progression-free survival rates (PFS)were 61%,57%,54 % and 40%, respectively.

Conclusions: BeEAC has demonstrated relative safety when used as conditioning regimen in ML. It is necessary to obtain further data to evaluate the effectiveness of the regimen and conduct a retrospective comparative analysis with other conditioning regimes for ML.

Clinical Trial Registry: ClinicalTrials.gov NCT03315520

Disclosure: None Declared

P163

Allogeneic Stem Cell Transplantation after total-body Irradiation using Helical Tomotherapy - A Single Center Experience

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Background: The role of helical tomotherapy (HT) as radiation technique for total body irradiation (TBI) prior to allogeneic stem cell transplantation (alloSCT) has yet to be defined. We report our initial experience using HT in patients with hematological diseases that had received their first allogeneic stem cell transplantation at our institution.

Methods: All consecutive patients who were treated with HT-TBI-based conditioning and transplanted from a sibling or unrelated donor for various hematological diseases between 1/2015 and 4/2019 were included. TBI was applied with 6 MV photons using helical tomotherapy (Accuray). After obtaining informed consent treatment planning was performed using computed tomography (Aquilion, Toshiba, 3 mm slices) with patients placed in a vacuum bag. Delineation of organs at risk was performed and a treatment plan including dose-volume histograms was generated. This plan was dosimetrically verified using

a phantom (Alderson). Irradiation dose deviations of up to 3 percent were deemed acceptable. Since the tomotherapy device has a longitudinal treatment limit of 160 cm patients with a body length exceeding this were irradiated caudally as far as possible and then turned around by 180 degrees to treat the remainder of the body. Primary endpoint of the study was leukemia-free survival (LFS). The study was approved by the local institutional review board.

Results: Twenty-six patients were included, 15 males and 11 females. Median age at time of alloSCT was 43 years (range 16 to 60 years). Indications for alloSCT were acute myeloid leukemia (AML) (n= 10), myelodysplastic syndrome (MDS) (n=5), acute lymphoblastic leukemia (ALL) (n=7), bi-phenotypic acute leukemia (n= 2), chronic myeloid leukemia in blastic phase (n=1) and paroxysmal nocturnal hematuria (n=1). Donors were matched related (n=4), matched unrelated (n=18) and mismatched unrelated (n=4). Conditioning regimens used were TBI/cyclophosphamide (n=12), TBI/VP16 (n=2), TBI/fludarabine (n=3) and FLAMSA-RIC (n=9). TBI doses ranged from 4 Gy given at a single fraction (n=9) to 8 Gy given at 4 fractions of 2 Gy over two days (n=3) to 12 Gy given as six fractions of 2 Gy over three days (n=14). Neutrophil engraftment was achieved after a median of 18 days (range 15 to 26 days). One patient experienced secondary poor graft function. Fifteen patients developed mukositis III-IV. Seven patients experienced a hematologic or molecular relapses at a median of 0.7 y (range 0.5 to 3y). Six patients developed an acute GVHD which was of grade I in all cases. Five patients developed moderate chronic GVHD, two of them after treatment of relapse using donor lymphocyte infusions in combination with sorafenib. After a median follow up of living patients of 2.6 y (range 0.6 to 4.8 y) three patients have died, one after 16 days due to sepsis, two others due to relapse, resulting in an estimated LFS at 2 y of 71%.

Conclusions: Our retrospective data show that using HT for TBI-based conditioning prior to alloSCT is feasible. Initial survival outcomes are encouraging. Longer follow-up is needed to assess late effects and define the role of HT in the context of TBI-based conditioning further.

Disclosure: Nothing to declare.

P164

Feasibility of CLAMSA-RIC as an Alternative Conditioning Regimen Compared to FLAMSA-RIC in Heavily Pretreated Refractory AML Patients - A Retrospective Single Center Analysis

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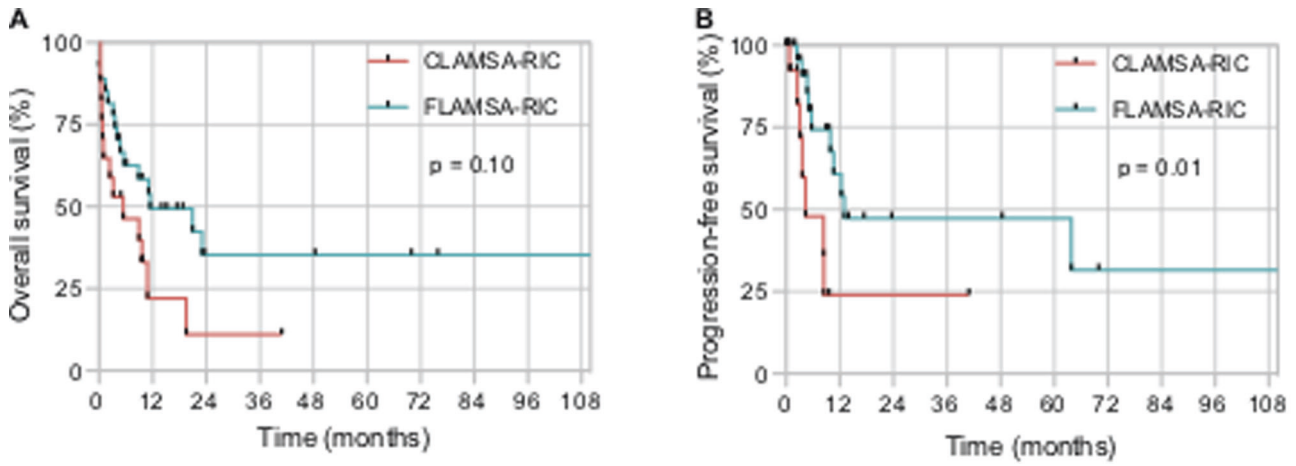
Background: The outcome of patients with relapsed/refractory acute myeloid leukemia (r/r AML) remains very poor even after undergoing allogeneic hematopoietic stem cell transplantation (alloSCT). In patients with very high relapse risk the conditioning regimen with fludarabine/amsacrine/cytarabine (FLAMSA) followed by reduced-intensity conditioning (RIC) has emerged as a very promising therapeutic concept. The second-generation purine analogue clofarabine has been reported to have a higher anti-leukemic activity compared to fludarabine, and promising results when incorporated in conditioning regimens for AML patients have been reported. As comparative data of the FLAMSA-RIC regimen with the clofarabine/amsacrine/cytarabine (CLAMSA) -RIC regimen are missing, we conducted a retrospective single center analysis.

Methods: In this retrospective, single center analysis 44 consecutive patients with r/r AML (median age 58 years, range 37-71) treated at our center between 2009 and 2019 were included. Per definition patients presented with primary induction failure to standard therapy (n=21), early refractory relapse (n=10), or had active AML with myelodysplasia-related changes and history of myelodysplastic syndrome (n=13). Patients either received fludarabine (30 mg/m2/day) (n=27) or clofarabine (50mg/day) (n=17) in combination with cytarabine (2 g/m2/day) and amsacrine (100 mg/m2/day) for 4 days. The RIC part consisted of busulfan (4x 0,8 mg/kg) and cyclophosphamide (60 mg/kg). Per institutional guidelines immunosuppression consisted of antithymocyte globulin, mycophenolatmotefil and a calcineurininhibitor. The primary endpoint of this study was overall survival (OS). Secondary endpoints were the rate of complete remission (CR), the rate of relapse-free survival (RFS) and cumulative incidence of acute graft-versus-host disease (GvHD) II-IV°.

Results: The median follow-up time was 53 months. The median OS (CLAMSA-RIC vs. FLAMSA-RIC) was 5.4 vs. 11.4 (p=0.10) months. The median RFS was 4.4 vs. 13.1 (p=0.01) months in comparison. Out of 17 CLAMSA-RIC treated patients, 10 (58%) achieved a CR, 2 were refractory and 5 died before response evaluation. In comparison 88% achieved a CR in the FLAMSA-RIC cohort and 3 had died before response evaluation. Cumulative incidence of acute GvHD II-IV° was 41% vs. 52% respectively. On average, patients in the CLAMSA-RIC cohort had received twice the amount of previous



[Figure 1: Comparison of the conditioning regimens CLAMSA-RIC and FLAMSA-RIC]

therapies compared to the FLAMSA cohort (3.2 vs 1.8). All patients within the CLAMSA-RIC group were either primary refractory or had refractory relapse and 58% had never achieved a CR. In comparison 13 (48%) patients in the FLAMSA-RIC group had undergone alloSCT without any previous chemotherapy.

Conclusions: Our study demonstrates that the incorpororation of clofarabin into conditioning prior to alloSCT in patients with r/r AML is feasible. Compared to the FLAMSA-RIC regimen the CLAMSA-RIC group showed inferior results in RFS. There was no significant difference in OS, however a clear trend towards the FLAMSA cohort. Comparison of the groups may be difficult as the 17 patients in the CLAMSA had higher disease activity and received more intense previous treatment regimens. However for extensively pretreated r/r AML patients with very poor prognosis, CLAMSA-RIC may be feasible as alternative conditioning regimen. Further prospective clinical trials are urgently required.

Disclosure: Nothing to declare.

P165

Flamsa-based High-dose Sequential Conditioning Regimen followed by Allogeneic Hematopoietic Stem Cell Transplantation(ALLO-HSCT): Is It Effective in Patients with Primary Refractory or Relapsed Acute Leukemia?

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Background: Advances in chemotherapy have improved the prognosis of patients with acute leukemia. However, patients with refractory disease or early relapsed still have a poor outcome. Allo-HSCT is the most effective anti-leukemic treatment. Nevertheless because of relapse and treatment-related complications, long- term survival is rare in advanced disease. Kolb and colleagues developed fludarabine/cytarabine/amsacrine (FLAMSA) regimen and reported the promising results in patients with acute myeloid leukemia. This reports describes our experience with the 45 patients who had high risk, primary refractory or relapsed acute leukemia and received FLAMSA-based high dose sequential conditioning regimen followed by allo-HSCT.

Methods: Patient characteristics are summarized in Table 1. We analyzed 45 consecutive patients (16 females, 29 males) with a median age of 39 years (range 19-62) transplanted after FLAMSA-based high-dose sequential conditioning regimen (36 RIC and 9 MAC) in our institution from October 2007 to November 2018. Six out of 45 patients received FLANG (fludarabine, cytarabine, mitoxantrone) instead of FLAMSA. In our cohort, five patients underwent the second allo-HSCT due to relapse of acute myeloid leukemia. Donors were HLA-identical siblings in 23 (51.1%) and unrelated donors in 22 patients (48.9%). The allograft source was peripheral blood stem cells in 42 patients (93.3%); two patient () received cord blood and one patient (2.2%) received bone marrow.

Results: There were 42 (93.3%) patients who were transplanted in the setting of active disease and 3 MRD^{+} patients in this retrospective analysis. Twenty-eight (62.2%) patients achieved complete remission (CR). Of these

fourteen patients relapsed, but CR was re-achieved all patients after chemotherapy and donor-lymphocyte infusions. After a median follow up of 12.4 months (range: 3.1-92.8 months), the incidence of non-relapse mortality was 30% (n=). Median time from diagnosis to alloHSCT was 18.2 months (range: 8.0-24.3 months). The median number of transplanted cells was 5,67±1,9x10^6CD34+ cells/kg (range 1.3-9.9 x10^6). Nineteen patients (42.2%) died from reasons not related to leukemia before day +100 (Table 1). Acute GvHD occurred in nineteen patients, reaching grade I in 3, grade II in 5, and grade III and IV in 11 cases. Of the 30 patients who survived more than day 100 chronic GvHD developed in 11 patients. The estimated 1-year progression free survival (PFS) and overall survival (OS) from the transplantation was %47,4±10,5 (median: 11.4 months, 95%CI 7.8-15.0) and %21.6±6.3 (median: 4.1 ay; %95 CI 3.1-5.1).

Conclusions: Although 62% of CR rate makes this approach attractive, high rates of relapse and transplant related mortality needs to be improved new transplant modalites.

Disclosure: Nothing to declare.

P166

Increasing in Serum total Amylase Levels After Total Body Irradiation Conditioning Regimen as a Predictive Marker of transplant-related Mortality in Pediatric Hematopoietic Stem Cell Recipients

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Background: Total Body Irradiation (TBI) represent one of the most used conditioning regimens for hematopoietic stem cell transplantation (HSCT) especially for malignant haematological disease. However, radiation susceptibility differs greatly among individuals and a biological dosimeter is warranted to predict individual risk of radiation exposure.

We have observed a variable increase in serum total amylase (TA) during TBI-based conditioning regimen. This study aims to determine a cut-off value of the TBI-related total amylase increase that might be a specific prognostic marker for transplant outcomes in the pediatric population.

Methods: The study included 78 pediatric patients with acute lymphoblastic leukemia (ALL) who received TBI-based standard myeloablative conditioning in preparation for an allogeneic HSCT between 2000 and 2018. We defined two TBI protocol groups: the first one was of total 12 Gy, delivered in 6 fractions; the second one was of 7.5 Gy in a single dose. A linear, accelerator-based, L-L irradiation was used. The lung was shielded with upper limbs in lateral position. In vivo dosimetry was performed using TLD only until 2003. Serum TA and pancreatic amylase were evaluated before and after the TBI, on a daily basis, until their normalization.

Results: TBI total dose was 12 Gy for 57 (73.1%) patients, and 7.5 Gy for 21 (26.9%) patients. Mean dose-rate ±SD was 14.0 ±2.0 cGy/min and 18.7 ±1.7 cGy/min respectively. The mean percent variation ±SD in dosimetry was -0.9 ±1.9% in 12 Gy group and 1.5 ±1.0% in 7.5 Gy group, under the acceptable 10% range. 71 (91.0%) patients had abnormal levels of TA values during TBI treatment. The mean ±SD of peak TA values was 368.4 ±348.2 U/L (n.r. 28-100 U/L). The difference in the maximum TA values between the two TBI groups was not significant ($P = 0,2111$). Maximum TA values were excellent in predicting the transplant outcomes as overall survival (OS) and disease recurrence. TA values >374 U/L had the best performance in predicting OS with AUC =0.773 and 95% CI = 0.66 - 0.86 ($P < 0.0001$), sensitivity 58.6% and specificity 95.9%. Diagnostic performance of maximum TA values >374 U/L in predicting the disease recurrence-related death was even better with AUC = 0.865 and 95% CI = 0.77 - 0. 93 ($P < 0.0001$), sensitivity 80.0% and specificity 88.9%. Kaplan-Meier curve analysis confirmed the statistically higher survival probability in patients with maximum TA values < 375 U/L ($P < 0.0001$).

Conclusions: Human population heterogeneity in radiosensitivity has been demonstrated in many studies due to polymorphic genetic variations. So far, the TBI protocols have not considered individual radiation susceptibility. In the era of precision medicine, the dosage of TA can be an useful tool to assessing the individual risk of radiation exposure.

Disclosure:

The authors declare. no conflict of interest.

P167

Evolution of Donor Chimerism after Haploidentical Stem Cell Transplant - Clinical Correlations

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Background: Donor Chimerism has been used in the post-hematopoietic stem cell transplant (HSCT) setting for monitoring graft and disease state.

Methods: Data from patients who underwent an haploidentical HSCT at our institution, between May 2014 and October 2019 was retrospectively collected from clinical files. The data regarding the evolution of lymphoid and myeloid lineage (CD3+ and CD33+, respectively) donor chimerism was then plotted on a dispersion chart. The patients were compared accordingly to type of conditioning, time to engraftment, and disease relapse to verify the presence of any correlation with chimerism state.

Results: We identified 29 patients; median age of 33 years (8-67) and follow-up of 32,8 months. A total of 19 patients had Hodgkin's Lymphoma (HL) and were conditioned with a reduced-intensity conditioning (RIC). Patients with acute leukemia or myelodysplastic syndrome (11 patients) were mostly conditioned with a myeloablative conditioning (MAC); only one AML patient was conditioned with RIC. A calcineurin inhibitor plus mycophenolate mofetil and post-transplant cyclophosphamide were used for graft-versus-host disease prophylaxis. The median time to neutrophil and platelet engraftment was 16 and 20 days in the MAC patients and 19 and 21 in the RIC patients.

A total of 27 patients achieved CD3+ full donor chimerism during follow-up; 4 patients lost CD3+ full donor chimerism but only 1 didn't re-achieve it during follow-up. The same 27 patients also achieved CD33+ full donor chimerism; 7 patients lost CD33+ full donor chimerism and 3 regained it during follow-up. Only 2 patients didn't ever achieve CD3+ and/or CD33+ full donor chimerism; one of them had primary graft rejection.

At day +30, average CD3+ chimerism was 84.5% vs 100% and average CD33+ chimerism was 91% vs 99.9% for RIC and MAC patients, respectively. At day +100 the same trend occurred, with average CD3+ chimerism 87.5% vs 99.6% and average CD33+ chimerism 87% vs 100% for RIC and MAC patients.

Of the 8 relapsing patients (6 HL, 1 AML, 1 ALL), 4 maintained CD3+ and CD33+ full donor chimerism, 2 lost only CD33+, 1 lost both CD3+ and CD33+ and 1 patient didn't achieve either. The occurrence of relapse wasn't related to the state of CD3+ chimerism and it wasn´t possible to find a correlation between time to engraftment and CD3+/CD33+ chimerism at D+30.

Conclusions: Haploidentical full donor chimerism established rapidly, earlier in the patients conditioned with MAC. Notwithstanding, most of the RIC patients also achieved full donor chimerism. There wasn't a correlation between loss of CD3+ chimerism and disease relapse. This suggest that other mechanisms may be underlying this phenomenon, although loss of graft-versus-disease effect may still be important. Diminished lymphocyte effector activity or loss of HLA haplotypes by the neoplastic cells are both possible avenues of study.

Disclosure: No conflitos of interest to declare.

P168

Thiotepa-busulfan-fludarbine as Conditioning Regimen for Patients with Myelofibrosis undergoing Allogeneic Hematopoietic Stem Cell Transplantation: A Single Center Experience

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Background: Allogeneic hematopoietic cell transplantation (HCT) is the only curative therapy for myelofibrosis (MF), nevertheless the optimal conditioning regimen has not yet been defined. Thiotepa-Busulfan-Fludarabine (TBF) is a promising regimen. However, only a small series of 12 patients receiving this conditioning regimen for MF with a short follow-up of 1 year has been reported, thus far. We therefore aimed to improve the assessment of outcomes associated to TBF in patients undergoing HCT for MF.

Methods: We report a single-center, retrospective analysis of adult patients with MF undergoing HCT, with TBF as part of the conditioning regimen, between October 2013 and January 2019.

Results: Twenty-nine patients were included. The median age was 56 (range 41-71) years. Fourteen patients had primary and 15 patients had secondary MF. Thirteen patients (45%) were female and 8 patients (28%) had received 2 or more previous lines of treatment. Eighteen patients had a JAK2 mutation (including 2 with an associated CALR mutation), 6 had single CALR mutation, 1 had MPL mutation and 4 patients were triple negative. According to the refined Dynamic International Prognostic Scoring System (DIPSS-plus) for primary myelofibrosis, patients were stratified as intermediate-1 (n=2), intermediate-2 (n=10), and high (n=15) risk. The majority (n=21) of patients were in progressive disease at the time of HCT, including two patients with blast transformation.

Ruxolitinib was given to 16 patients prior to HCT. The median time from diagnosis to HCT was 11 (range 1-249) months. Graft source was peripheral blood stem cells in 27 patients and bone marrow in 2 patients. Donor type was HLA-matched related (n=5), matched unrelated (n=16), mismatched unrelated (n=1), and haploidentical (n=7). Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine and ATG for all patients, combined with mycophenolate mofetil in 25 patients. High dose post-transplant cyclophosphamide was added in haploidentical HCT. All patients engrafted except 2, who died during aplasia. The median time to neutrophil recovery was 14 days (range, 9-34). The median times to achieve platelet engraftment, >20 G/L and >50G/L, was 18 (range 1-387) and 20 (range 8-497) days, respectively. Six patients (21%) experienced grade II-IV acute GVHD. Among these, 4 had grade IV acute GVHD. Chronic GVHD occurred in 9 patients (31%). Only one severe form of chronic GVHD (pulmonary) was observed. The median follow-up was 35 (range, 10-57) months. Overall survival (OS) was 69 ± 9% at 2 years. Nine patients died: 5 of infection, 2 of GVHD and 2 due to multi-organ failure. No relapse was observed. OS was significantly lower among patients who had Ruxolitinib before HCT compared to patients who had not (50% versus 92%, p=0.02), respectively. A trend towards better OS was observed for patients who underwent HCT before the median time period of 11 months (86% versus 53%, p=0.05).

Conclusions: Our findings confirm that TBF is a valid conditioning strategy in patients with MF, and allows for a high incidence of engraftment, good disease control and promising OS. Previous use of Ruxolitinib and delay from diagnosis to HCT seem to negatively influence survival.

Disclosure: Nothing to declare.

P169

The Results of Allogeneic Hematopoietic Stem Cell Transplantation from HLA-haploidentical Donor with post-transplant Cyclophosphamide Regimen in Children

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Background: Hematopoietic stem cell transplantation is a commonly accepted treatment option for high-risk hematological and immunological patients. The strategy of using stem cells of a HLA-haploidentical related donor combined with using post-transplant cyclophosphamide provided good control of the graft versus host reaction while maintaining the efficacy of HSCT

Methods: Between 2013 and 2019, 44 haplo-HSCTs with post-transplant cyclophosphamide regimen were performed in 40 patients, of which: acute lyphoblastic leukemia (n = 13), acute myeloid leukemia (n = 16), juvenile myelomonocytic leukemia (n = 7), severe combined immunodeficiency (SCID) (n = 3), aplastic anemia (n = 1). The average age of the patients was 3.6 years (6 month - 15 years). Stem cell sources were bone marrow (BM) (n = 39) and peripheral blood stem cells (PBSC) (n =5). Patients received regimen: busulfan-based (n = 13), threosulfan-based (n = 21), full-dose total body irradiation TBI 12 Gray (n = 5), non-myeloablative TOT and cyclophosphamide (n=1). In case of primary graft rejection second HSCT was performed for 4 patient with threosulfan and melphalan conditioning (n=2) and melphalan only conditioning (n=2). Post-trasplant cyclophosphamide was administered for all patients +3 and +4 days in 50 mg/kg dosage.

Results: The median day for neutrophil engraftment was 22 days for BM HSCT and 19 days for PBSC. The following complications occurred: oral mucositis: grade 1 (n=9), grade 2 (n=30), grade 3 (n=5); neutropenic enterocolitis: grade 1 (n=8), grade 2 (n=27), grade 3 (n=7), grade 4 (n=2); toxic hepatitis (n=22), hemorrhagic cystitis (n=6), systemic inflammatory syndrome (n=15), polyneuropathy (n=2), TMA-HUS (n=2). Viremia: cytomegalovirus (n=15), herpes virus type 6 (n=6), adenovirus (n=4) - with negation in the short term. Acute GVHD with skin rash symptoms of grade 1 (n=5), grade 2 (n=25), grade 3 (n=5), grade 4 (n=2); GVHD with gastrointestinal manifestation of grade 1 (n=7), grade 2 (n=15), grade 3 (n =7), grade 4 (n = 2); hepatic GVHD (n=5) of degree 3 of severity; chronical form (n=9). The transplant-related mortality occurred in a patient with TMA (n=1).

Complete +30 day donor chimerism was achieved in 80% patients (35/44). The risk of primary graft failure was 13.6% and was higher in 5/13 patients (38%) treated with busulfan, compared with 1/21 patients within threosulfan group (4.8%). Also the relapses occurred more frequently among busulfan treated patients (30%) than among threosulfan treated (19%).

Patients with SCID who had respiratory insufficiency of a 2-3 degree before conditioning had improved and resolved complications up to 45-60 days after HSCT. The 5 out of 6 patients with primary graft failure had HLA-C mismatched transplant. Of 40 patients 31 is currently alive (79%).

Median follow-up has been 2 years (range 3 months - 6 years).

Conclusions: Our experience shows that haplo-HSCT with post-transplant cyclophosphamide regimen is effective treatment for high-risk patients with acceptable toxicity and low transplant associated mortality rate. Early control of infection and anti-virus immune response stimulation are the issues to be resolved. It is still disputable whether threosulfan-based regimen is beneficial for engraftment. High incidence of GVHD requires administration of adaptive supportive care.

Disclosure: Nothing to declare.

P170

Analysis of Differences in Preventive Measures after high-dose Cyclophosphamide Among Belgian Stem Cell Transplant Centres

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Background: Cyclophosphamide is used in high dose in the conditioning regimen of allogeneic and autologous stem cell transplantation and early post-transplant as prophylaxis of graft-versus-host disease (GVHD). The risk of bladder toxicity and hemorrhagic cystitis is well established. However, preventive measures differ depending on local protocol.

Methods: We conducted a survey among Belgian transplant centres to identify differences in preventive measures after high dose cyclophosphamide. All 15 JACIE accredited Belgian transplant centres were asked to complete a short questionnaire. Centres who did not use high dose cyclophosphamide (n=2) were excluded from the analysis.

Results: A total of 13 centres were included in the analysis. High dose cyclophosphamide was used in conditioning regimen pre-allogeneic stem cell transplantation in 11 centres (84,6%) and pre-autologous stem cell transplantation in 5 centres (38,5%). In 11 centres (84,6%) high dose cyclophosphamide was used as GVHD prophylaxis.

Preventive measures included hyperhydration and forced diuresis, administration of mesna and insertion of a bladder catheter. Hyperhydration with or without forced diuresis was reported in all centres (100%). Mesna was used in all centres (100%), however dosing depended on local protocol ranging from 500mg/m2 in bolus injections (each 3 hours) to a daily total dose of mesna estimated equal to 80% to 160% of the total dose of cyclophosphamide either administered in bolus injection or continuous infusion.

Three centres (23,1%) reported insertion of a bladder catheter as a standard precaution in all patients. Motivation included either historical reasons or previous cases of severe hemorrhagic cystitis. No centres reported continuous bladder irrigation as a standard practice, but one centre (7,7%) used continuous irrigation in high risk patients with contraindication for hyperhydration.

In three centres (23,1%) a standard interval for diuresis was defined (with waking patients up at night). In most centres (92,3%) urine output was monitored with a specific target urine output defined in 4 centres (30,8%).

Conclusions: Major differences in preventive measures after high dose cyclophosphamide could be found between the Belgian transplant centres. In particular, the use of bladder catheters and the dosing of mesna vary depending on local protocol. Bladder catheters may cause discomfort and are not without complications. As the majority of Belgian centres do not use this as standard procedure, this study can serve as a benchmark and may encourage to question the systematic use of bladder catheters in this setting. More evidence is needed to identify best practice and obtain a more uniform and standardised approach.

Clinical Trial Registry: not applicable

Disclosure: Nothing to declare.

P171

Irradiation-free Re-conditioning for T-cell Depleted haplo-identical Stem Cell Transplantation

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Background: Haplo-identical stem cell transplantation (hHSCT) is an option for patients requiring stem cell transplantation who lack an HLA-matched donor. We focus on transplantation of T-cell depleted HLA-haploidentical stem cells (TCD hHSCT) from a parent to their child, which is associated with a risk of graft rejection in 10%. We identified 9 patients who rejected a first TCD hHSCT and received a salvage TCD hHSCT from the other parent following a irradiation-free lymphodepleting reconditioning regimen.

Methods: Our cohort of 9 patients (7 female, 2 male, 4 with an initial indication of malignancy, 5 for non-malignant diseases) received their second TCD hHSCT either due to graft-rejection (5/9), or due to non-engraftment (4/9) after their first TCD hHSCT, conducted from 2011 to 2018. No acute GvHD was observed. Their median age was 2.3 years (3 months - 10 years).

In all cases, one parent donated with peripheral stem cells for the first transplantation, the other for the re-transplantation. The conditioning for the first, failed haplo-transplantation was fludarabine and thiotepa for all patients, 7 also received anti-thymocyte globulin, 2 thymoglobulin or alemtuzumab. The final conditioning components were treosulfan and melphalan in 4, and TDM busulfan in 1 patient.

The second transplantation was 6 to 26 days (median: 16 days) after the first. All patients were conditioned with fludarabine, thymoglobulin, and thiotepa. No radiation was administered. T-cell depletion of PBSC was employed in 6 patients by $CD34^+$ selection and in 3 patients with CD3/CD19 depletions. The median of transplanted stem cells was higher than in the first transplantation.

Results: Leucocyte engraftment was achieved in all patients 9 to 15 days post-transplantation (median: day 12). 5 of the 9 patients exhibited no symptoms of GvHD, 2 had grade I aGvHD, and 2 had grade II aGvHD limited to the skin. By day 100 the aGvHD had resolved in all 4 affected patients.

The follow-up times ranged from 4 months to 7 years (median: 11 months). 8 of the 9 patients were alive at last follow-up. All of these patients showed a sustained engraftment and complete donor chimerism. At last follow-up no patient showed symptoms of a cGvHD.

One patient died due to a leukemia relapse and multi-organ failure. Of the 8 surviving patients, 4 had a CMV reactivation, 1 suffered from a transfusion related acute lung injury shortly after transfusion, and 1 from a BK-virus-associated hemorrhagic cystitis.

Of the 8 surviving patients, all but one received no transplantation related medication and were in good health. The most recent patient is at day 218 in stable health after a severe episode of autoimmune hemolytic anemia (AIHA). The Lansky Scores for all patients reached 80% to 100% at day 100.

Conclusions: With a median follow-up of 11 months, the overall outcome after irradiation-free re-conditioning is promising. Omitting irradiation spares side effects and reduces the infection risk. With all patients showing a robust engraftment and only few complications post-transplantation, this conditioning seems to be a promising regimen, notwithstanding the relatively small cohort size of 9 patients.

Disclosure: Nothing to declare.

P172

Low Graft CD4 Cell Dose Predicts Relapse in the Atg-based Myeloablative Conditioning Regimen

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Background: T cells, on the peripheral blood stem cell (PBSC) allogeneic allogeneic hematopoietic stem-cell transplantation (HSCT) play a crucial role of the immunologic effect of graft-versus-host disease (GVHD) and graft-versus-tumor (GVL). However, the exact doses of subsets of lymphocytes CD4, and CD8, and that effect on outcome is not well characterized, and may changes between different types of conditioning and GVHD prophylaxis.T

To determine the impact of graft T-cell doses on incidence of disease relapse, acute and chronic GVHD after allogeneic HSCT with ATG-based myaloablative conditioning regimen, in adult patients with hematological malignancies.

Methods: this is a prospective, single-institution cohort (N=32) of patients with hematological malignancies (28 AML, 2 ALL, 2CML), who received allogeneic HSCT from February 2013 to February 2019. At time of transplant, all AML and ALL patients were in CR. Myeloablative conditioning regimen consisted to intravenous Busulfan (Bu) - Fludarabine (Fu) for AML and CML, and Bu- Melphalan for ALL patients. GVHD prophylaxis included ATG (thymoglobulin) 2.5 mg/kg on D-2 and D-1, ciclosporin and methotrexate. All patients received PBSC from an identical HLA-related donor. Analysis of Graft subsets lymphocytes by flow cytometry (BD CANTO cytometer, II 8 colors). None of patients received prophylactic DLI.

Results: median age at transplant was 32 years (18-62), including 19 men and 13 women. Median CD34+/ kg cells and CD3 + lymphocytes infused were 4.5 x 10^6 (2.24-7) and 2.32 x 10^8 (0.72-6.24) respectively. Median time for absolute nuclear cells > 0.5×10^9/L was 13 days (6-25), and unsupported platelet counts of at least 20 x 10^9/L was14 days (10-43). Median CD4 and CD8 cells infused were 0.84 x10^8(0.09-2.88), and 1.13x10^8(0.08 -4.14). There were no significant correlations between the CD8 graft content and risk of relapse (P=0.09), however higher CD4 cell doses (cutoff >0.81x10^8) were associated with trend lower risk for disease relapse 11% vs 43% (p= 0.05), without a significant increase risk acute or chronic GVHD 36% vs 33% (p=0.89), and 21% vs 39% (p=0.32) respectively.

Conclusions: A potential strategy for optimizing graft T-cell doses, apear to be useful to improve outcome in patients

received allogeneic HSCT with ATG based myeloablative conditioning regimen.

Disclosure: No **conflict of interest**

P173

Abstract already published.

P174

Haplo-identical Hematopoietic Stem Cell Transplantation (HSCT) in high-risk Hematological Malignancies, Algerian Experience

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Background: The haplo-identical HSCT is currently a rescue procedure in patients (pts) with high risk hematological malignancies when identical HLA donor is not available. We propose a retrospective study of 71 pts who benefited from this procedure.

Methods: From May 2013 to May 2019, 71 haplo-identical HSCT were used in 71 pts with hematological malignancies (15 AML, 39 ALL, 10 CML, 1 lymphoblastic NHL, 4 AL biphenotypic, 2 MDS). Median age was 26 years (4-61) and sex-ratio (M/F):2.7. At the time of the transplant, 15 pts were in first complete remission (CR), 48 pts in second CR and 8 pts in active disease. The donors used were parent (35), siblings (29) or offsprings (7). The degree of compatibility (HLA A, B and DR) is 3/6 (50 cases), 4/6 (15) and 5/6 (6). Two successive conditioning regimens were used; the first was inspired to Pekin (HP) associated: Busilvex 9.6mg/kg, Aracytine 8g/m^2, Cyclophosphamide 3.6g/m^2 for 36 pts in HEPA filtered rooms; the GVHD prophylaxis included the combination Ciclosporin-Methotrexate- Mycophenolate-Thymoglobulin (10mg/kg) and received an unmanipulated bone marrow (BM) transplant and Peripheral blood stem cells (PBSC). The second one (TBF) associated Fludarabine (150mg/m^2)-Thiotepa (10 mg/kg)-Busilvex (9,6mg/kg) for 35 pts in rooms without HEPA filters; the GVHD prophylaxis included the association Ciclosporin-MMF-Endoxan 50mg/kg day3-5 and received PBSC. Median dose infused CD34+ cells: 8.15.10^6/kg (1.43-32) and nuclear cells: 4,89.10^7/kg (0.59-7,44). At September 2019, the minimal follow-up delay was 4 months and maximal 76 months.

Results: Aplasia was observed in all pts with median duration of 18 days (10-38). The median day of neutrophils engraftment was 13 days (11-27). Two cases of VOD were observed. Four pts presented Thrombotic Micro-angiopathy (TMA). Four pts (5%) presented an early rejection. Acute GVHD occurred in 32 pts (48%) including 30 (93%) grade II-IV. Chronic GVHD was seen in 19 pts (43%) with extensive form in 9 pts (47%). twenty eight pts (42%) showed CMV reactivation. Forteen cases (21%) of haemorrhagic cystitis (HC) are observed. Thirteen pts (18%) relapsed, of which 5 pts were blast crisis at the time of the transplant. After a median follow-up of 32 months (4-76), 29 pts (40,8%) are alive and 42 pts (59,2%) died within 30 pts (42%) from TRM (GVHD:10, severe infection:10, HC: 1, TRALI syndrome: 1, TMA :1, V0D :2, early rejection :3, multi-visceral failure: 1, cerebral hemorrhage :1) and 12 pts (17%) after relapse, There was no significant difference between the two conditioning regimens (HP Vs TBF) in terms of aGVHD (48%Vs48%; p= 0.87), cGVHD (34% Vs55%; p= 0.13), CMV (48%Vs36%; p= 0.32), HC (21% Vs21%) and relapse (33%Vs12%; p= 0.13) except for TRM (27%Vs57%; p=0.02). The overall survival and disease free survival at 76 months are 37% (at 36 months: 46% Vs29,5%; p=0.5) and 37,2% (at 36 months: 44,15% Vs30,17%; p=0.9) respectively without significant difference.

Conclusions: Haplo-identical HSCT is, currently, a well-validated procedure in pts with high-risk haematological malignancies who do not have sibling HLA donor. However TRM is relatively high essentially in TBF procedure may be explained by the different conditions of realization (absence of laminar flow).

Disclosure: Nothing to declare.

P175

Interruption of Conditioning for allo-HCT does not affect Clinical Outcomes other than Chronic GVHD

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Background: Conditioning regimens for hematopoietic cell transplantation (HCT) should be performed according to usual standards and timescales. However, an interval of one or two days is occasionally required during the

conditioning because of hospital closure, predetermined HCT dates or simultaneous HCTs for multiple patients. This interrupted conditioning may have negative effects on the clinical outcomes of the HCT, and we tested this hypothesis in patients who had undergone HCT in our hospitals.

Methods: We retrospectively evaluated 83 pediatric patients (median age 9.7 years; range 1.5-19.9 years) with a malignant disease who had received 12 Gy or 13.2 Gy total body irradiation (TBI) as part of their conditioning regimen before allo-HCT at Sapporo Hokuyu Hospital or Hokkaido University Hospital. Among these patients, 19 patients had experienced interrupted conditioning and the remaining 64 patients received conventional uninterrupted regimens. The five-year overall survival (OS), event free survival (EFS), the median number of days of neutrophil engraftment and the incidence of acute and chronic graft versus host disease (GVHD) were compared between the two groups. The interrupted group had a mean interval duration of 1.4 days (range 1-2 days), and the interval during TBI was set in 8 of the 19 patients (42%). Most of the patients were diagnosed as hematologic malignancies (92%). Patient characteristics were compared between the conventional and the interrupted conditioning groups in terms of age, sex, diagnosis, disease status at HCT, graft source, related or unrelated donor, drugs used for GVHD prophylaxis and conditioning regimen; these were almost consistent across the two groups except for the type of calcineurin inhibitor administered.

Results: The differences in five-year OS and EFS were not statistically significant between the group without interval and the group with interval (OS: 50% vs 47%, p=0.925, and EFS: 43% vs 40%, p=0.892). Moreover, the median number of days of neutrophil engraftment was not significantly different in patients who had received uninterrupted regimens or those who experienced treatment intervals (median 18 days, range 11−46 days vs median 19 days, range 14−26 days, p=0.976). However, the interrupted conditioning group showed a marginally significant tendency toward the higher incidence of chronic GVHD than the conventional conditioning group. (19% vs 42%, p=0.063). Consequently, the association between an interrupted conditioning regimen and chronic GVHD was investigated through logistic regression analysis with clinical variables that were significant in the univariate analysis (p< 0.1). In the multivariate analysis, an interval during conditioning for allo-HCT was significantly associated with chronic GVHD (odds ratio, 3.72, 95%CI, 1.04-13.3, p=0.043). (Table 1)

Conclusions: Our study of patients with malignant diseases who had undergone allo-HCT with 12 Gy or 13.2 Gy TBI indicates that an interval during HCT conditioning does not affect clinical outcomes such as OS or EFS. However, interrupted conditioning can affect the occurrence of chronic GHVD, and this association requires further investigation.

Disclosure: Nothing to declare.

P176

Reduced Intensity Conditioning followed by Haploidentical Hematopoietic Cell Transplantation (Ric-haploHCT) and post-transplant Cyclophosphamide as Graft versus Host Disease Prophylaxis, for Hematological Disorders: Single Centre Experience

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Background: Haplo-HCT has emerged as a viable option for patients without matched sibling donors. With the use of Reduced intensity conditioning(RIC) and post-transplant cyclophosphamide (PTCy), the outcomes of haplo-HCT are improving steadily. We conducted a retrospective audit of our experience to assess real world transplant outcomes in the Indian scenario.

Methods: This is a retrospective chart review of patients with hematologic disorders who underwent RIC-HaploHCT and PTCy at our centre between August 2012 and September 2019. Demographic data, clinical features and outcomes were analyzed using standard descriptive statistical methods and survival analysis.

Results: Of a total of 64 HaploHCT done in the study period, 21 patients underwent RIC-HaploHCT, of which 17 were malignancies [AML(5), Acute Lymphoblastic Leukemia (2), Hodgkin lymphoma (5), NHL(2), MDS (2), CML (1), Aplastic Anemia (3), Fanconi anemia (1)]. The median age was 34 years (range: 10-60 years) and 55.5% (n=15) patients were males. 3 patients were in first complete remission (CR1), 11 were in CR2 or CR3, and 7 patients had active disease[Aplastic anemia - 3, MDS - 2, Fanconi anemia-1, CML-1] at the time of transplantation. The most common conditioning regimen used was fludarabine and melphalan (n=14). Donor types were sibling (n=13), parent (n=4), cousin (n=1) and child (n=3). Stem cell source was peripheral blood stem cell graft in all patients. The median CD34 cell dose infused was 5 x 10^6 cells/ kg. 76.2% (n=16) patients achieved >95% chimerism at D+28. D+100 survival was 58% (n=12)[5 patients (23.8%) died pre-engraftment (neutropenic sepsis - 4, grade 4 VoD - 1) and 4 (19%) died post-engraftment (bacterial sepsis - 2, relapse - 1, graft rejection - 1)]. Acute GVHD was seen in 38%

(n=8) patients with grade III/IV acute GVHD in 19% (n=4). Steroid refractory persistent GVHD was seen in 2 patients. Chronic GVHD developed in 14.2% (n=3) patients. One patient with MDS had disease relapse. In the entire cohort, median survival was 4.8 months while the estimated 3 year survival was 40%. 80.9% (n=17) patients had surveillance cultures (Faecal or throat) positive for 1 or more multi-drug resistant organisms (MDRO). All of them were gram negative bacilli (GNB) and included 38% carbapenem resistant organisms. During the peri-transplant period, 9 cultures were positive: gram negative bacilli in 6 and gram positive cocci, Fusarium and Aspergillus in 1 culture each.

Conclusions: RIC-HaploHCT for hematological disorders is associated with modest overall outcomes in our study with early mortality affecting the survival. Higher non-relapse mortality due to MDRO infections is of urgent concern. Relapse rates were however low.

Number of patients	n= 21
Participating center	1
Median age and range	34 years(10 to 64 years)
Male :Female	15:6
Malignancies (AML, ALL, MDS, NHL, Hodgkin Lymphoma, CML)	17
Other hematological disorders (Aplastic anemia/ marrow failure)	4
Patients in Complete remission at transplant	14
Patients with Active disease at transplant	7

[Patient Characteristics]

Disclosure: Nothing to declare.

P177

Describe and Explore a Patients´ Outlook on Dental Care in the Context of their Medical Diagnosis and Treatment Prior to and following Allogeneic HSCT

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Background: Within the United Kingdom, national guidance recommends patients receive a dental assessment, and necessary treatment prior to haematopoietic stem cell transplant, due to the resulting immunosuppression and increased risk of sepsis. It is uncertain from the current literature what benefits pre-HSCT dental interventions have on patients' outcome post-HSCT.

Methods: This study involved a qualitative approach with the use of face-to-face semi-structured interviews. A topic guide was used to facilitate the discussion in the interview. Areas of interest such as diagnosis and medical background, views on the care pathway and dental service, impact and feelings around dental treatment and advice provided, oral complications and future views on dental care were explored.

Patients were recruited from a late effects clinic >100days following allogeneic HSCT. All potential participants were given the opportunity to discuss the study and completed a consent form if they wished to proceed to interview. Ethical approval was granted for this study.

Results: From a potential 12 participants, 7 completed the face-to-face semi-structured interview. The interviews ranged from 15 minutes to 45 minutes in duration. The recorded interviews were transcribed verbatim by the researcher. Thematic analysis was used to analyse the results.

From the results, 4 main themes emerged:

1. **Preventing transplant related complications:** Overall particiants understood the need for a dental assessment prior to HSCT, and that improved oral hygiene could improve post-HSCT oral complications. However they highlighted the diffculties in completing oral hygiene practices whilst being an in patient due to their levels of fatigue and medical complications.
2. **Patient experience of the care recieved:** Generally participants were reassured by seeing a specialist dental unit prior to HSCT however there was differing expectations as to the treatment available and follow up process. Participants suggested having further information regarding the dental service so that they could tailor their expectations.
3. **Consequences of medical management:** Participants discussed both oral and medical complications of their transplant including GvHD, sepsis along with mucositis, xerostomia and dysguesia.
4. **Psychological impact of treatment:** Participants highlighted anxiety regarding their medical treatment but also a number of them experienced dental anxiety. The participants appeared pragmatic with regards to their dental anxiety with many of them stating their anxieties around dental treatment had reduced following the expereince of HSCT.

Conclusions: To conclude, completion of this study will enable changes to the current care pathway for patients including provision of more written information as to the reason for dental assessment, importance of continued oral hygiene and follow up dental care post-HSCT. It also provides a base for future research to build upon with regards to improving the oral health care for this patient group.

Clinical Trial Registry: N/A

Disclosure: Nothing to declare.

P178

Safety and Efficacy of low-dose Benda-EAM as Compared to Beam Conditioning for Autologous Transplantation of Refractory/relapsed Lymphoma Patients

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Background: The standard of care in relapsed/refractory lymphoma is consolidation with high dose chemotherapy and autologous stem cell transplantation (ASCT). BEAM has been widely used as a conditioning regimen for ASCT since 1990. However, issues such as pulmonary toxicity and scarcity of carmustine (BCNU) have led centers to seek alternative agents such as bendamustine. The optimum dose of bendamustine is not well defined, with total doses reported in the literature ranging from 100mg/m^2 to 400mg/m^2. Higher doses have been associated with increased renal toxicity. At our institution, we used BEAM from 2008 until 2017 at which point we made Benda-EAM our standard. After reviewing the experience of other centers, we chose a total dose of Bendamustine 320 mg/m^2 to minimize side-effects. The objective of this study is to compare the two conditioning regimens in terms of overall survival (OS), relapse free survival (RFS), and adverse events

Methods: Global summary and bivariate analyses of patients comparing Bend-EAM vs BEAM type of conditioning was made to describe the baseline and post-ASCT events characteristics.

Overall survival and relapse-free survival (defined as the first event between relapse and death) since ASCT were illustrated with the Kaplan-Meier method and curves were compared thanks to the log-rank test. Hazard-Ratios of univariate and multivariate analyses (incorporating baseline variables that was significantly different between conditionings and significant on univariate analyses as adjustment co-variables) were estimated with Cox regressions.

Results: A total of 71 patients were evaluated (BEAM n= 54, Benda-EAM n=17). There were no significant differences in the baseline characteristics of the two groups, with the following notable exceptions: pre-transplant status with less complete response [1/17 (5.88%) vs 7/53 (13.21%) (p=0.016)] and more ICE salvages [(14/17 (82.35%) vs 27/54 (50.00%), p=0.023)]in Benda-EAM versus BEAM respectively.

In terms of non-hematological toxicity, there was a higher incidence of significant mucositis (≥Grade 3) in the Benda-EAM group [82.3% vs 48% (p=0.02)]. There were no significant differences in pulmonary adverse events (n=2 and n=6 (p=0.82) or in renal toxicity [11.4 % vs 7.5 % (p=0.75)] between Benda-EAM and BEAM respectively. No severe cases of renal toxicity (≥Grade 3) were observed. Transplant related mortality (TRM) was 5.9% (1/17) in the Benda-EAM group and 3.7% (2/54) in the BEAM group (p=1.0).

Neutrophil and platelet engraftment favored Benda-EAM over BEAM, (10 vs 14 days (p= < 0.001) and 16 vs 27 days (p= < 0.001) respectively. The cumulative incidence of relapse 15 months after ASCT was 36% in Bend-EAM and 24% in the BEAM group (p=0.369).

Median OS was not reached in either group. The probability of OS at 18 months for the Benda-EAM and BEAM groups was 94.12 % and 91.89% respectively (p=0.66).

Conclusions: Benda-EAM utilizing a total bendamustine dose of 320mg/m^2 is a safe and efficacious conditioning regimen. Renal toxicity utilizing this dose is minimal. BendaEAM is associated with more GI & mucosal toxicity even with reduced dose. TRM and other adverse effects were not significantly different as compared to BEAM. Benda-EAM is non-inferior to BEAM conditioning in terms of RFS and OS.

Disclosure: Nothing to declare.

P179

Conditioning Regimen with Fludarabin/treosulfan Compared to Busulfan/cyclophosphamid Prior to Allogeneic Stem Cell Transplantation in Younger Patients with AML And MDS: A Single Center Retrospective Analysis

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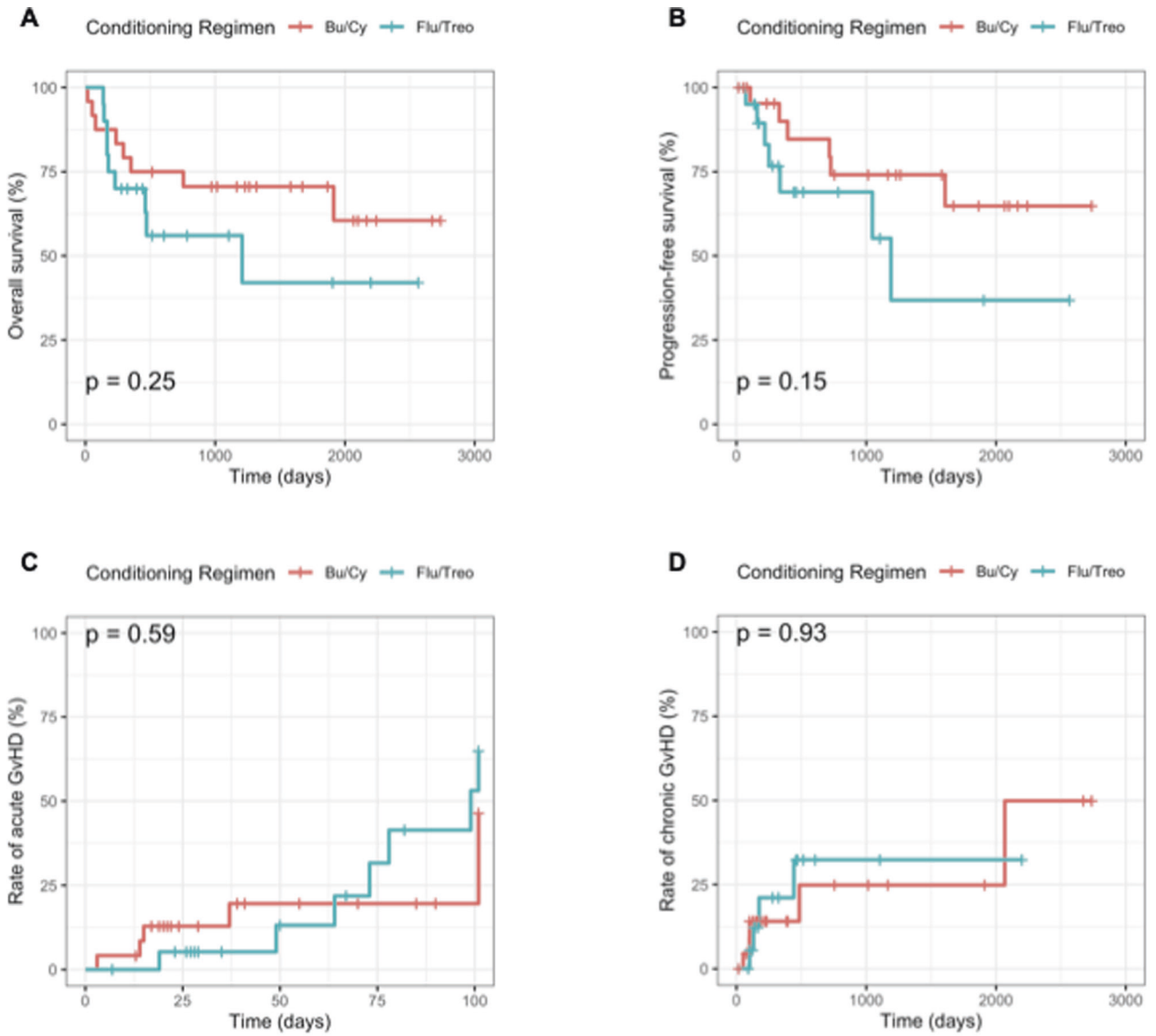

[Figure 1. Comparison of the conditioning regimens Bu/Cy and Flu/Treo, p-values using log-rank-test.]

Background: Non-myeloablative conditioning regimens such as Fludarabin/Treosulfan (Flu/Treo) enable allogeneic stem cell transplantation (alloSCT) for a broad range of patients with hematologic malignancies due to reduced toxicity rates and transplant related mortality. Beelen et al. showed, that conditioning with Flu/Treo provides excellent disease control and low rates of treatment related mortality in older and comorbid patients.[1] Nevertheless, myeloablative conditioning regimens (MAC) such as Busulfan/Cyclophosphamide (Bu/Cy), which are associated with higher toxicities, are often conducted in younger patients, because it is thought that those regimens lead to a better disease control[2]. Yet it is still of debate if younger patients could profit from a less toxic MAC regimen. This retrospective, single center analysis compares conditioning with Flu/Treo to Bu/Cy prior to alloSCT in younger patients with myeloid malignancies concerning outcome, toxicity and Graft-versus-Host-Disease (GvHD).

[1] Beelen, D. W., R. Trenschel, M. Stelljes, et al. Treosulfan or busulfan plus fludarabine as conditioning treatment before allogeneic haemopoietic stem cell transplantation for older patients with acute myeloid leukaemia or myelodysplastic syndrome (MC-FludT.14/L): a randomised, non-inferiority, phase 3 trial. The Lancet/Haematology 2019, published online October 9, https://doi.org/10.1016/S2352-3026(19)30157-7.

[2] Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. J Clin Oncol 2017; 35: 1154-61.

Methods: In this single center, retrospective study 44 patients aged between 25-55 with hematologic malignancies (AML (34), sAML (2), tAML (2), MDS (5), tMDS (1)) receiving either Flu/Treo (20 patients, 9 female, average age 48,9 years, 15 patients in complete remission before alloSCT) or Bu/Cy (24 patients, 19 female, average age 40,4 years, 23 patients in complete remission before alloSCT) conditioning before alloSCT at our institution between 1998 - 2019 were analyzed. Data concerning outcome, toxicity and GvHD were evaluated retrospectively. Patients were eligible for allogeneic transplantation based on their underlying malignancy and to institutional guidelines. All patients received either anti-thymocyte globuline and cyclosporine in combination with mycophenolatmofetil or Methotrexat short.

Results: Median overall survival (Bu/Cy vs. Flu/Treo, median (days): 1293 vs. 452, p=0,25) and progression free survival (Bu/Cy vs. Flu/Treo, median (days): 1201 vs. 331, p=0,15) did not differ between the two groups (Figure A, B). Non-relapse mortality was 33% in both groups. The rate of acute GvHD (only Grade 3 and 4 considered) did not differ significantly between both groups (25% in the Bu/Cy, 35% in the Flu/Treo group, p=0,59, Figure 1C). The rate of chronic GvHD (only extensive considered) did neither differ significantly between the two groups (12% in the Bu/Cy, 32% in the Flu/Treo group, p=0,93, Figure 1D).

Conclusions: This retrospective analysis reveals that the conditioning regimen Flu/Treo has comparable outcomes concerning overall survival, progression-free survival and rates of acute and chronic GvHD to Bu/Cy. The tendency to a more favorable overall survival within the Bu/Cy group might partially be explained by the higher rate of active disease and older patients within the Flu/Treo group. Therefore the comparison of the Flu/Treo conditioning regimen with MAC should be studied in a randomized, prospective trial.

Disclosure: Nothing to declare.

P180

Atg in Conditioning for Sibling Allogeneic Stem Cell Transplantation; Single Center Experience

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Background: The majority of hematologic diseases, especially the malignant group, are attributed with low survival rates. The modern medicine copes with finding the optimal treatment protocol. Allogeneic stem cell transplantation holds the biggest curative potential for this group of diseases. But still acute and chronic graft versus host disease (GvHD) represents a major problem to solve.

Methods: Our goal was to present our experience in conditioning candidates for sibling allogeneic stem cell transplantations by adding ATG balancing between GvHD prevention, infectious complications and survival.

We have made a 5 year retrospective analysis of 29 patients where sibling allogeneic stem cell transplantation was done in our transplant center. We have included not only malignant hematological diseases, but also patients with aplastic anemia. We did not detail the patients in terms of previous treatment intensity, and made a more general analysis of outcome in patients where ATG was used in conditioning and where it wasn`t the case. We administered mainly anti-human T-lymphocyte immunoglobulin (Grafalon) 8-10 mg/kgTT.

Results: We have included 29 patients. 16 were male (55%), and 13 females (45%). The mean age was 39.7 years. The majority of patients, 15 (51%) were diagnosed with AML, 6 (20.6%) with MDS, 3 (10.3%) with ALL, 2 (6.8%) with myelofibrosis, 2 (6.8%) with CML, 1 (3.4%) with AA. As sibling donors we used 12 females (41.3%) and 17 (58.7%) males. ATG was applied in the conditioning of 12 patients (41%). The median number of cells, mainly mononuclear cells, used in the graft in the ATG group was 3.3, while in the non ATG group 3.8. There was no significant difference in days to engraftmen, 13.7 in the ATG group, compared to 12.9 in the non ATG group. We used standard MTX+CsA immunosuppression posttransplant. In the majority of patients Bu-Cy-ATG was used as conditioning protocol. In the ATG group, in 35% of the patients some kind of infectious complication was confirmed, even with some multiresistant strains like E.Coli ESBL+ or Vanvomicin resistant Enterococcus (VRE), while in the non ATG group, only 11% had infectious complications, mainly catheter associated. But, if we analyze the GvHD, in the ATG group, acute GvHD it was diagnosed in 22% of the patients, while in the non ATG group it doubled the incidence of acute GvHD, and it was near 42%, gr III-IV was most prevalent and it could be related to 40% of the deaths in the non ATG group. The relapse rate in the ATG group was 10%, ehile in the non ATG group, around 12%, but we must emphasize that the risk profile of the patients was much worse, and nearly all of them were transplanted in nearly active disease.

Conclusions: ATG should be recommended in conditioning for sibling allogeneic stem cell transplantation in hematological diseases. More rigorous control and

treatment of infectious complications must be and can be provided with adequate use of antibiotics. The higher rate of infections does not outweigh the benefit of lower rate for GvHD, predominantly acute GvHD making allogeneic HSCT safer and more applicable.

Clinical Trial Registry: Not aplicable

Disclosure: Nothing to declare.

Experimental stem cell transplantation

P181

2nd allo-hsct for Patients who Diagnosed Recurrence all after the 1st allo-hsct

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Background: Recurence of ALL after Allo-HSCT is described with poor prognosis and very low long-time survival rate. At present, there are no definite effective treatment measures for these patients. The results of 2nd Allo-HSCT in patients with this group leukemia in our center was analyzed in order to understand whether the therapeutic effect can improve prognosis on the patients.

Methods: Retrospective analysis, from July 1st, 2015 to November 1st,2019, all patients undergo 2nd Allo-HSCT who diagnosed as R/R ALL after Allo-HSCT. Total 28 cases. Male 16/ Female 12; 27 cases diagnosed as B-ALL (10 cases with BCR/ABL1, 1 with IKZF1 mutate, 1 with IKZF1 and ETV6 mutate; 1 with Ph-like; 2 cases with E2A/PBX1) and 1 diagnosed as T-ALL. Conditioning regimen in 1st Allo-HSCT 5 cases are TBI/CY/ATG/Me-CCNU and 23 cases are BU/CY/ATG/Me-CCNU. In contrast Conditioning regimen in 2nd Allo-HSCT conditioning regimen, 23 cases are TBI/CY/ATG/Me-CCNU and 5 cases are BU/CY/ATG/Me-CCNU. 22 cases accepted CART before 2nd Allo-HSCT.

Results: Recurrence time had significant effect on overall survival(OS) and leukeamia free survival(LFS). recurrence time more than 6months vs less than 6 months: 1-year OS 58.4% vs. 33.3%, p=0.029; 2-year OS 58.4% vs. 33.3%, p=0.029; 1-year LFS 53.3% vs. 33.3%, 2-year LFS 42.7% vs. 33.3%; incidence of viral disease 67.9% (19/28), CMV46.4%(13/28), EBV-PTLD 10.7%(3/28), others 10.7%(3/28); Cause of mortality: total 11cases, viral disease 8cases (including 2cases PTLD), septic shock 1case, TMA1case, GI-GVHD 1case.

Conclusions: 1. 2nd Allo-HSC can improve the prognosis of Recurrence ALL after 1st Allo-HSCT who reached CR. 2. Recurrence time less than 6months had significant effect on OS and LFS; 3. Another CR even FCM-MRD negative could be reached who undergone CART therapy, access to 2nd Allo-HSCT; 4. The main early complications of 2nd Allo-HSCT were viral disease; 5. The main causes of death after 2nd Allo-HSCT were none relapse mortality, mainly viral diseases.

Disclosure: Nothing to declare.

P182

Establishing a Transplant Sharing Program

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Background: Autologous stem-cell transplantation (ASCT) is a prevalent therapy with firmly established efficacy and safety indices. However, to perform this procedure is necessary to transfer patients to referral centers with obvious implications for patients and their relatives. Besides, the increasing demand of autologous and allogeneic transplants may cause transplant delays.

Based on previous studies carried out in Canadian centers (Crump. Bone Marrow Transplant. 1992), an autologous transplant sharing program has been set between 3 centers in Spain to increase the availability of ASCT, avoid transplant delays and improve patient and family comfort.

Methods: Retrospective, observational and analytical study of the ASCT enrolled in this program between July 2017 and October 2019.

Selected ASCT candidates for multiple myeloma (MM), lymphoma and acute myeloid leukemia (AML) from Infanta Leonor (ILH) and Nuestra Señora del Prado Hospitals (NSPH) were included after signing the informed consent.

Uniform clinical protocols were used between the 3 hospitals. A clinical transplant update program for nurses and physicians was set up before the program started.

The program is divided into 2 stages: First stage: Pre-transplant patient evaluation, stem-cell apheresis collection

and cryopreservation as well as administration of high-dose therapy and hematopoietic stem-cell infusion were performed at 12 de Octubre hospital (H12O). Second stage: in absence of significant clinical events patients were transferred to the referring center (NSPH and ILH) on day +1 for supportive care.

Results: Results:

- **Population**: 12 patients (4 female, 8 male). Median age: 58 years (23-71). **Diagnosis:** multiple myeloma (MM): 9, acute promyelocytic leukemia (APL): 1, follicular lymphoma: 2. Conditioning regimens: Melfalan 200 (75%), CyBU (8%), BEAM (17%) All patients received standard prophylaxis with acyclovir, fluconazole and cotrimoxazole. G-CSF was allowed from day +5.

- **HSCT and engraftment:** no patient needed an additional bridge therapy because of transplant delay. All 12 patients were transferred on day +1. Median time to neutrophil (> $0.5x10^9$/l) and platelets (> $20x10^9$/l) engraftment was 11 days (10-14) and 12 days (11-20) respectively. Secondary graft failure: 1/12 patients.

- **Adverse events:** Febrile neutropenia was observed in all patients with microbiological documentation in 42%. Documented pathogens: bloodstream infections due to Pseudomonas Aeruginosa, Enterobacter cloacae and Streptococcus gallolyticus. Urinary tract infection: Klebsiella pneumoniae. 1 infectious colitis caused by Campylobacter jejuni. Engraftment syndrome was observed in 2 patients (17%) and grade ≥ 3 mucositis in 6 patients (50%). 7 patients (58%) required parenteral nutrition.

- **Results:** 11 patients were successfully discharged. 1 patient died due to secondary graft failure. Follow up was provided as needed in the referring center. Patients were reviewed in H12O on day +100 and annually therafter.

Conclusions: The sharing transplant program is a feasible and safe network that eases the access of patients to this therapy avoiding delays and prolonged stays in reference centers, with the consequent psychological and social benefit for patients and their families. Outcome and adverse events were according to literature. This is a pilot study that aims to extend to other centers within the PETHEMA group.

Clinical Trial Registry: No applicable

Disclosure: Nothing to declare.

Experimental transplantation

P183

Impact of Gut Fungal Composition on Outcome after Allogeneic Hematopoietic Cell Transplantation

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Background: Alterations of gut bacterial microbiota composition have been shown to impact outcome after allogeneic hematopoietic cell transplantation (alloHCT), including overall survival (OS), graft versus host disease (GVHD) and relapse incidence (RI). Furthermore, the role of eukaryotic gut virome in GVHD was recently shown (Legoff et al., Nature Medicine, 2017). In contrast, the impact of gut fungal microbiota is still unknown in the alloHCT setting. Earlier studies in patients with inflammatory bowel diseases or primary sclerosing cholangitis, suggested that gut fungal microbiota dysbiosis and composition contribute to disease severity.

Methods: With this background, we examined the role of fungal microbiota in patients undergoing alloHCT. Our goal was to attempt to correlate the fungal microbial shifts and changes with patients' outcome. Fecal specimens were collected at day 0 of alloHCT (before graft infusion). The gut intestinal microbiota was characterized by 454 pyrosequencing of the ITS2 genes [ITS2 (sense) 5'-GTGARTCATCGAATCTTT-3′ and (antisense) 5′-GAT ATGCTTAAGTTCAGCGGGT-3′ and the optimized and standardized ITS2-amplicon-library preparation protocol (Metabiote, GenoScreen)]. Phylogeneic classification was obtained using the UNITE ITS database (version 12_11). Association of fungal microbiota with clinical predictors and outcomes were evaluated.

Results: In all, we analyzed 68 patients (34 males and 34 females). Median age was 60 (range, 22-74) years. Disease risk index was low-intermediate in 38 patients, high-very high in 27 patients (not assessed in 3 patients with aplastic anemia). 49 patients received a myeloablative reduced toxicity conditioning regimen, while 19 patients received a reduced intensity conditioning regimen. 16 patients received their graft from a matched sibling donor, 18 from a haploidentical donor, and 34 from an unrelated donor. 97% of patients received antithymocyte globulin as part of their conditioning regimen, and patients undergoing alloHCT from a haploidentical donor also received post-transplant cyclophosphamide.

Overall we found a low fungal diversity score of the fungal microbiota at day 0 in all patients from this cohort, with little variations. Therefore, it proved difficult to establish any statistically significant correlations between fungal diversity and patients' outcome. Nevertheless, we observed a dominance by Candida albicans in alloHCT patients, and patients with higher number of Candida

albicans at day 0 of alloHCT have a significantly lower overall survival and GVHD-free, relapse-free survival (p=0.026 and p=0.013 respectively. In multivariate Cox hazard analysis including the most important parameters associated with patients' outcome, higher number of enterococcus, enterobacteria and Candida albicans was associated with a lower OS and GRFS, while bacteria belonging to the clostridiales were associated with a higher OS and GRFS.

Conclusions: In conclusion, we find an important disruption of gut fungal microbiota in patients undergoing alloHCT, as evidenced by the very low fungal diversity observed at day 0. Furthermore, increased numbers of Candida Albicans species at time of alloHCT were predictors of mortality and GVHD-free, relapse free survival, independently of clinical parameters and bacterial microbiota composition.

These results indicate that in addition to bacterial and viral microbiota, fungal microbiota is another important factor influencing outcome after alloHCT. Validation studies and exploration of the link between fungal and bacterial microbiota are warranted.

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The other authors declare. no competing financial interests.

P184

Monitoring Hematopoietic Cell Microparticles in Allografts and Transplant Recipients

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Background: Peripheral blood microparticles (MPs) are released from plasma membrane of activated or apoptotic cells and carry cell surface markers of the mother cells. Platelet- and endothelial-derived MPs have been detected in a wide variety of clinical conditions as well as in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, the role of MPs during and after allo-HSCT and their possible immunomodulatory effects is under investigation. The objective of this project was to study the role of MPs isolated from lymphocyte and stem cell populations of patients undergoing allo-HSCT.

Methods: Samples were collected from the grafts and the peripheral blood of 19 patients who underwent allo-HSCT in our department. Nine patients were diagnosed with acute myeloid leukemia (AML), 9 with acute lymphoblastic leukemia (ALL) and 1 with myelodysplastic syndrome (MDS). Informed consent was obtained from all patients. Eighteen patients received peripheral blood stem cell transplant from sibling donors and 1 from a matched unrelated donor (MUD). All patients were at complete remission before allo-HSCT. Conditioning regimen administered to 4 AML patients was myeloablative (BuCy), whereas 5 received reduced-intensity (RIC) regimens, ie Flu/Treo in 3, Flu/Bu in 2 and FluCy in 1 patient. Six ALL patients ie 1 received myeloablative condiotioning, received BuCY, 5 TBI/Cy, and 2 received RIC, ie Flu/MEL. The MDS patient received RIC conditioning, ie Flu/Treo. residual

MPs were isolated from plasma centrifugation and their number was determined by flow cytometry after incubation with Annexin V and CD34, CD3 or CD56. The number of MPs has been estimated in the graft as well as in the peripheral blood of the patients at days 0, 4 and 14 (day0, +4d, +14d) post allo-HSCT. Statistical analysis was performed using t-test, Pearson´s and Spearman´s depending on the normality of the distribution of variables.

Results: MPs were detected in the graft and in the peripheral blood of the recipients after allo-HSCT. MPs can also be detected in grafts. The number of total measured patient AnnV+ CD34+, CD56+, CD3+MPs on +14d was decreased compared to day0 and +4d. CD34+MPs of the graft were significantly associated with patient CD34+MPs on +14d after allo-HSCT (r=0.643, p=0.003). The median time to CD34+cell engraftment was 13 days after HSCT and was not correlated to patients and graft CD34+MPs. The number of CD3+MPs were low on days 0, 4 and 14 post-HSCT. The number of CD3+MPs on +4d was positively correlated to the CD3+MPs of the graft (r=0.579, p=0.009). Although CD3+MPs were not significantly associated to relapse, CD3+MPS were positively correlated with CD3+cell engraftment (r=0.622, p=0.008). CD56-derived MPs were positively correlated with CD3 cell engraftment (r=0.501, p=0.015). CD56+MPs on day 0 and those of the graft were positively correlated (r=0.517, p=0.23). CD34+, CD56+ and CD3+MPs were not significantly associated with chimerism on day 30 and 90.

Conclusions: Stem cell derived and T-lymphocyte and NK-derived MPs were detected in the graft and in patients undergoing allogeneic-HSCT. The number of MPs derived from T lymphocyte (CD3+MPs) and NK cells (CD56+MPs) were related to the T cell reconstitution. Therefore

MPs may represent a valuable marker after allogeneic-HSCT

Disclosure: Nothing to declare.

Gene Therapy

P185

Ex-vivo Autologous Haematopoietic Stem Cell Gene Therapy in Mucopolysaccharidosis Type IIIA

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Background: Mucopolysaccharidosis type IIIA (MPSIIIA) is progressive lysosomal storage disorder (LSD) caused by a mutation in the SGSH gene. A deficiency of the enzyme N-sulfoglucosamine sulfohydrolase prevents the degradation of heparan sulfate(HS), and substrate accumulation causes a predominantly neurological phenotype that result in early death. Allogeneic HSCT does not modify the disease phenotype even when performed early and with fully donor engraftment.

Preclinical data from our group has demonstrated correction of the disease phenotype with engraftment of gene-modified cells, with enzyme over-expression, including in the brain. Here we report the findings of a first-in-man, autologous, ex-vivo modified, haematopoietic stem cell gene therapy transplant for MPSIIIA from a first patient and discuss our open clinical trial for this disease.

Methods: A 2 years old patient underwent collection of autologous, mobilised, peripheral blood stem cell cells using G-CSF and plerixafor. The cells were transduced using a lentiviral vector incorporating the SGSH gene with the CD11b, myeloid specific promoter. The patient received myeloablative busulfan only conditioning and infusion of the cryopreserved gene modified stem cell product.

Results: The patient had neutrophil engraftment (ANC >0.5x10^9/L) on day +16 and platelet engraftment (>20x10^9/L) by day +39. The patient was discharged from hospital on day +33.

Enzyme analysis, substrate reduction and engraftment have been monitored following the transplant.

Enzyme levels are very significantly greater than normal in leucocytes, all leucocyte fractions and plasma and these supra-physiological enzyme levels are sustained. Substrate analysis shows reduction of HS to normal in urine (never achieved in allogeneic transplant) (Fig 1a), and plasma, and substantial reduction in CSF HS at an early time point. There is sustained, multilineage engraftment of gene-modified cells, and the incorporated VCN in engrafted cells in shown in Fig 1b.

Conclusions: We report the first patient to be treated with autologous ex-vivo haematopoietic stem cell transplant for MPSIIIA and demonstrates successful engraftment with sustained, supraphysiological high enzyme levels expressed with little toxicity. We report early neurodevelopmental data in this otherwise rapidly progressive, ultimately fatal neurological disease. A phase I/II trial of this approach is open and recruiting patients.

Disclosure: Nothing to diclare

Graft-versus-host disease – clinical

P186

Identification of Predictive Models Including Polymorphisms in Cytokines Genes Associated with Acute Graft versus Host Disease and overall Survival after Identical HLA-allogeneic Stem-cell Transplantation

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Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative treatment for patients with hematologic malignances. However, 40% of patients develop post-transplantation complications such as acute graft versus host disease (aGVHD). Immune system genes like cytokines play a role in inflammatory process that occur during aGVHD. The aim of this study was to select polymorphisms in interleukins and chemokines genes to build models to predict the development of aGVHD and overall

survival after allo-HSCT from an HLA-identical sibling donor.

Methods: We retrospectively selected 90 patients with hematological malignancies who received an allo-HSCT from an HLA-identical sibling donor from 2000 to 2015. At aGVHD analysis we did not include two patients due to early death. The genotyping was performed using an NGS panel (include 73 interleukins and 59 chemokines genes) in a HiSeq platform (Illumina, USA). The bioinformatics analysis was carried out with the GeneSystems software (Sistemas Genómicos, Spain). We analyzed variants located in coding regions, splicing sites, UTR, and 5´upstream and 3´downstream zones (+/- 200pb). The SNPs selected corresponding to non-synonymous variants, with read depth ≥30X in the canonical isoform with an allele frequency ≥0.4 and represented in at least 5% in our cohort. To compare the differences among groups we used fisher test for aGVHD and Kaplan-Meier for OS. Multiple logistic regression models were performed using combination of polymorphisms selected previously that could be applied to clinical practice to predict aGVHD. The models with the highest AUC value, sensitivity and specificity value and the lowest number of genetic variants used were selected. Statistical Package for the Social Sciences (SPSS, Chicago, USA) was used for statistical test.

Results: The cumulative incidence rates for aGVHD of grades II-IV and III-IV at 100 days after transplantation were 48.93% and 18.08%, respectively. And OS at 2 years was 60%. The clinical variables (age, gender, pathology, stem cell source and previous transplantation) were not correlated with aGVHD nor OS, except conditioning regimen that was significant at III-IV aGVHD (p= 0.041) and OS (p=0.034). Using filters defined previously, we detected 820 polymorphisms. Specifically, 14 SNPs were correlated with II-IV aGVHD, 13 SNPs with III-IV aGVHD and 47 SNPs with OS.

We developed multiple logistic regression models for II-IV, III-IV aGVHD and OS in interleukins and chemokines genes. According to predictive models, we classified patients at risk and low risk based on cut-point by ROC curve. Based on predictive scores the 80% of high-risk patients vs 12% of low-risk patients developed grades II-IV aGVHD and the 60% of high-risk patients vs 3% of low-risk patients developed grades III-IV aGVHD at 150 days after allo-HSCT. In the case of OS, the 7% of high-risk patients vs 94% of low-risk patients at five years after allo-HSCT were alive.

Conclusions: These predictive models allows the classification of patients at low and high risk of developing aGVHD, who could benefit from personalized management through immunosuppression and other drugs. However we must validated these polymorphisms in a prospective cohort and in others types of allo-HSCT.

Disclosure: The authors have nothing to disclose

P187

Search for Circulating Endothelial Cells of Donor Origin after Allo-HSCT: Potential Clinically Relevant Implications in the Context of graft-versus-host Disease

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Background: We have confirmed that Circulating Endothelial Cell (CEC) count changes represent a valuable marker to monitor endothelial damage in patients undergoing allogeneic hematopoietic stem cell transplant (allo-HSCT) and hold the potential to enter clinical routine as a suitable tool to assist clinicians in GVHD diagnosis. At the same time, we have repeatedly documented that statistically significant higher CEC counts (P>0.003) are scored at engraftment in patients who will not manifest GVHD versus those who will develop GVHD (Transplantation 2014; Bone Marrow Transplantation 2017; Scientific Reports 2019). By considering the organ transplant setting, it has been recently reported that endothelial cells from the grafted organ, besides being a continuous source of alloantigens, can downregulate alloreactivity exerting tolerogenic responses. Therefore, by inference to the allo-HSCT field, the presence of donor CEC might result in a putative protective effect against GVHD presentation.

Methods: With the aim to test the hypothesis that at time of engraftment CEC present in peripheral blood (PB), besides coming from cells shedding from patient vasculature, could partly belong to donor, originating from the cellular graft, we conducted a two step study: 1) an exploratory set, and 2) a confirmatory set. In the exploratory set, we performed FISH analysis on flowcytometry-sorted CEC ($CD45^{neg}/CD34^{bright}/CD146^{pos}$, Lyotube #623920, BD Biosciences) (n=3) and on whole PB derived

culture-expanded CEC (n=3) (EGM-2 BulletKit, Lonza), obtained at engraftment in sex-mismatched allo-HSCT. In the confirmatory set (n=15), single CEC were recovered from PB, at engraftment (T1) and at 90 days (T2) after allo-HSCT, through the DEPArray™ technology (Menarini Silicon Biosystems), after preliminary bulk separation step carried out with the CellSearch® System. Single recovered CEC was whole genome amplified (Ampli1™ WGA Kit) and short tandem repeat (STR) profile determined (Ampli 1™ STR kit) on each single CEC. To confirm host/donor origin, single CEC STR profile was compared to that determined on patient and donor cells before allo-HSCT. Moreover, donor CEC presence was evaluated by CISH analysis on formaline fixed and paraffin-embedded biopsy sections obtained at least three months after sex mismatched allo-HSCT.

Results: By positive findings of the exploratory set, we proved, at the single cell level in the confirmatory set, the presence of donor CEC at engraftment (T1) in 4 out of 15 patients (see Table). Of them, 2 did not manifested GVHD, despite a GVHD risk score of 2, and the other 2 presented GVHD grade I. On the contrary, among the 10 patients in whom no donor CEC were detected, 6 experienced GVHD grade II-III, while 4 did not manifested GVHD, despite a 1-3 GVHD risk score.

Conclusions: Our results represent the proof of principle that D-CEC may flow in host PB early on from hematopoietic recovery and seldom persist thereafter at steady-state conditions. These puzzling findings will require in depth investigations with the aim to shed brighter light on tissue tolerance in the context of GVHD, opening up unexpected scenarios on the protective role potentially played by donor CEC.

Clinical Trial Registry: NCT04038827

Disclosure: Francesca Fontana and Nicolò Manaresi are employee of Menarini Silicom Biosystem; Gianluca Rotta is employee of Becton Dickinson Biosciences Italia.

P188

Double Lung Transplantation in Adults for Chronic Pulmonary Graft versus Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Severe pulmonary chronic graft versus host disease (cGVHD) is a life-threatening complication that may occur following allogeneic hematopoietic stem cell transplantation (HSCT). Lung transplantation (LTx) is a potential therapeutic modality in this setting but evidence of tolerability and efficacy is restricted to case reports and small series. We aim to report our experience of double lung transplants in adults with severe pulmonary cGVHD after allogeneic HSCT.

Methods: We retrospectively reviewed all adult patients who underwent LTx for pulmonary cGVHD after allogeneic HSCT at our centre. Medical health care records were analysed for patient demographics, indication for allogeneic HSCT, induction and consolidation treatment received, HSCT details (including donor details, conditioning regimens, GVHD prophylaxis), post-HSCT complications (occurrence and severity of acute and chronic GVHD, pulmonary infections), details of LTx and post-transplant outcomes (including infections, acute rejection, chronic lung allograft rejection (CLAD)), survival after HSCT and after LTx. Survival outcomes were compared by Kaplan-Meier analysis.

Results: A total of 18 patients underwent bilateral LTx for chronic pulmonary GVHD between 2003 and 2019. The median(range) age at time of LTx was 38(19-55) years. Chronic myeloid leukemia (33%;n=6) was the most common indication for HSCT followed by Acute Lymphoblastic Leukemia (22.2%;n=4) and Acute Myeloid Leukemia (16.7%;n=3). Stem cell donors were matched related, matched unrelated, and haplo-identical in 80%, 13.3%, and 6.7% cases, respectively. All patients received myeloablative conditioning regimens with 84.6% (n=11) receiving total body irradiation at a median dose of 1200cGy. Acute GVHD of any grade was seen in 70% patients. Skin (66.7%) was the most common site of extra-pulmonary cGVHD followed by mouth (50%) and eyes (41.7%). Bronchiolitis obliterans (83.3%; n=15) was the most common pathological diagnosis of pulmonary cGVHD followed by pleuro-parenchymal fibro-elastosis (16.7%;n=3). The median(range) time to LTx following HSCT was 9.9 (1.2-19.2) years.

Post Lung transplant immunosuppressive therapy included a calcineurin-inhibitor (Cyclosporine or Tacrolimus), a cell-cycle inhibitor (Azathioprine or Mycophenolate) and Prednisone. In the first 2 years following LTx, four patients (22.2%) developed acute-cellular rejection, necessitating augmented immunosuppression (IV methylprednisolone in all patients plus Anti-Thymocyte globulin in 1 case). CLAD was observed in 44.4% patients (n=8), with the median time to developing CLAD being 5.1 years. After a median follow up of 31 months, 50%(n=9) patients died. Estimated survival

at 5-years for patients undergoing LTx for pulmonary GVHD and LTx for other indications(during the same time period) were 48.1% and 59.4% respectively(p value-0.4). Sepsis (66%) was the most common cause of death followed by CLAD (33%). One patient suffered a relapse of their primary malignancy(CML) after lung transplant and is currently in remission.

Conclusions: Double lung transplant is a viable treatment modality for adults with severe pulmonary cGVHD after allogeneic HSCT with a satisfactory 5-year post lung transplant survival. When compared to lung transplants for other indications, there is a trend towards increased mortality associated with infection. Due to the rarity of this disease as a transplant indication, multicenter prospective studies are needed to accurately quantify the benefit of this approach, appropriate timing of lung transplant, and elucidate factors predicting favourable outcomes.

Disclosure: Nothing to declare.

P189

Reduced Inflammatory Tissue Infiltration during Intestinal steroid-refractory GVHD

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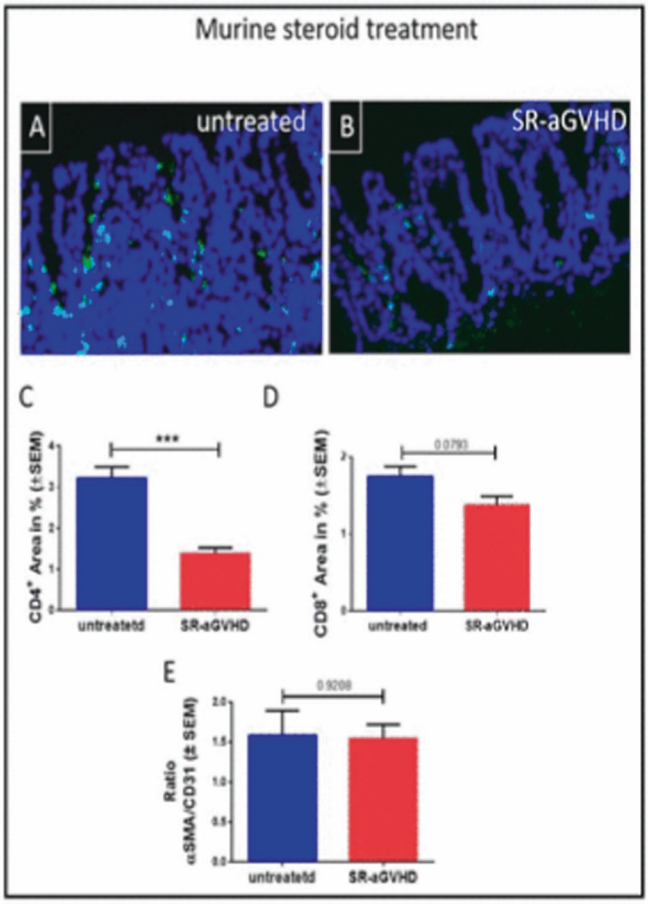
Background: Mortality in patients who fail initial steroid treatment (steroid-refractory GHVD; SR-GVHD) is very high because immunosuppressive treatments for SR-GVHD showed disappointing clinical results. SR-GVHD pathobiology is poorly understood and there were no experimental models of SR-GVHD, thereby hindering the development of novel therapeutic approaches. To shed light on SR-GVHD pathobiology we developed two murine SR-GVHD models and we analyzed intestinal patient biopsies from two independent alloSCT centres.

Methods: Murine models: To mimic SR-aGVHD, we used the chemotherapy based murine models 129→B6 (minor-mismatch) and B6→B6D2F1 (haploidentical) by administering i.p. 0.5 mg/kg/day dexamethasone upon clinical presentation of GVHD. Dexamethasone was used in mice instead of prednisolone due to practical reasons (longer lasting effects allowing once daily dosing). Intestinal tissues were harvested during non-treated GVHD versus SR-GVHD and were stained against CD4, CD8, CD11b and F4/80 as well as the endothelial marker CD31 and pericyte marker alpha smooth muscle actin (αSMA). Positive stained area in the intestinal mucosa was quantified by fluorescence microscopy and Image J.

Human data: Formalin fixed tissue sections from intestinal biopsies from independent patient cohorts with GVHD at diagnosis vs. SR-GVHD (Charité Berlin and Medical University Hannover) were stained against CD45, CD3 and Caspase 3. Cohort 1 included colon and duodenum biopsies from 6 and 5 patients at aGVHD onset vs. 6 and 5 patients during SR-GVHD, respectively. Cohort 2 included colon biopsies from 11 patients. In each of these patients two biopsies were taken: first at onset of aGVHD and second at diagnosis of SR-GVHD.

Results: In two independent clinical cohorts as well as in the experimental model we found considerably reduced inflammatory infiltration in intestinal biopsies in SR-GVHD compared with aGVHD at diagnosis (Fig 1). In mice, the predominant remaining cell populations in colon during SR-GVHD were CD4+ and CD8+ T cells, CD11b+ and F4/80+ myeloid cells; with significant lower levels of CD4+ and CD8+ T cells in SR-GVHD versus aGVHD without steroid treatment (Fig.1A-D). In patients, significant CD45+ leukocyte reduction (Fig.1F, G, H, I, J) was mainly mediated by significantly lower infiltration of CD3+ T cells (Fig.1K, L, M, N, O) in colon and duodenum biopsies during SR-GVHD vs. aGVHD at time of diagnosis. In H&E sections, we found massive tissue damage during SR-GVHD. Analyzing endothelial pathology in intestinal samples, we found endothelial damage as quantified by pericyte coverage (αSMA) reduction in colon vessels (CD31) was equally severe in SR-aGVHD and untreated aGVHD mice (Fig.1E). In line, Caspase 3 staining in patient intestinal biopsies demonstrated a high level of endothelial apoptosis during aGVHD both at diagnosis as well as during SR-GVHD (Fig.1P).

Conclusions: Our data indicates that despite severe tissue damage during SR-GVHD, the inflammatory activity in intestinal tissues is reduced after clinically unsuccessful steroid treatment. In the context of disappointing clinical results of SR-GVHD treatment by immunosuppressive agents, our current results provide a rationale for non-immunosuppressive therapies, e.g. tissue protection or regenerative approaches.



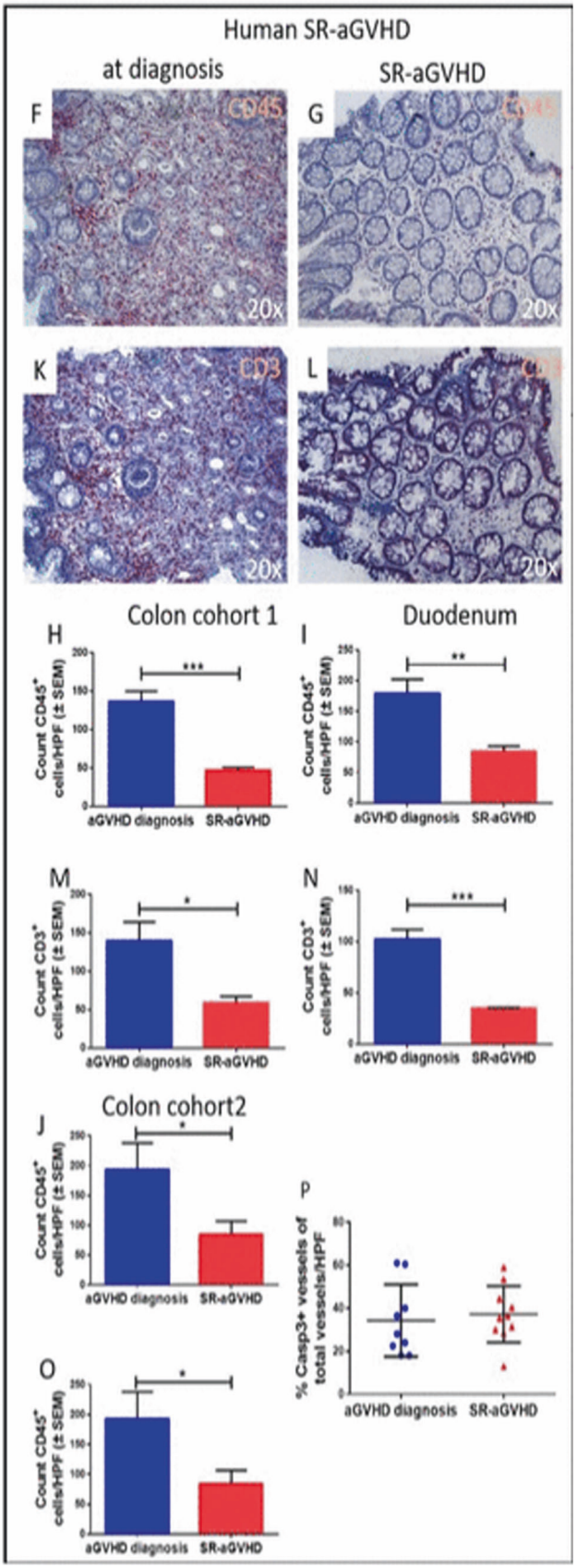


Figure 1: CD4⁺ staining (green) in murine colon mucosa of **(A)** control PBS treated (untreated) aGVHD and **(B)** Dexamethasone treated aGVHD (SR-GVHD) (B6-BDF model). Quantification of CD4⁺ **(C)** and CD8⁺ **(D)** area and endothelial damage by ratio of αSMA⁺ area/CD31⁺ area **(E)** in colon mucosa of untreated aGVHD versus SR-aGVHD. Significance was tested by student's *t*-test (****P* < .001; n=5 animals per group). Error bars indicate mean ± standard error of the mean (SEM). Human intestinal biopsies at aGVHD diagnosis and during the course of SR-aGVHD stained against CD45 **(F,G)** and CD3 **(K,L)**. Quantification of CD45 and CD3 infiltrates at aGVHD diagnosis versus SR-aGVHD in colon **(H,M)** and duodenum **(I,N)** biopsies of cohort 1 and in colon biopsies of cohort 2 **(J,O)**. **(P)** Quantification of Casp3⁺ events in colon endothelium of biopsies of cohort 2 at aGVHD diagnosis vs. SR-aGVHD given in % of vessels in HPF. Significance was tested by student's *t*-test (****P* < .001; n= 4-6 patients per group). Error bars indicate mean ± standard error of the mean (SEM).

[Figure 1: Inflammatory infiltration and endothelial damage in experimental and human SR-aGVHD.]

Clinical Trial Registry: not applicable
Disclosure: Nothing to declare.

P190

Impact of Antithymocyte Globulin Dose for graft-versus-host Disease Prophylaxis in Stem Cell Tansplantation from Unrelated Donors

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Background: Despite the wide use of anti-thymocyte globulin (ATG) for GVHD prevention after allogeneic HCT convincing evidence about an optimal dose is lacking.

We assessed the impact of Thymoglobulin® dose on main clinical outcomes in HCT from HLA-matched unrelated donors (MUD).

Methods: We report a retrospective analysis of 453 adult patients who received HCT for hematological malignancies at three Transplant Centers from January 2005 to December 2016. Primary endpoints included cumulative incidence of acute (aGVHD II-IV and III-V), and moderate/severe chronic GVHD, cumulative incidence of relapse (RI) and nonrelapse mortality (NRM). Secondary endpoints included Overall survival (OS), Event-free survival (EFS) and Refined GVHD/relapse-free survival (GRFS).

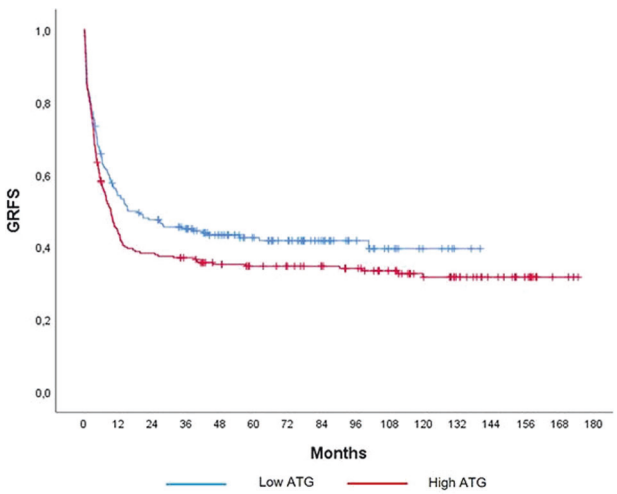
Results: Patients were divided into lower-ATG group (5mg/kg ATG, N= 213) and higher-ATG group (range 6-7.5 mg/kg ATG, N=240). Median age at transplant was 51 years, groups were balanced for major characteristics (EBMT risk score, disease type, female donor into male recipient, GVHD prophylaxis, graft source, active disease at transplantation) except for age (51.3 vs 50.7 years, p=0.035), higher proportion of HLA mismatched transplantations (56,7% vs. 31,6%, p< 0.001) and use of reduced intensity conditioning regimen (35% vs. 24,9% p=0.024) in the higher ATG group.

Median follow up was 83.7 months.

Cumulative incidence of grade II-IV aGVHD, grade III-IV aGvHD and moderate/severe cGVHD did not differ (6-month grade II-IV aGVHD 30.1% in the lower-ATG group vs 33.2% in the higher-ATG group, p=0.22; 6-month grade III-IV aGvHD 10.4% vs 12.5%, p=0.42; 3 years moderate-severe cGVHD 18,2% vs 21.8%, p=0.2; respectively) By multivariate analysis, HLA-mismatch regardless of ATG dose, significantly affected the cumulative incidence of II-IV aGVHD (HR 1.66, p=0.003) and III-IV aGVHD (HR 2.61, p=0.001). Conversely, only female donor into male recipient (HR 1.82, p=0.027) and reduced intensity conditioning (HR 0.54, p=0.021) affected moderate/severe cGVHD, while the risk was not significantly increased in patients with mismatched donors.

Likewise, cumulative incidence of relapse and NRM did not differ according to ATG dose (HR 1.03, p=0.8 and HR 1.29, p=0.18 respectively). By multivariate analysis, age and active disease had an impact on relapse incidence (HR 0.98, p=0.001 and HR 2.49, p< 0.001 respectively) and NRM (HR 1.03 p=0.001 and HR 1.52, p=0.03 respectively). Estimated median OS and RFS were 77.3 months and 20.8 months respectively though not different between groups (p=0.16 and p=0.17, respectively). By multivariate analysis, the only factors associated with OS were age (HR 1.01 p=0.041) and disease status at transplantation (HR 1.96, p< 0.001), while only the latter impacted on EFS (HR 2.2, p< 0.001). By univariate analysis, a trend for a higher probability of GRFS was observed in the lower-ATG group (2 years 47,5% vs 38,3% respectively, HR 1.2 p=0.069). **(Figure 1)**. When adjusted by multivariate analysis, the only factor significantly associated with GRFS was disease status at transplantation (HR 1.84, p< 0.001)

Conclusions: In conclusion, in this analysis an ATG dose higher than 5mg/kg as GVHD prophylaxis showed no significant benefit in any of the outcomes analyzed, in particular it did not result in a significant improvement in GVHD control.



[Figure 1.]

Disclosure: Nothing to declare.

P191

Decreased Soluble HLA-e Levels in Patients after Allogeneic Stem Cell Transplantation are Associated with Severe Acute and Extended Chronic graft-versus-host Disease and Inferior overall Survival

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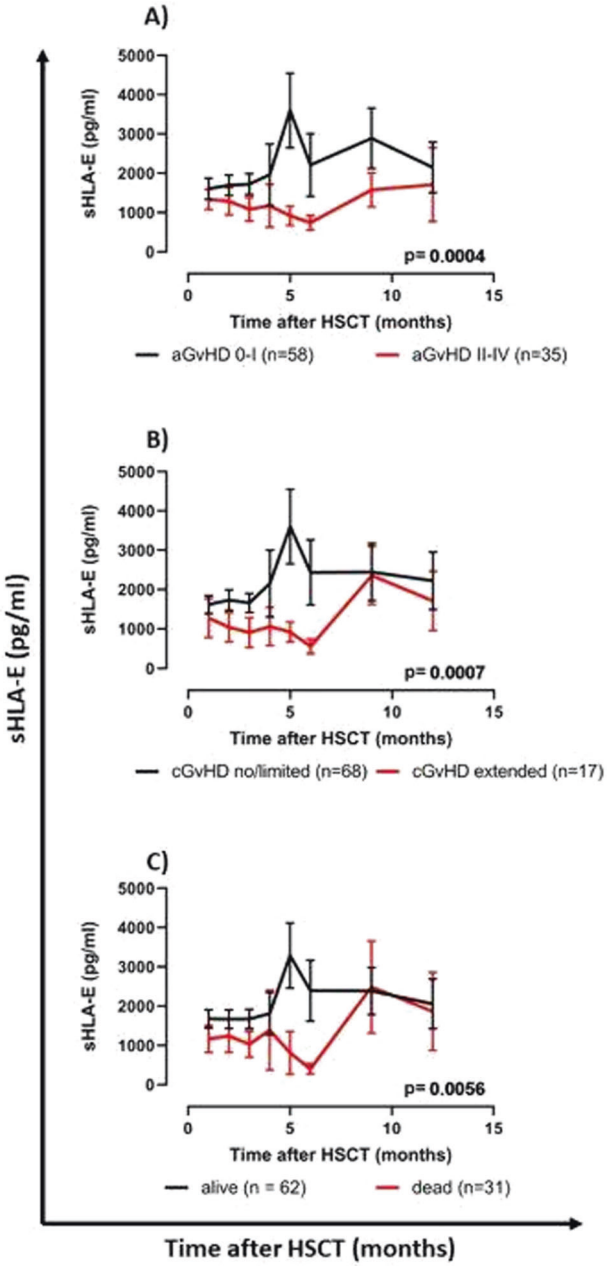
Background: HLA-E is a non-classical HLA molecule and by interaction with activating or inhibitory receptors of NK and T cells, HLA-E can lead to immune activation or suppression. Recently, the non-classical HLA molecules gained more attention in the setting of allogeneic hematopoietic stem cell transplantation (HSCT). Most studies so far have focused on the two most frequent genotypes (HLA-E*01:01, HLA-E*01:03) and investigated their potential association with clinical endpoints of HSCT, like graft-versus-host disease (GvHD), relapse, and overall survival (OS). However, these studies have produced inconsistent results. We therefore here investigate soluble HLA-E (sHLA-E) levels in patients following HSCT and relate this to clinical endpoints.

Methods: Plasma samples of 93 patients were procured 1, 2, 3, 4, 5, 6, 9 and 12 month(s) before and after transplantation. To capture sHLA-E the monoclonal antibody 3D12 (eBioscience, Frankfurt, Germany) was used. Recipients and donors were typed for HLA-E with a sequence-specific primer-PCR. Genomic DNA was isolated from buffy-coats using QIAamp® DNA Blood Mini Kit (QIAGEN GmbH, Hilden, Germany). HLA-E amplifications were performed in a Geneamp 9700 PCR thermal cycler (Applied Biosystems, Waltham, USA). Statistical analyses were performed by using SPSS 23.0 (SPSS Inc., Chicago, IL, USA) or GraphPad Prism V8.1.2 software (GraphPad Software, San Diego, CA, USA). Data are presented as mean ± standard error of mean (SEM). Continuous variables were compared by T-test, non-parametric Mann-Whitney test or two-way analysis of variance. For categorical data, 2-sided Fisher's exact test was used.

Results: Patients with acute GvHD grade II-IV after HSCT displayed significantly (p=0.0004) reduced sHLA-E levels (mean +/-SEM) compared to patients with acute GvHD 0-I (Figure 1A). Similarly, sHLA-E levels were significantly (p=0.0007) diminished in patients with extended chronic GvHD compared to patients without or with limited chronic GvHD (Figure 1B). Furthermore, lower sHLA-E levels were significantly associated with mortality post HSCT (p=0.0056, Figure 1C). Using receiver operating characteristic analyses specific thresholds were identified being indicative for severe acute GvHD, extended chronic GvHD or inferior OS. We could not detect any association of the course of sHLA-E levels post HSCT with the three most frequent HLA-E genotypes (HLA-E*01:03/*01:03, HLA-E*01:01/*01:01, HLA-E*01:01/*01:03). However, there was an association of HLA-E*01:03 homozygosity with inferior 5-year-OS.

Conclusions: Our results indicate that clinical endpoints of HSCT like acute and chronic GvHD and OS have to be associated rather with sHLA-E than with HLA-E polymorphisms. These findings shed some light on the possible impact of reduced sHLA-E levels after HSCT on GvHD and OS. Thus, sHLA-E appears to be a novel promising candidate for the prediction of clinical HSCT outcome concerning extended cGvHD and OS.



[Figure 1]

Figure 1: Association of reduced sHLA-E levels with severe GvHD and inferior OS following HSCT. sHLA-E in patients with (A) aGvHD grade II-IV (red line) versus aGvHD grade 0-I (black line), (B) extended cGvHD (red line) versus no/limited cGvHD (black line) or (C) patients having died (red line) versus patients being alive (black line) during the follow-up time.

Disclosure: Nothing to declare.

P192

Effect of Extracorporeal Photopheresis on Production of Serum Soluble CD163: Relationship to Immunosuppression and Disease Activity in Chronic Graft Versus Host Disease

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Background: Extracorporeal photopheresis (ECP) is a second line therapy for steroid refractory, dependent or intolerant chronic GVHD (cGVHD). In cGVHD, activated tissue macrophages contribute to fibrosis of the skin, lung and liver. CD163 is a scavenger receptor expressed by monocytes and macrophages, which is released as soluble CD163 (sCD163) following activation and is increased in the serum of patients with systemic scleroderma and pulmonary fibrosis (1). Plasma sCD163 is elevated in active cGVHD and de novo cGVHD patients compared to HSCT patients without cGVHD and healthy controls (2). We have previously shown in a pilot study that ECP reduced sCD163 levels in a subset of patients (3). Here, we have tested whether this holds in a larger sample and how sCD163 levels relate to immunosuppression and skin and liver disease activity.

Methods: Serum samples were collected from 72 cGVHD patients (39 male /33 female; age range: 25-74) and 17 age-matched healthy controls (10 male / 7 female) before ECP and at 3 month intervals up to 1 year. Patients had GVHD affecting skin (61/72), mucosal membranes (16/72), liver (14/72), joints (8/72), gut (17/72), eye (8/72), genital (4/72), and respiratory involvement (4/72). Serum sCD163 was assessed by ELISA (R&D Systems). Data were analysed using GraphPad Prism 6. Statistical tests performed include 2-tailed Mann-Whitney, Pearson's correlation test, and 2-way ANOVA with repeat measures, as appropriate.

Results: Chronic GVHD patients had significantly elevated serum levels of sCD163 (P=0.0026; median of 723ng/ml, IQR 536-1101) compared to healthy controls (median of 466ng/ml, IQR 353-553). Stratification into sCD163 quartiles showed that ECP patients with an initial sCD163 level in the upper quartile (sCD163hi ; >1101 ng/ml) had significant reduction in sCD163 after 3 months of ECP (P< 0.05), but this was not sustained to the 6 month interval and remained substantially higher than in patients in the lower quartile (sCD163lo). Glucocorticoids and cyclosporine affect monocyte function, but there were no significant differences in prednisolone or cyclosporine dosages between the sCD163 quartiles at pre-ECP baseline or in the rate of steroid tapering. Where data were available, there was no significant relationship between Modified Rodnans skin scores and pre-ECP sCD163 levels. In measurements of liver inflammation, pre-ECP patients in the sCD163hi quartile had highly significantly increased levels of serum alanine amino-transferase (ALT) liver enzyme levels compared to sCD163lo patients (P< 0.0001), which was significantly reduced after 3 months of ECP (P< 0.003). Serum aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT), but not bilirubin, each had significant correlations with sCD163 (r=0.44: P< 0.0001, r=0.56;P< 0.0001and r=0.52;P< 0.0001 for ALT, AST and GGT, respectively), but only ALT and AST were reduced with ECP.

Conclusions: We confirm that sCD163 is significantly raised in a subset of cGVHD patients compared to healthy controls, which is reduced by ECP. Further, the data suggest that ECP therapy reduces hepatocellular injury as indicated by serum ALT and AST liver enzyme levels in sCD163hi patients.

Disclosure: NCM has received grant funding and attended advisory board for Mallinckrodt.CB has received grant funding from Mallinckrodt. AA has received speaker fees and grant funding from Mallinckrodt

P193

Post-transplant High-dose Cyclophosphamide Overcomes the Detrimental effect of a single-locus HLA Mismatched in Unrelated Donor Allogeneic Hematopoietic Stem Cell Transplantation

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Hospital Clinic, Barcelona, Spain

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) from mismatched unrelated donors (MMUD) at a single HLA locus -A, -B, -C, or -DR (7/8) are associated with worse survival outcomes compared to 8/8 matched unrelated (MUD). Despite that, 7/8 MMUD grafts remain a viable option for allo-HSCT, particularly in patients who lack suitable donors or in those with aggressive hematologic malignancies for whom the risks of disease progression due to delays in identifying optimal donors is offset in part by the benefits of earlier transplantation. We hypothesized that post-transplant high-dose cyclophosphamide (PTCy) could overcome the detrimental effect of a single-locus HLA MMUD.

Methods: We retrospectively analyzed 110 patients (median age 50y, range 42-62) who received 7/8 MMUD (n=56) or 8/8 MUD (n=54) allo-HSCT all of them with PTCy in our institution. Unrelated donor selection was performed according to standard criteria, including high resolution typing for alleles at HLA-A, -B, -Cw, DRB1 and DQB1.

Results: AML/ALL and MDS accounted for 66% of all diagnostics. Disease Risk Index (DRI) was low in 11%, intermediate in 47%, and high in 42%. Forty-nine percent of patients had a HCT-CI ≥3. All patients, except four received peripheral blood stem cells (PBSC). Conditioning regimens (most of them fludarabine plus busulfan or TBI) were myeloablative (MAC) in 50 patients (45%) and RIC in 60 (55%). GVHD prophylaxis consisted on PTCy 50mg/kg IV on days +3 and +4 followed by tacrolimus (n=99) or MMF (n=1) or tacrolimus plus MMF (n=10). All but one patient engrafted; the median time to neutrophil (>500/mL) and platelet (>20,000/mL) recovery was 19 days (IQR 16-22) and 14 days (IQR: 12-22), respectively. Eight patients (7%) developed an invasive pulmonary Aspergillosis, 25 (22%) had severe bacterial infection, 57 (52%) CMV reactivation, 10 (9%) cytomegalic disease and one EBV reactivation. The CI of 1-year TRM, 100-days acute grade II-IV, 100-days grade III-IV GHVD, and 1-year moderate-severe chronic GHVD were 14%, 12%, 5%, and 13%, respectively. The CI of 1 and 2-year relapse rate was 20% and 23%. After a median follow-up of 1 year (0.05-6.4), 5-year OS and DFS were 60% and 58%. 5-year survival free of relapse and free of moderate-severe chronic-GVHD was 48%. Patient's age >50 years was associated to worse OS (HR 3.3, p=0.009), PFS (HR 2.2, p=0.03), and NRM (HR 3.5, p=0.05). Other variables such as HCT-CI (< vs. ≥3), DRI (low vs. intermediate vs. high), conditioning type (MAC vs. RIC), 1 vs. 2 immunosuppressors, and HLA matching (7/8 vs. 8/8) had not impact on post-transplant outcomes.

Conclusions: PTCy after unrelated PBSC allo-HCT results in low incidence of acute and chronic GVHD with no differences between 7/8 MMUD and 8/8 MUD in survival outcomes. An immunosuppressive schema of intermediate intensity such as PTCy followed by single-agent tacrolimus provide an adequate GVHD prophylaxis in both MMUD and MUD transplants. HLA 7/8 MMUD transplantation using this strategy is a suitable alternative to MUD.

Disclosure: Nothing to declare.

P194

Allogeneic Peripheral Blood Transplantation with post-transplant Cyclophosphamide and Sirolimus from Haploidentical and Matched Donors: "sir-PTCY" Results in 249 Patients

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Background: Post transplant cyclophosphamide (PT/Cy) has recently emerged as a very promising GVHD prophylaxis in the setting of allogeneic HSCT from haploidentical donors, and more recently in matched donor transplants. Herein, we compare long-term outcomes of allogeneic HSCT using GVHD prophylaxis with PT/Cy and sirolimus ("Sir-PTCy"), from haploidentical and matched related and unrelated donors.

Methods: Between 2013 and 2017, a total of 249 adult patients received either HLA-matched related (MRD), HLA-matched unrelated (MUD) or haploidentical donors for high-risk haematological malignancies in our center. According to Institutional algorithm, patients were assigned to haploidentical source if not available a matched donor > 9/10 in the due time for planned HSCT. Conditioning regimen was based on treosulfan and fludarabine; 86% received an intensified conditioning with the addition a 2nd alkylating agent (melphalan or thiotepa). Patients received unmanipulated PBSCs. Patients received PT/Cy on days 3 and 4, and sirolimus from day 5; mycophenolate mofetil (MMF) was added from day 5 to day 30, in MUD and haploidentical donors. All patients were treated according to current institutional programs upon written informed

consent for transplant procedures and use of medical records for research.

Results: In the haploidentical donor group (n=151), we documented a cumulative incidence of grades II-IV and III-IV acute GVHD at 100 days of 35% and 20%, and a cumulative incidence of chronic GVHD of 42% at 3 years. The cumulative incidence of relapse and non-relapse mortality (NRM) was 35% and 27% at 3 years, respectively. The 3-year overall survival (OS) was 44%, while progression-free survival (PFS) was 38%; the composite end-point of GVHD/relapse-free survival (GRFS) was 24% at 3-years.

In the HLA-matched donor group (MRD, n=48, MUD, n=50), the cumulative incidence of grades II-IV and III-IV acute GVHD at 100-days was 23% and 9%, respectively. The cumulative incidence of chronic GVHD was 25% at 2 years. The cumulative incidences of relapse and NRM were 31% and 9% at 2 years, respectively. The 2-year OS was 72% and PFS 60%; GRFS was 52% at 2-years.

Comparing by multivariate analysis the main transplant outcomes across the different donor groups under study, we observed a higher risk of severe acute GVHD and chronic GVHD in the haploidentical setting. Moreover, haploidentical HSCT performs worse in terms of NRM, OS, PFS and GRFS at 2 years. However, more patients in the haploidentical group presented high/very high disease risk index (DRI; Armand et al), higher HCT-comorbidity index and more time elapsed from diagnosis to transplant. In patients presenting a low-intermediate DRI transplant outcomes were superimposable among the three donor groups. In this subgroup of patients GRFS at 2 years was 53% in MRD, 65% in MUD and 46% in haploidentical HSCT (p=0.33), respectively.

Conclusions: Sirolimus-PT/Cy platform is safe and offers a valid alternative to CNI-based GVHD prophylaxis for all donor, deserving further investigations and a formal prospective comparison with the other GVHD prophylaxis strategies currently in use. This strategy provide low mortality and superimposable severe GVHD in patients presenting a low-intermediate DRI, translating in a relevant long-term survival.

Clinical Trial Registry: NA

Disclosure: None

P195

A New Hope in the Treatment of steroid-refractory Graft Versus Host Disease (Sr-GVHD) after Allogeneic Hematopoetic Stem Cell Transplantation (AHSCT): Ruxolitinib

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Background: Steroid refractory graft versus host disease (SR-GVHD) remains a clinical challenge and significantly contributes to nonrelapse morbidity and mortality after allogeneic hematopoetic stem cell transplantation(AHSCT). Recently, retrospective studies have reported that ruxolitinib, appears to be safe and effective in the both acute and chronic SR-GVHD, with upward of 80% of patients responding. Herein, we share a real-life experience using ruxolitinib in the treatment of SR-GVHD.

Methods: This multicenter retrospective study conducted in 13 different stem cell transplant centers included 77 adult patients diagnosed with acute or chronic SR-GVHD. We treated off-label these patients from June 2016 to November 2019 with ruxolitinib with a dose of 5 or 10 mg P.O. twice daily, depending on the hematological parameters. The physicians of the patients classified organ sites affected; acute GVHD(aGVHD) and chronic GVHD (cGVHD) grading before starting ruxolitinib according to Glucksberg staging system and the National Institues of Health(NIH) 2014 criteria. Steroid refractory chronic GVHD was defined as any disease that failed to respond to previous immunosuppressive therapy with steroids at least 4 weeks or inability to taper it w/wo additional immunosuppressive drugs.

Results: The baseline characteristics of the patients are listed in Table 1. Ruxolitinib was initiated for SR-aGVHD in 25 patients, whereas 52 patients received ruxolitinib for cGVHD. Patient characteristics are outlined in Table 1. Among patients treated for aGVHD; 4 patients(16%) had refractory skin GVHD, 2 patients(8%) had refractory gastrointestinal(GI) GVHD and remaining 19 patients(76%) had multisite refractory disease, involving the skin, GI tract and liver. A median of three(range; 1-6) prior therapies,

including steroid administration, were administered before ruxolitinib. On initiation, 13 patients(52%) had grade II, 3 patients(12%) had grade III and 9 patients(36%) had grade IV GVHD. At day 28 after ruxolitinib initiation, 84% (21/25) of patients with aGVHD achieved CR or PR(CR, 15 patients; PR, 6 patients). Four non-responders (SD, 1 patients; PD, 3 patients) had grade IV GVHD at initiation of therapy.

As expected mouth(55.8%) and skin(78.8%) were the most frequently involved organs and 53.8 %(28/52) of patients showed evidence of cGVHD in more than two organs. A median of four prior treatment(range, 1-8) was administered before ruxolitinib. By 28days, 80.7% of patients(42/52) demonstrated evidence of response to therapy with 19(20.5%) patients in CR and 23(44.2%) patients experiencing improvement in at least one organ system. Three patients had stable disease under the ruxolitinib treatment and still continue receiving. Analysis by organ domain showed the best overall response in the GI tract 86.4%(19/22), lung 80%(12/15), skin 73.8%(31/42), and liver 72.7%(16/22). The four out of seven nonresponders had severe sclerodermatous skin GVHD. Ruxolitinib appeared to be well tolerated, and SR-cGVHD patients remained on therapy for median four months.

Conclusions: This retrospective, multicenter study of a limited patient number, treated with ruxolitinib due to SR GVHD, highlights the excellent results with good tolerance and minimal adverse effects, even in difficult cases such as lower GI tract involvement and lung disease. Further prospective studies would be appropriate to confirm our observations and to better define patients who would benefit from ruxolitinib treatment.

Disclosure: Nothing to declare.

P196

Abstract already published.

P197

Evaluation of the Prognostic Value of Histologic Assessment of Acute graft-versus-host-disease of the Upper Gastrointestinal Tract According to Lerner Early after Allogeneic Hematopoietic Cell Transplantation

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Background: Acute graft-versus-host-disease (aGvHD) is a major cause of morbidity and mortality following allogeneic hematopoietic cell transplantation (alloHCT). Early after alloHCT, patients with persistent nausea, vomiting or anorexia represent a clinical challenge. Therefore, we set out to study the association between upper gastrointestinal tract (GIT) symptoms early after alloHCT, histological grade according to Lerner, overall clinical grade of aGvHD and mortality.

Methods: We performed a retrospective study on 174 patients, who received alloHCT between January 2007 and June 2018, presented with symptoms of aGvHD of the upper GIT within the first 42 days after alloHCT and underwent endoscopic examination.

Results: Indications for alloHCT were AML/MDS (66%, N=115), ALL (11%, N=19), Lymphoma/Myeloma (11%, N=20) and other diagnoses for the remaining 11% (N=20). The median age of patients was 56 years. Donors were HLA-identical siblings (15%, N=26), haploidentical relatives (6%, N=11), HLA-compatible (8/8) unrelated donors (57%, N=100), and partially matched (9/10) unrelated donors (21%, N=37). Conditioning regimens were myeloablative (36%, N=63), reduced-intensity (57%, N=99) or non-myeloablative (7%, N=12). GVHD-prophylaxis included a calcineurin-inhibitor for 94% (N=164) and ATG for 36% (N=63) of patients.

Abnormal macroscopic findings were reported for 86% of patients. Edema/erythema were seen in 59%, erosions/ulcers in 22% and an accompanying esophagitis in 23% of patients, respectively. Overall, histologic findings resulted in the pathological diagnosis of upper GIT aGvHD in 51% of patients. 43% of patients showed Lerner grade I, 4% grade II and 4% grade III-IV mucosal changes. The highest Lerner grade was found in biopsies taken from the duodenum in 82%, from the antrum in 41% and from the gastric corpus in 20% of patients.

Severity of overall aGvHD was rated grade II in 33%, III in 12% and IV in 13% of patients (N=100). Assessment of symptoms, macroscopic findings and histology resulted in subsequent systemic treatment in 91 patients (52%). Endoscopic and histologic evaluation resulted in a diagnosis other than aGvHD in 6 patients (3%): CMV infection (N=3), concomitant CMV/Giardia lamblia infection (N=1), esophageal stenosis (N=1) and suspected mycophenolate-induced gastropathy (N=1).

Eleven out of 14 patients who showed Lerner grade ≥II in the upper GIT had an overall severity of aGvHD grade III-IV. Hence, histological grade and the maximum overall

grade of aGvHD correlated tightly ($p < 0.001$). The 1-year cumulative incidences of non-relapse mortality (NRM) of patients with upper GIT aGvHD Lerner grade I versus II-IV were 20% and 36%, respectively (Gray-Test, p=0.3). NRM was not statistically different for patients with aGvHD Lerner grade I versus 0. In landmark analyses from day +100, the 1-year NRM and relapse of patients with aGvHD overall clinical grade 0-I, II, and III-IV was 9%, 12% and 37% (Gray-Test, p=0.02) and 11%, 16% and 13% (Gray-Test, p=0.9), respectively.

Conclusions: Histologic grade of upper GIT aGvHD and overall clinical grade are tightly correlated. Histologic findings Lerner grade I in the upper GIT, themselves, were not associated with an increased risk of NRM. In contrast, Lerner grades >I in biopsies taken from the upper GIT often indicated life-threatening aGvHD.

Disclosure: Nothing to declare.

P198

Cyclosporine a Alone versus Mycophenolate Mofetil Plus Cyclosporine a Based GVHD Prophylaxis For Patients With AML undergoing Mud Transplantation. A Study from the ALWP

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Background: Acute GVHD (aGVHD) remains an issue after allogeneic transplantation from matched unrelated donors (MUD). Since the introduction of mycophenolate mofetil (MMF) for GVHD prophylaxis, the association of Cyclosporine A (CsA) and MMF has rapidly increased in the setting of reduced intensity conditioning (RIC). Nevertheless, the use of CsA alone or in combination with MMF has not yet been reported in a large cohort of patients.

Methods: We retrospectively investigated the outcomes of 497 adult patients with AML in complete remission (CR) undergoing a MUD transplantation between 2007-2017 and receiving CsA+MMF or CsA alone as GvHD prophylaxis who were registered with the ALWP of the EBMT.

Results: GVHD prophylaxis consisted in CsA alone (n=183) or CsA+MMF (n=314). All patients underwent a RIC regimen with fludarabine 30mg/m^2 from day -6 to day -2 and busulfan 130mg/m^2 from day -5 to day -4 and received anti-thymocyte globulin as part of the conditioning. The median age at transplant was similar (59 and 60 years in the CsA and CsA+MMF group, respectively). The median follow-up was not significantly different between the two groups (CsA: 33 vs CsA+MMF: 34 months). Disease status at transplant was first complete remission (CR1) for 81% in CsA group and 86% in CsA +MMF group (p=NS). Peripheral blood stem cells (PBSC) was the graft source in 93% of patients receiving CsA alone and in 96% of patients who received CsA +MMF (p=0.17). All but 2 patients engrafted. The 100 day cumulative incidence (CI) of grade II-IV and grade III-IV acute GvHD were 30% and 10%, respectively. The 2-year CI of chronic GvHD was 35% (CI of extensive cGvHD was 15%). The 2-year CI of non-relapse mortality (NRM) and relapse were 19% and 25%, respectively. Disease recurrence (n=31), GvHD (n=20) and infection (n=17) were the most common causes of death in the CsA group. Relapse (n=53), GvHD (n=28) and infection (n=28) were the most frequent causes of death in the CsA+MMF group. The 2-year GVHD-free relapse-free survival (GRFS), leukemia- free survival (LFS), and overall survival (OS) were 45%, 56% and 60%, respectively. In multivariate analysis (MVA), no statistically significant differences were found among the two groups with respect to relapse, NRM, LFS, OS, acute and chronic GvHD. A positive cytomegalovirus serology of the donor was associated with higher NRM [HR=2.03, p< 0.001] and higher cGvHD [HR=1.44, p=0.03] and a lower OS [HR 1.66, p< 0.001], LFS [HR=1.69, p=0.001] and GRFS [HR=1.75, p< 0.001].

No differences were detected between the two groups for relapse, NRM, LFS, OS, or aGvHD when conducting a subgroup analysis in patients who received PBSC in CR1. Patients who received CsA alone tended to have a higher cGvHD (p=0.05). However, this finding was not statistically significant in MVA.

Conclusions: We observed comparable outcomes for patients with AML in CR1 who underwent MUD

transplantation and RIC with CsA+MMF or CsA alone as GvHD prophylaxis. This suggests that both strategies may be considered valid approaches. Prospective randomized trials are needed to assess which patients could benefit from the addition of MMF as GvHD prophylaxis

Disclosure: No conflict of interests

P199

Transplant-associated Thrombotic Microangiopathy is Independently associated with Ruxolitinib Administration in Patients with graft-versus-host-disease

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Background: Recent data suggest that several novel biologic agents, such as imatinib, are associated with an increased risk of thrombotic microangiopathy (TMA). However, little is known about ruxolitinib, a JAK2 inhibitor. Given the latest approval of ruxolitinib administration in graft-versus-host-disease (GVHD), we aimed to investigate factors and outcomes associated with transplant-associated TMA (TA-TMA) in patients with GVHD.

Methods: We enrolled consecutive allogeneic hematopoietic cell transplantation (alloHCT) recipients followed-up for treatment of extensive overlap or chronic GVHD at our JACIE-accredited Unit (01/2016-06/2019). Ruxolitinib has been administered off-label in these patients since 2016. Patient data including details of transplantation procedure (donor, disease phase and type, conditioning, age, CD34+ cells infused), disease status, acute and chronic GVHD occurrence and treatment, Cytomegalovirus (CMV) or Epstein-Barr reactivation (EBV), disease-free (DFS) and overall survival (OS) were extracted from our prospectively acquired database. Charts from patients with TA-TMA were re-reviewed to identify diagnostic and therapeutic features. TA-TMA was diagnosed according to the International Working Group Criteria and treated according to our previously published protocol.

Results: Among 160 GVHD patients, 18 (11%) were diagnosed with TA-TMA. TA-TMA developed at a median of 150 post-transplant day (range 98-3013 days). Median ADAMTS13 activity was 62% (range 38-112%). Patients with TA-TMA had previously received GVHD treatment with: steroids (18/18), mycophenolate mofetil or cyclosporine inhibitor (18/18), extracorporeal photopheresis (ECP, 12/18), ruxolitinib (7/18), ibrutinib (2/18), and antithymocyte globulin (ATG, 3/18). TA-TMA management included: steroids (18/18), cyclosporine inhibitor cessation when applicable (9/18), plasma infusions (2/18), plasma exchange (8/18), and eculizumab (5/18).

Among studied pre- and post-transplant factors, diagnosis of TA-TMA was associated only with ruxolitinib administration ($p< 0.001$). With a follow-up of 38.4 months (4.6-83.9) in surviving patients, 5-year DFS was 48.4% and OS 52.9%. OS was independently predicted by TA-TMA ($p=0.001$), severe (grade 3-4) acute GVHD ($p=0.002$) and CD34+ cells infused ($p=0.002$). Ruxolitinib was not associated with survival rates in the whole population or in TA-TMA patients.

Conclusions: Our real-world data in a large cohort of GVHD patients suggest for the first time that ruxolitinib is associated with TA-TMA. Given the confounding comorbidities in these patients, increased awareness is needed by treating physicians to identify TA-TMA. Further studies are warranted to confirm these findings and unravel possible pathogenetic mechanisms.

Disclosure: Nothing to declare.

P200

Diagnostic Significance of Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) in Acute Intestinal graft-versus-host Disease (GVHD)

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Background: Allogeneic stem cell transplantation (alloSCT) is considered a potentially curative treatment for many refractory and high-risk hematologic malignancies that would otherwise be fatal, even with most of the current conventional therapies. Following alloSCT intestinal GvHD is a frequent complication, associated with a significant morbidity and mortality. Previously, we have shown, that FDG-PET can be used for diagnostic purposes and might have a prognostic value for patients suffering from intestinal GvHD. The objective of this retrospective study was to further elucidate diagnostic and prognostic value of FDG-PET in patients with intestinal GvHD.

Methods: Between 06/2011 and 02/2019, 101 patients with suspected acute intestinal GvHD underwent FDG-PET examination. Complete clinical and FDG-PET data sets were reviewed for presence of intestinal inflammation. 74 of the 101 patients had a clinically and/or histologically proven intestinal GvHD and signs of inflammation in FDG-PET. These patients were analyzed in detail regarding the response to GvHD therapy and survival. Different quantitative PET parameters, as well as clinical data, were compared between patients with fast and slow / no response to immunosuppressive treatment.

Results: For patients with suspected intestinal GvHD, sensitivity and specificity of FDG-PET for detection of intestinal GvHD was 92.8% (95% CI: 84.9 - 97.3) and 72.2% (95% CI: 46.5 - 90.3), respectively. Patients with subsequent rapid relief of GvHD symptoms had significantly higher standard uptake values for SUVmax (mean 13.5, 95% CI: 10.7 - 16.4) and SUV peak levels (mean 9.2, 95% CI: 7.3 - 11.1) compared to patients with slow or no response to immunosuppressive therapy (mean SUVmax: 7.7; 95% CI: 7.0 - 8.4; mean SUVpeak: 5.4, 95% CI: 4.9 - 5.8; p .005). Since immunosuppressive therapy with corticosteroids had already been initiated in 52 of 74 patients at the time of PET-CT examination, SUVmax/SUVpeak as prognostic parameters did not show significant influence on overall survival. However, overall survival at 12 month in patients with fast response to immunosuppressive therapy was significantly better than in patients with slow response (fast response: 66.7%; 95% CI: 44.5 - 88.9; slow/non-response: 33.2 %; 95% CI: 20.4 - 46.0; p .005).

Conclusions: This retrospective analysis indicates diagnostic value of FDG-PET in intestinal GvHD. Of further interest, our results suggest potential significance of FDG-PET in predicting treatment response following immunosuppressive therapy. Before implementation into clinical guidance of GvHD treatment and to strengthen these findings, prospective clinical trials are needed.

Disclosure: Nothing to declare.

P201

Long term Outcomes of Ruxolitinib Therapy in steroid-refractory graft-versus-host Disease in Children and Adults

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Background: Steroid-refractory graft-versus-host disease (srGVHD) is still one of the major causes of mortality after allogeneic stem cell transplantation (allo-HSCT). We conducted a prospective study of efficacy of ruxolitinib in both acute and chronic srGVHD in children and adults underwent allo-HSCT.

Methods: The study included 75 patients with srGVHD (32 acute, 43 chronic, 41 adults and 34 children). Indications for allo-HSCT were AML - 29%, ALL - 24%, MPD - 19%, LPD - 10%, non-malignant disorders - 18%. Severity of acute srGVHD was II gr. - 11 pts., III gr. - 10 pts., IV gr. - 11 pts. Skin was involved in 91%, gastrointestinal tract (GL) in 56% and liver in 37%. Among patients with chronic GVHD 14% had moderate disease and 86% - severe disease. Most commonly skin (91%), mouth mucosa (81%), GI (56%), liver (51%) and eyes (74%) were involved. Lung involvement was observed in 40% of patients with 13% of moderate and severe cases. Among patients with clinically significant chronic skin GVHD 39% had scleroderma.

Results: Median follow up was 28 months, range 23-47 months. In patients with acute srGVHD overall response rate (ORR) was 75% (95%CI 57-89%), including 63% of patients with complete response (CR) cases (95%CI 44-79%) and 13% with partial response (PR) (95%CI 4-29%). Median time to PR in patients with acute GVHD was 20 days (range 1-112). Median time to CR was 53 days (range 9-255). Patients with grade III-IV GVHD (p=0.0292) and patients with grade IV gastrointestinal GVHD (p=0.0033) had significantly reduced ORR. Patients with chronic srGHVD had ORR of 81% (95%CI 67-92%), including 21% of CR (95%CI 10-36%) and 60% of PR (95%CI 44-75%). Median time to PR was 71 days (range 18-783) and median time to CR was 425 (27-635 days). Initial severity of organ involvement was not predictive for response except for lung GVHD severity (p= 0.0023). No differences in response was observed in adults and children (aGVHD - p=0.31, chGVHD - p=0.35). Hematological toxicity was the most common adverse event (Hb< 80/transfusion dependence - 86%/85%, thrombocytopenia 4 gr.- 77%/15%, neutropenia 4 gr.- 53%/5% in aGVHD and chGVHD respectively). After ruxolitinib initiation 59% had either persistence or de novo CMV reactivation. Seventy four percent received additional antibiotic treatment, 62%

additional systemic antiviral treatment and 32% additional antifungal treatment. OS in acute GVHD group was 59% (95%CI 49-74%). OS In chronic GVHD group was 85% (95%CI 70-93%). The major factor predicting survival in acute GVHD group was grade III-IV GI involvement (29% vs 93%, p=0.0001). Neither overall severity of chronic GVHD, nor organ involvement, nor the age of patients were predictive for overall survival. No differences in survival was observed between adults and children (65% vs 53%, p=0.44).

Conclusions: The study demonstrated the high efficacy of ruxolinib for srGVHD in both adults and children with an acceptable toxicity profile.

Disclosure: Nothing to declare.

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Abstract already published.

P203

Efficacy and Toxicity of Ruxolitinib in Patients with steroid-resistant Acute and Chronic graft-versus-host Disease after Hematopoietic Cell Transplantation

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Background: Steroid-resistant (SR) acute and chronic graft-versus-host-disease (aGVHD - cGVHD) represent a major complication of allogeneic hematopoietic stem cell transplantation (HSCT). Ruxolitinib is the first treatment having received FDA approval on May 2019 for SR-aGVHD.

Methods: We retrospectively evaluated the efficacy and toxicity of ruxolitinib in patients treated for SR- GVHD in our center. Primary objective was to evaluate the 28-day complete remission (CR) and partial remission (PR).

Results: Eighteen patients with aGVHD and 10 patients with cGVHD, and who had previously presented aGVHD, transplanted between 01.01.2015 and 31.10.2018 were included, 71.4% male and 28.6% female. Median age was 58 years (range, 21 to 73).

Among patients treated for grade II to IV SR-aGVHD, 11.1% had skin, 55.6% gastrointestinal, 11.1% liver and 22.2% multisite disease. A median of 3 prior therapies (range, 2 to 4), including steroids, were administered before ruxolitinib. Ruxolitinib was initiated at a median of 132 days (IQR: 44 to 248) post-transplant and 28 days (IQR: 12 to 71) after onset of aGVHD. At day 28 post-ruxolitinib initiation, 8 patients (44%) achieved CR and 4 patients PR (22%), maintained through day 56. Five out of six non-responders had grade IV GVHD and finally died because of GVHD. Median duration of treatment was 133 days (IQR: 58 to 443), with one patient remaining on ruxolitinib at last follow-up.

The median follow-up, for all alive, post-transplant and post-ruxolitinib initiation was 1206 (IQR: 1153 to 1234) and 445 days (IQR: 372 to 532) respectively. The estimated 6-month failure-free survival (FFS) was 44.4% and the estimated 6-month and 1-year overall survival (OS) 72.2% (standard error, SE=14.6%) and 50% (SE = 23.6%), respectively.

47%, 78% and 67% of patients presented grade III neutropenia, thrombocytopenia and anemia, respectively.

67%, 72% and 18% of patients presented at least one documented bacterial, viral and fungal infection respectively.

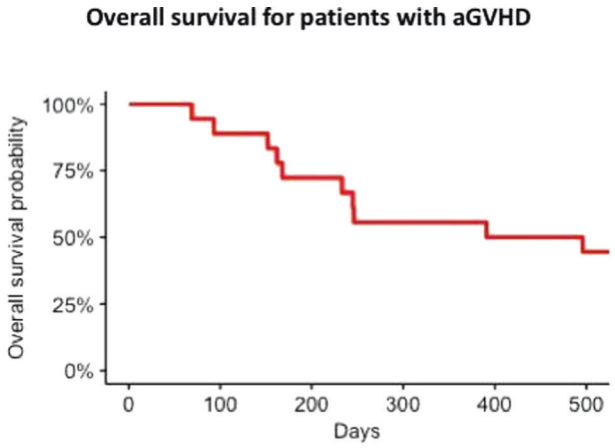
Among cGVHD patients treated with ruxolitinib, 40% had moderate cGVHD and 60% severe. Organ involvement included at least skin in 70% of patients. A median of 2.5 prior therapies (0 to 5) were administered before ruxolitinib. By day 28, nine patients (90%) obtained a CR or PR and only one patient failed and who finally died because of GVHD. The median duration of therapy was 269 days (IQR: 42 to 426). Ruxolitinib was withdrawn in one patient in CR. Concerning toxicities, one patient interrupted ruxolitinib because of hematologic toxicity, one because of relapse and seven patients are still under ruxolitinib at last follow-up.

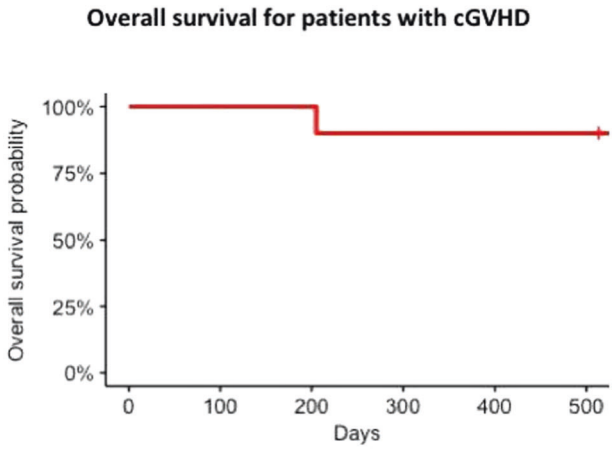
The median follow-up, for all alive, post-transplant and post-ruxolitinib initiation was 1352 days (IQR: 990 to 1592) and 374 (IQR: 126 to 713), respectively. The estimated 6-month and 1-year FFS was 62.5% and the estimated 1-year and 3-year OS 90% (SE: 10.6%) and 77.1% (SE: 18.7%), respectively.

Anemia grade III was observed in only one patient.

Five patients presented documented bacterial and three viral infection; no fungal infection was observed.

Conclusions: Ruxolitinib represents a promising treatment for SR-GVHD, allowing satisfying response rates in patients having already received several lines of GVHD therapy. Careful infectious monitoring is nevertheless required.





[Overall Survival]

Disclosure: "Nothing to declare."

P204

Patient Characterization and Survival Outcomes in Paediatric Chronic Graft versus Host Disease Patients - A population-based Study in Sweden

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Background: There is a scarcity of data describing incidence and real-world outcomes in paediatric chronic Graft versus Host Disease (cGVHD) patients.

Methods: Longitudinal population-based registries held by the National Board of Health and Welfare in Sweden were used to identify patients < 18 years of age that underwent allogeneic hematopoietic stem cell transplantation (HSCT) between 2006 and 2015. End of follow-up was 2017. Patients surviving ≥6 months post-HSCT were classified as having cGVHD by timing and extent of systemic immunosuppressive treatment. cGVHD was defined as those who received systemic corticosteroid treatment for ≥ 3 months alone (mild) or with extracorporeal phosphoresis (ECP) and/or other immunosuppressive treatment (moderate-severe) in children with malignancies, and systemic corticosteroid treatment for ≥ 3 months and/or ECP in children with non-malignant indications for HSCT. Our method may contrast with the standard NIH 2014 guidelines; i.e. the standard method for making decisions about treatment and enrollment in clinical trials. Crude survival rate (SR) and cause-specific mortality were evaluated by estimation of cumulative incidence. Morbidities were analyzed by multivariate negative binomial regression models to adjust for follow-up year and age. Median follow-up times were 5.8 (interquartile range [IQR] 2.8-8.7 [malignant]) and 6.2 (IQR 4.3-9.4 [benign]) years.

Results: Among patients surviving ≥6 months post-HSCT (n=327), 176 and 151 had underlying malignant and benign disease, respectively. The 1- and 5-year SRs were lower for patients with malignant [86.9, 95% CI 82.1-92.1 and 78.5, 95% CI 72.6-84.9] versus benign [98.7, 95% CI 96.9-100 and 95.2, 95% CI 91.8-98.7] disease. The incidence of cGVHD was higher in patients with malignancies (59.1%) versus for benign disorders (37.7%). For patients with malignancies, the 1-year SR from 6 months post HSCT increased with increasing cGVHD severity: 79.2 (95% CI 70.3-89.1) [non-cGVHD], 88.2 (95% CI 79.8-97.5) [mild cGVHD], 96.2 (95% CI 91.2-100) [moderate-severe cGVHD] (p=0.016), however this difference evened out at 5-years of follow-up (p=0.797). Similarly, he cumulative relapse-related mortality (RRM) after one year was higher in non-cGVHD [20.83, 95% CI 13.28-32.68] versus moderate-severe cGVHD [3.77, 95% CI 0.97-14.7] patients. Over the entire follow-up period, cGVHD

status was not associated with survival in patients with benign disorders (p=0.14). Among patients with malignant and benign disorders, respectively, there were no differences in SR when comparing different stem cell sources, (p=0.38, p=0.076), donor relatedness (p=0.2, p=0.51), calendar periods [2006-2010, 2011-2016] (p=0.33, p=0.43) and age [≤11,≥12 years] at HSCT (p=0.56, p=0.64). When comparing morbidities among non- and moderate-severe cGVHD patients with malignancies, the most pronounced differences were observed for injury, poisoning and certain other consequences of external causes [IRR 0.03, 95% CI 0.02-0.05], diseases of the musculoskeletal system and connective tissue [IRR 0.16, 95% CI, 0.08-0.33] and diseases of the circulatory system [IRR 0.23, 95% CI 0.06-0.85].

Conclusions: The incidence of cGVHD was higher in patients with malignant versus benign disorders. Overall, the cGHVD incidence was higher compared to previous reports in Sweden, indicating that this diagnosis may be underreported in clinical practice. For patients with malignancies, increasing cGVHD severity was associated with higher survival rates the first follow-up year.

Disclosure: Dr Mattsson, Dr Remberger, Dr Toporski declare.s no conflict of interest. Dr Schain is owner of and employed by Schain Research AB and work as a consultant for Janssen and has previously been an employee of Janssen. Dr Baculea is employed by Janssen. Mrs Batyrkekova and Dr Dominicus are employed by Scandinavian Development Services AB and work as consultants for Janssen.

P205

Cytokine Levels following Allogeneic Hematopoietic Stem Cells Transplantation. A match-pair Analysis of Home Care Versus Hospital Care

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Background: During two decades more than 250 patients were treated at home as an alternative to isolation in the hospital during the neutrophenic phase after allogeneic hematopoietic stem cell transplantation. Home-care patients had less acute GVHD and improved survival compared to patients isolated in the hospital (Svahn et al. Blood 2002). Many days at home was correlated to a low risk of acute GVHD.

Methods: We analyzed cytokines, chemokines and growth factors during the first three weeks after HSCT and compared patients treated at home (n=42) with matched patients isolated in the hospital (n=37).

The patients in the hospital were matched with the home-care patients for age, diagnosis, remission status, timing, HLA-match and type of donor sibling or matched unrelated donor.

We used Laminex and analyzed; EGF, Eotaxin, G-CSF, GM-CSF, IFNγ, IL-10, IL-12 p40, IL-12 p70, IL-13, IL-15, IL-17A, IL-1RA, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IP-10, MCP-1, MIP-1α, MIP-1β, TNFα, TNFβ and VEGF.

Results: In multivariate analysis, patients treated at home had decreased GM-CSF, IFN-γ ($p< 0.01$), IL-13 and IL-5 ($p< 0.05$). GM-CSF, IFN-γ and IL-13 are associated with GVHD. Patients with blood stream infections had reduced eotaxim, G-CSF and IL-1a and increased IL-15 ($p< 0.01$). Patients who developed acute graft-versus-host disease had increased G-CSF and IP-10 and decreased IL-7 and IL-8 ($p< 0.01$). In addition, anti-thymocyte globulin, G-CSF treatment, immunosuppression, age, conditioning, related vs unrelated donors, graft source and total body irradiation affected various cytokine levels. Acute GVHD grades III-IV was 10% and 16% in the home-care and hospital-care patients, respectively. One year transplant-related mortality was 7% and 16% and overall survival at 5 years was 69% and 57% in the two groups, respectively.

The more similar outcome between home- and hospital-care in this analysis, may be due to that patients in more recent years spent a shorter time at home. Furthermore, several improvements in hospital-care were introduced to mimic home-care, such as better nutrition, more exercise and the possibility for walks outside the hospital.

Conclusions: Patients treated at home had decreased levels of GM-CSF, IFN-γ and IL-13, which may contribute to reduced acute GVHD.

Disclosure: Nothing to declare.

P206

Incidence of Chronic graft-versus-host Disease - Results from a Prospective Multicentre Analysis of 2 Cohorts

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Background: Incidence of chronic Graft-versus-Host Disease (cGvHD) is ~45%, but varies significantly depending on conditioning regimen, choice of donor, stem cell source, age and GvHD prophylaxis. In the past, increasing cGvHD incidence was reported due to accumulation of risk factors, but recent studies capturing the effect of new prophylaxis strategies are lacking.

Methods: This study was conducted as joint analysis of 308 patients from two cohorts - cohort 1 included patients (pts) transplanted 2017 at University Hospital Zagreb (Croatia), and St. Anna Children`s Hospital, Vienna (Austria), cohort 2 included consecutive pts documented in period from July 2015 to September 2018 within the German-Austrian-Swiss GvHD register.

Results: Cohort 1 consisted of 98 (55% male), mainly adult pts (70%), who underwent allogeneic hematopoietic stem cell transplantation (alloHSCT) at median age of 40 (range 0-66) years, and cohort 2 out of 210 (65% male) pts transplanted at median age of 56 (range 19-70) years. Most frequent indications for alloHSCT in both cohorts were acute leukaemia (51.9%), myelodysplastic/myeloproliferative diseases (19.2%), lymphoma (15.6%), plasma cell disorders (5.5%), non-malignant diseases (7.2%), and solid tumours (0.7%). 65% of all alloHSCT were performed from unrelated donors, 23% from matched related donors and 12% from haploidentical donors (25% in cohort 1 vs. 6% in cohort 2). Peripheral blood stem cells were applied in 73%, while 27% received bone marrow grafts. For both cohorts, at median follow-up of 333 (range 0-1149) days, the overall survival (OS) was 71% and cumulative incidence (CI) of treatment related mortality (TRM) 19%. CI of malignant disease relapse was 21%, and occurred at median of 154 (range 0-757) days after alloHSCT. Acute GvHD was reported with CI of 42% (6% for stage III/IV) in period of 100 days. For cohort 1 late acute GvHD had CI of 10% (1% for stage III/IV) and occurred at median time of 166 (range 110-424) days after alloHSCT and for cohort 2 CI was 11% (3% for stage III/IV) and occurred at median time of 217 (range 106-562) days.

In cohort 1 CI of cGvHD was 14% and all pts had NIH moderate/severe global score at onset which occurred at median of 197 (range 62-700) days with de novo, progressive and quiescent onset in 42%, 25% and 33%, respectively. In cohort 2 CI of cGvHD was 39% (19% moderate/severe) at onset at median of 197 (range 92-588) days with de novo, progressive and quiescent onset in 37%, 1% and 62%, respectively. Four pts of cohort 2 were diagnosed with cGvHD with other manifestations such as glomerulonephritis or cerebral vasculitis. Among cGvHD pts from cohort 1 most involved organs at onset were mouth (82%), skin (73%), and eyes (64%) followed by liver (55%), gastrointestinal tract and lung (each 27%) and genital tract (18%) with a median Karnofsky/Lansky score of 80% (range 50-100). In the joint analysis, 71% pts required second line treatment.

Conclusions: This study shows for the first time a decreasing incidence of cGvHD compared to previous publications which may reflect the change in practice pattern in prophylaxis and treatment of GvHD.

Disclosure: This work was supported by European Cooperation in Science and Technology (COST), through action number CA17138 - Integrated European Network on chronic Graft versus Host Disease.

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P207

Early Introduction of Ruxolinitib for Children with Graft versus Host Disease - A Stitch in Time Saves Nine

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Background: Algorithms for the management of graft versus host disease need to be revisited as the use of steroids and agents such as etarnacept and tociluzimab increases the risk of viral reactivation. Newer drugs such as ruxolinitib are oral JAK ½ inhibitors with little immunosuppressive effect making this an attractive option as the first line drug rather than salvage therapy for graft versus host disease in this setting. We describe our experience with early introduction of ruxolinitib in acute and chronic graft versus host disease and the outcomes in children.

Methods: A retrospective analysis of 50 children who had received Ruxolinitib between September 2017 and September 2019 on compassionate basis use was analysed. All children with acute graft versus host disease (GVHD)

had Ruxolinitib introduced within 48 hours of commencing steroids and those with chronic graft versus host disease within four weeks. The grading of acute GVHD and the organ involved was documented as per Glucksberg grading and chronic GVHD the organ involved and if limited or extensive. Data analysed was regarding efficacy, toxicity and viral reactivation rates. Ruxolinitib was used at a dose of 2.5 mg twice a day in less than 20 kg and 5 mg twice a day in more than 20 kg children.

Results: The indication was acute GVHD in 18 children and chronic GVHD in 32 children. Gut was the most common organ affected in the acute group and skin and mouth in the chronic group. The response rate was high with resolution of symptoms over 5 to 7 days in 16 of 18 children with acute GVHD. Steroid taper was possible over 4 to 6 weeks and the viral reactivation was seen in 10 of 18 children. In the 32 children with chronic graft versus host disease, 30 had responded to the medication. Ruxolinitib was effective in limited rather than sclerosing chronic graft versus host disease and effective even in lung and eye graft versus host disease. There was no viral reactivation seen in this group and three children died due to leukaemia relapse. Thrombocytopenia was seen in over 65% of children in chronic graft versus host disease and over 90% in the acute GVHD group. In children less than 8 kg hypothermia was a peculiar side effect noted. There were no significant drug interactions.

Conclusions: Ruxolinitib offers a new avenue of care in children with graft versus host disease. The dramatic response rates of 88% in acute and 93% in chronic GVHD makes it an invaluable agent in this setting. Early introduction helps rapid taper of steroids and reduced rates of viral reactivation and mortality in acute GVHD. Morbidity due to steroids including hypertension, diabetes and avascular necrosis of the femoral head could be prevented in children with chronic GVHD if the drug is used early rather than as salvage therapy. The high cost of the medication is a challenge in developing countries and the Managed Access Patient (MAP) programme allows access to this medication on compassionate basis in children.

Disclosure: Twelve children obtained Ruxolinitib through the Novartis MAP programme on compassionate basis free of cost

P208

Post-transplant Cyclophosphamide as an Effective Strategy For GVHD Prevention in both HLA-matched and Mismatched Allogeneic Transplants

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Background: High-dose post-transplant cyclophosphamide (PTCy) has proven feasible and effective in overcoming the negative impact of HLA disparity on survival after haploidentical SCT. However, the optimal prophylaxis regimen for GvHD in the setting of matched or mismatched allogeneic transplants is not well-defined.

Methods: We retrospectively evaluated the combination of PTCy and a second immunosuppressive agent for GVHD prophylaxis in 64 consecutive adult patients diagnosed with high-risk haematological malignancies who received an allo-SCT in our institution between 2016 and 2019. Patient characteristics are shown in Table 1.

Results: At a median follow-up for survivors of 535 days (range: 30-1324), 44 patients (68%) were alive and in remission. The 1-year OS after identical sibling, MUD and MMUD allo-SCT was 82%, 86% and 66%, respectively ($P = 0.1$). Six patients had graft failure and 4 of them were successfully re-grafted using a different PTCy-based conditioning regimen. One patient died from severe bacterial infection before day +30. The median days to neutrophil (w/o G-CSF) and platelet recoveries were + 22 (range: 16-36) and +24 days (range: 10-249), respectively. The incidence (C.I.) of grade 2-4 aGVHD was 12% in sibling donor, 11% in MUD and 35% in MMUD donor groups (p=0.06), respectively, with 4 steroid-refractory cases (6%). Of the 52 evaluable patients, the 1yr. C.I. of moderate-severe chronic GVHD was 8.5% (95%C.I.: 4-14). The C.I. of relapse at 1 year was 31% in the MRD, 20% in the MUD group and 22% in the MMUD group (p=0.7), while NRM at 1-yr was 9.4%, 12% and 38%, respectively (p=0.06), with opportunistic infections being the most frequent cause of death (36% of 14 deaths), followed by relapse (28%) and GvHD (14%). Figure 1 shows the C.I of aGvHD and NRM according to donor type.

Conclusions: Our experience shows that single agent GvHD prophylaxis and PTCy can be combined outside the haploidentical setting with low incidence of both acute and chronic GvHD and acceptable relapse rates. There was a trend toward worse long-term outcomes after MMUD transplant which remains to be confirmed in future studies.

Age, median (range) ≥ 50 years	55 (19-72) 39 (61
Sex, male	34 (53)
Underlying disease AL and MDS NHL/ Hodgkin Myelofibrosis or other MPN Others	33 (51) 15 (23) 9 (14) 7 (11)
Advanced disease at transplant	27 (42)
Sex mismatch: female to male	8 (12)
Donor type HLA Identical Sibling 10/10 matched URD / 1-allele mismatched URD	19 (30) 20/25(31/39)
Disease risk index: High/Very high	12 (41)
Conditioning Fludarabine-Busulphan (RIC) Fludarabine-Melphalan (RIC) MiniTiothepa-modified RICs Fludarabine- TBI or Busulphan (MAC)	11 (17) 13 (20) 23 (36) 17 (26)
Stem cell source (PBSC)	62 (97
Second immunosuppressive agent: Single-agent Tacrolimus/Sirolimus	61/3(95/5)

[Patient characteristics (N=64)]

Disclosure: Nothing to declare.

P209

Serum Autoantibodies in Allogeneic Hematopoietic Cell Transplantation (HCT) Patients: A Pilot Study

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Background: Allogeneic hematopoietic cell transplantation (HCT) is the only curative option for several hematological malignancies including high-risk and relapsed/refractory acute myeloid leukaemia (AML). Allogeneic HCT is often associated with immune-mediated complications such as graft-vs-host disease (GVHD). As some of these complications are T cell-mediated, several anti-thymocyte therapies have been developed, including anti-thymocyte globulin (ATG) and post-transplant cyclophosphamide (PTCy). In contrast, less is known about the contribution of humoral immunity to GVHD. We sought to investigate the role of humoral immunity in the development GVHD through identification of novel autoantibodies in HCT patient serum.

Methods: In this pilot study, we investigated five patients who underwent HCT for de novo AML in first complete remission (CR1). Serum samples were collected on days -6, 0, +14, +30, +60 and up to day +150 post HCT. Autoantibodies were purified from serum by protein G magnetic beads and incubated with a pooled human tissue lysate containing >7,000 proteins, extracted from human liver, colon, skin and lung. After washing, antibody-bound protein antigens were trypsin-digested and positively identified on the Q-Exactive H-FX high-resolution mass spectrometer (MS) (Thermo Fisher Scientific, San Jose, California). Raw files were uploaded into Proteome Discoverer v.1.4 (Thermo) and searched against the Human Swiss-Prot database. A filtering algorithm was developed which excluded autoantibodies against highly abundant proteins, those present at baseline at high titers and those whose titers did not increase compared to baseline.

Results: Of the five patients, four were female. Median age was 45 (range 21-61). Three patients had a matched related donor, one had a haploidentical related donor and one had a matched unrelated donor. Two patients received myeloablative conditioning, while three received reduced intensity conditioning. GVHD prophylaxis consisted of ATG, PTCy, methotrexate (MTX) or cyclosporine A (CsA). Median follow up time among survivors was 141 days (range 130-157).

Of the five patients, three developed grade 1-4 acute GVHD. In two of these, we identified 19 autoantibodies which demonstrated a more than 2-fold increase in titer compared to baseline; no autoantibodies were detected in the third patient. Of the 19 autoantibodies, three were detected in both patients, including those against isoform 2 of clathrin heavy chain 1 (CLTC), isoform 4 of myosin-11 (MYH11), and talin-1 (TLN1). The titers of anti-MYH11, anti-TLN1, and anti-CLTC autoantibodies displayed a > 2-fold peptide count increase compared to baseline in patient 1 (peptide count correlates with protein abundance). In addition, titers of anti-MYH11, anti-TLN1, and anti-CLTC autoantibodies displayed a > 2-fold peptide count increase compared to baseline in patient 5. Two patients had no GVHD; no autoantibodies were discovered in these individuals.

Conclusions: Using immuno-mass spectrometry, we demonstrate that serum autoantibodies of potential clinical significance can be detected in patients at early time points post-HCT. Some of these autoantibodies, including those against CLTC, MYH11 and TLN1, are detected in patients with GVHD. Our finding of common autoantibodies in patients with GVHD suggests that these autoantibodies may potentially serve as biomarkers of GVHD and warrant further prospective studies to determine their role in the pathophysiology of GVHD.

Disclosure: Nothing to declare.

P210

Optimized Starting Dose of Cyclosporine Reduces Risk of Acute GVHD after Allogeneic Hematopoietic Cell Transplantation: A Single Center Experience

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Background: Allogeneic hematopoietic cell transplantation (allo-HCT) is a curative option for many patients with hematologic malignancies. Acute (aGVHD) and chronic graft-versus-host disease (cGVHD) are the most common early and late complications after allo-HCT impacting outcome. Previous results have shown that close monitoring of cyclosporine A (CsA) dosing with active adjustments to maintain therapeutic levels above 195 µg/L in the first 10 days after allo-HCT, could significantly reduce aGVHD (Bianchi et al. Annals of Hematology; 2019; 98: 971-977).

Methods: In this retrospective analysis of patients undergoing allo-HCT, we correlate CsA levels on day 10 and its effect on the incidence of aGVHD vs. cGVHD and outcome [progression-free survival (PFS) and overall survival (OS)]. We hypothesized that with a higher starting dose, more patients will have levels higher than the desired minimum within the first 10 days as determined by ROC, and that consequently GVHD incidence would be lower.

Results: We evaluated 535 patients with primarily myeloid (65%) and lymphoid malignancies (32%). 160 (30%) patients received a CsA starting-dose of 5mg/kg (CsA5) and 375 (70%) patients a starting dose of 3mg/kg (CsA3). In patients with clinically relevant aGVHD grade ≥ 2, mean CsA level was lower on day 10 compared to patients without aGVHD (176µg/L ± 58 vs. 202µg/L ±64, respectively; $p < 0.001$). In our cohort, the optimal CsA cutoff was >193µg/L as suggested by receiver operating curve analysis and Youden's index at day 10 to reduce aGVHD and was similar to published results. The CI of aGVHD grade ≥ 2 in patients with initial CsA level ≤193µg/L vs. >193µg/L was 49% (95% CI: 42%-55%) vs. 35% (95% CI: 28%-41%, p=0.0023), respectively. The frequency of patients achieving the desired CsA level of >193 µg/L at day 10 after HCT was significantly higher with CsA5 starting dose with 85/159 (54%) vs. 147/365 (40%) in patients with CsA3 starting dose, respectively (p=0.005). Correspondingly, the CI of aGVHD with grade ≥ 2 was significantly higher in patients within CsA3 (45%, 95%CI: 40%-51%) compared to patients with the CsA5 starting dose (36%; 95% CI: 28-44; p=0.024). Interestingly, in patients with CsA ≤193µg/L vs. >193µg/L on day 10 post allo-HCT, the 1-year CI of cGVHD was significantly decreased with 42% (95%CI: 36%-49%) vs. 53% (95%CI: 45-60%, p=0.038), respectively.

In addition, the 1-year PFS in the CsA5 group was significantly higher with 69% (95% CI: 60%-76%) compared to the CsA3 group with 59% (95% CI: 54%-64%; p=0.020). This translated into a longer 1-year OS in the CsA5 group with 81% (95% CI: 74%-87%) vs. 70% (95% CI: 66%-75%; p=0.001) in the CsA3 group, respectively.

Conclusions: With a higher CsA starting dose of 5mg/kg, significantly greater rates of aGVHD preventing drug levels above 193 µg/L on day 10 after allo-HCT could be achieved and resulted in advanced outcome with prolonged PFS and OS. Additionally, the degree of immune suppression during the early post-HCT phase may also influence late complications such as cGVHD.

Disclosure: Nothing to declare.

P211

Success of Immunosuppression in Patients with Chronic GVHD: Analysis on 108 Adult long-term Survivors after Matched and HAPLO HSCT

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Background: Allogeneic stem cell transplantation (HSCT) is today a mainstay for the cure of malignant and non-malignant diseases. Over time, the application of HSCT has increased dramatically, but control of graft-versus-host disease (GvHD) is still unsatisfactory.

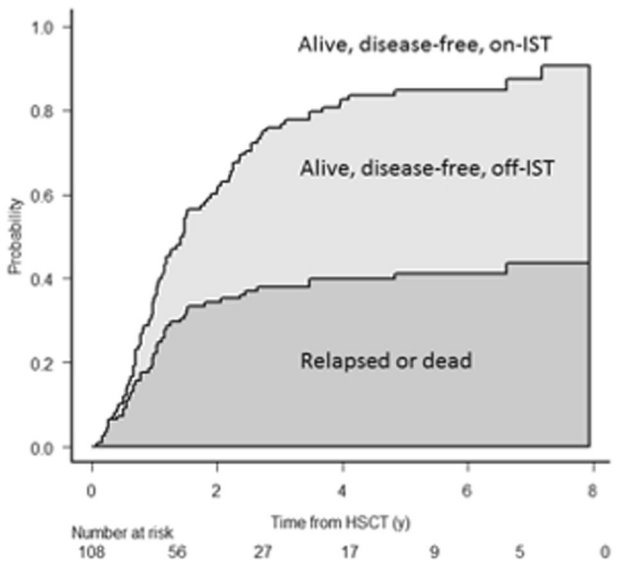
As recently confirmed by a FHCRC study on 250 patients with chronic (ch)GvHD followed for more than 5y after diagnosis, patients with chGVHD usually receive multiple lines and years of IST (immunosuppressive therapy), with only a third permanently off-IST, alive, and free of malignancy.

Primary endpoint of our study was to assess outcome of chGvHD as for overall survival, exposure and discontinuation of IST therapy. Secondary endpoint was to evaluate the power of our immune reconstitution (IR) prognostic score in predicting the possibility of IST discontinuation since chGvHD declaration.

Methods: The study cohort included 108 adult patients who had previously undergone HSCT at our Institute between Jan-2011 and Dec-2014 and subsequently received IST for chGVHD starting from a median time after HSCT of 189 days (range 31-1304). All patients received as 1st line therapy prednisone 0.5-1mg/Kg and NIH criteria were applied for diagnosis and response evaluation. Patients were eligible regardless of graft source, donor type, or GVHD prophylaxis.

Results: Patient characteristics are summarized in Table-1.

After a median follow-up of 5,8 years for all survivors, 19 (18%) were still on-IST (median time of IST exposure 1752 days - range 1189-2820), regardless of previous attempts to discontinue IST. Fifty patients (46%) were alive, in complete remission and off-IST (median time of IST exposure 373 days - range 93-1399). Thirty-nine (36%) have relapsed or died (Figure-1).



[Figure 1. Cumulative incidence of events]

In univariate analysis the probability of being alive, disease free and off-IST at 2 and 5 year was 41% and 64% for patient with moderate chGvHD vs 7% and 20% for patient with severe chGvHD ($p < 0,001$), 31% and 56% for patient with classic GvHD vs 21% and 28% for patient with overlap GvHD respectively (p 0,007); 40% and 72% for patient with IR-score low vs 30% and 44% for patient with IR-score intermediate vs 14% and 18% for patients with IR-score high ($p< 0,001$). Disease risk index, donor/patient sex, conditioning, stem cell source, donor, GVHD prophylaxis, prior acute GvHD did not differ in univariate analysis.

In multivariable logistic regression analysis, successfully stopping IST was associated with NIH GvHD severity: patients with severe chGvHD have less probability of being alive, disease free and off-IST (HR, 10.3; 95% CI, 3.38 to 31.5; $p < 0.0001$).

Conclusions: Patients with chGVHD are exposed to long-time IST: less than half of the patients is off-IST, alive, and free of malignancy at 5y after chGVHD diagnosis. Definition of parameters and biomarker able to predict the trajectory of chGvHD and the probability of survivorship disease-free and IST-free are warranted.

Donor	**MRD**	30 (28%)	**MUD**	31 (29%)	**MMRD**	47 (43%)		
GvHD prophylaxis	**CsA-based**	25 (23%)	**Sirolimus-based**	87 (76%)	**Other**	1 (1%)		
chGvHD type	**Classic**	61 (56%)	**Overlap**	47 (44%)				
chGvHD grade	**Mild**	13 (12%)	**Moderate**	39 (36%)	**Severe**	56 (52%)		
IR score	**Low**	38 (35%)	**Intermediate**	27 (25%)	**High**	28 (26%)	**not evaluable**	15 (14%)

[Table 1. Patients characteristics]

Disclosure: Nothing to declare.

P212

Incidence and Outcome of Liver Chronic graft-versus-host Disease During Tapering or after Stopping Calcineurin Inhibitors in Allogeneic Hematopoietic Stem Cell Transplant Recipients

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Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients sometimes develop liver

chronic graft-versus-host-disease (cGVHD) during tapering or soon after stopping immunosuppressant. However, the clinical characteristics of liver cGVHD during low dose immunosuppressant are still unclear.

Methods: We retrospectively analyzed 242 patients who underwent their first or second allo-HSCT at our center between January 2007 and December 2016, survived more than 100 days after allo-HSCT and experienced dose reduction of calcineurin inhibitors (CI) to lower doses (less than 40mg of cyclosporin A or 0.4mg of tacrolimus by oral administration) for clarifying the risk factors and the clinical characteristics of liver cGVHD during low dose CI. Liver injury was defined as an elevation of any liver enzyme levels (total bilirubin (T.Bil), direct bilirubin (D.Bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP)) to more than 2× upper limit of normal (ULN) or more than 5×ULN if initial liver enzyme levels during low dose CI were more than 2×ULN. We categorized liver injuries into "proven", "probable" and "possible" cGVHD according to the definition by the German Working Group on Bone Marrow and Blood Stem Cell Transplantation and we defined proven and probable liver injury as liver cGVHD in this study. We also compared the clinical characteristics of liver GVHD during low dose CI to that in other periods. In addition, we evaluated the treatment efficacy with CI or corticosteroid for cGVHD during low dose CI.

Results: Sixty patients (25%) developed liver cGVHD during low dose CI. Multivariate analysis showed donor age of ≥40 years (HR 2.20, P=0.02), myeloablative conditioning (HR 2.19, P=0.02), female donors to male recipients (HR 2.53, P< 0.01) and recipient seropositivity for herpes simplex virus (HR 2.52, P< 0.01) were identified as significant risk factors of liver cGVHD during low dose CI period. Peak AST and ALT levels were higher in patients with liver cGVHD during low dose CI period than those in other periods, but T.Bil, ALP and ALP/ALT ratio showed no significant differences. Eighteen (30%) cases received no treatment because cGVHD improved spontaneously, whereas 27 (45%) cases were initially treated with restart or increase of CI and 21 patients responded to CI treatment. Eighteen (30%) patients were treated with corticosteroids and 13 patients responded to corticosteroids therapy.

Conclusions: The risk factors of liver cGVHD during low dose CI shown in this study were similar to previously reported risk factors of cGVHD. Some liver cGVHD during low dose CI could improve without treatment or with CI but others needed corticosteroids therapy. Peak T. Bil was identified as a significant factor to predict the response to corticosteroid therapy.

Disclosure: Nothing to declare.

P213

Post-transplant Cyclophosphamide after Matched Sibling and Matched Unrelated Compared to Haploidentical Donor Transplants in Patients with Acute Myeloid Leukemia, a Study on Behalf of Geth

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Background: Post-transplant cyclophosphamide (PTCy) effectively prevents GVHD in unmanipulated haploidentical (Haplo) transplants, and results in lower rates of GVHD in the HLA matched donor setting compared to standard prophylaxis.

Methods: In this retrospective study, we analyzed adult patients with AML who underwent a first allogeneic HSCT with PTCy from MSD and MUD (n=62) performed between 2013 and 2018, and Haplo donors (n=132) performed between 2012 and 2017 and reported in the GETH registry (Grupo Español de Trasplante Hematopoyético y Terapia Celular). Median follow-up was 15 months for the MSD/MUD cohort and 17 months for the Haplo cohort.

Results: Median age of the patients was 51 years for both cohorts (16-75). HCT-CI/age score was 0-2 in 56% of MSD/MUD patients and 54% of Haplo patients. Compared to MSD and MUD, Haplo patients included a higher proportion of high/very high disease risk index AML (65% vs 30%). Disease status at transplantation was CR1 in 66% and

68%, respectively. Peripheral blood (PB) was used as the stem cell source in 81% and 86%, respectively. MAC conditioning was used in 66% of MSD/MUD transplants and in 54% of Haplo transplants. Most used regimens contained busulfan/fludarabine in Haplo transplants (87%) while MSD/MUD received busulfan/fludarabine in 56% and TBF in 42%. All Haplo transplants received PTCy on days +3+4 followed by CNI+MMF from day +5. MSD/MUD transplants were performed with PTCy days +3+5 with CNI from day 0 in 14%, PTCy +3+4 with CNI alone from day +5 in 21%, and PTCy +3+4 with CNI+MMF from day +5 in 65%. No patient received anti-thymocyte globulin. Cumulative incidence of neutrophil recovery at 35 days for MSD/MUD and Haplo was 100% and 98%, in a median of 16 days and 17 days, respectively. The cumulative incidence of acute GVHD grade II-IV and III-IV at 180 days were 14% vs 49% (p=0.002) and 0% vs 7% (0.006), respectively. The 2-year chronic GVHD rate were 36% vs 48% (p=0.7), respectively. Cumulative incidence of relapse and non-relapse mortality at 1 year were 17% and 19% (p=0.59) and 20% and 18% (p=0.67) for MSD/MUD and Haplo cohorts, respectively. Event-free survival and overall survival at 1 year for the whole cohort were 62% (95% CI 54-71) and 68% (95% CI 59-76), respectively, with no significant differences between both cohorts. The most frequent cause of non-relapse related death was infection for both MSD/MUD (n= 5, 38%) and for Haplo (n=12, 48%).

Conclusions: PTCy as GVHD prophylaxis in HSCT from MSD, MUD and Haplo for patients with AML using mostly PB stem cells effectively prevents GVHD and provides comparable rates of relapse, NRM and survival. Acute GVHD II-IV and III-IV rates were markedly low in the MSD/MUD cohort. Prospective studies are needed to confirm these results and to assess the optimal immunosuppression combination for PTCy in the setting of PB stem cell transplants.

Disclosure: The authors have no conflicts of interest to declare.

P214

T-lymphocyte Transcriptional Signature in ECP-treated Paediatric Patients with Acute graft-versus-host Disease

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Background: Acute graft-versus-host disease (aGVHD) remains a leading cause of morbidity and mortality following allogeneic haematopoietic stem cell transplantation (allo-HSCT). Extracorporeal photopheresis (ECP) treatment for aGVHD is believed to be immunomodulatory specifically targeting activated T-lymphocytes with in vitro evidence suggesting involvement of regulatory T-lymphocytes (Tregs). Our objective was to investigate cellular and transcriptional changes in T-lymphocytes in aGVHD treated with ECP.

Methods: Transcriptional analysis was performed on T-lymphocytes from 3 responding and 2 non-responding paediatric patients pre and post ECP for treatment of aGVHD following allo-HSCT. The Ion AmpliSeq Transcriptome Human Gene Expression Kit was utilized to generate barcoded libraries. Differential gene expression analysis was performed using the ampliSeqRNA plugin. Pathway analysis was done using Ingenuity Pathway Analysis (Qiagen). Immunophenotypic analysis for naïve T-lymphocytes ($CD3^+CD4^+CD45RA^+CD31^+$), Tregs ($CD3^+CD4^+CD25^{hi}CD127^{lo}$) and activated T-lymphocytes ($CD3^+CD4^+HLA\text{-}DR^+$) was performed using the Fortessa X-20 flow cytometer.

Results: ECP responders demonstrated reduced frequency of activated T-lymphocytes and increased naive T-lymphocytes with treatment progression correlating with clinical improvement. Treg frequency increased in the ECP-responders; however, this occurred at different time points in treatment. In the evaluation of Treg function, alloreactive T-lymphocyte proliferation initially declined in the ECP responders, increasing at the end of treatment, indicating most effective Treg suppression of T-lymphocyte proliferation mid-ECP treatment, and becoming less effective at the end. Non-responders demonstrated the opposite trend. The transcriptional profile of the ECP-responders identified significant downregulation in genes involved in effector T-lymphocyte (Teff) metabolism compared to that of the non-responders. Whole transcriptome analysis in responders pre- and post-ECP treatment identified significant downregulation of the ERRα (a metabolic regulator of Teffs) and GαS (important for Th1 and Th17 differentiation and function) T-lymphocyte activation pathways. ERRα downregulation in the setting of ECP therapy may reduce aGVHD-causing Teff production and function, and divert T-lymphocyte differentiation towards Treg or naive T-lymphocyte generation. There was reduced gene expression of cytokines associated with the pathogenesis of aGVHD (IL-3, IL-5, IL-26, IL-27). The Type I interferons (IFN) comprised the largest subtype of differentially expressed cytokines. Reduced type I IFNs in T-lymphocytes after a successful response to ECP parallels thymic recovery and increased naïve T-lymphocytes observed in these patients.

Conclusions: These findings indicate that the T-lymphocyte transcriptional signature from ECP responders is characterized by decreased expression of genes important for Teff function and a reduction in proinflammatory genes. These data suggest that ECP reduces T-lymphocyte activation, potentially via ERRα and GαS pathways. This transcriptional signature is previously unreported and may be unique to ECP therapy. Further evaluation in additional responding and non-responding ECP patients is required, as well as analysis to determine if ERRα and GαS down-regulation are causative of these observed effects.

Disclosure: Educational grant from Mallinckrodt Pharmaceuticals

P215

Efficacy of low-dose Ruxolitinib as Savage Therapy in Heavily Pretreated Patients with Moderate/severe steroid-refractory Chronic graft-versus-host Disease

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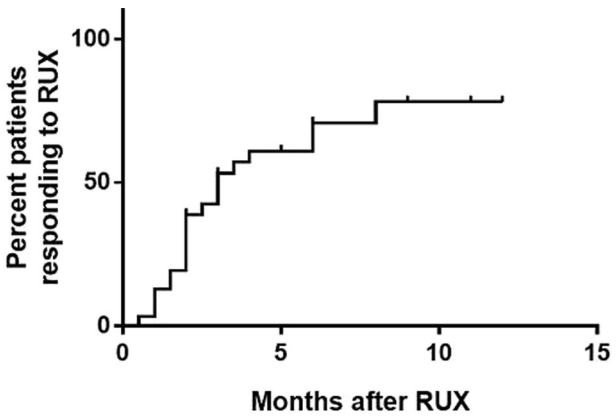
Background: Moderate/severe chronic graft-versus-host disease (cGVHD) remains a devastating complication after allogeneic hematopoietic stem cell transplantation (allo-SCT), especially for the heavily pretreated patients. Inhibition of the Janus-associated kinases (JAK) with ruxolitinib (RUX) reduces GVHD in preclinical and clinical models. We aimed to assess the efficacy and safety of low-dose RUX in the treatment of moderate/severe steroid-refractory cGVHD (SR-cGVHD) after allo-SCT.

Methods: This retrospective study included 31 allograft recipients (males n=22; median age: 30 yrs (range: 17-56)) with moderate/severe SR-cGVHD in a single institution, who received RUX as ≥3nd line salvage between December 2017 and June 2019. The stem cell source was peripheral stem cells. The donors were from matched sibling donors (MSD, n = 7) and HLA-haploidentical related donors (HRD, n = 24). The regimens were based on the myeloablative BuCy regimen. ATG Fresenius 10mg/kg was applied to patients with HRD. The patients received cyclosporine A plus short-time MTX ± MMF as GVHD prophylaxis. For the salvage treatment of SR-cGVHD, RUX was administered orally at 5 mg twice daily for patients ≥ 50 kg or 5 mg once daily if < 50 kg.

Results: The median number of previous lines of therapy was 5 (range 3-8). Overall 21 patients achieved response (ORR, 67.7%), including 8 (25.8%) CR and 13 (41.9%) PR. The response (complete/partial) rate per organ was 94.7% for oral, 90.9% for cutaneous, 91.7% for ocular, 90.0% for hepatic, 66.7% for musculoskeletal, 55.5% for gastrointestinal, 57.1% for scleroderma and 50.0% for pulmonary chronic GVHD (bronchitis obliterans, BO), respectively. Among the 21 responders, responses occurred at median time of 60 days after RUX and were sustained which enabled discontinuation (6/21, 28.6%) or reduction of steroids to physiologic doses (13/21, 61.9%). Among 31 patients in the study cohort, only five of patients (5/31, 16.1%) experienced at least one CMV reactivation, and no one develop CMV disease. Fifteen patients (5/31, 25.8%) experienced EBV reactivation, but no post-transplantation lymphoproliferative disorder was observed. Eight patients (8/31, 25.8%) were complicated with severe pulmonary infection >= 3 grade. The incidence of severe pulmonary infection was significantly higher in BO group than in non-BO group (46.67% vs. 6.25%, p=0.01). HBV Hepatitis B virus (HBV) was reactivated in two patients (6.45%). After a median follow-up of 325 days (range 48-654) after RUX, relapse of the underlying malignancy occurred in 14.3% (3/21) of the patients with SR-cGVHD. The 1-year overall survival estimate and 1-year non-relapse mortality after RUX was 73.6% (49.0%-87.7%, 95%CI) and 15.9% (1.0%-33.1%, 95%CI), respectively.

Conclusions: Low dose ruxolitinib in the real-life setting is an effective treatment option for GVHD, which could successfully spare long-term steroids use, with an ORR of 67.7% for refractory moderate/severe cGVHD, in heavily pretreated patients. However, lung is the worst responsive organ. And pulmonary infection events deserve more attention, especially in patients with bronchitis obliterans.



[Percent patients responding to RUX]

Disclosure: Nothing to declare.

P216

Restrictive use of Intravenous Antibiotics in Allogeneic SCT Pts with Fever due to Cytokine Release Syndrome Allows Microbiota Protection without Increase of Infections and TRM

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Background: Loss of early microbiota diversity has been reported as a major risk factor of gastrointestinal GvHD and early mortality following allogeneic SCT. Use of intravenous broad spectrum antibiotics (ABX) is a major risk factor of microbiota damage but empiric immediate treatment is needed in pts with fever and the risk of neutropenic infections. As previously shown, most broad spectrum ABX induce severe microbiota damage; thus changes in strategy might be more helpful in microbiota protection than selection of individual ABX.

Methods: Therefore, we introduced a restrictive policy regarding use of ABX in pts with fever and a high likelihood of cytokine release syndrome (e.g. due to antithymocyte globuline) based on repeated careful clinical examination and defined risk criteria since 9/2017. Initiation of broad spectrum ABX was postponed to the next period of fever for 24hrs in these pts. We now compared 146 pts with standard use of ABX from 2014-2015 with a cohort of 130 consecutive pts treated according to the restricted policy.

Results: Advanced stages (41%) and unrelated donors (75%) were equally distributed between the 2 cohorts, all pts received rifaximin as an oral prophylaxis. Overall, the restricted strategy led to a significant reduction of the use of ABX prior to the day of SCT from 49.3% to 28.7% (p 0.003), which translated in a significantly delayed start of systemic ABX (3d before vs 1.8 d after SCT (p 0.000) and an overall reduced length of ABX treatment (21.2 vs 16.6 d, p 0.001) in the restricted use cohort. As a result, urinary indoxylsulfate levels at day 7 were significantly higher in the restricted use group indicating prolonged partial protection of commensal bacteria. Incidence of bacteremia was unchanged in both cohorts, and no increase in neutropenic sepsis (4.3 vs 3.3%) or early treatment related mortality until 30d (3.8% vs 0.8%) was observed. Incidence of GI GvHD grade 2-4 (13% vs 8%) and 1 yr TRM (16% vs 7%) even showed a trend for further reduction in the cohort receiving restricted ABX.

Conclusions: Overall, these data indicate that improved antibiotic stewardship may help to reduce microbiota damage in allogeneic SCT provided careful timely and continuous clinical supervision of pts is warranted.

Clinical Trial Registry: Not applicable

Disclosure: Ernst Holler - advisory board MaatPharma all other authors nothing to declare.

P217

Extracorporeal Photopheresis (ECP) as first-line Treatment for Acute GVHD (AGVHD) in Pediatric Patients who underwent T-depleted Haploidentical Stem Cell Transplantation (APLO-HSCT)

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Background: Intensive immunosuppressive therapy administered for aGVHD is a risk factor for infections, disease relapse, organ failure and adversely affects quality of life. In the pediatric setting these aspects are worsened by impaired growth with negative impact on emotional and social life. To reduce the risk of infections, cronic GVHD (cGVHD) and relapse in high-risk patients, ECP was adopted as first-line therapy in pediatric patients with aGVHD to avoid long-term steroid administration. Indeed, ECP is an outstanding therapeutic chance, carrying the advantage of high tolerability and maintaining at the same time the graft-verus-leukemia effect.

Methods: Eleven pediatric patients, median age of 11 years(range 5-17), underwent αβT/CD19B-cell-depleted(5/11) and regulatory and conventional T-cell adoptive immunotherapy(Treg/Tcon)(6/11) aplo-HSCT between September 2016 and May 2019 with ≥2 grade aGVHD. Eight of them were affected by B-ALL, two by AML and one by aplastic anemia. Mother was donor in ten cases, father in the other one. All patients received a myeloablative conditioning regimen; total body irradiation was employed in 8/11 patients. 8/11 patients received Rituximab 200 mg/mq as PTLD prophylaxis. No patient received post-transplantation pharmacological GVHD prophylaxis. At a median of 28 days from transplant (range 6-80),5/11 patients developed grade 2 (3 liver-only, 1 lung-skin, 1 skin-only) aGVHD,4/11 patients grade 3 aGVHD (2skin-

bowel-liver, 2skin-bowel),2/11 grade 4 (skin-bowel-liver) aGVHD. All patient received early systemic steroids with a median dose of 2 mg/Kg (range 1-3 mg/Kg). At a median of 3 days (range 2-5) from diagnosis of aGVHD, all patient starting ECP treatment, with 3 procedures/week (7/11 patients) or 2 procedures/week (4/11 patients) at median of 6 weeks, then two procedures/week and finally one/week. All patients were treated with ECP using the off-line method (MNCs collection by a cell separator device followed by irradiation in the presence of 8-methoxypsoralen and reinfusion into the patient). The total median number of procedures performed for each patient is 27 (range 8-76). The add-on therapies administered were calcineurin inhibitors (6/11), mycophenolic acid (5/11), Infliximab (3/11) and Ruxolitinib (4/11).

Results: The early start of photopheresis allowed the tapering of steroid therapy at a median time of 8 days (range 6-30) in all patients. We registered 5/11 cases of Adenovirus infection, 6/11 of Cytomegalovirus, 2/11 of HHV-6, and one Aspergillosis invasive infection. No patient died for these infectious complications.

2/11 patients developed cGVHD, both are currently alive and disease-free. With a median follow-up of 19 months (range 1-35), one patient with B-ALL relapsed. Seven patients (64%) were alive at time of the last follow-up, only two of them with cGVHD.4/11 patients died, two for 4 grade aGVHD, one for relapse of B-ALL, one for thrombotic microangiopathy. The alive patients are all disease-free, five of them also cGVHD-free.

Conclusions: These preliminary data in pediatric patients with ≥ 2 grade aGVHD showed that ECP as first-line treatment for severe aGVHD is an effective therapeutic option even in aplo-HSCT setting. Indeed, it allowed in all patients an early tapering of steroid therapy, the incidence of infectious complications was low and so was cGVHD incidence. The overall survival was 64% and disease and cGVHD-free survival of alive patients is 71%.

Disclosure: Nothing to declare.

P218

Micro RNA Profiling of acoustically-isolated Extracellular Vesicles Identifies Potential Biomarkers for post-allo-hsct Complications

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Background: Extracellular vesicles (EVs) contain a number of disease- and tissue-specific microRNAs and they can be isolated non-invasively from plasma samples. This makes them ideal candidates for biomarker discovery approaches. Traditionally, EVs are isolated by ultracentrifugation (UC). However, UC is laborious and requires large sample volumes, which makes it difficult to perform longitudinal studies on larger patient samples. We therefore investigated the use of a recently-developed, semi-automatic acoustic trapping device for EV isolation from small plasma volumes to identify EV miRNAs as potential biomarkers for post allogeneic hematopoietic stem cell transplantation (allo-HSCT) complications.

Methods: Plasma samples (n=89) were collected from 10 patients (age: 22-58 years) with high-risk or refractory/relapsed diseases undergoing allo-HSCT. Samples were collected before transplantation and post-transplant (weekly until discharge, bi-weekly thereafter up to 12 weeks). Patients received mobilized PBSC from related (n=2) and unrelated donors (n=8), respectively, after standard conditioning. All patients received cyclosporine and methotrexate as GvHD prophylaxis. EV isolation was performed by acoustic trapping using the AcouTrap device. Acoustic trapping uses a local λ/2 acoustic standing wave generated by a piezoelectric transducer over a capillary. EVs are captured in the acoustic field in 12 μm polystyrene bead seeding particle clusters and are then released for downstream analysis. Number of EVs and size distributions were analyzed by nanoparticle tracking analysis. miRNA profiling was performed with a miRNA panel consisting of 179 miRNAs (Qiagen). EVs were enriched from 50μl and 300μl of diluted plasma for nanoparticle tracking analysis and miRNA profiling, respectively.

Results: Acoustically enriched EVs were intact, round and predominantly 30 - 200 nm in size. Median numbers of EVs isolated from 50 μl diluted plasma (1:2) were 1.9 x 10 (range 3.7 x 10^8 - 5.5 x 10^9) pre-transplant compared to 2.9 x 10^9 (range 4.4 x 10^8 - 1.5 x 10^{10}) after transplantation. The majority of patients had increased numbers of EVs in their plasma over time (> 2 fold) and EV size was slightly increased after transplantation. Sufficient quantities of RNA for miRNA analysis were obtained from all samples and EV miRNA profiles differed from whole plasma profiles. As a proof of principle, platelet-specific miR-142-3p in EVs was shown to correlate with platelet counts as expected. Infectious episodes (defined as use of i.v. broadspectrum antibiotics, fever > 38.5°C and CRP > ULN) were recorded in 7 patients. Nine patients developed GvHD at a median onset of 6 weeks after transplantation (range: 2 - 12). Eight patients had GvHD grade I (skin), one patient developed grade III GvHD. Of note, EV analysis identified miRNAs

that positively correlated with infection (miR-15a-5p, miR-375, miR-106a-5p, miR-25-3p, miR-486-5p) and GvHD (miR-15b-3p, miR-30a-5p, miR-342-3p, miR-130a-3p and miR-145-5p), respectively. Additionally, we also identified miRNAs that were consistently negatively correlated with these two complications, (infection: miR-328-3p, miR-342-3p, miR-30a-5p, miR-133b and miR-141-3p; GvHD: miR-141-3p, miR-486-5p, miR-93-5p, miR-18a-5p and miR-92b-3p).

Conclusions: Acoustic enrichment of EVs from small sample volumes enabled the identification of miRNAs that correlated with infection and GvHD. Thus, analysis of acoustically-enriched EVs is a promising tool for biomarker development in allo- HSCT.

Disclosure: TL and SS are co-founders and shareholders of Acousort AB, Lund, Sweden

P219

Colonization Plays an Important Role in the Outcome of Allogeneic Transplantation

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Background: The role of gut pathogens colonization in eliciting both infective complications and graft-versus-host disease (GVHD) has been largely established. Candida is a member of the Micobiome and its colonization in the gut has been considered a risk factor in pathophysiology of acute GVHD (aGVHD). We present a retrospective analysis to evaluate the role of colonization in patients undergoing allogeneic transplant for haematological diseases at our institution.

Methods: We retrospectively evaluated 223 patients undergoing to allogeneic transplants (HSCT) for hematological malignancies during the last 5 years (from 2013 to 2018). Patients characteristics are summarized in Table 1. COL is defined as detection of exogenous micro-organism in the rectal, oral, upper airway swab and urine colture at baseline: yeast (F), gram positive (G+) and negative bacteria (G-). Patients were divided in 2 different cohorts depending on the preexistent colonization (COL) at the time of HSCT. A close monitoring of acute or chronic GVHD, relapses, CMV reactivation after HSCT was carried out. Comparison of non-continuous variables was done by Chi-square test, Kaplan-Meyer curves were used to assess OS, GVHD & Relapse free survival (GRFS).

Results: The majority of patients were COL by Candida non albicans (16), KPC (14), VRE (8), S aureus (7) and S. maltophilia (5). No correlations were found between occurrence of COL and onset of either aGVHD or cGVHD (p=ns). In patients experiencing aGVHD, F colonization was related to gut localization (p=0,032).

Overall gut pathogens COL was associated with a trend to lower OS (median OS was 9,7 mts and 49,86 mts) p=ns; among them different micro-organisms, only F colonization had a negative impact on both OS (p=0,000) and on GRFS (p=0,005).

Conclusions: Exogenous colonization of intestinal microbioma has a negative impact on HSCT outcome. In our experience, yeast colonization plays a major role in determining both the onset of aGVHD and Overall survival. A careful strategy to prevent and treat such event may remarkably improve the outcome of this life-saving procedure.

	Global	Colonized	Not Colonized	p
aGVHD (%)	81 (36)	28 (13)	53 (23)	0,11
cGVHD (%)	62 (28)	12 (6)	50 (22)	0,07
OS mts	34,4	9,7	49,86	0,000
GRFS mts	4,7	3,76	5,06	0,176

[Table 1]

Clinical Trial Registry: not applicable
Disclosure: no disclosure

P220

Endothelial Activation and Stress Index (Easix) Score at the Onset of Acute graft-versus-host Disease in Predicting Outcome of Allogeneic Stem Cell transplantation-a Retrospective Analysis

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Background: Endothelial dysfunction links thrombotic microangiopathy to steroid-refractory graft-versus-host disease (GVHD) after allogeneic stem-cell transplantation (allo-SCT). Endothelial Activation and Stress Index (EASIX) is a simple score comprised of standard laboratory

parameters (creatinine, LDH and thrombocytes) developed as a potential tool to predict allo-SCT mortality by Luft and colleagues. They validated EASIX retrospectively and showed that EASIX taken at the start of acute GVHD (EASIX-GVHD) can be used as an independent predictor of overall survival (OS) and transplant related mortality (TRM) after allo-SCT.

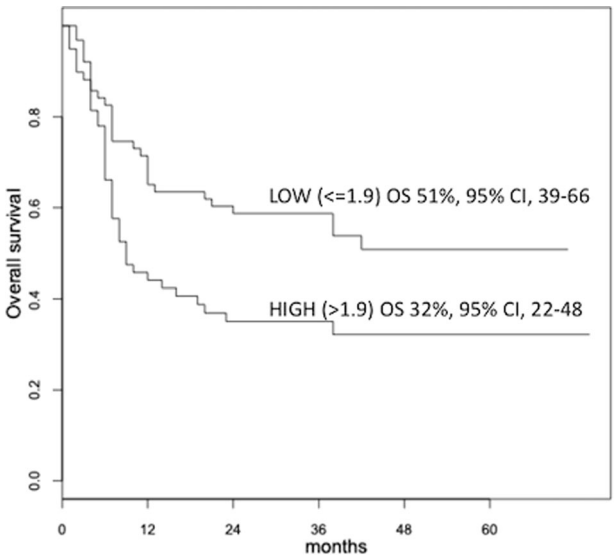
Methods: The aim of our study was to retrospectively evaluate EASIX-GVHD as a predictor of OS and TRM in cohort of consecutive patients who underwent allo-SCT in the University Hospital Center Zagreb. Group comparisons between patients with low and high GVHD-EASIX score were done using the log-rank test or Gray test for competing risks outcomes. A multivariate analysis evaluated the association of OS with relevant variables by using a Cox's regression model and with TRM by the use of semi-parametric proportional hazards model of Fine and Gray.

Results: Our study group included 308 patients who received allo-SCT in our institution between 2012 and 2017. We further identified a cohort of 122 patients who developed acute GVHD. Among them, 68 (56%) had stage I-II, and 54 (44%) stage III-IV acute GVHD. 48 (40%) were female, 74 (60%) were male with the median age 49.6 years (range 18-67) at the time of the transplant. The most frequent diagnosis were acute leukemia (71 pts, 58%) and myelodysplastic/myeloproliferative diseases (26 pts, 21%). Thirty-nine pts (32%) underwent myeloablative and 83 (68%) reduced-intensity conditioning (RIC) regimen, 32 (26%) had a matched related, 81 (67%) unrelated and 9 (7%) haploidentical donor.

The median EASIX score was 1.9 at the time of acute GVHD onset (range 0.29-38.63). With a median follow up of 19.5 months (range 1-74), the OS at 24 months was 51%, (95% CI, 39-66) for the low EASIX (< =1.9) and 32%, (95% CI, 22-48) for the high (>1.9) EASIX group (p=0.01). Moreover, high EASIX group had significantly higher TRM compared to low EASIX score group; 58%, (95% CI, 44-70) vs 31% (95% CI, 19-43), respectively (p=0.001). In the multivariate analysis, high EASIX stayed an independent predictor of worse OS (HR 1.98; 95% CI, 1.18-3.36, p=0.01) and higher TRM (HR 2.49; 95% CI 1.41-4.39, p=0.001).

As EASIX-GVHD was previously reported as a powerful predictor of OS after GVHD particularly in patients who underwent RIC, we further analysed EASIX-GVHD in our RIC subpopulation (83 pts). By using the 3.43 cut-off proposed in the Luft study, we confirmed the low EASIX score to be associated with better OS (48%; 95% CI, 36-65,) compared to high EASIX score (18%; 95% CI, 7-44, p=0.0004).

Conclusions: Our retrospective data support previous data and suggest that EASIX-GVHD could potentially serve as a valid tool for prediction of allo-SCT outcomes. As a simple biomarker panel, EASIX could easily be implemented in clinical decision making in the field of allo-SCT. These retrospective data need validation in a prospective study which is currently being conducted.



[OS for low vs high EASIX score]

Disclosure: No disclosures.

P221

Carfilzomib In addition to Standard Cyclosporine/ Methotrexate Combination Effectively Prevents Acute graft-versus-host Disease after Allogeneic Stem Cell Transplantation from Unrelated Donors

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Background: Acute graft-versus-host disease (GVHD) remains a major obstacle for successful allogeneic stem-cell transplantation from matched-unrelated donors. Novel preventive regimens are thus in need. The proteasome-inhibitor bortesomib has immune modulatory effects that were shown to be beneficial in several studies adding a short treatment course to the standard calcineurin/ methotrexate regimen in matched and mismatched unrelated-donor transplants. Carfilzomib is a second generation irreversible proteasome-inhibitor that produces sustained proteasomal inhibition. It

is more selective than bortesomib and was shown to be more effective in relapsed/ refractory multiple myeloma. There is no data on the effect of carfilzomib in GVHD prevention.

Methods: The study enrolled 26 patients with AML (n=19) in CR1 (n=13) or CR2 (n=6) or previously untreated MDS with less than 10% blasts (n=7). Patients were given a 10/10 (n=21) or 9/10 (n=5) unrelated-donor transplants. The conditioning regimen included fludarabine combined with intravenous busulfan at reduced (n=8) or myeloablative doses (n=14) or treosulfan (n=4). We explored a novel GVHD prevention regimen consisting of 2 doses of carfilzomib at 20 mg/m2, given on day 1 and 2 after transplantation combined with standard cyclosporine/ methotrexate. All patients were also given antithymocyte-globulin (ATLG Neovii, total dose 15 mg/kg). Transplantation outcomes were compared to a historical group of 100 patients with similar patient and transplant characteristics given unrelated-donor transplant with a standard cyclosporine/ methotrexate regimen.

Results: The median age was 63 years (range, 30-73). Twenty-three patients completed the planned two days of carfilzomib. One patient had only one dose and two none due to adverse events that dictated stopping treatment by protocol. The median follow-up is 34 months (range 18-56). All patients engrafted with a median of 15 days (range, 9-31) compared with 14 days (range, 9-23) in the control group (P=0.14). There was no difference in the rate of grade ≥3 organ toxicities, 20% and 30%, respectively (P=0.36). Acute GVHD grade II-IV occurred in three patients in the study group (grade II, III and IV, one each), cumulative incidence 11% (95%CI, 4-32) compared with 39% (95%CI, 30-50) in the control group (P=0.01). Chronic GVHD occurred in 11 patients, cumulative incidence 49% (95%CI, 32-75) compared with 41% (95%CI, 33-52), respectively (P=0.98). Nine patients had mild disease and the incidence of moderate to severe chronic GVHD was 8% and 18% (95%CI, 11-30), respectively (P=0.52). Non-relapse mortality (NRM) occurred in 3 patients in the study group, 2 died of acute GVHD and one of multi-organ failure. The cumulative incidence of NRM was 11% (95%CI, 4-33) and 22% (95%CI, 15-32), respectively (P=0.41). Three patients relapsed in the study group, cumulative incidence 16% (95%CI, 5-49), compared to 26% (95%CI, 18-36) (P=0.09). In all, 20 patients are alive with an estimated 2-year survival of 81% (95%CI, 66-100) compared to 56% (95%CI, 46-66) in the control group, respectively (P=0.07).

Conclusions: Carfilzomib in addition to standard cyclosporine/ methotrexate is safe and allows better prevention of acute GVHD without compromising the graft-versus-leukemia effect, resulting in favorable outcome after unrelated-donor transplant. Larger randomized prospective studies are required to confirm these initial promising results.

Disclosure: Nothing to declare.

P222

Comparison of Exclusive Postransplant Cyclophosphamide versus a Calcineurin Inhibitor Based Regimen as GVHD Prophylaxis in Allogeneic Bone Marrow Transplantation from HLA Identical Sibling

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Background: Post transplant cyclophosphamide (PtCy) as graft versus host disease (GvHD) prophylaxis was initially employed in haploidentical transplant and its use is progressively expanding to different settings.

We conducted a pilot study using exclusively high dose PtCy as GvHD prophylaxis and compared the results with historic controls using cyclosporine (CsA) + Methotrexate (Mtx) or Mycophenolate (MMF). Our primary objective was to analyze engraftment, overall survival (OS), event free survival (EFS) and the characteristics of GvHD. Secondary objectives were incidence of complications, transplant related mortality (TRM) and relapse.

Methods: From March 2017 to October 2019, PtCy 50 mg/kg was used on day +3 and +4 in 10 patients, 80% affected by a myeloid malignancy, median age of 44 years (30-56) with an allogeneic stem cell transplantation (allo-SCT) from a HLA identical sibling using mobilized bone marrow. G-CSF was not routinely used to shorten duration of neutropenia. For each case we selected one matched control with similar clinical and demographic characteristics. For details check table 1.

Results: An absolute neutrophil count (ANC) of 500 was reached on days 18 (12-25) and 15 (11-21) (p=0.04) in PtCy and CsA group; and 50,000 autologous platelets on days 26 (13-46) and 14 (11-34) (p=0.036), respectively. OS and EFS at median follow up of 12 months (3-29) in PtCy group were 100%. In CsA group, median follow up was

59 months (5-81); at 12 months OS and EFS were 100% and 90%.

Two patients developed acute GvHD in PtCy group (grade II), with a median time to onset of 43 days (32-55). Steroids were employed during 43 and 77 days in these patients. In CsA group 5 patients developed acute GvHD ≥ grade II (4 grade II, 1 grade III); with a median time to onset of 28 days (15-127). Steroids were used for a median time of 33 days (25-109).

In PtCy group, 6 cases of chronic GvHD were diagnosed (3 mild, 2 moderate, 1 severe) with a median time to onset of 145 days (116-327). Four patients required systemic immunosuppression for a median time of 185 days (68-616). In CsA group, tapering of immunosuppression started at day 60 and median days of treatment was 165 (126-964). Eight patients experienced chronic GvHD (3 mild, 2 moderate, 3 severe) with a median onset of 154 days (62-204) and 7 required additional immunosuppression with steroids for a median time of 510 days (126-1755).

Incidence of complications was similar in both groups (≈ 50%) with no difference between infectious (p=0.3) and non-infectious (p=0.6). In CsA group, 2 patients died beyond day 100 due to TRM (infection, GvHD) and 1 due to relapse.

Conclusions: Use of PtCy as exclusive immunosuppression after a mobilized bone marrow allo-SCT from HLA identical sibling **seems** to decrease the incidence of acute and chronic GvHD compared to a CNI based regimen, without affecting relapse and overall survival and allows 60% of patients not to require additional immunosuppression. Longer follow up and a controlled randomized trial comparing these schemes are needed to confirm this results.

Disclosure: Nothing to declare.

P223

Sirolimus versus Cyclosporine with post-transplant Cyclophosphamide and Mycophenolate as graft-versus-host Disease Prophylaxis in Haploidentical Transplants: a Retrospective Analysis of One Single Institution

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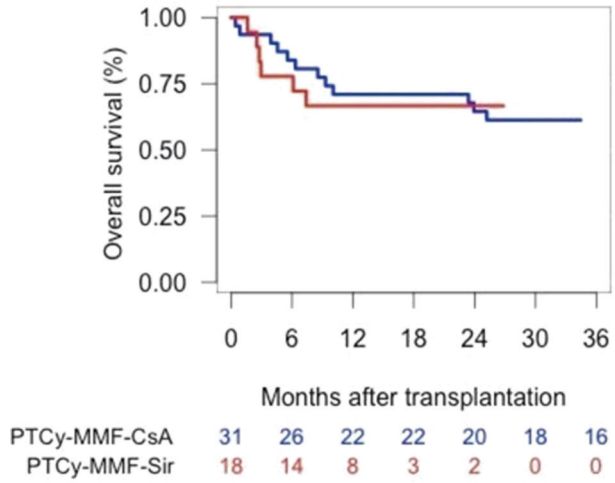
Background: In the last decade, the use of a CNI (Calcineurin-Inhibitor)-free GVHD prophylaxis with post-transplantation cyclophosphamide (PTCy) and sirolimus has been extended to haploidentical stem cell transplantation (Haplo-SCT). However, there are no randomized studies that compare the outcome with classical CNI-based regimens.

Methods: This study included all consecutive adult patients with haematological malignancies who underwent first Haplo-SCT at our institution between October 2012 and December 2018 using PTCy plus mycophenolate and cyclosporine (PTCy-MMF-CsA) or PTCy plus mycophenolate and sirolimus (PTCy-MMF-Sir) as GVHD prophylaxis. Primary end point was the assessment of OS. Secondary end points included GVHD, NRM, cumulative incidence of relapse (CIR), DFS and GRFS. Other post-transplant events such as VOD, acute kidney injury (AKI), thrombotic microangiopathy (TMA) and hypercholesterolemia were also evaluated.

Results: Forty-nine patients received an Haplo-SCT with PTCy-MMF-CsA (n = 31) or PTCy-MMF-Sir (n = 18) as GVHD prophylaxis. Median age of the entire series was 55 years (range, 18 - 69). There were no differences in patient or disease characteristics between both groups. Forty-seven (96%) patients underwent RIC regimen. Conditioning regimen was CBF in 94% of the patients with PTCy-MMF-CsA and TBF in 72% of the patients with PTCy-MMF-Sir (P < 0.001). All patients received peripheral blood as stem cell source. Thirty (61%) of the 49 patients remained alive with a median follow-up of 37 months (range, 9 - 80) after SCT. In the PTCy-MMF-CsA group median follow-up was 51 months (range, 26 - 80), whereas in PTCy-MMF-Sir group it was 14 months (9 - 26). The 2-year OS was 67% and 65% in the PTCy-MMF-CsA and the PTCy-MMF-Sir groups, respectively (P = 0.75) (Figure 1). There were no statistical differences in GVHD, NRM, CIR, DFS or GRFS (Table 1). The 6-month cumulative incidence of VOD, AKI, TMA and hypercholesterolemia was 6% versus 11% (P = 0.6), 58% versus 22% (P = 0.01), 29% versus 0% (P = 0.013), and 13% versus 39% (P = 0.04), for the PTCy-MMF-CsA or PTCy-MMF-Sir groups, respectively.

Conclusions: Despite the limited number of patients, the relatively short follow-up and the retrospective assessment, this study suggests that CNI-free regimens with PTCy-MMF-Sir as GVHD prophylaxis in Haplo-SCT have similar outcomes than CsA-based schedules, and may have a better safety profile. Prospective randomized trials are required to confirm this hypothesis.



[Figure 1: Overall survival according to GVHD prophylaxis]

Outcome	Global	PTCy-MMF-CsA	PTCy-MMF-Sir	P
aGVHD grade II-IV, 100-d CI (%)	45	42	50	0.3
aGVHD grade III-IV, 100-d CI (%)	12	10	17	0.45
cGVHD all grades, 2-yr CI (%)	38	28	69	0.09
cGVHD moderate/severe, 2-yr CI (%)	16	14	21	0.62
NRM, 2-yr CI (%)	27	23	33	0.31
CIR, 2-yr CI (%)	13	19	0	0.07
DFS, 2-yr (%)	59	58	67	0.8
GRFS, 2-yr (%)	48	48	50	0.85
OS, 2-yr (%)	63	65	67	0.75

[Global outcomes according to GVHD prophylaxis]

Disclosure: Nothing to declare.

P224

Targeted Sequence Capture Metagenomics (Virocap) to Detect Virus in Stool Samples of Hematopoietic Stem Cell Transplantation Patients

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Background: Gastro-intestinal (GI) symptoms in pediatric allogeneic hematopoietic stem cell transplantation (HSCT) patients are common and may be caused by viruses, Graft-Versus-Host-Disease (GVHD) or both. Currently, little is known about the GI viriome in SCT patients, hindering the study of the pathogenicity and role in GVHD. We used ViroCap, a viral target enrichment method, in combination with Next Generation Sequencing (NGS) to detect viruses in stool samples of HSCT patients and compared to PCR results.

Methods: Using ViroCap, nucleic acid of a broad range of RNA and DNA viruses infecting vertebrate hosts was enriched in banked stool samples of HSCT patients. Upon enrichment, samples were sequenced by NGS on an Illumina MiSeq system and detected viral sequences were analyzed using the automated Genome Detective pipeline (GD) and/or directly aligned (DA) to a reference sequence of a specific virus, using Genious software. Where possible, presence of newly detected viral pathogens was confirmed by virus-specific qPCR.

Results: Stool samples of 11 patients, age range 1-17, that had undergone HSCT for a variety of indications were selected for ViroCap analysis. All selected patients suffered from GI-symptoms. Ten were diagnosed with grade I-IV GI-GVHD according to consensus guidelines. In 6 samples adenovirus (ADV), norovirus or both had been previously detected by clinical diagnostic qPCRs (Diagnosis D), while in 5 samples no viral GI pathogens were found (No diagnosis ND). In all D samples the presence of the initially found virus could be confirmed upon ViroCap analysis. ADV was most commonly found and Ct values grossly correlated with the number of sequence specific reads upon ViroCap GD and DA analysis. In addition, ViroCap led to the detection of multiple, possibly clinically relevant viral pathogens in D samples, including human herpesvirus-6B (HHV6B) (n=1), BK polyomavirus (BKV) (n=2), ADV (n=1) and human rhinovirus (HRV) (n=1). Presence of BKV and HRV was confirmed by qPCR. Furthermore, in 4/5 ND samples viral pathogens were detected. These included human herpes Virus 7 (HHV7) (n=1), BKV (n=1), HRV (n=2) and Astrovirus (AV) (n=1). HRV presence was confirmed by qPCR, HHV7 was not tested. BKV could not be confirmed, but other clinical samples from the same patient taken closely before/after the specific stool sample were BKV positive. Further analysis of the AV sequences revealed that the routine PCR failed to detect this virus due to extensive sequence mismatches in the primer/probe binding regions. This AV clade was classified as an AV VA3 (JX857868.1).

Conclusions: In summary, application of viral target enrichment strategies with limited pathogen detection bias, such as ViroCap, increase the sensitivity of NGS for virus detection and can lead to discovery of novel variants. As

such, it might be a useful screening tool to study associations of viral pathogens with GI-symptoms and GVHD.

Disclosure: Nothing to declare.

P225

Extracorporeal Photopheresis and Production of Serum IL-34 and Elafin in Chronic Graft Versus Host Disease

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Background: Extracorporeal photopheresis (ECP) is a second line therapy for steroid refractory, dependent or intolerant chronic GVHD (cGVHD). In cGVHD, tissue macrophages produce factors that contribute to the formation of fibrotic lesions. IL-34 is secreted by activated keratinocytes and promotes proliferation and differentiation of skin macrophages [1]. Recent data shows that serum IL-34 levels are raised in patients with systemic sclerosis and interstitial lung disease compared to healthy controls[2]. Elafin is a serine-protease inihibitor produced by epithelial cells, including keratinocytes, and high levels of serum elafin have been identified as a biomarker for skin GVHD[3]. Since sclerosis is a symptom of skin cGVHD, we conducted a pilot study to investigate whether IL-34 levels are raised in cGVHD patients, if ECP affects its production and its relationship to elafin

Methods: Serum samples were collected from18 cGVHD patients (12 male /6 female;age range: 16-70) and 8 healthy controls (5 male / 3 female;age range: 25-58) before ECP and at 3 month intervals up to 9 months. Patients had cGVHD affecting skin (16/18), mucosal membranes (5/18), liver (4/18), gut (4/18), eye (2/18), joints (1/18) and no genital or recorded respiratory involvement. Serum IL-34 and elafin levels were assessed by ELISA. Data were analysed using GraphPad Prism 6. Statistical tests performed include a two-tailed, unpaired Mann-Whitney, 2-way ANOVA with Tukey's post-test and Pearson's correlation coefficient, as appropriate.

Results: cGVHD patients had significantly elevated serum levels of IL-34 (n=18) compared to healthy controls (n=8) (P=0.0042; median of 12.43pg/ml, IQR 7.37-16.70 vs 0pg/ml, IQR 0-5.7 respectively). Sub-analysis by grouping patients according to whether IL-34 levels were above (IL-34^{hi}) or below (IL-34^{lo}) the median at pre-ECP baseline, showed IL-34 was significantly higher in ECP-treated IL-34^{hi} patients at month 9 (p=0.0392). In contrast, similar analysis of elafin in matched serum samples revealed that elafin^{hi} patients had a significant reduction in elfain levels after 3 months of ECP (P=0.0098; mean±SD: 48.51±36.6ng/ml vs 22.91±13.44ng/ml, respectively), which was sustained up to 6 months (P=0.0297; mean±SD: 26.18±15.47ng/ml), whereas, elafin^{lo} patients (mean±SD: 11.02±5.29ng/ml) showed no significant change over the same period. Although keratinocytes produce both IL-34 and elafin there was no correlation between them (r=0.16). Where clinical data were available, there was no correlation between IL-34 and Modified Rodnan's skin score (r=0.14;n=10). However, there was a significant inverse correlation between IL-34 and FEV1 pre-ECP (r=-0.62;P=0.0234;n=13).

Conclusions: As previously reported in different autoimmune diseases including systemic sclerosis, serum IL-34 was significantly elevated in cGVHD patients compared to healthy controls. Further, pre-ECP IL-34 concentration was significantly inversely correlated with FEV1 in the absence of lung cGVHD. Whereas ECP was associated with a significant reduction of serum elafin in elafin^{hi} patients up to 6 months, consistent with lack of correlation, there was no reduction in serum IL-34 suggestive of both the different modes of release and respective roles in cGVHD.

Disclosure: NCM has received grant funding and attended advisory board for Mallinckrodt. CB has received grant funding from Mallinckrodt. AA has received speaker fees and grant funding from Mallinckrodt.

P226

Impact of Upper and Lower Acute Gastrointestinal graft-versus-host Disease on Grading And Outcome of Allogeneic Stem Cell Transplantation: A Retrospective Analysis in 122 Consecutive Patients

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Background: Acute graft-versus-host disease (aGVHD) is the leading cause of morbidity and mortality in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT): gastrointestinal (GI) aGVHD plays a pivotal role on outcome. The adverse prognostic role of lower GI aGVHD is well established while the influence on outcome played by upper GI aGVHD remains uncertain.

Methods: We retrospectively analyzed outcomes of 122 consecutive adult patients undergoing allo-HSCT between January 2015 and August 2019 in our center. Primary endpoint was to assess the differential prognostic role of upper and lower GI aGVHD in terms of non-relapse

mortality (NRM); secondary endpoints were to evaluate the 2-years overall survival (OS) and relationship between aGVHD grading and outcome.

Results: With a median follow up of 29 months, 73 patients (60%) developed aGVHD. Overall 34 patients developed GI aGVHD, 14 of them involving both upper and lower aGVHD, diagnosed at the same time. 28 patients (23%) developed upper GI aGVHD and among them, grade 2 and grade 3-4 aGVHD were diagnosed in 19 and 9 patients, respectively. Upper GI aGVHD occurred in combination with low stage (1-2) skin aGVHD in 10 patients and in 3 patients occurred as isolated: these patients received diagnosis with grade 2A aGVHD. Incidence of lower GI aGVHD was 16% (20 patients): 12 patients presented stage ≤ 2 GI aGVHD (10%) and 8 patients presented stage 3-4 GI aGVHD (6%). No patients developed lower GI aGVHD after diagnosis of upper GI aGVHD: all patients with isolated upper GI aGVHD obtained a complete response with oral beclomethasone.

Overall 12-months NRM was 29%. All the 13 patients with grade 2A aGVHD at 12 months were alive, while 12-months NRM of patients who developed grade 0-1, 2B and 3-4 aGVHD was 18%, 38% and 53%, respectively ($p< 0.001$). Patients with diagnosis of lower GI aGVHD had the highest 12-months NRM (58%).

2-years OS of the entire cohort was 50%. Selected patients by aGVHD grading, 2-years OS in patients developing grade 2A aGVHD was similar to patients with grade 0-1 aGVHD (63% vs 61%, respectively, $p=0.39$), while it was higher as compared to patients developing grade 2B (63% vs 44%, $p=0.08$) and grade 3-4 aGVHD (63% vs 24%, $p=0.003$).

Conclusions: GI aGVHD remains an important obstacle to the success of allo-HSCT, in particularly lower GI aGVHD represents a potentially fatal complication of allo-HSCT. Upper GI aGVHD presents a minor impact on survival and patients with aGVHD classified as grade 2A have similar outcome as those with lower grade aGVHD.

Disclosure: Nothing to declare.

P227

Preliminary Experience with the use of Ruxolitinib, Ibrutinib or Imatinib for the Treatment of Acute or Chronic GVHD

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Background: Steroid-refractory (SR) GvHD after alloHSCT is a major challenge and is associated with significant morbidity and mortality. There is no therapeutic standard defined beyond calcineurin inhibitors (CNI) and steroids.

The aim of the study was to analyze patients treated with ruxolitinib, ibrutinib or imatinib for acute or chronic GVHD at our institution between September 2014 and September 2019.

Methods: We conducted a retrospective study on 29 patients (median age 49 years, range 18-67) with haematological malignancies [n= 9 (31%) AML, n=8 (28%) HL/NHL, n=5 (17%) MDS, n= 4 (14%) ALL, n=2 (7%) MPN, n=1 (3%) MM] who received ruxolitinib, ibrutinib or imatinib for the treatment of SR acute or chronic GVHD. Response was assessed in patients treated for a minimum of 30 days. Donors were matched sibling (n=13), matched unrelated (n=13) or haploidentical (n=3). Patients received either myeloablative (86%) or reduced intensity (14%) conditioning. GVHD prophylaxis included CNI-MTX (n=15, 52%), CNI-MTX-ATG (n=10, 34%), CNI-MMF (n=4, 14%) and post-transplant cylophosphamide in haploidentical HSCT. Stem cell source was peripheral blood for all patients.

Results: Eight patients received ruxolitinib for SR grade III-IV aGVHD. One died of SR-aGVHD before completing 30 days of treatment. Among 7 evaluable patients, the ORR was 72% (n=3 CR, n=2 PR); 1 patient had SD and 1 patient PD. Five patients were able to discontinue steroids after a median of 44 days (range 14-128), one patient died during steroid tapering. Median duration of treatment with ruxolitinb was 55 days (range 30-205).

Overall, 21 patients with cGVHD were treated with ruxolitinib (n=11), ibrutinib (n=7) or imatinib (n=10); 5 patients were treated with more than one study drug for intolerance or lack of response to previous drugs. One patient received imatinib as first line therapy for steroid intolerance.

Patients presented moderate (n=7) or severe (n=14) cGvHD and the median number of previous therapies was 3 (range 1-6).

Eleven patients discontinued the study treatment: 5 due to side effects, including nausea, neutropenia, gastrointestinal symptoms and 6 for inefficacy.

Results are presented in Table 1.

cGVHD	Ruxolitinib (11)	Ibrutinib (7)	Imatinib (10)
Steroid-dependent cGVHD	3	0	3
Median dose of steroids at time of initial treatment (mg/kg/die)	1 (0.5-1)	0	0.5 (0.1-1)
	0.2 (0-0.4)	0	0.3

cGVHD	Ruxolitinib (11)	Ibrutinib (7)	Imatinib (10)
Median dose of steroids after 3 months of treatment (mg/kg/die)			
Number of patients discontinuing steroids	2 (67%)	0	2 (67%)
Steroid-refractory cGVHD	8	7	7
ORR	37.5% (1CR, 2 PR)	43% (3 PR)	14% (1 PR)

[Table 1]

Conclusions: Our preliminary results suggest that ruxolitinib is a safe and effective option for the treatment of SR-aGVHD. Two thirds of the patients receiving ruxolitinib/imatinib for steroid dependent GVHD were able to discontinue steroids. A favorable ORR has been observed in patients with SR-GVHD with rates ranging from 14% to 43%. A larger number of patients is required to confirm our results.

Disclosure: Nothing to declare.

P228

Ruxolitinib with or without Ibrutinib as an Alternative First Line Therapy free of Corticosteroids or Calcineurin Inhibitors in Treatment of Acute graft-versus-host Disease

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Background: Acute graft-versus-host disease (aGVHD) is a common and serious life-threating complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Corticosteroids(steroids) and calcineurin inhibitors(CNIs) are the primary therapy of aGVHD, but they have several side-effects, especially the increased risk of infections, relapse(Deeg, Blood 2007). Janus kinase (JAK) 1/2 has been implicated in the pathogenesis of aGVHD via common gamma chain signaling and dendritic cell activation(Spoerl et all, Blood 2014). Ruxolitinib is an oral JAK 1/2 inhibitor, currently approved for the treatment of myelofibrosis and salvage therapy of steroid-refractory aGVHD(Zeiser et all, Leukemia 2015). Ibrutinib is an irreversible molecular inhibitor of Bruton tyrosine kinase(BTK) and interleukin-2-inducible T-cell kinase(ITK), which targets B cell, Th2 cell, and become a FDA-approved second-line therapy for steroid-resistant chronic GVHD(Miklos et all, Blood 2017). We evaluated the efficacy and safety of ruxolitinib with or without ibrutinib as an alternative primary therapy free of steroids or CNIs in patients with aGVHD.

Methods: We performed a respective study in 19 patients with aGVHD who had received ruxolitinib with or without ibrutinib as the first line therapy (Table 1). We evaluated the aGVHD responses across involved organ, infection, primary disease relapse, survival, and treatment-related side effects after treatment with ruxolitinib or ruxolitinib plus ibrutinib. Ruxolitinib at a daily dose of 5mg to10mg, and ibrutinib 140mg per day was administered orally until GVHD progression or the development of unacceptable toxic effects.

Results: At a median follow-up of 11.5 months (range, 10-19.5months), after the patients received ruxolitinib alone or the combined treatment; the overall response rate was 100%; the complete response of ruxolitinib group is 84.62% (11/13), and the combined group is 83.33% (5/6). The median time to a minor response was 4(3-7) and 5.5 (2.75-11.25) days respectively. All involved organs responded to treatment. Specifically, the Tacrolimus (FK-506), Cyclosporine (CSA) and Mycophenolate mofetil (MMF) dose was reduced more than half in 55.56% (5/9),75% (3/4), and 30% (3/10) of patients taking ruxolitinib, and 80% (4/5) of patients receiving the combination ruxolitinib and ibrutinib reduced the does of FK-506. Besides, 35.71% (5/14), 25% (1/4), and 26.67% (4/15) responders discontinued FK, CSA, and MMF respectively. No patients died during study treatment period or follow-up. The most common adverse events during follow-up were thrombocytopenia (in 5.26%); other adverse reactions were insignificant.

Conclusions: Ruxolitinib or ruxolitinib plus ibrutinib is an effective substitute for steroids or CNIs as first line therapy, and safe in patients with aGVHD.

Characteristics	Total (N=19)
Median age (range), year	31 (22-45)
Male/female	12 / 7
Mean follow up time(range), month	11.5 (10-19.5)
Underlying diagnosis AML ALL MDS NHL CML	7 (36.84%) 5 (26.32%) 2 (10.53%) 3 (15.79%) 2 (10.53%)
Stem cell source PB PB+BM	13 (68.42%) 6 (31.58%)
The courses of GVHD After HSCT Reduce the dose of FK/CSA Discontinue FK/CSA Others	5 (26.32%) 12 (63.16%) 1 (5.26%) 1 (5.26%)
The grade of GVHD II III IV	12 (63.16%) 4 (21.05%) 3 (15.79%)

Characteristics	Total (N=19)
Involved organ Skin Liver Gastrointestinal	17 (89.47%) 6 (31.58%) 2 (10.53%)
Number of involved organs 1 2 ≥3	13 (68.42%) 5 (26.32%) 1 (5.26%)

[Table 1. Clinical characteristics of the patients]

Disclosure: The authors declare. no competing financial interests.

P229

Calcineurin-inhibitors or Sirolimus PTCy-MMF Based GVHD Prophylaxis: Comparative Study in 132 Pts

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Background: Haploidentical stem cell transplantation (haplo-SCT) using post-transplant cyclophosphamide (PTCy) has spread rapidly worldwide. Nevertheless, studies comparing different GvHD prophylaxis regimens are lacking. We aimed to evaluate two regimens using either tacrolimus (FK506) or cyclosporine (CS) compared to sirolimus in addition to PTCy and Mycophenolate (MMF) in terms of engraftment, acute and chronic graft-versus-host disease (aGvHD and cGvHD) and endothelial complications.

Methods: One-hundred and thirty-two consecutive adult patients receiving a haplo-SCT as their first allogeneic transplant between January 2012 and December 2018 were included in this study. Thirty-five patients were transplanted at center #1 and received either CSA or FK506 (platform-1) as GvHD prophylaxis, 97 patients were transplanted at center #2 and received sirolimus (platform-2) as GvHD prophylaxis. Furthermore, in both centres GvHD prophylaxis relied upon PTCy (day +3 and +5 in platform 1, day +3 and +4 in platform 2).

Results: Median age was 59 (25-69) yrs for platform-1 and 57 (19-76) yrs for platform-2 (p=0,593). Stem cell source was bone marrow for platform-1 and peripheral blood for platform-2. Thirty out of 35pts (86%) in platform-1 received a busulfan-based conditioning regimen while 94 out of 97pts (97%) in platform-2 received a treosulfan-based regimen. Neutrophil (PMN) engraftment on day +30 was not statistically different from platform-1 and platform-2 and was 84+/-6% and 82+/-4%, respectively (p=0.553). Instead, platelet (PLT) engraftment at day +30 was higher for platform-2 (61+/-5%) compared to platform-1 (53+/-9%) (p=0.004). On day +60 PMN engraftment was 95+/-5% and 97+/-2% (p=0.553) and PLT engraftment 73+/-8% and 85+/-4% (p=0.004) for platform-1 and platform-2, respectively. Cumulative incidence (CI) of day +100 aGvHD 2-4 and 3-4 was similar between the two groups and was as follows: 41 +/-10% for platform-1 and 40+/-5% for platform-2 (p=0.61), and 14+/-7% for platform-1 and 25+/-5% for platform-2 (p=0.18), respectively.

In multivariate analysis we didn't find any risk factors neither for aGvHD 2-4 or for aGvHD 3-4.

The 2-year CI of moderate-severe cGvHD was 35 +/-12% in platform-1 vs 48+/-6% in platform-2 (p=0.366). In multivariate analysis risk factors for a higher CI of moderate-severe cGvHD was a previous aGvHD 2-4 (HR 1.04; CI: 1.008-1.074, p=0.013).

Hemorrhagic cystitis occurred in 6 out of 35pts (17,1%) in platform-1 and in 14 out of 97pts (14.4%) platform- 2 (p=0,445). Overall 9 out of 132pts (7%) developed endothelial complications, 7 out of 35pts (20%) in platform-1 (20%), 2 out of 97pts (2,1%) in platform-2 (p= 0,001). For both platforms endothelial complications were associated to transplant related mortality (TRM): 8 out 9 patients with endothelial complications died for TRM (6 in platform 1, 2 in platform 2) and five out 8 patients died before day +100. All patients who experimented endothelial complications in platform-1 have received a busulfan-based conditioning regimen.

Conclusions: The association of both calcineurin-inhibitors or sirolimus to PTCy and MMF gives similar results in terms of aGvHD and cGvHD incidence after unmanipulated haplo-SCT. Patients receiving calcineurin-inhibitor-based GvHD prophylaxis showed higher incidence of endothelial complications.

Disclosure: Nothing to declare.

P230

Impact of KIR/HLA Incompatibilities after Posttransplant Cyclophosphamide based T cell-replete Haploidentical Hematopoietic Stem Cell Transplantation

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Background: Posttransplantation cyclophosphamide (PTCy) based T cell replete haploidentical (haplo) hematopoietic stem cell transplantation (HSCT) is a valid option for patients with indication for allogeneic HSCT without a human leucocyte antigen (HLA) matched donor. The impact of killer cell immunoglobulin-like receptor (KIR)/HLA incompatibilities (inc.) in this setting is unclear. Russo et al. (Blood 2018) reported that PTCy eliminates most mature donor NK cells infused with the graft, including single KIR^+ NK cells, thereby blunting NK cell alloreactivity. Aims of our study were to evaluate the impact of (i) KIR/HLA inc., (ii) donor KIR genotype and (iii) HLA-DP mismatch status on outcome in our homogeneously treated, independent patient cohort.

Methods: We retrospectively analyzed the outcome of 51 consecutively transplanted patients (AML/MDS (n=28/5), ALL (n=9), HD (n=2), NHL (n=5), CML (n=1), PMF (n=1)) receiving a PTCy based T cell-replete haplo HSCT between 01/2011-12/2018. All patients received a myeloablative conditioning regimen (fludarabine/total body irradiation or thiotepa/busulfan/fludarabine) with unmanipulated bone marrow (98%) as the preferred graft (median CD34+ cells: 3.02 x 10^6/kg (range, 1.50-6.90) and median CD3+ T cells: 3.54 x 10^7/kg (range 1.52-43.74)). GvHD prophylaxis with cyclosporine A started on day 0, mycophenolate-mofetil on day +1, PTCy was applied on day +3 and +5.

Results: Patient, donor and transplant characteristics were well balanced between the inh. KIR/HLA inc. group (n=29) vs. no inh. KIR/HLA inc. group (n=22) with the exception of the median donor age (41.7 (range, 23.4-73.7) vs. 33.6 (range, 19.0-56.2), resp. All patients engrafted. At day +28 (range, 20-29; n=26) CD3+ cells were 88.5/nL (range, 3-665), CD3+CD4+ cells 22.5/nL (range, 0-277.0), CD3+CD8+ cells 117.0/nL (range, 7-478), CD19+ cells 1.0/nL (range, 0-12), $CD56^{bright}$ cells 74.4/nL (range11.1-93.4), $CD56^{dim}$ cells 25.5/nL (range, 6.4-88.9) measured by flow cytometry and without differences between the inh. KIR/HLA inc. group vs. no inh. KIR/HLA inc. group. CMV reactivation occurred in 73.3% of patients at risk and median time of occurrence was 32 days (range, 12-97) without difference between groups. Median follow-up for surviving patients was 26.1 months (range, 2.8-92.8) and we found no significant differences in 2-year overall survival (OS; 65.3±10.3 vs. 89.6±7.0, p=0.311), 2-year relapse-free survival (RFS; 66.0±9.4 vs 77.8±10.2, p=0.235), GvHD- and relapse-free survival (GRFS; 48.4 ±9.8 vs 60.5±12.0, p=0.182) as well as cumulative incidence in relapse (23.3% vs 16.2%, p= 0.283), acute GvHD grade 2-4 (27.6% vs 31.8, p=0.563), moderate-severe chronic GvHD (22.2% vs. 9.9%, p=0.227) and NRM (16.3% vs 5.3%, p=0.283) between the inh. KIR/HLA inc. group vs. no inh. KIR/HLA inc. group. This was also the case for donor KIR genotype AA vs AB (n=46; 2-y OS: 74.9±13.0% vs. 73.0±9.9%, p=0.844; 2-y RFS: 60.0 ±14.8% vs 74.5±8.4%, p=0.645) and HLA-DP-ident/permissive mismatch vs non-permissive (n=45; 2-y OS: 70.7 ±10.0% vs 72.7±13.4%, p=0.945; 2-y RFS: 73.2±8.2% vs 63.6.0±14.5%, p=0.798)

Conclusions: In our limited patient cohort, we did not find significant differences in clinical relevant HSCT outcomes supporting the hypothesis of PTCy eliminating mature donor NK cells infused with the graft and thereby reducing the impact of alloreactivity in this setting.

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Elevated PTH Levels among Chronic graft-versus-host Disease Patients and other Long term Survivors after Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Chronic Graft-versus-Host disease (cGvHD) is the leading cause of late non-relapse morbidity and mortality following allogeneic hematopoietic stem cell transplantation (alloHSCT). Metabolic bone disease is frequently seen after alloHSCT and is related to vitamin D deficiency and to GvHD - especially corticosteroids therapy and gastrointestinal (GIT) involvement. Elevated parathyroid hormone levels (PTH>6 pmol/L) were noticed alongside vitamin D deficiency presumably causing excessive bone resorption. However, high PTH level could be also a marker of systemic inflammation in cGvHD. In this study we investigated an association of cGvHD and vitamin D with PTH levels among long-term alloHSCT survivors.

Methods: Data were collected on a prospective cross-sectional study protocol in patients who underwent alloHSCT and were evaluated by the institutional multidisciplinary cGvHD team from 6/2013 to 11/2019. Laboratory tests and detailed history were obtained, and patients with cGvHD were evaluated according to NIH 2005 criteria. Exclusion criteria were active acute GvHD, and for non-cGvHD group of patients also ongoing immunosuppressive treatment.

Results: Study population consisted of 89 alloHSCT survivors (46% female), median age 48 (11-72) years, median of 672 (77-9478) days after alloHSCT. 62 (69.7%) had cGvHD and were evaluated at median of 376 (0-8869) days after the diagnosis was established. Majority of cGvHD patients had severe (38.7%) or moderate (38.7%) NIH global score, 41.9% had active cGvHD by clinician impression, and 58.1% were receiving systemic immunosuppression (41.6% of them corticosteroids). Median number of organs involved by cGvHD was 3, and most frequently involved organs were skin (58.0%), eyes (53.2%), and mouth (51.6%). GIT was involved in 11.3% of the patients. There was significantly more patients with history of acute GvHD ($p< 0.0001$), peripheral blood stem cell source ($p=0.0029$), higher median days from transplant to assessment ($p=0.0082$) and higher median age at assessment ($p=0.0083$) in cGvHD group. Elevated PTH was found in 25.8% of study population. Although PTH median levels were similar, (4.2 (0.2-16.05) in cGvHD vs. 3.9 (1.2-8.2) pmol/L in non-cGvHD group), elevated PTH levels were noticed in 32.3% cGvHD patients comparing to 11.1% non-cGvHD patients, but the difference did not reach statistical significance ($p=0.067$). Prevalence of vitamin D deficiency was 30.3% without significant difference between groups ($p=0.97$). PTH level has shown significant correlation with older age ($r=0.44$, $p< 0.0001$) and lower calcium level ($r=-0.297$, $p=0.0048$), but not with vitamin D levels ($r=0.027$, $p=0.8461$), NIH cGvHD global score ($p=0.1$), organ involvement (GIT $p=0.529$, others not shown), current use of corticosteroids ($p=0.83$) and intensity of immunosuppression ($p=0.267$).

Conclusions: Results of this study demonstrate elevated PTH levels among one in four of alloHSCT long-term survivors. Patients with cGvHD show a trend towards higher rates of elevated PTH levels than non-cGvHD patients. PTH levels correlate significantly with older age and lower calcium, but not with vitamin D levels or cGvHD severity. These results suggest other factors besides calcium metabolism driving PTH levels. The role of PTH as an inflammation marker after alloHSCT should be further investigated in larger cohort of patients.

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P232

Concurrence of GVHD and non-infectious Neurological Complications of Hematopoietic Cell Transplantation

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Background: Graft-versus-host disease (GVHD) is a common occurrence after hematopoietic cell transplantation (HCT), however, the association, and the quantification thereof, of GVHD with certain post-HCT neurological complications (NCs) remains to be elucidated.

Methods: Herein, we conducted a systematic electronic search regarding the occurrence of non-infectious NCs and of GVHD in HCT recipients, gauging the concurrence of GVHD with each complication to establish a possible association.

The medical literature was searched as per the PICO criteria. Studies meeting the inclusion criteria consisted of case reports, case series, clinical trials, and retrospective studies; those excluded were systematic reviews, meta-analyses, review articles, and pre-clinical studies. Recipients of all modalities of HCT, autologous and allogeneic, were eligible for inclusion.

Complication	Comp+/aGVHD+ ---------- Total Comp+	Comp-/aGVHD+ ---------- Total Comp-	P-Value (by Z test) for aGVHD	Comp+/cGVHD+ ---------- Total Comp+	Comp-/cGVHD+ ---------- Total Comp-	P-Value (by Z test) for cGVHD
Seizures	37/50	30/139	P < .00001	17/21	4/18	P = .00024
PRES	43/69	203/552	P = .0002	3/17	41/207	P = .82588
MG	-	-	-	1/1	2/3	P = .50286
Stroke	-	-	-	-	-	-
PN	-	-	-	-	-	-

[GVHD occurrence rates, categorized by complication and the presence/absence thereof, with associated P-values, where applicable, for GVHD associations]

The NCs studied included: Seizures, Posterior Reversible Encephalopathy Syndrome (PRES), Myasthenia Gravis (MG), Stroke, and Peripheral Neuropathy (PN).

Medline and other databases were searched as per standard protocol. In all, articles from 1983-2017 were retrieved. As per a preliminary ruleset, data from 82 articles were extracted. Then, where available, data on the concurrent reportage by each such study of GVHD occurrence in patients both with and without the complication of interest were retrieved, to analyze a more natural post-HCT GVHD occurrence.

Results: aGVHD frequency per complication was as follows: Seizures (118/188; 62.77%); PRES (65/116; 56.03%); MG (8/10; 80%); Stroke (15/27; 55.55%); and PN (60/123; 48.78%). Corresponding cGVHD frequencies were as follows: 21/29 (72.41%); 15/69 (21.74%); 15/17 (88.24%); 8/27 (29.62%); and 74/103 (71.84%). Further analysis then, detailed in Table 1, of only those studies wherein there was equal reporting of the occurrence of GVHD in patient populations stratified as given above revealed a statistically significant association between the following: concurrence of aGVHD and PRES (P = .0002); cGVHD and seizures (P = .00024); and aGVHD and seizures (P < .00001). Unfortunately, lack of adequate data precluded analysis of the concurrence of GVHD with Stroke and PN, and of aGVHD with MG.

Conclusions: The occurrence of acute and chronic GVHD is prevalent amongst HCT recipients, with notable differences in frequencies amongst patients experiencing each NC studied. Furthermore, when analyzed according to a more natural distribution of occurrence borne out of stricter analysis criteria, a statistically significant association was established between the concurrence of GVHD and certain NCs.

This study underscores the importance of accurate reporting of GVHD in a precisely stratified HCT recipient population and increased awareness amongst treating physicians of the above-established associations.

Disclosure: Nothing to declare.

P233

Acute GVHD Incidence in Mismatched Unrelated Donor HSCT in Paediatric Ad Adult Patients: A Study from the Turin Metropolitan Transplant Center

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Background: The search for a full match unrelated donor (UD) may be difficult and sometimes an urgent HSCT is necessary. In order to proceed quickly to UD HSCT clinicians may accept mismatched donors. Here we report our multicenter experience in paediatric and adult patients given a mismatched UD (mUD) HSCT from 2012 to 2018.

Methods: One hundred and 11 patients received a mUD HSCT for malignant and non-malignant disease. Among diagnosis the main indication for mUD HSCT was acute leukemia (AML=42 and ALL=30), median age 33 years (range 1-69). Forty-six patients were below 18 years old. A total of 54 donor- recipient pairs were HLA-A mismatched (MMA), 24 for HLA-B (MMB), 29 for HLA-C (MMC), 25 for HLA-DQB1 (MMDQB1). Twenty-one patients received an HSCT with two MM involving both HLA-class 1 and HLA-DQB1, while 8 patients had a double MM over HLA-class 1. The GvHD prophylaxis was based on 2 approaches: Cyclosporin A-Methotrexate-Serotherapy (N=80) vs. Tacrolimus-Mofetil Mycofenolate-Cyclophosphomide post HSCT (N=31).

Each donor-patient pair were typed by high resolution DNA technique and each typing was confirmed by a secondary test in our laboratory according to the Italian Bone Marrow Donor Registry (IBMDR) indications. The primary

endpoint of this study was the acute GvHD (aGvHD) incidence while the secondary endpoints were the overall survival (OS) and the chronic GvHD incidence (cGvHD). Data are reported as median and ranges, while the incidence are reported as cumulative incidence and standard errors by using NCSS software. OS was calculated by SPSS statistics version 19. A P value below 0.05 was considered statistically significant.

Results: Four patients died before engraftment and finally they were excluded from the analysis (3%). The median day of ANC engraftment (>0.5x10^9/L) was achieved on day 16 (range 10-30) and platelets engraftment (>50x10^9/L) on day 21 (range 10-154). The median day of aGvHD occurrence was 23 (range 7-77), the median day of cGvHD occurrence was 141 (range 113-1400). The overall incidence of aGvHD II-IV was 29.1% (±0.047). It was 29.5% (±0.066) for MMA, 41.3% (±0.106) for MMB, 15.8% (±0.084) for MMC, and 28.6% (±0.092) for MMDQB1 (P=NS). When a double MM involving DQB1 was found, we had 26.3% (±0.104, P=NS). For the few patients with a double MM in HLA class 1, aGvHD incidence was 30% (±0.049, P=NS). When patients were stratified according to GvHD prophylaxis (CyA-MTX-ATG vs. Tacrolimus-MMF-Cyclophosphamide post HSCT) aGvHD incidence was 41.3% (±0.062) vs. 3.3% (±0.033, P< 0.000). The cGvHD incidence for all population was 28.5% (±0.047), whereas it was reduced to 10% when the GvHD prophylaxis with Tacrolimus-Mofetil Mycofenolate-Cyclophosphomide post HSCT was chosen (P=0.04). The 5-year OS for the entire population was 60% (±0.055).

Conclusions: The univariate analysis of our study confirms that a single MM do not impact significantly the aGvHD occurrence, but a trend for a lower GvHD II-IV risk for MMC and higher for MMB has been highlighted. Here we confirm the role of Tacrolimus-Mofetil Mycofenolate-Cyclophosphomide as sparing agent of early immunological complications.

Clinical Trial Registry: None

Disclosure: Nothing to declare.

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Practical Implementation of the NIH Diagnostic Criteria for Oral Chronic GVHD in a Multidisciplinary Team in the Late Follow Up of Allogenic HSCT Patients

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Background: Chronic graft versus host disease (cGVHD) is a major cause of late non-relapse morbidity and subsequent mortality after allogeneic hematopoietic steam cell transplantation (HSCT). Its incidence has an average of 50% depending upon donor and transplant characteristics. Although it can be a multiorgan disease, skin and mouth are the most affected sites and also might be the first place where it presents or persist during systemic remission. The study aimed to describe the experience of a multidisciplinary team and the application of the National Institutes of Health (NIH) diagnostic criteria for oral cGVHD.

Methods: 192 patients who attended routine consultations between 2017 and 2019 were evaluated. Oral exam was performed as part of the clinical examination using a flashlight, gauze and wooden spatula. Criteria used for clinical diagnosis were based on the NIH diagnostic criteria for cGVHD of 2005 revised in 2014.

Results: A total of 192 patients were evaluated, 60.9% men and 39.1% women, with an average of 10 years follow up (1±23). 83.3% (n=160) developed cGVHD (skin, mouth, liver, lung, eye, gastrointestinal tract, joint/fascia, genital) being skin and mouth the most affected areas. Oral cGVHD developed concomitantly with other sites in 96 patients and was graded accordingly to the NIH diagnostic criteria that stated the presence of lichen planus-like changes, characterized by hyperkeratotic white lines and lacy-appearing lesions observed mainly on the buccal mucosa and tongue in approximately 70% of all patients diagnosed with cGVHD. Most patients (70%) scored 1, being mild symptoms but not limiting oral intake and nearly 27% of patients scored 2 showing moderate symptoms with partial limitation of oral intake. 3 patients scored 3 with severe symptoms and major limitation of oral intake. All patients with scores 2 and 3 showed other features like ulcerations and major erythema. Common features according to the NIH criteria were xerostomia 67,7% followed by mucosal atrophy 67,7%, ulcers 24% and mucocels 5,4%. The latter was more patient referred due to the rapid cycle of evolution. In about 65% of the cases there was a combination of these features. Oral biopsies were performed in 26 patients in which there was a need to rule out other diseases and/or to discard malignancy.

Conclusions: Diagnosis of oral cGVHD should be performed based on history and clinical examination by a qualified professional and, when appropriate, ancillary tests like a oral biopsy should be considered to confirm the disease and rule out differential diagnosis. It is important to emphasize the increased risk of oral cancer related to the history and the treatments for cGVHD and the mouth is one at the most high risk sites. Patients undergoing HSCT must be accompanied by a multidisciplinary team, critical to the treatment and improvement of comorbidities involved and the specialized oral medicine professional should be closely

inserted to the team in order to perform early diagnosis of oral GVHD, as well as act in local management of this condition, whose early and correct diagnosis is essential for survival with satisfactory quality of life.

Disclosure: Nothing to declare.

P235

The Impact of antibiotic-mediated Modification of the Intestinal Microbiome on Outcomes of Allogeneic Hematopoietic Cell Transplantation: Systematic Review and meta-analysis

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Background: Accumulating evidence point towards a protective role of intestinal microbiota diversity on outcomes of allogeneic hematopoietic cell transplantation (alloHCT).

Methods: The primary outcome of this systematic review and meta-analysis is to measure the effect of the intestinal microbiome modification caused by antibiotics on main alloHCT outcomes [graft-versus-host disease (GVHD), treatment-related mortality (TRM), overall survival (OS)]. The secondary outcome concerns the association of antibiotic-mediated disruption of microbiota as indicated by microbiome markers with alloHCT outcomes.

We searched MEDLINE, COCHRANE, EMBASE through 14th of October 2019 for eligible randomized controlled trials (RCTs), case-control or cohort (prospective/retrospective) studies that investigate the role of antibiotics and microbiome (as expressed though cultures or markers) on alloHCT outcomes. We excluded only editorials, case report/series studies and narrative reviews. Two independent reviewers screened, extracted data and assessed risk of bias (RoB).

Results: Among 402 screened references, 23 studies we deemed eligible for qualitative synthesis; 15 of which were included in meta-analysis. The impact of gut decontamination (measured by genomic or non-genomic markers of microbiota diversity) on GVHD or OS has been analyzed in 14 studies; among them 2 were RCTs.

In studies with non-genomic markers, the gut decontamination group tended to have a favorable outcome despite the lack of statistical significance [OR 0.42 (0.13, 1.27), I^2= 48%, p=0.12, Graph]. However, in recent studies which used genomic markers, the occurrence of grade II-IV acute GVHD was significantly reduced in patients not receiving broad-spectrum antibiotics as prophylaxis or treatment [OR 1.59 (1.22, 2.08), I^2= 0%, p=0.0006, Graph]. When we incorporated RoB on the outcome of intestinal GVHD, we found a positive correlation of intestinal GVHD with gut decontamination [OR 1.77 (1.29, 2.44), I^2= 0%, p=0.004]. Patients who received antibiotics as prophylaxis or treatment of neutropenic fever had 10% reduction on OS [RR 0.90 (0.77, 1.06), I^2= 78%, p=0.23] compared with controls. Nevertheless, heterogeneity remained high and the outcome was not statistically significant even after the incorporation of RoB, or subgroup analysis of genomic versus non-genomic microbiota methods. Moreover, we confirmed that antibiotic administration increased the risk of TRM by 75% [RR 1.75 (0.96, 3.17), I^2= 75%, p=0.07]. Patients with higher microbiota diversity had 86% increase in OS compared to patients with lower diversity [RR 1.86 (0.94, 3.66), p=0.07]. Nevertheless, heterogeneity was high (I^2= 88%) due to the lack of a unanimous approach regarding the definition of microbiota diversity. Unfortunately, data were not sufficient to estimate the effect of microbiota on TRM.

Conclusions: Our systematic review and meta-analysis confirms that broad-spectrum antibiotics increase the incidence of acute GVHD. Similarly, gut decontamination increases the risk of intestinal GVHD. Despite trends toward statistical significance, available data are not sufficient to support an association of microbiota diversity with TRM and OS. Further RCTs using standardized markers of microbiota diversity are needed to clarify its impact on survival.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare.

P236

Clinical Application of Mesenchymal Stem Cells from Wharton's Jelly in Patients with graft-versus-host Disease

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Background: Mesenchymal stem cells (MSCs) provide an interesting therapeutic option to treat acute (aGvHD) and chronic (cGvHD) graft-versus-host disease (GvHD). MSCs isolated from Wharton's jelly (WJ-MSC) are a preferable because of the ease and safety of the harvesting procedure, and the high number of cells in the umbilical cord. Here, we present the results of the clinical application of WJ-MSCs in patients with GvHD.

Methods: WJ-MSCs were derived from third party unrelated donors. The intravenous injections were used as salvage therapy in 35 patients, refractory to earlier-line GvHD therapy. The median age was 7.04 years at transplantation and 7.96 years at the first infusion. The patients were divided into two groups based on primary disease: hematological malignancy (HM) (patients with ALL, AML, MDS, ALCL, MPF, or CML) and non-hematological malignancy (NHM) (patients with SCID, WAS, HLH, SAA, CGD, or MPS1). Thirty-one patients were diagnosed with aGvHD (12 with grade IV, 17 with grade III, 2 with grade II) and 7 patients with cGVHD (6 with extensive cGvHD). Almost all patients expressed steroid-refractory disease (23/25 in the HM group and 10/10 in the NHM group). Adverse events (AE), health condition improvement, drug demand, and mortality rate were recorded. The effects of therapy were clinically evaluated.

Results: The median dose of WJ-MSCs was 1.86×10^6 cells/kg body mass. In the HM group, 9 patients had 1 infusion, 8 received 2, 4 received 3, 1 had 4, 1 had 5 and 2 had 6. In the NHM group, 2 patients had 1 infusion, 1 had 2, 6 had 3, and 1 patient had 6. One patient in the HM group reported AE (anxiety, feeling unwell, facial flushing, tightness in the chest). Twenty patients experienced overall improvement (11 in the HM group and in 9 in the NHM group). After treatment, the number of patients with grade IV GvHD decreased from 12 to 5, and those with grade III GvHD decreased from 17 to 3. In.5 patients, symptoms decreased from grade III to I, in 2 from IV to III, in 2 from III to II and in 1 from IV.to.I. Symptoms completely subsided in 9 patients (5 patients with III, 2 with IV and 2 with II grade at baseline). The demand for other drugs decreased in 11 (11/25) patients in the HM group and in 9 (9/10) patients in the NHM group. In the HM group, improvements were noted in skin lesions in 6 of 19 patients, diarrhea in 6 of 21 patients, decreased stool volume in 3 of 21 patients, and in liver functions in 1 of 6 patients. In the NHM group, skin lesions improved in 3 of 10 patients, diarrhea in 2.of.7, and the level of bilirubin in 2 of 3 patients. Eleven of 35 patients died: 9 in the HM group and 2 in the NHM group. The most common causes of death were sepsis (3 patients), kidney failure (2 patients), and sudden cardiac arrest (2 patients).

Conclusions: The infusion of allogeneic WJ-MSC in GvHD is a safe procedure with promising efficiency.

Disclosure: Michał Piątek, Izabela Zdolińska-Malinowska, Maciej Rojek and Dariusz Boruczkowski are employees of the Polski Bank Komórek Macierzystych S.A. (FamiCord Group), Warsaw, Poland

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Predictive Role of Endoscopic/histological Examinations for gastro-intestinal Acute Graft versus Host Disease after Allogeneic Stem Cells Transplant: "a Posteriori" Analysis in a Single Center

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Background: Gastro-intestinal complications, particularly GUT-GVHD, represent the main causes of morbidity and death in patients undergoing allo-HSCT, and the diagnosis of GUT-GVHD is often a challenge. Given the lack of non-invasive surrogate markers for the differential diagnosis with other HSCT complications, endoscopic and histological tools are often required A number of clinical experiences recognized rectal biopsy as the most performing test for diagnosis of GUT-GVHD, also in patients just with upper symptoms but these data are still limited.

Methods: Tha aim of the study was the analysis of endoscopic and histological diagnostic reliability in patients with a posteriori diagnosis of GUT-GVHD. We retrospectively analyzed data of 78 adult patients undergoing allo-HSCT for different hematological malignancies between January 2016 and December 2018 in Ancona University Hospital; 21 of whom undergo endoscopic examination for the suspicion of GUT-GVHD. In details, 19 received EGDS (esophagogastroduodenoscopy), 8 rectosigmoido/colonscopy, always with multiple biopsies sampling (random or lesion-guided); in 6 of them both examinations have been performed. The diagnosis of GUT-GVHD, established with "a posteriori" strategy was based on international[AO1] [GT2] or autoptic criteria, and confirmed in 13 patients.

Endoscopy was judged positive for GUT-GVHD when moderate/severe edema and/or erosions/ulcerations and/or

epithelial atrophy were found. Histology was judged positive when apoptotic figures and/or loss of glandular crypts and/or granulocyte infiltrate in the intestinal crypts were found with immunostagining negative for pathogens.

Results: Upper endoscopy showed 0.75 (CI95% 0.49-0.91) of sensitivity power and 0.43 of specificity (0.22-0.67) while lower endoscopy showed a 0.67 of power of sensitivity (0.29-0.92) and 1.0 of specificity (0.59-1.00). The addition of histology kept absolute specificity but with poor sensitivity (0.42 in the upper and 0.67 in the lower biopsies). The concordance with final diagnosis, calculated with Coen's k, reached a maximum of 0.5 for lower examinations (both endoscopy and histology). For patients undergoing both upper and lower endoscopies, histologic analysis reached 0.80 (0.34-0.98) of sensitivity and 1.0 of specificity. Positive predictive value was 1.0 (0.52-1.00) and negative predictive value 0.5 (0.14-0.86) with a concordance K of 0.57.

Conclusions: The simple endoscopic evaluation shows a poor diagnostic reliability for GUT-GVHD. The histology has good performance and moderate agreement with "a posteriori" diagnosis of GUT-GVHD. Therefore, in the evaluation of patients with suspected upper symptoms we suggest to proceed with EGDS and subsequently with rectosigmoido/colonscopy in case of negativity of first examination. Conversely in those patients with lower or generalized symptoms, we suggest to proceed with rectosigmoido/colonscopy. Moreover, the completion of the procedure with the biopsy sampling is mandatory, even in the absence of mucosal lesions.

Disclosure: nothing to declare.

P238

The Incidence, Risk Factors, and Outcomes of Acute graft-versus-host Disease in Pediatric Haploidentical Hematopoietic Stem Cell Transplantation

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Background: The specific description, risk factors, and outcomes of acute graft-versus-host disease (aGVHD) in pediatric haploidentical hematopoietic stem cell transplantation (haplo-HSCT) have not been well described previously.

Methods: We retrospectively evaluated the incidence, risk factors, and outcomes of aGVHD in 350 consecutive pediatric haplo-HSCTs (median age 11 years, range 1-17 years) using the Glucksberg and NIH aGVHD classifications between January 2015 and December 2017.

Results: The cumulative incidences of grade I, II, III, and IV aGVHD were 28%, 29.7%, 8.3%, and 5.1%, respectively. None of the considered variables significantly influenced the incidence of grade III-IV aGVHD. The 3-year overall survival (OS), disease-free survival (DFS), cumulative incidence of nonrelapse mortality (NRM) and relapse rate of the whole group were 77.2%, 75.6%, 6.9%, and 17.5%, respectively. The occurrence of severe grades of aGVHD (III-IV) significantly influenced NRM and survival in both malignant disease and nonmalignant diseases but did not influence the rate of relapse. The 3-year OS, DFS, NRM, and relapse rate between the severe grades of the aGVHD (III-IV) group and the grade 0-II aGVHD group were 65.6% vs. 80.1% ($P = 0.013$), 64.1% vs. 77.5% ($P = 0.015$), 19.3% vs. 5.0% ($P < 0.001$), and 16.7% vs. 17.5% ($P = 0.86$), respectively.

Conclusions: The incidence of aGVHD was similar regardless of malignant disease and nonmalignant diseases, and better prevention of severe grades of aGVHD (III-IV) needs to be explored.

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Prognostic CT findings around the Onset of Acute Gastrointestinal graft-versus-host Disease

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Background: Acute graft-versus-host disease (aGVHD) is an important complication after allogeneic stem-cell transplantation. GVHD is caused by alloreactive donor-derived T lymphocytes and involves various organs such as the skin, liver, and gastrointestinal (GI) tract. Among them, GI-aGVHD is associated with severe morbidity and ahigh rate of mortality. Abdominal CT has been the major modality, showing abnormal findings in GI-aGVHD which correlate with pathological and clinical grading. Despite noninvasive nature of CT, there are only a small number of reports discussing about the role of abdominal CT in the assessment and prognosis of patients with GI-aGVHD. The aim of this study was to analyze abdominal CT findings around the onset of GI-aGVHD.

Methods: Between 2010-2018, patients with a clinical diagnosis of acute GI-aGVHD were evaluated. Abdominal CT was performed within 6 days before or after the onset of GI-aGVHD. CTs were examined for intestinal and extra-intestinal abnormalities, and correlated with GI-aGVHD staging and outcome.

Results: Thirty-nine patients were included in this study. At the median follow-up of 454 days (range; 34-3119), estimated overall survival (OS) rate at 2 years was 52.6%. The median age of the patient was 45 years (range; 20-65 years). Median onset day of GI-aGVHD was 29 after allogeneic stem-cell-transplantation (range 10-103). Median abdominal CT performed day was 0 from the onset of GI-aGVHD (range -5 - 6). Thirty patients had GI-aGVHD clinical Stage 1-2 and 9 had Stage 3-4. Twenty-seven patients received systemic corticosteroid treatment for GI-aGVHD, and 7 of the patients needed additional treatment. Thirty-five patients had abnormal CT appearances. Ascites (n=16, 41%), gastric wall thickening (n=16, 41%), and large bowel dilatation (LBD) (n=14, 36%) were the most consistent findings. Other manifestations included large bowel wall thickening (n=12, 31%), small bowel wall thickening (n=10, 26%), small bowel dilatation (n=8, 21%), periportal edema (n=11, 28%), and biliary abnormalities (n=9, 23%). In a multivariate analysis using Cox regression model, patients with LBD [hazards ratio (HR) =3.18 (95%CI; 1.28-7.91), p=0.013] and ascites [HR=3.01 (95%CI; 1.24-7.32), p=0.015] were independently associated with worse OS. Six patients had both appearances and 2-year OS of these patients was 0%. LBD was associated with severity of GI-aGVHD (p=0.002) and lower response rate to corticosteroid treatment (p=0.038), while ascites was not statistically correlated with both factors (p=0.695 and 1.0, respectively).

Conclusions: Around the onset of GI-aGVHD, CT manifestations of LBD and ascites were associated with poor prognosis, especially when these factors exist concomitantly.

Disclosure: Nothing to declare.

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Thymoglobulin and Grafalon effect on Allogeneic Stem Cell Transplant - Pooled Data from Wroclaw Medical University, Poland and University Medical Center Ljubljana, Slovenia

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Background: Anti-thymocyte globuline is standard of care for graft versus host disease (GvHD) prophylaxis in the setting of allogeneic stem cell transplant (alloSCT). The aim of our retrospective study was to compare the impact of two formulations of rabbit anti-thymocyte globuline, Thymoglobuline Sanofi (Thymo) vs. ATG Grafalon (ATG-G), on the outcome of alloSCT in patients with acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS).

Methods: Patients with ALL, AML and MDS who underwent myeloablative (MAC) or reduced intensity conditioning (RIC) alloSCT from HLA identical siblings (SD), matched (10/10) unrelated donor (MUD) or mismatched (9/10) unrelated donor (mMUD) between November 2017 and November 2019 were included in the analysis. Data was collected from our institutional databases.

Results: We analyzed 118 patients with ALL (n=27), AML (n=76) and MDS (n=15). They received MAC (n=99), RIC (n=10) or reduced toxicity conditioning (n=9) for alloSCT and graft from SD (n=33), MUD (n=71) and mMUD (n=14). Thymo was used in 36/71 (51%) patients who were transplanted with MUD and 1/14 of patients (1%) transplanted with mMUD at the median dose of 5 mg/kg (range, 1,5-5). ATG-G was used in 11/33 (33%), 20/71 (42%), and 12/14 (86%) patients transplanted with SD, MUD, and mMUD, respectively, at the median dose of 30 mg/kg (range, 10-30). Two patients died before engraftment. No differences were found in severe clinically or microbiologically documented infections after Thymo and ATG-G treatment (11% vs. 10%, p=0.85) during aplasia.

Grade 2-4 acute GvHD was observed in 24/116 patients (21%), with no difference between patients treated with Thymo and ATG-G who had alloSCT with MUD (6% vs.13%, p=0.41). Extensive moderate or severe chronic GvHD occurred in 18 of 105 evaluable patients (17%), similarly with no differences between Thymo and ATG-G group (15% vs. 7%, p=0.40). In multivariate logistic regression analysis the only risk factor for G2-4 acute GvHD and moderate/severe chronic GvHD was treatment without ATG (OR 4.76, 95%CI 1.33-17.2; p=0.016, and OR 4.35, 95%CI 1.12-15.9, p=0.032, respectively). After the median follow-up time of 11 months overall survival (OS) and leukemia-free survival (LFS) rates in the whole study group at 18 months were 80% and 72%, respectively. The only adverse prognostic factor for OS and LFS was disease risk index (HR 3.28, 95% 1.64-6.57, p< 0.001, and HR 2.10, 95% 1.20-3.66, p=0.009, respectively). Non-relapse mortality (NRM) and relapse incidence (RI) in the whole study group was 9% (95%CI 5-16) and 15% (95%CI 9-25), respectively, with no significant differences found between two types of ATG in MUD alloSCT.

Conclusions: In summary, our results indicate that Thymoglobuline Sanofi and ATG Grafalon similarly decrease the risk of grade 2-4 acute GvHD and extensive moderate and severe chronic GvHD. Moreover, we did not find any differences in OS, LFS, NRM and RI after alloSCT in patients treated with Thymo and ATG-G.

Disclosure: Authors have no conflict of interest.

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The Role of low-dose Anti-thymocyte Globulin in Matched Sibling Donor Peripheral Blood Stem Cell Transplantation for Hematologic Malignancies

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Background: High chronic GVHD rates have been one of the major drawbacks for matched sibling donor peripheral blood stem cell transplantation.

Methods: To study the safety and efficacy of low dose Anti-thymocyte Globulin (ATG) as standardized part of the conditioning in patients with matched sibling donor peripheral blood stem cell transplantation,72 MSD-PBSCT patients or donors age ≥40 years with hematological malignancies who displayed similar baseline characteristics, either received rATG (n=42) or no ATG (n=30), in addition to cyclosporine, methotrexate and mycophenolate mofetil as standard GVHD prophylaxis regimen. The modifications included that the dose and type of ATG was 5mg/kg Thymoglobulin(rabbit ATG, Sanofi), and the timing was -5 and -4 before graft infusion.

Results: After a median follow-up of 874 days, the cumulative incidence of cGVHD were 37.3%(95% CI 17.8-57.0%) in ATG group and 52.1%(95% CI 31.0-69.5%) in no ATG group on 3-year respectively (p=0.00). The 3-year overall survival probability was 71.0 % (95% CI 56.3-89.4%) for the ATG group and 62.0 % (95% CI 46.5-82.6%) for the no ATG group (p=0•047). The 3-year disease free survival probability was 66.7 % (95% CI 51.4-86.7%) for the ATG group and 58.4 % (95% CI 42.8-79.7%) for the no ATG group (p=0•026). The 3-year GRFS probability was 66.7 % (95% CI 51.4-86.7%) for the ATG group and 40.0 % (95% CI 25.3-63.4%) for the no ATG group (p=0•000). There were no difference for the 2-year cumulative incidence of NRM and relapse between ATG group and no ATG group.

Conclusions: These data suggest that rATG at a 5mg/kg total dose administered over 2 days (day-5 to -4) for GVHD prophylaxis is well tolerable and efficacious in patients receiving MSD-PBSCT.

Clinical Trial Registry: ClinicalTrials.gov Identifier: NCT02677181

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P242

Nephrotic Syndrome after Allogeneic Stem Cell Transplantation as a form of Chronic Graft versus Host Disease: Single Center Experience

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Background: Chronic graft versus host disease (cGHVD) remains the leading cause of morbidity and late non-relapse mortality after allogeneic stem cell transplantation

	Case 1	Case 2	Case 3	Case 4	Case 5
Sex / Age / Disease	Female / 65 / MDS	Male / 53 / AML	Male / 50 years / Aplastic anemia	Female / 50 / MM	Male / 60 / AML
Donor type / SC Source	MUD 12/12 / PB	Identical sibling / PB	Identical sibling / BM	Identical sibling / PB	Identical sibling / PB
Conditioning régimen / GVHD prophylaxis	Fludarabine + Busulfan / CsA + MTX	Busulfan + Cyclophosphamide / CsA + MTX	Cyclophosphamide + ATG / CsA + MTX	Fludarabine + Melphalan / CsA +MTX	Cyclophosphamide + Busulfan / CsA + MTX
GVHD	No	No	Chronic	No	Acute
Months after transplant / Proteinuria gr/day	36 months / 8	30 months / 4.5	17 months / 15	12 months / 4	15 months / 8.9
Renal failure	No	Yes, mild	No	Yes	No
Renal biopsy (histology)	Membranous Glomerulonephritis	Membranous Glomerulonephritis	Minimal Change Glomerulopathy	Focal segmental glomerulosclerosis	Membranous Glomerulonephritis
Renal GVHD treatment	CsA + steroids	CsA + steroids	CsA + steroids	MMF + steroids	CsA + steroids + Photopheresis
Response / Evolution to chronic renal failure	Complete / No	Complete / No	Partial / No	Parcial / Yes Chronic renal failure on dyalisis Renal transplantation	Partial / No

[Patients, transplantation and renal GVHD's characteristics]

(AlloSCT). Nephrotic syndrome (NS) is a rare clinical manifestation of GVHD, with a reported incidence of around 1%.

Methods: We retrospectively analyzed 417 patients who underwent AloSCT in our center between January 2005 until December 2017. We found 5 cases of nephrotic syndrome (defined by proteinuria greater than 3.5 gr / day, edema, hyperlipemia and hypoalbuminemia) attributed to renal cGVHD, which means a prevalence of 1.19%. The initial symptoms was hypoalbuminemia +/- edema, confirmed with proteinuria and renal biopsy. Two of the 5 patients developed the NS during the decrease of immunosuppressive therapy; another at 2 months of donor lymphocyte infusion. The most frequent histology found was membranous glomerulonephritis and in one case focal segmental glomerulosclerosis. See table.

Results: All patients received steroids, associated with Cyclosporine (Mycophenolate mofetil in case of renal failure), in addition to support with ACE inhibitors or AIIRAs and statins. The response to immunosuppressive treatment was complete in 2 patients. In the case of myeloma, the worst evolution could be due to previous underlying renal damage due to the underlying disease and a possible worse prognosis of glomerulosclerosis, which eventually leaded to renal transplantation. The case 5 precised the addition of extracoporeal photopheresis because of steroids dependence, with extraordinary and rapid proteinuria improvement.

Conclusions: In our experience, NS as a form of cGVHD, is rare and appears late. It seems advisable to consider this manifestation, in case of hypoalbuminemia and edema, performing serial proteinuria and renal biopsy if proteinuria is demonstrated. More studies are needed to establish the most appropriate therapeutic regimen, as well as its duration, to avoid recurrences or long-term renal disfunction.

Disclosure: Nothing to declare.

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Correlation among Total Nucleated Cells (TNC), CD34+, CD3+ Cell Content in G-CSF-primed Bone Marrow Collections and their Relative Influence on Development of Acute GVHD

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Background: Traditionally the amount of stem cell product to be infused is calculated based on Total Nucleated Cell (TNC) count for bone marrow (BM) and CD34+ cells for Peripheral Blood Stem Cell collections (PBSC). CD3+ cell dose is another critical parameter associated with engraftment and Graft Vs Host Disease (GVHD) (Urbano-Ispizua et al. Blood 2001 Jan 15;97 (2):383-7). While most studies have correlated transplant

outcomes with one of the above measurements there is paucity of information on the relationship between the numbers of TNC, CD34+ and CD3+ cells in G-CSF-primed marrow collections, the degree of variation of the above cell populations among individuals and the relative influence of TNC, CD34+ and CD3 cell doses on the occurrence of aGVHD.

Methods: We analysed 96 successive bone marrow harvests done at Sankalp-People Tree Centre for Paediatric BMT where we routinely measured TNCs, CD34+, CD3+ cell count to see how they correlate with each other. We also studied the variations of CD34+ and CD3+ cell counts for a given TNC count range in the harvest sample. From our earlier analysis we recognised that poor quality marrow as defined by the ratio of marrow TNC to donor peripheral WBC count on the day of harvest less than 0.9 is a strong risk factor for GVHD (https://ash.confex.com/ash/2019/webprogram/Paper125111.html). Out of 73 consecutive matched sibling BMTs for low risk thalassaemia 16 were not included in this analysis because of suboptimal grafts as defined above and already at high GVHD risk. Finally, we compared TNC, CD34+ and CD3+ cell doses per kilogram weight of the recipient in 57 patients who received optimal quality marrow using logistic regression analysis to assess which of these cell doses best correlated with GVHD risk

Results: We observed a strong relationship between TNC count and CD34+ (p=0.0066) as well as CD3+ (p=0.0005) cell counts in G-CSF-primed marrow collections and even stronger relationship between CD3+ and CD34+ (p = < 0.0001) and CD4+ counts (p = < 0.0001). Though there was a strong correlation between these counts, we observed a significant variation in CD34+ and CD3+ cell content for any given range of TNC doses (Table 2). These variations were pronounced in good quality harvests as seen in the scatter diagrams (Fig 1-3). When TNC, CD34+ and CD3+ cell doses were compared in terms of aGVHD risk in patients receiving good quality marrow, only CD3 cell dose seemed to be relevant (p=0.0069) as opposed to TNC (p=0.9024) and CD34+ cell doses (p=0.9546) (Fig 4-6).

Conclusions: In G-CSF-primed bone marrow collections there is significant variations in CD34+ and CD3+ cell counts for any given range of TNC counts. With optimal quality marrow (day 0 marrow/donor WBC counts > 0.9) CD3+ cell doses had the strongest association with the risk of aGVHD compared to TNC and CD34+ cell doses. We advise to count CD3+ cells in G-CSF-primed BMTs in order to avoid the administration of excessive T-cells amounts and decrease GVHD risk.

Disclosure: No conflict of interests to disclose

P244

Prediction for Lethal Acute Graft versus Host Disease and non-relapse Mortality By Early Plasma Biomarkers; a Single Center Retrospective Study in Japan

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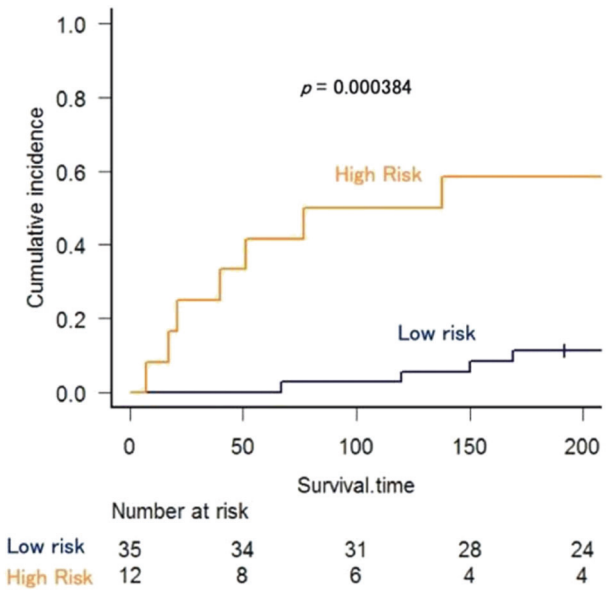
Background: Non-relapse mortality (NRM) such as severe graft-versus-host disease (GVHD) is a major cause of allogeneic HSCT(aHSCT). Nevertheless, no laboratory test can predict the risk of NRM and severe GVHD after aHSCT prior to the onset of GVHD symptoms. Recently reported 2-biomarker (ST2 and REG3α) algorithm (Hartwell et al. JCI Insight 2017) may predict severe GVHD early after aHSCT; however, it is unknown whether this algorithm (called MAGIC algorithm) is similarly available for Japanese patients. Thus, to elucidate the availability of this algorithm for Japanese patients, we performed this retrospective study.

Methods: We retrospectively analyzed consecutive 47 patients who received aHSCT at Kansai Medical University Hospital from July, 2010 until April, 2016. Plasma samples obtained 7 days after transplantation and measured the concentrations of ST2 and REG3a. The results of 2 biomarkers were analyzed with previously reported biomarker algorithm (Hartwell et al. JCI Insight 2017) to evaluate a risk of 6-month NRM for individual patients. GVHD clinical staging, NRM, relapse mortality, and overall survival (OS) were analyzed. Differences in cumulative incidence of NRM and relapse between HR and LR groups were calculated by Gray's test. OS was estimated by the Kaplan-Meier method and differences between groups were calculated using the log-rank test. This study was approved by the Research Ethics Committee of the Faculty of Medicine, Kansai Medical University.

Results: Of the 47 patients (male 24, female 23), the median age was 52.0 years (range, 22-69 years). Eleven patients received PBSCT from HLA matched-related donor, 24 patients received bone marrow transplantation from HLA-matched unrelated donor, and 9 patients received umbilical cord blood. Twenty patients received non-myeloablative conditioning regimen. The median survival time (MST) and 1-year OS rate were 375 days (range, 7-3236 days) and 53.2%, respectively. The overall cumulative incidences of 6-month NRM was 23.4%. The incidence of grade II-IV and III-IV acute

GVHD were 34%, and 14.9%, respectively. The median day of acute GVHD onset was 28 days after aHSCT. According to the biomarker algorithm, a threshold of $\hat{p} = 0.13$ separated high-risk (HR) and low-risk (LR) groups to identify a maximum number of HR patients with a near-maximum difference in NRM. Thirty-five patients were defined as LR group, and 12 patients were defined as HR group. The incidence of grade III-IV acute GVHD in LR group and HR group was 11.4% and 25%, respectively. Six-month cumulative incidence of NRM in HR patients was significantly higher than that of LR patients (HR: 58.3% vs. LR: 11.4%, $p< 0.001$), whereas the relapse rate did not differ between risk groups. HR patients were approximately 4 times more likely to die from GVHD than LR patients (HR: 33.3% vs LR: 8.6%, $p< 0.05$). Six-month OS rate was significantly worse in HR patients compared to LR patients (HR: 33.3% vs LR: 71.4%, $p< 0.05$).

Conclusions: A biomarker algorithm based on ST2 and REG3a measured 7 days after aHSCT can identify a HR group for GVHD and non-relapse mortality in Japanese patients.



[Figure 1]

Disclosure: Nothing to declare.

P245

Ruxolitinib in the treatment of corticosteroid-refractory graft-versus-host Disease (GVHD). One Single Center Experience

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Background: Corticosteroid-refractory GVHD is one of the main causes of non-relapse mortality and morbidity after allogeneic stem cell transplantation (allo-SCT). Treatment options are available with a response rate of 20-40%. The JAK1/2 inhibitor Ruxolitinib is being evaluated in clinical trials because of its potent anti-inflammatory properties.

Methods: We performed a retrospective cohort study of patients who underwent an allo-SCT between 2014 and 2018 and were treated with Ruxolitinib after being diagnosed of steroid-refractory GVHD.

Results: 17 patients were included, 10 women (59%)/ 7 men (43%), median age: 52 (19-73). Underlying disease: 7 (41%) AML, 3 (17.64%) MDS, 2 (11.76%) ALL, 2 T-non Hodgkin Lymphoma, 1 (5.88%) CML, 1 SMF and 1 PML. Disease status: 13 CR (76%). Type of HSCT: 5 HLA identical related donor (29.4%), 8 haploidentical (47.05%) and 4 unrelated donor (23.53%). Conditioning regimen: 13 myeloablative (76%), 4 reduced-intensity (24%). All patients were in complete response (CR) after transplant.

4 patients (24%) that developed acute GVHD were included: Grades II-IV 1 (25%) and 3 grades III-IV (75%). Organ involved: 1 Skin (25%) and 3 gut (75%). The majority of patients had chronic GVHD (n=13, 76%), between mild and moderate (50% each). Mucosal involvement was the most frequent in cGVHD (7 oral (53.84%) and 3 genital (23.08%).), followed by skin in 9 (69%) and lung in 5 patients (38.46%), also liver (n=3, 23.08%), pericardial and esophagus (1 each, 7.60%).

The 82.36% (n=14) of patients remained in corticosteroid therapy prior to the onset of Ruxolitinib, that was indicated after 3 prior lines of treatment in half of patients (n=9, and after 2, or more than 3 lines in the other half. The treatment was started after a median of 2 months (range 0-26) of the beginning of corticosteroids, the initial dose was 10 mg/ 12 h in the 82.35% (n=14) of patients. Monotherapy was used in the 29.4% (n=5), extracorporeal photopheresis (ECP) was the most frequent combination (41%, n=7). The dose of corticosteroids was reduced in 86.6% (n=13) and in 60% (n=9) of patients was withdrawn.

The median time on treatment was 5 months (range, 0.5 - 24 months).

The most frequent reasons for discontinuation were response (n=5) and infectious complications (n=4). Other reasons: Toxicity (2 hematological and 1 non-hematological), deaths (n=3) and non-response (n=1).

13/17 patients (70.6%) achieved a partial response (PR), 12 after 1 month of treatment and 1 after 3 months, 3 of them finished the treatment due to hematological toxicity, they persisted in PR. 2/12 PR patients achieved a CR after 3 months of treatment. 4 patients were non-responders: 2 died due to complications secondary to acute GVHD and 2 finished the treatment because of infectious complications.

Conclusions: Ruxolitinib is a useful and safe treatment strategy that can be incorporated from the 2nd line in steroid refractory GVHD in daily clinical practice, like we demonstrated in this retrospective study with a response rate of 70.6%. It is also an alternative to be explored in combination in prospective randomized trials.

Disclosure: Nothing to declare.

P246

Outcome of Patients alive at 1-year Post Allogeneic Stem Cell Transplantation: A Retrospective Analysis from a Single Institution

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Background: Allogeneic stem cell transplantation (allo-SCT) is associated with a significant number of life-threatening complications, especially within the first year. Patients alive after this period are expected to become long-term survivors. However, data on quality of life and occurrence of late-onset complications, including chronic GVHD or relapse, is scarce.

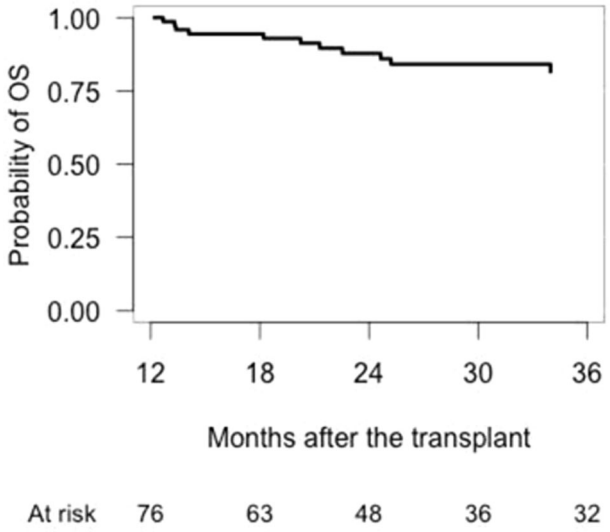
Methods: This retrospective study included all consecutive adult patients with haematological malignancies who underwent first allo-SCT at our institution between January 2015 and October 2018 and remained alive one year thereafter. Primary endpoints were OS and late-onset chronic GVHD. Secondary end points included NRM, cumulative incidence of relapse (CIR), DFS and GRFS.

Results: Seventy-six (69%) of the 111 patients who received an allo-SCT survived one year thereafter. Median age at transplant was 52 years (16-70). Most patients had either acute leukaemia (n=32, 42%) or lymphoproliferative disorders (n=28, 37%). Fifty-six (74%) recipients underwent RIC regimen, being TBF (24, 36%), CBF (13, 17%) and FluMel (13, 17%) the most common regimens used. Thirty (40%), 23 (30%) and 23 (30%) patients were allografted from MUD, MRD and Haplo, respectively. One year after the transplant, ECOG scale was 0 in 56 (74%) patients. Forty-four (58%) and 33 (43%) patients had previously developed acute or chronic GVHD, respectively. Thirty-two (42%) patients had active GVHD at that moment and 28 (37%) were still under immunosuppression (IS). Five (7%) of the patients had previously relapsed. At last control, sixty-five (85%) of the 76 patients remained alive with a median follow-up of 33 months (range, 13 - 56) after allo-SCT. The 3-year OS was 82% (95% C.I., 71-92%) (Figure 1). In multivariable analysis, absence or grade 1 transaminitis (HR 0.25, 95% C.I., 0.08-0.76, P = 0.01) and 1-year ECOG 0 (HR 0.3, 95% C.I., 0.11-0.81, P = 0.02) were the independent variables associated with OS. Interestingly, history of acute GVHD or use of IS at one year after transplant did not impact OS. Eleven patients died: seven (63%) of relapse, and 4 due to the following complications: GVHD (n=2, 18%), infection (n=1, 9%), and idiopathic encephalopathy (n=1, 9%). Late-onset chronic GVHD developed in 11 (29%) of 48 eligible patients (none of them severe). Only 3 (29%) of them required introduction or additional IS therapy. OS, GVHD and secondary end points are summarized in Table 1.

Conclusions: This study suggests that surveillance of late-onset chronic GVHD is mandatory, though the severity or the probability of using IS are low. Relapse is the major cause of mortality in survivors one year after allo-SCT, which hampers the clinical benefit for a small but significant part of patients.

Outcome	Eligible patients, n	3-year CI or probability, % (CI)
OS	76	82 (71-92)
Chronic GVHD	48	35 (18-52)
NRM	76	6 (0-12)
CIR	71	11 (3-20)
DFS	71	82 (71-92)
GRFS	44	76 (61-91)

[Outcomes at 3 years after the transplant]



[Overall survival at 3 years after the transplant]

Disclosure: Nothing to declare.

P247

Ruxolitinib in steroid-refractory Chronic graft-versus-host Disease: Experience in our Centre

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Background: Graft-versus-host disease (GVHD) is a mainly cause of morbidity and mortality in allogeneic hematopoietic stem cell transplantation (HSCT). Ruxolitinib is a selective JAK inhibitor that has been evaluated in recent years as rescue therapy in patients with acute or chronic GVHD in whom corticosteroids first-line treatment has not been effective.

Methods: A single-centre (Miguel Servet Hospital, Zaragoza, Spain), retrospective study was made including 7 patients who underwent an allogeneic HSCT, developed steroid-refractory chronic GVHD and received ruxolitinib after failure of previous treatments, between January 2015 and November 2019. Patient characteristics are shown in Table 1 and Image 1.

Results: Chronic GVHD was diagnosed between day 30 and day 669 (median: 162 days) after allogeneic HSCT. Organ-specific manifestations of chronic GVHD in our cohort of 7 patients were most commonly in skin, 85.7% (n=6), followed by 42.9% (n=3) with ocular disease. Liver, lung, upper gastrointestinal tract and musculoskeletal systems were involved in 14.3% (n=1). According to the international consensus of National Institutes of Health (NIH), the severity of the disease was moderate and severe in 28.6% (n=2) and 71.4% (n=5) of the cohort, respectively. The median of time since onset of GVHD to initiation of ruxolitinib was 748 days (range: 185-2312). Before ruxolitinib, patients had received a median of 5 previous lines of treatment (range: 2-9). The median ruxolitinib dose administrated was 20 mg daily. The median ruxolitinib therapy duration was 128 days (range: 21-1399). 85.7% (n=6) of our cohort received extracorporeal photoapheresis (ECP) before or during ruxolitinib administration. Over 85.7% (n=6) of the cohort was receiving corticosteroids at the time ruxolitinib therapy was initiated. 83.3% (n=5) of these patients had corticosteroids discontinuation during this line of treatment, between day 7 and day 300 (median: 30 days) after starting ruxolitinib. Overall response rates (ORR) were 85.7% (n=6), with complete response (CR) in 14.3% (n=1) and partial response (PR) in 71.4% (n=5) of our cohort. The median duration of response was 105 days (range: 15-580). Treatment failure was observed in 28.6% (n=2), one patient presented no improvement of GVHD and adverse effects and another patient had GVHD progression after 90 days of failure-free survival. Both patients discontinued ruxolitinib. Ruxolitinib adverse effects observed in 14.3% (n=1) were cytopenias and infection (pneumonia). There were no death events in our cohort.

Conclusions: Ruxolitinib throws hopeful results as a new therapy in refractory chronic GVHD as most patients in our cohort with moderate or severe disease, after failure of previous treatments, presented PR without adverse effects. One patient with moderate skin GVHD presented CR. Ruxolitinib also made possible steroid discontinuation in most of them. The patient with no ORR had severe disease at three different systems, failure of nine previous therapies and adverse effects at day 30 of treatment.

Gender ratio (Male:Female)	1:1.3
Median age (range)	54 (27-65)
Related HLA identical donor transplant	7 (100%)
Myeloablative conditioning regimen	5 (71.4%)
Reduced-intensity conditioning regimen	2 (28.6%)

[Patient baseline characteristics]

Disclosure: Nothing to declare.

P248

Low-dose of Ruxolitinib: An Effective Therapy for Refractory Bos Patients

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Background: Bronchiolitis obliterans syndrome (BOS) is a severe complication after allogeneic Hematopoietic stem cell transplantation (allo-HSCT). Patients who lack of response to traditional therapies are more likely to have poor prognosis.

Methods: We retrospective analyzed 10 patients diagnosed with BOS by pulmonary function tests (PFTs), lung symptoms and CT scans after allo-HSCT. Before the analysis, all patients had been treated with but refractory to steroids and other second-line drugs. The patients were **given** low-dose of Ruxolitinib (5mg/bid), systemic steroids (4-8mg/qd), FAM (inhaled Budesonide1-2mg/bid, Azithromycin 0.25g/d, Montelukast 10mg/qd) and anti-infectious prophylaxis (Itraconazole 100mg/bid, Compound sulfamethoxazole 0.48g/bid).

Results: The median age of patients was 15 (range 11-56) years. Seven were male and three were female. Diseases at transplant included AML (n=5), ALL-B (n=3) and MDS (n=2). Transplantation type contained unrelated Cord Blood Transplantation (n=8) and HLA-matched sibling HSCT (n=2). Symptoms included dry cough (n=7), fever (n=2), wheezing (n=6)and shortness of breath (n=8, 6 after walking on the plat ground, 2 after climbing steps and 2 at rest). Duration of lung symptoms was 7 (range 2-13) months after HSCT. 2015 NIH lung symptom-based scores were as follows: 1 (n=6), 2 (n=2), 3 (n=2). Duration between lung symptoms and PFT was 2 (range 1-12) months. The average FEV1% of the first PFT was 50% (range 29%-76%). FEV1%-based scores were as follows: 1 (n=2), 2 (n=5), 3 (n=3). NIH Global Severity of cGVHD: moderate (n=2), severe (n=8). The median time of Ruxolitinib therapy was 4 (range 1-11) months. Symptoms were improved quickly especially dry cough and wheezing which disappeared after 1 to 4 weeks. FEV1% recovered slowly but maintained at a stable level. 2 had a complete response (CR) with lung symptoms score 0 and FEV1% reached normal after 1 month. 8 had a partial response (PR), 4 of them with FEV1% increased over than 10% and another 4 with lung symptom score decreased by 1 or more points. None of them progressed. All patients except two withdrew Ruxolitinib. The median time of survival was 10.6 (range 6-27) months and all of them survived until the last follow-up. One AML patient relapsed 11 months after Ruxolitinib retreat then received chemotherapy and now is alive. None of patients were found side effects attributable to Ruxolitinib.

Conclusions: Lung symptoms especially long-termly and repeated dry cough or wheezing may indicate lung injury early. Physicians should pay attention to symptoms and monitor PFT. Combination therapy with low-dose of Ruxolitinib has obvious curative effects on refractory BOS patients. Lung symptoms can be improved quickly and FEV1% may recovered slowly but can maintain at a stable level.

Disclosure: Nothing to declare.

P249

Detection of Biomarkers Predictive of graft-versus-host Disease in Allogeneic Hematopoietic Cell Transplantation (HCT) Patients: A Pilot Study

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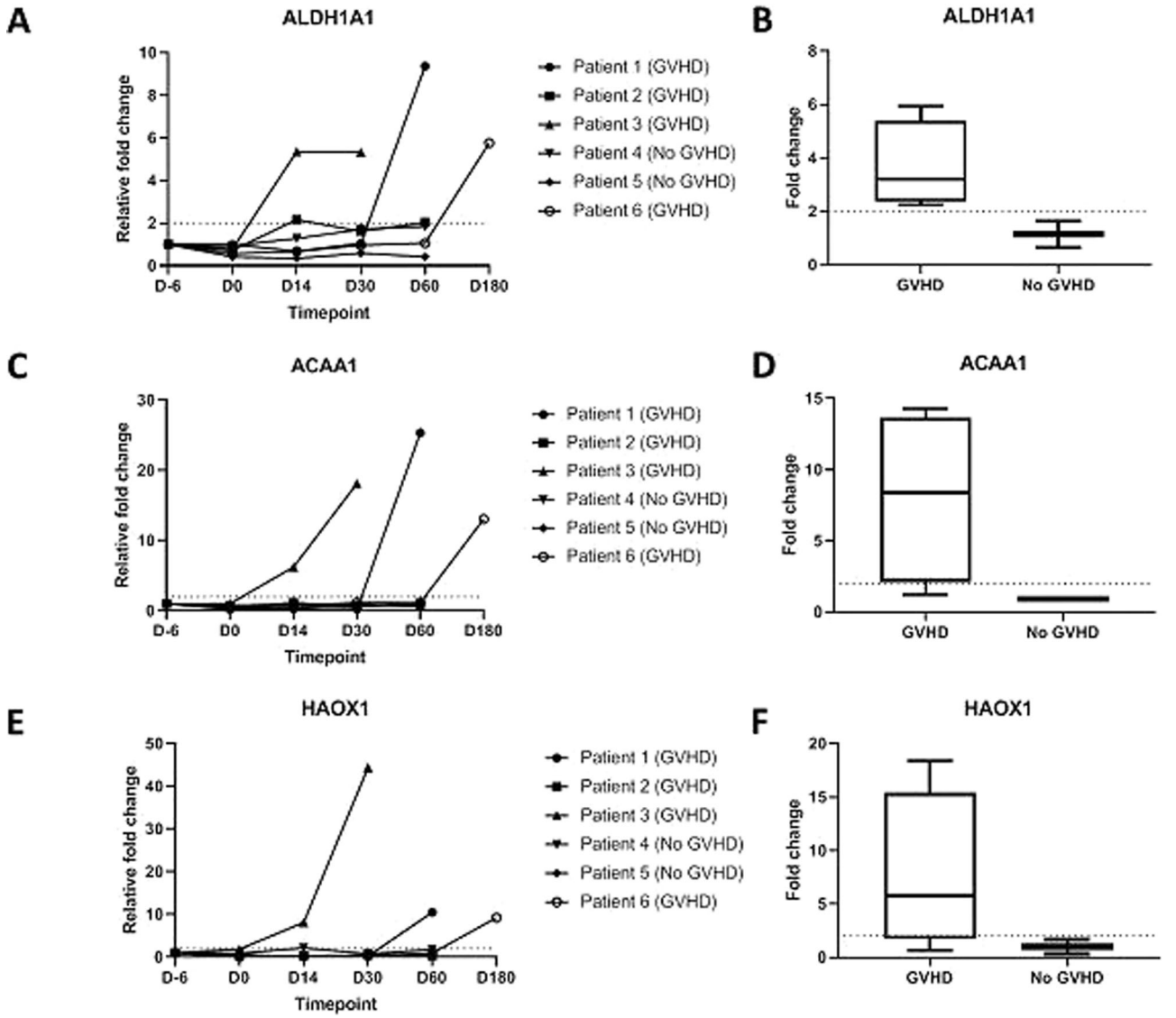
Background: Allogeneic hematopoietic cell transplantation (HCT) remains the only curative option for hematological malignancies including high-risk acute myeloid leukaemia (AML), but is often associated with morbidity and mortality due to complications such as graft-vs-host disease (GVHD). Although biomarkers predictive of GVHD may potentially be useful, few have been described to date. We report the use of a novel 1000-protein multiplex proximity extension method for the potential discovery of novel biomarkers of GVHD.

Methods: In this pilot study, we investigated six patients who underwent HCT for de novo AML in first complete remission (CR1). Serum samples were collected on days -6, 0, +14, +30, +60 and up to day +180. Samples were analyzed for relative protein concentration changes using a multiplex proximity extension assay (Olink Proteomics, Boston, MA). Over 1,000 protein markers were assayed. Raw data were provided in terms of a normalized protein



[Changes in serum levels of ALDH1A1, ACAA1 and HAOX1 in patients with and without GVHD]

expression (NPX) value. Values that were below the limit of detection (LOD) were reported as the LOD. The NPX values were transformed using the formula 2NPX and the pre- versus post-HCT fold change was calculated for each protein across all patients. Only those candidates which showed a ≥2-fold increase in expression post- compared to pre-HCT in patients with GVHD but not in patients without GVHD were included.

Results: Of the six patients, 4 (67%) were female. Median age was 53 (range 21-72). Two patients (33%) had a matched sibling donor, three patients a matched unrelated donor (50%) and one patient had a haploidentical donor (17%). Five patients (83%) received reduced-intensity conditioning. GVHD prophylaxis consisted of anti-thymocyte globulin (ATG), post-transplant cyclophosphamide (PTCy) and cyclosporin A (CsA) in five patients (83%); the remaining patient received ATG, CsA and methotrexate. Median follow up was 254 days (range 30-298). Among the six patients, two (patients 2 and 3) developed grade II-IV acute GVHD and two (patients 1 and 6) developed moderate/severe chronic GVHD. In these four patients, we identified 503 candidate biomarkers which demonstrated ≥2-fold increase in relative expression post- compared to pre-HCT. Among the 503 proteins, nine were detected in all four patients with GVHD, including Aldehyde Dehydrogenase 1 Family Member A1 (ALDH1A1, Figure 1A). Further twenty-eight markers were detected in three out of four patients with GVHD, including

Acetyl-CoA Acyltransferase 1 (ACAA1, Figure 1C) and Hydroxyacid Oxidase 1 (HAOX1, Figure 1E) while seventy-nine markers were detected in two out of four patients with GVHD. In the case of all biomarker candidates, expression increase was seen only in those patients who developed GVHD and not in those who did not (Figure 1B, D and F).

Conclusions: Using the proximity extension assay, we identified proteins of potential clinical significance in the serum of HCT patients. Furthermore, some of these proteins, including ALDH1A1, ACAA1and HAOX1 were increased in several patients with GVHD. Our findings suggest that these proteins may potentially serve as biomarkers of GVHD and warrant further prospective study in a larger cohort to determine their role in the pathophysiology of GVHD as well as other post-transplant complications.

Disclosure: Nothing to declare.

P250

Outcomes of Allogeneic Hematopoietic Stem Cell Transplantation (ALLO-HSCT) After PD-1 Blockade in Relapsed/Refractory (R/R) Lymphomas -A Single Center Experience

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Background: PD-1 blockade is an effective bridge therapy to allo-HSCT for R/R lymphomas. However, this immune modulation alters allo-HSCT outcomes: it can increase graft-versus-tumor effect but also graft-versus-host disease (GVHD). Our aim was to assess the incidence and severity of the latter.

Methods: We analyzed retrospectively 10 patients (median age: 39, range 16-66, 60% male) with R/R Hodgkin (80%) and T-cell lymphomas (20%) who underwent allo-HSCT and previous anti-PD-1 monotherapy, with Nivolumab (240 mg / 2 weeks) (80%) or Pembrolizumab (200 mg / 3 weeks) (20%). All being III-IV Ann Arbor, high risk IPS and heavily pretreated (median lines: 4, 3-6). See transplantation characteristics (Table1).

Results: Median number of anti-PD1 cycles: 8 (2-18), 60% of patients experienced immune-mediated adverse events, mainly toxicoderma, none being severe or discontinuing therapy. Median time from last dose to allo-HSCT: 92 days (38-232).

At the time of transplantation, overall response rate was 100% (70% complete, 30% partial). 8 patients (80%) developed acute GVHD (aGVHD) at median 32 days (18-55) after allo-HSCT, applying the MAGIC criteria, as follows: 2 (20 %) grade I, 4 (40 %) grade II, 1 (10%) grade III, 1 (10%) grade IV. 7 of them experienced a complete resolution with steroids and immunosuppressants and 1 died due to severe steroid-refractory aGHVD. Chronic extensive cutaneous and ocular GVHD occurred in 2 of these 8 patients, 1 controlled (steroids and CsA), another partially (adding extracorporeal photopheresis).

During median follow-up (13 months), overall survival was 60 %. Four patients (40%) died of: infection (2), progression (1), aGVHD (1).

Conclusions: We observed a higher rate of aGVHD (80%) regardless of the GVHD prophylaxis used compared to historical rates (25-40%). This high incidence may be explained by all the graft sources being peripheral blood and by the persistent PD1 blockade on T lymphocytes that, based on literature, can persist for up to 10 months (way beyond the therapy half-life of 1 month).

Furthermore, we found no direct relation between the risk or severity of GVHD and previous anti-PD1 adverse events, total number of cycles or time elapsed since the last administration.

After our data analysis, we found that PD-1 inhibitors may be a highly effective bridge therapy to allo-HSCT, but their use carries an increased risk of GVHD related morbidity and mortality. This knowledge should lead to a careful selection of candidates in the pre-allo-HSCT setting and, when performed, to a close monitoring for signs of GVHD and slower immunosuppression reduction.

Patient	Type of allo-HSCT	Conditioning regimen	GVHD prophylaxis	GVHD grade	Alive	Cause of death
1	Haplo-identical	TT/Bu/Flu	T-cell depletion	III	No	Infection
2	HLA-identical sibling	Mel/Flu	CsA and MTX	I	No	Refractory disease
3 and 4	Haplo-identical	Cy/Flu/Bu	PT-Cy, MMF and CsA	II	Yes	-
5	Umbilical cord blood	TT/Bu/Flu	FK and steroids	-	No	Infection
6	HLA-identical sibling	Mel/Flu	CsA and MTX	-	Yes	-
7	HLA-identical sibling	Mel/Flu	CsA and MTX	IV	No	Refractory GVHD
8	Haplo-identical	Cy/Flu/Bu	PT-Cy, MMF and CsA	I	Yes	-
9	Haplo-identical	Cy/Flu/Bu	PT-Cy, MMF and CsA	II	Yes	-
10	HLA-identical sibling	Mel/Flu	CsA and MTX	II	Yes	-

[Table 1. Transplantation characteristics.]

Disclosure: Nothing to declare.

P251

CD3+ Dose in Peripheral Blood Progenitor Cells Products for Allotransplant from Matched Unrelated Donors for AML: Impact on Chronic Graft Versus Host Disease and Survival

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Background: Chronic graft versus host disease (cGVHD) remains one of the most important causes of morbimortality in allogeneic stem cell transplantation (allo-SCT). CD3+ cells contained in grafts may have an important role in development of this entity, but there is no consensus on dose limit and its impact on transplant's outcome. Several studies have been performed in this setting, with different results.

Methods: We retrospectively analyzed 38 patients with acute myeloid leukemia who underwent allo-SCT from matched unrelated donor in our center from January 2008 to May 2019. All transplants were performed with myeloablative conditioning and stem cells source was peripheral blood in all cases. We divided them into 2 groups according to median dose of CD3+ cells contained in stem cell product: 192,3x10^6/kg. All patients received Cyclosporine + Methotrexate as GVHD prophylaxis except one patient from group CD3+>192,3x10^6/kg who received also Thymoglobulin. Statistical analysis was performed with T-test, Pearson Chi-Square and Fisher´s Exact Test according to type and distribution of the variable. Survival curves were obtained with Kaplan-Meier method.

Results: Table 1 shows the main characteristics of patients and transplant procedures. Median CD34+ dose was 6x10^6/kg in both groups. Incidence of aGVHD was higher in the CD3+>192,3x10^6/kg group (62,5 vs 37,5%; p=0,693) and cGVHD was significantly higher in this group (63,2 vs 26,3%; p=0,022). Cumulative incidence of cGVHD is shown in figure 1. Relapse rate was 26,3% in both groups. Survival curves show an increased mortality for CD3+>192,3x10^6/kg group in the first three years post-transplantation (Log-rank p=0,044), see figure 1.

Conclusions: In our experience, higher doses of CD3+ cells in peripheral blood stem cell graft lead to an increased risk of cGVHD development and a negative impact on survival in this homogeneous population. Further studies are needed to support these findings and to define a standard cut-off value of CD3+ dose in grafts.

	CD3+<192,3x106/kg (n=19)	CD3+>192,3x106/kg (n=19)	p value
AGE // GENDER (M/F)	59 (24-70) // 13 (68,4%) / 6 (31,6%)	40 (19-65) // 10 (52,6%) / 9 (47,4%)	0,041 / 0,319
CONDITIONING: BUCY / FLUBU / CY-TBI	12 (63,2%) / 6 (31,6%) / 1 (5,2%)	13 (68,4%) / 3 (15,8%) / 3 (15,8%)	0,210
ABO COMPATIBILITY: COMPATIBLE / MAJOR / MINOR	11 (57,9%) / 4 (21,1%) / 4 (21,1%)	9 (47,4%) / 5 (26,3%) / 5 (26,3%)	0,810
DISEASE STATUS: CR / CR MRD+ / ACTIVE	11 (57,9%) / 6 (31,6%) / 2 (10,5%)	14 (73,7%) / 4 (21,1%) / 1 (5,2%)	0,579
CMV STATUS(D/R): +/+ // +/- // -/+ // -/-	12 (63,2%) / 0 / 6 (31,6%) / 1 (5,2%)	6 (31,6%) / 3 (15,8%) / 9 (47,4%) /1 (5,2%)	0,133
SEX STATUS (D/R): M/M // M/F // F/M // F/F	9 (47,4%) / 5 (26,3%) / 3 (15,8%) / 2 (10,5%)	7 (36,8%) / 3 (15,8%) / 3 (15,8%) 6 (31,6%)	0,432
GVHD PROPHYLAXIS: CSA + MTX / CSA + MTX + ATG	19 (100%) / 0	18 (94,7%) / 1 (5,2%)	1,000
CD34+x106/kg	6 (3,2-7,2)	6 (3-6,6)	0,799
ENGRAFMENT (DAYS) LEUKOCYTE / PLATELETS	20 (11-31) / 14 (10-41)	17 (12-29) / 14 (8-54)	0,084 / 0,632

[Table 1. Patient and transplant's characteristics]

Disclosure: Nothing to declare.

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A Role of Methotrexate in the Therapy of Chronic graft-versus-host Disease - A Multicenter Observational Study on Behalf of Polish Adult Leukemia Group (PALG)

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Background: Methotrexate (MTX) has a fixed position in the therapy of autoimmune diseases due to anti-inflammatory and antiproliferative proprieties. On the other hand, it is not commonly prescribed in the treatment of chronic graft-versus-host disease (cGVHD) even though the overall response rate (ORR) is assessed on 77% in the meta-analysis.[1, 2] The use of MTX leads to quite permanent suppression of activated T-cells and the expression of adhesive molecules.[3] The concerns about hematological and hepatic toxicities probably limit the use of MTX in this transplant setting.[2, 4, 5] However, another meta-

analysis published in 2018 showed MTX as the best cost-effectiveness option in cGVHD.[6] Therefore, a study among Polish transplant centers was initiated to evaluate MTX usage, efficacy and toxicity in cGVHD setting.

Methods: We evaluated retrospectively data of 24 patients who underwent allogeneic hematopoietic cell transplantation (HCT) due to hematological malignancies. The latest NIH Consensus diagnostic and response cGVHD criteria were used. A dose of MTX 5 - 15 mg per week was administered with folic acid support.

Results: The median age was 36 years old at HCT. In 50% of patients, acute GVHD preceded cGVHD. The median time to cGVHD diagnosis was 5 months (3 - 40) post-HCT. Corticosteroid (CS) refractoriness or dependence was diagnosed in 46% of patients. MTX was prescribed in moderate or severe cGVHD, mostly as second (54%) or third line (29%) of therapy with a weekly dose of 15 mg in 61% of patients.

MTX was added to CS (5 patients) or to CS plus other agent(s) (15 patients). The best response was achieved in the case of the joint/fascia (ORR 87%), skin (ORR 78%), liver (ORR 57%), and mouth (ORR 55%) involvement. In 17 patients (85%), a dose of CS could be at least reduced by 50%. The main or major role of MTX in amelioration of cGVHD symptoms was indicated by treating physicians in 42% of patients. In one case, MTX monotherapy caused remission of deep sclerodermatous cGVHD.

Infections (bacterial and/or viral) were recorded in 38% of patients. The toxicity profile included hematological (2 patients), mucosal (1), hepatic (1), and kidney (1) toxicity. The MTX therapy was discontinued in 9 patients (37%) due to: cGVHD remission (1), treatment failure (3), infections (2), relapse (2), toxicity (1). One patient died due to a relapse in the follow-up period.

Conclusions:

Our observational study confirmed a high response rate in selected organs (joints/fascia, skin) and the acceptable toxicity of MTX. Therefore, MTX should not be omitted as a component of therapeutic cGVHD protocols.

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Disclosure: Nothing to disclose

P253

Evaluation of Extracorporeal Photopheresis used as second-line Treatment for graft-versus-host Disease After Allogeneic HSCT in a Brazilian Center

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Background: Graft-versus-host disease (GvHD) is an important complication following allogeneic hematopoietic stem cell transplantation (HSCT) with significant impact on short- and long-term morbidity and mortality. Corticosteroid is considered the first-line treatment for GvHD. Extracorporeal photopheresis (ECP) is an option as second-line treatment, albeit expensive and hemotherapeutic resource demanding, available in our service only by individual judicialization. As one of the few Brazilian public health services working with ECP, we aimed to evaluate our experience using this treatment as second-line therapy for steroid-refractory GvHD in patients transplanted at Barretos Cancer Hospital.

Methods: Data was retrospectively gathered by review of medical records of adult patients with GvHD who underwent therapy with ECP from 2012 to 2018. The full course of treatment consisted of 31 ECP sessions, according to the institutional protocol defined by the Bone Marrow Transplantation Center of Instituto Nacional do Cancer (INCA). The response criteria were evaluated according to "The 2014 Response Criteria Working Group Report".

Results: Two hundred and four allogeneic transplants were performed between 2012 and 2018. ECP was used as second-line therapy for acute and chronic GvHD (aGvHD and cGvHD) in 15 patients with a mean age of 39 years (20-55). Among these patients, 14/15 (93%) underwent ECP to treat severe cGvHD, while only one patient (7%) was treated for grade IV aGvHD, not included in statistics. From those treated for cGvHD, 11/14 (79%) performed 1 treatment course, and 3/14 (21%) performed 2 treatment courses and the average number of sessions per course was 24.4 (range 13-31 sessions). The mean time to start treatment was 540 days, with median of 373 days (range 21-2144 days). The mean duration of courses was 129 days (range 36-504 days). Among those patients, 14% had 3, 29% had 4, 29% had 5, 21% had 6 and 7% had 8 organs involved in cGvHD. Thus, from all patients evaluated for cGvHD, seven (50%) responded to treatment

and were able to reduce the steroid dose. After the ending of each course, 5 (30%) were able to reduce ≥ 80% of the steroid dose. Nevertheless, none of the patients enrolled to a second course responded to ECP.

Conclusions: The treatment of steroid-refractory GvHD is a major challenge due to the lack of effective therapeutic options and their high costs. ECP has a good safety standard, as it does not cause marked immunosuppression, does not increase the risk of infectious complications and recurrence of malignant disease.

ECP was the first Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved photoimmune cell therapy for the treatment of malignant diseases, however, it is not by now affordable for the Brazilian public health system, used as second or third-line rescue therapy. The ability in diminishing clinical manifestations and reducing the dose and duration of steroid therapy, especially in cGvHD, are the main goals of treatment, but the best results are obtained when started early, therefore, as soon as steroid refractory cGvHD is diagnosed.

Disclosure: Nothing to declare.

P254

Analysis of Histology's Impact in Patients with Acute Graft versus Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Acute graft versus host disease (aGvHD) is one of the main complications of hematopoietic stem cell transplantation. It affects different organs with varying manifestations and response to the different treatments available, being characterized by reducing patient's quality of life. Diagnosis is based on clinical symptoms, although a histological study of the organ affected is recommended to confirm the diagnosis. Our aim is to establish a relationship between the level of response to corticosteroids and histological diagnosis of aGvHD.

Methods: A one center retrospective study, with data obtained from the electronic clinical history. Descriptive analysis; measures of central tendency and dispersion for central numerical variables, absolute and relative frequencies for the qualitative variables. Association between performing biopsies and histology compatible with response to corticosteroid treatment; Pearson's chi-squared test. p-value < 0.05 is considered significant. The data was analyzed with IBM SPSS Statistics 19 software.

Results: Of a total of 139 patients with allogeneic hematopoietic stem cell transplantation in Granada from 2014 to 2018, 101 developed acute graft versus host disease (72,75%), biopsies being performed on 81 of them (80,2% of the aGvHD), of which a compatible histological diagnosis was obtained in 44 of the cases (54,3% of the biopsies). The relationship between clinical and histological severity is not clear. It is not possible to establish a significant statistical relationship between patients with a biopsy of affected organ and grade of response to corticosteroids (p=0,15). Similarly, there is not significant statistical relationship between histological diagnosis of aGvHD and response to corticosteroids (p=0,5).

			Corticosteroid reponse			
			No response	Sensitive	Dependent	Total
Histological diagnosis of aGvHD	No	Count	7	15	15	37
		%	36,8%	53,6%	44,1%	45,7%
	Yes	Count	12	13	19	44
		%	63,2%	46,4%	55,9%	54,3%
Total		Count	19	28	34	81
		%	100,0%	100,0%	100,0%	100,0%

[Corticosteroid response in histological aGvHD group]

Conclusions: Allogeneic hematopoietic stem cell transplantation has a high incidence of acute graft versus host disease. The response to first line treatment with corticosteroids is variable, with frequent steroid dependency. From our experience, a biopsy is not an indispensable method of diagnosis for the management of acute graft versus host disease, as the relationship between the level of response to corticosteroids and an accurate histological diagnosis has not been established.

Disclosure: Nothing to declare.

P255

Ruxolitinib in Chronic Graft Versus Host Disease: Single Center Experience

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Background: Allogeneic stem cell transplantation is a treatment modality with a potential of cure in hematological malignancies. But, in a subset of these patients Chronic Graft Versus Host Disease (cGVHD) leading to significant mortality and mobidity can be observed. Ruxolitinib is a JAK 1/2 inhibitor and there is data showing that JAK inhibitors may reduce GVHD by inhibiting donor T-cell expansion and inflammatory cytokine production, regulatory T-cell (Treg) function and viability. In this study, we aimed to analyse the results of our patients who received Ruxolitinib for cGVHD treatment.

Methods: We analysed the results of 32 patients who received Ruxolitinib at a dose of 5mg for 2 times aday for cGVHD treatment between September 2016 and September 2019.

Results: The median age was 35(18-64). The primary diagnosis was ALL in 15 (46%) patients, AML in 9 (28%) patients, Lymphoma in 2 (6%) patients, MDS in 2 (6%) patients and other in 4 (12%) patients. The donor type was HLA-identical sibling in 13 (40%) transplantations, unrelated in 14 (43%) transplantations and haploidentical in 5 (15%) transplantations. 90,6% of the patients (29) had skin GVHD, 62,5% of the patients (20) had liver GVHD, 53,1 % of the patients (17) had lung GVHD, 12,5% of the patients (4) had GIS GVHD. Clinical characteristics of the patients are shown in Table 1.

Conclusions: According to our results, Ruxolitinib can be used for the treatment of of patients with cGVHD with a high response rate and tolerability.

Extracorporeal Photopheresis before Ruxolitinib	27(84,4%)
Median cycles of Extracorporeal Photopheresis before Ruxolitinib (range)	10(2-22)
İmatinib before Ruxolitinib	27(84,4%)
Duration of İmatinib before Ruxolitinib, months;median(range)	6(1-27)
Reason for stopping İmatinib: Ineffectiveness, Toxicity	21(77,7%), 6(22,2%) (respectively)
Time from transplantation to Ruxolitinib, months;median(range)	27,5(7-71)
Total time of Ruxolitinib usage, months; median(range)	9(1-34)
Number of patients who discontinued Ruxolitinib	11(34,4%)
Response to Ruxolitinib treatment: Partial response, No response, Response could not be determined because of the death of the patient	23(71,9%), 6(18,8%), 3 (9,4%) (respectively)

[Table 1: Clinical characteristics of pateints]

Disclosure: Nothing to declare.

P256

Impact of post-transplant Cyclophosphamide(CYPT) for graft-versus-host Disease (GVHD) Prophylaxis in Allogenic Hematopoietic Stem Cell Transplantation (ALLO-HSCT). Unicentric Experience

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Background: Post-transplant cyclophosphamide associated with other immunosuppressive agents is emerging as a promising pharmacological strategy in allo-HSCT. The safety and efficacy profile in reducing both acute and chronic GVHD in haploidentical transplant is contributing to its extended use to other types of allo-HSCT (HLA matched sibling and matched unrelated donor), with acceptable rates of GVHD, and mortality.

The study aim is to evaluate the incidence of both acute and chronic GVHD in patients receiving allo-HSCT using CYPT as GVHD prophylaxis, regardless the type of donor, compared to those who received a traditional GVHD prophylaxis.

Methods: This is a retrospective, unicentric and observational study using data from 40 patients from Quirón Public Health group in Madrid who underwent allo-HSCT from January 1, 2015 until July 30, 2018. Statistical analysis was performed with the STATA statistical package version 15.1.

In our serie, 17 HLA matched sibling donor (MSD) (42.5%), 17 haploidentical donor (42.5%), 4 HLA matched unrelated donor (MUD) (10%) and 2 mismatch related donor (5%) were used.

18 transplants use a non-myeloablative conditioning regimen (45%) and 22 myeloablative conditioning regimen (55%). In 100% the source of hematopoietic progenitors were peripheral blood.

Regarding to the GVHD prophylaxis scheme, CYPT was used according to Baltimore protocol in 25 transplants (62.5%), of which 17 were haploidentical, 3 MSD, 4 MUD and 1 in mismatch related.

Results: In our serie, acute GVHD was reported in 20 patients (50%) (Grade I-II: 30%; grade III-IV: 20%) and chronic GVHDi n 16 patients (40%) (Grade I-II: 30%; grade III-IV: 10%).

Among patients who received CYPT, acute GVHD was detected in 12 patients (48%); 1 patient (33.3%) who underwent MSD allo-HSCT, 8 patients (47.06%) who received haploidentical allo-HSCT, 3 with MUD allo-HSCT. No acute GVHD was detected in mismatch related donor allo-HSCT.

In contrast, 8 patients (32%) presented chronic GVHD among the population who received CYPT prophylaxis. 6 patients (35.29%) with haploidentical allo-HSCT, 2 (50%) with MSD allo-HSCT. None after allo-HSCT from MSD and mismatch related donor.

The relationship between prophylaxis with CYPT and acute GVHD showed a Relative Risk (RR) of 0.9 (95% IC 0.48-1.68) with a non-statistically significant p ($p = 0.74$). Since all patients undergoing haploidentical HSCT received CYPT prophylaxis, they were excluded from the risk analysis. The subgroup analysis showed no differences in acute GVHD.

The relationship between prophylaxis with CYPT and chronic GVHD showed a RR of 0.6 (95% IC 0.29-1.26) with a non-statistically significant p ($p = 0.18$).

The chronic GVHD, not including patients who received haploidentical HSCT, also showed no statistically significant differences with a RR = 0.47 (95% IC 0.13-1.7) and a $p = 0.19$.

Conclusions: The incidence of both acute and chronic GVHD have not been statistically significant between the different prophylaxis schemes. It is true that the sample size and the median follow-up are short to assess the appearance of chronic GVHD.

It is necessary to design an individualized prophylaxis scheme and to develop prospectives, randomized studies with a higher number of patients in order to draw conclusions with greater evidence.

Disclosure: No disclosures to declare.

P257

Early Recovery of Lymphocytes after Hematopoietic Stem Cell Transplantation is Risk Factor of CGVHD

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Background: There are few studies that investigate an association between severity of lymphopenia and clinical outcome during chemotherapy or HSCT. We investigate this problem by using the index which reflect the duration and intencity of lymphopenia by reference to D-index used in many studies to evaluate the severity of myelosuppression. We called this index LD-index and retrospectiely analyzed LD-index of the patients who underwent allo-HCT in our hospital.

Methods: There are 101 pediatric and young adult patients who underwent allo-HSCT in our hospital from April 2007 to August 2019. We excluded the patients who did not gain the lymphocyte recovery (>500/μl) due to treatment-related death or death from disease. Consequently, we targeted 92 cases (male 54, female 38) with allo-HSCT. The LD-index is the area over the lymphocyte curve plotting the lymphocyte count during lymphomenia (< 500/μl), calculated from depth and duration of lymphopenia. The median age at transplant was 10.3 (range 0.4-28.1), and number of patients diagnosed with hematological malignancy was 54, solid tumor was 14, benign disease was 17, respectively. We compared the association between LD-index and the age at HSCT, sex, donor source, HLA typing, donor source, number of transplantations, infectious complication during HSCT, the incidence of aGVHD and cGVHD, TRM, and OS.

Results: The median LD-index is 9285 (range, 2217-36064). Among them, only the incidence of cGVHD was significantly associated with LD-index. LD-index of patients with or without cGVHD is 8298.5 (range, 3725-13521), 10112.5 (range, 2217-36044) respectively. The patients with cGVHD had a significantly lower LD-index compared to the patients without cGVHD ($p=0.004$). Therefore we analyzed predictive factor for cGVHD to 92 cases with allo-HSCT. In multivariate analysis, high levels of LD-index (LD-index > 9040, calculated by ROC curve) and transplantation by bone marrow were significantly low incidence of cGVHD ($p=0.029$, 0.011, respectively). We have studied similar analysis by using LD-index(< 300/μl), and high levels of LD-index was signigicantly low incidence of cGVHD($p=0.010$). So we have proved that early recovery of lymphocytes after HSCT is risk factor of cGVHD.

Conclusions: The duration and intensity of lymphopenia after HSCT have an effect on cGVHD, but have no impact on the incidence of infectious complication, TRM, OS. Altough there are still limitations in analysis of various diseases in children and young adults, and we hope that similar study will lead to better post-transplant management.

Disclosure: Nothing to declare.

P258

Combined Therapy with MSC Infusions to Overcome steroid-dependency in a Case of Severe Pulmonary CGVHD

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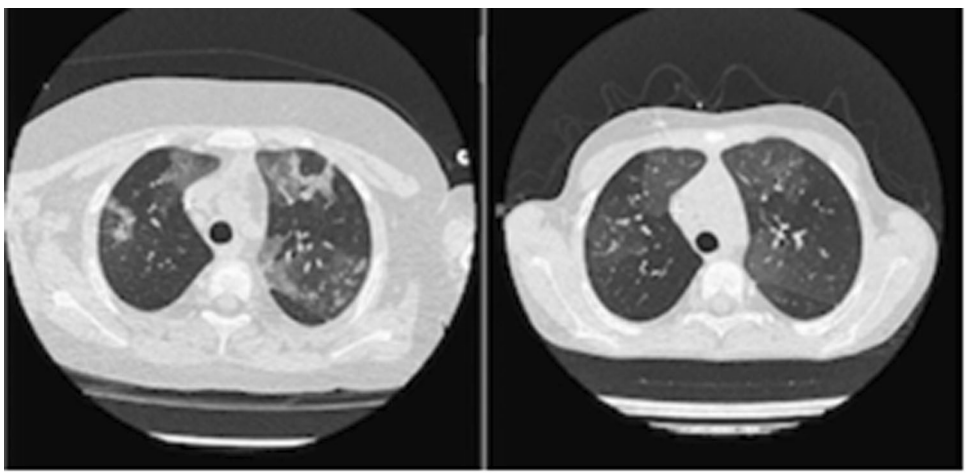
Background: Severe pulmonary chronic graft-versus-host disease (cGvHD) correlates to poor quality of life, reduced performance status and reduced survival prognosis with both higher NRM and worse OS, mainly in symptomatic patients and with unstable disease. Treatment strategies are based on steroids and other immunosuppressive/immunomodulatory drugs which may induce disease stabilization but, together with the baseline condition, increase the risk of frequent respiratory tract infections (RTI). In pediatric patients, given the longer life expectancy, this long-term complication may have a great impact on quality of life and physical activity. The main issue remains treatment modality, since in the pediatric setting it is understudied.

Methods: We herein report a case of a boy with severe pulmonary cGvHD after allogeneic HSCT for a Myelodysplastic Syndrome. Since cGVHD onset on June 2016, he was treated with oral steroid as first line therapy, together with supportive therapy with bronchodilators, azithromycin and anti-leukotriene as anti-fibrotic. To improve results, extracorporeal photopheresis (ECP) was associated, and a first attempt at tapering steroids was performed. After few months, due to lack of improvement, a double immunosuppressive and anti-fibrotic treatment with Imatinib and Everolimus was started. Despite the new regimen, he underwent several acute exacerbations, mainly due to respiratory tract infections (RTIs). Thus, based on literature, high dose steroid administration was attempted with limited results, followed by treatment with Rituximab. The patient's clinical condition remained stable, and after almost two years of treatment the main issue remained his steroid-dependence. Based on their immunomodulatory role, we decided to start mesenchymal stromal cells (MSC) infusions while tapering steroids. MSC were infused monthly for one year, then every two months as a maintenance therapy, without adverse effects. Steroids were definitely stopped after the first 3 months of MSC therapy. During the following 18 months, Pulmonary functional tests (PFT) remain unchanged whereas his performance status improved notably, no acute exacerbations due to RTIs were observed and chest CT scan showed a significant improvement on pulmonary parenchyma.

Results: MSCs are multipotent cells with immunomodulating and anti-inflammatory properties. MSC seem to have an important role in favoring reconstruction of damaged tissues including respiratory mucosal cells, leading to airways remodeling and more rapid repair. Pulmonary cGvHD, with its restrictive/obstructive patterns of lung injury as the result of persistent and dysregulated inflammation after HSCT, could benefit from this strategy. Even if limited to a single experience, we were able to achieve encouraging results, showing that MSCs may have a role in controlling steroid-dependency, in reversing the pulmonary parenchymal damage, without favoring infections and acute exacerbations.

Conclusions: MSC infusions may help to improve the pulmonary parenchymal damage leading to a reduced risk of acute exacerbations, improved quality of life and performance status, and to allow a significant reduction in prednisone exposure. Prospective clinical studies are needed in this setting.

Disclosure: Nothing to declare.



[Thorax CT scan before and after MSC infusions]

P259

Multiple Strictures of the Small Intestine Demanding Surgical Intervention as a Complication of Graft versus Host Disease - Case Report

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Background: Surgical complications of gastrointestinal graft versus host disease (GvHD) include hemorrhage, perforation and strictures in various parts of the gastrointestinal tract. Small bowel obstruction is extremely rare.

Methods: We describe the case of a child with multiple strictures of the small intestine secondary to steroid-resistant GvHD.

Results: A 7 year old girl underwent the second allogenic hematopoetic stem cell transplantation (HSCT; 2,76x10^6 CD34+/kg b.w.; 0,6 x10^8 CD3/kg b.w.) from 10/10 matched unrelated donor for CALR-positive post-ET myelofibrosis and its relapse after the first HSCT. CsA, „short" MTX and ATG were used in GvHD prophylaxis. HSCT was complicated with grade IV steroid-resistant GvHD (skin and intestinal tract). The patient was treated with CsA (from day -1 until day +227 after HSCT), methylprednisolone (day +8 until +574), etanercept (8 doses 0,4mg/kg - from day +412 until +440 after HSCT), ECP (74 procedures - from day + 120 until +435). Complete resolution of skin GvHD was achieved, but gastrointestinal GvHD persisted. Due to malabsorption symptoms and anorexia the patient required total (at the onset of GvHD) and then partial parenetral nutrition for 15 months after HSCT. On day +457 the laparotomy was performed due to increasing symptoms of mechanical bowel obstruction. Ten critical cicatricial strictures of the small intestine with substantial wall thickening in the strictures were revealed. Nine segmental resections of the strictured segments of the small intestine and 6 intestinal anastomoses were done during one surgical procedure. In total, about 45 cm of the small intestine were resected. The postoperative period was uncomplicated, oral feeding was gradually implemented, achieving full coverage. Pathological examination of the resected parts of the intestine confirmed the diagnosis of overlap syndrome of acute and chronic GvHD. Therefore, therapy with ruxolitinib at a dose of 2,5 mg per day started on day +484, while still methylprednisolone at a dose of 0,35 mg/kg b.w. per day was administered. Corticosteroid therapy was withdrawn on day +574. The patient continues treatment with ruxolitinib at a reduced dose. No recurrence of GvHD and no gastrointestinal disturbances were observed at 29 months after the second HSCT. The patient remains in good general condition and in hematological and molecular remission of CALR-positive post-ET myelofibrosis.

Conclusions: GvHD therapy is largely based on conservative treatment, but a patient with permanent changes in the wall of the gastrointestinal tract needs to undergo surgical intervention to ensure its efficient functioning.

Disclosure: Nothing to declare.

P260

A Remarkably Long Remission Achieved with Ibrutinib Monotherapy in a Patient who was Diagnosed with Steroid Refractory Sclerosing Chronic GVHD

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Background: Chronic sclerosing steroid refractory skin GVHD remains as a clinical challange despite the advent of novel therapeutic approaches. One of the most promising option in this scenario is Ibrutinib. We present a case of ours who was refractory to both steroid, imatinib and photopheretic treatment approaches.

Methods: 20 years-old female patient was diagnosed with intermediate risk AML in October 2015 and underwent an allogeneic stem cell transplantation with myeloablative conditioning regimen from her matched sibling donor on December 2015. Stem cell source was peripheral blood. After discharge she did well until the seventh month of transplant with rapidly resolving grade 2 skin and gastrointestinal acute GVHD when her systemic symptoms started. She complained of sore mouth, thickening and edema of skin mainly involving distal extremities and limited movement on elbow and wrist. Physical examination revealed an edematous and sclerotic skin with lichenoid lesions throughout the oral mucosa and deminished lung sounds on both sides. She was diagnosed with severe chronic sclerosing GVHD with pulmonary, oral and skin involvement with a global cGVHD score of 8. She has received steroid first but was refractory to steroids and received extracorporeal photopheresis and imatinib as a combination approach. Unfortunately she did not respond to combination therapy and while she was on therapy she was hospitalized due to recurring pulmonary infections and attacks of non-infectious edematous fasciitis mimmicking capillary leak syndrome which responded well to IVIG but gradually worsened the range of motion of affected joints.

After obtaining an off-label drug approval from health authority she was put on to Ibrutinib 420 po.

Results: After the initiation of Ibrutinib in 20 days she was able to achieve a partial response and in two months partial response was evolved to a complete response. Her global chronic GVHD score was 3 at the end of first month of Ibrutinib treatment. She is on the 26th month of Ibrutinib with no drug related complications and no worsening in the sclerosing chronic GVHD.

Conclusions: Sclerosing chronic GVHD after allogeneic HSCT is an un-met clinical need despite evolving armamentarium. Ibrutinib has recently approved by FDA for the treatment of chronic GVHD. Our patient is receiving Ibrutinib with a full-resolution of symptoms and signs attributable to sclerosing chronic GVHD with a novel question arising 'when to stop the treatment' which needs to be answered by well designed phase 2 or 3 trials.

Our case designates a proof of consept of the capability to reverse and suppress a severe sclerosing chronic GVHD with a Bruton Tyrosine Kinase inhibitor for a reasonably long period of time surpassing two years.

Clinical Trial Registry: not applicable

Disclosure: Nothing to declare.

P261

Increased Risk of Acute GVHD in Patients with Myelofibrosis after Allo Transplant in the Absence of jak-stat Inhibition

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Background: Acute graft-versus-host disease (GVHD) is a multisystem disorder that is a common, life-threatening complication of allogeneic transplant, it is driven by alloreactive donor T cells, and it remains a major cause of morbidity and nonrelapse mortality in allo-HSCT recipients. JAK-STAT signaling pathways help regulate the development, proliferation, and activation of immune cell types important for GVHD.

Methods: We report in this case series the findings in three of our patients who underwent allogenic transplant for Myelofibrosis. All three patients received treatment with ruxolitinib for Myelofibrosis for at least 6 months before the transplant, however this treatment was stopped at least 2 weeks before the transplant. All three patients continued to have splenomegaly and pancytopenia after engraftment. Patient number 2 required frequent Platelets transfusion, while patient number 1, and 3 required frequent red cell transfusions. Despite having good donors, and GVHD prophylaxis, all three patients had severe grade IV steroid refractory acute GVHD, and required the addition of ruxolitinib to control their disease. The timing and the rapid progression of their Acute GVHD, which started during the taper of their immune suppression and about 109 -140 days from the last dose of ruxolitinib. Our treatment approach was to initiate ruxolitinib after they failed high dose steroids. In our group of patients, we noticed that the combination of stopping ruxolitinib before transplant, and the lack of the inhibition of JAK1/JAK2, after transplant might have contributed to the development and the severity of Acute GVHD.

Results: All three patients noticed improvement in their symptoms after the treatment with ruxolitinib was started. The lack of JAK-STAT signaling inhibition could have contributed to the development, proliferation, and activation of immune cell types important for GVHD, also increased the production of proinflammatory cytokines, and the trafficking of T cells and innate immune cells to tissues. Furthermore, the loss of this inhibition after the transplant could have contributed to the higher grade of Acute GVHD and the severity of their symptoms. We noticed that starting ruxolitinib to treat GVHD after they failed the initial course with high dose steroids, helped in controlling their symptoms, and the stabilization of their disease.

Conclusions: ruxolitinib is an oral selective inhibitor of JAK1/JAK2. It has been approved for the treatment of steroid refractory Acute GVHD. In our group of patients with Myelofibrosis the common denominator was the treatment of myelofibrosis with ruxolitinib for at least 6 months before the transplant, and stopping it at least 2 weeks before the transplant. It is worth noting that continuing to establish the inhibition of JAK1/JAK2 after the transplant might be needed to reduce the risk of this group of patients of developing Acute GVHD.

patient	Age	Myelofibrosis/ grade	Ruxolitinib stop date prior to SCT	Conditioning regimen	Donor	Onset of Acute GVHD	Ruxolitinib initiation day
1	70	MF-2/grade 4	2 weeks	RI Bu/Flu/ rATG	12/ 12 MUD	Day 95	Day 7 of high dose steroids
2	55	MF2/Grade 3	4 weeks	RI-BU/FLU	12/ 12 MRD	Day 98	Day 15 of high dose steroids
3	61	MF2/Grade 3	4 weeks	RI- BU/FLU	16/ 16 MRD	Day 110	Day 10 of high dose steroids

[Table 1 patients characteristics]

Clinical Trial Registry: N/A

Disclosure: member of the Incyte Speakers Bureau

P262

Autoimmune Myositis as Paraneoplastic Complication of a Squamous Cell Carcinoma of the Tongue after Severe Chronic Graft versus Host Disease

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Background: Chronic graft versus host disease (cGVHD) and secondary malignant diseases are major complications late after allogeneic hematopoietic stem cell transplantation (HSCT). Especially after cGVHD of the oral mucosa secondary leukoplakia and squamous cell carcinoma are common complications and require specific prevention and therapy. Here we describe a case of a patient in our interprofessional long-term follow up program with severe cGVHD and multiple secondary carcinoma, complicated by paraneoplastic autoimmune myositis.

Methods: All patients are assessed for signs of cGVHD every 3 month, GVHD is graded according to the NIH consensus, GVHD of the oral mucosa is evaluated according the Schubert scale.

This case report is based on retrospective data, collected within the clinical routine.

Results: A female patient underwent HSCT of HLA ident sibling in 2008 at the age of 53 years after diagnosis of acute myelogenous leukaemia (AML) (FAB M1, 46XX, FLT3-ITD positive, ELN high risk) in CR1. Conditioning regimen consisted of 12 Gy TBI and cyclophosphamide combinded with GVHD prophylaxis with ciclosporin A. After HSCT AML remains in molecular complete remission. 4 months after HSCT the patient acquired aGVHD of the skin II° overall I° with need of local treatment with corticosteroids. 12 months after HSCT the patient acquired de novo cGVHD of the oral mucosa III° and joints I° overall severe. Local steroids were used as mouth rinses and systemic immunosuppression with corticosteroids was needed. In 2013 leukoplakia of the tongue was diagnosed first. In 2014 a squamous epithelium carcinoma of the tongue was diagnosed followed by partial glossectomy and neck dissection. Up to now the patient relapsed three times with need of further partial glossectomies and neck dissections and local radiation (30Gy) in 2018, complicated by enhanced inflammation of the oral mucosa and infections with different pathogens (herpes simplex, candida albicans, pseudomonas aeruginosa)

After another relapse of the carcinoma of the head and neck in 2019 the patient acquired a myositis with strong pain of all muscles as well as paraparesis with elevated creatine kinase (CK) up to 2042 U/l and elevated C-reactive protein values. Skeletal muscle antibodies were detectable. Due to clinical need prednisolone 2mg/kg was started. Symptoms and laboratory values declined rapidly, and the treatment was continued in our outpatient clinic for 3 weeks. When tapering the prednisone to 0,5mg/kg symptoms returned and CK raised. To spare steroids we discussed different antibody depleting strategies such as plasma-exchange or plasma-filtrating approaches and CD20 antibody rituximab. Due to patient wish we stared rituximab weekly (375mg/m^2) and continued this for 4 weeks. CK again declined to normal levels and skeletal muscle antibodies were not detected anymore, the patient remained clinically well without any symptoms.

Conclusions: This case reports describes a paraneoplastic immune myositis in a patient suffering from secondary malignancy as complication of a persisting cGVHD. To our knowledge this is a very rare event and this long term follow up of a patient with secondary malignancy following chronic GVHD is an example for the successful multidisciplinary approach in taking care of long-term survivors.

Clinical Trial Registry: -

Disclosure: Nothing to declare.

P263

Unusual Cause of Dyspnea in post-transplant Patient

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Background: Pericardial effusion related to graft-versus-host disease (GvHD) it is a rare complication after allogenic hematopoietic stem cell transplantation (alloHSCT). The incidence, risk factors, morbility and mortality have not been well defined.

Methods: Case report from a patient with a pericardial effusion and constrictive pericarditis attributable to chronic graft-vs-host disease.

Results: A 27 years old man diagnosed from a lymphoma Hodgkin with previous allogeneic transplantation of bone marrow from identical HLA related donor.

At six month post-transplant the patient developed a chronic GVHD affecting initially the liver and gastrointestinal tract, that responded to treatment with

ursodeoxycholic acid and prednisone. Four months later, he developed a cutaneous GVHD that required prednisone. After this event, he had a relapse of his lymphoma that responded with brentuximab and bendamustine. At 21 month post-transplant, the cutaneous GVHD got worse affecting 15% of body surface requiring prednisone and extracorporeal photopheresis for 6 months without respond. Cyclosporine and PUVA therapy were started, but they were suspended because of infections related to immunosuppression by cyclosporine. The affection by the cutaneous GVHD progressed and ruxolitinib was started with the reintroduction of extracorporeal photopheresis, keeping this treatment until the next emergency visit in month 29.

At 29 months post-transplant, the patient went to the emergency department with dyspnea. A chest radiography was performed showing effusion that required thoracentesis. A CT was performed and revealed a large pericardial effusion and the echocardiogram showed a constrictive pericarditis. All these symptoms appeared in association with a cutaneous GVHD that affected more than 50% of the body surface area. All the differential diagnoses were ruled out included infectious diseases. Lastly, the final diagnosis was pericardial effusion related to GVHD. The patient was treated with heart failure and immunosuppressive therapy, initially with corticosteroid in high doses associated with cyclosporine. In the absence of response to treatment, mycophenolate mofetil was added showing a complete resolution of pleural and cardiac effusion and partial response in skin symptoms.

Conclusions:

Pericardial effusion related to GVHD is a rare event, there is only a few cases described in the literature and it is a diagnosis of exclusion. The prevalence is around 0,89% especially affecting patients with a moderate to severe GVHD and the median time to onset is between 42 and 525 days post-transplant. The treatment requires the use of multiple immunosuppressive therapies.

Disclosure: Nothing to declare.

Graft-versus-host disease – preclinical and animal models

P264

Enhancing Regulatory T Cell Function and Homing to the Gut to Improve graft-versus-host Disease Prevention after Adoptive Transfer in Allogeneic Hematopoietic Transplantation

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Background: Adoptive immunotherapy with donor conventional T cells (Tcons) and $CD4^+CD25^+FOXP3^+$ regulatory T cells (Tregs) can prevent Graft-versus-Host Disease (GvHD) after haploidentical transplantation (Haplo-HCT) without post-transplant pharmacological immunosuppression. This protocol allows for ~70% chronic GvHD/relapse-free survival in patients with acute myeloid leukemia in any remission. However, acute GvHD (aGvHD) occurs in about 30% of patients (Pierini et al., submitted). We are evaluating the impact of Treg homing to target tissues on aGvHD control. Moreover, since the number of freshly isolated peripheral blood Tregs is limited, we are investigating strategies to boost Treg function before adoptive transfer.

Methods: Thirty-one colon biopsies from patients with suspected aGvHD were stained with anti-CD3 and anti-FOXP3 antibodies.

Human $CD4^+CD25^+$ T cells were incubated for 60 hours with IL-2 (10 UI/ml) with or without TNF-α (20 ng/ml). Treg proliferation and Treg-mediated suppression of Tcon proliferation were evaluated by CFSE assay.

Results: We analysed clinical signs of the last 21 patients with acute leukemia who were diagnosed with grade II-IV aGvHD after Haplo-HCT with Treg/Tcon immunotherapy. Median time to onset was 41 days post-transplant. aGvHD was refractory to steroids in 6 patients (29%). Fourteen patients are alive and off-therapy (67%). Seven patients died due to aGvHD (4), encephalitis (2) and relapse (1). Organ involvement at the onset was: gut in 20 patients, skin in 10 patients and liver in 9 patients. Ten patients (47%) presented with early-onset gut aGvHD without any skin involvement. We hypothesize that preferential targeting of the gut is the consequence of defective homing of Tregs. In fact, Tregs express higher levels of skin homing receptors (such as CCR4 and CLA-4), but lower levels of the gut homing receptor α4β7-integrin compared with Tcons. When we analysed the infiltration of Tregs and Tcons in colon biopsies from patients with suspected aGvHD, we found that number of Tregs and Treg:Tcon ratio were higher in patients who were not diagnosed with aGvHD compared with those who were ($p < .05$).

We are evaluating the effects of a short-term activation with low-dose IL-2 and TNF-α (IL-2/TNF) on human Tregs. In fact, recent studies showed that activation of mouse Treg with TNF-α improves their effectiveness in controlling

GvHD. Compared with Tregs stimulated with IL-2 alone, IL-2/TNF-primed human Tregs expressed higher levels of FOXP3 and CD25, displayed enhanced proliferation, and suppressed Tcon proliferation more efficiently in vitro. Importantly, priming with IL-2 or IL-2/TNF up-regulated α4β7-integrin expression on human Tregs compared with freshly isolated cells ($p < .01$), possibly improving gut homing. IL-2/TNF priming increased expression of genes associated with Treg activation, differentiation and function (Myb, CD83, OX-40, CCR8, CD39, CD69 genes) and components of the non-canonical NF-kB signaling pathway in whole transcript expression analyses.

Conclusions: After Haplo-HCT with Treg/Tcon immunotherapy, aGvHD preferentially targets the gut and is generally responsive to steroids without the need for long-term immunosuppression. The present study suggests that Treg homing in target tissues could be critical for aGvHD control and IL-2/TNF-priming could promote human Treg function and homing to the gut, improving GvHD control after Treg/Tcon immunotherapy.

Disclosure: Nothing to declare.

P265

LYG1-deficient Donor Splenocytes Attenuated the Severity of Acute graft-versus-host Disease Via Skewing $CD4^+$T Cell Polarization Towards Treg Cells

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Background: Acute graft-versus-host disease (aGVHD) is a lethal complication after allogeneic hematopoietic stem cell transplantation (HSCT). As a complex immunopathology, aGVHD depends on the recognition of host antigens by donor T cells and induces augmented response of alloreactive T cells. Previously, we reported LYG1 (Lysozyme G-like 1) as a novel classical secretory protein promoting anti-tumor activity of T cell. In this study, the role of LYG1 in aGVHD was investigated.

Methods: Lyg1-knockout (C57BL/6 background, $Lyg1^{-/-}$) mice and LYG1 recombinant protein (rhLYG1) were used, and a major MHC-mismatched aGVHD mouse model was adopted by transferring splenocytes and bone marrow cells (BMs) from C57BL/6 mice into lethally irradiated BALB/c mice.

Results: Firstly, using MLR assay in vitro, we found LYG1 deficiency reduced activation of $CD4^+$T cells and Th1 proportion, but the proportion of Treg cells was increased. Then we established aGVHD model by transferring splenocytes from wild-type (WT) or $Lyg1^{-/-}$ mice with WT BMs into BALB/c mice. The recipients receiving $Lyg1^{-/-}$ donor splenocytes showed higher survival rates, lower clinical aGVHD scores and milder damage in liver, lung and colon than those who received WT splenocytes, indicating LYG1-deficient donor splenocytes attenuated the severity of aGVHD. The activation of T cells and the proportion of Th1 decreased, whereas the proportions of Treg increased in spleens and livers in recipients receiving $Lyg1^{-/-}$ donor splenocytes. Further, rhLYG1 intraperitoneally administration in mouse aggravated aGVHD by promoting the activation of $CD4^+$T cells and Th1 differentiation, which confirmed the results established using $Lyg1^{-/-}$ mice. More importantly, LYG1 deficiency in donor splenocytes did not affect GVT (graft-versus-tumor) effects in mouse model. Finally, we explored the potential application in translational medicine. Patients with grade 2-4 aGVHD exhibited higher LYG1 levels in serum than patients with grade 0-1 aGVHD and LYG1 expression was correlated with the initiation and development of aGVHD.

Conclusions: LYG1 as a new target impacted aGVHD via skewing $CD4^+$T cell polarization and LYG1 blockade in aGVHD patients might have therapeutic potential.

Disclosure: No potential conflicts of interest were disclosed.

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P266

Attenuation of Murine Chronic Graft versus Host Disease by the Nrf2 Activator Mangiferin

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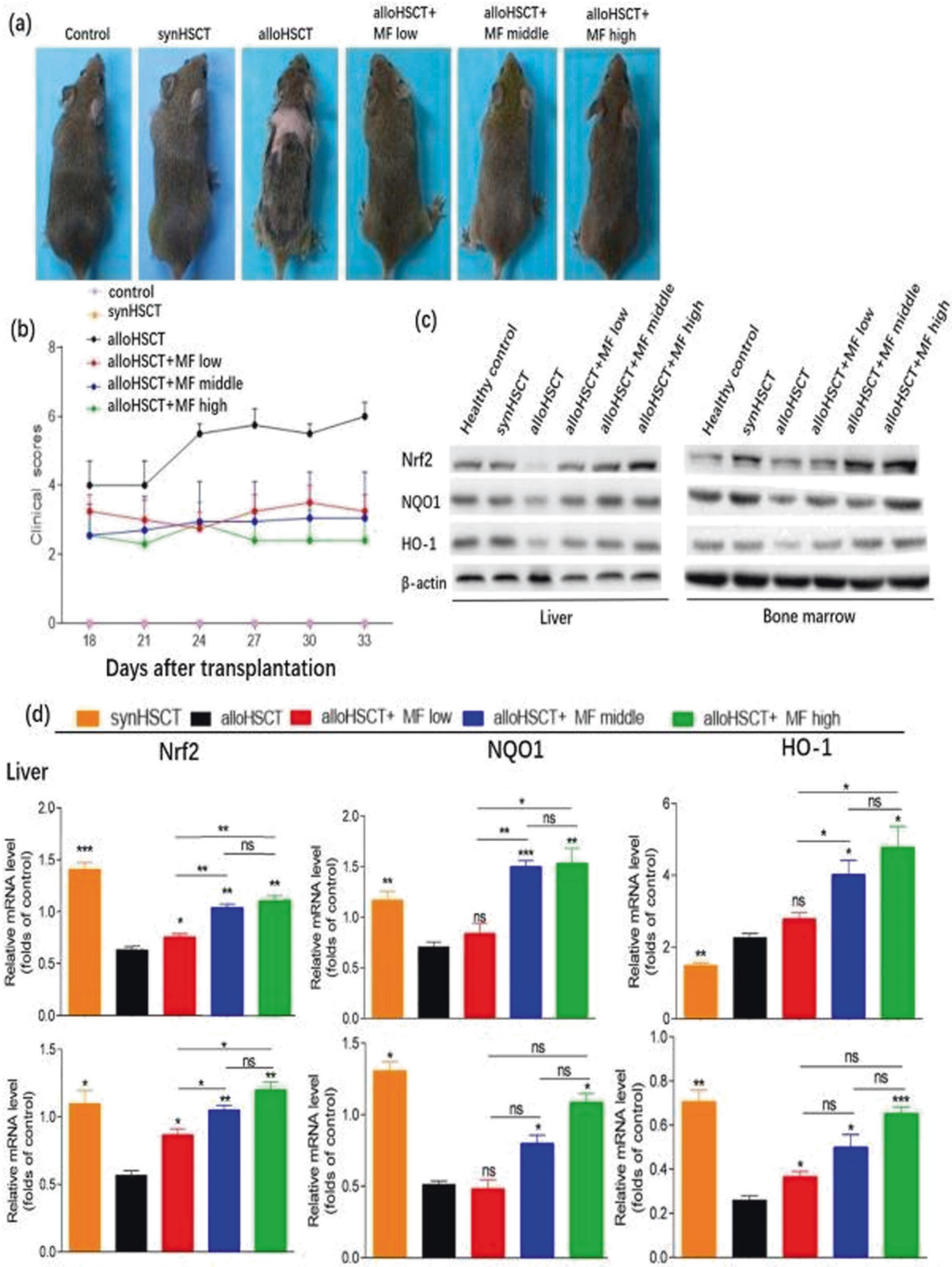
Background: Chronic graft-versus-host disease (cGVHD) is the primary cause of long-term morbidity and mortality after allogeneic hematopoietic stem cell transplantation (alloHSCT). NF-E2-related nuclear factor 2 (Nrf2) is a vital transcriptional factor which induces expression of antioxidant genes including NAD (P) H: quinone oxidoreductase 1 (NQO1) and heme oxygenase 1(HO-1). Our previous study has observed that Nrf2, NQO1, HO-1 mRNA levels were significantly decreased in the liver and bone marrow of allogeneic HSCT mice compared to those of syngeneic HSCT mice, suggesting that Nrf2 suppression


(a)
Control
synHSCT
alloHSCT
alloHSCT+ MF low
alloHSCT+ MF middle
alloHSCT+ MF high
(b)
control
synHSCT
alloHSCT
alloHSCT+MF low
alloHSCT+MF middle
alloHSCT+MF high
Clinical scores
Days after transplantation
(c)
Healthy control
synHSCT
alloHSCT
alloHSCT+MF low
alloHSCT+MF middle
alloHSCT+MF high
Nrf2
NQO1
HO-1
β-actin
Liver
Bone marrow
(d)
synHSCT
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alloHSCT+ MF low
alloHSCT+ MF middle
alloHSCT+ MF high
Nrf2
NQO1
HO-1
Liver
Relative mRNA level (folds of control)

[Figure]

could be involved in the pathogenesis of cGVHD. We therefore evaluated the potential impact of Mangiferin (MF), an activator of Nrf2, on the cGVHD development in vivo by using an established murine cGVHD model.

Methods: 10- to 12-week-old CB6F1 female mice as recipients were randomly divided into control, synHSCT, alloHSCT, alloHSCT+MF low dose, alloHSCT+MF middle dose, alloHSCT+MF high dose group (Three mice in each group). Irradiated recipients were transplanted with 8 × 10^6 male Balb/c bone marrow cells and 7 × 10^7 male Balb/c spleen cells (allogeneic) or 8 × 10^6 female CB6F1 bone marrow cells and 7 × 10^7 female CB6F1 spleen cells(syngeneic). 20,50,100mg/kg body weight MF and equal amount of vehicle solution were respectively administrated to the MF low, middle, high dose groups and alloHSCT group by gavage once daily starting from day 1 to day 14 after HSCT. All mice were sacrificed on day 27-33 after HSCT. Clinical cGVHD score and histologic analysis were used to evaluate cGVHD. Oxidative activity in PBMCs was assessed by intracellular reactive oxygen species (ROS) production. The mRNA levels and protein levels of Nrf2, NQO1, HO-1 in liver and bone marrow were examined by RT-PCR and western blotting.

Results: MF significantly ameliorated cGVHD responses and diminished the clinical and histopathological evidence of cGVHD in a dose dependent manner(Fig.a). cGVHD scores were reduced in MF-treated mice compared with allogeneic vehicle recipients (Fig.b). ROS levels in low, middle, high dose MF treatment groups were obviously lower than that in alloHSCT vehicle group.(3.02±1.07,1.46±0.19,1.06±0.03 vs 19.58±0.98, P< 0.01). Moreover, MF could notably upregulated Nrf2, NQO1, HO-1 protein levels (Fig.c) as well as mRNA levels (Fig.d) in bone marrow and liver dose-dependently. Data shown are mean ± SEM. *P < 0.05; **P < 0.01; ***P < 0.001;ns not significant.

Conclusions: The study firstly demonstrates the favorable effects of MF against murine cGVHD, rendering this compound a promising agent for the treatment or prevention of cGVHD.

Disclosure: Nothing to declare.

P267

Chemotherapy and Inflammation Induced Damage of Intestinal Epithelium is associated with Increased T Cell Chemotaxis

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Background: Tissue damage is a risk factor for the development of intestinal Graft-versus-Host Disease (GvHD) after allogeneic bone marrow transplantation (allo-BMT). In previous work we have shown that donor T cells are present in close proximity to the intestinal stem cell (ISC) containing crypts and that T cell secreted interferon-gamma (IFNy) causes ISC apoptosis. Recent studies have proposed that in GvHD in vivo donor T cells directly interact with intestinal epithelium, but the underlying mechanisms are not yet completely elucidated. Here, we study the influence of IFNy- and chemotherapy-induced intestinal epithelial damage on direct epithelial cell-T cell interactions and T cell migration.

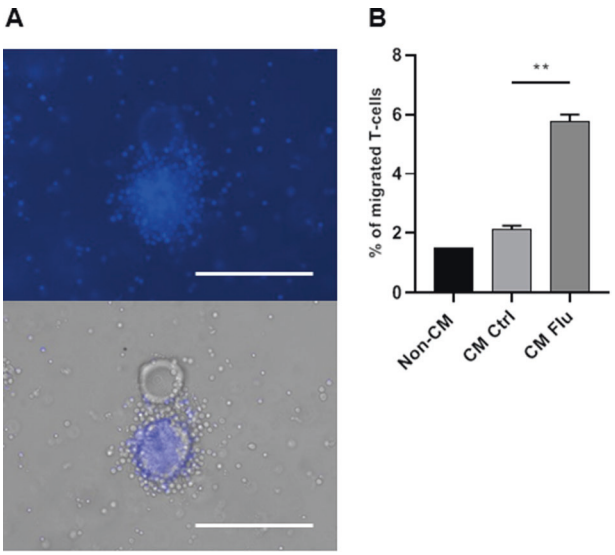
Methods: We developed a co-culture system of human intestinal organoids and polyclonally activated T cells in which we could study possible T cell-epithelial interactions. Organoids were treated with IFNy or Busulfan (Bu), Fludarabine (Flu), Clofarabine (Clo) to investigate the level of toxicity to organoid growth and survival. Furthermore, we investigated changes in epithelial expression of T cell immunogenic markers (HLA-type I, II and chemokines) upon damage. Medium obtained from organoids, here referred to as conditioned media (CM), was assayed by Luminex for chemo-attractants and used to assess the potential to influence T cell migration in a transwell system.

Results: Using the co-culture system, we observed that activated T cells assemble in close proximity to the organoids (Fig. 1A). RNA-seq analyses of IFNy-treated organoids indicated significant upregulation of T cell chemotaxis associated genes including CXCL9, 10 and 11, among many others, and luminex analysis of CM confirmed release of these chemokines in co-cultures versus controls. In addition, stimulation of organoids with IFNy led to upregulation of HLA-I and HLA-II at both the RNA and membrane protein expression level, setting the stage for possible direct T cell epithelial interaction.

Next, chemotherapy-induced damage of the intestinal epithelium was characterized. After chemotherapy treatment we observed a dose-dependent decrease in the number of surviving organoids, smaller organoid size, decrease in proliferation and induction of apoptosis, as seen by the presence of increasing levels of activated caspases. In addition, chemo-damaged intestinal epithelial cells showed impaired ability to reconstitute organoids in a concentration dependent manner. Chemo treatment did not affect HLA-I-II qPCR mRNA expression, but a donor-dependent

upregulation of membrane HLA-I protein expression upon exposure to Bu was observed. In a transwell migration assay we established that CM from chemotherapy-treated organoids exerts increased T cell chemotaxis compared to control medium (Fig. 1B).

Conclusions: In conclusion, intestinal epithelial damage induced by (T cell-derived) IFNy- and chemotherapy can lead to T cell migration in vitro, resulting in direct contact between allogeneic T cells and co-cultured human intestinal epithelium. As such, IFNy signaling and conditioning-related injury may contribute to GvHD pathogenesis in vivo by promoting recruitment to the intestinal crypt epithelium.



[Figure]

Disclosure: Nothing to declare.

P268

Inkt Cells Promote Immune Tolerance by Selective Dendritic Cell Apoptosis

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Background: Graft-versus-host disease (GvHD) is one of the main causes of morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT). Invariant natural killer T (iNKT) cells bear phenotypical features from both T and NK cells and interact preferentially with CD1d molecules through a semi-invariant T-cell receptor (TCR). We recently showed that donor iNKT cells can be expanded ex vivo being able to prevent activation and proliferation of alloreactive donor T cells while promoting efficient graft-versus-leukemia effects. However, the underlying mechanism remains unknown. Here, we demonstrate how human iNKT cells execute their protective function against GvHD by selective interaction with dendritic cells.

Methods: Monocyte-derived dendritic cells (mo-DCs) were cultured with expanded iNKT cells. Mo-DC apoptosis was analyzed by subsequent multiparametric flow cytometry and cytokines were measured via multiplex analysis. Transwell assays and imaging flow cytometry were performed to elucidate cell-cell interactions. Different receptors were blocked using specific antibodies to analyze their function for iNKT-cell activation. Furthermore, DC subsets from whole blood were isolated and purified with fluorescence-activated cell sorting. T-cell activation and proliferation were assessed after co-incubation with T cells to investigate the effect of iNKT cells.

Results: iNKT cells and mo-DC co-cultures demonstrated that iNKT cells induce apoptosis of allogeneic mo-DCs. Transwell assays and imaging showed that this occurs in a cell-contact-dependent manner resulting in the release of perforin, granzym B and granulysin as observed in the multiplex analysis. Furthermore, blocking experiments revealed that the HLA-I-like molecule CD1d is required for the induction of DC apoptosis. We observed an increased CD1d expression on mDCs in comparison to pDCs and this correlates with the results obtained in the T-cell activation and proliferation assays. mDCs were shown to induce higher expression of early and late T-cell activation markers as well as increased proliferation of alloreative T cells than pDCs. By addition of iNKT cells to T-cell and DC co-cultures, selective apoptosis of mDCs and significant decrease in T-cell activation and proliferation could be observed when compared to co-cultures without iNKT cells.

Conclusions: We propose a new mechanism how culture-expanded iNKT cells prevent alloreactivity and protect from GvHD in humans. iNKT cells modulate alloreactive T-cell responses by selective apoptosis of DC subsets in a CD1d-dependent manner Preferential apoptosis of mDCs leads to a relative expansion of pDCs that are known to contain tolerogenic properties, resulting in protection from GVHD while enabling beneficial immune responses following HCT.

Disclosure: Nothing to declare.

P269

A Murine Model Reveals A Critical Role for Reactive Oxygen Species in Hyperacute graft-versus-host Disease

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Background: Hyperacute graft-versus-host disease (GVHD) is a severe and rapidly fatal disease and is clinical defined as a GVHD occurring within 14 days after allogeneic haematopoietic stem-cell transplantation (allo-HSCT). Despite numerous studies, the pathological process and the crucial factors driving this disease remain undefined. Myeloid derived suppressor cells (MDSCs) have a beneficial role in transplantation and can suppress alloreactive T-cell responses with the help of reactive oxygen species (ROS).

Methods: BALB/c (H-2Kd) or C57BL/6 (H-2Kb) mice (8-12 weeks age) were used as donor mice and age- and gender-matched C57BL/6 (H-2Kb) or gp91phox-/- (B6.129S6-Cybbtm1Din, H-2b) chronic granulomatous disease (CGD) mice were used as recipient mice to establish a completely mismatched or completely matched major histocompatibility antigen (MHC) murine model.

Results: In this study, we established a murine model of hyperacute GVHD, allowing us to discover that NADPH oxidase deficiency causes the mice to rapidly die of hyperacute GVHD developed before engraftment and depending only on allogeneic cell infusion. Furthermore, the donor splenic T cells are critical for the development of hyperacute GVHD, while alloreactive T cells are activated massively, proliferate and obtain strong killing ability during hyperacute GVHD. We find that NADPH oxidase-dependent ROS production by MDSCs is essential for preventing alloreactive T cells from over-activation. Moreover, treatment with ROS agonist rescues the defects of hyperacute GVHD in NADPH oxidase-deficient mice, while there is a link between low ROS level and the development of hyperacute GVHD symptoms in patients after allo-HSCT.

Conclusions: Together, our findings suggest that NADPH deletion impairs the ability of MDSCs to produce ROS, leading to the activation and proliferation of alloreactive T cells and subsequently hyperacute GVHD. Thus, we provide new insights into the pathogenesis of GVHD, which may improve the clinical management of this fatal complication.

Disclosure: Nothing to declare.

P270

Mapping the Road of GVHD and GVT. A Longitudinal Study of immune-transcriptome Signatures as Novel Approach to Solve post-allogeneic Transplantation Dilemmas

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Background: Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT) is currently the only curative therapy for high-risk hematologic malignancies.

Despite extensive research, very few predictors of GVHD and GVT have so far been identified. Additionally, GVHD diagnostics can be challenging due to overlapping therapy- or and infection-related organ toxicities manifestations, thus further complicating prediction and stratification algorithms.

We designed a multicenter study to study the mechanisms of GVHD and GVT through a novel approach, that captures longitudinal immune signatures, as dynamic "snapshots" of the patient's immune system after alloHSCT. The method is called Transcriptome Fingerprint Assay (TFA). It is a multiplex q-PCR based assay linked with modular functional transcriptome analyses, uniquely tailored for answering complex questions on immune perturbations through frequent profiling of gene expression signatures from small quantities of blood. TFA has been successfully applied to stratify patients prognosis in autoimmune diseases and viral infections.

The study is based on the hypotheses that fluctuations over-time in the gene expression of alloHSCT patient's immune system reflect the pathologic/disease control programs (GVHD/GVT) and may be tested as diagnostic and predictive biomarkers.

Thus, the objective of the study is to systematically measure gene expression signatures in immune perturbations post-alloHSCT, in order to:

a. identify GVHD-related immune signatures consistent with GVHD clinical diagnosis

b. predict and stratify therapy-resistant GVHD and severe chronic GVHD, according to immune signatures.

identify links (causative and consequential) between GVHD, GVT, relapse, and other post-transplant immune perturbations, as infections.

Methods: The study design entails the recruitment of 250 alloHSCT patients and 50 donors (healthy controls cohort) to populate a "GVHD cohort" and a "non-GVHD cohort" of 50 patients each.

Patients donate micro-quantities of blood (50 to 600 microliters), every week until day 100 post-transplant and every 2 weeks thereafter until 2 years after alloHSCT. Detailed clinical, lab and therapy annotations are captured during the follow-up. The gene expression of 265 immune-related genes for every sample are analyzed through Fluidigm q-PCR system, and normalized on a pool of 8 housekeeping genes. Data interpretation is performed through TFA modular analyses and correlated with the clinical annotations.

Results: The preliminary results of the first 8 patients have been analyzed with a follow up of 93 to 304 days after transplant. All patients underwent myeloablative alloHSCT (3 MUD, 5 MRD), for 1 of them the graft was depleted for CD45RA T cells, for 1 the source was BM. Seven out of 8 patients developed a steroid responsive-aGVHD, with some differences in the clinical response (responders/slow responders/GVHD-flairs). Three patients developed cGVHD after aGVHD. The series of transcripts expressed over time, grouped in modules are displayed. Of note, IFN signatures faithfully followed the clinical course of the patients, peaking with aGVHD, dropping with steroids responsiveness, and reappearing with GvHD flairs.

Conclusions: We hope to contribute through this novel approach to fill knowledge gaps instrumental to solve clinical dilemmas related to alloHSCT complications, and to improve the clinical outcomes of alloHSCT patients.

Disclosure: Nothing to declare.

P271

Cell-free DNA Levels are Increased in Acute graft-versus-host Disease in Patients and Mice

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Background: Cell-free DNA (cfDNA) and DNA binding proteins in circulation are markers of cell-damage, which play an important role in various inflammatory diseases. However, the role of cfDNA in acute Graft-versus-Host Disease (aGvHD), a major complication of allogeneic hematopoietic stem cell transplantation (HSCT), is unknown. Conditioning treatment preceding allogeneic HSCT and tissue damage during ongoing GvHD may cause the release of cfDNA, which may in turn stimulate the anti-host immune response in aGvHD. The aim of the present study was to investigate cell-free DNA in the form of nucleosomes in aGvHD using a translational approach: first, we measured nucleosomes in aGvHD patients and second we monitored nucleosome levels in a xenotransplantation model for aGvHD.

Methods: Thirty-eight patients admitted for allogeneic HSCT were included in the study. Blood samples were collected at baseline (before allogeneic HSCT) and 1, 3, 6, 12 and 24 months after allogeneic HSCT. Only patients with early onset (< 100 days) of acute GvHD were included. Cell-free DNA in the form of nucleosomes as well as cytokines were measured by ELISA; in addition we set up a xenotransplantation model using NOD-SCID IL-2rγ^{null} (NSG) mice challenged with human PBMCs to induce aGvHD. Chimerism, nucleosomes and cell-free DNA specific for mouse and human, respectively, was assessed before and after clinical development of aGvHD.

Results: Nucleosome levels, as a measure for total cfDNA, measured in plasma of 38 allogeneic HSCT patients were equal at baseline between patients that did (n=19) and did not develop aGvHD (n=19). However, nucleosome levels were significantly increased 1 month after aHSCT in aGvHD patients. In addition, in a majority of aGvHD patients there was a sample available just before and/or after the diagnosis of aGvHD. Nucleosome levels measured in samples before (n=9) or after diagnosis of aGvHD (n=14) were significantly higher as compared to the baseline levels. In the xenotransplantation model, severity and lethality of aGvHD increased in parallel with increasing doses of PBMC (1x10E5/g, 6.3x10E5/g, 1x10E6/g and 2.5x10E6/g, respectively). Nucleosome levels increased in parallel with the amount of PBMC administered and the severity of aGvHD. This was evidenced by the significant correlation of nucleosome levels with clinical and pathology scores of GvHD and chimerism levels ($r>0.70$, $p< 0.005$). Using a species-specific PCR, we found that this cfDNA is mainly of human origin and to a lesser extent of mouse origin, indicating that cfDNA can both be attributed to (proliferating) human PBMC and damaged mouse cells.

Conclusions: We demonstrate for the first time that nucleosome levels as a measure for cell-free DNA significantly increase during aGVHD. Furthermore, we show

mice suffering from aGvHD to have increased levels of nucleosomes and that cfDNA is mainly attributable to human hematopoietic cells and to a lesser degree by (damaged) non-hematopoietic tissue. We propose nucleosome levels as a marker to monitor severity of GvHD

Disclosure: no conflicts of interest reported

P272

DS-2741a, anti-orai1 Antibody, Showed Ideal Profile of Immunosuppressant for GVHD Treatment by Biased Inhibition on Effector T Cells without Affecting Regulatory T Cells Function

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Background: Adequate prophylactic control of graft-versus-host disease (GvHD) has considerable impacts on the prognosis of treatments for leukemia and aplastic anemia. Calcineurin inhibitors (CNIs) are standard of care to manage the GvHD risk, but difficulties exist in prescribing CNIs due to their nephrotoxic potentials, and drug-drug interaction. ORAI1 is a component of calcium release-activated calcium (CRAC) channels in immune cells, and mediates calcium-calcineurin-nuclear factor of activated T cells (NFAT) signaling pathway for T cell activation. Patients with ORAI1 homogenous non-functional mutations exhibit Severe Combined Immunodeficiency (SCID), but no defects are observed in kidneys. Accordingly, inhibition of ORAI1 would be a promising strategy to suppress T cell activities without nephrotoxicity, which is the ideal characteristics compared to CNIs. Here, we obtained a channel-blocking humanized anti-ORAI1 antibody, DS- 2741a, and evaluated its pharmacological actions in isolated human T cells and efficacy in the mouse disease models.

Methods: Effects on human PBMCs and T cell subsets

Naïve $CD4^+$ T cells isolated from human peripheral blood mononuclear cells (hPBMCs) were differentiated into Th1, Th2, Th22 or regulatory T cell (Treg) by stimulation with anti-CD3/28 antibodies and relevant cytokines. Inhibitions of cytokine productions from these T cell subsets or hPBMCs with DS-2741a (0.3 pM - 60 nM) or calcineurin inhibitor, Tacrolimus (10 nM) following PMA/Ionomycin stimulation were determined by commercially available ELISA kits. For Treg differentiation assay, number of $Foxp3^+$ cells were evaluated by FACS.

Effects on Treg suppression activity on effector T cells

$CD4^+CD25^-$ effector T cells (Teff), and $CD4^+CD25^{high}$ Treg cells isolated from hPBMCs were co-cultured in the presence of $CD3^-$ accessory cells and anti-CD3/ CD28 antibodies with or without DS-2741a (0.1-10nM). In the presence of Treg cells, the Teff activity were determined by [methyl-^{3}H]-tymidine uptake.

Efficacy in acute GvHD (aGvHD) mouse model

Male NSG mice were X-ray irradiated and injected i.v. with hPBMCs on Day 0. DS-2741a (3-30 mg/kg) was administered i.v. once per week (Day-1, 6, 13), and tacrolimus (10-30 mg/kg) were administered p.o. daily from Day 0 to 28.

Results: Effects on human T cell subsets

The maximum inhibition level of DS-2741a on cytokine production from hPBMCs or several T subsets was as strong as that of tacrolimus. DS-2741a did not inhibit differentiation into $Foxp3^+$ Treg cells from naïve CD4 cells nor Teff suppression activity unlike Tacrolimus

Efficacy in aGvHD mouse models

Decrease in body weight of the recipient mice was evident within 14-21 days post-transfer of hPBMC. DS-2741a treatment completely suppressed the body weight loss. The maximum efficacy of DS-2741a on this model was equal to or greater than that of tacrolimus.

Conclusions: DS-2741a, inhibited activities of each effector T cell subset, and its inhibitory potency was comparable to that of tacrolimus. Unlike tacrolimus, DS-2741a didn't inhibit Treg cell differentiation and Teff suppression activity. DS-2741a prevented aGvHD in the mouse model with comparable or superior potency to that of Tacrolimus. These results demonstrate promising therapeutic potential of DS-2741a to prevent clinical aGvHD events with desirable efficacy/safety profiles compared to CNIs.

Disclosure:

Masatsugu Oh-hora

Joint research fund: DAIICHI SANKYO CO., LTD.

Anri Aki, Hiroaki Maeda and Kiyoshi Morimoto

Nothing to declare.

P273

B-t Cell Interactions in graft-versus-host Disease

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Background: Cytotoxic T cells (CTLs) are the final key-players in GVHD and also B cells are well known contributors.

B-cells role in the pathogenesis of immune responses is multifold, including antibody-mediated and -independent mechanisms, such as antigen presentation and cytokine production, including chemokine release, targeted to T cell attraction. In chronic GVHD (cGVHD), B cells are mostly studied for their antibody production, while their cellular immune involvement is less understood.

We explored the cellular interactions of B cells with CD8 cells in patients suffering from late acute and cGVHD. In a retrospective study, we described the evidence of peripheral blood CD19-CD8 cell coupling shortly after the onset of GVHD. This phenomenon was easily detectable in regular flow-cytometry screenings, where couplets were identifiable by size and by double positive CD19-CD8 antibody markers. Also in GVHD tissue biopsies, coupling was clearly visible between the cells. Even if quite rare (usually < 1% in blood), couplets significantly distinguished patients with GVHD after transplantation, from patients without GVHD and from normal donors. B cells in the couplets showed an activated phenotype, with high expression of CD80 and CD86 (Deola, BMT 2017).

CD19-CD8 interactions might theoretically be also present in lymphoid structures even in acute GVHD (aGVHD), when B cells are not yet circulating. Preliminary experiments in an OT-I/m-act OVA aGVHD mouse model actually confirmed the presence of B-CD8 couplets in Payer's Patches of mice with overt aGVHD. Distinction by CD45 donor-recipient mismatch chimerism showed a donor origin of couplets.

In order to unravel the significance of CD19-CD8 coupling, we built an in-vitro model with PBMCs of healthy donors.

Methods: Flu and CMV antigen-specific CTLs of healthy-donors are expanded with cognate peptides and IL2 for 1-2 weeks, then immune-selected for CD8 antigen by Miltenyi microbeads negative-selection and incubated (2-18 hours) with fresh autologous CD19-B cells immune-selected with the same method. CD19-CD8 couplets are measured through flow-cytometry (SymphonyA5 BD) and video-imaging (Confocal LSM 880+Imaris analysis software).

Results: B-CTL couplets are formed by alpha-beta TCR + CD8+ CD45RA++ CTLs preferentially targeting CD27 + CD19+ cells. Interactions may last from 5 minutes to roughly 1 hour. CTLs spike a discrete Ca++ flux after interaction and leave B cells intact. Couplets frequency is partially decreased by interference with MHC class I through blocking antibodies, although the cognate antigen recognition on B cells is not involved. Indeed, when B cells are artificially mounted with cognate peptide are promptly killed by T cells. Also, in a mixed population of Ag-specific expanded CTLs (10-30% Ag specific for CMV or Flu peptide) both Ag-specific and non Ag-specific CD8 seek interactions with B cells.

Conclusions: CTLs are the ultimate line of "tissue attack" in GVHD and several diseases, as autoimmune diseases, cancer, viral diseases, sharing a common pathological program definable as "immune rejection". B cells are key players in immune rejection, but a link between these 2 types of cells is still unclear.

We are currently exploring the significance of these cell interactions, to assess their relevance in the immune system responses and in particular in GVHD.

Disclosure: Nothing to declare.

P274

Identification of Potential Microbiome Markers for AGVHD Early Diagnosis

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Background: Graft versus host disease (GvHD) is a condition that might occur after an allogeneic transplant. It has been shown that shifts in the gut bacterial flora and loss of microbiome diversity may predict acute GI GvHD. Gut microbiota is also known to regulate the immune function.

Methods: Stool and blood samples were collected from 69 subjects undergoing Allogeneic hematopoietic stem cell transplantation (allo-HSCT) at St. Istvan and St. Laszlo Hospital, Semmelweis University Budapest, Hungary, at 6 Time Points (before the allogenic transplant [-7 to 0], 7,14,21,28 and 100+ days after the transplant). The microbiome composition was obtained by 16S rDNA sequencing on the Illumina MiSeq platform and QIIME based analysis. The LEfSe modules were applied to discover the biomarkers that identify differences between two or more clinical conditions.

The blood transcriptome of the immune function was obtained using transcriptome fingerprinting assay (TFA) of 273 genes combined in 66 expression modules (R Banchereau et al. Cell 165 (6), 1548-1550. 2016. PMID 27259156.)

Results: preliminary data from microbiome analysis showed that Bacteroidetes and Firmicutes steadily dropped

as the days progressed in GvHD patients, comparatively the Non-GvHD patients. At phylum level, GvHD patients displayed an increase in Proteobacteria starting from Day 21 onwards. At the Genus level data revealed the prominence of the Escherichia-Shigella and Enterobacter on the 100 +day timepoint in the GvHD patients. LEfSe analysis indicated that the common microbes Ruminococcaceae, Lachnospiraceae, Agathobacter etc. were abolished in the GvHD patients as the days progressed. TFA analysis is in progress.

Conclusions: the architecture of the microbiome is altered in GvHD patients and identifying these early biomarkers may help in an effective therapeutic regime targeting a faster restore of immune function.

Disclosure: Nothing to declare.

Granulocyte and osteoclast disorders

P275

Haploidentical Hematopoietic Stem Cell Transplantation with post-transplant Cyclophosphamide for Osteopetrosis

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Background: Malignant infantile osteopetrosis (MIOP) is a rapidly progressing hereditary disorder characterized by excessive bone overgrowth due to a defect in bone marrow resorption by osteoclasts. This condition causes progressing irreversible cranial nerve damage and bone marrow insufficiency. Allogeneic hematopoietic stem cell transplantation (HSCT) is curative and may stop disease progression but needs to be done as soon as possible before permanent damage such as blindness ensues. Haploidentical HSCT is a feasible option for MIOP patients who do not have a matched donor, but engraftment failure and graft loss are common. Post-transplant cyclophosphamide (PT-Cy) regimens for haplo-HSCT are gaining popularity and recent reports in malignant and non-malignant transplants show promising results. We report our experience with five MIOP patients who were transplanted with a haploidentical donor with PT-Cy.

Methods: We collected data from all patients with MIOP who underwent HSCT using PT-Cy at Hadassah Medical Center. The collected data included age and clinical presentation at diagnosis, genetic diagnosis, conditioning regimen, time to engraftment, clinical course and outcome.

Results: Five patients with MIOP have been transplanted from haplo-identical donors with PT-Cy during the years 2015 to 2019 at Hadassah Medical Center. In the first two cases the PT-Cy transplant was a second transplant following engraftment failure after CD34 selected PBSC haplo-transplants. The first is alive and well and the second died from sepsis and ARDS twelve days post his second transplant. The third case was a successful transplant using PT-Cy upfront, and is currently more than three years post HSCT, alive and well. The fourth case was transplanted at the age of 8 months from his haplo-identical father using PT-Cy and died from overwhelming klebsiella sepsis eleven days after the transplant. The fifth case gradually lost his graft after PT-Cy transplant from his 7/10 matched sister and underwent a second transplant from the same donor with a CD34 selected PBSC graft. As of today, four months post his second transplant, he is alive and well.

Conclusions: In our experience, haplo-identical transplant for osteopetrosis with PT-Cy is a feasible option. However, considering the risk of engraftment failure and graft loss we still prefer choosing an unrelated donor if available, even with a one-locus mismatch, over a haploidentical donor.

Disclosure: Nothing to declare.

Haematopoietic stem cells

P276

Clonal Dynamics and Genomic Integrity of Hematopoietic Stem and Progenitor Cells in Human Allogeneic Transplantation Recipients

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Background: Hematopoietic stem cells (HSCs) support the lifelong production of blood cells, and are used therapeutically for transplantation of patients suffering from various, otherwise lethal, diseases (HSCT). Administration of sufficient numbers of undamaged HSCs is crucial to restore hematopoiesis in the recipient, and to maintain long-term polyclonal blood formation. However, the number of HSC clones that regenerate the recipient's blood, and the consequences of transplantation on the genomic integrity of HSCs, remain elusive. We aimed to determine the clonal contribution of individual HSCs to blood regeneration upon

transplantation, and to unravel the mutational consequences of transplantation.

Methods: Here, we adopted retrospective lineage tracing, using naturally occurring somatic DNA mutations as "barcodes" to identify and trace single HSCs. We included three pediatric HSCT recipients and their sibling donors. All recipients were transplanted because of acute lymphoblastic leukemia, with bone marrow stem cells after myeloablative conditioning. We isolated hundreds of HSCs from the bone marrow graft, and from blood of the HSCT donor and recipient. To obtain sufficient DNA for whole genome sequencing, we clonally expanded these cells in vitro. Of each donor-recipient pair, we selected six clones for in-depth mutation capture by whole genome sequencing. Subsequently, we validated the presence/absence of these mutations in the additional HSC clones and in each of the mature cell populations by targeted sequencing. Using bioinformatic pipelines, we reconstructed the clonal dynamics of the transplanted HSCs up to six years after transplantation.

Results: We found that the number of mutations in single HSCs of the donor and recipient corresponded to normal age-dependent mutation accumulation in the HSCT donor. We observed a median of 269 (range 213-269) base substitutions in single HSCs of the HSCT donor, which was similar to the expected number of base substitutions based on the biologic age of the HSCs (median 298, range 241-298). This indicates that the impact of transplantation on HSC mutagenesis in this cohort was negligible. We did not find any difference in the type of mutations, nor in mutational signatures between HSCs obtained prior and after transplantation. Using population dynamics based on shared mutations, we reconstructed the hematopoietic lineage tree for each HSCT donor-recipient pair and quantified the contribution of single HSCs to each of the mature cell populations.

Conclusions: This study provides comprehensive data on the clonal dynamics of HSCs in human allogeneic transplantation recipients. Surprisingly, our findings demonstrate that transplantation does not damage the genome of the HSCs. In future studies, we will investigate the impact of stem cell source and donor age on HSC mutagenesis in the recipient. Ultimately, this work may improve clinical transplant protocols and contribute to map the landscape of human fundamental HSC biology.

Clinical Trial Registry: N/A

Disclosure: Nothing to declare.

P277

Abstract already published.

P278

Treatment of Pure Red Cell Aplasia after Major ABO Incompatible Allogenic Stem Cell Transplantation: A French Retrospective Study

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Background: Pure Red Cell Aplasia (PRCA) following allogenic hematopoietic stem cell transplantation (AHSCT) is mainly related to major ABO incompatibility. Delay of erythrocyte recovery is responsible for fatigue and iron overload. Management and treatment of this complication are still controversial and non-evidence based.

Methods: We conducted a retrospective study in four French hematologic academic centers, which included all patients who received a major or bidirectional ABO incompatible AHSCT between January 2009 and December 2018 excluding cord blood AHCST. PRCA was defined at 60 days post-transplant as anemia requiring red blood pack transfusions associated with reticulocytopenia below 10 G/L. Early disease progression, primary graft dysfunction and alternative PRCA diagnosis were excluded. The primary endpoint was the cumulative incidence of transfusion independence, considering death as a competing event. We evaluated the impact of specific treatment administration on the primary outcome usinga cause-specific cox model with time-dependent covariate. The analysis of Erythropoietin administration was performed separately.

Results: Among the 633 AHSCT, 66 patients experienced PRCA and the cumulative incidence was 10.5% [8.2-13]. The median duration of PRCA was 171 days [116; 261]. No significant differences between treated or untreated subjects were observed (HR=0.8 CI95 [0.41; 1.58], p=0.53) in univariate analysis. Interestingly, acute graft versus host disease (aGVHD) during the first 60 days post-transplant significantly prevented the occurrence of PRCA (p=0.001). Twenty-one patients (31.8%) received at least one specific treatment of PRCA at a median time of 116 days [77; 211] post-transplant. Seventeen patients

received an anti-CD20 monoclonal antibody (Rituximab, weekly 375mg/m2 infusion during 1 to 4 courses) as a first line treatment for most of them, whereas donor lymphocytes infusions (DLI, 7 patients) were given mainly as a second line drug. Isolated patients received respectively steroids, thrombopoietin receptor agonist, boost of CD34+ selected cells or 2ndAHCST. Twenty-two patients (33.3%) received erythropoietin starting at a median time of 69 days [41; 106], there were neither significant reduction of the PRCA period (HR=0.87 CI95 [0.46; 1.6], p=0.65) in univariate analysis nor reduction of the red blood pack transfusions. Occurrence of a PRCA did not influence the survival in multivariate analysis (HR=0.95 CI95 [0.62; 1.45], p=0.81) just as gender (p=0.15), HLA matching (p=0.14) and myeloablative conditioning regimen (p=0.22) on the contrary, age (p< 0.001) and aGVHD (p=0.01) decreased overall survival. Otherwise PRCA patients who received a specific treatment had a significant reduction of survival (p=0.03) in univariate analysis.

Conclusions: Half of patients who experienced PRCA secondary to major ABO incompatibility resolved this complication during the first six months after ASCT with or without specific therapy. In this study no significant advantage was shown to use erythropoietin, Rituximab or DLI in terms of time for erythrocyte recovery or the number of red blood pack transfused in this setting.

Disclosure: Nothing to declare.

P279

Feasibility and Outcomes of a Third Allogeneic Haematopoetic Stem Cell Transplantation: A Retrospective Analysis from the ALWP of EBMT

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Background: Second allogeneic haematopoetic stem cell transplantation (HSCT2) is a frequently used approach for recurrence of acute leukemia (AL) post HSCT. However, many recipients of HSCT2 will suffer from subsequent relapse. No standard of care is established for this devastating clinical situation. Therefore, we evaluated feasibility, efficacy, and outcome of a third HSCT (HSCT3) for relapsed AL.

Methods: The EBMT/ALWP registry was screened for patients undergoing HSCT3 from an identical or alternative donor to treat AL in either haematological relapse or disease persistence of after HSCT2 between 2001 and 2018. Outcome and risk factors were analyzed retrospectively.

Results: Forty-five patients with acute myelogenous (AML, n=34) or lymphatic leukemia (ALL, n=11) were identified. Median patients' age at time of HSCT3 was 37 years (range: 12 - 71). The median interval from HSCT2 to HSCT3 was 12 months (range: 2 - 53). Reason for a third transplantation was relapsed (n=42) or refractory (n=3) disease after HSCT2. Before HSCT3, complete remission was achieved by salvage chemotherapy in 11 patients (24%), 34 (76%) patients were transplanted with active disease. Donors for HSCT3 were HLA-identical related (n=12), unrelated (n=17), haploidentical (n=11), cord blood (n=4), and syngeneic (n=1). Fifteen patients were transplanted from the same donor at all three transplants, 30 patients had 2 or 3 different donors. In particular, donor change was realized between HSCT2 and HSCT3 in 58% of patients.

After HSCT3, 38 patients engrafted, 7 died in aplasia. Twenty six (58%) patients achieved complete remission after HSCT3. After 1 year, cumulative incidences of leukemia relapse and non-relapse mortality were 47% and 51% respectively. Rate of acute graft-versus-host disease (GvHD) grade II - IV at day 100 was 19%, chronic GvHD was observed in 5 patients. Progression-free survival (PFS) and overall survival (OS) at 6 months, 1, and 2 years from HSCT3 were 29%, 11%, and 2%, and 42%, 20%, and 7%, respectively, with a median survival of 4 months. Patients transplanted with at least two different donors for their three transplants had a better OS and PFS compared with patients using the same donor for HSCT1-3 (1-year OS: 30% vs. 0%, p=0.009, 1-year PFS: 13% vs. 0%, p=0.007, log rank).

Conclusions: Results of third allogeneic transplantation for repeatedly relapsing acute leukemia are poor with 2 year LFS of 2% and a median survival of 4 months. Recurrent relapses of AL remain an unmet need and a major obstacle for successful HSCT. A third allogeneic transplantation should be based on an individual decision in carefully selected patients only.

Disclosure: None

P280

Changes in Viability Markers of Haematopoietic Stem Cells Following long-term Cryopreservation

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Background: Hematopoietic stem cell (HSC) products for autologous transplantation are cryopreserved and stored in vapour phase liquid nitrogen (-197ºC to -150ºC). Although most AutoHSC products are collected with a view to early use, increasing numbers of myeloma patients undergo second AutoHCTs many years later. Several groups have reported on a deterioration in the quality of HSC products in long-term storage. However, there is no consensus on a universal expiry date. We therefore used a standard set of viability markers to assess the effects of long-term storage on HSC products.

Methods: Viability testing was performed using an in-house standardised EBAO viability method, viable CD34+ cells were measured using BD™ Stem Cell Enumeration Kit and functional testing was performed using in vitro progenitor colony cultures assays (CFU-GM (Colony-forming unit-Granulocyte macrophage) & BFU-E (Burst Forming Unit-Erythroid) assay). Fifty-eight cryopreserved HSC products that were in storage for less than one year (median two months) and 44 cryopreserved HSC products that were in storage for between one and 22 years (median 9.9 years) were analysed. A post-thaw sample was taken directly from the clinical product bag for analysis. All were autologous PBSC products that had been harvested and cryopreserved in our institution using a largely consistent cryopreservation process over 25 years. All statistical analysis was performed using IBM SPSS software (Version 24).

Results: Analysis of these one hundred and two HSC products revealed a statistically significant decrease in PV, VCD34 and progenitors over time. The median EBAO % viability (PV) of the 58 HSC products in storage for less than one year was 90.7% and that of the 44 products in storage for more than one year was 83.2% (Fig. 1). The other median viability marker values in the respective cohorts were as follows: Viable C34+ cells (VCD34) 88.2% and 68.7%; BFU-E 105.9% and 47.7%, and CFU-GM 104.8% and 84.9%, respectively. The following statistically significant correlations between viability markers and time in storage were found: VCD34 recovery -1.7% per year ($p< 0.01$), BFU-E recovery -3.1% per year ($p< 0.01$), CFU-GM recovery -3.6% per year ($p< 0.01$). The relationship between the VCD34+ cell count ($x10^3$/mL) (both at harvest and post-thaw) and days to neutrophil engraftment was not statistically significant ($p=0.251$, $p=0.976$, respectively). However, there was a statistically significant correlation between the VCD34+ cell count (both at harvest and post-thaw) and days to platelet engraftment ($p< 0.001$, $p=0.001$, respectively).

Conclusions: We estimate a loss in HSC potency of approximately 2% per year in storage, based on the regression coefficients of -1.7% and -3.1% for VCD34 and CFU-GM recovery, respectively. This is unlikely to be of clinical significance for larger CD34+ doses. However, for patients whose cryopreserved cell dose is borderline, it may be relevant. A product with a dose of 2.0 $x10^6$/kg CD34 cells at collection may have a viable dose of 1.6 $x10^6$/kg after ten years of storage. '-2%/year' could be used as a rule-of-thumb to estimate the predicted post-thaw dose in products in long-term storage.

Disclosure: Nothing to declare.

P281

High pre-transplant Interleukin-18 is associated with Poor Hematopoietic Recovery after Allogeneic Stem Cell Transplantation and Predicts Increased non-relapse Mortality

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Background: Interleukin-18 (IL-18) is a pleiotropic immunoregulatory cytokine expressed in a variety of cells like monocytes, endothelial and epithelial cells. IL-18 acts on CD4+ and CD8+ T cells as well as on NK cells to induce Interferon-γ (IFNγ) production. Only unbound free IL-18 is biologically active. IL-18 is controlled by an inhibitor (IL-18 binding protein, IL18BPa). IL-18 is involved in endothelial activation and dysfunction and in the context of allogeneic stem cell transplantation (alloSCT), IL-18 has been associated with the pathogenesis of acute graft-versus-host disease (aGvHD). Our group has observed a significant association of higher pre-transplantant levels of IL-18 with increased non-relapse mortality (NRM) and worse overall survival (OS). Recently, attention was drawn to a possible relationship of IL-18 and hematopoietic proliferation. Hence, we investigate here whether free IL-18 serum levels measured before and on

day 0 of alloSCT are associated with hematopoietic recovery.

Methods: A training cohort (I) of 617 patients and a validation cohort (II) of 605 patients were included in this study. Pre-transplant serum samples were collected before alloSCT and cryopreserved at -80°C. Serum levels of pre-transplant IL-18 and IL-18BPa, together with the IFNγ-response marker CXCL9, were analyzed in patients of both cohorts, as well as in 43 normal subjects. Further, IL-18 and IL-18BPa levels were measured also on day 0-3 of alloSCT in 309 patients. Routine lab parameters were recorded pre-transplant and on days 0, +28 and +100 after alloSCT. These were compared to cytokine serum levels and outcome. Receiver operating characteristic (ROC) analysis was applied to analyze any potential influence of IL-18 serum levels measured before alloSCT and on day 0-3 on the platelet count < 50/nl on day+28.

Results: Pre-conditioning serum levels of total IL-18 were significantly higher in both patient cohorts (cohort I: 629 pg/ml, cohort II: 693 pg/ml) compared to healthy controls (median: 147 pg/ml). Cytokine serum levels further increased by approx. 25% until day 0-3. Pre-transplant IL-18 and free IL-18, but not IL-18BPa or CXCL9 were inversely correlated with platelet counts before and on days +28 and +100 after alloSCT in both independent cohorts. This inhibitory effect on platelet recovery was similar for IL-18 levels measured at the day of transplantation. IL-18 predicted platelet recovery on day +28. Low platelet counts on days +28 and +100 predicted 1-year non-relapse mortality in separate multivariable Cox regression analyses (confounders: age, disease stage, HLA-mismatch, donor/recipient sex, disease, ATG, conditioning intensity).

Conclusions: Serum levels of IL-18 were closely associated with platelet recovery after alloSCT. This effect did not depend on the IFNγ response markers IL-18BPa and CXCL9, suggesting a direct inhibitory effect of IL-18 on thrombopoiesis. Poor thrombocyte recovery predicts increased NRM. Strategies reducing IL-18 activity should be explored to potentially improve hematopoietic recovery and clinical outcome after alloSCT.

Disclosure: Nothing to declare.

P282

Microbial Diversity, Survival, and Acute GVHD in Adult Recipients of allo-hsct after Myeloablative Conditioning: Results of a Nutritional Intervention Trial

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Background: Loss of intestinal bacterial diversity has been associated with inferior survival and more acute graft-versus-host disease (aGVHD) among recipients of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Diet is a major determinant of gut microbiota composition. Whether nutritional support can modify microbial diversity and clinical outcome in allo-HSCT is not known. We used data from a randomized nutritional intervention trial to examine the effect on gut microbiota and its association with 1-year mortality and aGVHD (1).

Methods: We studied a subset of adult patients undergoing allo-HSCT enrolled in a two-armed randomized controlled trial with optimized energy and protein intake (n=23) compared to controls (n=24). Stool microbiota profiles were determined by 16S rRNA gene sequencing (V3-V4 region), and microbiota data from 82 stool samples were included in the final analysis (n=22 and n=19 from both study arms at baseline and 3 weeks, respectively).

Results: Six (26%) patients died during 1-year follow-up in the intervention group and 6 (25%) in the control group. Eighteen patients (78%) were diagnosed with aGVHD grade 0-1 in the intervention group and 18 (75%) in the control group. The number of patients with aGVHD grade 2-4 was 5 (21%) in the intervention group and 6 (25%) in the control group. The intervention and control groups had similar microbiota profiles at baseline and at 3 weeks post allo-HSCT. The groups were thus merged for further analysis. There was a major reduction in measures of intra-individual (alpha) diversity from baseline to 3 weeks ($p< 0.001$). Furthermore, at 3 weeks, the alpha diversity was lower in non-survivors compared to survivors during the first year (observed OTUs, $p=0.008$ and Shannon index, $p=0.024$), while the baseline diversity was not associated with mortality. Loss of the genus Blautia from baseline to 3 weeks ($p=0.047$), as well as low abundance at 3 weeks ($p=0.049$), were associated with 1-year mortality. No associations were observed between aGVHD and microbial diversity.

Conclusions: Reduced microbial diversity and low abundance of Blautia at 3 weeks post-HSCT was associated with 1-year mortality. The nutritional intervention did not appear to influence gut microbiota composition in this patient population.

1. Skaarud KJ, Hjermstad MJ, Bye A, Veierod MB, Gudmundstuen AM, Lundin KEA, et al. Effects of individualized nutrition after allogeneic hematopoietic stem cell transplantation following myeloablative conditioning; a

randomized controlled trial. Clinical nutrition ESPEN. 2018;28:59-66.

Clinical Trial Registry: ClinicalTrials.gov, ID NCT01181076

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P283

UK Experience in Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Activating PI3K Mutations

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Background: Mutations of the PIK3CD and PIKR1 genes increase lifetime risk of recurrent infection, autoimmune disease and lymphoma. They are accompanied by lymphopenia, increased circulating transitional B-lymphocytes and IgM, impaired vaccine responses, reduced recent thymic emigrants and impaired T-lymphocyte proliferative capacity. Allogeneic HSCT can achieve a complete cure with no further treatment; however, this is an evolving experience.

Methods: The data was collected retrospectively. The patients were identified by using APDS registry and by contacting the UK transplant centres via Inborn Error Working Party.

Results:

We present the clinical outcomes of UK patients who were transplanted for activating PI3K mutations.

Seven PIK3CD and 3 PIK3R1 affected patients received 10 and 5 procedures respectively. Age at first transplant ranged between 3-23 years (median 8). Active infection and non-infectious lung pathology were the most common comorbidities (60%). History of lymphoma/ lymphoproliferative disease (40%) and autoimmune cytopenia (30%) were present prior to first transplant.

Overall survival (OS) was 100% with median follow-up of 4 years (range 4 months-18 years). Three patients received multiple transplants due to graft failure (GF) and one also received CD34+ top-up for persistent neutropenia. Conditioning for 14 transplants were fludarabine (n=14) with treosulfan (n=9), Melphalan (n=3), Busulfan (n=1) or TBI (n=1). All received serotherapy (Alemtuzumab=10, ATG= 4). CD34+ dose ranged between 6.9-40.7x10^6/kg and the source was PBSC (n=10) or BM (n=4). Neutrophil engraftment was achieved at median 14 days (range 10-30). All patients had >90% donor engraftment in their last follow up appointments. Secondary GF was seen in 30% requiring multiple procedures. GVHD grade I-II was seen in 28%.

Conclusions: HSCT is a curative treatment for patients with activating PI3K mutation but almost a third of patients developed GF requiring an additional procedure.

Disclosure: Nothing to declare.

P284

Reconstruction of the donor-recipient Haematopoietic Cell Phylogeny Using Somatic Mutations to Establish Numbers of Engrafting long-term HSCS in real-world Transplantation

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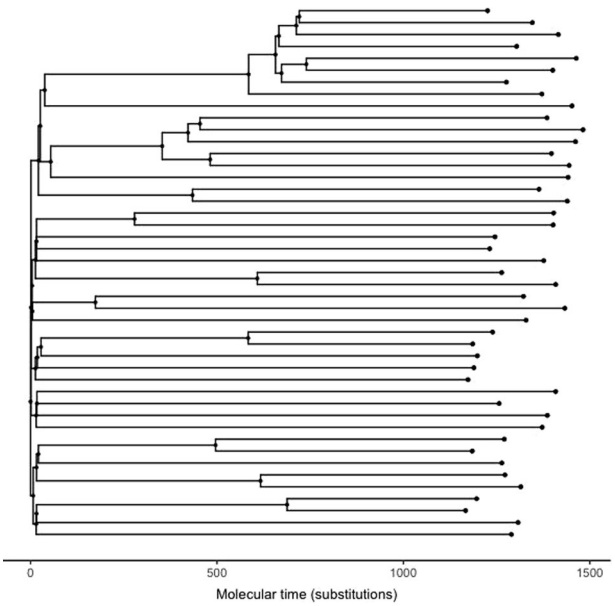
Background: The recommended minimum CD34+ cell dose in HSCT is $2x10^6$ per kilogram of recipient body weight. However, only a fraction are true long-term haematopoietic stem cells (LT-HSCs), and likely even fewer successfully engraft. In the autologous setting of lentiviral vector HSPC gene therapy, clonal tracking techniques estimate the number of active transplanted CD34+ clones at steady-state as ~1200, but for allogeneic HSCT, the figure is unknown and may be significantly lower given the allo-immune environment. By applying phylodynamic approaches to phylogenies inferred from somatic mutations, we aim to establish these for the first time.

Methods: We selected three donor/ recipient pairs who had undergone HSCT 9, 16 and 29 years previously. For each individual, CD34+ HSPCs from peripheral blood were plated in cytokine-supplemented methylcellulose medium. After 14 days of culture single colony-forming units (CFUs) were picked and the DNA extracted. Whole-genome sequencing (WGS) at a target of 10x coverage was performed on 50 and 200 CFUs from donors and recipients respectively - a total of 750 whole genomes - using the Illumina NovaSeq 6000 platform. Mutations were called using established variant-calling pipelines, then filtered to remove artefacts, germline variants, and in vitro mutations leaving only somatically-acquired mutations present in each CFU founder cell. Phylogenies were inferred from shared mutations using a maximum parsimony algorithm. Bayesian coalescence-based phylodynamic approaches will be applied to recipient phylogenies to infer size of the HSC population bottleneck representing the time of transplant. We will also establish the additional HSPC mutation burden acquired through transplantation.

Results: Full results are not yet available and will be presented at the conference. At the time of writing we have results from two transplant donors, and not their matched recipients - therefore transplant population inferences are not yet possible. However, donor CFU WGS reveals a consistent within-individual single-nucleotide variant (SNV) burden that correlates with age, in line with previous reports. One 74-year-old donor had a mean SNV burden of 1328 per cell (range 1167-1482) and a 65-year-old donor, 1135 (range 949-1367). Intriguingly, phylogeny structure in the 74-year-old donor (see figure) has considerably more mid-tree coalescences compared to the 65-year-old donor and a previously published phylogeny from a healthy 59-year-old.

Conclusions: Established barcoding strategies have furthered our understanding of HSCT dynamics in model organisms and in lentiviral vector HSPC gene therapy where use of vector insertion sites as clonal-tracking markers is intrinsic to the therapeutic modality, but are not ethically possible in human allogeneic-HSCT. In addition, barcoding strategies are limited by labelling over a restricted time window relative to the animal's lifespan post-transplant. In contrast, our approach uses "clonal markers" that are constantly created in vivo in the form of somatic mutations allowing retrospective inference of dynamic population changes. As well its relevance to basic HSC biology, extension of our approach to larger cohorts will reveal how engraftment dynamics are impacted by transplant variables such as conditioning regimen, cell dose and stem cell source. This may inform novel therapeutic approaches.



[Phylogeny of single HSPCs in a 74-year old who had been a transplant donor 9 year previously.]

Disclosure: Nothing to declare.

P285

Successful Clearance of Donor Specific anti-HLA Antibodies after Desensitization with Rituximab, Velcade and plasma-exchange followed by a Haploidentical Stem Cell Transplantion with post-transplantation Cyclophosphamide

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Background: T cell - replete haploidentical stem cell transplantation (haploSCT) is increasingly performed and has expanded donor pool and transplant option for many patients (pt). However, the presence of recipient antibodies against donor HLA antigens (DSA) have been reported to be associated with engraftment failure and may limit the access to transplantation as the only lifesafing treatment modality. Guidelines for detection and treatment of DSA have been recently published but no standardized

desensitization schedule exists so far. We report here the results of our institutional desensitization procedure initially developed for highly immunized patients with severe sickle cell disease undergoing haploSCT and then further adapted to all pt with DSA undergoing a mismatched allogeneic SCT.

Methods: From March 2014 to July 2019, 20 pt had detectable DSA and did perform desensitization before undergoing a haploSCT. The DSA level was determined by using the LUMINEX technique (One Lamda, Inc). In case of positivity, the single antigen test was done to identify each class I and II HLA antibody-specificity. The values were expressed in mean fluorescence intensity (MFI). DSA were considered positive if the MFI value was ≥ 1000. The desensitization treatment included Rituximab 375 mg/m^2, Velcade 1.3 mg/m^2 and Plasma-Exchange followed by intravenous polyvalent immunoglobulins. DSA level controls were done routinely during desensitization, before starting the conditioning regimen and the day before graft injection. Pt who did not decrease DSA levels were not considered for haploSCT.

Results: Median age was 61 years (range, 22-73). Diagnosis was acute myeloid leukemia in 6 pt, myelodysplastic / myeloproliferative syndrome in 10 pt, chronic lymphocytic leukemia in 1 pt and severe sickle cell disease in 3 pt. All donors were first-degree family members. Half of the pt were women [donor-recipient sex match: F/F=4; M/F=6; F/M=5; M/M=5pt]. The median MFI value before desensitization was 4700 (range, 1000-16000). Most pt (17) had DSAs against HLA class I antigens. Seventeen pt successfully decreased DSA levels to a median MFI value of 500 (range, 500-1200) and could proceed to haploSCT. They all engrafted and no DSA rebound was observed. One pt relapsed during the desensitization procedure and 2 pt with high DSAs above 10000 did not respond with remaining MFI of 16000 and 9500, respectively, and did not undergo haploSCT. One pt with CMML experienced primary graft failure for relapse and one pt with CLL did not engraft for unknown cause.

Conclusions: The presence of DSA under 10000 should not be a barrier to transplantation. Our report shows that the hereby described desensitization schedule effectively cleared DSA allowing engraftment after haploSCT. Further studies are needed to determine the role of specificity and strength of DSA in order to better predict the likelihood of successful desensitization.

Disclosure: Nothing to declare.

P286

Impact of pre-transplantation Minimal Residual Disease Determined by Flow Cytometry on Outcome of Acute Leukemia Patients after Allogeneic Stem Cell Transplantation: A Single Center Experience

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Background: Allogeneic hematopoietic cell transplantation (allo-HCT) is potentially curative for patients with high-risk acute leukemia, but disease recurrence remains the leading cause of treatment failure. Numerous studies have investigated prognostic significance of pre-transplantation minimal residual disease (MRD) with heterogeneity in results, likely attributed to differences in conditioning regimens and in MRD methods applied. Until the recent ELN MRD consensus, the standard definition of MRD in Acute Myeloid Leukemia (AML) especially has not been well established. Our study aims to determine the prognostic significance of the pre-HCT MRD by multiparameter flow cytometry (MPFC) in adult patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) in morphologic first (CR1) and second complete remission (CR2) in the pre MRD-standardization era.

Methods: We studied 167 adults patients receiving allogeneic HCT using 8/8 HLA matched sibling (n=63), 7-8/8 HLA matched unrelated donors (n=62), 4-6/6 HLA matched UCB (n=6) graft or haploidentical (n=33) donors for AML (n=108) and ALL (n=55) between Jan 2011 and Dec 2018, following myeloablative (MAC, n=) or reduced intensity conditioning (RIC, N=) regimen. Pre-transplant MRD by MPFC was performed from BM samples using our routine instituitional protocols.

Results: 5 year overall survival (OS) and progression free survival (PFS) were 54% and 47% for AML patients, and 67% and 51% for ALL patients, respectively. In multivariate analysis, pre-HCT MRD status was found to be associated with improved OS (HR 0.3, 95% CI 0.07-0.96; p=0.04) and PFS (HR 0.21, 95% CI 0.06-0.79; p=0.02) in ALL patients. In ALL patients with negative pre-HCT MRD (MRD -ve), the 5 year OS and PFS were 66% and 68%, respectively, and the corresponding OS and PFS for positive pre-HCT MRD (MRD +ve) ALL patients were 49% and 47%, respectively. However, pre-HCT MRD status has not been shown to have any significant impact on both OS and PFS in AML patients. The 5 year OS and PFS for MRD -ve AML patients was 54% and 48%, respectively, and the corresponding OS and PFS for MRD +ve AML patients were 54% and 55%, respectively.

Conclusions: Our study shows that pre-HCT MRD status has significant prognostic impact among ALL patients

but not in AML patients. Patients with high risk AML in remission should proceed with allo-HCT irregardless of their pre-HCT MRD status. In ALL patients, more studies on effective strategies to eliminate the disease burden pre-transplant are needed to further improve their outcome.

Disclosure: Nothing to declare.

P287

Economic Burden of Cytomegalovirus Infection in Allogeneic Hematopoietic Stem Cell Transplant Recipients: A Spanish Multicenter, Retrospective Study

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Background: Cytomegalovirus (CMV) is a great concern after allogeneic hematopoietic stem cell transplant (allo-HSCT). With the introduction of pre-emptive treatment, the incidence of CMV disease after allo-HSCT has been reduced. Nevertheless, antiviral agents of pre-emptive treatment may cause toxicities such as renal dysfunction or cytopenia and since CMV infection rates remains unchanged with this treatment strategy, indirect effects of CMV infection (graft-versus-host disease and other infections) could lead to further treatments and healthcare resource use. Therefore, we assessed the economic burden of CMV infection in allo-HSCT patients in the Spanish setting.

Methods: We retrospectively reviewed 734 patients who received a first allo-HSCT between 1 September 2014 and 31 December 2015 in 20 Spanish centers. Patients were considered with CMV infection when one of the following criteria was met: detection of CMV viral load value above the cut-off point of each center or diagnosis of CMV disease. Hospital resource use and costs were estimated from the allo-HSCT date to 12 months post-transplantation. Healthcare resources included were hospital length of stay (LOS) due to allo-HSCT, subsequent readmissions, outpatient and emergency visits, medical procedures and laboratory tests, CMV pre-emptive drugs and other pharmacological treatments associated to the management of clinical complications. Costs were estimated by applying the unitary cost of the resources considered to the number of resources consumed per patient (€ 2019).

Results: Of the 734 patients evaluated, CMV infection was detected in 390 (53%) patients. Total average LOS in patients with CMV infection was 20.3 days longer than in patients without CMV infection (95% CI: 13,9 - 26,7 days; p=< 0.001). The average total costs per patient with CMV infection were €84,946, which represented a 21% increase compared to patients without CMV infection (€70,242; p< 0.001). The average cost per patient was higher in the cohort of patients with CMV infection regarding all types of healthcare resources, except for outpatient and emergency visits. Transplant admission and readmission costs represented approximately the 70% of the total annual cost of the patient management (table 1).

Conclusions: This study shows that CMV infection in allo-HSCT recipients increased healthcare resource use and cost. New therapeutic options to prevent CMV infection, including prophylaxis, may help to reduce the economic burden related to transplant admission and medical procedures for the Spanish National Healthcare System.

Type of resource (SD)	CMV infection N = 390	No CMV infection N = 344	p-value
Transplant admission	32,894.49 (30,757.80)	28,110.99 (14,819.23)	0.010
Subsequent Readmissions	27,594.8 (25,906.27)	22,206.24 (15,596.16)	0.092
Outpatient and emergency visits	4,846.32 (3,627.74)	5,121.27 (3,880.35)	0.240
Medical procedures and laboratory tests	11,599.33 (7,084.18)	9,747.45 (5,937.25)	<0.001
CMV pre-emptive treatment	1,275.39 (2,023.04)	0 (0)	-
Other pharmacological treatments	6,735.41 (15,633.86)	5,055.88 (10,192.74)	0.444
Mean total cost	84,945.74 (50,286.33)	70,241.84 (29,095.5)	<0.001
SD: Standard Deviation			

[Table 1. Average annual cost per patient (€, 2019)]

Disclosure: The study was financed by Merck Sharp & Dohme, Spain, a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, USA. The study implementation and statistical analysis for this study was done by Pharmacoeconomics & Outcomes Research Iberia S.L. All authors read and approved the final abstract.

P288

Incidence and Outcome of Clonal and Malignant Transformation (CMT) Among Pediatric Patients with Inherited Bone Marrow Failure Syndromes (IBMFSS)

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Background: IBMFSs are a rare, heterogeneous group of genetic disorders that are characterized by single or multi-lineage cytopenias, and an increased risk of clonal and malignant transformation including clonal marrow cytogenetic abnormalities, myelodysplastic syndrome (MDS) and acute myeloid or lymphoid leukemia (AML /ALL); the development of any of the above is thought to have a negative impact on overall outcome. At King Faisal Specialist hospital and Research Centre, we examined the incidence of CMT in our patients with IBMFS and the treatment outcome in comparison with patients who did not develop CMT.

Methods: We retrospectively reviewed the clinical data of pediatric patients (Age ≤ 14 years at diagnosis) who were diagnosed and managed as IBMFSs at KFSHRC between (2005 - 2015). A total of 142 patients' profiles were reviewed, 82 (57.7%) were female. Median age at diagnosis was 6 years (Min 0.1- Max 14), 48 (33.8%) had single lineage, and 94 (66.2%) had multi-lineage abnormalities. 138 (97.2%) patients had classified IBMFSs and 4 had unclassified IBMFSs. The most common diagnosis was Fanconi Anemia (FA) in 94 (68.1%), followed by Diamond Blackfan Anemia (DBA) in 18 (13%), Severe Congenital Neutropenia (SCN) in 14 (10.1%) and Congenital dyserythropoietic anemia in 6 (4.3%). Median follow up time was 93.7±6.3 months from Diagnosis.

Results: In total, 21 out of 142 patients (14.8%) developed CMT. Twelve had MDS / hematological malignancy with or without clonal changes (6 had MDS, 3 AML, 2 ALL and one had acute Mixed Lineage Leukemia; AMLL). Nine patients had only clonal marrow cytogenetic abnormalities. When analyzed per primary diagnosis, 16 patients with FA developed CMT (Clone only: 6; MDS: 5; AML: 2; ALL: 2; AMLL: 1), 1 out 14 SCN patients developed AML, 1out of 18 DBA patients had Clonal abnormalities only. Among unclassified patients, 3 out of 4 developed CMT (Clone only: 2, MDS: 1). Monosomy7 was the most frequently recorded clonal change in 4 out of 17 (23.5%). 113 out of 121 patients in non CMT group and 20 out of 21 in CMT group underwent Hematopoietic cell transplantation (HCT). The 5-year overall survival (OS) was lower in CMT group 56.3 ±11.0 when compared to 81.4±3.6 in non-CMT group (P-Value: 0.013). In patients with malignant transformation, 11 patients underwent HCT, seven of them died. The causes of death were disease relapse (1), infection (4) and secondary malignancy (2). All 9 patients with clonal abnormalities underwent HCT, 4 died with graft failure.

Conclusions: In this study, the incidence of CMT among IBMFS patients was 14.8% and it was associated with lower OS compared to those who didn't develop CMT especially if they develop MDS/ Malignancy. Two of the FA patients developed ALL; this is a rarely reported phenomenon in the literature.

Disclosure: The Authors declare. no conflict of interest.

P289

Impact of post-transplant Immunosuppresion Wean vs. Boost in Early Mixed Chimerism following g-csf-primed Marrow Transplant in Thalassemic Patients

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Background: In leukemia mixed donor chimerism often prompts weaning immunosuppression in order to enhance graft vs. host malignancy, this however may not apply to the setting of thalassaemia transplants when G-CSF-primed bone marrow (G-BM) is used as a graft. The aim of this study is to compare the clinical outcomes (i.e. rejection, stable mixed chimerism with transfusion independence or improvement of donor chimerism by at least 10%) of two different approaches of managing early mixed chimerism: Immunosuppression (IS) wean vs. boost.

Methods: We retrospectively analysed 72 patients who underwent first matched related donor hematopoietic stem cell transplant between December 2013 and November 2018 for Thalassemia Major across 5 collaborating centres in the Indian subcontinent using Bu/Cy-based conditioning on 2 sequential protocols and were noted to have an early (< 60 days from transplant) level 2 or level 3 mixed chimerism (i.e. donor chimerism 5% to 74% and 75% to 90% respectively). Our practice had changed during the study period hence 58 patients received marrow primed with G-CSF (5 μg/Kg) for 5 days, 9 received marrow primed for 3 days and 5 were recipients of unprimed marrow. All patients had at least 1-year post-BMT follow-up.

Results: Among those with early mixed chimerism, 5 patients had received unprimed bone marrow and none rejected. Out of these 5 patients, 3 had IS wean, chimerism increased in all of them. Of the 2 with no intervention, chimerism improved in one and remained stable in the other.

Fifty-eight patients received marrow after 5 days of G-CSF priming. The following were the interventions: IS wean in 18, no intervention in 24 and IS boost in 16. In the IS wean group 15 (83.3%) rejected the graft, 2 (11.1%) had stable mixed chimerism and in 1(5.5%) chimerism improved. In the IS boost group of 16 patients 3 (18.7%) rejected the graft, 11 (68,7%) had stable mixed chimerism and in 2 (12.5%) the chimerism improved. In the no intervention group 3 (12.5%) rejected the graft, 7 (29.1%) had stable mixed chimerism and in 14 (58.3%) chimerism improved. (See Graph 1).

Out of the 9 patients who had 3 days of G-CSF priming none had IS boost, 4 had IS wean (1 rejected, 2 had stable mixed chimerism and 1 showed improvement) and in 5 no intervention was done (1 rejected, 1 ended with stable mixed chimerism and in 3 chimerism improved).

Every patient with first donor chimerism under 50 eventually rejected.

Conclusions: Our experience suggests that patients receiving G-BM may benefit from increasing or maintaining immunosuppression and weaning immunosuppression rapidly may be counterproductive in this setting. Whether G-BM was used should be taken into consideration when devising immuno-modulation strategies to deal with early mixed chimerism post bone marrow transplants in thalassaemia.

	Chimerism Improved	Chimerism not improved	Total
Unprimed marrow	3	0	3
G-BM (5 days)	1	17	18
Total	4	17	21

[Outcome of immunossupression wean. p-value by Fisher's exact test = 0.003]

Disclosure: Nothing to declare.

P290

Validation of Disease Risk Comorbidity Index (DRCI) for Overall Survival after Allogeneic Stem Cell Transplantation (HSCT) With Partially T-cell Depleted GRAFT

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Background: DRCI is a prognostic score integrating comorbidities (HCT-CI) and disease risk index (DRI) predicting 2-years overall survival (OS), disease-free survival (DFS), and graft-versus-host-disease (GVHD)-free/relapse-free survival (GRFS). DRCI has not been validated in an independent cohort and has not been investigated in patients allografted with in-vitro partially T-cell depleted graft (pTDEP). pTDEP is offered in our institution to patients in complete remission to reduce GVHD incidence.

Methods: All consecutive ≥18 years patients who received a first HSCT for haematological malignancy between 2008 and 2018 with data available for DRCI calculation were included. Haplo-identical donor were excluded. OS, DFS and GFRS were investigated with Kaplan-Meyer method.

Results: 404 patients were included, median age at transplant time was 53 years (range: 18-74), 39.6% were female, median Karnofsky index was 90 (80-100). 38% of graft were from sibling, 53% from matched-related donor and 9% from mismatched-unrelated donor. Stem cell source was peripheral blood in 94% and bone marrow in 6%. pTDEP was performed in 38% of HSCT. Reduced-intensity and myeloablative (MAC) conditioning was performed in 54% and 46%, respectively.

Among the 404 patients, 30 (7%) were assigned in the very low risk (VLR), 2 (0.5%) in the low risk (LR), 209 (52%) in the intermediate-1 risk (IR-1), 67 (17%) in the intermediate-2 risk (IR-2), 64 (16%) in the high risk (HR) and 32 (8%) in the very high risk (VHR). Because of the small number of patients in the LR, LR and VLR were combined for analysis. 2-years OS for LR was 84% (95% CI: 77-91%), for IR-1 was 61% (54-68%), for IR-2 was 46% (34-58%), for HR was 33% (21-45%) and for VHR was 29% (12- 46%) (p-value < 0.01). 2-years PFS for LR was 75% (95%CI: 60-90%), for IR-1 was 50% (43-57%), for IR-2 was 38% (24-50%), for HR was 23% (12-34%) and for VHR was 27% (11- 43%) (p-value < 0.01). 1-year GRFS was 75% (60-90%) for LR, 46% (37-53%) for IR-1, 42% (30-54%) for IR-2, 16% (7-25%) for HR and 19% (5-33%) for VHR (p< 0.01).

For pTDEP HSCT, HR and VHR were combined because of low number of patients. Among the 152 pTDEP, 20 (13%) were assigned in LR, 82 (54%) in IR-1, 37 (24%) in IR-2 and 13 (9%) in HR. 2-years OS for LR, IR-1, IR-2 and HR was respectively 90% (70-100%), 63% (52-74%), 50% (33-67%) and 37% (11-63%). 2-years LFS for LR, IR-1, IR-2 and HR was respectively 80% (62-98%), 54% (43-65%), 40% (24-56%) and 15% (0-35%) (p< 0.01). 1-year GRFS was 80% (62-98%) for LR, 59% (48-70%) for IR-1, 41% (25-57%) for IR-2 and 23% (11-35%) for HR (p< 0.01).

In addition to DRCI, Karnofsky >80, pTDEP, MAC and sibling donor had a positive impact on OS on univariate analysis. On multivariable analysis, only DRCI and Karnofsky index were confirmed to have an impact.

Conclusions: Our study confirms that DRCI predicts outcomes of HSCT in an independent cohort and validates this scoring system for pTDED HSCT. DRCI is a useful tool to guide physician in HSCT decision.

Disclosure: Nothing to declare.

P291

Allogeneic Stem Cell Transplantation in Patients with BCR-ABL-Negative Myeloproliferative Neoplasms Pretreated with JAK1/JAK2 Inhibitors

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Background: Primary myelofibrosis (PMF), post-polycythemia vera (post-PVMF), post-essential thrombocythemia (post-ETMF), and myelodysplastic/myeloproliferative neoplasms (MDS/MPN) are BCR-ABL-negative hematopoietic stem cell disorders (MPN) with variable prognosis. The aim of the study was to analyze the results of allogeneic hematopoietic stem cell transplantation (alloHSCT) in patients MPNs who did (MF+) and who did not receive (MPN-) target therapy with JAK1/JAK2 inhibitors.

Methods: Fifty four patients were included in the study with median age of 49 years (20-61). JAK1/JAK2 inhibitor therapy with ruxolitinib (25) or pacritinib (2) was performed during 7 months before alloHSCT and disease stabilization occurred in 15 patients, disease progression - 4, clinical improvement - 8 according to ELN criteria. Among them 26 patients received ruxolitinib 30-45 mg daily until D-1 and 10-15 mg/day from D+5 to D+100 and graft versus host disease (GVHD) prophylaxis with cyclophosphamide 50 mg/kg D+3,+4. Twenty-seven patients with MPN- (postPV-MF-2, PMF-10, CMML-9, aCML-3, MPN unclassifiable-3) were not treated with target therapy. GVHD prophylaxis in MPN- patients consisted of antithymocytic globulin (ATGAM 60 mg/kg or thymoglobuline 5 mg/kg) and tacrolimus/mophethyl-mycophenolate. All patients received conditioning regimen with fludarabine 180 mg/m^2 plus busulfan 8-10 mg/kg. AlloHSCT was performed from unrelated (37), related (10) and haploidentical (7) donor. Stem cell source was granulocyte colony-stimulating factor mobilized peripheral blood progenitor cells (43) and bone marrow (11). Median number of CD34 +cells/kg was 6,4 x 10^9 (1,4-11,9). In 20 patients analysis of ruxolitinib concentration in peripheral blood with high performance liquid chromatography-tandem mass spectrometry (Agilent technology, USA) at D0, D+7, D+14, D +21, D+30, D+60, D+100 was performed.

Results: Median follow up was 32 months (2-126). Primary engraftment was documented in 77% of patients. The rate of primary graft failure was 16% in MF+group and 29% - in MPN- (p=ns).

Analysis of Cthrough concentrations of ruxolitinib demonstrated accumulation of the drug from day+7 (median 17.7 ng/ml) to day+14 (median 43.8 ng/ml, p=0.028) and subsequent stable concentrations. Ruxolitinib value was not detected at day 0 in all samples due to drug intake interruption from day-1 to +4. Five MF+ patients died due to infection (4) and GI-bleeding(1).

Acute GVHD grade 2-4 and chronic moderate/severe GVHD was documented in 20% and 24% MF+, 29% and 43% of MPN-patients (p=ns). Viral reactivation occurred in 42% MPN-, 43% of MF+patients (p=ns). The rate of toxic hepatitis grade 3-4 and venoocclusive liver disease was similar between groups: 21% and 12% in patients with MPN-, 25% and 13% in MF+patients.

The 3-year overall survival was superior in MF+patients 74% compared to MPN- - 30% (p=0.007), as well as progression free survival (66% vs 24%, p=0.016).

Conclusions: Introduction of JAK1/JAK2 inhibitor in the pre- and posttransplant period might be one of the options to improve results of alloHSCT in MF patients.

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P292

The Determinative Role of patient-controlled-analgesia (PCA) in the Early Course of Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Early post-transplant toxicities, particularly mucositis, may affect the success of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Patient-controlled-analgesia (PCA), which is generally used for the palliation of mucositis-associated-pain in allo-HSCT recipients, is considered to improve patient's performance status (PS) and prevent further post-transplant complications associated with severe mucositis. The aim of this study was to evaluate the role and efficacy of PCA in allo-HSCT recipients and to clarify its possible association with early post-transplant toxicities.

Methods: Medical records of 452 allo-HSCT recipients (median age: 35(15-67) years; M/F: 285/167) were retrospectively reviewed. A total of 278 acute leukemia (61.5%), 51 lymphoma (11.3%), 34 aplastic anemia (7.5%), 29 myelodysplastic syndrome (6.4%), 25 multiple myeloma (5.6%), 14 chronic myeloid leukemia (3.1%), 10 primary myelofibrosis (2.2%), 5 paroxysmal nocturnal hemoglobinuria (1.1%), 4 thalassemia major (0.9%) and 2 chronic lymphocytic leukemia (0.4%) patients were included in the study. Toxicity grading was performed based on National Cancer Institute Toxicity Scale. Numeric Rating Scale was used for pain evaluation. Pain palliation with PCA was commenced in patients with pain score >3. The study cohort was divided into two subgroups as PCA^+ and PCA^-, based on the status of their PCA requirement.

Results: Patient-controlled-analgesia was more frequently used in younger patients (p< 0.001) and patients with acute leukemia (p< 0.001). Myeloablative conditioning (p< 0.001), total body irradiation (TBI) (p< 0.001) and methotrexate (MTX) use for graft versus host disease prophylaxis (p< 0.001) were identified as significant predictive factors for PCA requirement. Total parenteral nutrition (TPN) was more frequently used in PCA^+ group (p< 0.001). Neutropenic period (p=0.002) as well as the length of hospital stay (p< 0.001) were found to be longer in the same group of patients. Patients in PCA^+ group had a significant tendency to develop bacterial (p< 0.001) and fungal infections (p< 0.001) and organ toxicities including hepatic (p< 0.001), renal (p=0.033) and neurological toxicity (p=0.003) besides increased prevalence of veno-occlusive disease (VOD) (p< 0.001). A significant correlation was indicated between PCA use and nausea (p=0.011), vomiting (p=0.014), diarrhea (p< 0.001), constipation (p=0.001) and hypoxia (p=0.032). In multivariate Cox regression analysis, pre-transplant Eastern Cooperative Oncology Group (ECOG) PS (p < 0.001), European Group for Blood and Marrow Transplantation (EBMT) score (p=0.022), number of febrile days (p=0.005), hypoxia (p=0.031) and renal toxicity (p< 0.001) represented a significant prognostic impact on survival. Overall survival was found to be similar between PCA^+ and PCA^- groups (32.2% vs 37.7%, p>0.05).

Conclusions: In accordance with previous reports, myeloablative conditioning, TBI and MTX use were considered as major risk factors for development of mucositis. Transplant complications including VOD, infections, organ toxicities, prolonged hospital stay, prolonged neutropenia and delayed neutrophil engraftment were found to be more common in patients with severe mucositis who require PCA in the peri-transplant setting. Novel strategies to prevent or treat mucositis would reduce the risk of toxicities and improve transplant outcomes. The particular role of PCA,

which serves a better quality of life to the patient, seems to be associated with the severity of mucositis.

Disclosure: Nothing to declare.

P293

High Survival Rate and Low Incidence of AGVHD after CD34+ Stem Cells Selection and CD3+ T Cells Addback in Pediatric MUD HSCT

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Background: Only 25% of patients have an HLA-identical sibling, so in the absence of a suitable related donor, MUD is a good alternative source for HSCT in patients with hematological and non-hematological diseases.

CD34+ selection, used for counterbalance partial incompatible HSCT, is associated with sustained engraftment and effective reduction of T cells that minimizes GvHD. On the other hand, this approach could delay immune reconstitution and increase risk of viral and fungal infections. Since in our centre most part of patients are PID, we applied a procedure to minimize the risk of severe GvHD infusing a controlled number of CD3+ cells.

Methods: We report data about 95 pediatric patients who received 97 MUD HSCT (2 patients received 2 HSCT) between 2001 and 2019 in the BMT Unit of the Children´s Hospital of Brescia.

Patients received conditioning, according to the EBMT and ESID Guidelines.

CD34+ selection was realized by a magnetic column with an ideal addback of CD3+ of $30x10^6$/Kg.

Stem cell source was BM in 60 cases and PBSC in 37 cases.

Results: Median patients age at transplant was 2.1 years (range: 2.6 months-17 years). The mean numbers of infused cells were $11.5x10^6$/Kg CD34+ and $32.5x10^6$/Kg CD3+ in BM, $17.5x10^6$/Kg CD34+ and $30x10^6$/Kg CD3+ in PBSC. Mean time for engraftment was 15 days post-HSCT. Acute GvHD grade III-IV overall incidence was only 8.25% (8/97), while chronic GvHD was 3.1% (2 limited, 1 extensive/97). No major infections presented in the post-transplantation period and immunological reconstitution both cellular and humoral was completed by 12 months. Overall survival at 10 years is 78%.

Conclusions: The results demonstrate that GvHD severity can be minimized with a controlled addback of CD3+ lymphocytes. The method allows to graft PID patients even with PBSC without infusing too many T cells. Nevertheless, in case of an oncohematological patient, GvL effect is preserved.

Disclosure: Nothing to declare.

P294

Impact of ABO Incompatibility on Outcomes after Haploidentical Hematopoietic Stem Cell Transplantation for Severe Aplastic Anemia

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Background: The impact of ABO incompatibility on transplantation outcomes in severe aplastic anemia (SAA) patients receiving haploidentical hematopoietic stem cell transplantation (HSCT) remains controversial without published data.

Methods: A total of 199 SAA patients receiving haploidentical HSCT from ABO-matched (n=114), minor ABO-incompatible (n=47) or major ABO-incompatible donors (n=38) were included in this study.

Results: The median time and cumulative incidences of both myeloid and platelet engraftment in the ABO-compatible and ABO-incompatible groups were similar, and pure red cell aplasia was absent. Minor ABO incompatibility increased the rate of grade III-IV acute graft-versus-host disease (aGVHD) (ABO compatible: 6.14 ±0.05%, minor incompatible: 19.15±0.34%, and major incompatible: 10.53±0.25%; P=0.051), but did not influence the rates of grade II-IV aGVHD or chronic GVHD (cGVHD). Minor ABO-incompatibility was identified as an independent risk factor for grade III-IV aGVHD by multivariate analysis (hazard ration (HR) = 4.00 (1.48-10.80), P=0.006). Chronic GVHD, mortality, and treatment failure were not increased in the minor ABO-incompatible group.

Conclusions: For SAA patients receiving haploidentical HSCT, ABO compatible donors are better than ABO minor incompatible donors if several haploidentical donors are available.

Disclosure: Nothing to declare.

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Comparison of Outcomes after Haploidentical Versus Unrelated Donor Hematopoietic Cell Transplantation in Patients with Acute Leukemia: A Retrospective single-center Review

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Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is the most powerful therapy in patients with acute leukemia. Finding the suitable donor is an important factor in transplant success. transplantation (allo-SCT) from matched unrelated or haploidentical donors are potential alternatives for patients with acute leukemia in the absence of a matched related donor. We performed a retrospective study to compare the clinical outcomes of 203 patients with acute leukemia undergoing haploidentical (n=102) versus unrelated (n=101), (10/10 or 9/10) transplantation over 8 years at our institution.

Methods: The outcomes of 203 Adult and paediatric patients with acute leukemia (AML: 119, ALL: 84) whose have not suitable matched related donor underwent Allo-SCT between 2010 and 2018 were retrospectively analyzed. Comparison was made between Haplo with post-transplant cyclophosphamide (102 patients), MUD 10/10 (82 patients) and MMUD 9/10 (19 patients). The median follow up was 12.74 (range, 0.33-84.04) months. The myeloablative conditioning regimen comprised busulfan and cyclophosphamide were used in most of patients. Both of post-transplant cyclophosphamide (40mg/kg at +3,+4) and pre transplant ATG were used in most Haplo patients. unrelated patients received ATG as a conditioning regimen.

Results: In multivariate analyses using the Cox proportional-hazard model, pre transplant remission status (first remission vs second or more, p=0.016) and age of patients at time of transplant (< 40 vs >40, p=0.011) were independently associated with OS. After adjustment for patient age, donor/patient gender, primary disease, pre transplant remission status, type of conditioning and cell source (PB vs BM), the multivariate Cox model showed that donor type did not influence OS (p=0.98) and PFS (p=0.90) at 3 years, which the weighted 3-years overall survival (OS) and leukemia-free survival (LFS) were 43.8 ±5% and 43.7±5% for Haplo,48.6±6% and 48±6% for MUD 10/10, and 43±14% and 50±12% for MMUD 9/10 (p=0.98- 0.90), respectively. The type of donor was not significantly associated with either acute or chronic graft-versus-host disease incidence.(p=0.194)

Conclusions: We did not find any significant difference in outcome between transplants from Haplo and unrelated donor, suggesting that both can be equally used in the absence of match related donor. Haplo recipients did not experience worse outcomes compared to MUD 10/10 and MMUD 9/10. Considering primary risk and residual disease for best donor selection in hematologic malignancy is suggested in future studies.

Disclosure: Nothing to declare.

P296

Sequential Conditioning Regimen (Flamsa-bu-mel) in HLA-matched or Haploidentical Hematopoietic Stem Cell Transplantation in Refractory Myeloid Disease

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Background: Given the therapeutic challenge of refractory myeloid malignancies, allogeneic hematopoietic stem cell transplantation (HSCT) remains a valid strategy, albeit the high risk of relapse and the toxicity. The concept of sequential conditioning has been shown as a successful approach. However, few protocols have been reported with both HLA-matched and HLA-haploidentical donors.

Methods: In this monocentric retrospective study, we evaluated a sequential scheme including a cytoreduction phase by fludarabine (30 mg/m²/d), amsacrine (100 mg/m²/d), aracytin (2000 mg/m²/d) over 4 days (from D-13 to D-10), followed by a reduced intensity conditioning combining melphalan (140 mg/m² at D-6) and busulfan (3.2 mg/kg/d from D-4 to D-3). Prophylaxis of graft-versus-host disease (GvHD) combined anti-thymocyte globulin (ATG), cyclosporin A and mycophenolic acid for all patients, with the adjunction of high-dose post-transplant cyclophosphamide (HD-PTCy, 50 mg/kg/d at D+3 and D+4) for HLA-haploidentical HSCT recipients. A post-transplant consolidation treatment based on monthly cycles of low-dose 5-azacytidine and donor lymphocyte infusions (DLIs) was associated, whenever possible.

Results: Twenty-seven adult patients with refractory myeloid malignancies (22 acute myeloid leukemias, 4 myelodysplastic syndromes and 1 myeloproliferative disorder), with a median medullary blast count of 9% (1-60) in bone marrow, were included between May 2016 and November 2018. G-CSF mobilized peripheral blood stem

cells were used for all patients but one, from HLA-matched (n=14) or HLA-haploidentical (n=13) donors.

The median follow-up was 24.6 months (1.2-35.3). The 2-year overall survival was 84% (CI95% 48%-96%) in the HLA-matched group, and 38% (CI95% 13%-62%) in the HLA-haploidentical group (P=0.041). The 2-year disease-free survival was 54% (CI95% 23%-77%) and 38% (CI95% 14%-63%) in these groups, respectively (P=0.16). At 2 years, cumulative incidence of relapse was respectively 46% and 25% in these groups (P=ns). The only cause of death in the HLA-matched group was relapse (3/14). However, in the HLA-haploidentical group, the 2-year non-relapse mortality (NRM) reached 49% (95% CI 19%-73%). The main cause of death in this group was hemorrhagic events (4/13), favored by significantly delayed platelet reconstitution and a severe GvHD context.

Ten patients (37%) received a post-transplant consolidation with 5-azacytidine and/or DLIs. Only 1/10 patient relapsed during the observation period.

Conclusions: These data confirm the feasibility of a sequential conditioning for the treatment of refractory myeloid malignancies. Although no patient died from toxicity in the HLA-matched group, NRM was high in HLA-haploidentical recipients. Using bone marrow as main source of stem cells in haploidentical settings might reduce the incidence of GvHD. Avoiding ATG combined with HD-PTCy might minimize the risk of infections and associated cytopenia. More patients could therefore access post-HSCT consolidation strategies, which seem to provide encouraging results in this small series.

Disclosure: Nothing to declare.

P297

Investigation of Virological Features and Clinical Outcomes associated with pre-engraftment Cytomegalovirus Dnaemia in Allogeneic Hematopoietic Stem Cell Transplantation Recipients

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Background: Cytomegalovirus DNAemia is a frequent event after allogeneic hematopoietic stem cell transplantation (allo-HSCT), and it is usually documented after engraftment but it may develop before. Here, we investigated the virological characteristics and clinical outcomes of patients with CMV DNAemia prior to engraftment (preCMV). The information could be of value facing antiviral prophylaxis.

Methods: Retrospective, multicenter, cohort study including a total of 768 patients undergoing allo- HSCT from 2010 to 2019 at 18 different centres of Spain. Data was obtained by the registry of the Committee on Infectious and Non-Infectious Complications (GRUCINI) of the GETH. CMV DNAemia monitoring was performed using the Cobas Taqman CMV Test from Roche (50.5%), the Abbott CMV RealTime CMV (34.8%) and other PCRs (RealStar CMV PCR Kit from Altona Diagnostics and CMV R-gene from Argene, 14.7%). Financial support for this study was granted by Merck, Sharp and Domme (MSD)

Results: A total of 304 (39.6%) patients received allo-HSCT from matched Related donors (MRD), n=207 (27%) from matched unrelated donors (MUD), n=144 (18.8%) from haploidentical donors, n=88 (11.5%) from mismatched HLA related or unrelated donors (MMD) and n=25 (3.3%) from umbilical cord blood (UCB). 81% of recipients were CMV seropositive. Four hundred sixty three patients (60%) had CMV DNAemia during the first year after transplantation, at a median of 34 days (-29 to 354), of which 116 (25%) occurred prior to engraftment. preCMV

was less documented when the Cobas Taqman CMV Test from Roche was used (8.9% vs 24% with the Abbott CMV RealTime and 16% with other PCRs, P< 0.001). The incidence of preCMV was comparable across all transplant types. Neutrophil engraftment (>500 cells/μL) occurred at a median of 20 days [range, 5-57], irrespective of the transplant type. preCMV did not influence time to engraftment (median 21 days [5-57] vs median 20 days [6.57], P=0.36). The use of Sirolimus plus Mycophenolate mofetil plus post-transplant Cyclophosphamide (Siro/MMF/CP) as GvHD prophylaxis was associated with greater incidence of preCMV when compared to other combinations (34% vs 14%, P=0.001). Also, preCMV was more frequent in Acute Myeloid leukaemia (AML) than in other haematological diseases, 20% vs 13%, P=0.002.

No differences were observed regarding initial (median 2.14 $\log_{10}$ IU/ml [1.05-4.68] vs 2.35 [0.80-6.26]) and peak CMV viral loads (median 3.28 $\log_{10}$ [1.52-6.22] vs 3.34 [1.47-6.70], duration of episodes (median 32 days [7-428] vs 30 [7-450] and percentage of pre-emptive therapy (62% vs 68.5%) between CMV episodes occurring before or after engraftment, respectively. However, recurrent CMV DNaemia was more frequent in patients with preCMV (49% vs 34%, P=0.003). Cumulative Incidence (CI) of Non-relapse mortality (NRM) at day +100 and 1-year was similar in both groups (CI 6% [2-10] vs 7% [4-10]; P=0.63 and 22% [15-30] vs 20% [16-29]; P=0.37, respectively). No differences were observed on the incidence of GvHD or CMV disease between both groups.

Conclusions: preCMV DNAemia develops frequently following allo-HSCT and is associated with increased incidence of CMV recurrence. Nevertheless, virological features and clinical outcomes of these episodes did not differ from those occurring after engraftment.

Disclosure: Financial support for this study was granted by Merck, Sharp and Domme (MSD).

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CD34+ Hematopoietic Progenitor Cell Dose as a Predictor of Engraftment and Survival in Multiple Myeloma Patients undergoing Autologous Stem Cell Transplantation

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Background: High-dose melphalan and autologous hematopoietic stem cell transplantation (AHSCT) is the standard treatment strategy in Multiple Myeloma (MM) patients who are eligible for AHSCT. The recommended dose of CD34 + hematopoietic progenitor cells (HPC) for adequate engraftment is above $2x10^6$/ kg. The amount of CD34 + HPC that can be mobilized may vary depending on the factors such as disease status, age, and duration of previous chemotherapies. The aim of this study is to evaluate the relationship between CD34 + HPC dose and the survival in MM patients who underwent AHSCT at Hacettepe University Department of Hematology.

Methods: 271 MM patients who underwent AHSTC were included in this retrospective study.

Results: The median age of all patients was 54.8 (33-76) years. The median CD34 + HPC dose infused was $5.94x10^6$/kg (1.47-59.5 $x10^6$/kg). The median follow-up period was 54 months (4-211). The median overall survival of all patients was 103 months (110-144). Median neutrophil engraftment time was 10 (8-24) days and median platelet engraftment time was 11 (7-40) days. < $5x10^6$/kg and ≥ $5x10^6$ /kg CD34+ HPC were reinfused 38,1% and 61.9% of the patients, respectively. There was a negative significant correlation between reinfused CD34 + cell level and neutrophil/platelet engraftment times (r: -0.32, p:< 0.001; r: -0.27, p:< 0.001, respectively). The median overall survival times were observed as 103 months (110-144) for patients who were administered < $5x10^6$/kg of CD34+ HPC and 145 months (123-166) for patients who were administered ≥$5x10^6$ /kg of CD34+ HPC (p: 0.009).

Conclusions: The increased amount of CD34+ autologous hematopoietic stem cell dose after high dose melphalan chemotherapy in MM patients shortens platelet and neutrophil engraftment time and increases overall survival. Early platelet engraftment and administration of CD34+ HPC count ≥$5x10^6$/ kg can be considered as predictors of a better survival in patients.

Disclosure: Nothing to declare.

P299

Use of Plerixafor in Poor Mobilizer Patients with Myeloma and Lymphoma: Clonogenic Capacity and Engraftment Data

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Background: Plerixafor (PLX) reversibly blocks the binding of SDF-1 to CXCR4, resulting in hematopoietic stem cells (HSC) release from the bone marrow. It has been successfully used as a mobilizing agent in poor mobilizer (PM) patients. The best strategy is probably the "pre-emptive" use, as it allows an "on time" identification of PM, preventing collection failure and need for further mobilization. An important issue concerns the biological characteristics of the yields collected with PLX and their effects on the clinical outcomes.

Methods: We collected data from a total of 861 HPC apheresis consecutively performed at Niguarda Hospital in 627 autologous stem cell transplantation (ASCT) candidate patients (334 M, 293 F), affected by lymphoma and myeloma, mobilized between January 2011 and September 2019; a cohort of 67 PM patients was mobilized with PLX according to a pre-emptive strategy (Table 1). In this study the median value for PLX administration was 7,3/μL CD34 + cell count.

CD34+ cells enumeration was performed according to ISHAGE single platform. Clonogenic capacity of HSC was evaluated by the ability to produce in vitro colonies according to StemCell Technologies.

Patients were mobilized with different regimens: 1) Chemotheraphy+G-CSF; 2) Chemotheraphy+G-CSF +PLX; 3) G-CSF+PLX. A group of 140 healthy donors mobilized only with G-CSF has been considered to compare the clonogenic capacity of the collected HSC.

Results: PLX was used in 67 patients during 72 mobilization cycles resulting in 99 HPC collections. The median increase of CD34+ cells/μL after PLX was 3,6 fold, allowing to reach the recommended CD34 target doses for ASCT in 64/67 patients. Clonogenic capacity of the collected HSC, based on the $CD34x10^6/Kg/CFU\text{-}GMx10^4/Kg$ ratio, was compared in the above groups of patients (Table 1); moreover, clonogenic capacity of HSC was calculated (24,56 median value; 23,25 median) also in 140 healthy donors, mobilized with G-CSF, collected in the same period of time (216 HPC apheresis).

A total of 579 patients affected by myeloma (306) and lymphoma (273) underwent ASCT between January 2011 and September 2019. The same median engraftment time were detected in the three groups of patients (10 days); a difference was observed in the volume (mL) of HPC inoculated, clearly superior in the patients mobilized with PLX.

Conclusions: According to 9 years experience, PLX is effective in mobilizing HSC in PM and allowing an high percentage of them to undergo ASCT. In vitro and in vivo data are similar despite the different number of patients in the three groups.

Mobilization regimen	Chemotherapy +G-CSF	Chemotherapy +G-CSF +PLX	G-CSF +PLX
N° patients	560	54	13
N° mobilization	586	59	13
N° HPC apheresis	762	83	16
HPC apheresis /patient ratio	1,36	1,53	1,23
CD34+cells x10^6/Kg collected (median)	5,89	2,65	4,5
CD34+cells /CFU-GM ratio (median)	21,79	21,04	19,85
N° patients underwent ASCT	521	48	10
N° ASCT	572	48	13
Engraftment time (median)	10	10	10

[Table1]

Clinical Trial Registry: No applicable
Disclosure: Nothing to declare.

P300

Outcomes of Haploidentical Stem Cell Transplantation in Pediatrics: A Single Center Experience from India

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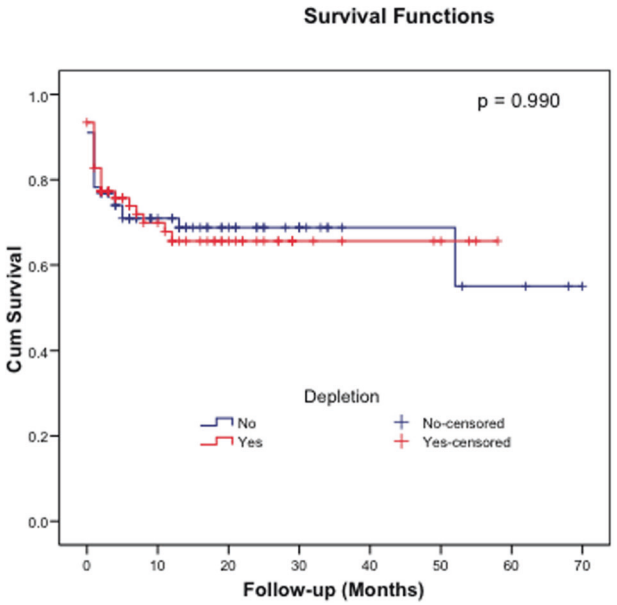
Background: Haematopoeitic stem cell transplantation (HSCT) is curative for several haemato-oncological conditions including benign and malignant disorders. The probability of finding a matched family donor is approximately 30%. Therefore, 70% patients require grafts from alternative donors. Related HLA haplotype-mismatched ('haploidentical') bone marrow transplantation (BMT) is an alternative method in those lacking fully matched donors.

Methods: We performed a retrospective study in the paediatric bone marrow transplant pediatric patients who underwent haploidentical stem cell transplantation from year 2014 to 2019 for various diseases.

Results: Total 150 children underwent 159 haploidentical HSCT (from parent/sibling). The mean age at transplantation was 82.55 months (range 5- 221 months) in which 100 were males and 50 were female. Diagnoses included: acute leukemia (n=64), hemoglobinopathies

(n=28), severe aplastic anemia (n=14), primary immunodeficiency diseases (n=15), Fanconi anemia (n=5), JMML /CML (n=8) and other (n=16). In this cohort, 80 patients were transplanted with T cell -depletion (TCD) while 79 patients received T-cell replete transplant followed by Post transplant cyclophosphamide. IN majority of the patients myeloablative conditioning was used. Predominate graft source was PBSC (PBSC=156, BM =3). GVHD prophylaxis consisted of PTCY with clacineurin inhibitor and MMF (n= 76, 47.7%), T cell depletion (n=52, 32.7%) and T Cell depletion with clacineurin inhibitor (n=28, 17%).



[survival graph]

Mean CD34+ cell dose was 12.95 × 106/kg. Eighty-seven percent patients engrafted; mean time to neutrophil and platelet engraftment was 14.34 (+/- 4.30) and 15.44 (+/- 7.22) days, respectively.

Sixty-eight (42.7%) children developed acute GVHD. The incidence of grade I/II acute GvHD was 41/159 (25.8%) and that of grade III/IV was 27/159(16.9 %). Acute GVHD rate was similar in T cell deplete and T replete group (38.8 % vs 46.8%; P =0.303). Eight patients had Chronic GVHD. Chronic GVHD rate was significantly not differed in T cell deplete and T replete group (3.8% vs 6.3%: P =0.457).

The mean follow-up time of the study group was 13.4 months (range, 3 months - 5.8 years). Day 100 post transplant survival of this cohort is 74.8%. The overall survival of this heterogenous patient cohort is 69.8% with a median follow up of 210 days. There were a total of 49 deaths. Infection (51%), GVHD (12%) and graft failure (8%) were the main causes of death. Other causes of death included were veno-occlusive disease, interstitial pneumonitis, hemorrhage and other causes.

Conclusions: Outcomes were acceptable and comparable in terms of engraftment, aGvHD, OS between the T cell deplete and T replete group. This retrospective study demonstrated that haploidentical HSCT is an option when no alternative donor is available even in resource limited settings.

Disclosure: Nothing to declare.

P301

Pre-emptive Use of Sorafenib Combined with DLI Post HSCT in AML FLT3+: A Single Center Experience

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Background: Fms-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) mutations are found in approximately one quarter of patients with AML Acute Myeloid Leukemia (AML). While initial remission rates are comparable to patients with FLT3-ITD wild type (WT), patients carrying this mutation are significantly more likely to relapse. FLT3 inhibitors seem to improve the outcome in this subset of patients, as in monotherapy or in combination. Allogenic hematopoietic stem cell transplantation (HSCT) represents a treatment option for patients FLT3-ITD AML in first complete remission. However, despite a durable disease-free survival (DFS), ranging from 19 to 58%, relapse remains a remarkable obstacle to long-term survival, even after HSCT. In this setting, FLT3 inhibitors seem to synergize with donor T cell to induce GvL (graft versus leukemia)

Methods: Here we report our experience on Sorafenib in association with DLI (donor lymphocyte infusion), to improve GVL effect in patients with FLT3-ITD/NPM positive AML, in molecular relapse after HSCT. The molecular monitoring of the disease was performed by PCR analysis in NMP positive patients, on day +60, +100 and every two months for two years after transplant. One patient NMP-/FLT3 pos was monitored at the same time points by multi parametric flow cytometry (MPFC). OS (overall survival), PFS (progression free survival), were analyzed. Moreover, adverse events related to Sorafenib and cGVHD incidence (chronic graft versus host disease) were evaluated.

Results: Between August 2015 and August 2018, 3 FLT3/NMP+ and 1 FLT3+/NPM-AML patients, underwent HSCT from unrelated donors. Three out of four patients were treated with a FLT3 inhibitor before HSCT. At the time of HSCT patients with FLT3/NMP+ were in complete hematological remission with a median value of NPM-1 of 424 copies (range 17 - 1027); the patient with FLT3+/NPM- showed 4% of blasts by MPFC. All patients showed persistence of MRD after HSCT. As pre-emptive therapy, Sorafenib and escalating doses of DLIs were administered, starting at a median time of 10 months from HSCT (range 4 - 18). Three patients receiving 3 doses of DLI, achieved molecular remission. One patient, still MRD positive 4 months from Sorafenib and 2 doses of DLI, developed a severe cGVHD togheter with mucocutaneous toxicity due to Sorafenib. After cGVHD a reduction of NPM-1 was observed up to 0 copies in peripheral blood and 0.38 in bone marrow. Sorafenib was discontinued while immunosuppressive therapy was started. After the resolution of cGVHD the patient started therapy with a second generation FLT3 inhibitor Gilteritinb.

Conclusions: Despite short follow-up and limited number of patients, in our experience the association of FLT3 inhibitors with DLI seems to be safe and effective. These preliminary results encourage clinical trial as well as biological evaluations to assess the impact of this combination in the immunological environment of transplanted patients.

Disclosure: The authors declare. no conflict of interest.

P302

Use of Eltrombopag for the Management of Poor Graft Function after Hematopoietic Stem Cell Transplantation in Children

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Background: Poor Graft Function (PGF) is a complication of Hematopoietic stem cell transplantation(HSCT)associated with high morbidity, withareported incidencebetween 5-27% and therapeutic options are limited. We present our experience using eltrombopag for the treatment of PGF after hematopoietic stem cell transplantation in children.

Themain objective wasto determine if treatment with eltrombopag in children diagnosed of PGF after HSCT can improve bone marrow function reflected in full blood count parameters (anemia, leukopenia and thrombocytopenia).

Methods: Retrospective study in patients under 18 years of age who had received an allogeneic stem cell transplantationin our unit between January 2013 and March 2019.

PGF was defined as peripheral cytopenia affecting two or three hematopoietic series (neutrophils < 0.5x10E9/L, platelets < 20x10E9/L and Hb < 7gr/dl or transfusion requirement and/or G-CSF), associated with decreased bone marrow cellularity in bone marrow aspirate or trephine with cellularity < 30%) in patients with complete donor chimerism (> 95% in peripheral blood or bone marrow). Cases of PGF occurring before day +28 after HSCT were defined as Primary PGF, and those occurring >= day +28 were named Secondary PGF.

Complete response was defined as neutrophils >1x10E9/L, platelets >50x10E9/L and Hb >8gr/dl independent of transfusion and G-CSF. Partial response was defined when the previously mentioned were reached in only one or two of the three hematopoietic series (but not all) or when a reduction of transfusion and G-CSF requirements was achieved.

Results: Out of 198 allogeneic HSCT, five patients met PGF criteria and were treated with eltrombopag. Four of those patients were diagnosed of severe acquired aplastic anemia and in one had dyskeratosis congenita. PGF was secondary in all cases and was documented at a median of 60 days after HSCT (range 40-90). Median time from transplantation to onset of treatment with eltrombopag was 120 days (range 90-720). Median starting dose was 50 mg/day (range 25-50) and median maximum dose was 75 mg/day (range 75-150). Median duration of treatment was 9 months (range 2-30). Response to eltrombopag was complete in three patients (60%), partial in 1 (20%) and absent in 1 (20%). The median dose required to achieve a response was 75 mg/day (range 75-150) and median time to achieve a response eigth weeks (range 5-12). Three patients (60%) have presented maintained response over time. Two patients (40%) required an additional CD34+ boost from the same donor. No patients discontinued treatment for side effects. With a median follow-up of 30 months (range 10-32), all patients are alive in complete remission of their underlying disease, with normal hematological counts. Four of the 5 patients discontinued the treatment with eltrombopag and one is now withdrawing treatment.

Conclusions: The use of eltrombopag in children with PGF achieved responses in 80% of cases and demonstrated to be an effective and safe therapeutic option in pediatric patients with secondary PGF.

Disclosure: No disclosure

P303

Treatment of Thrombocytopenia after Allogeneic Stem Cell Transplantation with Eltrombopag

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Background: Eltrombopag is an oral nonpeptide thrombopoetin receptor agonist, approved by the FDA for immune thrombocytopenia and aplastic anemia. After allogeneic stem cell transplantation, thrombocytopenia can be seen as a part of primary/secondary engraftment failure, poor graft function, autoimmunity or GVHD. The aim of this study is to analyze the outcome of off- label use of eltrombopag in transplant recipients retrospectively.

Methods: Twenty patients were evaluated (Table 1)

Results: Female to male ratio was 5: 15 and the median age at transplant was 52. The patients who failed to achieve adequate graft functioning and were given eltrombopag at 25- 75 mg/ day dose (except 150 mg/ d and 175 mg/ d in two patients). Persistent thrombocytopenia after stem cell transplant is classified as either primary isolated thrombocytopenia (PIT) or secondary failure of platelet recovery (SFPR). In our cohort, 12 had PIT and 8 had SFPR. 4 patients remained transfusion dependent. Median time to reach platelet recovery was 53 days (14- 193).

The median platelet count raised from 8000/ mL to 43000/ mL. The median duration of treatment was 82 days and the median platelet count increase was 38000/ mL which is found statistically significant ($p< 0,05$). The median eltrombopag dose was 50 mg/ d (Table 2). No serious adverse effects like hepatotoxicity or myelofibrosis related to eltrombopag were seen and the treatment cost was acceptable.

Conclusions: As thrombocytopenia is closely associated with transplant related mortality and overall survival, eltrombopag is an eligible option in posttransplant thrombocytopenia management.

It is considerably common for the hematopoetic stem cell transplant (HSCT) patients to experience delayed thrombocyte recovery, and many of them require thrombocyte suspensions throughout this process due to severe and deep thrombocytopenia. Within the last years, there have been few reports regarding eltrombopag use in HSCT patients. Eltrombopag is an effective molecule for both PIT and SFPR.

Platelet count before starting eltrombopag, median (range), mL	8.000/ mL (3- 15)
Platelet count increase, median (range), mL	38.000/ mL (3- 99)
Median time from transplant to eltrombopag (days)	145 (31- 330)
Median eltrombopag use duration (days)	82 (24- 464)

[Table 1. Results]

Disclosure: None

P304

Autologous Hematopoietic Stem Cell Transplantion in Multiple Myeloma Irreversibly Depletes Naïve T Lymphocytes

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Background: The particular immune signature that characterizes patients with multiple myeloma (MM) in long term complete remission (LTCR) after autologous hematopoietic stem cell transplantation (auto-HSCT), could reflect a "high quality" reconstitution of immunity associated with a long disease-free survival.

We evaluated whether this characteristic immune recovery was common to every MM patient treated with an auto-HSCT or exclusively of patients who reach a LTCR.

Methods: The study included 15 patients whose immune subsets were analyzed from their corresponding peripheral blood samples, every three months from months 3 to 24 after receiving an auto-HSCT. To this end, the different lymphoid subsets were quantified by multiparametric flow cytometry with an eight-color panel of antibodies designed to identify naïve T lymphocytes (T_N=CD45RA+CCR7+CD27+), central memory T lymphocytes (T_{CM}=CD45RA-CCR7+CD27+), effector memory T lymphocytes (T_{EM}=CD45RA-CCR7-CD27-) and CD45RA+ T_{EM} lymphocytes (T_{EMRA}=CD45RA+CCR7-CD27-). Two additional cohorts were also characterized: 25 age-matched healthy controls and 17 patients in LTCR for more than six years. The Kruskal-Wallis test and a posteriori test were carried out to evaluate differences between the groups.

Results: Absolute lymphocyte counts, as well as absolute numbers of CD8+ T-lymphocytes, were recovered at 3 months after auto-HSCT. Conversely, in a similar way to LTCR, neither the normal absolute values nor the percentage of total CD4+ T-cells were recovered at month 24 when compared to the healthy donors.

Regarding the different maturation stages, one of the most striking findings was that MM patients, including those in LTCR, never recovered the normal proportion or absolute counts of CD4+ T_N. Similarly, the number of CD8+ T_N in recently transplanted patients were lower than those of healthy donors till month 9. Later, CD8 T_N numbers were

not statistically different among the three groups of subjects but they were still lower in MM patients, both LTCR and the recently transplanted ones.

CD4+ T_{CM} absolute values were also lower in recently transplanted MM patients till late in the follow up. Interestingly, the proportion of CD8+ T_{CM} in both groups of patients was always higher than in healthy donors, particularly in LTCR subjects.

Both the proportion and the absolute values of T_{EM}, both CD4+ and CD8+, were or tended to be higher in patients, including LTCR ones, than in healthy donors. Finally, no differences were observed in the proportion or counts of T_{EMRA} lymphocytes, neither in CD4+ no in CD8+ T-cells.

Conclusions: The auto-HSCT results in a loss of naïve T lymphocytes which seems to be irreversible in many patients. This loss was compensated for by an increase in antigen experienced T-cells, including T_{CM} and $T_{EM,}$ that was maintained at least until the end of the follow up. We are now investigating whether individual differences in the magnitude of these changes are associated with LTCR.

Disclosure: Nothing to declare.

P305

Desensitization Protocol in Adult Allogeneic Hematopoietic Stem Cell Transplant Recipients with anti-HLA Donor-specific Antibodies (DSA): A single-center Experience

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Background: In the setting of haploidentical hematopoietic stem cells transplantation anti-HLA donor-specific antibodies (DSA) have an important role in the successful engraftment of donor cells. Besides pregnancy and transfusion of blood products are risk factor for developing anti-HLA antibodies. There are different methods for the screening of these, cell-based assays or solid-phase immunoassays. The assessment of functionality of anti-HLA antibodies can be done using solid-phase immunoassays modified like C4d, C1q and C3d assays. If there is not a donor available without the corresponding HLA antigens of DSA, to reduce the risk of primary graft failure, is mandatory to use a desensitization protocol to reduce or remove totally the DSA.

Methods: We conducted a retrospective review analyzing the incidence of anti-HLA antibodies and DSA in adult haploidentical hematopoietic stem cells transplantation recipients. We also analyze the results of the desensitization protocol effectuated in patients with DSA.

Results: From June 2017 to November 2019 we screened 64 haploidentical hematopoietic stem cell transplant recipients with hematologic malignancies for the presence of anti-HLA antibodies using the multianalyte bead assay with the Luminex platform. 22 cases (34%) showed anti-HLA antibodies: 9 (14%) of them showed DSA. Of these 6 patients were female, 3 male. All patients received blood transfusions and all the 6 patients female had previous pregnancies. In 4 cases with DSA, an alternative donor was selected. The other 5 patients, in absence of a donor available without the corresponding HLA antigens of DSA, were treated with desensitization strategy. Three of them present DSA against class II antigens, one against class I and one against class I and II. One patient with DSA was treated with desensititazion based on inhibition of antibody production by using anti CD20 monoclonal antibody (rituximab), antibody removal by plasmapheresis and antibody neutralization using intravenous immunoglobulin obtaining a reduction of the mean fluorescence intensity (MFI) of the DSA. The other four patients with DSA were treated with a desensitization protocol based on: inhibition of antibody production by using anti CD20 monoclonal antibody (rituximab) and inhibitor against alloantibody producing plasmacells (bortezomib), antibody removal by plasmapheresis and antibody neutralization using intravenous immunoglobulin or donor HLA antigens like white blood cell infusion. After the desensititazion in 3 patients we obtained the negativity of DSA; in one persisted the DSA with the C3d test negative. Donor neutrophil engraftment was reached in all patients (median time on days + 14). Donor platelet engraftment was reached in 4 patients (median time on days + 17). We not observed toxicity and complications related to the drugs and procedures used for the desensititazion.

Conclusions: The analysis of DSA for the choice of the best donor available it's mandatory. If there is not a donor without the corresponding HLA antigens of DSA, to reduce the risk of primary graft failure, it's necessary to use a desensitization method. The schedule of desensititazion that we used appears to be safe and effective to obtain a good engraftment. Further studies on larger number of patients are needed to define a standard desensitization protocol.

Disclosure: Nothing to declare.

P306

Association Between Metabolic Alteration with Type and Indication of Hematopoietic Stem Cell Transplantation

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Background: Identifying patients who may benefit from hematopoietic stem cell transplantation (HSCT) involves consideration of comorbidities and possible disease risk. The aim of this study was to evaluate the association of metabolic syndrome with type and indication of HSCT.

Methods: We performed an observational retrospective cohort of adult patients treated with HSCT at a fourth level referral center in Colombia from 2009 to 2018. Data on the patients' general condition as well as metabolic syndrome related indicators were assessed based on harmonized metabolic syndrome diagnostic criteria proposed in 2009. Evaluated metabolic alterations were metabolic syndrome, hypertriglyceridemia, low HDL cholesterol, hypercholesterolemia, atherogenic dyslipidemia, overweight, obesity, prediabetes, diabetes mellitus, hypertension and hyperuricemia. Indications for HSCT were lymphoma, myeloma, leukemia, autoimmune disorders and others.

Results: Information from 217 patients was available for analysis. 155 (71.4%) patients had autologous HSCT and 62 (28.6%) patients had allogeneic HSCT. Results for the 1st year were obtained from 171 patients, for 3rd year from 68 patients and 5th year from 20 patients. By indication of HSCT, for 1st year were associated metabolic syndrome (P=0.037), overweight (P=0.041) and hypertension (P=0.006); for 3rd year were associated overweight (P=0.018) and hypertension (P=0.011); and for 5th year were associated low HDL cholesterol (P=0.0.29), overweight (P=0.018) and hypertension (P=0.004). By type of HSCT, for 1st year were associated metabolic syndrome (P=0.016), overweight (P=0.002) and prediabetes (P=0.038) for both autologous and allogeneic HSCT; for 3rd and 5th year were associated overweight (P=0.001). Complete results are shown in table 1.

Conclusions: Overall, leukemia patients have higher risk of developing overweight, while metabolic syndrome was associated with lymphoma and multiple myeloma, this last group of patients were also associated with hypertension. Autologous transplant patients have higher risk of developing prediabetes and overweight, whereas metabolic syndrome was associated with allogeneic transplant, which can be related to pre-transplant conditioning treatment and the use of medication related to insulin resistant during the first post-transplant year.

Disclosure: Nothing to declare.

P307

Retrospective Analysis of Survival Outcomes for Patients Receiving Umbilical Cord Blood Transplants at the Royal Marsden Hospital Between 2007 and 2017

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Background: Allogeneic haematopoietic stem cell transplantation remains the only curative option for many patients with haematological malignancy. Unfortunately, matched siblings and unrelated donors are not always available for patients. An important alternative source of haematopoietic stem cells for these patients is umbilical cord blood transplant. Here we present our data on 10 years' worth of patients who have received umbilical cord blood transplants for haematological malignancy.

Methods: Data was collected from 52 patients who had received an umbilical cord blood transplant between 2007 and 2017. All patients were aged 18 years or over at the

		Lymphoma n (%)	Myeloma n (%)	Leukemia n (%)	Autoimmune n (%)	Others n (%)	P value
1st year	Metabolic syndrome	5 (8,6)	5 (8,9)	9 (20)	1 (16,7)	3 (50)	0,037
	Overweight	26 (44,8)	27 (48,2)	12 (26,7)	2 (33,3)	0	0,041
	Hypertension	7 (12,1)	9 (39,3)	8 (17,8)	2 (33,3)	2 (33,3)	0,006
3rd year	Overweight	30 (51,7)	28 (50)	13 (28,9)	2 (33,3)	0	0,018
	Hypertension	9 (15,5)	22 (39,3)	8 (17,8)	2 (33,3)	3 (50)	0,011
5th year	Low HDL cholesterol	19 (67,8)	18 (100)	25 (67,6)	2 (33,3)	3 (75)	0,029
	Overweight	30 (51,7)	28 (50)	13 (28,9)	2 (33,3)	0	0,018
	Hypertension	11 (19)	23 (41,07)	8 (17,8)	3 (50)	4 (66,7)	0,004

[Table 1. Association between metabolic alteration and indication of HSCT]

time of their transplant, with the median age of 42.28 years. Patients who had received either full intensity (34.6%) or reduced intensity conditioning protocols (65.4%) were included in the study. The majority of the patients were diagnosed with AML; 51.9% of the patients. The other diagnoses included ALL, MDS, Hodgkin's lymphoma, non-Hodgkin's lymphoma, myeloma, PLL and CML.

The survival outcome of full intensity versus reduced intensity conditioning was compared, in addition to disease related outcomes.

Results: Our median overall survival from transplant for all patients was 63.2 months. The median time from transplant to death in all patients was 115 days. The majority of the deaths were related to either sepsis (47.8%) or disease relapse (34.7%).

The median survival time for full intensity conditioning from transplant was 112.2 months and 52.1 months for reduced intensity conditioning (p= 0.091). Overall survival at 1 year was 77.7% for full intensity conditioning and 58.8% for reduced intensity conditioning (p=0.178).

Across all disease types, patients who received reduced intensity condition had reduced outcomes compared to those who had received full intensity conditioning; however, this was non-significant in all cases.

Conclusions: This data demonstrates that in our centre, those patients who receive full intensity conditioning regimens for umbilical cord transplants have an excellent survival outcome. From our data if the patient survives the first 4 months post-transplant they are highly likely to remain alive for at least 2 years. Of the deaths we saw 50% (n=2) were sepsis related and 25% (n=1) were related to relapse. Survival as expected is less in those patients who received reduced intensity conditioning regimens. However, it has to be considered that patients receiving reduced intensity conditioning are unlikely to be suitable for full intensity regimens possibly due to age, co-morbidity scores or previous therapies.

Clinical Trial Registry: n/a

Disclosure: Nothing to declare.

P308

Higher Cost and no Survival Benefit with Addition of Rituximab to Beam Conditioning for Autologous Transplantation in Patients with Relapsed/Refractory DLBCL

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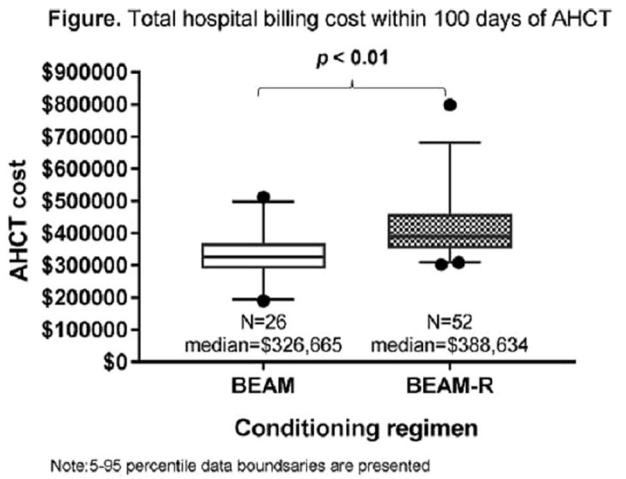
Background: High dose conditioning chemotherapy followed by autologous hematopoietic cell transplantation (AHCT) has been the standard of care for patients with chemosensitive relapsed/refractory (Rel/Ref) diffuse large B-cell lymphoma (DLBCL). The practice of adding rituximab (R) to commonly used BEAM (BCNU, etoposide, cytarabine, melphalan) conditioning has been driven by non-randomized single-institution data (Khouri et al., JCO 2015). Equivalent survival after BEAM and BEAM-R regimens was recently reported by the CIBMTR (Jagadeesh et al. Abstract 785, ASH 2019), however the true cost associated with addition of Rituximab to BEAM remains unknown.

Methods: We analyzed a retrospective cohort of BEAM (n=26) and BEAM-R (n=52) recipients with Rel/Ref DLBCL who were 1:2-matched by closest dates of AHCT performed between 2005 and 2019 at the Moffitt Cancer Center. Rituximab was administered at the dose of 375 mg/m^2 IV on days +1 and +8 of AHCT per our institutional protocol. Primary study endpoint was the total cost of AHCT within first 100 days (D100) post-transplant. Secondary endpoints included post-AHCT complications within D100, cumulative incidence of progression, and progression-free survival (PFS). Conditional logistic regression and Kaplan-Meier methods were used to analyze binary and survival outcomes, respectively.

Results: BEAM and BEAM-R recipients were largely comparable according to major demographic, disease, and transplant characteristics such as age (median 60 [range 39-79] vs. 62 [25-80] years, respectively, p=0.5), gender (p=0.4), race (p=0.8), pre-AHCT salvage lines of therapy (median of 1 for both, p= 0.2), presence of bulky (p=0.5) or FDG/PET-positive disease (p=0.9) prior to AHCT. Both cohorts had also similar rates of major infectious complications by D100 such as febrile neutropenia ± sepsis ± enterocolitis ± pneumonia (p=0.3), mucositis (p=0.4), anemia (p=0.7), and neutropenia (ANC< 1,500/mm3 by day 100; p=0.8). As consistent with the recent CIBMTR study, both the long-term PFS (log-rank p=0.4) and cumulative incidence of DLBCL progression (log-rank p=0.2) were similar between BEAM and BEAM-R cohorts. In contrast, BEAM-R-based AHCT was associated with significantly higher cost compared to BEAM-based AHCT (p< 0.01, see Figure below). The median difference of $61,970 USD/patient in hospital billing cost appeared to be driven by rituximab use.

Conclusions: Our pair-matched single-institution analysis demonstrates that BEAM-R does not appear to confer an

advantage over BEAM regimen for patients with R/R DLBCL and it is associated with significant cost in the absence of survival benefit. We therefore recommend against R use as a part of AHCT for DLBCL.



[Total hospital billing cost within 100 days of AHCT]

Disclosure: Aleksandr Lazaryan; EUSA Pharma LLC: SAB member (scientific advisory board)

P309

Association Between Metabolic Alterations with Age and Gender of Patients with Hematopoietic Stem Cell Transplantation

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Background: Aging and male gender may be a significant risk factor for worse outcomes after hematopoietic stem cell transplantation (HSCT). This study was performed to evaluate the association between HSCT with gender and age.

Methods: We conducted an analytical and observational retrospective cohort of adult patients treated with autologous and allogeneic HSCT at a fourth level referral center in Colombia from 2009 to 2018. The evaluated metabolic alterations were metabolic syndrome, hypertriglyceridemia, low HDL cholesterol, hypercholesterolemia, atherogenic dyslipidemia, overweight, obesity, prediabetes, diabetes mellitus, hypertension and hyperuricemia. Age was divided into 3 groups, < 20-year-old, 20-60-year-old and >60-year-old.

Results: A total of 217 patients were included, 53% were men and mean age was 46 years. 155 (71.4%) patients had autologous HSCT and 62 (28.6%) patients had allogeneic HSCT. Results for the 1st year were obtained from 171 patients, for 3rd year from 68 patients and 5th year from 20 patients. For 1st year, there were no significant associations between metabolic alterations and age, however, metabolic syndrome (P=0.007), low HDL cholesterol (P=0.013) and hyperuricemia (P=0) were associated with sex. For 3rd year, only atherogenic dyslipidemia (P=0.04) was associated with age, while metabolic syndrome (P=0.004), low HDL cholesterol (P=0.014) and hyperuricemia (P=0) were associate with gender. For 5th year, atherogenic dyslipidemia (P=0.02) and hyperuricemia (P=0.047) were associated with age, while metabolic syndrome (P=0.003), low HDL cholesterol (P=0.024) and hyperuricemia (P=0) were associated with sex. Complete results of significant data are shown in table 1.

Conclusions: Aging is a heterogeneous process with changes across many domains, although there is no relation between categorized age and the different studied metabolic alterations. Otherwise, male gender presents higher risk of developing metabolic syndrome, low HDL cholesterol and hypertriglyceridemia, which can be related to estrogen's action on insulin resistance and lipids.

Year	Metabolic alteration	<20-year-old n (%)	20-60-year-old n (%)	>60-year-old n (%)	P value
3rd year	Atherogenic dyslipidemia	0	25 (37.9)	5 (83.3)	0.04
5th year	Atherogenic dyslipidemia	0	27 (39.7)	6 (85.7)	0.02
	Hyperuricemia	2 (40)	33 (27)	16 (48.5)	0.047

[Table 1. Association between metabolic alteration and age]

Disclosure: Nothing to declare.

P310

Haploidentical HSCT in Children with very high-risk Haematologic Malignancies: A single-centre Experience

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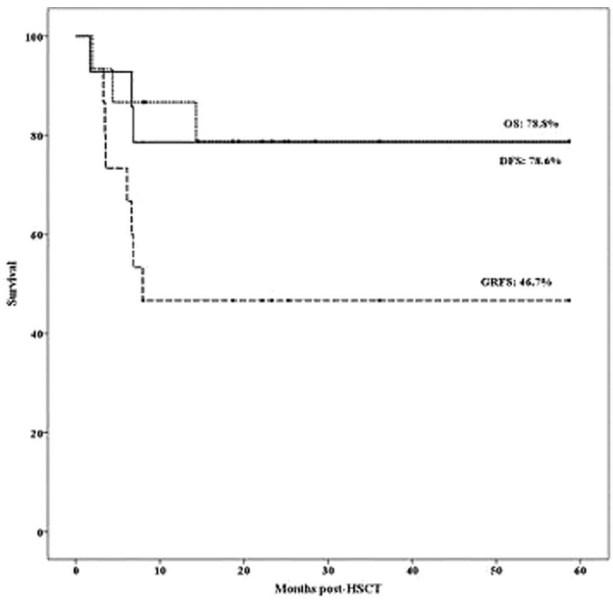
Background: The use of haploidentical stem cell transplantation (haplo-SCT) in paediatric patients without a suitable HLA-matched donor has become an opportunity over the recent years.

Methods: In this retrospective study, 15 patients (8 males, 7 females) with very high-risk haematologic malignancies underwent haplo-SCT over a 5-year period at the Royal Children´s Hospital, Melbourne, Australia. Two patients underwent haplo-SCT twice following primary graft failure. Nine of them were diagnosed with acute lymphoblastic leukaemia, four with acute myeloid leukaemia and 2 with juvenile myelomonocytic leukaemia. Five of them relapsed following previous HSCT and two patients had active disease going into the haplo-SCT. All patients received T-cell deplete (TCD) graft between year 2014 and 2016. Between 2017 and 2018, patients stratified to very high-risk disease at diagnosis and those undergoing second transplant were preferentially elected to receive T-cell replete (TCR) graft while the others received TCD transplant. Conditioning regimens used for most of the TCR and TCD transplants were fludarabine/melphalan/cyclophosphamide/TBI and busulfan/fludarabine/thiotepa/ATG respectively. GVHD prophylaxis consisted of post-transplant cyclophosphamide on Day +3,+4 with cyclosporine (CSA) and mycophenolate mofetil (MMF) for TCR transplant, whereas for TCD transplant, combination of CSA and MMF or monotherapy with MMF was given if the T-cell depletion was inadequate.

Results: Out of the 17 transplants, 8 were TCR while the remaining were TCD. The donors were mainly the father (52.9%) or the mother (41.2%), and majority (88.2%) of them had peripheral stem cells harvesting. Median age at transplant was 5.4 years (range 8 months to 15.5 years) while median duration of follow up post-transplant was 1.6 years (range 3 months to 4.9 years). Median CD34+ cells infused was 8.98 x 10^6/kg (IQR 25th 5.96; 75th 11.10). Median duration of neutrophil and platelet engraftment were 14 days (range 9 to 25 days) and 25 days (range 15 to 87 days) respectively. Thirteen patients (86.7%) had complete donor chimerism at Day+30.

Although no significant bacterial or fungal infections were observed in this study, eleven (73%) patients had at least one episode of viral reactivation. One patient developed fulminant liver failure following adenovirus viremia and succumbed at Day+133. The overall incidences of aGVHD grades II-IV and grades III-IV were 48.1% and 14.3% respectively. Meanwhile, the incidence of cGVHD and extensive cGVHD were 35.7% and 28.6% respectively. The estimated 3-year OS and DFS were 78.8% and 78.6% respectively. Three patients relapsed following haplo-SCT, making the 1-year cumulative incidence of relapse post-HSCT of 21.4%. Two of the relapsed patients died from disease progression while the other patient underwent a second TCR transplant.

Conclusions: From our study, the overall survival of patients with very high-risk haematologic malignancies following haplo-SCT was encouraging. However, longer duration of follow-up is needed to study the late events and long-term effects of the haplo-SCT.



[Kaplan-meier curve for overall, disease-free and GVHD-free/relapse-free survival.]

Disclosure: Nothing to declare.

P311

Infused Total Nucleated Cell Dose is not Associated with Engraftment in Autologous Stem Cell Transplantation

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Background: in some haematological malignancies the autologous hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy. Many studies have shown the effect of CD34+ cell dose on engraftment because a higher CD34+ cell dose correlates with a faster neutrophil and platelet engraftment. However, the effect of total nucleated cell (TNC) dose on engraftment has not been studied in autologous haematopoietic transplantation.

Methods: we have examined the impact of both TNC and CD34+ cell dose on time to neutrophil and platelet engraftment in 353 patients with haematological malignancies who underwent to their first stem cell autologous transplantation. The restrospectively evaluable patients were 323, 181 males (56%) and 142 females (44%), 174 with multiple myeloma (54%), 106 with non Hodgkin lymphoma (33%) and 43 with Hodgkin lymphoma (13%). The median age was 55 years (range 20-71). Neutrophil engraftment was defined as the first day of an absolute neutrofil count > 500/μL on three consecutive measurements; platelet recovery was defined as the first day of two consecutive measurements of > 50,000/μL. The median dose of infused TNC and CD34+ cells was $35.7x10^7$/Kg (range 28 - 182.8) and 5.3 x 10^6/Kg (range 2-15) respectively.

The patients were categorized into three group according to TNC [25th percentile 22.45 x 10^7/Kg (group 1), 75th percentile 56.05 x 10^7/Kg (group 2), high value 182 x 10^7/Kg (group 3)] and into three group according to CD34+ [25th percentile 4.2 x 10^6/Kg (group 1), 50th percentile 5.3 x 10^6/Kg (group 2), 75th percentile 6.9 x 10^6/Kg (group 3)].

Results: for all patients the Spearman coefficient for TNC versus CD34+ cells was -0.051 (95% CI:-0.15-0.051) suggesting that no correlation exists between ratio CD34+/TNC and engraftment. Moreover, by univariated analysis we did not find any correlation between TNC dose and neutrophil or platelet engraftment ($p=0.89$ and $p=0.055$, respectively). Instead, we shown that CD34+ cell dose was associated with a faster neutrophil engraftment ($p< 0.0001$), but we have failed to show a correlation between CD34+ dose and time to platelet engraftment ($p=0.097$), may be because we considered higher threshold levels of platelet engraftment than others studies.

The median engraftment time for neutrophils was 10 days, and for platelets was 14 days.

Conclusions: on the basis of our retrospective analysis it does not exist any correlation between infused total nucleated cell dose and time to engraftment in autologous stem cell transplanation.

Clinical Trial Registry: None

Disclosure: None interest conflict

P312

A Comparison of Allogeneic Stem Cell Transplantation And BFM 95 Chemotherapy Protocol in Adult Patients with Acute Lymphoblastic Leukemia

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Background: Acute lymphoblastic leukemia (ALL) is a hematological malignancy with heterogenous patterns of response to differing treatment options. Hence, there is no single treatment modality in patients with ALL. The main problem encountered in the treatment of adult ALL patients is that difficult to enter into complete remission (CR), and additionally CRs are short-lived. Therefore, allogeneic stem cell transplantation (AHSCT) isoffered in patients with a full-matched donor during the early course of the complete remission state. Maintenance chemotherapy is one of the treatment options for patients without full matched donor or not suitable for transplantation. This study aims to compare the efficacy of the induction and maintenance BFM95 chemotherapy regimen with allogeneic bone marrow transplantation (AHSCT) in adults with ALL in first remission.

Methods: One hundred and nine patients with ALL who were followed at Hacettepe University in 2003-2019 years, were enrolled in this retrospective study. Of 109 patients, 84 underwent AHSCT and 25 received maintenance chemotherapy. Of 84 transplanted patients, 40 received The Hyper - Cyclophosphamide - Vincristin - Adriamycin - Dexamethasone (Hyper-CVAD) chemotherapy, 21 received Cancer and Leukemia Group B (cyclophosphamide, daunorubicine, vincristine, prednisolon and L-asparaginase) chemotherapy and 23 received Berlin -Frankfurt - Munster 95 (BFM 95) (prednisolone, vincristine, daunorubicine and L-asparaginase) chemotherapy and AHSCT was performedearly after obtaining a complete remission. In total, 25 patientscompleted maintenance chemotherapy, induction, consolidation, re-induction, and maintenance therapy of BFM 95 chemotherapy. All of the patients who underwent AHSCT received transplantation from a HLA fully-matched donor.

Results: Median age of the study population was 28 years (range 17 to 67). Of 109, 41 (37.6%) were female and 68 (62.4%) were male. 86 (78.9%) were B-ALL and 23 (21.1%) were T-ALL. Philadelphia chromosome was positive in 2 patients with B-ALL. As prognostic factors, T

phenotype (19% vs 28%, p = 0.110), median leukocyte count at the time of diagnosis (27 vs 31 x 10^3/mm3, p = 0.420), median age (23 vs 30 years, p = 0.120) and first remission duration (42 vs 47 days, p = 0.820) were not different between the groups. The median time to AHSCT was 6.7 months (range, 2 to 11.2 months) after the diagnosis. Overall (OS) and relapse free survivals (RFS) at 3 years were 72% and 61% in patients receiving maintenance chemotherapy, and 70% and 58% in patients underwent AHSCT, respectively. Between the two groups, OS and RFS were not statistically different (p = 0.910 for overall and p = 0.880 for relapse-free survival). Relapse disease was observed in 5 (20%) of 25 patients receiving maintenance chemotherapy and 24 (28.5%) of 84 patients underwent AHSCT (p = 0.420).

Conclusions: These results suggest that whether if there exist any advantage of AHSCT over BFM-95 chemotherapy regimen for adults with ALL in first remission large prospective randomized studies are needed before reaching a definitive conclusion.

Disclosure: nothing to declare.

P313

Treosulfan Combined with Fludarabine as Conditioning Regimen in Allogeneic Stem Cell Transplanation of Myeloid Diseases, Allows High Overall Survival with Low Related Toxicity

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Background: Allogenic stem cell transplantation (alloHSCT) is a potentially curative option in acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). The replacement of Busulfan by Treosulfan in the conditioning regimen of these patients may result in a lower toxicity, especially in patients with high comorbidity index (HCTI).

The primary objective of our study is to evaluate the efficacy of this regimen for overall survival (OS) and disease-free survival (DFS); as secondary objectives we include the description of the pharmacological toxicity, the transplant-related mortality (TRM) and the cumulative incidence of acute and chronic graft versus host disease (GvHD).

Methods: Twenty-eight patients with AML (20) and MDS (8) who received Treosulfan (14 g/m^2 x 3) and Fludarabine (30 mg/m^2 x 5) between 2012 and 2019 were retrospectively analyzed.

Patients´characteristics are shown in Table 1. The median age was 57 years (13-73). Among the AML group, 12 patients (60%) were in 1st CR, 14 patients (70%) had positive MRD, and 8 patients (40%) had an adverse cytogenetics. Most patients with MDS had active transplant disease.

The DRI was high in 11 patients (39%) and the HCT-CI score $\geq$3 in 20 (71.4%). The donor was matched unrelated in 16 patients (57%) and haploidentical in 6 patients (21.4%). The stem cell source used was bone marrow in 15 patients (53%). In 10 patients (33%) treosulfan was used in the contidioning regimen of a 2nd transplant (5 autologous and 5 alogenic).

Results: All patients engrafted. Median time for neutrophil (>0.5 x 109/L) and platelet (>20 x 109/L) engraftment was 17 days (10-27) and 17 days (10-47) respectively. With a median follow-up of 36 months, 19 patients (67.8%) are alive (13 AML and 6 MDS), with OS at 1 and 3 years of 77 % (95% CI: 74% -79%) and 69% (95% CI: 64% -71%) respectively. DFS at 1 and 3 years was 73% (95% CI: 69% -76%) and 69% (CI 95%: 65% -72%), respectively. At 3 years, 6 of the 8 patients with MDS are alive

Two patients developed a post-transplant lymphoproliferative disorder. Grade ≥3 gastrointestinal and heart toxicity was seen in 5 patients (18%) and 1 patient (4%), respectively. None patient developed liver or lung toxicity grade ≥3. The cumulative incidence of TRM was 11% (95% CI: 2.7% -26%). Five patients (17.8%) died due to relapse of the disease and one patient with Li-Fraumeni syndrome due to a second neoplasm.

The cumulative incidence of grades II-IV and III-IV acute GvHD was 26% (95% CI: 11% -43%) and 18.6% (95% CI: 6.6% -35%), respectively. Chronic GvHD at 2-year was 56.7% (95% CI: 34% -74%), with 28.6% being moderate-severe (12%-47%).

There were no specific differences in elderly OS> 60 years, DRI, HCTI, adverse cytogenetics, pre-transplant MRD and donor.

Conclusions: Treo-FLU conditioning is effective in patients with a high risk of relapse including recurrence after previous transplantation, with a low MRT rate despite high HCT-CI, especially in patients with MDS.

Disclosure: Nothing to declare.

P314

Outome of Relapsed Acute Lymphoblastic Leukemia in Children and Adolescents Post Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains a crucial treatment method for pediatric patients suffering from acute lymphoblastic leukemia (ALL). However, the data about those who relapsed after allo-HSCT are sparse. Primary objective of this retrospective single-center study was to evaluate the incidence, further treatment and general outcome of patients with ALL who relapsed post first allo-HSCT.

Methods: Retrospective chart review of children (n=69) diagnosed with ALL who underwent allo-HSCT in Department of Pediatric Hematology, Oncology and Bone Marrow Transplantation in Wrocław, Poland in years 1995-2019, and then relapsed after transplant was performed. Clinical and epidemiological features as well as possibility of subsequent transplantation were assessed. Overall survival (OS), leukemia free survival (LFS) and transplant related mortality (TRM) were primary endpoints of this study. Statistical analysis was performed using R software package ver. 3.4.2.

Results: Among 287 children who underwent allo-HSCT due to ALL, 69 (24%; 45 males and 24 females) aged from 6 months up to 18 years (median 7.8 yrs) relapsed. Seventeen (24.6%) of them received first allo-HSCT in first complete remission (CR), 39 (56.5%) in 2CR, while 12 (17.4%) were beyond 2CR at the moment of transplant. Median time from first HSCT to relapse was 6.3 months (range 0.9-51.4). Twenty patients (29%) were able to achieve subsequent remission and underwent second alloHSCT. Median time between relapse and second allo-HSCT was 4.3 months (range 1.2-54.1). There was a noticeable difference in TRM after first and second allo-HSCT (6.8% vs 50%). Seven patients (35%) relapsed after second allo-HSCT, of which five died. Two children received third transplant and remain in fourth CR.

Median survival time in relapsed ALL after allo-HSCT was 4.2 months. The probability of survival at 1 year after relapse was 29.8% (95% CI 19.1%-41.2%), at 3 years 19.3% (95% CI 10.5%-30.1%), and at 5 years 17.2% (95% CI 8.8%-27.9%). Patients who underwent their first allo-HSCT in 1CR had significantly better survival (29.4%; 95% CI 7.8%-55.6%) than other patients (p=0.003), while there were no correlation between type of graft donor and OS. Children who underwent first allo-HSCT in less advanced stage of disease (1 or 2CR) had relevantly greater chances of achieving subsequent remission post relapse (95% vs 5%; p=0.05) and therefore being eligible for second transplantation. For those who achieved remission and received second allo-HSCT the probability of survival at 1, 3 and 5 years after second transplant were estimated at 55.4% (95% CI 29.9%-74.9%), 49.3% (95% CI 24.7%-69.8%) and 32.8% (95% CI 7.6%-61.8%) respectively.

Conclusions: Despite unequivocal curative potential of allo-HSCT in ALL, considerable number of patients relapses post-transplant. General outcome of those patients remain poor. The prognosis, however, depends closely on the timing of allo-HSCT - those who underwent transplantation in first or second CR had significantly greater chances for obtaining remission after relapse and better OS comparing to patients transplanted in more advanced stages of disease (beyond 2CR).

Disclosure: Nothing to declare.

P315

Motivation for Antifungal use in Pediatric HSCT Patients in an Institution in Southern Brazil

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Background: Invasive fungal infections are responsible for high morbidity and mortality rates in pediatric HSCT recipients. The diagnosis of fungal infections is delayed due to lack of positive cultures from blood or from tissues, which requires invasive procedures to obtain and are often difficult to perform in these critically ill patients. Early initiation of empirical antifungal therapy, delayed diagnostic procedures

and lack of financial and technological resources decrease pathogen identification rates. In order to identify fungal infections in our patients, considering the difficulties in establishing all probable and proven diagnoses, we reviewed the use of antifungal agents as a way to identify clinical situations treated as fungal infections and evaluated the number of ICU admissions and mortality.

Methods: We retrospectively analyzed the motivation of antifungal prescribing in HSCT pediatric patients between 2009 and 2018 at Hospital de Clínicas de Porto Alegre, a public institution in south of Brazil.

Results: 138 patients were submitted to 150 allogeneic HSCT, the median age was 9y (5m - 18y). 80 children had malignant diseases. Fluconazole was the main prophylactic antifungal agent, used in 131 transplants, 12 used voriconazole, 1 itraconazole and 2 posaconazole as secondary prophylaxis. Were identified 90 antifungal treatments in 78 patients. During the transplant hospitalization, 63 patients received therapeutic antifungal agents, mainly deoxycholate amphotericin; 33 were treated for febrile neutropenia and no fungal pathogens were identified; the other 30 diagnosis were candidemia (4), hepatosplenic candidiasis (1), oropharyngeal candidiasis (2), pulmonary aspergillosis (15), fungal rhinosinusitis (4), soft tissues aspergillosis (2), Saccharomyces cerevisiae fungemia (1), Fusariosis (1). There were 26 hospitalizations after first discharge (median day 208 post-transplant) with therapeutic antifungal prescriptions for febrile neutropenia (6), sepsis (6), pulmonary aspergillosis (10), fungal rhinosinusitis (3) and hepatosplenic candidiasis (2). Among 78 patients who received therapeutic antifungal agents, there were 39 intensive care unit admissions (50%) and 34 non relapse related deaths (43,6%), compared with 14 ICU admissions (23,3%) and 13 non relapse related deaths (21,7%) in 60 patients who hadn't received antifungal agents (p = 0,04 and 0,08, respectively).

Conclusions: Pediatric HSCT patients are at high risk to develop fungal infections and its treatment either empirically, as part of febrile neutropenia protocols, or targeted to specific pathogens, are frequent. In our institution, therapeutic use of antifungal agents is related to more severe clinical situations, with more ICU admissions and worse outcomes.

Disclosure: Nothing to declare.

P316

Impact of the Use of Granulocytic colony-stimulating Factor after Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Granulocyte colony-stimulating factor (G-CSF) has been used to accelerate neutrophil recovery and thus reduce the period of aplasia after allogeneic hematopoietic stem cell transplantation (HSCT). However, some studies have associated it administration with an increased risk of graft versus host disease (GVHD) and platelet engraftment delay. Currently its use is controversial since it is unclear what risk or benefit G-CSF brings after HSCT. The objective of this study is to analyze the impact of the use of G-CSF by comparing 2 cohorts of patients undergoing HSCT in our center.

Methods: We conducted a retrospective observational study that included 40 patients with hematological disease who underwent HSCT in our center between 2015 and 2018. We compared patients who received G-CSF from day +5 to post-transplant neutrophil recovery with those who did not receive G-CSF. To compare the use of G-CSF with other qualitative variables, the Chi-square test was used. We applied Kaplan-Meier test to analyze the overall survival (OS) using the SPSS v18 program for Windows. Cumulative incidence (CI) rates were calculated using the statistical package R v3.3.2.

Results: Data from 40 patients who underwent HSCT were retrospectively analyzed (Table 1). Median follow-up period was 17.8 months in G-CSF cohort and 34.1 in no-GCSF group. Median age was 56 and 55 in G-CSF and no-GCSF cohort, respectively. In both groups, the most common indication for transplantation was acute myeloid leukemia. Peripheral blood was the stem cell source used in all cases. In G-CSF cohort, the CI of grade 1-4 aGVHD and grade 3-4 aGVHD at 100 days was 43% and 25%, respectively. CI of chronic GVHD (any grade) at 2 years was 61%. CI of non relapse mortality (NRM) at 2 years was 22% and OS at 2 years was 59%. On the other hand, in no-GCSF cohort, the CI of grade 1-4 aGVHD and grade 3-4 aGVHD at 100 days was 50% and 18%, respectively. CI of chronic GVHD (any grade) at 2 years was 50%. CI of NRM at 2 years yas 12% and OS at 2 years was 57%. In both cohorts, all patients had haematological recovery. We found no difference in time to reach neutrophil engraftment >0.5 $x10^9$/l. Conversely, patients given G-CSF after transplant took a longer time to reach platelet count >20 $x10^9$/l. Thus, CI of platelet engraftment at 20 days was 87% in no-GCSF group vs. 50% in G-CSF group. We found no association was found between the use of G-CSF and post-transplant complications (graft failure, engraftment syndrome,

hemorrhagic cystitis, acute and chronic GVHD, relapse, non-relapse mortality and overall survival).

Conclusions: Our study did not find relationship between the use of G-CSF and post-transplant complications. Similarly, we did not find differences in time to neutrophil engraftment. However, we detected a delay in time to platelet count >20x10^9/l in patients who received G-CSF. The use of post-transplant G-CSF had no impact on NRM and OS at 2 years. Our study shows that adding G-CSF does not provide any benefits after HSCT.

Disclosure: Nothing to declare.

P317

Abstract already published.

P318

Phase II Study of Plerixaflor and G-CSF as Mobilizing Therapy for Double Autologous Transplantation Patients with Relapsedrefractory Diffuse Large B Cell, Pet Positive after Two R-DHAP

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Background: Relapsed/Refractory Diffuse large B-cell Lymphoma (DLBCL n HL) tipically follows an aggressive clinical course and management is challenging with treatment decision based on patients and disease characteristics.

As demonstrated by Scholar 1 study, in addition to IPI score, mutation or over expression of Myc, Bcl2 or p53, refractory status play a really important role to determine the prognosis.

Methods: In this subset of patients also High dose chemotherapy and Autologous Stem Cell Transplantation (ASCT) evidence a poor outcome with 50% of failures at a median of 5.6 months.

In such a population of patients, still Pet+ after salvage, we planned a different approach other than a single ASCT in the attempt to better the response and the outcome in term of PFS and OS.

Within the framework of Rete Ematologica Pugliese (REP) we designed a prospective multicentric study to perform a double ASCT or a tandem ASCT/RIC Allo, if refractoriness was demonstrated by Pet after two cures of RDHAP. (CETIM0109 Trial).

In these evenience we aimed to mobilize a large number of CD34+ cells able to perform double ASCT.

Results: Primary endpoint was to collect CD34 + ≥ 6*106 Kg mobilized, after first cure of RDHAP, by G-CSF and Plerixafor at day four of G-CSF. Number of apheresis, to reach 6*10 6 Kg CD 34+ cell, engraftment kinetics and outcome were secondary endpoint

Median CD 34+ cell/Kg collected were 10.5x10.6

93% of collections exceeded 6*10.6 Kg.

Median Apheresis to target was 1 (1-3) in 73 %.

Median number of infused CD 34+ cell at first transplant was 4.75* 10.6 Kg, with 99 % of viability.

Pet Neg CR after first ASCT were documented in 20 pt (64%). CR rate of the double transplant was 67.5 % (CR 20+5).

Relapse Rate at first year was 10%, PFS at first year and third year were 78 e 65 % respectively.

Conclusions: Considering our follow-up of two years after first ASCT and after second ASCT, the result in term of ORR, PET negative CR and PFS in our Cohort of patients, are very promising and prove the capability to increase CR rate.

Early intensification and Pet driven treatment program could be the possible positive explanation.

In the future it's to better define, in the real life, the impact of cellular therapy with Car-T cell in refractory DLBCL (ZUMA trial and JULIET trial), after failure of ASCT, in this particulary subset of patients.

N.Apheresis, Median(range)	1(1-4)
1	28(76%)
>=2	9(24%)
N.PLX vials, Median (range)	2(1-4)
<=2 vials, n(%)	25(68%)
Median time to collection from diagnosis, months(range)	8.3(4-103)
CD34+ x 10^6/Kg Median (range)	10.5(2.5-51)
<=6 x 10^6/Kg, n(%)	35(95%)

[Mobilization and collection data]

Clinical Trial Registry: The clinical trial obtained approval by Local Ethics Committee

Disclosure: All authors have no potential conflict of interest

P319

The Effect of CD34+ Hematopoietic Progenitor Cell Dose on the Hematopoietic Recovery and Survival in Acute Lymphoblastic Leukemia (ALL) Patients Underwent Allogeneic Stem Cell Transplantation

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Background: Although the influence of the amount of the transplanted CD34+ hematopoietic progenitor cells (HPC) on neutrophil/ platelet engraftment time and influence on the transplantation outcomes has been controversial, greater than $2x10^6$/kg CD34+ cells are commonly accepted for adequate engraftment. The aim of this study is to evaluate the relationship between CD34 + HPC dose and the survival and engraftment time in ALL patients who underwent Allogeneic Stem Cell Transplantation (Allo-HSCT).

Methods: In this study, 84 patients underwent Allo-HSCT and followed at the Hacettepe University Faculty of Medicine Department of Hematology were enrolled. Patient data and the hospital records were analyzed retrospectively. All patients received HLA-identical sibling donor Allo-HSCT and the CD34+ HPC were mobilized with granulocyte colony-stimulating factor.

Results: The median age of all patients was 30,5 (17-64) years. The median follow-up time was 42,6 months (2-199,6). The features of the engraftment in 48 (57.1%) patients allografted using the reduced-intensity and 36 (42,9%) myeloablative conditioning regimen were analyzed. The patients received a median of 6.3×10^8/Kg mononuclear cells (range 1.2 to 28), and a median of $7,4 \times 10^6$/Kg CD34 cells (range 1.4 to 30) for Allo-HSCT and when analyzed it has been found that $< 5x10^6$/kg and $\geq 5x10^6$ /kg CD34+ HPC were transplanted in 28 (33,3%) and 56 (66,6%) of the patients, respectively. There was no patient who failed engraftment; in those patients, the median time to achieve neutrophil engraftment 11 days (range 8 to 16), and the median time to platelets engraftment was 12 days (range 9 to 38). Although there was a significant negative correlation ($r = -0.260$, $p = 0.018$) between the neutrophil engraftment time and CD34+ HPC given, there was no correlation between platelet engraftment time and CD34+ HPC given ($r = -0.160$, $p = 0.130$). Furthermore, the number of mononuclear cell count and the time for recovery had no association. Graft versus host disease (GVHD) was observed in 41 (48.8%) patients. In patients who received CD34+ HPC greater than $5x10^6$ /kg doses, GVHD was seen more common (34 vs 7 patients, $p = 0.05$). When the cut-off value was accepted as $5x10^6$ /kg for CD34+ HPC, median overall survival (OS) and progression free survival (PFS) showed no difference (for $< 5x10^6$ /kg, median OS = 187.9 vs median PFS = 51.4 months, $p = 0.290$ and for $\geq 5x10^6$ /kg, median OS = 118.5 vs median PFS = 41.4 months, $p = 0.780$).

Conclusions: The number of CD34+ infused cells was significantly related to the neutrophil engraftment time and the GVHD rate of the patients when $\geq 5x10^6$ /kg for CD34+ HPC transplanted to the ALL patients who underwent Allo-HSCT.

Disclosure: nothing to declare.

P320

The Eventual Role of Donor and Recipient Vitamin D Levels in Allogeneic Hematopoetic Stem Cell Transplant Setting

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Background: Vitamin D (VitD), which regulates several immun system functions including hematopoietic stem cell proliferation and differentiation, may be considered to have a potential role in hematopoietic stem cell transplantation (HSCT) setting. The aim of this study was to evaluate the possible impact of donor and recipient VitD levels on HSCT outcome.

Methods: A total of 123 donor [median age: 44 (18-70) years; M/F: 66/57] and allogeneic HSCT (allo-HSCT) recipient [median age: 46 (18-68) years; M/F: 72/51] pairs were included in this retrospective study. The association of pre-HSCT VitD levels with certain HSCT parameters were analysed statistically. Subjects were classified into two subgroups, as low- (< 20 μg/L) and high-VitD (>20 μg/L) groups. Patient and transplant characteristics are summarized in **Table 1**.

Results: Median pre-HSCT VitD levels were 16(3-62.6) μg/L and 12.8(3-63.3) μg/L in donor and recipient groups respectively. Neutrophil engraftment day was found to be longer in low-VitD group compared to high-VitD group in allo-HSCT recipients [14(10-26) days vs 12(10-21) days; p=0.032]. A negative correlation was demonstrated between recipient VitD levels and chronic graft versus host disease (GvHD) (p=0.011, r=-0.235). Among donor and recipient arms, no statistical difference was observed

between low- and high-VitD subgroups in terms of post-HSCT complications including veno occlusive disease (VOD), cytomegalovirus (CMV) reactivation, mucositis, acute and chronic GvHD. At a median follow-up of 16(1-67) months, overall survival (OS) was better in low-VitD group compared to high-VitD group in both donor [53.1% vs 49.2%, p>0.05] and recipient [60.9% vs 29.4%, p>0.05] arms, without statistical significance. On the other hand, the probability of progression free survival (PFS) was found to be higher in high-VitD group compared to low-VitD group in donor [68.4% vs 71.7%, p>0.05] and recipient [63.5% vs 72.5%, p>0.05] arms, without statistical significance. Multivariate Cox regression analysis revealed pre-HSCT European Society for Blood and Marrow Transplantation (EBMT) score (p=< 0.001), Karnofsky score (p=0.013) and VOD (p=0.002) as significant prognostic factors for OS.

Conclusions: Prevalence of VitD deficiency was shown to be extremely high among allo-HSCT recipients like healthy individuals. Based on its effects on immunological network and hematopoietic cell compartment, several studies have demonstrated a potential association of VitD with acute/chronic GvHD, CMV reactivation, post-HSCT relapse and survival. In the current study, a significant association of pre-HSCT VitD levels with neutrophil engraftment and chronic GvHD was also observed. Donor and recipient VitD levels did not represent distinct effect profiles on post-HSCT complications. However, a discordance was indicated between the impact of pre-HSCT VitD levels on OS and PFS, which did not reach statistical significance. Eventually, we can conclude that VitD requires more evidence to be considered as a potential prognostic marker in allo-HSCT setting even if remarkable data was provided in the previous reports.

Primary Diagnosis [n(%)]	
Acute Myeloid Leukemia	53(43.1)
Acute Lymphoblastic Leukemia	34(27.6)
Lymphoma	14(11.4)
Multiple Myeloma	1(0.8)
Aplastic Anemia	1(0.8)
Myelodysplastic Syndrome	11(8.9)
Chronic Myeloid Leukemia	3(2.4)
Chronic Lymphocytic Leukemia	1(0.8)
Primary Myelofibrosis	5(4.1)
Pre-transplant Disease Status [n(%)]	
Complete remission	84(68.2)
Partial remission	8(6.5)
Refractory or progressive	24(19.5)
Unknown	7(5.7)
Donor Type [n(%)]	
Matched-sibling	113(91.9)
HLA-matched relative	4(3.3)
Haploidentical	6(4.9)
Conditioning Regimen [n(%)]	
Myeloablative	63(51.2)
Reduced intensity	60(48.8)

[Table 1. Patient and Transplant Characteristics]

Disclosure: Nothing to declare.

P321

Average Length of Hospital Stay for Pediatric Blood and Marrow Transplants in the Backdrop of Cell Source, Transplant Type and Outcome

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Background: Blood and marrow transplant is a high-cost procedure. In countries, where such treatment options are made available to the masses by government agencies, average length of hospital stay (ALOS) is considered as a surrogate marker to estimate cost per transplant. In this backdrop, timely availability of accurate and updated information according to the primary indication of disease and transplant category is of prime importance.

Methods: A total of 475 patients underwent 503 transplants, from Jan 2015 to December 2018. Medical and electronic records were reviewed retrospectively and their In-patient admission duration, engraftment status, outcome and length of stay for the transplant from the start of conditioning regimen till first discharge were recorded. In 274 (54.5%) the stem cell source was a fully matched donor (FMD) followed by Haplo-identical (Haplo) (89, 17.7%), Cord blood (COB) in (69, 13.7%) and Matched Unrelated Donor (MUD) in (16, 3.2%); 55(10.9%) were autologous transplants. In terms of Primary Diagnostic Related Groups, Non-malignant Hematological Disorders constituted 170 (33.8%), followed by malignancies (n=161,32%), Immune Disorders (n=104,20.7%), Histiocytic Disorders (n=41,8.2%) and Metabolic Disorders (n=27,5.4%).

Results: For a total of 24868 patient-days, ALOS for all transplants was 49.4 days (Range: 6-379), regardless of their survival status or engraftment outcome. It was 76.8 in patients transplanted using COB, followed by 67.4 for

MUD, 51.2 in Haplo, 44.7 in FMD and 30.5 in autologous transplants. Regarding hospital-days for in-patient stay (24868 days); MUD transplants contributed to 49.3% (12258 days), COB 21.3% (5296 days), Haplo 18.3% (4559 days), autologous 6.7% (1677 days) and MUD 4.3% (1078 days). In term of indications for transplantation, ALOS for patients transplanted for Metabolic disorders was 74.3 days (hospital days: 2007, 8.1%), Immune Disorders 62.1 (hospital days: 6457, 26%), Histiocytic Disorders 57.4 (hospital days: 2354, 9.5%), Malignant Disorders 43.6 (hospital days: 7016, 28.2%) and Non-malignant hematological disorders 41.4 (hospital days: 7034, 28.3%). ALOS for Engrafted transplants (n=449) was 46.2 (range, 18-379); 72.2 for COB, 69.8 for MUD, 47.6 for Haplo, 44.5 for FMD and 28.7 for autologous transplants. Regarding hospital-days for this subgroup (20750 days); FMD transplants contributed to 57.3% (11890 days), Haplo 17.7% (3663 days), COB 12.5% (2600 days), autologous 7.5% (1550 days) and MUD 5.0% (1047 days).

Mortality rate in our cohort was 22.7% (108 of 475) for all transplants with an ALOS of 63.4 days (range, 6-379; Hospital days: 6851). ALOS for expired patients for MUD was 90 days (Hospital days: 270, 3.9%) followed by FMD 80.7 (Hospital days: 3389, 49.5%), COB 58.2 (Hospital days: 1687, 24.6%), Haplo 50.2 (Hospital days: 1255, 18.3%) and autologous 27.8 (Hospital days: 250, 3.6%). Expired patients contributed to 27.5% of total hospital stay (6851 days) compared to those who are alive and engrafted 69.4% (17252 days), 83.4% (20750 days) respectively.

Conclusions: ALOS in pediatric transplants depends on multiple factors and should not be taken as a single independent measure to decide on the economics of pediatric blood and marrow transplantation. Further analysis for causes of prolonged ALOS will help developing different strategies to reduce both ALOS and cost per transplant case.

Clinical Trial Registry: NA

Disclosure: NA

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One Center Experience in Offline Technique Validation with Biological Quality Tests

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Background: Extracorporeal photoapheresis (ECP) is an immunomodulatory cell therapy based on leukapheresis that was first developed for the treatment of cutaneous T-cell lymphoma (TCL).

It has proven effective in treating rejection of solid organ transplantation, graft-versus-host disease (GVHD), systemic inflammatory diseases (eg, Crohn´s disease), and some autoimmune and dermatological diseases.

Two systems are used to perform ECP: the online system Therakos and the off-line method.

Because this technique involves the ex vivo treatment of white blood cells, a quality control (QC) is necessary to validate the process. In our apheresis unit the off-line method is used, mononuclear cells (MNC) are collected by leukapheresis and then exposed to ultraviolet light (UVA) after adding a photosensitizing agent, 8-methoxy-psoralen (8-MOP) the cells light up to later reinfuse the patient.

In our center, we performed hematological controls for each apheresis bag and microbiological analysis of each product obtained.

The data published in the literature on the mechanism of action of ECP suggest that DNA damage induced by ECP is closely related to the apoptotic process and for this reason, it was decided to use the percentage of MNC apoptosis as a test for the biological validation of ECP.

Methods: To analyze the kinetics of apoptosis induced by the ECP procedure and to quantify the early and late apoptosis in ECP in treated and untreated CMNs; as a test for the biological validation of ECP. The ECP was performed according to our internal protocol, using the MacoGenic G2 photoiluminator from Macopharma.

In this study, we used the binding of annexin V labeled with FITC to phosphatidylserine (PS) in association with propidium iodide (PI) staining to analyze the kinetics of apoptosis induced by the ECP procedure and to quantify early and late apoptosis in ECP in MNC treated and untreated.

A total of 8 consecutive extracorporeal photopheresis procedures belonging to 5 patients were analyzed; 2 patients with GVHD and 3 patients with TCL.

Results: Our data on the kinetics of apoptosis demonstrated that there is a significant difference in the percentages of living and apoptotic cells between the pre- and post-FEC samples at 48 h where the percentage of apoptotic cells increased considerably.

In 87.5% of the 8 ECP procedures studied, Delta APOPTOSIS was> 15%.

Red blood cell contamination (% Hct), which is thought to interfere with UVA irradiation when> 2.5%, was < 2% low in our apheresis bags.

Conclusions: Our data suggest that flow cytometry is a promising tool in this context.

The measurement of apoptosis seems to be a reliable method to validate FEC procedures, but we are aware that our results come from a limited number of procedures and we can not confirm this impression conclusively due to the small number of procedures analyzed.

However, our findings could provide the basis for research on a greater number of patients with different diseases.

Disclosure: No Disclosure

P323

The Outcome of Allotransplant using TBF Conditioning from Matched Sibling Related Donors in High Risk Myelodysplasia and Acute Myelid Leukemia: A Retrospective Single Center Experience

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Background: Busulfan plus cyclophosphamide (BuCy) or Busulfan Fludarbine based conditioning is the traditional conditioning regimens for allogeneic stem cell transplant (allo-SCT) for young, fit patients with high-risk myelodysplasia (MDS) and acute myeloid leukemia (AML) [1, 2]. The thiotepa-busulfan-fludarabine (TBF) protocol has recently demonstrated promising outcome in cord blood and haploidentical stem cell transplantation [3, 4]. Recent EBMT registry study showed an impressive lower rate of relapse in a large cohort of AML patients transplanted from matched sibling and matched unrelated donors [1]. Here we will report on twenty adult allotransplant recipients from matched related donors, who received TBF conditioning at King Hussein Cancer Center during January 2017-July 2019.

Methods: We included twenty consecutive patients with high risk MDS and AML, who received TBF conditioning regimen for allotransplant from January 2017-July 2019. Patients- disease and transplant related characteristics listed in Table-1. Fourteen patients received a myeloablative conditioning regimen consisting of thiotepa (5mg/kg/day)infused on day -6 and -5, fludarabine (30mg/m^2/day) on day -4 to day -2; and busulfan (3.2mg/kg/day) on day -4 to day-2. GvHD prophylaxis consisted of calcineurin inhibitor, started on day -3 with short course methotrexate on days +1, +3, +6 in myeloablative and Mycophenolate Mofetil, started on day zero in reduced intensity transplants. All recipient received GCSF mobilized PBSC graft.

Results: Twenty patients (100%) engrafted. Median time to granulocytes and platelets engraftment was 15 days (range: 12-19) and 14 days (range: 9-25) respectively. 74% had full donor chimerism on day+100. After a median follow up of 6.9(2.0- 12.1months), the cumulative incidence of Grade II-IV and III-IV acute GVHD (aGvHD) was 20% and 15% respectively. Four patients (20%) developed chronic GvHD, 2 of which extensive, one after preemptive azacytidine. six patients (30%) relapsed at a median of 113 days (60-465), one extramedullary in the CNS, three of which (50%) died due to disease progression and only one patient successfully salvaged, in complete remission (CR) with full donor chimerism at last follow up. Eleven patients (55%) had CMV reactivation, one-third within the first 100 days post-transplant. The day 100 NRM 5% (N=1), due to grade IV gut aGvHD and flare up of pulmonary proven fungal infection. At last follow up, 14 patients (70.0%) were alive; all except two are in continuous complete remission with negative minimal residual disease and full donor chimerism.

Conclusions: TBF conditioning regimen appears to be safe, allows high rate of engraftment and low NRM among high-risk MDS/AML patients and can lead to a long-term disease control.

Disclosure: Nothing to disclose

Sex	Disease	Disease status at transplant	Conditioning	day30:mor.CR day30: Mol.CR	Day100MorCR Day100MolCR	Day30 Chimera	Median CD34 x10E6/kg Median CD3 x10E7/kg	Patient´s Status
F/M	AML/ MDS	CR1 ≥ CR2 Not in CR	MAC RIC	yes yes	yes yes	Full Mixed		Alive Dead
07(35.0%) 13(65.0%)	17(85%) 03(15%)	07(35.0%) 10 (50%) 03 (15.0%)	14(70%) 06 (30%)	20(100%) 06 (60%)	16(80.0%) 14 (70%)	18(90.0%) 02(10.0%)	17.2(3.80194) 21.5(12.0-30)	14(70.0%) 06(30.0%)

[Table- 1: Patients- disease and transplant characteristics (N = 20)]

P324

Efficacy and Safety of Post Hematopoietic Stem Cell Transplantation Donor Lymphocyte Infusion in Patients with Acute Leukemia. Retrospective Analysis in Our Center

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Background: Relapse of acute leukemia (AL) after allogenic hematopoietic stem cell transplantation (alloHSCT) worsens patients' prognosis. Donor lymphocyte infusion (DLI) may be an effective therapy in these patients

Methods: Retrospective analysis of 30 patients with AL who received DLI after alloHSCT from 2000 to 2018.

Patients in 2nd or further complete remission (CR), positive MRD or adverse cytogenetics were considered at high risk for relapse.

Median age was 37 years (5-71). Twenty one patients were males. The baseline characteristics of the patients are shown in table 1.

Twenty two patients had a matched donor (14 related, 8 unrelated), 5 patients received a mismatched graft and 3 patients a haploidentical graft.

Fourteen patients received DLI therapeutically, 11 pre-emptive and 5 as prophylaxis. At DLI, only one patient had mild chronic graft versus host disease. All patients were off immunosuppresive therapy at DLI. Seven patients received reinduction chemotherapy before the DLI.

Fifty eight doses of DLI were administered, with a median of 1 (1-5) dose per patient. The maximum infused dose varied, depending on the type of donor and degree of HLA disparity: 5,4 (1 -15,3), 4,2 (1-10), 1,9 (0,2-4,6) and 0,5 (0,2-1) x10^7/kg in matched related donor, matched unrelated donor, missmatch and haploidentical, respectively. The dose was higher in the therapeutic group.

Median time until triggering event of DLI (relapse, appearance of MRD or loss of chymerism) was 132 days (21-547) and median time from alloHSCT until first DLI was 179 days (38-771)

Results: Nine out of 14 patients in the therapeutic group reached CR and 1 PR. Among 11 patients in pre-emptive group, 5 reached CR. Four out of 5 patients in the prophylactic group remained in CR. The median follow up after DLI was 49 (range, 14-163) months.

Median OS and LFS for the entire cohort were 14 (IC 95%, 3, 9 to 24,1) and 9 (IC 95%, 1,1 to 16,9) months, respectively.

Median OS and LFS in the therapeutic group were 11 (CI 95%, 5,5-16,5) and 4 (CI 95%, 0-12,5) months, respectively. Median OS and LFS in the pre-emptive group, were 14 (CI 95% 7, 7-20,3) and 5 (CI 95%, 0-38) months, respectively.

In the prophylactic group, the median OS (p=0,029) and LFS (p=0,01) were not reached. The LFS probability at 1, 2 and 3 years was 80% (IC 95%, 77 to 82).

Patients in CR after DLI (n=14) had a median LFS of 17 months (IC 95% 5,5 to 28).

After DLI, the cumulative incidence of acute GvHD grades II-IV was 20.4% (95% CI: 8.1-36.6) and chronic GvHD was 33% (95% CI: 15.4-51.9). Two patients with chronic GvHD died of related complications.

The causes of death were: relapse (n=14), severe infection (1), demyelinizing neuropathy (1) and 2 unknown

Conclusions: Our data suggest that prophylactic DLI could improve LFS in high risk patients. Therapeutic and pre-emptive DLI was useful in a subgroup of patients with relapsed leukemia or positive MRD.

DLI was a safe treatment, GVHD being the most frequent complication but with a low incidence of severe forms

Disclosure: Nothing to declare.

P325

Cardiovascular Risk in Patients before and after Hematopoietic Stem Cell Transplantation

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Background: Hematopoietic stem cell transplantation (HSCT) survivors are at higher risk of developing adverse cardiovascular risk (CVR) and metabolic syndrome, leading to cardiovascular comorbidities. The aim of this study was to evaluate the CVR in patients before and after HSCT.

Methods: We conducted an analytical and observational retrospective cohort of adult patients treated with autologous and allogeneic HSCT at a fourth level referral center in Colombia from 2009 to 2018. To calculate CVR,

metabolic syndrome, hypertriglyceridemia, low HDL cholesterol, hypercholesterolemia, atherogenic dyslipidemia, overweight, obesity, prediabetes, diabetes mellitus, hypertension and hyperuricemia were evaluated. Cardiovascular risk was measured before and one year after HSCT with Framingham scale, a gender-specific algorithm used to estimate the 10-year cardiovascular risk.

Results: Information from 103 patients were analyzed for CVR before HSCT, and information from 55 patients were available for CVR after 1 year of HSCT. Before HSTC, low CVR was identified in 69 patients (67%), moderate CVR in 26 patients (25%) and high CVR in 8 patients (8%). After one-year follow-up, low CVR was identified in 36 patients (66%), moderate CVR in 14 patients (25%) and high CVR in 5 patients (9%). Average CVR by Framingham was 12.1% before HSCT and 12.86% one-year after HSCT.

Conclusions: It is clear that HSCT survivors have a higher prevalence of cardiovascular disease, HSCT survivors presented a Framingham score of 10-20%, which is categorized by the American Heart Association (AHA) as intermediate CVR, which remained even one year after HSCT. This exposes the need of aggressive screening for CVR such metabolic syndrome to establish prevention strategies and decrease morbidity, poor quality of life, and premature mortality.

Disclosure: Nothing to declare.

P326

Peripheral Blood Stem Cell Transplantation in Pediatric Recipients in Peru: Experience of a Referral Center

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Background: Stem cell transplantation (SCT) is a curative treatment for children with relapsed/refractory malignancies. The aim of this study was to determine survival of children who have received peripheral blood stem cell transplantation (PBSCT) at a referral center in Peru.

Methods: A total of 20 children (≤14 years) who underwent related allo- or auto-PBSCT from October 2014 to December 2017 were included in the study. The event-free survival (EFS) and overall survival (OS) at two years was evaluated.

Results: We report 13 males and 7 females with a median age of 9.5 years (1- 14). Eighteen patients received allo-SCT and 2 auto-SCT. Pre-SCT complete remission (CR) was achieved in 19 cases: 8 (38%) CR1; 8 (38%) CR2 and 3 (14.2%) CR3. Median follow-up was 12 months (1-39). The 2-year OS and EFS were 75.7% and 51.6%, respectively. Children with ALL older than 3 years of age, who did not receive radiotherapy-based conditioning regimen, the OS and EFS were 51.9% and 45.1%, respectively. Acute graft-versus-host disease (GVHD), chronic GVHD, transplantation-related mortality (TRM) and relapse were 27.7%, 11.1%, 4.7%, and 28.5%, respectively

Conclusions: EFS and OS are comparable with published data. However, survival of children with ALL older than 3 years of age is less than international historical reports. Higher number of cases and longer follow-up time are needed to reach definitive conclusions

Disclosure: Nothing to declare.

P327

Haematopoietic Stem Cell Product Viability: A Comparative Study Between Bags and Vials

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Background: The Cellular Therapy Laboratory (CTL) at the South African National Blood Service (SANBS) is responsible for processing and storing Hematopoietic Stem Cells (HSC) for 16 transplant units across South Africa.

To assess HSC viability prior to reinfusion, a sample vial is tested for viability using flow cytometric and manual trypan blue investigations. An aliquot of the processed HSCs is placed in the vial during processing and stored under the exact same condition as the HSC product ("bag"), giving a "best representation" of the bag content. Studies have shown that this test vial may be an under representation of HSC product viability because thaw rate (and subsequent cell death) is inversely proportional to volume.

The transplant units have varying degrees of access to laboratory testing, however none have quick access to flow cytometric analysis to assess HSC viability. There is an urgent need for a point of care/ bedside viability test to assess bag viability, specifically in cases where vial viability is poor.

This pilot study compared vial viability performed at our institution to bag viability performed at the patients' bedside.

Methods: This study included fifteen samples.

Vials were tested for CD45 and CD34 % viability using the Beckman Coulter FC500 flow cytometer and the Stem-Kit ™ reagents. Vials were also tested using a manual trypan blue (0.4%, Gibco) staining method and viability

detected using a contrast phase microscope. The manual trypan blue and automated trypan blue methods were 94% comparable (results not shown).

At the bedside, HSC product bags were thawed for immediate reinfusion. A sample was stained with 0.4% trypan blue (Gibco) and tested using the automated trypan blue (Bio-rad TC20 Automated Cell Counter) method as per manufacturer instructions.

Results: Vials with high HPC viability (≥80%) showed equally or higher bag viability. However, vials with low viability associated bags had far higher viability. Vials with 40-60% viability had bag viability >80% while vials with viability of 30-40% had bag viability of 60-80%.

Conclusions: SANBS offers a country wide service for processing and storage of HSC using one centralized processing facility and multiple national transplant units. While this allows patients throughout South Africa access to HSC transplants, it has various limitations with regards to access to near-patient laboratory testing.

There is a great concern that the vials being tested at CTL is not a direct representation of the bag content that will be reinfused. The results presented here show that high vial viability correlates with high bag viability; however, low vial viability does not correlate with bag viability. This study indicates bag viability of vials that has a viability below 50%, is often almost double that of the vials.

This pilot study showed that while vial viability testing is essential for release of the product, the result is often underestimated when compared to bag viability. This has clinical significance, especially when vial viability results are poor (< 50%). Our suggestion is that bedside bag viability should strongly be considered in all HSC transplants, specifically those with low vial viability.

Disclosure: Nothing to declare.

P328

Transfusion Support in the First 30 and 100 Days after Haploidentical versus HLA-matched Related Donor Hematopoietic Stem Cell Transplantation

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Background: Haploidentical hematopoietic stem cell transplantation (haplo-HSCT) has increased in recent years as an option for patients without available HLA-matched donor. Transfusion support could be higher due to increased risk of delayed engraftment and genetic disparity, but data are still scarce. The objective of this study was to compare transfusion requirements (red blood cell [RBC] and platelet concentrates [PC]) during the first 30 and 100 days after haplo-HSCT versus HLA-matched related donor HSCT (allo-HSCT).

Methods: Thirty-four haplo-HSCT performed between 2013 and 2019 were included in this single-center retrospective study. Patients with graft failure (n=4) were excluded. Allo-HSCT performed between 2003 and 2018 were used as controls. PC were made based on pooling 5 interim platelet units and were obtained by REVEOS™ processing system. All RBC and PC units were leukodepleted and irradiated.

Results: Twenty haplo-HSCT recipients were matched with 20 allo-HSCT recipients with the same baseline patient and transplant characteristics (Table 1). Nearly all patients were transfused in the first 30 days (PC: 95% haplo-HSCT vs. 90% allo-HSCT [p=1.000], RBC: 90% haplo-HSCT vs. 75% allo-HSCT [p=0.407]) and 100 days (PC: 65% vs. 42% [p=0.152], RBC: 65% vs. 53% [p=0.433]). Among the transfused patients, the number of PC transfused was higher in haplo-HSCT than in allo-HSCT group by day 30 (median of 7 [range 2-24] vs. 2 [1-33], p=0.065), but no significant differences were noted in PC transfused by day 100 or in RBC units by day 30 and day 100. Platelet engraftment (>20 $\times 10^9$ platelets/L) was delayed in haplo-HSCT compared to allo-HSCT (median of 28 days [14-112] vs. 13 days [10-115], p< 0.001), but not neutrophil engraftment. No significant differences were observed between haplo-HSCT and allo-HSCT in 2-year probabilities of overall survival (33% [95% CI, 14%-54%] vs. 50% [95% CI, 27%-69%], p=0.635), relapse incidence rate (21% [95% CI, 6%-42%] vs. 35% [95% CI, 15%-56%], p=0.343) and non-relapse mortality (46% [95% CI, 22%-66%] vs. 35% [95% CI, 15%-56%], p=0.665).

Conclusions: Our findings suggest that platelet transfusion requirement is higher in the first 30 days after haplo-HSCT compared to allo-HSCT, probably related to delayed platelet engraftment. No differences were observed in RBC requirement.

Disclosure: Nothing to declare.

P329

Haploidentical Hematopoitec Stem Cell Trasplantation with Macs in a Peruvian Health Childrens Institute: three-year Experience

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Background: In the year 2016, the Peruvian Health Children's Institute of San Borja (Lima, Peru) became the pioneer in the development of the Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) program. It was necessary to stablish an alternative strategy for the treatment of the almost one thousand cases of hematological malignancies in pediatric population that are reported in Peru in which only between 20% of the patients that required a HSCT had a compatible Human Leukocyte Antigen (HLA) donor.

Since then, 35 Allo-HSCT have been accomplished within the remaining 80% of the mentioned pediatric population. Whom, three years ago was forced to access international donor registries that extended the awaiting time and also conditioned the progress of the disease.

Additionally, we have found that this program also contributes to the reduction of the risk of Graft-versus-Host Disease (GvHD) and it has allowed many pediatric patients to access a efficient and safe treatment as it has been demonstrated with the depletion of positive TCRα/β+ and B cells procedures for allo-HSCT.

Methods: The total universe (n = 35) of patients treated from December 2016 to December 2019 with Allo-HSCT with Magnetic Activated Cell Separation (MACS) were included in this report. All of the diagnostics were performed according to international protocols and overall survival was calculated within the three-year period.

Results: The Overall Survival (OS) of patients diagnosed of Acute Lymphoblastic Leukemia (ALL) is of 44% and 33% for those diagnosed of Acute Myeloid Leukemia (AML). Additionally, the OS of patients diagnosed of Severe Aplastic Anemia (AAS) reaches a 60% and those diagnosed of Fanconi Anemia is of 43 %.

Conclusions: The evaluated data confirms that Allo-HSCT with MACS is an effective and safe strategy and it has a notable cost-benefit ration that makes it feasible in Latin-American countries like Peru.

It has been identified a great need to modify early diagnostic protocols and to revalidate viral prophylaxis as found in the significative improved results of the last 12-month period.

Disclosure: All authors declare. no conflict of interest.

P330

Collection, Cryopreservation and Autologous Transplantation of Peripheral Blood Stem Cells in Kaunas, Lithuania 2015-2019

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Background: Peripheral blood stem cells (PBSCs) are widely used for autologous blood stem cell transplantation (auto-SCT) around the world. Post-thaw viable $CD34^+$ cell count is the important parameter for quality assurance of the cryopreserved cells. The $CD34^+$ cell post-thaw viability was analysed and its relationship with clinical parameters was evaluated in this study.

Methods: The study included 236 apheresis, 329 products and 106 hematopoietic SCT on 100 patients undergoing auto-SCT in the Hospital of Lithuanian University of Health Sciences Kaunas Clinics from 2015 to 2019 August. Patient's plasma and DMSO (final concentration of 10%) was used for PBSC cryopreservation. All PBSC products were initially cryopreserved in a controlled freezer, then stored in vapor phase nitrogen. PBSC were thawed before use in water bath at 37°C. Viability was assessed immediately after thawing using BD FACS Canto flow cytometer and BD Stem Cell Enumeration Kit. A multivariate regression model and Pearson correlation were applied for statistical analysis.

Results: In total 100 patients (51 females, 49 males) with a median age of 59 (range 18-73) years were harvested after G-CSF (10 g/kg) or Cyclo+G-CSF or additional mobilizing agents such as plerixafor (0,24mg/kg, n=4) for auto-SCT. Indications were multiple myeloma (n=82), non-Hodgkin lymphoma (n=15), germ-cell testicular tumor (n=1), sarcoma (n=1) and autoimmune encephalitis (n=1). Most patients received one auto-SCT. 24 patients received double SCT and 1 patient triple SCT. PBSC transplantations were

performed for patients with the following diagnosis: 94 myeloma, 7 lymphoma, 3 germ-cell testicular tumors, 1 CNS lymphoma and 1 autoimmune encephalitis. The median post-thaw $CD34^+$ viability was 79% (range 42-96). Median leukocytes (>1.0 x 10^9/l) engraftment on two consecutive days was 11 (range 8-13) days, and 15 days for platelets (>50 x 10^9/l), ranging 9-23 days after SCT. Volume, $CD45^+$ count, $CD34^+$ count, the total count of $CD34^+$ cells, $CD34^+$ viability in leukapheresis product, number of frozen bags and duration of apheresis were tested and found in linear dependence with cell post-thaw viability (r^2=0,304). Statistically significant (p< 0,05) negative correlations were observed between $CD34^+$ cell post-thaw viability and $CD45^+$(r=(-0,395)); $CD34^+$ count (r=(-0,269)); volume of leukapheresis product (r=(-0,329)).

Conclusions: These findings suggest that the cryopreservation method using 10% DMSO final concentration is acceptable, all patients had successful engraftment. Lower counts of $CD45^+$ and $CD34^+$ cells and leukapheresis volume had a better impact on post-thaw cell viability. Further studies will be needed to confirm these findings and to find a way how to increase post-thaw PBSCs viability.

Disclosure: Nothing to declare.

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P331

Evaluation of Overall Survival in Allogeneic Hematopoietic Stem Cell Transplantation (ALLOHSCT). Unicentric Experience

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Background: AlloHSCT is a therapeutic strategy increasingly used in patients with malignant hematological pathologies. Overall survival (OS) and disease-free survival are two variables that should always be studied to evaluate the results of a center or procedure. OS is interfered by many other factors involved in alloHSCT, such as prophylaxis for graft versus host disease (GVHD), the stem cells source, or the presence of concomitant diseases.

Methods: Observational, unicentric, analytical and retrospective study. The alloHCST were carried out in the Public Health Group Quirón between January 1st, 2015 until July 30th, 2018. The transplants were divided into two groups, those who received a traditional GVHD prophylaxis and those who received a post-transplant cyclophosphamide (CYPT) strategy.

We applied Kaplan-Meier test to analyze the OS and analysis of Cox in variables that interfere in the OS with the STATA statistical package version 15.1.

Results: Our study consists of 40 transplants. 53% male (n = 21) and 47% female (n = 19). Average age was 50 years, SD 11.22 years (19-68).

25 (62.5%) patients underwent transplantation in complete remission (CR), 6 (15%) in partial response and 9 (22.5%) patients in relapse or visible disease. In addition 6 (15%) patients previously received an alloHSCT.

18 (45%) patients underwent in non-myeloablative conditioning and 22 patients (55%) underwent in myeloablative conditioning. Peripheral blood was the source of hematopoietic progenitors in all cases.

According to the Baltimore protocol CYPT was used in 25 transplants (62.5%), where 17 were haploidentical (100% of haploidentical), 3 in HLA Identical siblings, 4 in MUD, and 1 mismatch related donor.

After alloHSCT, 9 patients (22.5%) relapsed, 6 of whom had received prophylaxis with CYPT. The incidence of death was 39.47% (n = 15). The OS after 100 days of transplants was 89.2% with a SD of 0.05 (95% CI 0.74-0.96). The OS after 365 days was 69.6% with a SD of 0.08 (95% CI -0.82). The main cause of death was the relapse of the underlying disease (40%).

When analyzing by subgroups, according to prophylaxis for GVHD, we observed that patients who subjected traditional regimens, OS after 100 days was 93% with an SD of 0.0644 (CI95% 0.6126- 0.9903) while the OS in patients receiving CYPT was 68% with a SD of 0.189 (95% CI 0.2047-0.9085).

The OS after 300 days among those who received a scheme without CYPT was 80% with an SD of 0.103 (CI95% 0.50-0.939), and among patients who received

CYPT (n = 8) it was 33% with an SD of 0.193 (CI95% 0.047-0.68).

When performing a Cox regression, prophylaxis being the factor to be studied as a survival variable and excluding haploidentical transplants, the results showed a Hazard Ratio of 3.44 (IC95 0.77-15.44) not being statistically significant, at get a p of 0.105.

Conclusions: Our study shows a higher mortality in patients who receive a CYPT scheme without presenting significant differences after the statistical study. The biggest problem of our work is the sample size, future work will help us confirm these results.

Disclosure: Nothing to declare.

P332

Refractory T-cell Cutaneous Lymphoma Treated with Allogeneic Haploidentic Hematopoietic Stem Cell Transplantation- A Case Report

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Background: Folliculotropic mycosis fungoides (fMF) is an aggressive clinical course variant of cutaneous T-cell lymphoma (CTCL) - classic mycosis fungoides (MF), with distinct clinical and pathological characteristics, and it is less responsive to skin-directed therapies. For diseases in advanced stages, chemotherapy, autologous hematopoietic stem cell transplantation (HSCT) or immunomodulator drugs may provide remissions with limited duration and the treatment remains substantially palliative. These dismal results have induced to explore the therapeutical approach with allogeneic hematopoietic stem cell transplantation (HSCT) in such patients. Early studies have shown encouraging results also in patients with advanced disease, suggesting a major therapeutical role played by the graft versus lymphoma (GVL) effect.

Methods: Case presentation : A 46-year-old female patient with refractory subtype B follicular fungal mycosis (fMF) T-cell lymphoma, diagnosed in 2012, clinically characterized by exfoliative erythroderma, widespread plaques on the trunk and limbs, tumoral lesion on face, pruritus and bilateral inguinal, submandibular and cervical lymphadenomegaly. After failure to respond to five conventional treatment lines: methotrexate; PUVA; interferon; acitretin and extracorporeal photopheresis, a haploidentic allogeneic HSCT from her brother was indicated.

The non-myeloablative conditioning consisted of fludarabine (160mg / m2), melphalan (140mg / m2) and total body irradiation (ICT) (200cGy). Bone marrow infusion occurred on 1/16/2019 (D0). Graft versus host disease (GVHD) prophylaxis was performed with cyclosporine (3mg / kg), mycophenolate mofetil (1.5g / day) after D + 5 and cyclophosphamide (50mg / kg /) on D + 3 and D + 4. Donor lymphocyte infusion(DLI) (1 x 106 CD3 + / kg / recipient cells) was performed on 5/23/19 (D + 127) as planned by our protocol

Results: After conditioning there was improvement of pruritus and involution of the cutaneous condition. On D+ 55 presented aGVHD in upper gastrointestinal tract- grade 2A, treated with prednisone (1mg / kg / day) with complete clinical resolution. On D + 132 presented cutaneous lichenoid phenotype and oral lichen as manifestations of cGVHD treated with topical medication. D + 139 started breathing with persistent dry cough, dyspnea and after fever initially treated as an infectious condition, with antibiotic therapy and antiviral therapy for influenza. Chest tomography showed bronchiectasis and areas of air trapping suggestive of pulmonary GVHD (treated with prednisone 1mg / kg / day) with complete regression of the respiratory and cutaneous lesions.

Conclusions: the clinical response of the presented case confirms what has been reported in the literature. CTCLs appear to be particularly susceptible to GVL, which makes HSCT a potential cure for advanced CTCLs in eligible patients. The timing to perform HSCT in the clinical course of the disease remains a matter to be settled.

Disclosure: no conflicts

P333

Autologous Stem Cell Transplantation: A single-center Experience Over Last Years

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Background: Autologous stem cell transplantation (ASCT) is considered currently the standard of care as consolidation in first-line therapy in fit multiple myeloma (MM) patients or in relapsed fit patients with lymphoproliferative disorders, being also a therapeutic option in first-line therapy in high-risk lymphomas and other types of cancer. Although ASCT has a wide well-known range of potential complications, it is

considered a safe procedure when performed in fit patients in centers with enough experience. The aim of this study is to review the results of ASCT in one single tertiary center.

Methods: We retrospectively evaluated in terms of progression free survival (PFS) and overall survival (OS) all patients who underwent ASCT in our center from 2010 to 2017.

Results: We performed 100 ASCT in 96 patients: 42 patients with MM, 38 with non-Hodgkin lymphoma, 13 patients with Hodgkin lymphoma, 2 with acute leukemia and one with germ cell tumor. The medium age was 50 years (range 19.71), 32% older than 60 years. The conditioning regimen most used was BEAM in 46 patients followed by Melphalan in 45 patients. The procedure data are showed in more detail in the table below. Table 1:

	N=100
Demographic characteristics: - Age (mean, range) - Sex: male (%, frequency)	50 (19-71) 63% (63/100)
Base disease: - Lymphomas (Hodgkin and non-Hodgkin) - Multiple myeloma - Others	51% (51/100) 46% (46/100) 3% (3/100)
Response to ASCT: - Complete response - Very good partial response - Partial Response - Stable Disease - Progression disease	40.6% (39/96) 10.4% (10/96) 42.7% (41/96) 4.3% (4/96) 2% (2/96)
Pre-transplant treatment lines: - One line - Two lines - Three or more lines	29.6% (29/98) 54.1% (53/98) 16.3% (16/98)
Conditioning Regimen: - BEAM - Melphalan - Others	48.4% (46/95) 47.3% (45/95) 4.3% (4/95)
CD34+ cells infused x10e6/Kg (medium, range)	6.27 (2.2-24.6)

[Table 1: ASCT Baseline Characteristics.]

B..

PFS was 53.49 months on average (95% CI: 43.65 - 63.33). OS was 93 months on average (95% CI: 84.06 - 120.04). Predictors for worst outcome in terms of PFS and OS were: MM, poor disease status and age over 60 years. We recorded 10 cases of second malignancies during follow-up, of which only 2 were hematologic. Three patients suffered late related ASCT toxicities: 2 of them cardiotoxicity and one neurotoxicity. There were no deaths during hospitalization for ASCT. Mortality within the first 100 days after transplant occurred only in 2 patients: one due to infectious complications and the other one due to disease progression. During the follow-up 21 patients died mostly due to disease progression (66.6%).

Conclusions: In our center ASCT appears to be a safe treatment option with low risk of both morbidity and mortality, especially in young patients with good control of the underlying disease at the time of transplant. Further studies are needed to compare this procedure with new therapies currently available.

	N=100
Demographic characteristics: - Age (mean, range) - Sex: male (%, frequency)	50 (19-71) 63% (63/100)
Base disease: - Lymphomas (Hodgkin and non-Hodgkin) - Multiple myeloma - Others	51% (51/100) 46% (46/100) 3% (3/100)
Response to ASCT: - Complete response - Very good partial response - Partial Response - Stable Disease - Progression disease	40.6% (39/96) 10.4% (10/96) 42.7% (41/96) 4.3% (4/96) 2% (2/96)
Pre-transplant treatment lines: - One line - Two lines - Three or more lines	29.6% (29/98) 54.1% (53/98) 16.3% (16/98)
Conditioning Regimen: - BEAM - Melphalan - Others	48.4% (46/95) 47.3% (45/95) 4.3% (4/95)
CD34+ cells infused x10e6/Kg (medium, range)	6.27 (2.2-24.6)

[Table 1: ASCT Baseline Characteristics.]

Clinical Trial Registry: No appicable
Disclosure: Nothing to declare.

P334

Causes of Complications in Adults during the First Year after Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Allogeneic hematopoietic stem cell transplantation is the treatment of choice for cure of many haematological disorders. Allo-HSCT is associated with a significant risk because of the high toxicity of the conditioning regimen and the period of inmmune suppression. These patients are subject to numerous complications in the first year after transplantation.

A better understanding of the incidence and causes of complications in adults undergoing allo-HSCT may improve quality of care and outcomes. The aim of this retrospective study was to describe the causes of complications in adult patients undergoing allo-HSCT during the first year.

Methods: A retrospective study was performed in patients who received a allo-HSCT between January 2013- December 2018. The following complications were considered: Fever, Infection, GVHD, graft failure and graft dysfunction. Demographic and clinical information was collected from patients medical records, data

was analyzed in SPSS v21 using none parametrical statistical.

Results: We analyze 68 patients, 57.4% were male, median age 29 years (15-60y), diagnostic of ALL 59%, AML 31%, NHL 7.5%, myelofibrosis 1.5% and CML 1.5%. Forty-seven percent had a prior treatment line before allo-HSCT, 35% with two lines and 17.6% with three lines of chemotherapy. Sixty patients (88%) were HLA identical and 8 patients (12)% haploidentical.

Eighty-eight percent of patients who received allo-HSCT developed some kind of complication during the first year. Fever was in 75%, 67% had an infection: 33% mucous membranes, 24% respiratory tract, 19% urinary tract. The causal germ was only isolated in 37% (81% bacterial, 14% viral and 5% fungal), 9% of the patients required ICU. Acute GVHD was in 28%, chronic in 31% and graft failure in 6% of the cases.

Thirty-four patients (50%) re-admitted to the hospital as a result of some complication after allo- HSCT, 41% due to infection, 24% due to relapse, 15% due to GVHD. One, two and more than three readmissions to hospitalization were in 32%, 10%, and 7% respectively.

The relapse was 30%, 55% received reinduction with chemotherapy (only 15% received a second transplant), and 45% received palliative care. Twenty-three patients (34%) died, 74% related to relapse and 26% not related to relapse. The median time to death due to relapse was 8.4 months, 1.9 months due to infection, 3.2 months due to GVHD.

Conclusions: Allo-HSCT has a high frequency of complications, it requires a lot of health resources for patient care, most complications can be solved, however relapse is still the most frequent cause of death.

Variables	100% identical n=60	n=8 Haploidentical
Infections	45 (75%)	6 (75%)
Acute GVHD	6 (10%)	2 (25%)
Chronic GVHD	10 (17%)	0
Graft failure	4 (6.7%)	0
Subsequent hospitalizations	31 (52%)	3 (35.7%)
Relapse	19 (32%)	1 (12.5%
Dead	22 (37%)	2 (25%)
Relapse mortality	16 (76%)	1 (50%)
Non Relapse mortality	5 (24%) 5 (24%)	1 (50%)

[The characteristics by type of transplant table 1]

Disclosure: The authors declare. that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Haemoglobinopathy and inborn errors

P335

High Dose Stem Cell Therapies, Like MGTA-456, Enable Complete Neural and Peripheral Disease cross-correction Through Rapid and Robust Hematopoietic Engraftment

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Background: Allogeneic hematopoietic stem cell transplant (HSCT) is a potentially curative approach to halt disease progression of select inherited metabolic disorders (IMDs). For IMDs that affect the central nervous system (CNS), donor-derived cells, like microglia, cross-correct defects via production of normal enzyme. The typical cell dose used in HSCT can be sub-optimal and, in gene therapy applications, copy number has been shown to be variable. We developed MGTA-456, a high dose cell therapy that led to rapid neutrophil recovery and 100% engraftment in patients with malignant and non-malignant diseases (Wagner et al Blood 2017; Orchard et al AAN 2019). The impact of cell dose on disease correction, however, is unknown. Here, we show that fast and robust hematopoietic and microglia recovery via high cell dose therapies, like MGTA-456, leads to rapid and complete disease resolution of Hurler syndrome through hematopoietic-derived microglial engraftment in the CNS.

Methods: For mouse transplant studies, bone marrow cells were transplanted into wild-type or $Idua^{-/-}$ mice following myeloablative busulfan or treosulfan conditioning and analyzed weekly from 1-16 weeks post-HSCT. For MGTA-456 mouse studies, the high cell dose therapy, MGTA-456, was transplanted into busulfan conditioned NSG mice and analyzed weekly. Flow cytometric, enzymatic, substrate, and functional assays were performed.

Results: At 1-16 weeks post-HSCT, transplant of increasing doses of bone marrow cells following myeloablative busulfan conditioning led to a dose-dependent increase microglial engraftment (26-fold for $10x10^6$ cells vs $0.3x10^6$ cells, $p< 0.01$), with 91-99% peripheral donor chimerism. In $Idua^{-/-}$ mice, high cell doses led to an improvement in CNS disease endpoints, such as IDUA enzyme production (n=5, $p< 0.01$), reduced substrate

accumulation (n=5, p< 0.01), and normalization of behavioral activity to wild type levels at 4 and 16 weeks post-HSCT. Reduction of substrate to wild type levels was observed as early as 1 week after transplant with $10x10^6$ cells (p< 0.01). In contrast, transplant of $10x10^6$ cells into mice conditioned with a myeloablative dose of treosulfan, an agent that does not permit brain microglial engraftment, did not correct CNS defects, suggesting that donor engraftment in the CNS is required for disease correction.

Relative to low cell dose therapies, transplant of MGTA-456, a high cell dose therapy with two normal IDUA gene copies, led to robust, long-term immune recovery (n=88 animals), 60-fold greater microglial engraftment as early as 2 weeks post-HSCT (n=8, p< 0.001), and >600-fold higher IDUA enzyme levels (n=2 donors, p< 0.001). Mechanistically, brain microglia are derived from CD34+CD90+ cells, which are present at high numbers in MGTA-456.

Conclusions: We show that high dose HSCT leads to rapid and durable improved disease correction, including normalization of behavioral outcomes, via robust microglial engraftment. High dose cell therapies, like MGTA-456, may resolve neurologic disease in patients with IMDs and other neurodegenerative diseases caused by defective microglia.

Disclosure: Goncalves: Intellectual Property Rights, Ownership Interest and Salary

Hyzy: Ownership Interest and Salary

Brooks: Ownership Interest and Salary

Hertzler: Nothing to Declare

Boitano: Intellectual Property Rights, Ownership Interest and Salary

Cooke: Intellectual Property Rights, Ownership Interest and Salary

P336

HLA set-up is a major Predictor of Engraftment in haplo-identical Transplant for Severe Thalassemia (ST) using post-cyclophosphamide (PTCY)

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Background: Severe thalassemia syndromes (ST) are the most common non-infectious life-threatening disease of children in South-Asia and Bone marrow transplant (BMT) is only curative option currently available. Only 30-35% of patients have a matched related donor available hence substantial proportion of patients requires alternative donors. Rejection is a major problem in haplo-identical transplants in thalassemia due to multiple donor exposure leading on to significant alloimmunisation and there is paucity of literature on predictors of successful engraftment in this setting. Our previous experience suggests that Host Vs Graft (HVG) and Graft Vs Host (GVH) vectors are associated with rejection and engraftment respectively and donor specific antibody (DSA) was a predictor of rejection (Marwah et al. BMT 2019).

Methods: We assessed 48 consecutive patients with ST with a median age of 5.4 years (range 1.5 to 14.4), all with low-risk features, defined as liver size ≤ 2 cm from costal margin, who underwent Haplo-PTCy BMT between March 2017 and Oct 2019 in 3 centers in India, South East Asia Institute for Thalassemia in Jaipur (31 cases), People Tree Hospital in Bangalore (12 patients) and Care Institute of Medical sciences in Ahmedabad (5 patients). All received partially matched grafts, 16 from the father and 32 from the mother with a uniform regimen modified from Anurathapan et al. BMT 2016. Bone marrow was the source of stem cells and all have at least 1-month post-transplant follow up. We explored the contribution of various patient characteristics towards rejection to identify a subgroup of patients whose rejection risk is low.

Results: Out of 48 patients 12 rejected their graft (25%). Of the risk factors studied DRB1 and/or DQB1 match (Class 2 match) (p=0.016), unbalanced DRB1 and/or DQB1 donor homozygosity (Class 2 GVH vector) and/or Class 2 match (p=0.0021) were strong predictors of engraftment and unbalanced HVG was predictors of rejection. Using the old and newly identified risk factors we defined a favourable group (Class 2 match and/or Donor Class 2 homozygosity and/or GVH vector and no unbalanced HVG vector or DSA) were the rejection rates were very low 1/26 (3.8%) as opposed to those who did not have a favourable HLA set up (unfavourable group) 12/22 (54.5%) (p=0.002). Isolated class 1 allele match is a risk factor for rejection (5/9 rejected) (p=0.03), whereas with isolated class 2 allele match was associated with low risk of rejection (1/14 rejected) (p=0.02). Three out of 4 patients with HVG vector with no other favourable set up rejected, among those were the only two patients with class 2 HVG vector.

Conclusions: In favourable HLA setting the rejection risk is very low. Patients with favourable HLA setting can be offered the choice of haplo-identical transplant and those with unfavourable setting further intensification of conditioning regimen may be warranted. Class 2 HLA antigens seem to play a major role in promoting engraftment whereas class 1 allele matches may be associated with increased rejection.

Disclosure: Nothing to declare.

P337

Lentiglobin Gene Therapy Treatment of Two Patients with Transfusion-dependent β-thalassemia

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Background: Gene therapy with autologous CD34+ cells encoding a $\beta^{A\text{-}T87Q}$-globin gene (LentiGlobin for thalassemia) is being evaluated in patients with transfusion-dependent β-thalassemia (TDT) in the phase 3 studies Northstar-2 and Northstar-3. Here, we report two case reports for patients with different severity of TDT: a 23-year-old male with a β^0/β^+ genotype (patient A, Northstar-2) and a 7-year-old female with a $\beta^0/\beta^{+\ (IVS\text{-}I\text{-}110)}$ genotype (patient B, Northstar-3).

Methods: Following hematopoietic stem cell collection via mobilization and apheresis, CD34+ cells were transduced with the BB305 lentiviral vector. After receiving pharmacokinetic-adjusted, single agent busulfan myeloablation, LentiGlobin was infused intravenously (7.9 $x10^6$ [patient A] and 4.7 $x10^6$ [patient B] CD34+ cells/kg).

Results: Baseline characteristics and treatment parameters are presented in Table 1. After LentiGlobin infusion, patients A and B received RBC transfusions for 1 and 2 months, respectively, and have since not received transfusions for 18.1 and 14.3 months as of last follow-up. Total hemoglobin (Hb) values for patient A were 12.0, 12.3, and 12.8 g/dL at Months 6, 12 and 18 and for patient B were 10.1, 10.7 and 10.4 g/dL at Months 6, 9 and 16. Endogenous Hb values were 2.9 g/dL for patient A at Month 18 and 1.42 g/dL for patient B at Month 12. In both patients, gene therapy-derived Hb, Hb^{AT87Q}, increased continuously reaching levels above 9 g/dL within approximately 6 months after LentiGlobin infusion. At 12 months after DP infusion, the myeloid:erythroid ratio improved towards normal levels in both patients (Table 1). Both patients achieved and maintained transfusion independence (weighted average Hb ≥9 g/dL without RBC transfusions for ≥12 months). Weighted average Hb during transfusion independence was 12.4 g/dL for patient A and 10.3 g/dL for patient B. Neither patient experienced any serious or LentiGlobin-related adverse events (AEs). After LentiGlobin infusion Grade ≥3 AEs occurred which were considered to be related to myeloablative conditioning regiment by investigator included anemia, neutropenia, leukopenia and thrombocytopenia in both patients. No AEs related to BB305 vector insertion occurred.

Conclusions: Following treatment with LentiGlobin gene therapy for β-thalassemia, two patients with TDT (25 and 7 years old) and a β^0/β^+ and $\beta^0/\beta^{+\ (IVS\text{-}I\text{-}110)}$ genotype, respectively, were reaching levels above 9 g/dL of gene therapy-derived HbA^{T87Q} within approximately 6 months, enabling both to become transfusion independent, irrespective of the different genetic asset. In both patients, improvement of myeloid:erythroid ratio towards normal levels was observed. The safety profile of LentiGlobin was consistent with that of busulfan myeloablation.

	Patient A (Northstar-2)	Patient B (Northstar-3)
Age at diagnosis, months	12	19
Annualized transfusion number (volume) 2 years prior to enrollment	24.5 (240.5 mL/kg/year)	19 (189.9 mL/kg/year)
Liver iron concentration, baseline	7.2	1.2
Cardiac T2*, baseline	35.3	39.3
Vector copy number per diploid genome/% transduced cells	3.7/83	3.4/78
Average daily busulfan area under the curve, μM*min	4988	6351
Neutrophil and platelet engraftment, days	26/44	34/50
VCN in peripheral blood (range during follow up)	1.00-1.52	1.61-2.2
Myeloid:erythroid ratio, baseline/Month 12	1:5.5/1:1.3	1:4.7/1.2:1

[Summary of transfusion history, baseline characteristics and treatment parameters]

Clinical Trial Registry: Northstar 2: HGB-207; NCT02906202; https://clinicaltrials.gov/ct2/show/NCT02906202

Northstar 3: HGB-212; NCT03207009; https://clinicaltrials.gov/ct2/show/NCT03207009

Disclosure: MA is a consultant for bluebird bio and has received honoraria from Miltenyi.

FL has the following conflicts: Amgen: Honoraria, advisor; Bellicum: Consultancy, advisor; bluebird bio: Consultancy; Miltenyi: Honoraria; Novartis: Consultancy, advisor.

All other authors are employees of bluebird bio Inc.

P338

Bone Marrow Transplant in Patients with Sickle Cell Anaemia. Experience in One Centre

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Background: Sickle cell disease (SCD), despite the improvement in the medical management, is still associated with severe morbidity and decreased survival. Waiting further development in gene therapy, allogenic hematopoietic stem cell transplantation (allo-HSCT) currently provides the only curative therapy. A report is presented on our experience in children with SCD, who underwent allo-HSCT.

Methods: A single centre descriptive study on patients with SCD

who underwent a bone marrow transplant from an HLA-identical sibling donor between May 2010 and June 2019.

Transfusion therapy was started 3 months before HSCT and hydroxyurea was increased or started one month before HSCT in order to maintain reticulocyte count under 100 000/mm3. Conditioning regimen: Busulfan, cyclophosphamide, alemtuzumab until January 2015, graft versus host disease (GvHD) prophylaxis with CsA and MTX. Afterwards we changed to myeloablative but reduced toxicity conditioning: Thiotepa, Treosulfan, Fludarabine, antithymocyte globulin, GvHD prophylaxis with CsA or tacrolimus with MMF. Seizure profilaxis during immunosuppression treatment. During transplant we maintain a platelet threshold of 50.000/mcL, hemoglobin of 11 g/dL and avoid hypertension and hypomagnesemia to decrease neurological complications. Ovarian tissue is cryopreserved since 2015.

Epidemiological, clinical and analytical parameters were collected with a follow-up to December 2019. Data are presented as frequencies, percentages, and medians (range).

Results: 38 Allo-HCST was performed in 37 patients (14 males) with a median age of 6.0 years (2.0-13.8). A stable graft was achieved in 35 out of 37 patients (33 of them with complete donor chimerism, and two patient with stable mixed chimerism after 20 months and 4.8 year of allo-HSCT respectively). Two patients experienced secondary graft failure, one of them achieved complete donor chimerism after a second allo-HSCT from same sibling donor, the other one still continue without SCD symptoms after 18 months but with 84% receptor chimerism. Median time to neutrophil and platelets recovery was 20 days (13-27) and 24 (16-94) respectively. Complications of allo-HSCT were: arterial hypertension 33/38, acute renal failure 9/38, CMV reactivation 24/38, neurological complications 10/38 (subarachnoid haemorrhage, seizure or toxicity related with drugs), and acute GvHD (aGvHD) of the skin 16/38 all of them grade I or II, except one patient who developed grade IV intestinal aGvHD, causing his death (day 51). None of the patients developed chronic GvHD. The overall survival and event-free survival was 97.4% and 91.6%, respectively, with a median follow-up of 2.6 years (0.1-9.5). Comparing both periods of study with different conditioning regimens (2010-2014; 2015-2019), overall survival was 90.9% versus 100% and event-free survival 81.8% versus 96%.

Conclusions: SCD families and physicians alike debate the burden of morbidity and mortality from a chronic disease, versus the curative option with transplantation and the risk of transplant-related complications and mortality. The outcome of our center, the largest HCST series in Spain is similar to the international cohort and confirms the role of HLA-identical sibling transplantation for children with SCD. Since 2015 we improved our results, with less toxicity and without mortality.

Disclosure: Nothing to declare.

P339

Outcomes in Cerebral Adrenoleukodystrophy after Hematopoietic Stem Cell Transplantation: Single Center Experience

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Background: Cerebral adrenoleukodystrophy (cALD) is a x-linked, neurodegenerative and rapidly progressing disease. Functional disabilities are the worst complications of the disease. Hematopoietic stem cell transplantation is the only curative treatment especially in early stages.

Methods: This study involves 25 boys with cALD who underwent transplantation between January 2012-September 2019 in Medical Park Göztepe/Antalya Hospitals. Loes scoring was performed for cerebral involvement. Loss of communication, cortical blindness, tube feeding dependence, total incontinence, wheel chair dependence and complete loss of voluntary movement were classified as major functional disabilities (MFD).

Results: The characteristics of 25 patients was revealed in Table-1. Busulfan based myeloablative conditioning was used for all transplants. After severe hemorrhagic cystitis occurred in two patients transplanted between 2012-2014, cyclophosphamide was replaced with fludarabine for the further conditioning regimens between 2014-2018 and no more severe hemorrhagic cystitis was observed. Acute graft versus host disease (GVHD) grade 2-4 developed in 5 patients (20%). We observed full donor chimerism in 20 patients (80%) and mixed chimerism in 4. Graft rejection occurred in 2 patients and they underwent second transplantation from different matched unrelated donors. At the time of the last follow up, 19 patients were alive. Six patients died after transplantation and cause of deaths were disease progression (n=3), severe hemorrhagic cystitis (n=1), acute gastrointestinal GvHD (n=1) and sepsis (n=1).

With a median follow up of 24 months (1-84 months) overall survival (OS 3-yr) was 73.3 (95% CI 54.5-92.1) and MFD free survival 3-yr was 69.9 (95% CI 50.4-88.8). Cumulative transplant related mortality for this cohort was 14.5% (95% CI 5.0-42.4). According to pre-transplant Loes scores (Loes< 8 vs Loes≥8), while overall survival was 100% and 48.8%, respectively (p=0.007), MFD free survival was 100% and 42.7%, respectively (p=0.015). Five patients who had no functional disability but only mild neurologic dysfunctions before transplantation developed MFD after transplantation. Loes score was observed as a significant prognostic factor for MFD development after transplantation (Loes< 7 vs Loes≥7, 100% vs0% p=0.011).

Conclusions: Although hematopoietic stem cell transplantation is the only curative treatment for cALD, disease progression after transplantation is the most undesired outcome. According to our findings, better OS and MFD free survival depend on pre-transplant Loes score and this could be used for prediction of the success of transplantation for ALD. These findings warrant further evaluation in larger patient series.

Patient Characteristics	cALD (n=25)
Median Age at Transplant, month	96 (41-158)
Donor Type	
Match Related	8 (32%)
Match Unrelated	14 (56%)
Haplo	3 (12%)
Stem Cell Source	
Bone Marrow	15 (60%)
Peripheral Blood	7 (28%)
Bone Marrow + Peripheral Blood	3 (12%)

[Table-1: Patient Characteristics]

Disclosure: Nothing to declare.

P340

Neurodevelopmental Outcomes of Hematopoietic Stem Cell Transplantation for Mucopolysaccharidosis Type II: A Prospective, Longitudinal Study

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Background: The aim of the study was to prospectively evaluate the long-term neurodevelopmental outcomes of Mucopolysaccharidosis type II (MPS II) following treatment with hematopoietic stem cell transplantation (HSCT).

Methods: A total of eleven patients with the severe phenotype of MPS II underwent standardized neurodevelopmental evaluations pre- and post-HSCT. For five patients, a known family history of MPS II allowed for HSCT at < 18 months of age, prior to the onset of overt neurological deterioration. The remaining six patients were treated at ≥18 months. Within-family comparisons were made for families with multiple affected relatives who were discordant for HSCT status or treatment age.

Results: The median follow-up duration was 6.1 years. All patients treated with HSCT at < 18 months gained skills across multiple developmental domains post-transplantation. For three patients treated at < 24 months, post-HSCT cognitive development proceeded at a rate comparable to that of age-matched peers. In comparison, most patients treated after 18 months failed to gain skills. Within-family comparisons showed that patients transplanted at < 18 months of age experienced better outcomes than relatives who were not transplanted or were treated after the onset of substantial brain involvement.

Conclusions: If performed early, HSCT prevents neurological deterioration in MPS II patients.

Disclosure: Maria Escolar is on the Regenxbio MPS II Advisory Board and the Takeda MPS II Advisory Board, is a consultant for Denali Therapeutics, and performs contracted research for Regenxbio and Denali Therapeutics. Paul Szabolcs performs contracted research for Regenxbio.

P341

Hematopoietic Stem Cell Transplantation for Sickle Cell Disease: The Spanish Experience

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Background: Sickle cell disease (SCD) is the most common haemoglobinopathy. The prevalence is higher in Sub-Saharian Africa, Middle East, India, Brazil and the Caribbean Islands but due to the slave trading and contemporary immigration, SCD has spread through other countries (UUEE, France, UK). In Spain the incidence is much lower, in 2019 there were a total of 1218 patients registered in the National Registry of Hemoglobinopathies (REDHem), with 0.32 SCD cases/ 1000 live births.

The natural history of SCD is highly variable. Besides the acute complications (vaso-occlusive crisis, chest syndrome, stroke) patients present progressive ischemic organ damage. For this reason, SCD remains a systemic disease with a high morbidity and mortality.

To date, HSCT remains the only curative option for SCD patients, however, only a small group of patients have benefited from HSCT.

Methods: National multicenter retrospective study. Data was collected from GETMON (Spanish group of HSCT in children) Registry. Children who underwent a MSD transplant were included.

Primary endpoints: event free survival and overall survival. Secondary endpoints: neutrophil engraftment, graft failure, acute and chronic graft versus host disease (GvHD).

Results: From 1999 to 2018, 45 patients received a MSD transplant for SCD. Patients and transplant characteristics are shown in Table 1.

Median age at transplantation was 9.15 (2.09-19.08) years. Elevan patients (24.4%) were < 5 years old at the time of the transplant. Twenty five patients were males (55.5%). Most of the patients received a myeloablative conditioning regimen (n= 30; 66,6%) based on busulfan and cyclophosphamide and the rest (n=15; 33,3%) received a reduced - intensity conditioning regimen with treosulfan, fludarabine and thiotepa. Most regimens included in vivo T cell depletion (n=42) with either anti - tymocyte globulin (n=30) or alemtuzumab (n=12). The stem cell source was bone marrow for most of the patients (n=42), cord blood for 2 and the combination of bone marrow and cord blood for 1.

All except one patient engrafted. Median time to granulocyte recovery was 20 days (15-29). One patient presented secondary graft failure with autologous reconstitution. Five patients had sustained mixed chimerism (11.1%).

Grade II-IV aGvHD was(17.7%) and grade III-IV (6,6%). The cumulative incidence of cGvHD was 6,6% (2 patients moderate and 1 severe).

Most frequent complications, apart from infections, were those related to the endothelium (posterior reversible leukoencephalopathy, thrombotic microangiopathy and sinusoidal obstruction syndrome).

Overall, 3 patients died from primary graft failure (n=1), GvHD (n=1), infection (n=1). With a median follow-up of 36 months (5-221) the OS and EFS were 93% and 91% respectively; for patients aged < 5, both OS and EFS, were 100%.

Conclusions: SCD represents a chronic and multisystemic disease with a high morbidity and mortality. Results with MSD transplant are excellent; therefore it is important to refer these patients to centers with experience and promptly assess the indication of HSCT.

Disclosure: Nothing to declare.

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Long-term Quality of Life in Patients with Thalassemia Major following Hematopoetic Stem Cell Transplantation in Childhood

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Background: More than 90% of patients with thalassemia major currently survive after the hematopoietic stem cell transplantation and disease-free survival is around 80%. But information about the long-term quality of life are limited.

The aim of this study was to determine the long-term quality of life in patients with beta-thalassemia major after allogeneic hematopoietic stem cell transplantation in childhood and to compare the results to healthy people in the same age group.

Methods: The study included patients over 5 years of age who had undergone hematopoetic stem cell transplantation for thalassemia major between 2005 and 2017 in Ege University- Pediatric BMT Unit. Healthy children in the same age group and young healthy adults were selected as the control group. The Universal quality of life scale -Pediatric Quality of Life Inventory (PedsQLTM) Version 4.0-were used to assess the quality of life in children aged 5-18 years. The World Health Organization Quality of Life Instrument, Short Form (WHOQOL-BREF) also was used over 18 years of age. Education and working status of the patients were evaluated with separate questionnaires.

Results: A total of the 38 patients included in the study, 16 were female and 22 were male with a mean age of 16.1 ± 4.3 (min 6.5, max 25.3) years. 13 patients were above 18 years old. The mean time from transplantation to study was 7.3 ± 3.2 years (min 2 - max 11.6 years). The total of the 38 healthy cases selected to the control group, they have similar age and sex.

In pretransplant evaluation; 21% of 38 patients were evaluated as Class 3 according to Pesaro criteria, liver dysfunction was detected in 16 cases (42%), endocrine complications in 7 cases (18%). The donor was MSD (76%) in 29, MRD (5%) in 2 and MUD (18%) in 7 patients. Four patients had second transplantation because of graft failure.

When the late complications were evaluated; extensive chronic GVHD was found in 3 cases and endocrine complications in 17 cases (44.7%).

Both university-level education and the rate of working in a job was higher in the control group over 18 years of age.

No statistically significant difference was found between patient and healthy group in the total quality of life scores of all group. There was also no statistically significant difference in quality of life between the patient and control groups in adult cases over 18 years of age.

When the patients under the age of 18 were examined according to the age groups, the comparison of the quality of life in the 8-12 age group, there were significant differences in physical, emotional, school and total scores.

Conclusions: No difference was found between peers and total quality of life scores of the patients in all age groups. However, when comparisons are made according to age groups; Education levels and work rates were lower in adult patients and lower physical energy, less adaptation to school and more emotionally fragility were observed in school children between 8-12 years of age.

Disclosure: nothing to declare.

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High Incidence of Autoimmune Cytopenias after Allogeneic Stem Cell Transplantation in Pediatric Patients with Thalassemia and Sickle Cell Disease: The Impact of Matched Unrelated Donor

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Background: We retrospectively examined pediatric patients with transfusion dependent Thalassemia or Sickle cell disease that were subjected to allogeneic stem cell transplantation in our unit from January 2004 till March 2019. During this period, 65 patients received a graft from a matched sibling donor (MSD) and 19 patients received a graft from a matched unrelated donor (MUD). We compared the two groups of patients concerning the probability of overall survival (OS), of graft failure, the cumulative incidence of acute Graft versus Host Disease (aGvHD), the incidence of mixed chimerism at 100 days and 6 months post transplantation and the incidence of complications, more precisely reactivation of viruses, other infections, veno-occlusive disease of the liver (VOD) and autoimmune cytopenias.

Methods: Of the 65 patients that had MSD, 40/65 were boys (61.5%) and 25/65 girls (38.5%). The median age of this group was 6.9 years. The group of the 19 patients that had MUD consisted of 11 boys (58%) and 8 girls (42%) with a median age of 3.4 years. 15/19 of these patients (79%) had a donor with a 10/10 HLA compatibility, whereas 4/19 (21%) had a donor with a 9/10 HLA compatibility (2 patients with a difference in HLA-DQB1,1 patient in HLA-A and 1 patient in HLA-B). OS and thalassemia-free-survival were estimated according to the Kaplan-Meier method. Probabilities of graft failure, GVHD and complications were calculated by using the cumulative incidence estimator.

Results: The probability of OS did not differ significantly between the 2 groups of patients (96.5% in the MSD group and 92.3% in the MUD group, p=0.66).

The probability of graft failure in patients with MSD was 6%, in contrast to the 35.7% probability of graft failure in the MUD group. The difference between the 2 groups was statistically significant, p=0.0377.

The cumulative incidence of aGvHD was found to differ strongly between the 2 patient groups, p=0.00027. More specifically, the incidence of aGvHD was 7.7% in the MSD group versus 42.1% in the MUD group.

The incidence of mixed chimerism in 100 days and 6 months after transplantation did not appear to differ significantly in the 2 patient groups.

Morbidity after transplantation was evaluated by the incidence of complications (iemia, infections, VOD and autoimmune cytopenias) and differed statistically significantly between the 2 groups of patients, p=0.007. In particular, it was defined as 46.2% in the MSD group versus 84.2% in the MUD group. Moreover, impressive was the increased incidence of autoimmune cytopenias in the MUD group, (32% vs 0% in the MSD group, p< 0.0001).

Conclusions: The experience of our unit shows that transplantation in pediatric patients with hemoglobinopathies using a MUD involves higher percentage of graft rejection and significantly greater morbidity, in the context of GvHD and complications, especially autoimmune cytopenias, compared to transplantation with a sibling donor.

Disclosure: Nothing to declare.

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Abstract already published.

P345

A Phase II Stratified Trial to Assess Haploidentical t-depleted Stem Cell Transplantation in Patients with Sickle Cell Disease with no Available Sibling Donor

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Background: Sickle cell disease (SCD) represents a worldwide health problem and is a progressively debilitating multi-organ disease. At least 2% of the world population carry a hemoglobin S variant and cause over 80% of hemoglobin disorders which contribute to the equivalent of 3.4% of mortality in children aged under 5 years. Matched sibling donor (MSD) availability is < 20% so that alternative donor HSCT is an unmet need.

Methods: This is a phase II multicenter, open-label study in patients aged 1 to 35 years with SCD. Patients who fulfill inclusion criteria will be stratified according to donor availability. Patients with MSD (10/10 allelic match) will be stratified into the control arm. Patients with no MSD will receive a TCRαβ/CD19 depleted graft from a relative. The myeloablative conditioning regimen for both arms is identical with the exception that anti-thymoglobulin (ATG-Neovii®) is dosed at 15mg/kg for T-haplo and 10mg/kg for MSD HSCT and given upfront on day -10 to -8 in T-haplo and on day -3 to -1 in MSD HSCT. Chemotherapy consists of thiotepa 10mg/kg, fludarabine 160mg/m^2 and treosulfan 42g/m^2, given between days -10 and -2. The duration of treatment consists of app. 10 days conditioning and stem cell infusion, followed by an in-patient follow-up of app. 20-40 days. Total follow-up for this trial is 2 years.

Primary efficacy endpoint: Composite Endpoint: Event free survival (EFS). Event is defined as incidence of acute GvHD (Grade III - IV), chronic GvHD (moderate/severe), graft failure (GF), or death (from any reason). Key secondary endpoint(s): (i) Overall survival (OS); (ii) Disease-free survival (DFS); (iii) Graft failure (GF); (iv) Immune reconstitution; (v) Quality of life (QOL); (vi) Fertility

Key inclusion criteria: Homozygous hemoglobin S disease or heterozygous hemoglobin SC or S 0/+ with pre-existing severe or moderate SCD related complications: Clinically significant neurological event (stroke) or deficit; silent crisis, neurocognitive deficit; pathological angio-MRI with TOF Sequence; TCD velocity >200 cm/s at 2 occasions >1 month apart; More than 5 vaso-occlusive crises (VOC) in the past 1 year or more than 20 VOC in a lifetime; Two or more episodes of acute chest syndrome (ACS) in a lifetime or one episode of ACS in the past 24 months; Chronic transfusion requirement or more than 8 transfusions or one exchange transfusion in a lifetime; Transfusion-refractory allo-immunization; More than five SCD-related hospitalizations in a lifetime; Beginning pulmonary hypertension; Osteonecrosis at more than 2 sites; Beginning SCD Nephropathy; Recurrent priapism (>2)

Results: The enrolment of the first patient is planned in April 2020 and will involve app. 25 centres in 10 countries. First patient in to last patient out is 72 months, duration of the entire trial is 84 months, the recruitment period is 48 months to enroll in total 212 patients.

Conclusions: The objective of this trial is to prove that EFS following T-Haplo-SCT is non-inferior to MSD HSCT as well as evaluation of safety/tolerability and feasibility of haploidentical PBSC grafts depleted of TCRαβ and CD19 cells in adult and paediatric patients with sickle cell disease

Clinical Trial Registry: EudraCT number: 2018-002652-337.

Disclosure: Nothing to declare.

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Hematopoietic Stem Cell Transplantation for Inborn Errors of Metabolism using Alternate Donors: A Prospective Single Study

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Background: Inborn errors of metabolism (IEM) are rare genetic disorders that lead to significant neurologic deterioration and early death during in childhood period in the majority of affected patients. Allogeneic hematopoietic stem cell transplantation (HSCT) has been established as an effective therapy for inherited metabolic disorders for many years. Here we report an analysis of 20 HSCTs for IEM that was performed in Children Medical Center, the biggest children hospital in Iran, between October 2016 and March 2019.

Methods: The HSCT indications included mucopolysaccharidosis (n=10), osteopetrosis (n=5), metachromatic leukodystrophy (n=2), Niemann-Pick type B (n=2), and adrenoleukodystrophy (n=1). Twelve of patients were male. The median age at transplantation was 3.7 years (range: 0.3-8 years). The majority of transplants utilized other related donor stem cells (n=12, 60%) and the others were transplanted with sibling (n=4, 20%) and unrelated donor stem cells (n=4, 20%). All related donors were selected from normal homozygotes individuals using enzyme level. Totally 95% of the HSCTs were performed using peripheral blood stem cells and the other 5% was done with the bone marrow stem cells. myeloablative conditioning regimen consist of Busulfan and Cyclophosphamide with or without Antithymocyte globulin, was used for all patients. The graft versus host disease (GvHD) prophylaxis regimen included a combination of CsA and short course of Methotrexate.

Results: Except of two patients (1 mucopolysaccharidosis and 1 Niemann-Pick type B) who died due to the cardiopulmonary failure before day +15, primary engraftment was occurred in all patients. One patient experienced secondary graft failure after 2 months. The mix chimerism in two patients and full chimerism in 15 others was obvious. The grade I-II and grade III-IV acute GvHD were developed in 20% and 20% of patients, respectively. Limited chronic GvHD occurred in one patient (5%). The development of hemorrhagic cystitis in one patient and the CMV infection in five patients was controlled effectively. With the mean follow up of 13.5 months, 15 patients (13 with full chimerism and 2 with mixed chimerism) are alive without any evidence of disease progression. The causes of death were cardiopulmonary failure (n=2), disease progression (n=2), infection (n=1).

Conclusions: The results show that in the lack of HLA-identical siblings, HSCT using full matched other related or unrelated donors is associated with good results. Early transplantation before disease establishment should consider for improving patients' outcome.

Disclosure: There is no conflict of interest.

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Pearson Syndrome in a Patient Transplanted for diamond-blackfan Anemia

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Background: Diamond-Blackfan Anemia (DBA) and Pearson Syndrome (PS) share important features including early onset of severe anemia and variable nonhematologic manifestations. Here we present a patient whom the leading clinical diagnosis was DBA actually have PS.

Methods: The patient presented to a center at the age of 2 months due to severe pallor. Because of the severe anemia with hemoglobin level of 2.6 gr/dl, bone marrow aspiration was performed and DBA was diagnosed due to erythroid aplasia. Methylprednisolone 2 mg/kg was started, however it was discontinued after 4 months of treatment because of development of cataract. Meanwhile, RPS19 gene sequence analysis was reported as normal. As the patient had a full-matched sibling donor, the patient admitted to our center at the age of 20 months for hematopoetic stem cell transplantation (HSCT).

He was administered busulfan at a myeloablative dose, 150 mg/m2 fludarabine, 10 mg/kg thiotepa and 30 mg/kg anti-thymocyte globulin (ATG-Fresenius) as the preparatory regimen. He was transplanted with bone marrow stem cells with a dose of 10×10^8/kg total nucleated cells and 7×10^6/kg CD34(+) cells. Graft versus host disease (GVHD) prophylaxis was carried out with cyclosporine, and 10 mg/m2 methotrexate at days 1, 3, and 6.

Results: There was no problem in the post-transplant period except for severe mucositis. Neutrophil and thrombocyte engraftments occurred at days 16 and 9, respectively. On the 24th day, the patient had sepsis with hypoglycemia and hyperammonemia and lactate increased

to 10-12 mmol/L. In the same period, the patient developed direct hyperbilirubinemia due to liver GVHD and it was decided to switch to tacrolimus and to add 2 mg / kg methylprednisolone. Although his general condition gradually improved and cholestasis regressed, lactate level remained elevated. The patient was considered to have metabolic disease. Therefore, it was decided to screen for PS, which has a clinical condition similar to DBA. In the study, which was analyzed from DNA separated before transplantation, a mitocondrial deletion was found in favor of PS. The patient was discharged on the 69th day for outpatient follow-up with improved GVHD. However, because of some social problems, the patient was followed-up in another city and developed sepsis at the fourth month of HSCT. Despite support, he worsened rapidly and lost on 167th day.

Conclusions: In patients presenting with congenital anemia, it is recommended that not only DBA but also PS should be screened even if the general condition is good and there are no syndromic findings. Although bone marrow transplantation is also a treatment of choice in Pearson syndrome, it is essential to determine the diagnosis in terms of follow-up.

Disclosure: Nothing to declare.

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Haploidentical Stem Cell Transplantation for Class 3 Thalassemia major using post-transplant Cyclophosphamide

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Background: Allogeneic hematopoietic cell transplantation (allo-HCT) is the only available curative therapy for thalassemia major (TM), although promising results from gene therapy are emerging. However, access to transplant is limited for many patients due to lack of suitable match donors. The use of haolpidentical allo-HCT will increase the donor pool for patient with TM.

Methods: case report

Results: A 3-year-old baby girl, the first child in the family, was diagnosed at the age of 6 months to have TM. She was referred to king Hussein cancer Center (KHCC), for possibility of allo-HSCT. She was on regular blood transfusion and not on regular iron chelation. On exam she had hepatosplenomegaly, liver was 4 cm and the spleen was 3 cm below costal margin, ferritin level was 3600 ng/ml. Routine liver biopsy showed secondary hemochromatosis, grade I, stage III, with fibrosis (Stage III).

Donor selection

No full HLA match donor was found, however, her mother shared 7/10 antigen matching at DR and DQ antigens, with different blood groups. The mother is A positive; and the recipient was AB positive with moderate positive donor specific antibodies. The patient underwent 2 sessions of plasmapheresis before stem cell infusion from her mother and was given one dose of IVIG 1gm/kg and rituximab 375mg/m2 on days -12 and -13 before stem cell infusion, respectively.

Conditioning regimen, GVHD prophylaxis, and supportive care:

Autologous stem cells were collected in advance. She was given 2 cycles of pre-transplant immunosuppression therapy with 5 days Fludarabine 40mg/m2 and dexamethasone 25mg/m2, followed by reduced toxicity conditioning of rabbit ATG(thymoglobulin) 4.5mg/kg, Busulfan, Thiotepa(5mg/kg) and a single fraction of total lymphoid irradiation 500 cGy, followed by T cell repleted peripheral blood stem cell. Total nucleated cells were 14x10^8, CD 34 were 10x 10^6 and CD3 cells were 48x10^7. Cyclophosphamide 50mg/kg on days +3 and +4 post stem cells infusion, cyclosporine A and Mycophenolate mofetil were used as GHVHD prophylaxis. Prophylactic antiviral, anti-fungal and anti PCP prophylaxis given according to our institution guidelines. She was given defibrotide, ursodeoxycholic acid and Spironolactone as veno-occlusive disease prophylaxis. The patient has achieved neutrophil and platelet engraftment on days 13 and 19 respectively.

Complications post-transplant:

· Clostridium difficile acute gastroenteritis,

· Enterobacter cloacae sepsis,

· Decrease hemoglobin, there was no evidence of hemolysis, normal retics, stable mixed chimerism, hemoglobin electrophoresis showed thalassemia trait, and donor blood group, a trial of steroids was given, with improvement in hemoglobin level without blood transfusion, and tapered slowly.

Chimerism and immune reconstitution:

Post-transplant days	30	100	200	360		450
Whole blood Chimerism	91%	80%	41%	47%	76% lymphoid engraftment	47%

[Post-transplant chimerism]

Immune reconstitution by flowcytometry was done one year after transplant and it showed normal B-cells, normal T-cells and normal NK-cells.

Conclusions: We report a successful transplant from haplo-identical mother for Pesaro class III thalassemia major patient, with stable mixed donor chimerism, transfusion independent and no viral reactivation or chronic GVHD with normal immune reconstitution.

Disclosure: no conflict of interest

Immunodeficiency diseases and macrophages

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Hematopoietic Stem Cell Transplantation for Severe Combined Immunodeficiency in Japan: A Nationwide Retrospective Analysis

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Background: Hematopoietic stem cell transplantation (HSCT) is a curative therapy for most patients with severe combined immunodeficiency (SCID) but no comprehensive nationwide study has been performed in Japan.

Methods: To gain an overview of the transplantation for SCID in Japan, we retrospectively analyzed 182 patients with SCID, who underwent their first allogenic HSCT in Japan between 1974 and 2016 by using the Japanese HSCT database Transplant Registry Unified Management Program (TRUMP).

Results: 144 (79%) male patients and 38 (21%) female patients with a median age of 5 months (ranged between 0 and 23 months) at diagnosis received transplants at a median age of 7 months (ranged between 1 and 142 months). Causative genes were identifiable in 101 (55%) participants, among which IL2RG was the most common, accounting for 55 (54%) patients. 89 (49%) patients received transplants from related donors (RDs) and 54 (30%) from phenotypically matched RDs. 93 (51%) cases were from unrelated donors and 81 (44%) were from umbilical cord blood (UCB) donors. Overall survival (OS) rate after HSCT was 44% and retransplantation-free survival rate was 38% over a 25-year period. 10-year OS rate improved significantly according to HSCT date, 69% (2000-2016) vs 48% (1974-1999) respectively ($p=0.03$). The patients who received transplants before 4 months of age had better 10-year OS rate than those transplanted after 4 months old (83% vs 57%, respectively; $p = 0.03$). 10-year OS rates by each donor type were: 82% for matched RD, 81% for matched UCB, 63% for mismatched UCB, 53% for unrelated bone marrow, and 38% for mismatched RD. As a whole, the cumulative incidence of grade II-IV acute GVHD and chronic GVHD were 16% and 9% respectively, and did not show significant difference among donor types. Multivariate analysis of the patients who received transplants after 2005 revealed mismatched CB donors, conditioning other than fludarabine/busulfan or fludarabine/melphalan regimen, and performance status (PS) 2-4 were associated with worse OS.

Conclusions: Due to the satisfactory outcome of HSCT using matched UCB, which was a unique finding from our study, matched UCBT should be taken into consideration as a second alternative for HSCT for SCID in Japan. This advantage is probably due to various factors including homogeneity in HLA and/or minor histocompatibility antigens, gene polymorphisms of cytokines or drug metabolisms, or practice differences. However, outcomes of HSCT from mismatched UCB or mismatched RD were still poor. TCRαβ/CD19 depletion or gene therapy, which are not currently available in Japan, should be introduced for the patients who do not have matched RD/UCB donors. In addition, to keep better PS before HSCT, nationwide newborn screening for early diagnosis should be started in Japan.

Disclosure: Nothing to declare.

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Immunodeficiency - Centromeric Instability - Facial Dysmorphism (ICF) Syndrome: Evaluation of Characteristics and Outcome after Allogeneic Hematopoietic Stem Cell Transplantation

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Background: ICF syndrome is a disease characterized by immunodeficiency of variable extent, facial dysmorphism and centromeric instability. Genetically, four ICF syndrome subtypes have been identified: ICF1 (DNMT3B), ICF2 (ZBTB24), ICF3 (CDCA7) and ICF4 (HELLS). Current treatment regimens comprise antimicrobial prophylaxis, immunoglobulin substitution and treatment of infections, auto-immunity and/or malignancy. A handful of reports have been published about allogeneic hematopoietic stem cell transplantation (HSCT) in ICF syndrome, but a thorough description of characteristics and outcomes for HSCT-treated ICF syndrome patients is missing.

Methods: This EBMT-IEWP retrospective multicentre study included (pediatric) allogeneic HSCT-treated ICF patients. Information was obtained via a questionnaire containing items regarding clinical, biological, genetic and immunological features plus information on HSCT procedures. Data collection was performed by the EBMT-IEWP data office and in collaboration with the SCETIDE registry.

Results: We included 13 ICF patients from nine centers in six countries worldwide, transplanted between 2003 and 2018. All subtypes were represented: ICF1 (n=5), ICF2 (n=2), ICF3 (n=2), ICF4 (n=2). Two patients were diagnosed on clinical criteria. Patient and HSCT characteristics are summarized in figure 1. 85% of patients (n=11) were transplanted for (combined) immunodeficiency with severe recurrent respiratory/gastrointestinal tract and/or opportunistic infections. Chronic diarrhoea and failure to thrive (n=6), auto-immune cytopenia (n=2) and haematological malignancy (n=2) were additional HSCT indications. Donors were matched sibling+matched related (n=4), mismatched related (n=2) and (mis)matched unrelated (n=6). Unmanipulated bone marrow was used as stem cell source in nine cases (69%), peripheral blood stem cells (PBSC) in four patients (with ex vivo graft manipulation in two of these). Mainly busulfan-/treosulfan-based myeloablative conditioning regimes were applied in 10 patients (77%). Reduced intensity conditioning (RIC) was used in three patients with either organ damage or to reduce transplant-related toxicity. Serotherapy (ATG/alemtuzumab) was applied in 11 cases. All patients, except for one dying at day -1, engrafted with a median time to neutrophil recovery of 17 days. Acute graft versus host disease (GVHD) was reported in five patients (42%), grade I (n=2) to III (n=3). Chronic GVHD was not reported. During follow-up, 75% of patients experienced infectious problems, mainly viral infections/reactivations. Two patients developed auto-immune thyroiditis: for one patient, that also developed vitiligo, this was donor-derived. At time of analysis, 10 patients (77%) survived with a median follow-up of six years. Death was due to conditioning toxicity (n=1; day -1 in a patient with severe enteropathy and RIC), respiratory failure/viral infection (n=1; day +41) and multi-organ failure after prolonged adenoviraemia (n=1; day +145 after T cell-depleted PBSC). Both patients presenting with malignancy were among these deaths. All surviving patients demonstrated good T cell reconstitution and full donor chimerism at +1 year and 80% were off immunoglobulin substitution at this time point.

Conclusions: In this largest cohort of HSCT-treated ICF patients analyzed to date, we demonstrate good outcome in patients with predominantly severe infections and chronic gastrointestinal problems. We show acceptable GVHD rates and good immune recovery. Therapy-related mortality occurred mainly in the most vulnerable patients with active infections, organ damage and/or malignancy, pointing at possible advantages of earlier HSCT in these patients.

Disclosure: Nothing to declare.

P351

Thiotepa versus Melphalan Containing Conditioning Regimens in Hematopoietic Stem Cell Transplantations with TCRαβ/CD19 Graft Depletion for Primary Immunodeficiencies

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Background: Melphalan and thiotepa are alkylating agents widely used in pre-HSCT conditioning regimens. Most

studies report administration of just one or a combination of these drugs. To evaluate safety and efficacy of melphalan versus thiotepa containing conditioning regimens we performed this comparative analysis.

Methods: From 2012 to 2018 83 patients with non-SCID primary immunodeficiencies received allogeneic HSCT with thiotepa or melphalan containing conditioning regimens (CR) and TCRαβ/CD19 graft depletion in our center. The median age at HSCT was 3,6 years (range 0,4-17,6). In 21 patients - 9/10 and in 41 - 10/10 HLA matched unrelated donors; in 21 - mismatched related donors were used.

CR included treosulfan 36-42g/m2, fludarabine 150mg/m2 and either melphalan 140mg/m2 (n=45), or thiotepa 10mg/kg (n=38). In 80 patients thymoglobulin 5mg/kg and in 1 patient alemtuzumab 1mg/kg were administered. Two patients received no serotherapy. All but 3 patients also received rituximab 100mg/m2 on day -1.

In 58 patients from 1 to 3 immunosuppressive drugs were used until day +45 after HSCT, 25 patients received no post-HSCT immunosuppression.

Median FU of survivors was 19,4 months (range 12,2-62,4) in thiotepa and 49,5 months (range 13,8 - 75,5) in melphalan group.

Results: All, but 2 patients engrafted. Both non-engrafted patients had severe congenital neutropenia: 1 received melphalan, 1 - thiotepa containing CR. The median of neutrophil engraftment was 13,5 days in melphalan group and 12 days in thiotepa group, p=0,01. The median of platelet engraftment was 13 and 12 days after HSCT for melphalan in thiotepa groups, respectively, p=0,29. The cumulative incidence of graft failure was 0,16 (95% CI 0,08 - 0,31) in melphalan and 0,13 (95% CI 0,06-0,3) in thiotepa group, p=0,85.

Early toxicity, including skin, mucosal and renal did not vary significantly between 2 groups (p=0,4-0,47); however, there was more non-VOD liver toxicity after thiotepa usage (p=0,06): grade 1 in 4, grade 2 in 5 and grade 3 in 7 patients.

The incidence of acute GVHD was 0,2 (95% CI 0,12-0,37) and 0,25 (95% CI 0,14 - 0,44) (p=0,6), chronic GVHD 0,1 (95% CI 0,04-0,25) and 0,08 (95% CI 0,03-0,24) (p=0,97) in melphalan and thiotepa groups, respectively.

OS was 0,82 (95% CI 0,7-0,93) in melphalan and 0,82 (95% CI 0,7-0,94) in thiotepa groups, p=0,85.

Conclusions: No significant differences were found between the results of TCRαβ/CD19 depleted HSCT with treosulfan based CR containing melphalan and thiotepa. However, long term toxicity needs to be estimated in longer follow up.

Disclosure: authors have nothing to disclose

P352

Improved Transplant Survival and Long-term Disease Outcome for Children with CD40 Ligand Deficiency

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Background: Haematopoietic cell transplantation (HCT) is the only curative therapy for CD40L deficiency.

Methods: We examined the outcome of 22 children with CD40L deficiency who received first HCT at our centre between 1996-2019. From 2007, the conditioning was switched to Treosulfan-based chemotherapy. Outcomes of interest were OS, EFS (events were defined as death, graft failure or second procedures), toxicity, long-term disease outcome and graft function. Log rank test was used to analyse predictors of OS.

Results: The median age at diagnosis was 1.5 years (at birth to 12.2 years; 2 antenatal diagnoses). Prior to HCT, 11 (50%) had history of PCP, 5 (22%) crytosporidial infection and 4 (18%) chronic liver disease (3 sclerosing cholangitis; one hepatic fibrosis). The median age of transplant was 3.9 years (0.6-14.0). Donors: MFD (n=3); MUD (n=13); MMUD (n=4); haploid (n=2). Stem cell source: marrow (n=15), PBSC (n=7). 8 had ex-vivo T-cell depletion. Four had veno-occlusive disease (all had Busulfan). Eight (36%) had grade II-IV acute GvHD while 4 had (18%) had grade III-IV acute GvHD. None had chronic GvHD. Four had CMV viraemia, 5 adenoviraemia, 6 HHV6 viraemia and 2 EBV viraemia.

The 5-year OS for the entire cohort was 80% (55-92%), rising from 56% (20-80%) for the children >4 years of age to 100% for children transplanted at £4 years of age (p=0.01). Pre-transplant liver disease was associated with inferior OS, 25% (0-67%) (vs 94% (63-99%), p< 0.001). OS was 20% (0-71%) in MSD (n=3, 2 deaths had pre-transplant liver problems), 100% in MUD (n=2), 50% in MMUD (n=4) and 100% in haploid (n=2) (p=0.005). Year of transplant (p=0.06), pre-transplant cryptosporidium (p=0.11), conditioning (p=0.90), stem cell source (p=0.17) and ex-vivo T cell depletion (p=0.59) had no impact on OS. The 5-year EFS for the entire cohort was 57% (95% CI 32-76%). Four who had second procedures (3 stem cell boosts for slipping chimerism; one second HCT for primary reconstitution) were alive. Of four total deaths, 2 were due to liver failure, 1 cryptosporidiosis and 1 disseminated

adenovirus. The median age at transplant of deceased patients was 12.5 years (4.3-14 years).

Of 14 long-term survivors (> 1 year post-transplant), the median age at last follow-up was 8.9 years (5.1 to 23.6) with a median duration of follow-up 8.3 years (3.8-21.1). Median myeloid chimerism was 65% (5-100) and median T-lymphocyte chimerism was 80% (range, 7-100). Median CD4+ T cell CD40 ligand expression was 62% (6-94%). Three patients had post-HCT autoimmunity. Eleven (79%) were off immunoglobulin after a median of 12 months (6.2 to 45.8) months post-transplant. Three patients remained on immunoglobulin replacement after a median 7.4 years (3.8-14.5) post-HCT (2 on treatment for autoimmunity). None had significant infection. One patient had liver transplant at 3.2 years post-HCT for chronic liver failure secondary to liver GvHD after MMUD transplant. None had hepatobiliary cancer.

Conclusions: Age and pre-transplant liver disease had significant association with OS. Survival after matched unrelated and haploidentical donors were excellent. Long-term disease outcome of survivors is good.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare.

P353

Hematopoietic Stem Cell Transplantation Outcomes Including Immune Reconstitution in Primary Immunodeficiencies: 5 Years of Single Centre Experience

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Background: Primary immune deficiencies (PIDs), considered rare, are quickly increasing in number, mainly thanks to improved techniques for diagnosis. To date, more than 400 disorders with more than 350 defects in genes involved in immune host defense and immunoregulation have been described. Currently, hematopoietic stem cell transplantation (HSCT) represents a curative treatment for a broader spectrum of entities.

Methods: Retrospective observational study of pediatric patients with PID who underwent HSCT at Hospital Universitario La Paz (Madrid, Spain) from January-2015 to July-2019. Statistic analysis was made by SPSS Statistics 25.0.

Results: Thirty-three patients with PID were proposed for HSCT. Six patients were excluded because of: uncontrolled CMV/EBV infection (3), gene therapy (1), social reasons (1) and not suitable donor (1).

Twenty-seven patients underwent 34 HSCT (diagnosis classification according to UIS 2017 PID Committee Report on Inborn Errors of Immunity): Ia) SCID: 4, Ib) CID: 6, II) CID with associated or syndromic features: 2, IV) Immune disregulation disorders: 6, V) Congenital defects of phagocyte: 8, and VI) Defects in intrinsic and innate immunity: 1.

Median age at diagnosis was 55.55 months (0.3-186.3) and at transplant 70.41 months (3.1-196.67). Fifteen males and twelve females were transplanted from 13 related donors (MRD: 5, haploidentical: 8) and 21 unrelated donors (MUD: 11, MMURD: 10). Source of stem cells was bone marrow (50%), peripheral blood (41.2%) and umbilical cord blood (8.8%).

Nineteen patients (70.4%) are alive with median follow-up of 17.28 months (0.1-54.93). Mortality rate by diagnosis classification was: Ia) 25%, Ib) 50%, II) 50%, IV) 16.7%, V) 25% and VI) 0%. It was higher with haploidentical donor. Main cause of death was respiratory (Infectious/not).

Graft failure occurred in 7 HSCT (primary: 5, secondary: 2). Six patients received 2 transplants and 1 patient 3. Incidence of graft versus host disease (GVHD) was 17.6% for acute grade II-IV and 17.6% for chronic (any grade). 24 HSCT presented infectious complications: 65.7% viral, 40% bacterial, 5.8% fungal, and 5.8% others.

Median follow-up of immune reconstitution was 18.36 months (0.97-49.83). 44% patients have mixed chimerism. Only 3 patients need gammaglobulin replacement (one in decreasing dose) and 9 have started vaccinations. We observed that lymphocytes < $0.3x10^3$/μL (p=0.0362), CD3+ < $0.55x10^3$/μL (p=0.0145), >25% CD3+HLA-DR+ (p=0.0124), CD3+CD4+ < $0.175x10^3$/μL (p=0.0184), < 5% CD4+CD31+Ra+ (p=0.0175), CD19+ < $0.1x10^3$/μL (p=0.0013) and 0% of CD19+CD27+ (p=0.001), were related to mortality.

Conclusions: Complexity of PID patients requires specific knowledge for pre- and post-HSCT and consideration of single individual characteristics. For newer PIDs experience is scarce, complicating the decision-making process of who and when to transplant, so the risk of the procedure has to be balanced with the expected natural history of the underlying disease.

Thanks to advances in HSCT with alternative donors, lacking a MSD is no longer an obstacle to be transplanted. Though, results with haplo-HSCT donor in our experience are still not as good as when a MRD, MUD or MMURD is available.

Immune reconstitution correlates with transplant-related complications and could be a predictor of mortality after HSCT.

Disclosure: Nothing to declare.

P354

Outcomes of Stem Cell Transplant for RIPK1 Deficiency: Single Centre Experience

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Background: Loss of function mutations in Receptor Interacting Serine/Threonine Kinase 1 (RIPK1) cause primary immune deficiency associated with severe inflammatory bowel disease and arthritis (1). As the immune dysregulation is caused in part by increased production of IL1β, IL1 inhibitors have been suggested as a possible treatment of the inflammatory manifestations of the disease. HSCT has also been proposed as a potentially curative treatment, however only one successful transplant has previously been reported (Case 1 - (2)).

Methods: We reviewed the outcomes of 4 transplants from 2 sibships at the Great North Children's hospital between 2011 and 2019

Results: The transplant details are summarised in Table 1. Overall survival was 75% (3/4). A range of immune suppressive regimens were used in an attempt to control enteropathy pre transplant including steroids, infliximab and anakinra with no significant response to these medications. Case 2 developed grade 1 skin GVHD D+29 which responded to topical steroids.

Conclusions: Despite significant pre-transplant comorbidities transplant survival for RIPK1 deficiency is comparable to other immune deficiency/dysregulation disorders. Despite a sound theoretical basis for considering IL1 blockade as a potential treatment, our limited experience did not show any benefit. The severe inflammatory bowel disease was however responsive to HSCT with impressive resolution of bowel symptoms corresponding with engraftment. Our experience supports the safety and efficacy of early HSCT for patients with RIPK1 deficiency.

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Disclosure: Nothing to declare.

Year of transplant	Age at transplant	Donor	Conditioning	GVHD prophylaxis	Engraftment	Outcome	Latest chimerism
1 2011	12y M	8/10 MMUD PBSC (allelic A and C mismatches)	Fludarabine 180mg/m2, alemtuzumab 1mg/kg, treosulfan 14g/m2, thiotepa 10mg/kg	CSA + MMF	Neutrophil D+10, Platelet NA	Died D+46 (Multisystem organ failure from D+7. CVVH, intubation, inotropes. Encephalopathic. Sudden deterioration D+45 ?sepsis)	100%
2 2012	2y M	10/10 MUD PBSC	Fludarabine 150mg/m2, Treosulfan 42g/m2, Alemtuzumab 1mg/kg	CSA + MMF	Neutrophil D+15, Platelet D+13	Alive and well	100% 5years 7m post
3 2019	5y F	10/10 MUD PBSC	Fludarabine 150mg/m2, Treosulfan 42g/m2, Alemtuzumab 1mg/kg	CSA + MMF	Neutrophil D+12, Platelet D+14	Alive and well	CD15 100%, CD19 94%, T cell 89% D+124
4 2019	2y F	Maternal TCRα β/ CD19 depleted haploidentical PBSC	Fludarabine 160mg/m2, Treosulfan 42g/m2, Thiotepa 10mg/kg, ATG (grafalon) 15mg/m2), Rituximab 200mg/m2	Nil	Neutrophil D+10, Platelets D+16	Alive and well	100% D+62

[Patient and transplant characteristics]

P355

Improving the Result of Hematopoietic Stem Cell Transplantation For Primary Immunodeficiency with Serious Infection in Developing Countries using Ric Regiment

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Background: Allogeneic hematopoietic stem cell transplantation (HSCT) has provided a curative therapy in many patients with primary immunodeficiency (PID). Choosing an appropriate conditioning regimen has a major influence in the outcome of transplant especially in patients with history of recurrent infections and disseminated bacille Calmette-Guérin infection (BCG-osis) during transplantation. The aim of this survey was to investigate the result of HSCT using reduced-intensity conditioning (RIC) in children with PID.

Methods: A total of sixty-three patients with PIDs (39 male and 24 female) who underwent HSCT between November 2016 and October 2019 in the Children's Medical Center, Tehran, Iran were enrolled. The median age of patients at the time at transplantation was 4.3 years (range, 0,1-16). The most common indications for HSCT were severe combined immunodeficiency (SCID) (n=20), chronic granulomatous disease (n=12) and leukocyte adhesion deficiency (LAD) (n=9), followed by less frequent disorders including hyper IgE syndrome (n=6), Wiskott-Aldrich syndrome (n=5), familial erythrophagocytic lymphohistiocytosis (FEL) (n=4), Griscelli syndrome (n=2), LRBA deficiency (n=2), and also Chediak-Higashi syndrome, combined immunodeficiency and IL10RA deficiency each in 1 patient. Stem cell sources consisted of peripheral blood (n=56), Bone marrow (n=3) and umbilical cord blood (n=4) and were provided by HLA-identical sibling (32.8%), HLA-matched family (34.4%), HLA-matched unrelated (19.7%) and mismatched unrelated donors (13.1%). The median doses of infused mononuclear cells and $CD34^+$ cells were 8.0×10^8 cells/kg and 6.1×10^6 cells/kg, respectively. Except 2 patients with SCID who received HSCT form their HLA identical siblings without conditioning, other patients received the same RIC regimen consist of Fludarabine, Melphalan and antithymocyte immunoglobulin (ATG). Graft-versus-host disease (GvHD) prophylaxis was composed of Cyclosporine A and Methyl-prednisolone.

Results: A total of sixty-three patients received 66 HSCTs. Primary engraftment occurred in 61 patients. Tree patients (1 LAD, 1 FEL and 1SCID) received second transplantation due to primary graft failure in their first transplantation and 2 patients died due to infection before checking chimerism on day 15. Among 61 patients who engrafted, 48 mentioned full donor chimerism and 13 had stable mixed donor chimerism. Acute GvHD grad I-II and III-IV were developed in 22.2% and 23.8%, respectively. Limited chronic GvHD occurred in 4 patients.

With the median follow-up 8 months (range, 0.4-32), 48 patients are alive and regardless of having full or mixed chimerism are disease free with no manifestation of primary disease. The most common cause of death was infection (60%).

Conclusions: Although there are concerns about ability of RIC regimen to achieve engraftment and higher incidence of engraftment failure or mix chimerism following RIC-HSCTs,

It has created an opportunity for patients who are not eligible for myeloablative conditioning regimen. Use of RIC in developing countries where BCG vaccination are mandatory at birth can improve survival rates and mixed donor chimerism appears to be sufficient to control the disease in PIDs.

Disclosure: There is no conflict of interest

P356

Single-center Experience of Haploidentical Hematopoietic Stem Cell Transplantation With TCR αβ Depletion in Children with Primary Immunodeficiency Syndromes

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Background: Primary immunodeficiency syndromes (PIDs) are associated with high mortality and morbidity in childhood. Therefore early diagnosis and treatment are crucial. Allogeneic hematopoietic stem cell transplantation (HSCT) is used as a therapeutic option for primary immunodeficiency syndromes and HSCT at a younger age was found to increase survival rates. The best outcomes have been achieved with HLA-matched donors, but when a matched donor is not available, a haploidentical HSCT with

αβ T cell depletion can be done with low rates of graft failure and graft-versus-host disease, when urgent HSCT is needed. Here, we share our preliminary results on TCR αβ depleted haploidentical transplantation in patients with PIDs.

Methods: Twenty-four patients (median age, 1.4 years; range, .3 to 10.9) received 27 HSCTs from haploidentical donors (father n:10 mother n:17) after TCR αβ depletion. Most patients (74.1%) received reduced-toxicity myeloablative conditioning consisting of treosulfan (n=13) or busulfan (n=6), fludarabine and thiotepa. One patient with severe combined immunodeficiency (SCID) did not receive any conditioning. All conditioned patients received anti-human T-lymphocyte immunoglobulin. Fourteen patients received rituximab to reduce the risk of EBV-related post-transplantation lymphoproliferative disease. Mesenchymal stem cell was infused at day -1 and +5 to suppress alloreactive donor anti-host T-cell responses and to use their ability to promote angiogenesis and support microenvironment, which facilitate engraftment. Graft versus host disease (GVHD) prophylaxis consisted of cyclosporine in 10 patients, CSA +mycophenolate mofetil in 16 patients. All patients received immunoglobulin replacement until complete immune reconstitution. Immune reconstitution was monitored post-transplant monthly until complete reconstitution. The median duration of follow-up was 7 months (range, 1-56 months).

Results: Patients were transplanted with a median of $7.51x10^6$/kg (range, 2.49 to 19) CD34 cells, and the median number of TCR αβ cells in the graft was $0.2x10^6$/kg (range, 0 to 4.97). The median times to neutrophil, platelet and lymphocyte engraftment were 12 days (range, 10 to 72), 20 days (range, 11 to 66) and 30 days (range, 12 to 71). Acute GVHD were observed in 8 patients (grade I-II n=2 and grade III-IV n=6). Chronic GVHD was observed in only one patient. Preliminary data on immune reconstitution were very encouraging. Immunophenotypic analysis reveals a progressive increase in lymphocyte subset counts from day +30 through later posttransplantation time points. Patients had lymphocyte more than 1000 cells/mL, median on day 48 (range, 1-56 months). Eighteen patients (66.7%) had viral reactivation/infection post-transplant; 12/18 had one viral reactivation/infection, 6/18 had multiple viral reactivations/infections. Graft failure was observed in 8 patients. Two patients were successfully retransplanted with different rescue protocols. Probabilities of overall survival were 81.5% at day 100, 70.8% at one year and at five years. The cumulative incidences of transplant related mortality were 18% at day 100, 25.9% at one year and at five year.

Conclusions: We conclude that use of TCR αβ depleted haploidentical transplantation ensures a high engraftment rate; good immune reconstitution; low incidence of significant aGvHD, and acceptable posttransplantation morbidity in children with a range of PIDs and should be considered in children with PIDs lacking an HLA-matched donor, when urgent HSCT is indicated.

Disclosure: Nothing to declare.

P357

Haplo-identical Transplant Using post-transplant Cyclophosphamide (PTCY) in Children with Severe Combined Immunodeficiency - A Tertiary Care Centre Experience from South India

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Background: Severe combined immunodeficiency (SCID) is a universally fatal condition in the absence of haematopoietic stem cell transplant (HSCT). Most of the patients in the Indian setting present with active ongoing infection(s) due to lack of neonatal comprehensive screening programme and only less than 30% have a matched sibling donor. Mobilising matched unrelated donor (MUD) is not practical in a medical emergency and both MUD transplants and Cell manipulation techniques are expensive and beyond the reach of majority of our patient population.

Methods: We retrospectively reviewed the results of 8 consecutive haploidentical transplants in 6 SCID babies. The genetic diagnosis, phenotypic classification, condition at presentation, oxygen requirement, outcomes, latest donor chimerism and follow up duration were noted. All patients received bone marrow as stem cell source, post-transplant cyclophosphamide on day +3 and +5 at a dose of 50 mg/kg/day, Cyclosporine or Tacrolimus up to 6 months and Mycophenolate for 28 to 60 days. Conditioning regimen intensity varied depending on the clinical well-being of the child at transplant. Extensive immune reconstitution workup was not performed.

Results: Six patients received 8 Haplo-identical BMTs between Dec 2017 to June 2019 (details in Table 1). All, except Patient 2, presented with active infection. All patients improved with supportive care prior to bone marrow infusion except patient 6. Two patients (Pt 1 and 2) needed second transplant. Patient 2 succumbed to severe klebsiella sepsis post 2nd transplant on day +85. Patient 6 died of progressive sepsis with respiratory failure post-transplant before engraftment could be achieved. Four patients are doing fine, with a mean duration of follow-up 9 months post-transplant.

Conclusions: Reasonable outcomes can be achieved with haploidentical transplant with post- cyclophosphamide

in SCID patients with active infection as long as infection resolves prior to transplant even in resource limited settings.

Disclosure: Nothing to Declare

P358

Necrotizing Enterocolitis in a two-month-old Scid Patient after Bone Marrow Transfusion - Surgical Intervention At Day +1: Yes or No?

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Background: Necrotizing enterocolitis is a severe condition usually encountered in premature neonates. Pneumatosis intestinalis and portal venous gas are findings indicative of NEC and usually accompanied by rapid clinical deterioration. Treatment options include gastrointestinal rest, intravenous antibiotics and surgery. Involvement of the gastrointestinal system is one of the major complications and source of high morbidity and mortality following hematopoietic stem cell transplantation (alloHSCT). However, surgical intervention in complete aplasia shortly after bone marrow transfusion is associated with high mortality. Deciding on the right course of action poses a dilemma for the treating physician.

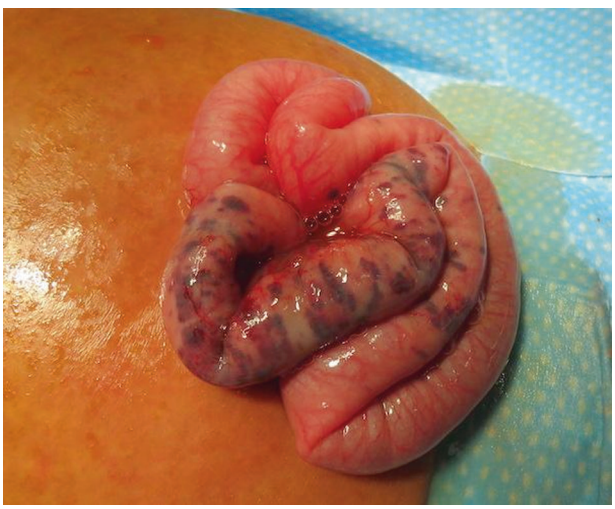
Methods: We report the case of a two-month-old boy with severe combined immunodeficiency (SCID, T-, B+, NK+) presenting with rapid onset of clinical features of acute NEC on day +1 after alloHSCT.

The patient was born on term and diagnosed with SCID of unknown genetic origin shortly after birth due to positive family history. Shortly after an early infection by Adenovirus (22nd day) he developed clinical manifestations of Omenn-syndrome including a severe papulous ichthyosis-like exanthema, elevated serum IgE-levels, marked eosinophilia and expansion of autoreactive oligo-potent T-cells. Treatment included cyclosporine and steroids, as well as Cidofovir infusions to clear Adeno-virus.

AlloHSCT was carried out early (60th day) using bone marrow of a healthy HLA-matched sibling. Conditioning regimen consisted of treosulfane, fludarabine and ATG, which was tolerated well. Shortly after graft infusion (d +1) the patient presented with symptoms of sepsis, including a severely distended, painful and livid abdomen, tachydyspnoea, and drop in oxygen saturation. Lab results showed an increase in CRP and drop in hemoglobin and thrombocytes. Immediate sonographic imaging revealed portovenous gas flow and widespread intrahepatic gas collection. After interdisciplinary discussion, calculating the risk of intra- and postoperative infectious complications, he was prepared for immediate explorative laparotomy suspecting fulminant necrotizing enterocolitis.

Results: Surgery showed petechial-like lesions predominantly antimesenterically restricted to the jejunum without perforation, consistent with an early-stage necrotizing enterocolitis. The remaining bowel, especially the colon was macroscopically unaffected. Intestinal decompression was achieved through manual orthograde massage of the bowel content. There was no necessity for resection or stoma formation. The patient was admitted to the PICU requiring respiratory and circulatory support for six days. Immediate postoperative sonographic imaging still showed pneumatosis intestinalis, but no more portovenous gas flow. Blood culture tests were positive for (3MRGN/ESBL) E. coli and antibiotic treatment was escalated accordingly. Already hours after surgery we observed a stabilization of the patient, followed by rapid clinical recovering without abdominal sequelae

Conclusions: Pneumatosis intestinalis and neutropenic enterocolitis have been described as complications after alloHSCT, primarily in patients suffering from GvHD. Usually, patients present mild to clinical symptoms like diarrhea, fever and thickening of the abdominal wall which can be successfully managed conservatively. Our case however, reports on an infant presenting with rapid onset of necrotizing enterocolitis and shock without signs of GvHD, necessitating an immediate decision on how to proceed. Clinicians should be aware of this rare post-HSCT complication in infants to ensure early sonographic imaging and assess need of early surgical intervention. Multidisciplinary management is necessary.



[Explorative laparotomy: petichial-like lesions in the jejunum consistent with early-stage NEC]

Disclosure: Nothing to declare.

P359

Long-term Enzyme Replacement Therapy (ERT) in ada-scid Patients: The Shadow of Malignancies

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Background: ADA-SCID is a rare disease (10-15% of SCID) due to the mutations of the ADA gene resulting in the accumulation of high systemic levels of ADA toxic metabolites. There are 3 treatment options: HSCT from matched sibling donor (the best therapeutic options), Enzyme Replacement Therapy(ERT) with PEG-ADA to manage disease in short term, autologous Gene Therapy (GT) or allogeneic HSCT from MUD/parents. Long term ERT is a therapeutic options although immune reconstitution may be sub-optimal in some patients. ERT is always being a life-saving treatment that normalized immune function and allowed a good quality of life for years, but has being a therapy at term. Therefore if no other therapeutic options are undertook, the risks for the patients could be severe infections and malignancies. Nowadays a new recombinant ERT is available with promising results in maintaining immunological reconstitution.

Methods: In our center 29 ADA patients were diagnosed, of which three were treated with ERT from diagnosis.

Results: The patients were diagnosed early: 1 prenatal diagnosis, at 2 months and 3 months of age. They started immediately ERT. Median time of ERT follow up is 20 years. They are well detoxified (median value of %dAXP is 0.65%), but have very low level of lymphocytes. An approach to correct the immunological situation by GT with peripheral stem cells, considering the bone marrow stem cell exhaustion in these patients, was hypothesized but was inapplicable. At diagnosis, approximately 20 years ago, gene therapy wasn't a consolidates therapy and ERT seemed the more solid therapeutic option. In the process of programming HSCT, unfortunately, one of these patients has developed plasmablastic lymphoma after 21 years of ERT.

Conclusions: Our experience shows that ERT gives a good therapeutic option as bridge therapy for HSCT. For patients in long-term ERT, would be beneficial the use of the newly approved recombinant PEG-ADA. Nevertheless strict monitoring would be necessary to check the results of this new therapeutical approach.

Disclosure: Nothing to declare.

P360

Haematopoietic Stem Cell Transplantation for X-linked Agammaglobulinaemia Complicated by Chronic Norovirus Enteropathy

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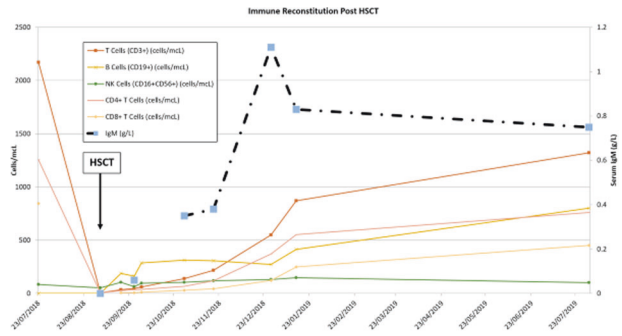
Background: The patient was diagnosed with X-Linked agammaglobulinaemia (XLA) (c.1750+2T>C) at eight months of age after investigations for a second episode of varicella which revealed agammaglobulinaemia. He was relatively well until six years of age, when he developed diarrhoea due to chronic Norovirus infection. He had protein-losing enteropathy requiring subcutaneous (SC) and intravenous (IV) immunoglobulin replacement therapy (IGRT) to maintain modest IgG trough levels. To maintain his weight, he required nasogastric (NG) feeds but quickly progressed to total parental nutrition (TPN) to prevent further weight loss. Trials of probiotics, bovine colostrum and ribavirin all failed to clear the Norovirus infection.

Methods: He underwent a 10/10 MUD PBSC HSCT with Fludarabine, Thiotepa, Treosulfan and Alemtuzumab. He received Ciclosporin and MMF for Graft versus Host Disease (GvHD) prophylaxis. He achieved neutrophil engraftment on D+19 and platelet engraftment on D+17. He had no transplant-related complications.

Results: Four months post-HSCT, he was clear of Type 2 Norovirus infection in the stool. This coincided with an improvement in stool frequency and cessation of TPN. He continued to gain weight on a normal diet with no supplements and was passing normal stools. Nine months post HSCT, IGRT was stopped. Five months after stopping IGRT (14 months post-HSCT), his IgG is 11.1g/L, IgA is < 0.02g/L and his IgM is 0.75g/L. His latest chimerism demonstrates 96% donor CD15+ cells, 97% donor B cells and 84% donor T cells. He has demonstrated satisfactory immune reconstitution (Figure 1).

Conclusions:



[Immune reconstitution post HSCT]

To our knowledge, this is the first HSCT for XLA in developed healthcare systems solely to cure XLA or its direct complications. Patients have previously been cured of XLA through HSCT, but only when HSCT was offered for a haematological co-morbidity (e.g. Sickle Cell Disease, Leukaemia). Similarly, HSCT is offered in developing healthcare settings where reliable access to IGRT is not possible where the risk-benefit ratio swings in favour of HSCT.

There are several complications of XLA unrelated to antibody deficiency and not amenable to IGRT. In addition to chronic Norovirus infection, inflammatory bowel like disease is well recognised. These complications are likely due to the lost regulatory role of B-Lymphocytes or loss of BTK function expressed in cells other than B-lymphocytes. While viral infections are not classically thought of as a problem in XLA (aside from CNS enteroviral infections), this case and other published cases demonstrate that persistent Norovirus infection is a recognised complication in XLA, similar to patients with CVID.

We propose that HSCT can play an active role in the management of XLA for patients with significant complications that are not amenable to IGRT or feasible alternatives.

Disclosure: Nothing to declare.

P361

Hematopoetic Stem Cell Transplantation in CD40 Ligand Deficiency

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Background: CD40 ligand (CD40L) is expressed on the T lymphocyte surface and its deficiency is caused by mutations in the glycoprotein CD40L (CD154) gene. However, no phenotype-genotype correlation causes difficulties in the treatment approaches including decision for hematpoetic stem cell transplantation (HSCT) which led us to review our ten HSCTs to contribute to the evidence about treatment approaches.

Methods: The patients with CD40L deficiency who were transplanted in Antalya and Göztepe MedicalPark Pediatric HSCT units between 2014-2019 and followed in Akdeniz University School of Medicine Department of Pediatric Immunology were retrospectively reviewed.

Results: Records of 8 male cases including a twin-case were evaluated retrospectively. As 2 transplants each were performed to twins, a total of 10 transplants were evaluated. The conditioning regimens were predominantly based on myeloablative protocols that consisted of treosulfan or busulfan with weight-based dosages, except for two twin cases wherein a non-myeloablative regimen was used in their first transplantation. Median neutrophil and platelet engraftment days were 13 (range 10-19) and 14 (range 10-42) days, respectively. Seven of ten patients had a CMV reactivation without morbidity and no other severe infections were developed other than one patient with a prolonged aspergillosis. Only one patient had a mild skin GVHD with a complete response and no other patient had either acute or chronic GVHD. Seven of 10 HSCTs resulted with success. All patients are alive and the median follow up was 1040 days, with a range of 160-1970 days.

Conclusions:

Our data show that HSCT for patients with CD40 ligand deficiency is a potentially effective treatment for long-term disease control.

Disclosure: Nothing to declare.

P362

Allogeneic Hemotopoietic Stem Cell Transplantation (HSCT) for Chronic Granulomatous Disease (CGD) in Childhood

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Background: Chronic granulomatous disease is a congenital disorder characterized by recurrent life-threatening bacterial and fungal infections secondary to a congenital defect in phagocyte NADPH oxidase leading to impaired phagocyte-killing mechanisms. The only curative approach is allogeneic stem cell transplantation. The aim of this study is to report our experience in patients with CGD.

Methods: From 10/2007 until 2/2019, 6 patients (1 girl) suffering from CGD (5 with X-CGD) were transplanted with median age 4 years (range 3,7- 5,7 years) without infection or autoimmune manifestations before the HSCT. The donor was a volunteer unrelated donor in 3 patients and a matched sibling donor in the other 3 patients. Four patients were conditioned with BU/CY, whereas 2 patients received TREO/FLU. Graft versus host disease (GvHD) prophylaxis consisted of ATG+CSA+MTX in 5 out of 6 patients. Five (5) patients received bone marrow graft and 1 umbilical cord (from unrelated donor).

Results: Engraftment was achieved in all patients. The median time to neutrophil and platelet engraftment were 25 (range 14-34) and 24 (range 11- 33) days respectively. Two (2) patients developed acute GvHD, grade II -III and none chronic. Immune recovery in the first year after HSCT was achieved in 4 patients. Two out of six (33%) patients had mixed donor chimerism and the remaining 4 had full donor chimerism at day+ 100. With a median follow-up of 58,28 months (range: 10,33 to 146,43) all patients are alive.

Conclusions: Allogeneic bone marrow transplantation in children with CGD conditioned with myeloablative regimens leads to sustained engraftment with high rates of full donor chimerism and immunological reconstitution without increased transplant related toxicity.

Disclosure: Nothing to declare.

Infectious complications

P363

Risk of Infectious Complications in Adult Patients After Allogeneic HSCT Depending on The Site of Central Venous Catheter Insertion - Multicentre Prospective Study

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Background: The current guidelines for prevention of infections in hematopoietic stem cell transplantation (HSCT) do not specify which central venous catheter (CVC) insertion site should be preferred in HSCT recipients - jugular or subclavian vene. The insertion site could influence risk of infectious and non-infectious complications in HSCT patients. So far there was no prospective multicenter study that addressed this question in adult allogenic HSCT patients.

In an attempt to answer this question, EBMT Infectious Diseases Working Party and Nurses Group of EBMT designed a prospective study comparing the risk of infectious and non-infectious complications between the two most common sites of CVC insertion - subclavian and jugular.

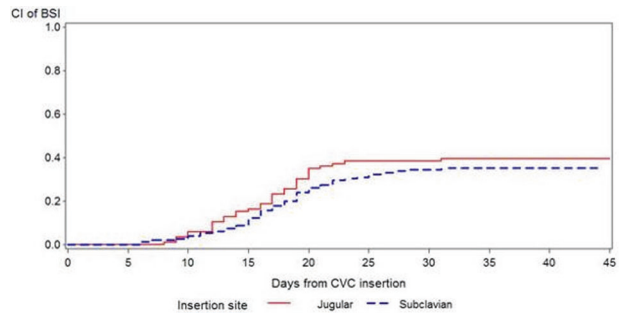
Methods: In collaboration between EBMT Infectious Diseases Working Party and Nurses Group of EBMT we designed a multicentre prospective trial that analysed the occurrence of complications depending on the CVC insertion site for the first CVC used for HSCT in allogeneic patients. Primary analysis endpoints were infectious complications in adult allogeneic HSCT recipients depending on CVC insertion site: a) any blood stream infection (BSI) b) confirmed CLABSI c) infections at the insertion site. Secondary endpoint was analysis of difference in relative risk of non-infectious complications at insertion or during follow up care in allogenic HSCT recipients depending on CVC insertion site. To support the uniformity of practices for CVC insertion the following inclusion criteria were used: a) adult allogenic HSCT, b) use of non-tunnelled CVC in majority of patients, c) lack of policy to routinely replace the catheters after a specific period of time d) lack of policy to remove the CVCs on the basis of fever alone, e)

surgical full barrier precautions at the insertion of CVC with body drapes covering sufficient area of the patients' body (drapes bigger than 60 x 60 cm) at the centre, f) availability or use of ultrasound during CVC insertion.

Results: There were in total 232 consecutive patients who underwent adult allogenic HSCT reported from 12 centres in 8 countries. 146 patients with subclavian CVCs and 86 with jugular CVCs. The groups had similar demographic characteristics.

The incidence of positive blood microbiologic cultures was similar in both arms - 40% for jugular vs 37% for subclavian (p=0.55). Figure 1 shows the cumulative incidence of BSI depending on insertion site. The confirmed CLABSI were more common in jugular than subclavian CVC - 16% vs 9% (OR Jugular vs Subclavian: 2.0 (0.9-4.5), p=0.095). The differences in CLABSI per 1000 days of CVC use favoured subclavian over jugular site (7.93/1000 days for jugular vs 2.79/1000 days for subclavian, p=0.002). There was one case of infection at the catheter exit site in subclavian arm. The frequency of all non-infectious complications was similar in both arms - 13% in jugular and 12% in subclavian (OR Jugular vs Subclavian: 1.1 (0.5-2.5), p=0.8).

Conclusions: This multicentre prospective study shows statistically significant lower confirmed CLABSI per 1000 days of CVC use without the higher risk of non-infectious complications related to subclavian insertion site in allogenic HSCT recipients.



[Cumulative BSI occurrence depending on CVC insertion site]

Disclosure: Nothing to declare.

P364

Infection Prevention Practices among EBMT Hematopoietic Cell Transplant Centers: A Survey of The Infectious Diseases Working Party of the EBMT

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Background: Patients undergoing HCT are at increased risk for infections. We aimed to describe the current status of infection prevention practices among EBMT transplant centers.

Methods: Questionnaires were designed and distributed to all EBMT transplant centers to capture clinical practices regarding anti-microbial prophylaxis, for patients undergoing auto and allo HCT.

Results: Of 553 transplant centers, 109 (20%) (adult, n=71; pediatric, n=18; both, n=20) responded with a completed questionnaire.

In alloHCT, G-CSF is provided in 52% of centers to enhance engraftment. Bacterial prophylaxis (BP) is employed in 72% of centers, primarily (77%) with quinolones, followed by beta-lactams, initiated concomitantly with the conditioning therapy (69%) and discontinued upon engraftment (63%). In patients without aGVHD, BP is continued in 43% of centers, with penicillin (52%) and/or quinolones (34%), throughout a year or more in 42%. In patients with aGVHD, BP is given in 48% of centers, with penicillin (42%) and/or quinolones (38%). BP is given to patients with cGVHD in 52% of centers. Systemic fungal prophylaxis (FP) is used by 84%, primarily with (66%) fluconazole, followed by voriconazole or posaconazole (20%) and echinocandines (12%). Without aGVHD, FP is maintained by 55%, until day 100 (67%) or until discontinuation of immunosuppression (IS) (20%). In the presence of aGVHD, FP is given by 97%, most often (50%) with posaconazole, until prednisone dose declines below 20 mg/d (15%), discontinuation of steroids (30%) or IS (22%). In the presence of cGVHD, FP is used by 86%. Posaconazole and voriconazole blood levels are monitored routinely by 40% of centers.

Viral prophylaxis (VP) against HSV is used by 99%, mainly (80%) with acyclovir, most often (41%) until discontinuation of IS; CMV prophylaxis is used by 19%, mostly (88%) by acyclovir/valacyclovir; VZV prophylaxis by 89%, during 1 year and/or until discontinuation of IS and/or resolution of chronic GVHD.

PCP prophylaxis with TMP-SMX is given by all centers.

IVIG is used by 85%, based on gamma-globulin serum levels (IGG< 400 mg%) with (15%) or without (63%) recurrent infections.

In autoHCT, G-CSF is provided in 78% of centers. BP is employed in 61% of centers, primarily (97%) quinolones, discontinued upon engraftment (92%). BP is continued only by 9%, with quinolones (89%) and/or beta-lactams (67%), up to 1 year.

FP is used by 71% of centers, primarily (78%) fluconazole until engraftment (92%).

VP against HSV and VZV is used by 90% and 63%, respectively, mostly (86%) acyclovir, up to 1 year. CMV prophylaxis is used by 7% of centers.

PCP prophylaxis with TMP-SMX is given by 83%, usually (85%) up to 6 months.

IVIG is used by 57%, based on gamma-globulin levels (IGG< 400 mg%) with (18%) or without (38%) recurrent infections.

Importantly, neither BP nor AP are used in 14% and 15% of centers, after alloHCT and autoHCT, respectively.

Conclusions: The survey shows a wide variety of prevention practices among transplant centers. The degree and causes of discordance between actual prophylaxis practices and evidence-based guidelines should further be explored.

Acknowledgement: We thank all the participating EBMT centers for their contribution.

Disclosure: Nothing to declare.

P365

HEV Infection In HCT Recipients - Retrospective Study of Infectious Diseases Working Party (IDWP) of EBMT

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Background: Hepatitis E virus (HEV) in industrialized countries is an emerging autochthonous infection. HCT recipients may be at particular high risk due to the possibility of acquiring the infection through transfusion and developing chronic infection. The aim of this study was to report the epidemiology and management of HEV infection in HCT recipients.

Methods: All EBMT centres were invited report cases of HEV infection in this retrospective IDWP study.

Results: From 06/02/2019 to 21/10/2019, 10 centres reported 30 cases of HEV infection (the Netherlands, 15; Germany 6; Switzerland, 5; Italy, 2; France, 2) (table 1); 17 (57%) were acute and 12 (43%) chronic HEV infections, with acute cases more frequent among patients from Germany and Switzerland (>80%).

In 93% of patients HEV-RNA tested positive, in 2 cases of acute infection only serology was performed. In 16 patients with provided HEV-RNA value the median level was 1.263.300 cp/ml (range, 60-1x1.8^8). IgG and IgM testing was performed in 10 and 13 patients with positive HEV-RNA, and resulted positive in 5 (50%) and 8 (62%).

The median leucocyte number was 6.4, only 2 patients were neutropenic (< 1000), 12 were thrombocytopenic, the median ALT and AST levels were 354 and 126 IU/ml, and the maximum ALT level during HEV infection was 1234 (106-2234). Patients with acute infection had significantly higher ALT levels at diagnosis compared to those with chronic infection (median 320, range: 24-1529 vs. 124, range: 17-354, p=0.014)

Extrahepatic manifestations were present in 5 patients: thrombocytopenia in 4 with pancytopenia, asthenia and encephalopathy in 1 case each, and haemolytic anaemia in 1.

The most probable reported source of infection was food (meat) in 9, transfusion in 7, and unknown in 14.

Upon the diagnosis of HEV infection, 6 patients had their immunosuppression reduced (20% in total, 24% among autologous and 15% among allogeneic HCT recipients), 12 received only ribavirin and in 1 both management strategies were provided.

Overall, 13 patients (43%) were treated with ribavirin (46% of these with acute infection and 54% of chronic), at a median dose of 800mg/day (range, 400-1800) and 10mg/kg/day. Four (31%) developed side effects: haemolytic anaemia in 2, neuropsychiatric effects and cytopenia in 1 each; which led to treatment discontinuation in 3 (23%).

HEV cure occurred in 26 patients (87%; 88% in acute and 85% in chronic infection; 85% ribavirin treated, 88% not treated), persistence was observed in 3 and relapse in 1.

Characteristics	Total, n=30	Acute leukaemia	8 (27%)	First HCT	23 (77%)	Reduced intensity conditioning	16 (64%)	aGvHD grade 2 or more before HEV	7 (28%)
Age at HCT (years), median (range)	49 (9-69)	Lymphoma	9 (30%)	Autologous	5 (17%)	T-cell depletion	12 (40%)	cGvHD before HEV	7 (28%)
Male	15 (50%)	Complete remission at HCT	16 (53%)	Allogeneic	25 (83%)	Median time from HCT to HEV infection, months (range)	4.5 (-3, 182)	Immunosuppressive therapy at the diagnosis of HEV infection	19 (63%)

[Patients' characteristics]

At the last follow up (32 months after HCT, range: 7-204), 9 patients (30%) were dead, with 1 due to infections with possible HEV-associated liver failure (3%).

Conclusions: There are geographical differences in HEV infection in general, and in the proportion of acute and chronic cases. Ribavirin treatment was provided to less than half of patients, both with acute and chronic infection, with one-third developing side effects. High cure rate and low mortality were observed.

Disclosure: Nothing to declare.

P366

The Role of Combination Prophylaxis in Preventing Cytomegalovirus (CMV) Infection after Ex Vivo Ab t-cell-depleted Haploidentical Hematopoietic Cell Transplant (HHCT) in Children

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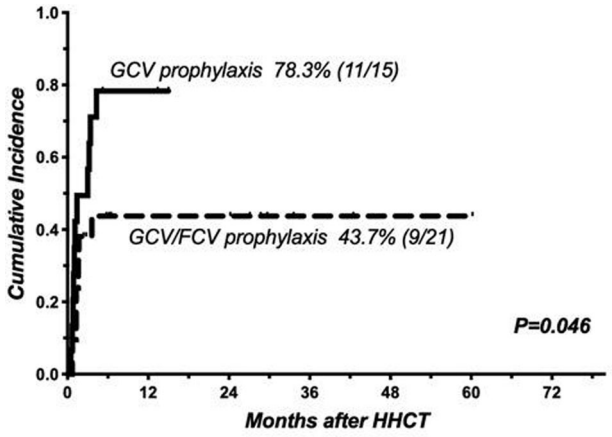
Background: Although haploidentical hematopoietic stem cell transplantation (HHCT) technique is constantly improving, CMV has always been one of the major concerns. However, few studies have examined CMV infection in these clinical settings, especially in the field of HHCT. This study evaluated the efficacy of ganciclovir (GCV), alone and in combination with foscarnet (GCV/FCV), for CMV prophylaxis in pediatric patients receiving ex vivo ab T-cell-depleted HHCT.

Methods: The medical records of 81 pediatric patients (36 non-malignant and 45 malignant disorders) who underwent their first HHCT using ex vivo ab T-cell-depleted grafts were reviewed. The GCV group received CMV-target prophylaxis with GCV during the conditioning period. Low dose acyclovir was given from day one post-transplant until engraftment. Ganciclovir or valganciclovir was administered thereafter until post-transplant day 100, and the CD4+ cell counts had recovered. The GCV/FCV group received GCV during the conditioning period with FCV starting from post-transplant day one until engraftment was confirmed. The valganciclovir was given thereafter.

Results: CMV reactivation occurred in 40 patients (50.8%) at a median of 41.3 days after HHCT. In univariate analysis of risk factors for CMV reactivation in non-malignant patients, GCV/FCV compared to GCV prophylaxis (p=0.046) and higher graft $CD3^{+}\alpha\beta^{+}T$ cells (p=0.047) showed a significant effect for preventing CMV reactivation. In multivariate analysis, GCV/FCV prophylaxis remained its significance (HR 0.396, 95% CI 0.162-0.970, p=0.043). Higher graft $CD3^{+}\alpha\beta^{+}T$ cells also showed a trend of effect on CMV prevention, although they did not reach statistical significance (HR 0.932, 95% CI 0.150-1.024, p=0.056). Higher $CD34^{+}$ cell counts of the graft were associated with higher CMV reactivation in patients with malignant disease (p=0.025). The significance was maintained in the multivariate analysis also (HR 3.370, 95% CI 1.073-10.591, p=0.038). For CMV disease, acute graft-versus-host disease (GVHD) was related to an increased risk of CMV disease in patients with malignant disease (p=0.043). During the study period, 8 cases were evaluated for antiviral resistance. There were 3 cases of the proven antiviral resistant strain. All strains expressed UL54 mutations. Two strains were resistant to both GCV and FCV, while one strain was resistant to FCV only. All three resistant strains were isolated from patients who received GCV prophylaxis. There was no significant difference in renal toxicity between GCV and GCV/FCV group

Conclusions: We conclude that GCV/FCV combination prophylaxis effectively prevents CMV reactivation in ex vivo ab T-cell-depleted HHCT, especially in patients

with non-malignant diseases. The GCV/FCV prophylaxis showed tolerable toxicity and not increasing the risk of developing antiviral resistant strain.



[The incidence of CMV reactivation in non-malignant disorders according to prophylaxis strategy]

No	Diagnosis	Mutation	Resistant antiviral agent	Prophylaxis group
1	ALL	Wild type (UL54, UL97)		GCV/FCV
2	AML	Wild type (UL54, UL97)		GCV/FCV
3	MDS	Wild type (UL54, UL97)		GCV/FCV
4	SAA	Wild type (UL54, UL97)		GCV/FCV
5	SAA	Wild type (UL54, UL97)		GCV/FCV
6	SAA	UL54-L822M	GCV/FCV	GCV
7	SAA	UL54-V715M	FCV	GCV
8	vSAA	UL54-V787L	GCV/FCV	GCV

[Genetic study for antiviral resistant strain]

Disclosure: Nothing to declare.

P367

Comparison of Immune Cell Response to Cytomegalovirus Proteins Versus Peptides using an IFN-γ Elispot Assay to Monitor cytomegalovirus-specific Immunity after Hematopoietic Stem Cell Transplantation

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Background: Impaired cytomegalovirus (CMV)-specific cellular immunity (CMV-CMI) is a major cause of uncontrolled CMV reactivation and associated complications in hematopoietic stem cell transplantation (HSCT). Reliably assessing CMV-CMI is desirable to individually adjust antiviral and immunosuppressive therapy. Standardized IFN-γ ELISpot assays based on the stimulation of peripheral blood mononuclear cells (PBMC) with pp65 and IE-1 CMV antigens can monitor CMV-CMI in immunocompromised patients. To better characterize the functionality of such assays, we compared the response of PBMC to CMV proteins versus respective peptides.

Methods: As part of a prospective, longitudinal, observational, multicenter study (AlloProtectCMV), IFN-γ ELISpot assays were performed on isolated PBMC stimulated in parallel either with T-activated® IE-1 and pp65 proteins (T-Track® CMV) or with the respective overlapping peptides. Quantitative (SFC/200,000 PBMC) and qualitative (positive/negative) test results of 39 paired assays from 15 HSCT recipients (10 D-/R+, 4 D+/R+, 1 D+/R-) were compared and evaluated in relation to the occurrence of CMV reactivation and disease, CMV viral load, total CD8+ counts as determined by flow cytometry from the same PBMC preparation, and occurrence of GvHD up to 7.5 months after transplantation.

Results: 29/39 (74.4%) overall test results (considering the response to both IE-1 and pp65) based on proteins vs peptides were concordant. The responses to pp65 proteins and peptides were comparable and the qualitative test results highly concordant (35/39 or 89.7%). By contrast, the response to IE-1 peptides was significantly higher than that to IE-1 protein (MWU p=0.001; Figure 1) and the respective qualitative test results showed lower overall agreement (26/39 or 66.7%). With a few notable exceptions,

quantitative test results in response to proteins and peptides were however in close range and discordant results were mainly borderline positive/negative tests. Strikingly, three IE-1 test results were truly discordant (orange circles). These were successive test results from one D-/R+ high-risk patient with CMV disease and high persistent viral load, together with high CD8+ counts, high IE-1 peptide response (75-514 SFC/200,000 PBMC) and sustained negative T-Track® CMV test results (IE-1 and pp65 protein responses < 2 SFC/200,000 PBMC).

Conclusions: Altogether, IFN-γ ELISpot response to CMV proteins and peptides were highly concordant. One out of 15 patients showed conflicting ELISpot test results in response to IE-1 peptides, possibly due to the concomitant elevated CMV viral load and total CD8+ counts which might measure the in vitro response of otherwise non-functional CMV-specific CD8+ T cells. Our data support the proposition that CMV proteins might more closely mimic the natural response to CMV infection (including the uptake, processing and presentation of antigens to specific T cells) and thus more accurately monitor the functionality of CMV-specific cellular immunity in immunocompromised transplant recipients.

Clinical Trial Registry: AlloProtectCMV (ClinicalTrials.gov identifier: NCT02156479); https://clinicaltrials.gov/ct2/show/NCT02156479

Disclosure: The participating clinical and measurement centers received research funding from Lophius Biosciences for this study. Ludwig Deml, Sascha Barabas, Traudel Schmidt, Harald Guldan and Anne Rascle are employees of Lophius Biosciences. Ludwig Deml is co-founder and Chief Scientific Officer of Lophius Biosciences. Ralf Wagner is Chairman of the Board of Lophius Biosciences. Ralf Wagner, Ludwig Deml and Sascha Barabas are shareholders of Lophius Biosciences GmbH.

P368

Human Herpesvirus Type 6 Reactivation after Haploidentical Hematopoietic Cell Transplantation: Risk Factors and Clinical Impact

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Background: Human herpesvirus type 6 (HHV6) reactivation is common after conventional allogeneic hematopoieticcell transplantation (HCT). However, few studies have assessed the risk factors for developing HHV6 reactivation and its impact on clinical outcomes after haploidentical (HAPLO) HCT with high-dose post-transplantation cyclophosphamide (PTCY).

Methods: We retrospectively evaluated 100 consecutive patients receiving a HAPLO with PTCY at our institution between January 2013 and December 2017. HHV6 plasma loads were monitored weekly by quantitative PCR during at least one month after transplantation.

Results: The median age at transplant was 51 (range 15-76) years and 61% of the patients were males. The median follow-up period was 36 months (range 11-76). The main indication for transplantation was acute leukemia (63%) and 46% of the patients were in complete remissionat the time of transplantation. Conditioning regimen was reduced intensity in 30%, myeloablative in 27% and sequential in 43%. Graft-versus-host disease (GvHD) prophylaxis consisted of PTCY, cyclosporine A and mycophenolate mofetil. In addition, 86% of the patients also received low-dose antithymocyte globulin. Graft source was predominately (76%) peripheral blood stem cells. The median absolute lymphocyte count (ALC) was 0.29 (range 0-0.67*10^9 cells/L) at day +30. HHV6 reactivation occurred in 56 % of the patients, at a median of 20 days (range day +8 to +122) after HAPLO. Cytomegalovirus (CMV) reactivation occurred in 53% of the patients and 31% had concomitant CMV and HHV6 reactivation. The cumulative incidence of CMV reactivation was 29%, 51% and 52% at day 30, 60 and 100, respectively. HHV6 reactivation was not associated with a higher incidence of CMV reactivation(p =0.59). Antiviral treatment (foscarnet, ganciclovir or cidofovir) was administered to 55% of the patients with HHV6+ but the majority (87%) of the treatments were initiated for other viral reactivations that were concomitant with HHV6, mainly for CMV. Six patients (6%) received a viral therapy specifically for HHV6 clinical manifestations: colitis (n=3), encephalitis (n=2) and liver disorders (n=1).

HHV6 reactivation was significantly more frequent in recipients with a low ALC at day +30 (below the median, ≤0.29*10^9 cells/L; p=0.002). Furthermore, HHV6 reactivation was associated with an inferior platelet recovery (50 G/L) at day +180 (HR 1.89, 95% CI 1.19-3.03; p< 0.007) in multivariate analysis. The cumulative incidence of acute grade II-IV GvHD was higher in case of HHV6 reactivation (39% versus 9%, p< 0.001). This finding was confirmed in multivariate analysis (HR 5.89, 95% CI 2.09-17.24; p< 0.001). HHV6 reactivation was more frequently observed in patients who experienced grade III-IV acute GvHD (n=12/13) (p=0.005). No significant impact on median ALC on day +90 or +180, chronic GvHD, overall survival,

progression-free survival and non-relapse mortality with respect to HHV6 reactivation was observed.

Conclusions: Our findings indicate that HHV6 reactivation is more frequent in patients with lower absolute lymphocyte count on the first 30 days after HAPLO with PTCY. Although HHV6 reactivation has no impact on survival outcomes it is associated with delayed platelet recovery at day + 180 and higher incidence of acute GvHD.

Disclosure: No disclosures to declare.

P369

Safety and Efficacy of Brincidofovir for Refractory Adenovirus Infection in Children Receiving Allogeneic SCT: A Retrospective Analyses from The Italian Pediatric Hematology Oncology Association (AIEOP)

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Background: Adenovirus (ADV) represents a major infectious complication after allogeneic hematopoietic stem cell transplantation (HSCT) in children, with up to 30% of mortality rate. Risk factors include: undelying disease, poor immune reconstitution, MUD or cord blood transplant, in-vivo or ex-vivo T-cell depletion and GvHD. Within the few therapeutic strategies, Cidofovir (CDV) is the only available approach. Brincidofovir (BCV, CMX001) is an orally bioavailable lipid-conjugate of CDV, effective against double-strand DNA viruses and with a lower toxicity profile. We report a retrospective analyses from AIEOP centers on use of BCV in transplanted children with CDV-refractory ADV infection.

Methods: 28 transplanted children (21 males) developed ADV infection. The median age at transplantation was 10 years (range: 9 months-19 years); underlying diseases were: acute lymphoblastic leukemia (ALL) (n=11), acute myeloid leukemia (AML) (n=6), non-Hodgkin lymphoma (NHL) (n=2), myelodisplastic syndrome (MDS) (n=1), chronic myeloid leukemia (CML) (n=1), juvenile myelo-monocytic leukemia (JMML) (n=1), immune deficiency (ID) (n=2) and other non-malignant diseases (n=4; 2 Fanconi's anemia, 1 aplastic anemia, 1 adrenoleukodystrophy). Donors were: haploidentical in 15 patients, MUD in 10, cord blood in 2, matched sibling in 1. Within patients with malignant disorders,11 patients were in first complete remission (CR) and 11 in ≥ II CR. 11 patients were receiving a second allogeneic HSCT. 27/28 patients received antiviral prophylaxis with Aciclovir. ADV viremia was checked once or twice a week by quantitative PCR. Organ samples were analyzed according to clinical symptoms.

Results: We registered 47 ADV infection episodes with positive viremia (median peak: 1.077.546 copies/mL, range: 15.100-75.000.000). Acute GVHD incidence was 46%, with 7 cases of grade > II. First ADV infection episode occurred at a median time of 3 months after HSCT (range: 20 days-14 months); 61% were receiving Cyclosporine and 61% had diarrhea. 38/42 episodes were characterized by organ diseases: enteritis (N=29), hepatitis (N=5), upper respiratory tract infections (N=3), pneumonia (N=4), and hemorrhagic cystitis (N=6). 22/47 episodes were treated with CDV (6 mg/Kg/week) as first line treatment and in 5 it was continued for a median time of 4 weeks (range: 1-12). A complete response (CR) with viremia negativization, a partial response (PR) with 2/3-log viremia reduction and a stable disease (SD) have been observed in 7, 1 and 2 patients respectively. Disease progression (DP) occurred in 12 patients. BCV (4mg/Kg/week) was used as first line treatment in 6 episodes and as rescue after Cidofovir failure/SD in 14 episodes, for a median of 2 weeks (range: 4 days-12 weeks). In 18/20 evaluable episodes, we observed 9 CR with negative viremia, 2 PR, 2 SD and 5 DP. At a median follow-up of 7.5 months (range: 1-43), 8 patients are alive in CR, 10 patients died of relapse and 10 of TRM, which was referred to ADV infection in 4. Overall ADV mortality rate was 14%.

Conclusions: BCV resulted effective and well-tolerated in treating CDV-refractory ADV infection in very high risk children after HSCT, the overall BCV response rate being 72%. BCV deserves to be tested in a prospective study.

Disclosure: No conflict of interest to disclose

P370

Subcutaneous Immunoglobulin Replacement Therapy in Patients who underwent Allogeneic Hematopoietic Cell Transplantation (HCT): A Prospective Study to Measure Feasibility, Safety and Health Care Resource Use

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Background: Allogeneic hematopoietic cell transplant (HCT) recipients are at an increased risk of infection secondary to hypogammaglobulinemia. Many centers administer intravenous immunoglobulin (IVIG) as replacement therapy to reduce the risk of infections. However, IVIG is costly, requires ambulatory infusion and ancillary nursing support. Subcutaneous immunoglobulin (SCIG) represents an alternative, allowing for self-administered home-based therapy. We evaluated feasibility, safety and total resource use of home-based SCIG administration in an allogeneic HCT population over a 6-month period. Safety, efficacy and overall cost were compared to a historical IVIG control group.

Methods: A total of 49 patients were approached, 20 of whom (41%) consented. Eligible patients were treated with SCIG (Hizentra, CSL Behring) at 0.1 g/kg/week for up to six months. Patients were matched by age (± 5 years) to a historical control group of 20 patients who received IVIG during the same 6-month period. Clinical outcomes collected were adverse reactions and infectious complications. Health care resource data collection included the number of doses delivered, IVIG infusion chair time, infection-related consultations, laboratory and diagnostic tests, hospitalizations and all antimicrobials used. Indirect costs were not considered. Quality of life (QOL) was measured using the EQ-5D scale. A patient satisfaction questionnaire was administered for those who completed the ScIG arm of the study. ClinicalTrials.gov Identifier: NCT03401268.

Results: Groups were comparable in terms of age, weight, gender and type of transplant. Of the 20 patients on ScIG, 14 transitioned from IVIG while 6 started ScIG as initial Ig replacement therapy. Median age in the ScIG group was 56 years (range 25-70). Median time from HCT to the start of the study was 36.5 months in ScIG patients versus 35 months in IVIG patients. Of the 20 ScIG patients, 5 (25%) had skin GVHD. Patients in the ScIG group received a median of 26 doses (6 g weekly) compared to 6 doses (27.5 g/4 weeks) in the control group. All 20 IVIG patients completed 6 months of therapy compared to 13 of 20 (65%) ScIG patients. Among the 7 patients who did not complete 6 months of therapy, 5 withdrew (3 cited intolerance and 2 were non-compliant) and 2 patients died from HCT-related complications.

There were no adverse reactions in the IVIG group, compared to 7 (35%) of patients who received ScIG. All adverse events were topical infusion-related grade I, transient and required no medical intervention. There were 24 infectious events in ScIG patients compared to 10 in IVIG patients, resulting in 41 and 9 days of hospitalization, respectively. Median cost was significantly lower with ScIG compared to IVIG ($9,756 vs. $13,780; $p = 0.046$). ScIG patients reported median preference and satisfaction scores of 100%. Over the 6-month period, the EQ-5D scores indicated stability in patient QOL.

Conclusions: ScIG was associated with a significant reduction in total health care costs compared to IVIG. Cutaneous GVHD did not impair ScIG administration. Patients were able to incorporate ScIG therapy into their weekly routine, with administrations being successfully performed at home.

Clinical Trial Registry: ClinicalTrials.gov Identifier: NCT03401268

Disclosure: Nothing to declare.

P371

Infectious Complications in Patients with Relapsed/refractory Hodgkin's Lymphoma after New Agents' Therapy and Allogeneic Stem Cell Transplantation

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Background: The introduction of new agents in the treatment of relapsed/refractory Hodgkin's lymphoma (r/r HL) increased the frequency of complete or partial responses. The infectious complications in r/r HL patients treated with the new agents after allo-HSCT has not been studied extensively.

Methods: Single center prospective observational study included 86 patients with relapsed/refractory HL who received allo-HSCT from 2002 to 2018. The median age was 27 (13-49) y.o., children (< 18 yo) - 13% (n=11). Allo-HSCT from MUD was performed in 45,4% (n=39), MRD - 24,4% (n=21), MMUD - 15,1% (n=13), haplo - 15,1% (n=13), with RIC (100%) and predominantly PTCY-based GvHD prophylaxis (71%). In 66% (n=57) patents recieved therapy with the new agents before allo-HSCT: nivolumab (nivo) - 8,7% (n=5), brentuximab vedotin (BV) - 59,6% (n=34) and combination nivo and BV - 31,6% (n=18).

Chemotherapy like "bridge-therapy" was used in 34% (n=29). In analysis considered only microbiologically confirmed infection episodes, invasive fungal disease (IFD) according the EORTC/MSG 2008 criteria. Infection episodes and outcome analysis evaluated events during one year after first allo-HSCT.

Results: In 45 r/r HL patients after allo-HSCT 90 infection episodes were registered: bacterial infections - 38,8% (n=35), IFD - 14,5% (n=13) and viral infections - 46,8% (n=42). The incidence of documented bacterial infections in the standard group (without new agents) was 34% (n=10), in the group with nivo and BV - 43,8, (p=0,4). Sepsis developed in 20% (n=6) vs 14% (n=8) in standard and new agents groups, respectively. The main etiology agent of sepsis was Klebsiella pneumonia (33% vs 25%) in both groups. The incidence of viral infections in standard group was 58% (n=17), in patients with nivo and BV - 43,8% (n=25) (p=0,19). The main etiology agent in both groups was CMV (88% vs 76%) with the main site of infection blood (100%). Reactivation of CMV developed more frequently in the standard group patients than after nivo+BV before allo-HSCT 51,7% vs 22% (p=0,04). The incidence of IFD in standard group was 20,6% (n=6), in new agents group - 12% (n=7) (p=0,3). The main etiology agent was Aspergillosis spp.: 66% (n=4) vs 85,7% (n=7) in standard and new agents groups. The main site of infection was lung (92%). The 1-year overall survival (OS) in patients with HL after allo-HSCT was 74,7%. Development of infectious complications after allo-HSCT do not decrease the 1-year OS rate: 71,4% - with infections vs 77,1% - without infections, p=0,381). Incidence of death attributive with infections in group with new agents and without was 3,5% vs 10,3% (p=0,248), respectively.

Conclusions: New agents in therapy r/r HL did not impact the development of infectious complications after allo-HSCT. Patients with chemotherapy prior allo-HSCT had higher incidence of CMV reactivation than patients with bridging therapy with nivo and BV (p=0,04). Development of infectious complications after allo-HSCT with current group size did not significantly impact the 1-year OS rate: 71,4% - with infections vs 77,1% - without infections, p=0,381). Incidence of death attributive to infections in the group with new the agents and without was 3,5% vs 10,3% (p=0,248), respectively.

Disclosure: Nothing to declare.

P372

Surveillance For Reactivation of *Toxoplasma Gondii* using Polymerase Chain Reaction Assay and pre-emptive Therapy Avoids Universal Prophylaxis and Prevents Symptomatic Infection

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Background: In patients undergoing an allogeneic stem cell transplant(allo-SCT), reactivation of Toxoplasma gondii occurs during periods of profound immunosuppression. In 2015, our center had three fatalities that were proven to be secondary systemic toxoplasmosis infection occurring early post allo-SCT. This prompted the introduction of a surveillance program using PCR and preemptive treatment of Toxoplasma gondii (T.gondii) reactivation. We report our experience using this screening and pre-emptive treatment approach.

Methods: All patients and donors undergo routine testing for previous exposure to T. gondii during transplant work-up, sero-positive recipients were identified as at a high risk of T. gondii reactivation irrespective of the donor serology. High risk patients were tested once weekly using a polymerase chain reaction (PCR) assay on whole blood from D+10 until cessation of immunosuppression. Any patient positive by PCR received standard anti-toxoplasmosis therapy with pyrimethamine and sulfadiazine, plus folinic acid until the PCR was negative.

For this analysis the end points were, T. gondii reactivation as evidenced by a positive PCR, outcome of therapy/intervention. Data were locked in October 2019.

Results: A total of 160 patients underwent an allo-SCT in the period between August 2016 and October 2019; 28 (17.5%) patients were considered high risk based on pre-transplant serology. Median age of the high risk population was 60 years. 17 patients had a 10/10 unrelated matched donor (VUD), 4 patients had 9/10 VUD,1 patient an 8/10 VUD, and 6 patients had a sibling matched donor.5/28 (17.8%) patients became PCR positive during monitoring. Median day of reactivation was day +29 post allo-SCT, range day +20 to + 96. None of the patients had symptoms of infection. PCR positive patients received prompt anti-toxoplasmosis treatment. All patients (5/5) were treated successfully, achieving a complete response (DNA negative by PCR). Median duration to achieve a response was 14 days. At the time of analysis 4/5 patients remain alive with one death due to disease relapse. No patients died from T. gondii related disease.

Conclusions: The use of risk stratification and surveillance PCR detected reactivation episodes of T. gondii before the development of symptomatic disease. Prompt treatment was effective in all cases with a return to PCR negativity. No patients developed symptoms.

Based on our experience we recommend assessment of toxoplasma serology and T.gondii risk stratification. High risk patients should have routine surveillance once weekly using PCR and preemptive therapy started when T. gondii DNA is detected by PCR. This policy was successful for early diagnosis of toxoplasmosis reactivation and prevention of the non-relapse mortality secondary to systemic toxoplasmosis. Moreover it has the advantage of avoiding toxicities of applying universal prophylaxis.

Age/ sex	Initial diagnosis	Transplant type (donor)	Days post allo-SCT to reactivation	Outcome
34/ Female	Hodjkin lymphoma	9/10 VUD	20	Alive - CR
58/ Male	T-Acute lymphoblastic leukemia	10/10 VUD	96	Death -Relapse
52/ Male	Acute promyelocytic leukemia	10/10 VUD	29	Alive - CR
20/ Male	Secondary Acute myeloid leukemia	10/10 VUD	90	Alive - CR
58/ Male	Biphenotypic acute leukemia	10/10 VUD	18	Alive - CR

[Patients and transplant characteristics of High risk patients who had Toxoplasma reactivation post allo-SCTdetected by PCR.]

Disclosure: None

P373

Cytomegalovirus (CMV) Impact on Clinical Outcomes and Resource use after Allogeneic Hematopoietic Cell Transplantation: The Influence of Recurrent Episodes of CMV Infection

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Background: Despite pre-emptive therapy (PET), Cytomegalovirus infection (CMVi) poses a negative impact on the outcome of allogeneic HCT recipients, and potentially on the use of resources for patient management.

Methods: This retrospective study analyses the impact of CMVi on clinical outcomes and resource use including hospital length of stay (LOS) in consecutive allogeneic HCT recipients (2009-2018), with a particular focus on recurrent CMVi episodes.

Results: 237 allogeneic HCT in 224 recipients were included: 138 men (58.2%); median age 45 years (16-69); 56.5% AML/MDS, 16% ALL, 15.6% chronic lymphoproliferative disorders, 6.3% myeloma and 5.5% other; 43.5% matched related, 30% cord-blood, 18.1% unrelated and 8.4% haploidentical donors; 52.3% myeloablative conditioning; 200 (84.4%) at risk of CMVi (donor and/or recipient positive serology); 74 (31.2%) had acute GvHD grades II-IV. CMV disease occurred in only 7 cases (3%; 3 pneumonia, 3 colitis, 1 multiorgan). Cumulative incidence of first CMVi was 54.85%, at a median day +35 post-HCT (23-56), and had an impact on overall survival (46.9% vs 61.4% at 2 years; p=0.024). Patients above median age had higher CMVi rates (51% vs 39% at 3 months and 65% vs 45% at 1 year; p=0.021). Compared to matched-related HCT, cord-blood and haploidentical HCT-recipients had higher CMVi rates (57% vs 39% at 3 months and 66% vs 49% at 1 year; p=0.001) and earlier onset (70% vs 32% within day +35 post-HCT; p< 0.001). Acute GVHD also increased CMVi rates (55% vs 41% at 3 months and 79% vs 46% at 1 year; p< 0.001). Among patients with a first CMVi, 49.2% had ≥2 and 13.5% had ≥4 recurrent CMVi episodes. CMVi recurrence ≥2 was also higher in cord-blood and haploidentical versus matched related HCT (HR 2.38; 95%CI 1.61-3.52; p< 0.001), age at the time of HCT (+1.6% per year OR HR 1.02 (1.016); 95%CI 1-1.03; p=0.024) and acute GVHD (HR 2.3; 95%CI 1.62-3.26; p< 0.001). Although most patients responded to first or subsequent lines of preemptive therapy, the rate of adverse effects derived from CMVi treatment increased from 27.6% with first-line to 50% after second-line. In terms of clinical burden, hospital LOS throughout the first year post-HCT was overall >30 days longer in patients with CMVi (vs without, p< 0.001; see attached). This increase in LOS was >45 additional days in patients with ≥2 recurrent CMVi, significantly higher than in those with only one CMVi episode (30 days; p< 0.001).

Conclusions: Despite preemptive therapy, CMVi remains a hurdle to the success of allogeneic HCT, with a significant impact on patients' outcome and use of resources. Recurrent CMVi episodes are very frequent, in particular in high-risk HCT-groups such as cord-blood, haploidentical and acute GVHD, pose a significant impact on outcomes and hospital LOS, and should be incorporated in registry studies and clinical trials in this field to provide a

full picture of the impact of CMVi on allogeneic HCT recipients and it's burden for the HCT program.

[Impact of CMV infection and recurrent infections on hospital admission length of stay.]

Disclosure: Nothing to declare.

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Fecal Microbiota Transplantation in Children to Treat Acute GVHD or multi-drug Resistant Bacteria Colonization

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Background: Fecal microbiota transplantation (FMT) is emerging as a new strategy to treat several medical conditions. In the HSCT setting the administration of healthy donor's fecal preparation has been explored to treat steroid-resistant acute GVHD (Kakihana et al., Blood 2016) or gut colonization by multi-drug resistant (MDR) bacteria (Bilinski et al., Clin Infect Dis 2017). Despite encouraging preliminary results in adults, no data are available in children.

Methods: Herein, we report on 7 pediatric patients (age range 1.4-18 years), 5 colonized by multi-drug resistant germs (4 patients by Enterobacteriaceae and 1 patient by Pseudomonas aeruginosa) and 2 affected by steroid-resistant acute GVHD (srGVHD), who received FMT at Bambino Gesù Children's Hospital on a compassionate use basis between March 2017 and August 2019 (Table 1 reports detailed patients and transplants characteristics).

Fecal microbiota donor was a relative or, in case of non-eligibility, an unrelated donor. Donor screening was performed according to European consensus guidelines on FMT (Cammarota et al. Gut 2017). FMT infusion was performed via esophagogastroduodenoscopy (EGDS), and stool emulsion placed in the duodenum. Four patients undergoing FMT for MDR decolonization received a three-day course of oral colistin before FMT to improve efficacy of the procedure.

Results: 9 infusion were performed (1 in each patient in need of decolonization and 2 in patients with acute GVHD); 3 from relatives and 6 from unrelated donors. The procedure was well tolerated and adverse events were mild in all cases except one; indeed, at the end of the first infusion, a 1.4-year old patient with acute srGVHD presented fever, chills and malaise. Blood test showed metabolic acidosis and a sharp increase of inflammatory markers; despite the seriousness of the clinical picture he recovered completely in the following 24 hours. A broad-spectrum antibiotic therapy was started, but all the blood cultures, as well as septifast® and t2 bacterial panel, resulted negative. One MDR colonized patient experienced a culture-proven sepsis (due to the colonizing bacteria) during the aplasia after hematopoietic transplantation.

Regarding efficacy, of the 2 patients with srGVHD one had a partial response after the first infusion and a transient complete response after the second administration, while the second did not respond to any of the 2 infusions. Of the 5 patients with MDR colonization, 4 achieved MDR decolonization within one week after the procedure, while at 1-month follow-up only 1 patient was decolonized.

Gut microbiota profiling showed a significant modification of recipient composition already one week after fecal transplantation, mimicking the donor's features. We also demonstrated a significant increase in the number of regulatory T cells and in the ration Treg/CD8+ in patients with srGVHD.

Conclusions: FMT before HSCT to eradicate MDR bacteria and after HSCT to treat srGVHD is feasible also in the pediatric setting. Safety profile seems good in patients colonized by MDR, while in those with active GVHD caution is needed. The number of patients in the cohort is limited to draw firm conclusions regarding efficacy; however, multiple infusions may be required to achieve long-term MDR bacteria decolonization.

Disclosure: Nothing to declare.

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Vaccination Against Tick-borne Encephalitis (TBE) after Autologous and Allogeneic Bone Marrow Transplantation

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Background: Tick-borne encephalitis, (TBE), is an emerging infection in Sweden and several other countries on the Eurasian continent. Severe disease and deaths are more common in immunocompromised hosts. TBE vaccination has not been evaluated after allogeneic (allo-) or autologous (auto-) stem cell transplantation (SCT).

Aims: To investigate feasibility, side effects and humoral response of four doses of TBE vaccine administered to patients after allo- and autoSCT.

Methods: Patients (n=104) were included at Sahlgrenska and Karolinska University Hospitals and at Uddevalla, Borås and Varberg hospitals, Sweden, median age 61 (24-72), in remission after alloSCT or autoSCT, with no recent immunoglobulin therapy, or ongoing infection. Twenty patients (pts) did not complete the study due to relapse (n=9), death (n=4), side effects (n=2), or other reason (n=5). Diagnoses in the remaining 84 pts were AML (n=22), ALL (n=2), myeloma (n=26), CLL (n=1), CML (n=3), lymphoma (n=21), myelofibrosis (n=1), MDS (n=4), and unknown (n=2). At first vaccination, 17 alloSCT pts were on immunosuppressive treatment: steroids (n=13), ciclosporin or tacrolimus (n=4). Three autoSCT pts were on maintenance lenalidomide or thalidomide.

Vaccination and analyses. Four vaccine doses (FSME-Immun®) were given at 9, 10, 12, and 21 months post transplant. Serum samples were obtained prior to each vaccination, and at 3 months after the last vaccination. Side effects were categorized as per the Common Terminology Criteria for Adverse Events (CTCAE) standards. To determine IgG antibodies to TBE in samples, the Enzygnost anti-TBE Virus ELISA test (Lot #48842, Siemens Healthcare AB, Sweden) was applied. Results were given in units per mL (U/mL) with an analytic interval of 7-700 U/mL. Values ≥10 U/mL were considered as positive.

Results: For the primary endpoint, we compared TBE serology before first vaccination versus 3 months after last vaccination in 84 pts (43 alloSCT, 41 autoSCT). There was no difference in antibody levels between alloSCT (mean 89 U/mL) and autoSCT (mean 94 U/mL). The median difference between pre- and post vaccination samples in all patients was 186 U/mL (range -12-597). Nine of 43 alloSCT pts, and 7 of 41 autoSCT pts had antibody levels below 10 U/mL. Seronegative alloSCT pts had received reduced intensity (n=5) or myeloablative conditioning (n=3).

Ongoing immunosuppression at inclusion (n=17) was associated with seronegativity (n=5) in the last sample (p=0.01;Fisher´s exact test). Of seronegative autoSCT pts (n=7), 3 myeloma pts had received maintenance therapy.

Adverse events: Local inflammatory reactions (tenderness, swelling) were reported in 13-17 pts after each vaccination. One pt withdraw consent after a pneumonia, and one pt was excluded due to urticaria after the first vaccination.

Conclusions: This is the first study of TBE-vaccination in hematological pts. We conclude that TBE vaccination was safe, and that 4 doses of vaccine, starting nine months post-Tx, induced seropositivity in a majority of pts after auto- (34/41=83%) and alloSCT (34/43=79%). The protective IgG level against TBE has not been defined, and our results may suggest that chronic GvHD, and/or its treatment, is associated with an impaired vaccination response. A similar trend was observed after autoSCT in patients on maintenance therapy.

Clinical Trial Registry: EudraCT-number: 2014-003573-42

Disclosure: Nothing to declare.

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Rifaximin use Favoured Micafungin Resistant *Candida* SPP Infections in Recipients of Allogeneic Hematopoietic Cell Transplantation

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Background: Damage to gut mucosa following conditioning regimens may favour bacterial infections that can trigger graft versus host disease (GvHD) in patients undergoing allogeneic hematopoietic cell transplantation (HCT). There is no general consensus regarding the need and the type of antibacterial prophylaxis, as bacterial epidemiology and resistance to antibiotics vary among centres. Antibiotic prophylaxis can also disrupt gut microbiome that may have an impact on GvHD onset and lethality. We historically chose a pre-emptive approach to bacterial infections in HCT patients avoiding the use of prophylactic antibiotics. We recently re-introduced antibacterial prophylaxis with rifaximin, an oral and non-absorbable antibiotic, effective in protecting HCT patients from bacterial infections and with low impact on microbiome (Weber et al. BMT 2016), to reduce bacterial infections in the gut and consequently acute GvHD.

Methods: In this study we compare the outcomes of rifaximin-treated patients with historical controls at our institution. We analysed transplants performed from January 2016 to August 2019. Rifaximin 200 mg/bid was given from the beginning of the conditioning to day+20 post-transplant. Micafungin 50 mg/die was used as antifungal primary prophylaxis, while lyposomal amphotericin-B (L-AmB) 1-3 mg/die was used as secondary prophylaxis.

Results: We retrieved data from 110 transplants (21 HLA-matched related HCT, 4 HLA-matched unrelated and 85 haploidentical). 21 received rifaximin, while 89 received no antibiotic prophylaxis. Incidence of neutropenic fever (100% with rifaximin vs 94% in controls) and the use of carbapenems (71% vs 76%) were similar between the two groups, but rifaximin reduced the number of documented sepses (24% vs 42%, $p< 0.05$). We did not observe any difference in GvHD incidence (43% vs 33%, Fig.1A). No patient died because of documented bacterial infection within 30 days after transplant.

Surprisingly, we found an increase in clinically relevant Candida spp. infections in rifaximin-treated patients (5 patients vs 1, 23.8% vs 1.1%, $p< 0.001$, Fig.1B). Three of the 5 rifaximin-treated patients experienced life-threatening candidaemia (2 C.Krusei, 1 C.Orthopsilosis). Rifaximin was the only factor that increased the risk of Candida spp. infection as such risk was not dependent upon type of malignancy, disease status at transplant, type of transplant, previous Candida spp. colonization, and GvHD prophylaxis. We observed that all the 6 Candida spp. infections happened in patients that were receiving micafungin despite all the isolates were sensitive to echinocandins at the antifungal susceptibility testing. We further analysed genotype of the two C.Krusei isolates and we found that both presented L701M mutation of the fks1 gene that is associated with in vivo resistance to echinocandins. In fact, shift from micafungin to L-AmB cleared infection in all the patients with candidaemia.

Conclusions: Our study proved that rifaximin favoured an outbreak of Candida spp. infections that were in vivo resistant to micafungin. Because of such unexpected complication, we decided to halt the use of rifaximin. Rifaximin could have contributed to microbiome disruption which made fks1-mutated Candida spp prevail. Despite rifaximin use was associated to a reduction of documented sepses, any evaluation of such prophylactic approach in HCT requires analysis of larger number of patients.

Disclosure: Nothing to declare.

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Baseline Characteristics and early poly-functional Assessment of T Cells to Identify Patients at Higher Risk to Develop Severe HCMV Reactivation after Allogeneic HSCT

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Background: Human cytomegalovirus (HCMV) infection is one of the main causes of mortality and morbidity after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Here, we analyze several baseline characteristics and T-cell parameters of HSCT recipients in order to early and precisely identify patients who will benefit from HCMV pre-emptive therapy and/or antiviral prophylaxis with letermovir, the recently approved antiviral drug.

Methods: We analyzed a previously described cohort of HCMV-seropositive patients, receiving allo-HSCT from June 2011 through May 2014 at Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. No patient received anti-HCMV prophylaxis; pre-emptive anti-HCMV therapy was administered after detection of HCMV DNA ≥30,000 copies/mL in peripheral whole blood. Baseline characteristics (gender, age at transplantation, donor HCMV serostatus, donor type, stem cell source, disease status at transplantation and type of conditioning) were collected. Moreover, total/HCMV-specific CD4+ and CD8+ T-cells and functional subsets of HCMV-specific CD8+ T-cells were measured at the earliest time-point available (1 month after transplantation). HCMV-specific immunity was determined by flow-cytometric analysis after stimulation with autologous infected dendritic cells and intracellular staining for three different cytokines.

Results: Sixty patients were divided into two groups based on their ability to resolve spontaneously HCMV-infection: i) 22 (37%) were able to spontaneously control HCMV reactivation ii) 38 (63%) were undergoing pre-emptive therapy for severe infections. The status of HCMV-seronegative donor was associated with a significant infection risk requiring pre-emptive therapy ($P< 0.001$). Both total and HCMV-specific CD4+ and CD8+ T-cells were significantly higher in patients spontaneously resolving HCMV infection than in patients requiring antiviral treatment (median total CD4+ T-cells/μl: 298 vs 90, $P=0.001$; CD8+ T-cells/μl: 308 vs 126, $P=0.017$; HCMV-specific CD4+ T-cells/μl: 0.69 vs 0.00, $P< 0.001$; HCMV-specific CD8+ T-cells/μl: 17.2 vs 1.2, $P< 0.001$). We identified two distinct functional subsets of HCMV-specific CD8+ T-cells: a tri-functional subset producing TNF-a, IL-2, IFN-g and a mono-functional subset producing IFN-g only. Patients requiring treatment presented an higher

percentage of mono-functional HCMV-specific CD8+ T-cells if compared with patients resolving the infection spontaneously (median 34.2% vs 16.4%, P=0.002). In addition to the above-mentioned parameters, also an unrelated donor graft (P=0.013) was associated with a significant risk of developing recurrent episodes of HCMV infection. In bi-variable models, we confirmed the significant prognostic impact of the percentage of mono-functional HCMV-specific CD8+ T-cells on treatment-free survival adjusted for total CD8+ and total and HCMV-specific CD4+ T-cells/μl.

Conclusions: A poly-functional assessment of the CD8+ T-cell compartment allows to better distinguish patients protected from a severe HCMV reactivation from those at high risk of developing this post-HSCT complication. Conversely to what reported by other authors, we also found a direct correlation between the amount of total and HCMV-specific CD4+/CD8+ T-cells detected one month after HSCT and the risk of HCMV reactivation requiring pre-emptive therapy. Taken together, these data suggest that poly-functional assessment of CD8+ T-cells may be used as an additional useful tool to better identify patients who will significantly benefit from anti-HCMV prophylaxis early after allo-HSCT.

Disclosure: Nothing to declare.

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Impact of HHV-6 Reactivation After T-reg/T-con Immunotherapy in Allogeneic Transplantation: A single-center Retrospective Study

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Background: Human Herpes Virus 6(HHV6) is a relevant early complication after Allogeneic Hematopoietic Stem Cell Transplantation(Allo-HSCT), associated with an increased incidence of acute graft versus host disease (GvHD) and non-relapse mortality(NRM) in children and in adults. Preliminary results of regulatory and conventional T cell adoptive immunotherapy in allogeneic transplantation (T-reg/T-con Allo-HSCT) in our Center proved that such approach effectively prevents GvHD and reduces risk of leukemia relapse, but data are still missing regarding the impact of specific viral infections such as HHV6 reactivation on T-reg/T-con Allo-HSCT outcomes.

Methods: We analyzed the impact of early(within 30 days post-transplant) HHV6 reactivation on clinical outcomes in adult T-reg/T-con Allo-HSCT recipients transplanted at our Institution from November 2015 until October 2019. All patients were weekly monitored by quantitative real-time PCR to detect HHV6-DNAemia, as copy number per mL of whole blood. In November 2015 we switched from TaqMan®-MGB to ELITe®-MGB reaction kits(both ©Elitech Group technology) increasing sensitivity.

Results: We collected data from 66 consecutive patients (43 AML,15 ALL,5 MDS,3 MM) with a median age at transplant of 52 years(range 18-70), who had received T-reg/T-con Allo-HSCT.HHV6 reactivation occurred early (median time was 13 days, range 6-21) at the time of engraftment. The presence of HHV6-DNAemia in the first 30 days after transplant was observed in 55 patients(83%), of whom 5 patients had rejection. The median first viral load was 5963 cp/mL(range 11-318066). Studies on separated plasma and white blood cell(WBC) populations showed HHV6 was detectable at higher concentration in WBCs of early engrafting patients (when neutrophils are more frequent) and persists in CD4+ T cells for a longer period of time. As prevalence of HHV6 reactivation was so high, it was impossible to analyze different outcomes according to HHV6 reactivation status. In HHV6 reactivating patients acute GvHD occurred in 15 patients(29%), chronic GvHD in 1(2%), relapse in 5(10%), rejection in 3 patients(6%). NRM was 23% with infectious complication being cause of death in 5 patients. We treated HHV6 reactivation(foscarnet 120 or 180 mg/kg i.v. daily for 10-14 days) only in case of clinical symptoms or signs of infection(rash, nausea, vomiting, possible organ involvement such as hepatic impairment). 34 HHV6-positive patients(62%) were treated for viral infections. Between treated or untreated patients, we noted this evidence: time of HHV6 reactivation(12 vs 15), overall survival(56% vs 84%), copy number at diagnosis(56870 vs 11667), incidence of GvHD(35% vs 14%).

Conclusions: Our retrospective analysis shows high prevalence of HHV6-positive patients, related to the presence of a more sensitive detection of HHV6 in our Institute and related to T-reg infusion without immunosuppression after transplant that represents a reservoir for early HHV6 infection and replication. Nevertheless we demonstrated that, after the recovery of white blood cells with specific immune reconstitution, the HHV6 viral load decreased, spontaneously, even without specific antiviral treatment. For this reason we do not perform anti-viral treatment in absence of clinical signs, despite high copy number. We observed a lower incidence of aGvHD, despite the presence of HHV6 and the absence of

immunosuppressive therapy after transplant. We confirm the absence of association of HHV6 reactivation and mortality.

Disclosure: Nothing to disclose

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Adenovirus Infections after HCT: Infectious Diseases Working Party Retrospective EBMT Registry Study

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Background: Infections with adenovirus (ADV) might contribute to morbidity and increased mortality after hematopoietic cell transplantation (HCT). The objective of this retrospective EBMT registry-based study was the analysis of clinical types, outcome and risk factors associated with ADV infection, in children and adults after allo- and auto- HCT.

Methods: Patients transplanted between 2000-2018 reported to the EBMT database, who had ADV infection, were analyzed in the study.

Results: Allo-HCT. A total number of 1614 patients were included to the study: 34.7% of them were reported by the centers participating in the survey "A survey on incidence and management of Adenovirus infection after allogeneic HCT (published in: Cesaro et al, BMT 2019)", while 65.3% by the other centers. In 64.5% patients in centers participating in the survey, regular screening for ADV infection was performed. In the entire cohort, 52.2% patients were children (< 18 yrs), and 47.8% adults. Primary diagnosis: 45.3% acute leukemia, 10.8% lymphoma, 19.6% chronic malignancies, 0.3% solid tumors and 24.0% non-malignant disorders. Stem cell source: PB in 45.7%, BM in 34.9%, and CB in 19.2%. Conditioning: myeloablative in 64.4%, reduced-intensity in 34.4%, not determined in 1.2%; TBI-based conditioning was used in 33.5% patients. Grade 2-4 acute GVHD was diagnosed in 48.9%, chronic GVHD in 23.9% (limited in 11.9%, extensive in 12.0%) of eligible patients. Patients were diagnosed for ADV viremia in 66.6% including septic shock in 0.7% cases; gut infection in 16.9%; cystitis in 4.3%; pulmonary infection in 2.9%; CNS infection in 0.3%, and other types of ADV disease in 9.0%. The 100 days overall survival (100d OS) after diagnosis of ADV infections was 70.9% (95%CI=68.5-73.0), including 70.2% (95%CI=66.2-73.9) in centers participating in the survey and 71.2% (95%CI=68.3-73.8) in others (ns). In patients in the centers with regular screening for ADV (participating in the survey) vs others, 100d OS was 70.2% (95%CI=65.2-74.7) vs 70.2% (95%CI=63.2-76.1) (ns). With respect to clinical form of ADV disease, the 100d OS was 86.7% (95%CI=78.2-92.0) in patients with gut infection, 67.4% (95%CI=62.2-72.1) with viremia, 44.4% (10/18 pts) with pneumonia and 71.0% (95%CI=58.0-80.7) with other ADV diseases (p=0.008). The 100d OS was 74.7% (95%CI=69.5-79.0) in children and 63.9% (95% CI=57.3-69.8) in adults (p=0.0007). In patients treated with brincidofovir+CTL (ADV-specific cytotoxic T-lymphocytes) the 100d OS was 85.6% (95%CI=70.7-93.3), and 69.0% (95%CI=63.5-73.8) in patients treated with cidofovir (ns). In multivariate analysis, bone marrow cell source and Karnofsky score (continuous variable) contributed to better OS in patients with ADV infection/disease.

Auto-HCT: Among 64 auto-HCT patients, 3/64 have died during 100 days after ADV infection/infection.

Conclusions: (1) The 100 days OS in patients with ADV infection was better in children than adults. (2) The use of brincidofovir and CTL contributed to improved outcome in patients with ADV infection. (3) The results of patients

from the centers participating in the survey were representative for entire cohort of patients.

Disclosure: All Authors have nothing to declare. with respect to this study.

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Clinical Impact of Colonization by Multidrug-resistant Enterobacteriaceae in Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Infection by multidrug resistant Enterobacteriaceae (MDRE) is an emerging issue in allogeneic hematopoietic stem cell transplantation (allo-HSCT). The impact of pre-transplant colonization by MDRE in clinical outcomes related to allo-HSCT is still a matter of debate.

The primary endpoint of this study is to analyze the epidemiology of colonization and its influence in infectious events. The secondary endpoints are to analyze the incidence of graft-versus-host disease (GvHD), infection-related mortality (IRM) and non-relapse mortality (NRM).

Methods: In this prospective, single-center study (ENTHERE-SCT Study PI16/01415) we evaluated data from 52 patients who underwent allo-HSCT from June 2017 to May 2019. Rectal swabs were collected preconditioning, weekly until day 30 after transplantation, every 2 weeks until day 100 and monthly until day 180 to screen for MDRE colonization. According to institutional protocol, no antibiotic prophylaxis was made.

Results: 536 rectal swabs were obtained with a median number of 11 (4-13) samples per patient. Pre-transplant MDRE colonization was found only in 5 patients (10%) and 27 (52%) were found to be carriers at any time point until the 6th month of transplant. Six (11.5%) patients were colonized by 2 different MDRE at different time points. Peak incidence of colonization took place during the first month after transplant. There were no differences between colonized and non-colonized patients baseline characteristics (table 1).

All of the isolated species in colonized patients were Gram-negative rods with the following distribution: 19 (58%) patients colonized by ESBL-producing bacteria, 11 (33%) by AmpC-producers, 2 (6%) by resistant to carbapenems and 1 (3%) by ESBL-producing and resistant to carbapenems. Distribution of species and patterns of resistance are summarized in table 2.

During neutropenic phase of allo-HSCT, 13 (25%) patients were colonized. There were no differences in neutropenic fever episodes between colonized and non-colonized patients (10 (77%) vs 35 (90%), p=0.347) but bloodstream infection (BSI) episodes in colonized patients were higher (7 (70%) vs 12 (34%), p=0.070). Despite that, only one colonized patient developed a BSI episode by a MDRE (the same pathogen isolated in the rectal swab). Once neutropenic phase resolved, there were 8 infectious episodes with confirmed bacterial isolation in the cohort of colonized patients and only 1 was a MDRE.

Acute GvHD incidence was similar between colonized and non-colonized patients (41% vs 48%, p=0.076) as well as chronic GvHD (46% vs 52%, p=0.772). There were no differences in acute GvHD between patients who had a BSI episode during neutropenic phase and those who hadn`t (7 (37%) vs 10 (42%), p=1).

There was no difference in IRM between colonized and non-colonized patientes (7.4% vs 16%, p=0.4) and only in one colonized patient mortality was attributed to MDRE infection. NRM in colonized patients compared with non-colonized patients was 11% versus 20% (p=0.4).

Conclusions: In our prospective study analyzing the course of colonization by MDRE in allo-HSCT the most common MDRE are ESBL-producing bacteria. Colonization by MDRE didn't have a significant impact on neutropenic fever episodes, acute and chronic GvHD, IRM and NRM in patients who underwent allo-HSCT, however it was associated with higher BSI episodes.

Disclosure: Nothing to declare.

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Post-allogeneic Transplantation Progressive Multifocal Leukoencephalopathy, Clinical and Biological Features, Treatment and Outcomes: A Retrospective Study from the SFGM-TC

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Background: Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating infection of the central nervous system caused by reactivation of the JC polyomavirus that occurs in the context of defective cellular immunity. Common underlying conditions that are associated with JC virus infection include advanced human immunodeficiency virus (HIV) infection, hematologic and solid-tissue cancers, hematopoietic stem-cell transplantation, and the use of certain immunosuppressive drugs.

Methods: We report a SFGM-TC retrospective study of post-SCT PML from 2005 to 2018. All patients with post-HSCT PML reported in the SFGM-TC registry were eligible for the present study. In total, 12 centers participated in the study. Referring local physicians were asked to confirm the diagnosis, clinical history and initial presentation, biological characteristics, histological subtypes, number and nature of the treatment lines, disease status at the time of allo-SCT, all data on the allo-SCT procedure and outcome including GvHD grade, and to update follow-up.

Results: A total of 19 patients, 13 males and 6 females, met the inclusion criteria. The median age was 52 years (range, 33-71). Nine patients were treated for acute leukemia, 2 for myelodysplastic syndrome, 5 for lymphoma and 3 for multiple myeloma. All, except one, underwent their first allo-SCT. Five patients received a MAC regimen and 14 a RIC or NMA. Among this cohort, 3 patients received a haplo-donor and 4 a UCB. PBSC was the main source of stem cell (76%). Seven patients developed an acute GVHD and 9 developed chronic GVHD. Seven patients had previous injections of rituximab. The median time to PML development was 19 months post-SCT (range, 1-46). Clinical presentation consisted in focal deficits (88%), epileptic seizures (35%), cognitive deficit and coma (12%). The median total lymphocytes count was 0.42 G/L (range, 0.17-1.7), CD8+ cell and CD4+ cell counts were 0.239 G/L and 0.214 G/L respectively. Sixty-eight percent of the patients were JCV PCR positive in the spinal fluid. RMI and magnetic resonance spectroscopy were used to establish the diagnosis of PML. Sera pre-transplant could be tested for one patient and his donor (relative): a mismatch could be found: he was JCV IgG positive and his donor was IgG negative. Combined therapeutic strategies were usually used: 3 patients stopped immunosuppressive treatment, 4 received antiviral treatment, 2 received DLI, 3 IgIV, 4 mirtazapine, and one mefloquine. Thirty-six percent patients were alive and 74% died from PML.

Conclusions: In this large cohort, delayed immune reconstitution, increased use of rituximab, and alternative donors appeared to be risk factors of PML. Antiviral treatment seemed to be ineffective. Serological mismatch between the donor and recipient could help to better understand the pathophysiology. Intervention to restore immunity should be considered as a priority together with stopping immunosuppressive treatment. Specific CTL and immune-checkpoint have recently showed promising results in this dramatic disease.

Disclosure: The authors have nothing to disclose

P382

Efficacy of Letermovir for Prophylaxis of CMV Reactivation after Allogeneic Hematopoietic Cell Transplantation: A Multi Center Retrospective Analysis among Japanese Patients

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Background: Cytomegalovirus (CMV) reactivation leads to increase the risk of mortality among patients with allogeneic hematopoietic cell transplantation (allo-HCT). A novel anti-CMV agent, letermovir (LTV) could reportedly reduce all-cause mortality with its high potential for preventing CMV reactivation.

Methods: We conducted a multi-center retrospective study to assess the impacts of prophylactic LTV on the incidence of CMV reactivation as well as transplant outcomes in clinical practice. 685 Japanese patients underwent allo-HCT between January 2015 and March 2019 at eight

institutions of Fukuoka Blood and Marrow Transplantation Group were analyzed, of whom 114 cases received LTV prophylaxis. Patients those who received other prophylactic CMV agents (n = 167), developed primary graft failure (n = 21), or died before engraftment (n = 62) were excluded in this analysis.

Results: The median age at transplantation was 57 (range; 15-76) years. The median onset of clinically significant CMV infection (csCMV infection; defined as CMV antigenemia required treatment and/or CMV-related diseases) was 90 days (range, 11-174 days) after transplant among patients with LTV prophylaxis, whereas 36 days (range, 7-149 days) among those without ($p < 0.001$). 180-day cumulative incidence of csCMV infection was significantly lower in LTV group than that in non-LTV group (44.7% vs 72.4%, $p < 0.001$). This beneficial effect was emphasized in recipients with high-risk for CMV reactivation (i.e., HLA-mismatched donor, CBT, or systemic steroid use for GVHD; 48.8% [range: 35.7-59.3%] in LTV group vs 80.6% [range: 76.4-84.1%] in non-LTV group, $p < 0.0001$) rather than low-risk for CMV reactivation (31.3% [range: 8.6-48.4%] in LTV group vs 43.5% [range: 33.9-51.8%] in non-LTV group, $p = 0.082$). In addition, LTV demonstrated the statistically significant efficacy for reducing the cumulative incidence of csCMV infection through day 180 in all subgroups analyzed as follows: 52.4% in LTV cohort vs 71.1% in non-LTV cohort among 137 patients with prior history of HCT ($p = 0.036$); 52.9% vs 81.3% among 85 adult T-cell leukemia/lymphoma patients ($p = 0.012$); 65.0% vs 81.1% among 108 patients receiving ATG ($p = 0.025$); and 24.0% vs 84.0% among 108 patients using PTCy regimen ($p < 0.001$), with the exception of 74 patients developing steroid-refractory acute GVHD, in which LTV had only a trend for reducing csCMV infection (75% vs 84.7%, $p = 0.065$) presumably owing to the small number of patients with LTV prophylaxis (n = 9) in this subgroup. Overall survival rate at 180-day after allo-HCT was 80.4% for patients in LTV cohort, significantly higher than that for patients in non-LTV cohort (73.1%, $p = 0.033$), although the median follow-up period among surviving patients was short with 231 days in LTV cohort and 416 days in non-LTV cohort, respectively.

Conclusions: LTV effectively prevents or delays CMV reactivation, that possibly contributes to improve transplant outcome, although long-term follow up will be required.

Disclosure: Nothing to declare.

P383

Standardized Monitoring of cytomegalovirus-specific Cellular Immunity can Improve Risk Stratification of Recurrent Cytomegalovirus Reactivation after Hematopoietic Stem Cell Transplantation

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Background: Increasing evidence suggests that impaired cytomegalovirus (CMV)-specific cell-mediated immunity (CMV-CMI) is a major cause of uncontrolled CMV reactivations and associated complications in hematopoietic stem cell transplantation (HSCT). No reliable test exists to predict patients at risk of primary and/or recurrent CMV reactivations following HSCT. Accurately assessing CMV-CMI might therefore improve the risk stratification of patients and allow optimizing and individualizing patient care. This study aimed to evaluate the suitability of an IFN-γ ELISpot assay (T-Track® CMV), which is based on the stimulation of peripheral blood mononuclear cells with T-activated® pp65 and IE-1 CMV proteins, to predict recurrent CMV reactivation following the end of treatment for a first CMV reactivation. The presented results are a follow-up of previously reported data.

Methods: A prospective, longitudinal, observational, multicenter study was conducted in 175 intermediate- and high-risk (Donor (D)+/Recipient (R)+, D+/R-, D-/R+)

HSCT recipients. Patients underwent preemptive antiviral therapy per institutional guidelines. CMV DNAemia was analyzed by quantitative PCR. CMV-CMI was measured at day 45, 60, 80, 100 and 120 post-transplantation, as well as at onset and following the end of preemptive treatment. Occurrence of recurrent CMV reactivation was monitored up to 7.5 months post-transplantation. 154/175 patients fulfilling the inclusion/exclusion criteria and having at least one valid T-Track® CMV test result were included in the analysis.

Results: 101/154 (66%) patients experienced at least one (treatment-requiring) CMV reactivation during the observational period. 40/101 (39.6%) patients with a first CMV reactivation faced at least one recurrent reactivation, mainly in the D-/R+ high-risk group. The positive predictive value (PPV) of T-Track® CMV (patients with a negative test after the first reactivation experienced at least one recurrent reactivation) was 84.2% (16/19) in D-/R+ patients. Kaplan-Meier analysis revealed a higher probability of recurrent CMV reactivation in high-risk patients with a negative test after the first reactivation (hazard ratio 2.73; p=0.007). A post-hoc analysis considering T-Track® CMV measurements at day 100 post-transplantation, a time point highly relevant for outpatient care, showed a PPV of 90.0% (9/10) in D-/R+ high-risk patients.

Conclusions: Altogether, the standardized IFN-γ ELISpot assay (T-Track® CMV) allows an improved risk stratification of CMV-related clinical complications, and can support clinicians in the identification and management of patients with increased risk of recurrent CMV reactivation following HSCT.

Clinical Trial Registry: AlloProtectCMV (ClinicalTrials.gov identifier: NCT02156479); https://clinicaltrials.gov/ct2/show/NCT02156479

Disclosure: The participating clinical and measurement centers received research funding from Lophius Biosciences for this study. Ludwig Deml, Sascha Barabas, Traudel Schmidt, Harald Guldan and Anne Rascle are employees of Lophius Biosciences. Ludwig Deml is co-founder and Chief Scientific Officer of Lophius Biosciences. Ralf Wagner is Chairman of the Board of Lophius Biosciences. Ralf Wagner, Ludwig Deml and Sascha Barabas are shareholders of Lophius Biosciences GmbH.

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Impact of Levofloxacin for Prophylaxis of Pre-engraftment Bloodstream Infections after Allogeneic HSCT: A single-center Matched Analysis in an Endemic Country for Carbapenem-resistant Gram-negative Bacteria

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Background: Gram-negative bacteria (GNB) blood-stream infections (BSIs), particularly if multidrug resistant (MDR), affect mortality in neutropenic hematological patients, worldwide. In the last decade, Italy has registered high prevalence of fluoroquinolone resistance and a worrisome spread of carbapenem-resistant (CR) GNB infections. In such a context, the benefit of fluoroquinolone prophylaxis is controversial, especially considering antibiotics' impact on enteric microbiome.

Methods: We aim to evaluate, retrospectively, the impact of levofloxacin for the prevention of pre-engraftment (PE) BSIs in adult patients affected by high-risk hematologic malignancies treated with allogeneic HSCT. Patients were treated according to institutional guidelines. We collected data of PE-BSIs: fifty-three patients who received levofloxacin prophylaxis (group-A, February 2018-October 2018) and fifty-eight patients who did not received antibacterial prophylaxis (group-B, February 2019-October 2019). Primary objective was to compare infection-related mortality (IRM) at day-30 in patients who developed GNB PE-BSIs. Secondary objective was the incidence, etiology and antimicrobial resistance of PE-BSIs.

Results: Two groups were superimposable for characteristics. The graft source was mainly unmanipulated peripheral blood, using a post-transplant cyclophosphamide strategy.

Overall, we reported data on 111 patients. Stem cell donors were family haploidentical (n=35), HLA-identical sibling (n=21), unrelated volunteer (n=50) or cord blood (n=5).

Among fifty-three patients of group-A, 18 episodes of PE-BSIs occurred in 17/53 patients (32%). Pathogens were GNB in 7/18 (3 Escherichia coli, Ec, 2/3 ESBL-producer; 2 Pseudomonas aeruginosa, Pa, 1/2 CR; 2 Klebsiella pneumoniae, Kp, 2/2 CR). Among GNB PE-BSIs, 71% were sustained by ESBL-producer or CR pathogens. Pre-transplant carriers were 6/53 (11%, 3/6 CR-Kp, 3/6 CR-Pa) and two of them developed PE-BSIs by the same pathogen (1 CR-Kp, 1 CR-Pa). After transplant, further 8/47 patients acquired MDR-GNB colonization (17%, 5/8 CR-Kp, 2/8 CR-Pa, 1 CR-Enterobacter) and one developed PE-BSIs by the same pathogen (1 CR-Kp).

Among fifty-eight patients of group-B, 36 episodes of PE-BSIs occurred in 30/58 patients (52%). Pathogens were GNB in 23/36 (12 Ec, 2/12 ESBL-producer; 6 Pa, 3/6 CR; 5 Kp, 2/5 ESBL-producer, 0/5 CR). Among GNB PE-BSIs, 30% were sustained by ESBL-producer or CR pathogens. Pre-transplant carriers were 3/58 (5%, 3/3 CR-Kp) and none of them developed PE-BSIs. After transplant, further 8/55 patients acquired colonization (15%, 2/8 CR-Kp, 5/8 CR-Pa, 1 CR-Enterobacter) and 2/8 developed PE-BSIs by the same pathogen (2 CR-Pa).

IRM due to GNB was 14% in group-A and 10% in group-B (p=0.8).

The incidence of PE-BSIs was significantly higher in group-B (p=0.04, RR 1.61). Withdrawing levofloxacin prophylaxis, we observed less PE-BSIs sustained by beta-lactamase producing GNB (ESBL-producer, CR) (p=0.052) and a similar rate of MDR-GNB colonization after HSCT (p=0.7).

Conclusions: Levofloxacin seems to have a minimal impact on IRM due to GNB PE-BSIs, confirming the safety of an approach based on its withdrawal. As expected, we observed an increased rate of microbiologically documented infections without prophylaxis, resulting in a higher rate of PE-BSIs sustained by susceptible GNB. Although small numbers, we documented an interesting trend towards a decrease in PE-BSIs sustained by MDR-GNB. Larger studies are ongoing to confirm the specific impact of fluoroquinolone prophylaxis on PE-BSIs after allogeneic HSCT.

Disclosure: Nothing to declare.

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Progressive Multifocal Leukoencephalopathy (PML) after HCT - A Retrospective Study of Infectious Diseases working Party EBMT

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Background: Most of human population is infected with JC virus (JCV) in early childhood with no clinical symptoms. In immunocompromised patients JCV may be reactivated and replicated in oligodendroglia of brain white matter causing the symptoms of progressive multifocal leukoencephalopathy (PML). PML is a demyelinating disease causing typical motoric disfunction with a rapidly progressive intellectual deterioration. There are limited data on PML after HCT. The aim of this study was to report the cases of PML after HCT

Methods: The data of 16 patients (6F:10M, median age -51.5y) who underwent alloHCT and 3 patients who underwent autoHCT (3F:0M, median age-63.0) between 2002 and 2018 and had been reported in MED-C forms by 15 participating centers was analyzed. All but one of the group were treated for hematological malignancies (allo: acute leukemia-6, lymphoma/myeloma-5, MDS-4, inherited disorder-1, auto: lymphoma/myeloma-3). Patients characteristics includes: the conditioning (allo: MAC/RIC-13/3, ATG used in 6, auto: MAC/RIC-3:0), the stem cell source (allo: PBSC/BM-12/4, auto: PBSC/BM-3/0), and for allo alone: the donor (identical sibling, haploidentical and matched unrelated in 7, 3 and 6 cases respectively; female donor to male recipient in 8 cases) and GvHD prophylaxis - CsA or Tacrolimus. PML was diagnosed according to American Academy of Neurology diagnostic criteria. For definite PML diagnosis all three criteria must be fulfilled: compatible clinical features, compatible neuroimaging findings and a positive PCR result for JC virus in cerebrospinal fluid (CSF). For probable PML diagnosis clinical or imaging criteria are allowed to be omitted. Possible PML diagnosis consists of CSF PCR positive result alone or, if negative, of two other positive criteria fulfilled concomitantly. Any other combination was not considered to be PML.

Results: The definite PML diagnosis was confirmed in 17 patients, probable and possible diagnosis was recognized in 1 case each, respectively. Median time from HSCT to PML diagnosis was 14 months (1-82). The most common neurological symptoms were motor weakness (16), speech disturbances (12), gait abnormalities (11),

incoordination (11) and sensory loss (6). Cognitive and behavioral changes were observed in 9 cases. Acute GvHD was present in most cases (15, grades 3-4 in 8), treated with an initial median steroid dose 1,2 mg/kg bw (0.3-2.0) and resolved (with the treatment cessation in 13 cases) before PML onset. Chronic GvHD was present in 7 cases at the time of PML diagnosis but only one patient was on corticosteroids at diagnosis. Other transplant complications include mainly viral reactivation before (and at the time of) PML onset: CMV-9(2), EBV-4(0), HHV6-1(2), BKV-1(2), VZV-3(1), ADV-1(0), HSV-0(1). The most common treatment approach in PML was immunosuppression dose reduction (7), Cidofovir (7), Mirtazapine (5) and Maraviroc (4), some of them combined. T cell therapies include infusions of cytotoxic T lymphocyte (CTL) lines in 1 and DLI in 3 cases (with a confirmed presence of anti-JCV antibodies in 1). 13 patients of 19 died due to PML (10-definitely, 3 -probably).

Conclusions: PML is a severe and lethal complication following HCT. Further detailed analysis is needed to determine PML risk factors in this group of patients.

Disclosure: Nothing to declare.

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Oral Ribavirin is a Highly Efficacious Treatment for Lower Respiratory Tract Infection due to Respiratory Syncytial or Parainfluenza Virus in Allogeneic Stem Cell Transplant Recipients

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Background: Lower respiratory tract infections (LRTI) due to parainfluenza (PIF) or respiratory syncytial virus (RSV) are associated with considerable mortality during the period of immunosuppression following allogeneic stem cell transplantation (allo-SCT). Due to the limited availability of antiviral agents and paucity of prospective trials, therapeutic options for those infections are debatable. We report our experience with the use of oral ribavirin alone or in combination with intravenous immunoglobulin (IVIG) in allo-SCT recipients with LTRI due to RSV or PIF.

Methods: A retrospective study among 3 transplant centers (2 adult and 1 pediatric) enrolled patients who received treatment with oral ribavirin for LRTI. LRTI was defined according to the European Conference on Infections in Leukaemia (ECIL-4). RSV or PIF in nasopharyngeal wash and/or BAL was detected by PCR assay. Ribavirin was administered at a daily dose of 20-30 mg/kg until significant symptomatic and radiological improvement. Combined therapy with IVIG (400 mg/kg/day for a total dose of 2 g/kg) was given at the discretion of the treating physician. Informed consent was provided by patients or their parents.

Results: Over a 9-year period, 49 episodes of LRTI due to RSV (n=34) or PIF (n=15) were reported in 44 allo-SCT recipients (7 children/37 adults) at a median age of 39 (range, 0.5-67) years. Three children and 2 adults had a second LRTI due to RSV at a median of 8 (range, 6-12) months after the first episode. Patient characteristics are shown on Table 1.

No. Patients/LRTI episodes	44/49
Disease: AML, MDS, CML/ ALL/ Lymphoma/ Immunodeficiency	29/7/5/ 3
Conditioning: Myeloablative/RIC	33/11
Donor: Matched Sibling/Unrelated/Haplo/Double Cord	9/26/5/ 4
Active GvHD and/or steroid treatment: Yes/No	30/19

[Table 1. Patient Characteristics]

All patients presented with fever and cough. High resolution CT scan was performed in 41 episodes, with bilateral small centrilobular nodules, bronchial wall thickening, and ground-glass opacities being the most common findings. Oxygen supplementation was needed in 32/49 episodes, and 7 patients required mechanical ventilation. All 49 episodes were treated with oral ribavirin, which was combined with IVIG in 37 cases. In 43 LRTI episodes, a rapid response to treatment was observed within a median of 3 (range, 2-5) days. Complete resolution of infection occurred after a median of 9 (range, 7-20) days of treatment, including 1 case with pneumonia due to PIF3 which required mechanical ventilation. Six deaths attributable to LRTI were noted. Recurrence of infection was detected only in 1 patient with LRTI due to RSV 10 days after the end of treatment. One child developed bronchiolitis obliterans syndrome (BOS) 9 months after resolution of RSV infection. Cryptogenic

organizing pneumonia (COP) was observed in two patients 1 and 2 months after resolution of LRTI due to PIF. Both responded to treatment with steroids.

Conclusions: Oral ribavirin was well-tolerated and resulted in fast and complete resolution in 88% of LRTIs due to RSV or PIF among allo-SCT recipients. Therefore, early intervention with ribavirin deserves further prospective study in the context of those life-threatening infections.

Disclosure: Nothing to declare.

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Timing of Induction Treatment for Reactivation of Cytomegalovirus Impacts Overall Survival in Pediatric Allogeneic Hematopoietic Cell Transplant

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Background: Despite significant advances in treatment and prophylaxis, reactivation of cytomegalovirus (CMV) remains a major complication following allogeneic hematopoietic cell transplant (allo-HCT). Methods to decrease the risk of CMV reactivation and long-term sequelae of CMV disease include controlling for known risk factors and administering appropriate antiviral treatments. Although they have been shown to be effective, these treatments carry considerable adverse effects that may limit their early or extended use. The optimal timing to initiate induction treatment remains unclear, especially in the pediatric population.

Methods: We performed a retrospective analysis of patients who received initial conventional or ex-vivo T-cell depleted (TCD) allo-HCT on the pediatric service from January 2010 - June 2018 at Memorial Sloan Kettering Cancer Center. CMV reactivation was defined as ≥ 1 CMV PCR >500 copies in whole blood or >137 in plasma within 180 days post-transplant. Induction treatment was typically initiated for CMV PCR ≥ 1000 copies in whole blood, ≥ 300 copies in plasma, or rising viremia from baseline. Hospital databases and medical records were utilized to identify patients and collect clinical data. Time-dependent Cox models and multi-state models to account for competing risks were performed. This study was approved by Institutional Review Board.

Results: Our study consisted of 227 patients (54 days - 27 years old) who underwent allo-HCT for malignant (N=143) and non-malignant (N=84) diseases. TCD represented 76% of all allografts. CMV donor (D) and recipient (R) serostatus were: D+/R+ N=90, D+/R- N=29, D-/R+ N=38, D-/R- N=70. Cumulative incidence of CMV reactivation was 24.8% within the first 180 days post-allo-HCT and 15 patients (27%) developed CMV disease. Median time to CMV reactivation was 24 days (IQR 14-33). Of the 56 patients who reactivated, 41 (73%) patients received induction treatment. Six patients were excluded for our analysis as they previously had CMV viremia and received anti-viral treatment within days prior to their allo-HCT. The median time from CMV reactivation to induction treatment was 6 days (IQR 1-15). D+/R+ serostatus was a predictor for CMV reactivation when compared to D-/R+ (HR=2.1, [95% CI 1.1 - 4, P< 0.001]). Overall survival (OS) varied significantly based on timing of induction in both conventional and TCD transplants (p=0.04). In the TCD only subgroup, timing of induction remained significantly associated with OS (p=0.02) with an optimal treatment time within 1 week of reactivation. There was no association found with the timing of induction treatment and risk of CMV disease. Interestingly, early treatment prior to fulfilling criterion for CMV reactivation was associated with lower OS.

Conclusions: A short interval between CMV reactivation and initiation of induction treatment was significantly associated with improved OS in combined conventional and TCD HCT, as well as in the TCD only subgroup. Earlier treatment did not translate into improved clinical outcomes, which may be confounded by high-risk patients receiving induction therapies earlier. Further evaluation into CMV prophylaxis and differences in timing of induction treatment on additional CMV outcomes will help optimize treatment options and improve clinical outcomes.

Clinical Trial Registry: n/a

Disclosure: Authors with nothing to declare.: Christine Camacho; Irene Rodriguez; Audrey Mauguen; Elizabeth Klein; Maria Cancio

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Prediction of Bloodstream Infection Risk using Citrulline as Biomarker of Intestinal Mucositis in hemato-oncology Patients

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Background: Bloodstream infections (BSI) remain important complications in hemato-oncology patients treated with intensive chemotherapy and hematopoietic stem cell transplantation (HSCT). Classically, neutropenia and central venous catheter (CVC) use have been considered the most important risk factors for BSI, thereby overlooking the impact of intestinal mucositis (IM). Preventive measures may therewith be partially misdirected and may result in overuse of antimicrobial agents, which impacts antimicrobial resistance and disruption of intestinal microbiota.

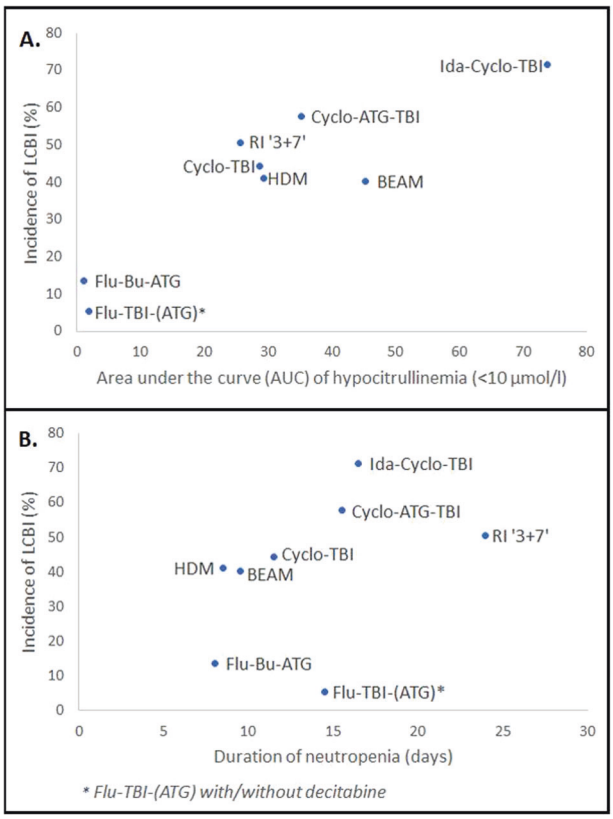
Earlier studies have suggested that severe IM, defined as hypocitrullinemia (citrulline < 10 μmol/l), is an independent risk factor for BSI.

The aim of our study was to grade the IM of commonly used chemotherapy and conditioning regimens and characterize its relationship with the incidence of BSI.

Methods: We performed a retrospective analysis of patients treated between January 2014 and January 2019, managed with a CVC for remission-induction chemotherapy ('3+7'), myeloablative conditioning (MAC) for autologous HSCT, and MAC or non-myeloablative/reduced intensity conditioning (NMA/RIC) for allogeneic HSCT. Patients received oral gram-negative antimicrobial prophylaxis. Data were collected on CVC characteristics (e.g. insertion site), neutropenia, BSI and cultured microorganisms. BSI definitions (laboratory-confirmed BSI [LCBI], mucosal barrier injury LCBI [MBI-LCBI], central-line associated BSI [CLABSI] and catheter-related BSI [CRBSI]) were scored according to Dandoy et al. (BMT 2017). In a subgroup of patients, citrulline levels were measured at baseline and 2-3 times weekly until 3-4 weeks post-chemotherapy. These results were evaluated using linear mixed model analysis. The relationship between the degree of intestinal mucositis, measured as the AUC of hypocitrullinemia ($AUC_{citrulline}$), and the incidence of LCBI, MBI-LCBI, CLABSI and CRBSI was analyzed.

Results: We included 644 episodes of CVC use in 513 patients. Citrulline levels were studied in a subset of 89 patients. A total of 272 (42.2%) LCBIs occurred, that could be classified as MBI-LCBI in 180 (28.0%), CLABSI in 116 (18.0%) and CRBSI in 58 (8.7%) episodes. CRBSI pathogens were mostly coagulase-negative staphylococci, whereas MBI-LCBIs were mostly oral viridans streptococci, gram-negative bacteria and enterococci. Age, sex and CVC characteristics were not associated with the incidence of BSI. However, the grade of IM was significantly correlated with the occurrence of LCBI (Figure 1A), MBI-LCBI and CRBSI. In NMA/RIC the $AUC_{citrulline}$ was < 10 with LCBI occurring in only 11.1% of episodes, despite a duration of neutropenia similar to those of MAC regimens. In '3+7' and most MAC schemes, LCBI occurred frequently (40.2%-57.7%) and the $AUC_{citrulline}$ was significantly higher, i.e. 25-45. The MAC outlier Ida-Cyclo-TBI had the highest incidence of BSI (57.7%), as well as the highest $AUC_{citrulline}$, i.e. 73.9. As expected with increasing IM the incidence of MBI-LCBI rose, but also, CRBSI was exclusively seen in mucotoxic regimens such as '3+7' and MAC conditioning. No correlation was found between duration of neutropenia and BSI incidence (Figure 1B).

Conclusions: The grade of IM of treatments is strongly correlated with the occurrence of BSIs in hemato-oncology patients. Determination of the grade of IM can aid in supportive care decisions, e.g. indication for antimicrobial prophylaxis.



[Figure 1. Correlation between LCBI and (A) AUC of hypocitrullinemia, (B) duration of neutropenia]

Disclosure: Nothing to declare.

P389

Prediction of CMV Reactivation by the Recipient IGG Titer Before allo-HCT

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Background: Recipient cytomegalovirus (CMV) seropositivity is known as a risk factor of CMV reactivation after allogeneic hematopoietic stem cell transplantation (allo-HCT), but it still remains unknown whether recipient pre-transplant CMV-IgG titer is associated with CMV reactivation after allo-HCT.

Methods: We retrospectively analyzed 308 patients who underwent allo-HCT in our institution between 2007 and 2017 with an available pre-transplant CMV-IgG titer data by enzyme immunoassay (EIA), and achieved neutrophil engraftment after allo-HCT. Patients who received letermovir prophylaxis were excluded. The general cut-off value of CMV-IgG titer for seropositivity was defined as ≥ 2.0 of EIA. CMV antigenemia was monitored from the time of engraftment using the C10/11 antibodies, and CMV reactivation was defined as ≥ 3 positive cells. Using receiver operating characteristics (ROC) curve analysis, we decided the best cutoff of CMV-IgG titer and analyzed the impact of CMV-IgG titer on CMV reactivation, CMV diseases, non-relapse mortality (NRM), relapse, and overall survival (OS).

Results: The ROC curve analysis showed that the best cutoff of CMV-IgG titer was 5.8 with an area under the curve of 0.746. We divided cohorts into three groups(≥ 5.8, 2.0-5.8, and < 2.0 groups as the "High-titer", the "Low-titer" and the "Negative" groups) according to the cutoff value.

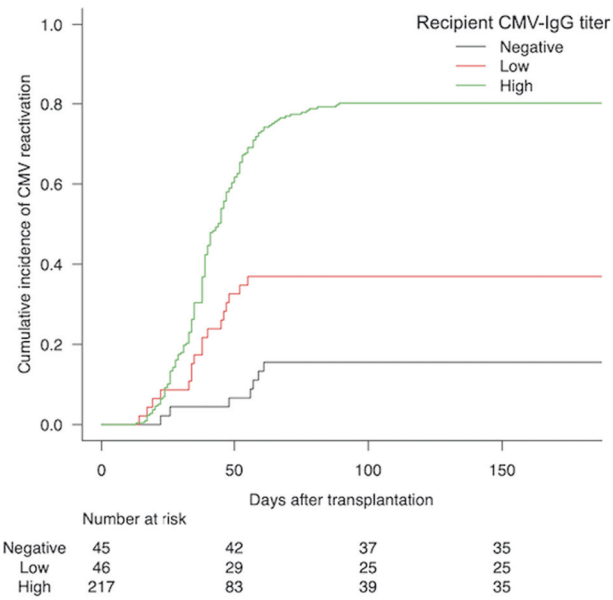
Among three groups, the "High-titer" group included significantly more patients with age ≥50, myelodysplastic syndrome or myeloproliferative neoplasm, and reduced-intensity conditioning, whereas the "Low-titer" group included more patients with ECOG PS 2 to 4.

CMV reactivation more frequently occurred in the "High-titer" group, compared with the "Low-titer" and "Negative-titer" group (80%, 37% vs. 16% at 180 days after allo-HCT, P< 0.01). In multivariate analysis, independent risk factors for CMV reactivation were identified as following: patients in the "High-titer" group [HR 9.61, P< 0.01] and the "Low-titer" group [HR 3.10, P=0.017], diagnosis of malignant lymphoma [HR 1.78, P=0.019], matched unrelated donor [HR 1.63, P=0.026], and the use of alemutuzumab [HR 2.26, P=0.015].

The cumulative incidence of NRM and relapse were not significantly different among the three groups[NRM 18%, 15% vs. 7%, P=0.344, relapse 34%, 27% vs. 22%, P=0.314 respectively], whereas OS tended to be lower in the "High-titer" group, than the "Low-titer" and the "Negative" group [2-year OS 56%, 60% vs. 80%, P=0.081]. In multivariate analysis, CMV-IgG titer was not associated with an increased risk of NRM, relapse, or OS.

No patients in the "Low-titer" and the "Negative" group developed CMV diseases after allo-HCT.

Conclusions: We demonstrated that the higher titer of recipient CMV-IgG before allo-HCT would predict CMV reactivation after allo-HCT, although it was not significantly associated with other survival outcomes. Recipient CMV-IgG titer should be considered in the risk stratification of CMV reactivation.



[Cumulative incidence of CMV reactivation after allo-HCT among three groups]

Clinical Trial Registry: No clinical trial registry
Disclosure: Nothing to declare.

P390

Comparison of Infectious Complications among Patients Receiving Unmanipulated Haploidentical Transplant followed by Post-transplant Cyclophosphamide and Selective Ex Vivo T-cell Depleted Haploidentical Transplant

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Background: Despite significant recent progress in haploidentical haematopoietic stem cell transplantation (haplo-HSCT), infection and graft-vs-host disease (GvHD) continue to be the major causes of transplant related mortality. We retrospectively analysed and compared the outcome of adult patients with haematological malignancies receiving haplo-HSCT using two different platforms for GvHD prophylaxis: selective ex-vivo T cell (TCRαβ and CD45RA+) depleted haplo-HSCT (Koh LP et al. Blood 2018; 132: 2093a) vs unmanipulated T cell replete haplo-HCT with high dose post-transplant cyclophosphamide (PTCy).

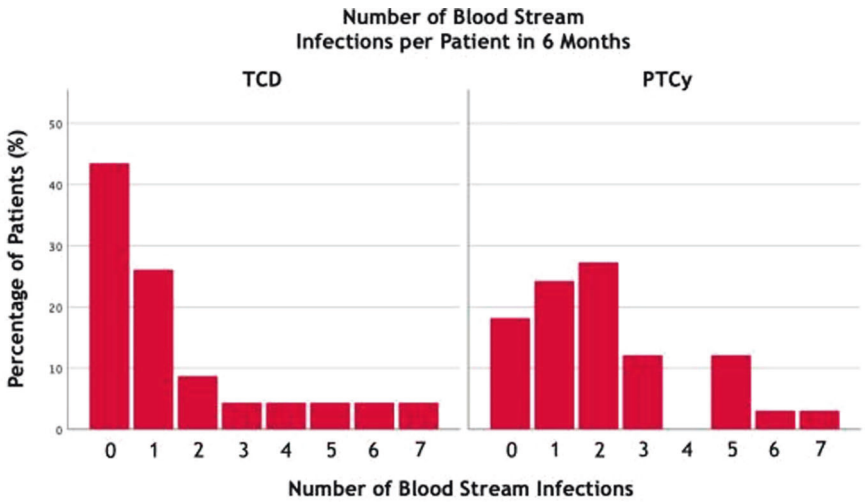
Methods: We studied the outcome of 56 consecutive adult patients with high risk haematological malignancies receiving haplo-HSCT in our institution between 2011 and 2019, comparing the incidence of infection within the first 180 days post-HSCT, between TCD (N=23) and PTCy (N=33) recipients.

Results: Other than age (median age TCD 36 years vs PTCy 46 years; p=0.038), both groups were comparable with regards to all other baseline characteristics (p>0.05 for all). TCD patients achieved earlier neutrophil recovery (median days to absolute neutrophil count >500 / μL = 10.5 vs 15, p< 0.001) as compared to PTCy patients. Day-180 cumulative incidence of grade 2-4 GvHD was significantly higher among TCD recipients (30.4% vs 15.2%, p=0.043).

There was no statistically significant difference in the median time to the onset of blood stream infection (BSI) (5 vs 10 days, p= 0.611) invasive fungal infection (IFI) (43 vs 41 days, p= 0.427), cytomegalovirus (CMV) reactivation (23 vs 25 days, p= 0.138) and BK viruria (56 vs 39 days, p= 0.335) for TCD and PTCy recipients, respectively.

There was no statistically significant difference in the day-180 cumulative incidence of BSI (56.5% vs 81.8%, p=0.064), IFI (30.4% vs 27.3%, p=0.709), CMV reactivation (73.9% vs 81.8%, p=0.916), or BK viruria (21.7% vs 33.3%, p=0.311) between TCD and PTCy recipients, respectively. There was a higher incidence of adenovirus infection in TCD recipients (17.4% vs 0%, p=0.014). There was a trend towards less frequent BSI events per patients among TCD patients as compared to PTCY patients (median event 1 vs 2, p=0.067) (Figure 1). However, there was no statistically significant difference in the incidence of gram positive and gram-negative BSI between both groups (p=0.889).

6-month cumulative incidence of infection-related mortality (IRM) was significantly higher for TCD (26.1% vs 6.1%, p=0.045). However, this difference did not translate into any significant difference in overall survival at 6 months for both groups (TCD 56.5% vs PTCy 78.8%, p=0.112).



[Figure 1 - Number of Blood Stream Infections per Patient in Six Months]

Conclusions: Our study shows comparable incidence of post-transplant infection between the two haplo-HSCT platforms, although infection related mortality was significantly higher among TCD recipients. This could be attributed to the higher incidence of acute GvHD seen among TCD recipients. More effective strategies are needed to eliminate the high risk of severe GVHD in these patients, while preserving antitumor and antimicrobial immunocompetence.

Disclosure: Louis-Pierre Girard received financial support from the Scottish Haematology Society, Aberdeen Medico-Chirurgical Society, and Santander Universities. All other authors have nothing to declare.

P391

The Cumulative Incidence of Multiple DNA Virus Reactivation is not Different in Non-depleted Haploidentical Stem Cell Transplantation and Unrelated Allogeneic Stem Cell Transplantation

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Background: Viral reactivation is frequent in haploidentical stem cell transplantation (haplo-HSCT) based on post-transplant cyclophosphamide and in matched-unrelated donor allogeneic stem cell transplantation using thymoglobulin (MUD-HSCT), probably due to delayed immune reconstitution. Few studies have compared the clinical impact of multiple DNA-virus reactivation in haplo-HSCT and MUD-HSCT.

Methods: We retrospectively analyzed 128 consecutive patients with hematological malignancies and severe aplastic anemia, who underwent haplo-HSCT or MUD-HSCT, excluding second allogeneic transplant, from 2010 to 2019. In the haplo-HSCT group, all patients have received mycophenolate mofetil (MMF), tacrolimus, and post-transplant cyclophosphamide (PT-Cy) and in the MUD-HSCT group, all patients received thymoglobulin, methotrexate and calcineurin inhibitor.

Viral monitoring was performed from graft infusion to D +180 by quantitative PCR (qPCR), which were done weekly for CMV and Adenovirus, and every 14 days for EBV. BK virus and HHV-6 were not routinely monitored and qPCR was requested in case of clinical suspicion. The event reactivation / viral infection was assessed in the first 6 months post -transplant.

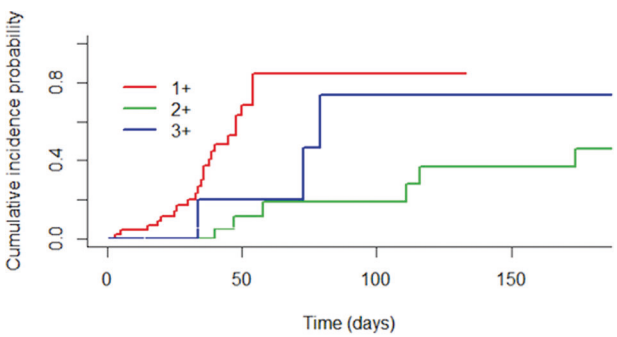
Results: In the haplo-HSCT group (N=59), the median age was 40 (4-76) years and 16 patients (27%), 20 (33%), and 23 (39%) used myeloablative (MA), reduced intensive conditioning (RIC) and non-myeloablative (NMA) regimen, respectively. All grafts were T cell replete and 44 (74,6%) of the haplo-HSCT used GCSF-stimulated bone marrow source. The median time to MMF suspension in the haplo-HSCT was on D+40.

In the MUD-HSCT group (N=69), the median age was 44 (1-76) years and 54 patients (78,3%), 13 (18,8%), and 2 (2,9%) used MA, RIC and NMA conditioning regimen, respectively. Bone marrow was the source of stem cell in 36 patients (52,2%). Fifty-five patients (79,7%) were 10/10 matched HLA and 14 (20,3%) were 9/10 matched HLA.

The cumulative incidence of multiple DNA viruses detection within 180 days post-transplant was high: 84,7% had 1 virus, 58,6% had 2 viruses and 65% had 3 or more viruses (Figure 1). Regarding the type of transplant, there was no difference in haplo-HSCT and MUD-HSCT. The cumulative incidence for 1 virus, 2 viruses and 3 or more viruses for haplo-HSCT and MUD-HSCT groups were 84,3% and 88,3 (p=0,8), 46% and 72,1% (p=0,13) and 73,3% and 50% (p=0,34), respectively.

Median time to first virus detection was 36 (3-67) days in haplo-HSCT and 31 (7-58) days in the MUD-HSCT. In the present study, multiple virus reactivation did not correlate with worse overall survival (p=0,46).

Conclusions: Multiple DNA-virus reactivation is frequent and similar in haplo-HSCT and MUD-HSCT, probably due to the intense immunosuppression related to both types of transplant. Specific strategies for prevention, prophylaxis and monitoring of viral reactivations should be discussed in the centers performing these types of transplants.



[Figure 1: Cumulative incidence of detection of multiple DNA viruses post-transplant]

Disclosure: Nothing to declare.

P392

Neutrophils Response to Human CMV Reactivation in Allogeneic Hematopoietic Stem Cell Transplant Recipients

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Background: Human Cytomegalovirus (HCMV) is a recognized cause of morbidity and mortality in allogeneic hematopoietic stem cell transplant (HSCT) recipients. Although neutrophils are able to promote HCMV dissemination as carriers, little is known about their biological response to the virus. Nonetheless, neutrophils represent the first reconstituting cells and almost the only players of the immune system in the first months after HSCT, when HCMV usually reactivates. This study aims at characterizing the response of neutrophils from HSCT patients to HCMV reactivation in terms of viability, activation, and cytokines expression and production.

Methods: In order to assess functional differences induced by HCMV, neutrophils isolated ex vivo from the peripheral blood of HSCT recipients, with (n=8) and without (n=8) HCMV reactivation, were purified and then evaluated using different methodological approaches (RT-qPCR, flow cytometry, ELISA assay). HCMV reactivation was defined as the presence of detectable viral DNA in plasma. Neutrophils from patients with HCMV reactivation were preliminary tested by RT-qPCR in order to establish that HCMV content in cells was consistent with the viral DNA load in plasma.

Results: According to flow cytometry quantification analysis, neutrophils from patients with HCMV reactivation (HCMV+ patients) showed a slightly increased viability as compared to neutrophils from HCMV- patients. An increased expression of surface markers of activation (CD11b) and adhesion (ICAM-1) was detected by flow cytometry in resting neutrophils from HCMV+ as compared to HCMV- patients. The expression of CD177, a neutrophil-specific membrane glycoprotein involved in mechanisms of activation, was also found to be up-regulated in neutrophils from HCMV+ patients. As expected, gene expression studies indicated an up-regulation of IFN-dependent genes (ISG15, IFIT1, IFI16) in resting neutrophils from HCMV+ as compared to HCMV- patients. In vitro experiments with neutrophils isolated ex vivo, purified, and cultured overnight with several stimuli (LPS, R848, TNFα, IFNα, GM-CSF), indicated that cells from HCMV+ patients displayed an impaired response to IFNα in terms of IFIT1 expression, thus suggesting a possible mechanism of viral immune evasion upon prolonged exposure to IFNα. Additionally, neutrophils from the same patients showed an up-regulation of pro-inflammatory genes such as IL-6, TNFα and CXCL8 (IL-8) upon stimulation with LPS and/or R848. ELISA assay confirmed that, when stimulated with R848, neutrophils from HCMV+ patients released higher amounts of TNFα as compared to neutrophils from HCMV- patients.

Conclusions: Our preliminary results confirm that HCMV+ neutrophils express molecules of activation and adhesion that favor their migration and therefore their ability to disseminate the virus through the body. Upon prolonged exposure to toll-like receptors agonists, HCMV+ neutrophils express and/or release pro-inflammatory agents such as IL-8, IL-6 and TNFα, potentially able to contribute to the pathogenesis of HSCT-related complications such as graft versus host disease (GVHD). Further data, obtained from a larger number of patients, will highlight possible relationships between HCMV reactivation, neutrophils and GVHD in HSCT recipients and will help to identify eventual targets for treatment of HCMV-related complications.

Disclosure: Nothing to declare.

P393

Clinical Efficacy of Letermovir Prophylaxis for CMV Infection after Allogeneic Hematopoietic Stem Cell Transplantation: A Single Center Experience

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Background: Cytomegalovirus (CMV) infection remains a common complication after allogeneic hematopoietic stem cell transplantation (aHSCT), which results in increased morbidity and mortality. Letermovir (LET) is a novel anti CMV drug that inhibits the CMV-terminase complex. The purpose of this retrospective study is to elucidate the real-world data on LET for CMV infection after aHSCT.

Methods: A total of one hundred thirteen patients underwent aHSCT for hematopoietic malignancies between Jan 2009 and Aug 2019. We compared the LET (+) chort with the prematched LET (-) cohort. Propensity score analysis with 1:1 matching with the nearest neighbor matching method was performed to select a control cohort among patients who were transplanted between Jan 2009 and Apr 2018 (before the advent of LET). The incidence of clinically significant CMV infection (CS-CMV; defined as CMV disease or CMV reactivation leading to preemptive

treatment), the time to engraftment, and non-relapse mortality through week 24 after aHSCT were assessed. CMV reactivation was monitored by the CMV pp65 antigenemia assay. Adverse events associated with LET through week 14 after aHSCT were analyzed. This study was approved by the Research Ethics Committee of the Faculty of Medicine, Kansai Medical University.

Results: Of 113 patients underwent aHSCT (median age 48 y (range 17-70 y), 27 patients received LET prophylaxis. Among patients who received LET, 20 patients (74.0%) were considered to be at high risk for CMV, including 6 patients (25.9%) having a haploidentical donor, 2 patients (7.4%) having an HLA mismatched unrelated donor, and 3 patients (11.1%) with an umbilical cord blood as the stem-cell source. LET prophylaxis was begun from the day of aHSCT. Age (>50) at transplantation, disease risk index, CMV serostatus, CMV risk, the use of antithymocyte globulin, prior aHSCT, HLA disparity, the use of reduced intensity conditioning regimen, and stem cell source were used to estimate the propensity scores. The incidence of CS-CMV by week 14 after aHSCT was significantly lower in the LET (+) cohort than that of the LET (-) cohort (11.1% vs 55.6%, P< 0.05). The onset of CS-CMV was late in the LET (+) cohort. Five of 7 patients were treated with glucocorticoid at the time of CS-CMV in the LET (+) cohort. One of 7 patient received antithymocyte globulin as a GVHD prophylaxis. CMV disease was uncommon; however, one patient developed colitis in the LET (+) cohort, and 2 patients developed CMV disease in the LET (-) chort. Non-relapse mortality through week 24 after aHSCT in LET (+) cohort was not significantly improved compared with that of LET (-) cohort (13.6% LET (+) and 22.6% LET (-)). The time to engraftment of neutrophil and platelet was similar in both cohorts. One patient discontinued LET 49 days after aHSCT because LET was suspected to be a cause of nausea.

Conclusions: Consistent with the phase III trial, our study shows that LET for the prophylaxis of CMV infection is safe, and considerably effective in a real-world setting.

Disclosure: Nothing to declare.

P394

At-home Foscarnet Administration in Allogeneic Hematopoietic Transplantantation Patients with Cytomegalovirus Infection: A Safety Feasible Model

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Background: Cytomegalovirus(CMV) infection is a relevant cause of morbimortality in patients receiving allogeneic hematopoietic cell transplantation(allo-HCT). Cytopenias and viral resistance limit the use of ganciclovir therefore patients received intravenous foscarnet(FCN). In this sense, an at-home FCN administration model has been designed for these patients. To evaluate model safety, we compared an at-home group with an in-patient group with similar characteristics.

Methods: Between March 2008 and December 2018, 80clinical records of patients were reviewed. For at-home patients it was mandatory a central venous catheter with one or two lumens. All patients received FCN infusion at 60mg/kg/12h for a glomerular filtrate(FG) >50 ml/min associated with hydroelectrolytic replacements tailored to blood levels. The first dose was administered at hospital. For single-lumen catheter, the nurse made two attendances at home, each for the corresponding FCN dose. Electronic infusion pump(BII)CADD-Legacy® was used for hydration between doses. For two-lumen catheter, the nurse made only one home visit to connect FCN morning dose and hydration solution simultaneously, then a BII at each lumen was connected, one for the next hydration solution, and the other for afternoon FCN. At least 3 laboratory tests were performed per week.

Results: 55patients (69%) received FCN at-home vs. 25 (31%) at-hospital; median(IQR) age was 52-years (43-61). The main diagnosis was acute leukemia in 50patients (63%), 52(65%) received a reduced intensity conditioning and 54(74%) from an unrelated donor. There were no statistically significant demographic differences between two groups, except in GvHD prophylaxis [at-home: post-transplant cyclophosphamide(PTCY) plus calcineurin inhibitor, 35(64%) vs. in-patient: 6(24%); p=0.002], CMV risk [at-home: high risk, 23(42%) vs. in-patient: 19(76%); p=0.005) and corticosteroids therapy [(at-home: 33(61%) vs. in-patient: 22(88%); p=0.02)]. Regarding toxicities, the cumulative incidence(CI) at 30 days of acute kidney injury (AKI) for the whole series was 59% and for severe AKI (grades 2-3) was 26%, there was no difference according to groups(see table). In this sense, FCN tailoring and IV hydration allowed to complete treatment in most patients. Sixteen patients(20%) showed genito-urethral ulcers(GUU) that in 11(14%) leaded to FCN discontinuation. The at-home group developed significative higher incidence of GUU [15(27%) vs. in-patient, 1(4%); p=0.02], thereof 11 (73%) were men and of these, 3 out of 4 had received PTCY-prophylaxis. We did not observe differences in other toxicities between both groups(see table). The median days (IQR) of FCN therapy was 15-days(9-36) and 722

admission days were saved in the at-home group. None of the at-home FCN patients required admission for CMV complications or FCN toxicities.

Adverse events	Total (n=80,%)	At-home (n=55,%)	In-patient (n=25,%)	p
AKI1 AKI2-3 AKI ≥2	17(21) 14 (18)	11(20) 9(16)	6(24) 5(20)	0.8
Digestive toxicity ≥2	4(5)	2(3)	1(4)	0.6
Liver toxicity ≥2	0(0)	0(0)	0(0)	-
Neurological toxicity ≥2	0(0)	0(0)	0(0)	-
GUU	16(20)	15(27)	1(4)	0.02
Infusion reaction	5(5.6)	3(5)	2(8)	0.7

[Table. FCN related toxicity]

Conclusions: Our at-home FCN administration model is feasible, safe and reproducible avoiding hospital admission. In order to reduce the frequency of GUU related to FCN, especially in men, a specific prevention protocol was implemented.

Clinical Trial Registry: no

Disclosure: no

P395

Effects of the Antibiotics Change or the Addition of Anti-mrsa Drugs for Persistent Febrile Neutropenia after Autologous Stem Cell Transplantation

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Background: When febrile neutropenia (FN) persists despite an administration of broad-spectrum antibiotics after autologous hematopoietic stem cell transplantation (auto-HCT), we empirically change antibiotics to the different class of antibiotics or add anti-methicillin resistant staphylococcus aureus (MRSA) drugs. However, the effectiveness of these approaches remains unclear, because the neutropenic duration after auto-HCT is relatively shorter than allogeneic HCT or induction therapy, although severe skin/mucosal injury occurs and central venous catheter is often inserted. Therefore, we conducted a retrospective study to evaluate the effectiveness of antibiotics change or the addition of anti-MRSA drugs for persistent febrile neutropenia after auto-HCT.

Methods: We retrospectively reviewed 209 patients who received auto-HCT at our institution between 2007 and 2019. FN that lasted for 4 days or longer was defined as persistent FN. We compared the time to defervescence between patients whose initial antibiotics were changed and/or who additionally received anti-MRSA drugs and those who did not. The antibiotics change, the addition of anti-MRSA drug or time of neutrophil engraftment were treated as time-dependent covariates.

Results: Neutrophil engraftment was achieved in all patients, and the median time of engraftment was 12 days (range 8-30 days). The cumulative incidence of FN was 93.8% (95% Confidence interval [CI] 89.5-96.3%), and only 8 cases (3.8%) were identified as bacteremia by blood culture. Persistent FN occurred in 140 patients (67%). When we evaluated defervescence after persistent FN as an event of interest, changes of antibiotics and neutrophil engraftment were not significant factors (hazard risk [HR] 0.80, p=0.35 and HR 1.30, p=0.27). On the other hand, an addition of anti-MRSA drugs was a risk factor for delayed defervescence after persistent FN (HR 0.57, p=0.0049). However, there was a bias due to patient background, as the time from auto-HCT to FN was significantly shorter in the anti-MRSA addition group (4 days vs 6 days, p< 0.001), and C-reactive protein at persistent FN was significantly higher in the anti-MRSA addition group (8.61 vs 3.58 mg/dL, p< 0.001).

Conclusions: In this study, the antibiotics change or the addition of anti-MRSA agents were not associated with defervescence after persistent FN in auto-HCT recipients. Although there were significant differences in patient background, the routine changes in antibiotics or the addition of anti-MRSA drugs may not be necessary to improve persistent FN after auto-HCT. However, a prospective study is warranted to confirm these results.

Disclosure: Nothing to declare.

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Therapeutic Drug Monitoring of Posaconazole and Subsequent Dosing in Allogeneic Hematopoietic Stem Cell Transplant Patients

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Background: Real-life data on posaconazole (POS) therapeutic drug monitoring (TDM) in allogeneic hematopoeitic stem cell transplant patients (allo-HSCT) are limited.

Methods: All allo-HSCT patients participating in the Swiss Transplant Cohort Study (STCS) who received POS as prophylaxis and/or treatment between 1.1.2016 and 31.12.2018 were identified through hospital-pharmacy and the STCS databases at the three allo-HSCT-centers in Switzerland. Allo-HSCT, POS-administration, POS-TDM, and other laboratory variables were recorded. Herein, we present preliminary data on POS-TDM distribution from 2 allo-HSCT-centers.

Results: A total of 1554 POS-TDM-levels were recorded in 230 patients in 2 allo-HSCT-centers: 1066 and 488 POS-TDM-levels were performed in 157 and 73 patients, who received POS-prophylaxis and POS-treatment, respectively. POS was administered for 120 days (mean, range: 2-1218): 117 and 137 days in the POS-prophylaxis and POS-treatment groups, respectively. The mean POS-TDM-level was 1.47mg/L (range: 0-8.28): 1.4 and 1.65mg/L in the POS-prophylaxis and POS-treatment groups, respectively (P-value< 0.001). POS-TDM-levels on day(D)7±3, 14±3, 28±3, 42±3, and 84±3 were available for 170, 131, 111, 82, and 40 patients, respectively. The mean POS-TDM-levels by D7±3, 14±3, 28±3, 42±3, and 84±3 were 1.03, 1.3, 1.55, 1.64, and 1.75mg/L, respectively. Amongst 157 patients who received POS-prophylaxis, 214/1066 (20.1%) of POS-TDM-levels were < 0.7mg/L. The mean POS-TDM-levels on D7±3, 14±3, 28±3, 42±3, and 84±3 were 1.02, 1.18, 1.57, 1.62, and 1.76mg/L, respectively. A total of 43/118 (36.4%) and 11/74 (14.5%) patients with POS-TDM-levels available by D7±3 and D28±3, respectively, had POS-TDM-level< 0.7mg/L. In multivariable analyses, allo-HCT at center-A was protective of POS-TDM-level < 0.7mg/L by D7±3 (odds ratio, OR:0.19, P-value:0.001). Amongst 73 patients who received POS-treatment, 149/488 (30.5%) of POS-TDM-levels were < 1.0mg/L. The mean POS-TDM-levels on D7±3, 14±3, 28±3, 42±3, and 84±3 were 1.06, 1.45, 1.51, 1.69, and 1.74mg/L, respectively. A total of 20/46 (43.5%) and 11/35 (31.4%) patients with POS-TDM-levels available by D7±3 and D28±3, respectively, had a POS-TDM-level< 1.0mg/L. There were no variables associated with POS-TDM-level< 1.0mg/L by D7±3.

Conclusions: Large variability in POS-TDM-levels is observed in allo-HCTr, with subtherapeutic POS-TDM-levels observed in up to 1/3 of patients and incremental changes attained with longer administration courses. Local practices are important determinants of POS-TDM-Levels.

Disclosure: Nothing to declare.

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Prophylaxis with Azithromycin in Allogeneic Cord Blood Transplant and Association with Relapse Rate and Transplant Outcomes

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Background: Azithromycin is a macrolide with antibacterial, anti-inflammatory and immunomodulatory effects. Since 2004, we use azithromycin 1g twice a week for Toxoplasma gondii prophylaxis in cord-blood transplantation (CBT) until patients' engraftment is stable and can tolerate switching to trimetropin-sulfametoxazol. Recently, the FDA warned against the use of azithromycin prophylaxis after allo-HSCT, as a result of an increased risk of disease relapse (compared to placebo) in the interim analysis of a randomized trial to prevent bronchiolitis obliterans (ALLOZITHRO1), which had to be interrupted prematurely. As our specific setting of CBT associates with relatively higher risk of infection and lower risk of disease relapse compared to other types of allo-HSCT, we decided to examine our experience to inform potential changes in clinical practice in our setting.

Methods: This retrospective study analyses the association between prophylaxis with azithromycin and transplant outcomes in all consecutive CBT recipients between 1999 and 2018.

Results: One hundred and thirty-seven CBT (1999-2018) in 128 recipients were included: 79 men (57,7%); median age 38 years (16-63) years; 52.5% AML/MDS, 32.8% ALL, 6,6% chronic lymphoproliferative disorders and 8.1% other; 96,4% myeloablative conditioning. Forty-two cases (30.7%) had acute GvHD grades II-IV. Since July 2004, 109 patients (79,6%) received prophylactic azithromycin with a median duration of treatment of 61 days (7-518). Azithromycin prophylaxis associated with a marked reduction in the incidence of Toxoplasma gondii infection from 14.3% (4/28) to 1.8% (2/109; p=0,004). However, no association was found with the incidence of disease relapse (17.6% vs 26.6%, no vs yes; p=0.339), with other immune-mediated outcomes such as acute GVHD

(30.3% vs 33.1%; p=0,848) or with overall survival (61% vs 58% at 1 year, 53% vs 47% at 2 years; p=0.243).

Conclusions: Our results show that azithromycin prophylaxis does effectively prevent Toxoplasma gondii infection in recipients of CBT. However, it does not seem to impair the incidence of disease relapse or other transplant outcomes in this setting. Therefore, in the setting of CBT, with an increased relative risk of opportunistic infections vs GVHD and disease relapse, our data would support a continued use of azithromycin prophylaxis to prevent Toxoplasma gondii infection. However, in other allo-HSCT settings the risks and benefits of this strategy should be studied to inform clinical practice.

Disclosure: Nothing to declare.

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Reactivated Varicella Zoster (VZV) Infection (Shingles), after Haematopoietic Stem Cell Transplant (HCT) for Haematological Disease in Children: A Significant Problem and Proposal for Future Management

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Background: There are limited data on the incidence and morbidity of VZV shingles post-cessation of antiviral prophylaxis in paediatric bone marrow transplant (BMT) patients. We have noted that it is a significant cause of morbidity after cessation of aciclovir prophylaxis, with hospital admission, pain including post-herpetic neuralgia, scarring and drug toxicity. Many children have described it as the "worst admission" of the entire transplant experience. Our practice has been to stop aciclovir with T-cell recovery. We surveyed our recent experience of VZV shingles, and considered how we might reduce the complication in the future.

Methods: The incidence of VZV shingles was recorded in all seropositive, paediatric patients transplanted between 2015 and 2018 in Manchester. We recorded the CD3, CD4 and CD8 T-cell count at onset of illness, and at time of withdrawal of aciclovir prophylaxis. The morbidities associated with that illness were recorded through telephone questionnaires and chart review.

Results: There were 88 responses. VZV (shingles) was common and 31 (35.2%) patients developed the complication. A majority of these patients were admitted to hospital for infection and pain management [16 (51.6%)] and for a median of 7 days. VZV shingles developed a median of 5 weeks post-cessation of antiviral prophylaxis, and was not related to T-cell reconstitution. 6 patients developed primary VZV infection. 3 patients developed VZV shingles whilst still receiving reduced dose antiviral prophylaxis.

Conclusions: This study shows a high incidence of VZV and significant morbidity within this paediatric BMT population. Reactivation of VZV occurred commonly, and despite immune reconstitution and despite continued low dose aciclovir prophylaxis (despite recent reports that such low dose treatment was adequate). Continued aciclovir prophylaxis is also not without adverse effects, and prolongs the "sick role" of the child beyond the transplant period, in the child returning to an otherwise full life. We propose, and discuss, a VZV vaccination strategy, with inactivated vaccine to reduce the incidence of this complication.

Disclosure: Nothing to declare.

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Letermovir Prophylaxis Reduces Inpatient Resource Consumption by Being Effective in Preventing Cytomegalovirus Reactivation after Allogeneic Hematopoietic Cell Transplantation: A Single Center real-world Experience

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Background: Reactivation of cytomegalovirus (CMV) still contributes essentially to morbidity and mortality after allogeneic hematopoietic cell transplantation (alloHCT). In January 2018, letermovir was approved by the European Commission for prophylaxis of CMV reactivation in seropositive patients who have undergone alloHCT. In a pivotal phase III trial letermovir significantly reduced the incidence of CMV reactivation (NEJM 2017;377:2433). Therefore, letermovir prophylaxis was established as standard policy at our institution in March 2018: letermovir is given in seropositive recipients from engraftment until day +100 or CMV reactivation. We conducted a retrospective study to investigate the effectiveness of letermovir prophylaxis for CMV reactivation and the impact on resource consumption.

Methods: The study cohort was formed by the first seropositive 80 patients who received letermovir prophylaxis at our institution (between March 2018 and March 2019). This patient cohort was compared with a control group containing another 80 patients who were transplanted

at our institution between January 2017 and March 2018, i.e. before the introduction of letermovir. CMV viremia was monitored by quantitative PCR twice a week during the inpatient period and weekly thereafter. Patients showing CMV reactivation prior to engraftment were not considered as event in both groups.

Results: The cohorts were completely matched for CMV donor/recipient sero-status and well matched for use of ATG, conditioning regimen, immunosuppressant use, underlying disease and donor type. The cumulative incidence of CMV reactivation on day +100 with altogether 11 reactivation events was 14% (95%CI 7-23%) in the letermovir group. This was significantly lower than in the control cohort (33 events, d +100 cumulative incidence 41% (95%CI 30-53%); HR 0.29 (95%CI 0.15-0.58); p< 0.0001). In terms of health economics, the cumulative expenses for foscarnet and valganciclovir until d +100 could be substantially reduced in the letermovir cohort: no therapy with foscarnet was necessary in the letermovir group compared to 7 out of 80 patients in the control cohort receiving foscarnet in the hospital with cumulative 407 inpatient days (256 days for initial alloHCT hospitalisation). The cumulative number of days on valganciclovir before d +100 was 368d for 80 letermovir patients vs 836d for 80 control patients. Four deaths occurred before d +100 in the letermovir group (three NRM, one PD) vs 7 deaths in the control group (five NRM, two PD).

Conclusions: By this retrospective study the efficacy and safety of letermovir for the prophylaxis of CMV reactivation after alloHCT could be proven in a real-world setting. Letermovir dramatically lowered the cumulative incidence of CMV reactivation to the same extent as observed in the pivotal trial. In terms of resource consumption, letermovir substantially reduced hospitalisation needs for foscarnet application enabling health care providers to allocate inpatient resources to other patients in need. Moreover, costs associated with administration of the therapeutic anti-CMV agents foscarnet and valganciclovir could be lowered substantially. In order to assess the impact of letermovir prophylaxis on overall and non-relapse mortality longer follow-up will be needed.

Disclosure: Patrick Derigs, Maria-Luisa Schubert, Paul Schnitzler, Tilman Schöning and Thomas Luft have nothing to declare.

Carsten Müller-Tidow, Peter Dreger and Michael Schmitt are members of a national advisory board of MSD Germany.

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Analysis of CMV Reactivation Risk after T Cell Replete Haploidentical and Matched Donor Allogeneic Hematopoietic Cell Transplantation

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Background: Cytomegalovirus reactivation is a frequent complication of allogeneic hematopoietic stem cell transplantation. We analyzed retrospectively the incidence of CMV reactivation after haploidentical donor transplantation using post-transplant high dose cyclophosphamide (ptCy) in comparison with standard matched sibling or unrelated donor transplants.

Methods: Data on patients who underwent first alloHCT at Institute of Hematology and Blood Transfusion in Prague between 2/2010 and 7/2019 was extracted from our transplant database. CMV was measured in peripheral whole blood by Q-PCR every week in early post-transplant period and later usually less frequently during outpatient controls. Detected CMV quantity was normalized to 10000 human genome equivalents assessed by quantification of albumin gene in the sample. Time to first clinically significant positivity (more than 100 copies of CMV per genomic equivalent) was calculated. Cumulative incidence estimates were calculated using R 3.6. GvHD prophylaxis was CSA +MMF in MSD transplants, CSA+MMF+ATG in MUD transplants and CSA+MMF+ptCy in Haplo transplants.

Results: 434 patients were included in the analysis: Donors were haploidentical (Haplo) in 11,3%, matched sibling (MSD) in 27% or match unrelated (MUD) in 61,8% of patients. Median age was 50/49/53 in Haplo/MSD/MUD group, respectively. Myeloablative regimen was administrated to 301 patients (70,3%), reduced intensity conditiong to 127 patients (29,7%). Majority of patients received peripheral blood progenitor cell grafts (90,6%), remaining patients received bone marrow. Allogeneic transplantation was performed mainly for acute myeloid leukemia (198 patients, 45,6%), acute lymphoblastic leukemia (62 patients, 14,3%), myeloproliferative diseases (51 patients, 11,8%) and myelodysplastic syndrome (50 patients, 11,5%). Donor-recipient CMV serology status was negative/negative in 12% (16% haplo, 9% MSD, 12.5% MUD), positive/negative in 36% (29.5% haplo, 14% MSD, 46% MUD), negative/positive in 11% (11% haplo, 14% MSD, 9% MUD), positive/positive in 41% (43% haplo, 61% MSD, 33% MUD).

Overall survival of the whole cohort was 57% and was not different among the groups. Cumulative incidence of

CMV reactivation was 13%, 29% and 31% after MSD, MUD and haploidentical donor transplantation (p = 0.001). In a subgroup analysis according to patient/donor CMV serostatus and donor type, the incidence of CMV reactivation did not differ significantly among groups except in patient positive/donor negative subset, where we have observed significantly lower incidence in MSD patients (9%) compared to haplo (42%) and MUD (54%), p = 0.005. Low number of patients in most serostatus/donor type groups limits the value of this analysis.

Conclusions: We observed no difference in the incidence of CMV reactivation after allogeneic HCT from haploidentical and matched unrelated donors. Patients who received transplant from matched sibling donors had significantly lower risk of CMV reactivation.

Disclosure: Nothing to declare.

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Incidence and Impact of Epstein-barr Virus Events in the Early Phase after Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Epstein-Barr virus (EBV) reactivation may evolve to a life-threatening complication after allogeneic haematopoietic stem cell transplantation (allo-HSCT). In this study, we investigated the characteristics of EBV loads in 382 consecutive allo-HSCT patients.

Methods: In a retrospective analysis of patients receiving allo-HSCT between 2010 and 2016 we determined the incidence rates of EBV-events and their association with recipient age, underlying disease, EBV IgG serostatus of donor/recipient, conditioning regimen, stem cell source, T cell depletion, graft-versus-host disease, and cytomegalovirus (CMV) events. EBV- and CMV-loads were determined by quantitative nucleic acid testing (QNAT) weekly for 3 months after transplantation. EBV- and CMV-surveillance was discontinued after 6 months after allo-HSCT, except in patients with at risk for EBV or CMV complications.

Results: We assessed 382 patients (166 female; 43.5%) suffering from AML n=137, lymphoma/myeloma n=77, MDS/MPN n=68, ALL n=48, CLL n=26, CML n=12, or others n=13, who had undergone myeloablative (278, 72,8%) and non-myeloablative (103; 27,0 %) allo-HSCT between 2010 and 2016. Acute GvHD (grade ≥2) occurred in 110/382 patients (28.8%). Chronic GvHD occurred in 90 (23.6%) of patients. Of 382 patients, 216 (56.5%) had EBV-events with a median value was 11935.50 GEq/mL (range 1000 - 4440000 GEq/mL). The median time interval from allo-HCT to EBV-events was 35 days (range 4 to 1879 days). The median time interval from allo-HSCT to the maximum EBV-events was 62 days (range 8 to 543 days). Donors were EBV IgG positive 328/382 (85.9%) and recipients 366/382 (95.8%). EBV-events were significantly correlated with EBV IgG donor serology (p=0.012), but not with EBV IgG recipient serology (p=0.285). EBV-events were associated with HLA mismatched HCT (p=0.035), donor type (p=0.001), GvHD prophylaxis (p=0.0001) and ATG use for GvHD prophylaxis (p=0.0001). EBV-events were not associated with conditioning regimen (p=0.071), stem cell source (p=0.231), CMV-events (p=0.469), acute GvHD (p=0.236), or chronic GvHD (p=0.657). However, overall survival was significantly shorter among patients with EBV-events (562 ± 468 days) compared to those without (640 ± 594 days; p< 0.0001). Twenty-six (26/382; 6.8%) patients received pre-emptive rituximab therapy at a median EBV load of 36.000 GEq/mL (range 3000 - 900000). The median number of rituximab applications was 3 (range, 1-5). Five patients developed PTLD. The median time to maximum EBV loads in these patients was 57 days after allo-HSCT (range 26 - 63 days). By comparison, 98 of 382 (25%) patients had CMV-events, consisting of asymptomatic CMV-DNAemia in 85 (86.7%) and 10 (10.2%) end-organ disease. CMV-events correlated significantly with acute GvHD (p< 0.0001).

Conclusions: Despite better approaches with weekly surveillance, monitoring and pre-emptive therapy for EBV, EBV-events are associated with reduced overall survival.

The impact of letermovir prophylaxis preventing CMV-events is expected to improve clinical management for CMV, but its impact on EBV-events is unknown.

Disclosure: Nothing to declare.

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Aspergillus Non-fumigatus Invasive Aspergillosis in Children and Adults after Hematopoietic Stem Cell Transplantation (HSCT) & Chemotherapy

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Background: Invasive aspergillosis (IA) is a major cause of morbidity in hematological patients. Aspergillus fumigatus is the most common etiologic agent of IA reported in severely immunocompromised patients. Aspergillosis caused by non-fumigatus Aspergillus species is poorly studied.

Methods: We design the retrospective study in order to investigate the epidemiology of IA caused by Aspergillus non-fumigatus as a single agent in large cohort of patients after HSCT and chemotherapy from 2013 to 2018 in R. Gorbacheva Memorial Institute of Children Oncology, Hematology and Transplantation (CIC725). During the observation period 30 patients with IA caused by Aspergillus non-fumigatus were identified and included into analysis. According to EORTC/MSG 2008 criteria 1 proven and 29 probable cases were diagnosed in children and adults with hematological malignances and non-malignant hematological diseases after allo-HSCT (n=27) and chemotherapy (n=3). The median age was 26 (3-60) y.o., males - 53%. The median follow up time was 10 months; for survivors - 17,5 months.

Results: The underlying diseases in patients with A. non-fumigatus IA were acute lymphoblastic leukemia (37%) and acute myeloid leukemia (30%), aplastic anemia (10%), lymphoma (10%), myelodysplastic syndrome (6,5%), and chronic myelogenous leukemia (6,5%). A. non-fumigatus IA was more common diagnosed in allo-HSCT recipients (90%) then after chemotherapy (10%). Most of the patients at the moment of IA diagnosed received antifungal prophylaxis with fluconazole (83%) or echinocandins (6,7%). Breakthrough IA (prophylaxis with voriconazole - 2, posaconazole - 1) was diagnosed in 10% of patients. Etiology agents were Aspergillus niger - 60%, A. flavus - 34%, A. glaucus - 3%, and A. terreus - 3%. The main sites of infection were lungs (80%), paranasal sinuses (10%), or combination lungs and paranasal sinuses (10%). For the diagnosed IA 26 BAL, 6 sinus fluids and 1 pleural fluid were examined. In 57% cases hyphae of molds was found by microscopy. A. non-fumigatus IA developed in combination with bacterial or other fungal infections in 20% (n=6): Klebsiella pneumonia - 33,3%, Pseudomonas aeruginosa - 33,3%, Kocuria kristinae - 16,7%, Trichoderma viride - 16,7%. The median time of onset of A. non-fumigatus IA after allo-HSCT was 155 (19-922) days. Antifungal therapy was used in all patients: voriconazole - 73,3%, lipid amphotericin B - 6,7%, posaconazole - 6,7%, combination therapy - 13,3%. A. non-fumigatus IA developed on the background of acute graft-versus-host diseases (GVHD) grade 2-3 + glucocorticoids therapy (25%) and CMV reactivation (19%). Overall survival at 12 weeks from the diagnosis of A. non-fumigatus IA was 83,3%. Death could be attributed to IA was registered in one case.

Conclusions: Aspergillus non-fumigatus invasive aspergillosis affected patients predominantly with acute leukemia (67%) and allo-HSCT recipients (90%). Aspergillus niger was the main etiology agent. In 20% cases IA developed in combination with other infections. Aspergillus non-fumigatus invasive aspergillosis was a late complication and developed on the background of CMV reactivation and acute GVHD. Overall survival at 12 weeks from the IA diagnosis was 83,3%.

Disclosure: Nothing to declare.

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Intravenous Pentamidine for *Pneumocystis Jirovecii* prophylaxis in Hematological Patients Treated with Chemotherapy, Hematopoietic Stem-cell Transplant (HSCT) and car-t Cell Therapy

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Background: Pneumocystis jirovecii pneumonia (PCP) prophylaxis with trimethoprim-sulfamethoxazole (TMT/SMX) is recommended in high-risk hematological patients. Nevertheless, intolerance of TMT/SMX and marrow suppression are relatively frequent and may necessitate alternative therapy. Intravenous pentamidine (IV-PEN) could be an alternative for these patients.

We retrospectively describe the experience with IV-PEN as PCP prophylaxis in 45 hematological patients.

Methods: Consecutive patients treated with chemotherapy, HSCT or CAR-T cell therapy receiving IV-PEN in our institution between January 2017 and November 2019 were analyzed.

Indications of IV-PEN were intolerance or allergy to TMT/SMX and marrow suppression. Besides, all patients treated with CAR-T cell therapy received IV-PEN at least once at the moment of lymphodepletion.

Monthly pentamidine dose was 4 mg/kg. Doses were premedicated with steroids.

Risk factors for PCP infection considered were allogeneic stem cell transplantation (allo-SCT), autologous stem cell transplantation (ASCT) or CAR-T cell therapy, lymphopenia, autoimmune disease, lung disease (asthma/COPD) and specific therapies including high doses of corticosteroids,

chemotherapeutic agents (purine analogs, cyclophosphamide, methotrexate, ABVD chemotherapy, vincristine, gemcitabine), anti-thymocyte globulin, cyclosporine and monoclonal antibodies (rituximab, alemtuzumab).

Reasons for discontinuing TMP/SMX, incidence of PCP while on prophylaxis, efficacy and side effects of IV-PEN were retrospectively studied.

Results: 249 patients received HSCT and CAR-T cell therapy (189 autologous-HSCT, 45 allo-HSCT, 12 CAR-T) and all of them received PCP prophylaxis (TMT/SMX: 209/249 (84%), IV-PEN: 37/249 (15%)). 8 additional patients received IV-PEN being high-risk PCP patients treated only with chemotherapy.

Overall, 45 patients (23 male/ 22 female) received IV-PEN (autologous-HSCT: 9/45 (20%) allo-HSTC: 16/45 (35%), CAR-T:12/45 (27%), chemotherapy: 8/45 (18%). Median age was 51.7.

Diagnosis of the patients: high grade NHL (11), low grade NHL (12), Hodgkin lymphoma (5), multiple myeloma (5), acute myeloid leukemia (6), myelodysplastic syndrome (3) and aplastic anemia (3).

Number of risk factors for PCP: 1-2, 17 (38%); 3-4, 27 (60%); >4, 1 (2%). Table 1.

Reasons for discontinuing TMP/SMX: intolerant/allergic: 10/45 (22%), pancytopenia: 32/45 (71%) and poor graft: 3/45 (7%).

The total number of IV-PEN doses administered was 128. Median number of doses per patient was 2 (1- 12) and 25 patients (55 %) received 2 or more doses.

Only 5 patients had adverse events with mild toxicity: paresthesia (4%), nausea (2%), abdominal pain (2%) and allergic rash (2%). No severe adverse events were described.

Reason for discontinuing IV-PEN: end of risk period 17/45 (38%), allergy to pentamidine 1/45 (2%), death 10/45 (22%), resume of TMT/SMX 8/45 (18%). IV-PEN prophylaxis is ongoing in 9 patients.

None of the 45 patients were diagnosed with PCP while on IV-PEN prophylaxis.

Conclusions: 11% of HSCT patients need an alternative therapy to TMT/SMX in this series. Our experience with IV-PEN shows a very low rate of adverse events. Although incidence of PCP infection is low, in this high-risk population IV-PEN seems not to increase the incidence of PCP and could be considered a safe and effective alternative.

Disclosure: Nothing to declare.

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Intensification of CMV Prophylaxis with the use of Ganciclovir during the Conditioning in Haploidentical Transplantation with post-transplantation Cyclophosphamide. Comparison with a Standard Strategy. 113 Patients

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Background: Cytomegalovirus reactivation in seropositive recipients of haplo stem cell transplantation is a common event. Letermovir is not yet universally available and there are published data which have shown that the addition of ganciclovir, during the conditioning, can decrease it. We present our experience with this strategy in the field of haplo transplant with cyclophosphamide post-transplantation (Haplo-PTCy).

Methods: We analyzed retrospectively all patients in our institution that underwent Haplo-PTCy from Jan 2015 to Oct 2019. In this study were included those who were seropositive for CMV and were alive at d+ 21. We compared the incidence of CMV reactivation, CMV disease, and toxicity between the groups who received ganciclovir to those who did not

Results: 113 patients met the inclusion criteria, 68 received ganciclovir, 5 mg/kg/bid from d-8 to -2, plus valacyclovir, 1.000 mg TID, or acyclovir, 500 mg/m2 TID, from day zero to +100 (intensive group), and 45 received only val/acyclovir from day - 8 to +100 (standard group). Both groups were monitored weekly for CMV reactivation and treated with val/ganciclovir if present.

The main characteristics of both groups are summarized in table 1. The foremost difference between them was that in the intensive group more patients received steroids and were younger

CMV reactivation occurred in 76% of the cases in the intensive group and in 80% in the standard (P: 0.6), the first positive viremia was on day + 39 (range 17-85) and + 40 (range 23-69) respectively (P: 0.64) Fig 1. The median time to first negative CMV viral load after treatment was 21 days (range 6-49) for the intensive and 22 days (range 6-48) for the standard. Four patients (6%) in the intensive group and 2 (4%) in the standard had CMV disease, however, there were no deaths due to the CMV in any group. Regarding the toxicity, 4% in both groups had acute kidney injury with complete resolution after the dose of offending medication was decreased

	Intensive Group	Standard Group	P
Age	22 (2-53)	35 (5-56)	0.001
< 18 y (%)	44%	19%	0.016

	Intensive Group	Standard Group	P
Malignancies (%)	85%	86%	0.084
Myeloablative Conditioning	90%	100%	0.055
Steroids > 0.5 mg/kg	36%	11%	0.008

[Table 1]

Conclusions: The incidence of reactivation in both groups was high, near to 80%. Whit the caveat that in the group those who received ganciclovir there were more patients on steroids, our study shows that in the field of Haplo-PTCy the intensification of CMV prophylaxis with the addition of full dose of ganciclovir for seven days during the conditioning to the standard strategy does not decrease neither the incidence of CMV reactivation nor the time of first viremia in seropositive patients. With the availability of new medication for CMV prevention in the market it is worth to explore the use of it in this high risk population

Disclosure: Nothing to declare.

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Prophylactic Dose Trimethoprim/sulfamethoxazole Does not Lead to Delayed Neutrophil and Platelet Engraftment in Allogeneic Haematopoetic Stem Cell Transplant Recipients

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Background: Toxoplasmosis and pneumocystis jirovecii pneumonia (PJP) are associated with high morbidity and mortality post-allogeneic haematopoetic stem cell transplant (allo-HSCT). Our first-line prophylaxis is trimethoprim/sulfamethoxazole (TMP/SMX). Due to graft failure concerns, our centre delays initiating TMP/SMX in recipient/donors who are toxoplasma seronegative (TPSN) and uses alternative PJP prophylaxis until stable engraftment. Only if the recipient and/or donor are toxoplasma seropositive (TPSP) is TMP/SMX commenced at conditioning. This analysis explores the effects of TMP/SMX during the peri-engraftment period.

Methods: A retrospective analysis was performed on adults undergoing sibling or matched unrelated donor (MUD) allo-HSCTs performed between January 2016 and December 2017 at the Royal Marsden Hospital, London. The primary outcome was time to neutrophil and platelet engraftment. TPSP recipients/donors received 480mg TMP/SMX twice a day, three days a week from conditioning and TPSN recipients/donors began prophylaxis after engraftment. European Society for Blood and Marrow Transplantation engraftment definitions were used.

Secondary endpoints included progression free survival (PFS), overall survival (OS), occurrence of toxoplasmosis, primary graft failure (failure to achieve a neutrophil count of $\geq 0.5 \times 10^9$/L for ≥3 days by day 28 post-HSCT) and secondary graft failure (persistent neutropenia $< 0.5 \times 10^9$/L and platelets $< 20 \times 10^9$/L for ≥3 months in disease absence). Time to engraftment, OS and PFS were calculated from the time of transplant using Kaplan-Meier analysis and compared using the Logrank test.

Results: 111 patients and 112 allo-HSCTs were included in the study; 34 patients received TMP/SMX at conditioning, 76 patients received TMP/SMX after engraftment, 1 patient received azithromycin and for 1 patient prophylaxis was undocumented. Median age at transplant was 55 years (range 18-72). 103 patients had reduced intensity conditioning; 9 were myeloablative. 32 patients had sibling donors; 80 had MUD.

Median time to neutrophil engraftment was 17 days in both groups (p=0.44). Median time to platelet engraftment was 16 days in both groups (p=0.81). The median PFS of the whole cohort was 34 months (with a median follow-up of 28 months) and the median OS has not yet been reached (the proportion of patients alive at 2 years was 54%). There was no significant difference in PFS between the two groups (hazard ratio 0.74, 95% CI 0.43-1.3, p=0.27) or OS (hazard ratio 1.1, 95% CI 0.61-2.0, p=0.73).

5 patients (4.5%) had primary graft failure, 2 in the TMP/SMX at conditioning group and 3 in the TMP/SMX post-engraftment group. 3 patients lost chimerism, 1 retained full donor and 1 died prior to analysis. 10 patients (8.9%) had secondary graft failure, 5 in each of the TMP/SMX at conditioning and post-engraftment groups. 4/15 graft failure patients had a second allograft and 3 received a donor lymphocyte infusion.

One patient developed toxoplasmosis disease, diagnosed on MRI. The patient had received TMP/SMX prophylaxis at conditioning as they were donor/recipient TPSP/TPSN.

Conclusions: There was no significant difference in time to neutrophil or platelet engraftment between patients receiving TMP/SMX prophylaxis from conditioning and those delayed until engraftment. Although the numbers were small, there did not appear to be a significant difference in PFS, OS or risk of graft failure between groups.

Disclosure: Nothing to declare.

P406

High Dose Valaciclovir as CMV Prophylaxis in Allogeneic Haematopoietic Stem Cell Transplantation

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Background: Cytomegalovirus (CMV) is a potentially devastating complication of allogeneic haematopoietic stem cell transplantation (alloHSCT). Universal antiviral prophylaxis strategies including letermovir are effective, but expensive and unsubsidised in Australia. Alternatively, prophylactic ganciclovir is myelotoxic and logistically challenging to deliver. Valaciclovir demonstrates anti-CMV activity in high doses, but little current data explore prophylaxis in the alloHSCT setting, particularly for haploidentical transplantation. We aimed to evaluate the clinical efficacy and tolerability of high dose valaciclovir (HDvala) as CMV prophylaxis in alloHSCT.

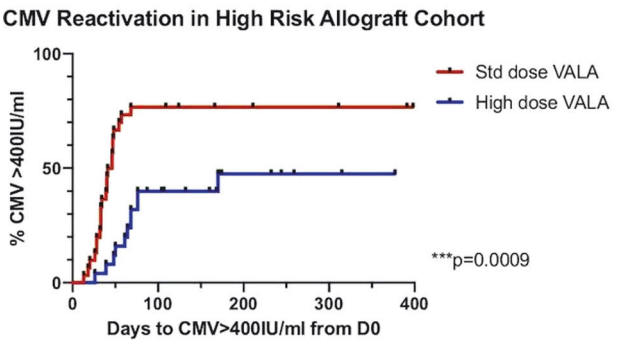
Methods: We performed a retrospective analysis of alloHSCT recipients at high risk of CMV (defined as recipient and/or donor CMV seropositivity, and undergoing T-cell depletion, haploidentical or cord transplantation), treated at the Royal Melbourne Hospital, Melbourne, Australia. Patients transplanted July 2018 - June 2019, treated with HDvala (2g TDS) from day +7 to +100 were compared to a historical cohort (transplanted July 2017 - June 2018) on standard dose valaciclovir (SDvala) (500mg BD until engraftment then 500mg daily). We compared the time to reach a CMV threshold of 400 IU/ml. Tolerability was also evaluated. Patient demographics are described in table 1.

Results: Of the SDvala cohort, (median follow-up 259 days), 23/31(74%) developed a viral load >400 IU/mL, requiring pre-emptive antiviral therapy. None had CMV disease. Median time to viral load >400 IU/mL was 39 days (range 13 - 68).

Of the HDvala cohort, (median follow-up of 209 days), 11/25 (44%) developed a viral load >400 IU/mL, requiring pre-emptive antiviral therapy. Three cases occurred post-cessation of HDvala. One patient developed CMV (gut) disease. Median time to CMV >400 IU/mL was 64 days (range 26-170 days). Time to CMV >400IU/ml was significantly different between the SDvala vs HDvala cohorts (mean ± SEM; 37.9±2.7 vs 67.8±11.3 days, **p=0.0015).

Median HDvala duration was 50 days (range 11-288). Six (24%) patients continued HDvala to day +100. Intolerance led to early cessation in 10 (40%) (acute kidney injury, n=6; cytopenia, n=3, both; n=1). Other patients ceased due to requirement for definitive CMV therapy (n=6) and unclear reasons (n=3).

Conclusions: In high risk alloHSCT recipients, HDvala is an effective CMV prophylactic strategy resulting in lower CMV infection rates and delays CMV reactivation. This may reduce requirement for myelotoxic CMV treatment and inpatient hospital admission. CMV infection following HDvala cessation remains a risk, and ongoing monitoring is required. Treatment tolerability remains a limitation.



[Figure 1: CMV Reactivation in High Risk Allograft Cohort]

	High Dose Valaciclovir Cohort (n=25)	Standard Dose Valaciclovir Cohort (n=31)
Median age, years (range)	52 (27-73)	51 (18-68)
Male/female (%)	16 (64%) / 9 (36%)	16 (52%) /15 (48%)
CMV serostatus (%): D+R+	11 (44%)	17 (55%)
CMV serostatus (%): D-R+ or D+R-	14 (56%)	14 (45%)
Matched Unrelated Donor	15 (60%)	26 (84%)
Haploidentical Donor	7 (28%)	4 (13%)
Sibling Donor	2 (8%)	1 (3%)
Umbilical Cord Blood Donor	1 (4%)	0
Conditioning: Myeloablative / Reduced Intensity (%)	10 (40%) / 15 (60%)	14 (45%) / 17 (55%)

[Table 1: Patient Demographics]

Disclosure: Nothing to declare.

P407

Invasive Mold Disease in a Real-world Hemato-oncology Setting: Value of a Diagnostic-driven Care Pathway

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Background: The incidence and management of invasive mold disease (IMD) in the hemato-oncology population varies according to local epidemiology, diagnostic capabilities and use of anti-mold prophylaxis. Hence, no particular strategy or care pathway has universal application.

We set out to determine the incidence of IMD and evaluate the diagnostic yield of combining serum galactomannan (GM) screening, low-dose CT scanning and broncho-alveolar lavage (BAL) in our institution.

Methods: We performed a retrospective study of IMD cases occurring during neutropenia in adult patients receiving intensive antileukemic therapy or myeloablative or reduced intensity allogeneic stem cell transplantation at the Radboud university medical center. Cases were classified according to the 2008 revised EORTC/MSG consensus criteria. Cases predating antileukemic treatment or neutropenia were excluded. The diagnostic care pathway included twice weekly serum GM screening and low-dose chest CT in cases with positive GM, persistent or recurrent febrile neutropenia (T $\geq 38.5^0$C) or clinical signs of lower respiratory infection. No universal mold-active prophylaxis was given. In patients with suspected pulmonary IMD, BAL was performed if clinically feasible. Anti-mold therapy was initiated while awaiting results of BAL, and could be stopped if no mycological evidence for IMD was found. Serum GM- index of 1x≥0.8 or 2x≥0.5 was deemed positive, BAL was positive if ODI ≥0.8, direct microscopy showed branching hyphae or with positive fungal culture. Additionally, PCR for Aspergillus spp was performed in selected BALs but results were disregarded for classification. SPSS version 25 was used for descriptive statistics.

Results: Between January 2014 and March 2019, 293 cases were screened with serum GM. In 190 cases a chest CT was performed, 3 were prompted by a positive serum GM. BAL was performed in 34 cases. The total incidence of IMD during the study period was 15 % (n= 45) with 15 cases of probable IMD (incidence 5%), 30 cases of possible IMD, and no cases of proven IMD (fig 1). Four cases were culture positive, 3 with Aspergillus fumigatus and 1 with Rhizomucor spp. Twenty-five cases could not be classified due to lack of radiological criteria or inconclusive mycology results. In total, 9 BALs were positive (26%), providing sole mycological evidence in 7 cases. In 6 cases positive serum GM provided mycological evidence and no BAL was performed. PCR was positive in 8/18 BALs, 2/8 BALs were otherwise negative.

Conclusions: The incidence of probable or proven IMD in this homogeneous population was 5%, comparable to previous studies (6-10%). Our diagnostic care pathway reduced the clinically suspected cases by 85%. Serum GM seemed of little value in prompting early CT-imaging, but CT scanning led to a supplemental BAL in 34 cases. The overall diagnostic yield of BAL was low compared to previous studies, suggesting suboptimal real-world diagnostic performance. Repeated screening with CT-imaging and targeted combined mycological sampling, including PCR might further improve the diagnostic value of IMD care pathways in the future.

Disclosure: Nothing to declare.

P408

Single Center Analysis on the Management of Acyclovir Resistant Herpes Simplex Virus Stomatitis in Patients after Allogeneic Hematopoietic Cell Transplantation

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Background: Despite antiviral prophylaxis patients undergoing allogeneic hematopoietic cell transplantation (aHCT) are at risk to develop Herpes simplex virus (HSV) reactivations, particularly stomatitis. HSV reactivations with acyclovir (ACV) resistant strains are a severe complication in aHCT patients. Guidelines suggest as therapy of ACV-resistant HSV-infection intravenous foscavir. Alternatively, local antivirals can be applied. However, data on local therapy of ACV resistant HSV-stomatitis after aHCT are scarce. Here we report on management and outcome of patients who developed severe ACV resistant HSV-1 stomatitis after aHCT at our center.

Methods: As part of our institutional guidelines all patients suffering from HSV stomatitis without clinical improvement after one week of i.v. high dose ACV were tested for ACV-resistance, either by cell culture or sequencing. Patients with documented ACV-resistance were treated either topically with 3% cidofovir solution (rinsing of the oral cavity) and 1% cidofovir gel (lips) or with topical

foscavir creme (Triapten[Tm]) or systemically with foscavir i.v. (40mg/kg, 3x/d).

Results: Among 214 patients who received aHCT at our institution between July 2010 and April 2019 nine (4%) developed ACV resistant HSV-1 reactivations. Six out of these nine patients presented an isolated HSV-1 stomatitis. The three remaining patients were excluded from the analysis due to disseminated HSV-infection (n=2) or simultaneous HSV-infection and severe oral chronic GvHD (n=2). All six patients who suffered from a severe (grade III n=1, grade IV n=5) isolated HSV-1 stomatitis, had the common clinical feature of relapsed AML after allogeneic HCT. The relapses occurred 11 (P1), 24 (P2), 1.5 (P3), 7 (P4), 3 (P5) and 3 months (P6) after aHCT, respectively. Two patients (P1 and P2) developed HSV-stomatitis during the acute phase of a second aHCT. The remaining four patients underwent relapse therapy due to active AML relapse after aHCT (P3: azacitidine, P4: FLAG-Ida, P5: FLAG-Ida, P6: sorafenib). ACV-resistant HSV stomatitis was treated in all six patients locally with cidofovir solution and gel, either as primary (n=4) or as 2nd line (n=2) therapy. Local foscavir creme was applied as primary (n=1) or 2nd line (n=1) therapy. Intravenous foscavir was used in 3 patients (1st line n=1, 2nd line n=2). All patients responded to therapy. Five of six patients developed a CR of HSV-stomatitis. However, five of six patients needed a 2nd line therapy. The median time to response was 42 days and to best response 61 days, respectively. CR were reached by local cidofovir (n=3), local foscavir (n=1) or intravenous foscavir (n=1). All patients with active AML and one patient who received 2nd allogeneic HCT died due to progression of leukemia. Only one patient survived.

Conclusions: ACV resistant HSV-stomatitis is a severe complication in AML patients relapsing after aHCT. It reflects the seriously impaired general condition of these patients. This analysis demonstrates that local therapy with cidofovir or foscavir can result in CR of ACV-resistant HSV-stomatitis in a majority of patients. It can be therefore used as an alternative therapy instead of i.v. foscavir.

Disclosure: Nothing to declare.

P409

Early Bacteremia following Allogeneic Bone Marrow Transplantation without the use of Prophylactic Antibiotic: Changing Epidemiology and Antimicrobial Resistance (2016-2018)

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Background: Bacteremia is a serious complication after allogeneic stem cell transplantation (ASCT). The aim of the study is to determine the incidence, epidemiology and risk factors of bacteremias in early post-ASCT.

Methods: Retrospective study conducted in patients who underwent ASCT from HLA-identical sibling donors between January 2016 and February 2018. Conditioning regimen consisted of Busulfex and Cyclophosphamide (Bu/Cy) or Fludarabine and Busulfex (F/Bu) in myeloid malignancies, TBI or thiotepa-based regimen in lymphoid malignancies and thymoglobuline and cyclophosphamide with or without fludarabine in aplastic anemia. Graft-versus host disease (GVHD) prophylaxis consisted of cyclosporine and short course of methotrexate. No patients received antibioprophylaxis. The first-line empiric antimicrobial therapy was piperacilline-tazobactam and aminosid in the absence of colonization with antibiotic-resistant germs. The adjustment was made according to colonization, the presence of clinical and/or microbiological documentation. Early bacteremia was defined as occuring between day-10 until day 100.

Results: One hundred and twenty patients were included, 26 episodes of bacteremia occured in 21 patients. Incidence was 0.2 episode by patient and 1.23 episode by infected patient. One patient had polymicrobial bacteremia (2 organisms). Ten episodes due to Gram-positive (GP) bacteria (38.5%) and 16 to Gram-negative (GN) bacteria (61.5%). GP/GN ratio was 0.44 in 2016, 0.5 in 2017 and 1.25 in 2018. The most frequent species was Pseudomonas. aeruginosa (n=4, 15.3%) and K.pneumonia (n=3, 11.5%) in GN bacteria and coagulase negative Staphylococci (CoNS) in GP bacteria (n=6, 23%). All CoNS were Methicillin resistant. ESBL-producing enterobacteriaceae and Multi-drug resistant P.aeruginosa were isolated in respectively, 80% (8 of 10) and 75% (3 of 4) of cases. One patient presented vancomycin-resistant enterococcal bacteremia. Nineteen (73%) episodes of bacteremia occured during the first 30 days after ASCT and 38.8% occurred in patients with acute myloid leukemia (AML), followed by aplastic anemia (30.8%). Episodes of bacteremia were catheter-related in 29.2% of cases. Risk factors for early bacteremia were, bone marrow as source of graft (p=0.02), aplastic anemia and AML (p=0.04), and corticotherapy (p=0.01). Mortality rate at 7 days after bacteremia was 4.8% (1 of 21). Early non-relapse mortality was 4.8% in patients with bacteremia versus 3% in patients without bacteremia (p=0.7). The 1-year overall survival was not significantly different between those with and without bacteremia (80.4% vs 92.8%, respectively, p=0.7).

Conclusions: Bacteremia was more frequent within the first 30 days after ASCT indicating the crucial role of neutropenia. Remergence of GP bacteremia and trend to increased multi-drug resistant GN bacteremia have been observed.

Disclosure: No conflict of interest

P410

Diagnostic Yield of Bronchoalveolar Lavage (BAL) in Haematological Patients after Allogeneic/Autologous Hematopoietic Stem Cell Transplantation (HSCT) - Comparison with BAL Performance in non-transplanted Patients

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Background: Pulmonary infections represent significant cause of mortality and morbidity in haematology patients especially after HSCT. However, due to different severity of immunosuppression and antimicrobial prophylaxis the spectrum of causative microorganisms as well as diagnostic yield of BAL and its contribution to adjustment of antimicrobial therapy could differ between individuals undergoing allogeneic or autologous HSCT and non-transplanted haematological patients.

The aim of this study was to evaluate the contribution of the BAL to the final diagnosis of lung infection and adjustment of therapy in above mentioned different patients' groups.

Methods: We retrospectively analysed results of BAL fluid performed between January 2005 and December 2018 in adult haematological patients with pulmonary infiltrates. The BAL was performed within 1 to 2 days after detection of pulmonary infiltrates on conventional chest radiography or CT. BAL sample was obtained from the area where the infiltration was most severe. All patients signed informed consent with the procedure. Treatment changes or modifications were defined as addition, change or prolongation of anti-infective agents.

Results: 390 BAL from 359 patients with median age 54 years (range 18-79 years) were included in the analysis. Severe (ANC< 0.5 x109/L) and moderate (ANC 0.5-0.99 x109/L) neutropenia was present in 176 (45%) and 40 (10%) of cases, respectively. 85 (21.7%) BALs were performed in patients after allogeneic HSCT, 53 (13.6%) in patients after autologous HSCT and 252 (64.6%) BALs in non-transplanted haematological patients.

Bilateral lung infiltrates were present in 72.9%, 75.4% and 69.4% of patients from above mentioned groups (n.s.). Antimicrobials were administered pre-emptively/empirically at the time of BAL in 92.9%, 90.5% and 90.8% of cases, respectively (n.s.).

Microbiological results and comparison between allogeneic/ autologous HSCT and non-transplanted groups are present in the table.

	Allogeneic SCT (n=85)	P value	Non-transplanted haematological pts. (n=252)	P value	Autologous SCT (n=53)
Proven/ probable infections, n (%)	46 (54.1%)	.1093	117 (46.4%)	.2578	22 (41.5%)
Bacterial pathogen, n (%)	24 (28.2%)	.2296	61 (24.2%)	.4051	12 (22.6%)
Fungal pathogen, n (%)	19 (22.3%)	**.0409**	36 (14.2%)	.2843	6 (11.3%)
Viral pathogen, n (%)	5 (5.8%)	.2843	11 (4.3%)	.4246	2 (3.7%)
Pneumocystis jiroveci, n (%)	3 (3.5%)	.0985	19 (7.5%)	.3191	5 (9.4%)
Two and more pathogens, n (%)	10 (11.7%)	**.0073**	11 (4.3%)	.3409	3 (5.6%)

[Table]

Antimicrobial treatment change according to BAL results were done in 35.2%, 30.1% and 27.7% (n.s.), however this percentage increased when BAL results proved infectious etiology (treatment change in 60.8%, 68.1% and 58.1% of cases, respectively (n.s.)).

Conclusions: The diagnostic yield of BAL and % of antimicrobial modification based of BAL results in patients after allogeneic/autologous HSCT do not differ from non-transplanted patients. However, higher percentage of fungal pathogens detected by BAL as well as higher frequency of polymicrobial infections in patients after allogeneic HSCT highlights the role of this semiinvasive procedure for early diagnosis of IFD in this subset of patients without mould active antifungal prophylaxis during hospitalisation in HEPA filtered room.

Disclosure: Nothing to declare.

P411

Versatile Effects of Letermovir Prophylaxis for Cytomegalovirus on Allogeneic Hematopoietic Stem Cell Transplantation: A single-institution Analysis

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Background: Cytomegalovirus (CMV) infection is a common, life-threatening complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Even in the era of preemptive antiviral therapy, the occurence of CMV reactivation is able to affect the cumulative incidence of transplant-related mortality (TRM) directly (e.g. CMV pneumonia) or indirectly (e.g. graft failure, co-infections, or graft-versus-host-disease (GVHD)). Letermovir (LET), a new anti-CMV agent, significantly reduced the incidence of CMV reactivation in a prospective study by prophylactic use. In the present study, we evaluated the suppression of CMV reactivation with this new antiviral prophylaxis could reduce these complications.

Methods: This study includes 31 patients (cases) undergoing first allo-HSCT with prophylactic use of LET and observed more than 100 days at our institution. We selected a patient (control) received first allo-HSCT with no CMV prophylaxis after 2008 at our institution for each case, matched for underlying disease, disease risk index, stem cell source and conditioning regimen. CMV reactivation was defined as the development of CMV antigenemia (at least one pp65 antigen-positive cell per 50000 leukocytes). Neutrophil and platelet engraftment were defined as absolute neutrophil count $>0.5\times10^9$/L in the first 3 consecutive days and platelet count $>50\times10^9$/L in the first 7 of consecutive days without transfusion.

Results: The median age of cases was 56 years (range, 18-69). The underlying diseases were acute myeloid leukemia (n=10), acute lymphoblastic leukemia (n=10), myelodysplastic syndrome (n=9), and malignant lymphoma (n=2). Sources of stem cells were bone marrow (n=15), cord blood (n=10), and peripheral blood (n=6). 10 cases (32%) were received grafts from an HLA-matched sibling or unrelated donor and about two thirds of the cases received HLA-mismatched allografts. 16 cases received cyclophosphamide plus total-body irradiation (TBI)-based myeloablative conditioning. The other 15 cases received fludarabine, melphalan, and low-dose TBI. GVHD prophylaxis consisted of tacrolimus and short-term methotrexate with or without low-dose anti-thymocyte globulin.

Until 100 days after allo-HSCT, only 3 patients of cases developed CMV reactivation. The frequency of CMV reactivation within the cases were significantly reduced compared with controls (9.7% vs 71%, respectively, $p< 0.001$). Preemptive antiviral therapy could be sufficient to suppress CMV end-organ disease, so only one patients of the controls developed CMV end-organ disease (retinitis) and no patients of cases developed until day100. The cumulative incidence of neutrophil and platelet engraftment until day 100 were almost comparable between cases and controls (neutrophil: 96.8% vs 100%, p=0.83; platelet: 64.5% vs 64.5%, p=0.58, respectively). The incidence of bacteremia and fungemia in the cases was slightly lower than in controls, but there was no significant difference (9.7% vs 16%, respectively, p=0.44). Whereas the cumulative incidence of all-grade acute GVHD until day 100 was similar between the two groups (51.6% vs 54.8%, respectively, p=0.74), the incidence of grade II-IV acute GVHD in the cases tended to be lower than in the controls (16.1% vs 35.5%, respectively, p=0.08).

Conclusions: The result of this study suggested that prophylactic use of LET might reduce TRM via not only suppression of CMV disease but also reduction of CMV-indirectly-related complications such as clinically significant acute GVHD.

Disclosure: Nothing to declare.

P412

Impact of a Change in Antibacterial Prophylaxis in Patients Receiving Autologous Stem Cell Transplantation in One Single Center

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Background: Antibacterial prophylaxis benefits in patients undergoing Autologous Stem Cell Transplantation (ASCT) remain unclear: some authors continue recommending its use but antibacterial resistances rates are growing, questioning both its efficacy and safety. In our center Levofloxacin prophylaxis was administered to all ASCT patients until January 2017 when we decided to stop this practice based in our community bacterial susceptibility patterns. The aim of this study is to review the impact of this action in terms of safety.

Methods: We retrospectively evaluated infectious complications in patients undergoing ASCT in our center between 2015 and 2018 comparing two temporary cohorts: patients receiving Levofloxacin prophylaxis versus patients who did not received it, before and after 2017 respectively. Medical records before 2017 were in paper, since then are digitized.

Results: Fifty-two patients underwent to ASCT in this period. Their baseline characteristics, summarized in the table 1, were similar between both goups. CD34 cells infused, engraftment and neutropenia febrile severity were also similar. Prophylaxis group patients received more days of antibiotic treatment on average (19.46 days versus 9.54; IC95%: 6.8-13.5; p=0,003). Other observations showed a trend without reaching stadistically significant differences: more carbapenms and aminoglycosids use (93.75% versus 38.1%; p=0.051; and 62,5% versus 19%; p=0.061; respectively), more glycopeptids added to treatment when fever persisted (100% versus 57.1%; p=0.26), and less febrile neutropenia episodes (53,8% versus 76,9%; p=0,8). Both groups had similar rates of antifungal treatment (25% versus 14,3%; p=0.68), central venous catheter removal (38,5% in both groups), mucositis (73,1% versus 76,9%; p=0.74) and total days of hospitalization (23.8 days on average versus 21,8; p=0,17). None of the patients had Clostridium difficile diarrhoea or died before 100 days after ASCT and multiresistant bacteria were only isolated in 4 patients in the non-prophylaxis group.

Conclusions: In our study antibacterial prophylaxis only shows a tendency in protecting against febrile neutropenia without improving outcome, being probably less cost-effective (as patients received more days of antibiotics) and increasing the probability of appearance of multiresistant bacteria. The fact that multiresistant bacteria were only found in non-prophylaxis group patients could be due to temporal bias: these patients were transplanted recently so multiresistent bacteria could be more spreaded and digitized medical records would be also more accurate.

	Prophylaxis Group (N=26)	Non-Prophylaxis Group (N=26)	Statistical Significance (p<0,05)
Age (average, range)	53.81 (28-67)	50,69 (18-70)	0.41
Sex (male, %)	19/26 (73,1%)	17/26 (65,4%)	0.54
Disease (n, %): Lymphoma, Multiple Myeloma, Acute Leukemia	10/26 (38,5%), 16/26 (61,5%), 0/26 (0%)	12/26 (46,2%), 13/26 (50,2%), 1/26 (3.8%)	0.47
Status Disease (n, %): Complete remission, Partial Remission, Very Good Partial Response, Stable disease	12/26 (46,2%), 5/26 (19,2%), 8/26 (30,8%), 1/26 (3,8%)	16/26 (61,5%), 0/26 (0%), 9/26 (34,6%), 1/26 (3,8%)	0.13
Karnofsky Performance Status (n, %): 100%, 75-90%, <75%	17/26 (65,4%), 8/26 (30,8%), 1/26 (3,8%)	21/26 (80,8%), 2/26 (15,4%), 0/26 (0%),	0.41
Conditioning Regimen (n, %): Mel200, BEAM, BEA	16/26 (61,5%), 10/26 (38,5%), 0/26 (0%)	13/26 (50%), 12/26 (46,2%), 1/26 (3,8%)	0.47

[Table 1: Patients Baseline Characteristics.]

Clinical Trial Registry: Not applicable
Disclosure: No potential conflict of interest

P413

Intravescical Instillation of Cidovofir is Efficient for the Treatment of BK Virus Hemorrhagic Cystitis after Allogeneic Transplantation

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Background: BK virus related hemorrhagic cystitis (BKV-HC) represents e serious complication after allogeneic stem cell transplantation (allo-HCT). There are no clearly defined treatment guidelines for the treatment of BKV-HC. The data on the effectiveness of intravescical instillation of cidovofir (ICI) to manage severe bleeding are very limited. Aim of this study was to evaluate the safety and efficacy of ICI to manage grade III-IV BKV-HC.

Methods: Criteria for the administration of ICI were grade III-IV (clinically significant hematuria with clots) BK-related hemorrhagic cystitis after allo-HCT which showed no improvement after symptomatic therapy with hyperhydration. Cidofovir was diluted in 60 mL of normal saline and installed via a Foley catheter which was blocked for 1 hour. Not knowing the level of absorption of the drug we decided to give probenecid prophylaxis in all patients. ICI was repeated weekly according to severity of symptoms. Urine and plasma BKV viral loads were quantified by RQ-PCR.

Results: In total, 8 patients (median age 41 years, 29-58) received ICI after allo-HCT. All patients had

haematological malignancies (AML 3, ALL 3, MDS 2). Seven patients received busilfex-based myeloablative conditioning regimen and 1 patient reduced intensity conditioning regimen. Seven patients received a graft from PBSC and 1 patient from BM, from a 7/8 HLA-matched (5 pts), 8/8 (2 pts) or haploidentical (1pt) donor. Median time for the onset of BKV-HC after allo-HCT were 49 days (range 23-117). All patients were under standard cyclosporine prophylaxis, 2 patients had prior acute GvHD and 1 patient had active acute GvHD at the time of onset of HC. The median PCR-BKV viral load at the onset of BKV-HC in urine and plasma were $3.45x10^8$ (range $0.15x10^8$-$59x10^8$) and 205.5 (range 0-1600), respectively. The median maximum PCR-BKV viral load in urine and plasma were $26.5x10^8$ (range $4.7x10^8$-$450x10^8$) and 1.350 (range 0-400.000), respectively. All patients had impaired renal function (eGFR < 60 ml/min, median 42 ml/min, range 33-53) at first ICI which was probably multifactorial. The median dose of intravesical cidofovir was 5 mg/kg (range 2.5-5 mg/kg) and a median number of 3.5 instillations (range 2-7) were given. Two patients received additional low dose iv cidovovir (1 mg/kg for one and two doses respectively). In 6/8 (76%) cases symptoms of cystitis improved dramatically without showing any deterioration of renal function or other systemic adverse effects. Virological response (at least 1 log reduction) was observed in 5 cases. After a median follow up of 156 days (range, 79-732) after allo-HCT, 3/8 patients are alive without cystitis symptomatology and 5 died (2 due to relapse and 3 due to TRM).

Conclusions: In this retrospective study we propose that local therapy of BKV-HC with ICI is safe and has high clinical and virological response rates. The administration of ICI after allo-HCT should be controlled in prospective randomized trials.

Disclosure: Nothing to declare.

P414

Risk Factors and Outcome of Early Clostridium Difficile Infection in Acute Leukemia Patients undergoing Allogeneic Hematopoietic Stem Cell Transplantation

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Background: C. difficile infection (CDI), the most common cause of hospital-acquired diarrhea, is very frequent after hematopoietic stem cell transplantation (HSCT) and it is reported to increase the risk of Graft Versus Host Disease (GvHD).

Methods: We evaluated incidence, risk factors and outcome of toxigenic CDI among 62 patients with acute leukemia undergoing allogeneic HSCT between January 2018 and September 2019. All patients performed rectal swab before conditioning. At the first episode of diarrhea, they underwent stool specimen collection and CDI diagnosis was detected by microarray-based Comparative Genome Hybridisation (CGH), identifying toxin producing strains. Levofloxacin routine prophylaxis was given to all patients undergoing HSCT. CDI infection was treated with oral vancomicin. Fidaxomicin was given in case of lack of stool CDI negativity after a 7 day-course of vancomicin treatment.

Results: Nine out of 62 patients (15%) developed toxigenic CDI at a median of 15 days (range 0-22) after HSCT. Comparing patients with and without CDI infection, we observed that patients with CDI infection were more likely to have an history of previous abdominal surgery (p=0.001), prior gram negative bacteria infection (p=0.013), higher hematopoietic comorbidity index (HCT-CI) (0.05) and transplant from mismatched unrelated donor (p=0.0004). Conditioning regimen intensity, mucosyte severity, incidence of gram negative bacteria infections and duration and type of antibiotic treatments during the aplasia period after HSCT were equally distributed between the 2 groups. Moreover, we did not identify any significant differences in the rate of patients developing acute GvHD (p=0.4), while patients with CDI were more likely to present subsequent CMV-DNA reactivation (p=0.02). Median time to reach stool CDI negativity was 11 days (range 5-30) after vancomicin (7 patients) or fidaxomicin in case of vancomicin failure (2 patients). Six month-Overall Survival (OS) was 66,6% for CDI group and 84% for control group (p=0.13)

Conclusions: We conclude that in our experience risk of early CDI infection after HSCT was increased by pretrasplant factors such as previous gram negative bacterial infections and prior abdominal surgery and by the choice of mismatched unrelated donor. Stool negativity was obtained in all patients with appropriate treatment and there was no increased risk of GvHD or OS impairment, suggesting that search for CDI at the first episode of diarrhea after HSCT and prompt treatment can definitively solve this infection without sequelae in allogeneic HSCT recipients.

Disclosure: nothing to declare.

P415

Risk Factors for Cytomegalovirus Infection in Children Undergoing Hematopoietic Stem Cell Transplantation

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Background: Cytomegalovirus (CMV) infection is a serious complication after hematopoietic stem cell transplantation (HSCT). The aim of this study was to analyze the incidence and risk factors for CMV infection in children undergoing HSCT.

Methods: We retrospectively investigated 443 consecutive children (median age, 10 years) who underwent peripheral blood stem cell (n=233; T-cell depleted: n=101) or bone marrow transplantation (n=210) in a single center. Two hundred seventy patients received allogeneic HSCT and 173 patients underwent autologous HSCT. Conditioning regimen was myeloablative in all cases and based on chemotherapy in 72% of transplants or total body irradiation in 28% of transplants. Antithymocyte globulin (ATG) was used in 150 patients (34% of transplants). In allogeneic transplantation, the donor was HLA-matched unrelated in 54% of transplants or a HLA-identical sibling in 31% of transplants. The CMV detection was performed by use of polymerase chain reaction (PCR) and pp65-antigen test.

Results: Thirty six of the 443 patients (8%) developed a CMV infection. Thirty five patients demonstrated a CMV reactivation and one patient suffered from a primary CMV infection. Risk factors for a CMV infection were age (>10 years, p=0.036), type of transplantation (allogeneic vs. autologous, p=0.001), donor (unrelated vs. sibling donor, p=0.012), a positive CMV serostatus of the patient in allogeneic (p< 0.001) as well as in autologous (p=0.008) transplanted patients, conditioning regimen using ATG (p=0.042), and a viral co-infection (p< 0.001). A comparison of both CMV detection methods PCR and pp65-antigen test revealed a significant difference in the duration of CMV detection (p=0.001). By use of PCR the CMV infection could be detected earlier (p=0.008) and longer (p=0.002).

Conclusions: Risk factors for CMV infection after HSCT in childhood are age > 10 years, allogeneic transplantation, especially if an unrelated donor is used, a positive CMV serostatus of the patient, conditioning regimen using ATG, and a viral co-infection. PCR was more sensitive than the pp65-antigen test for detection of CMV infection. Therefore, PCR is more useful to quantify CMV in those children with above mentioned risk factors to initiate early pre-emptive therapy for CMV infection.

Disclosure: Nothing to declare.

P416

Impact of Hypogammaglobulinemia on Outcome of Allogeneic Hematopoietic Stem Cell Transplantation in Adult Acute Lymphoblastic Leukemia Patients

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Background: There is limited experience on the impact of hypogammaglobulinemia on Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) outcome.

The aim of this study was to evaluate the impact of hypogammaglobulinemia on transplant outcome in adult patients affected by Acute Lymphoblastic Leukemia (ALL).

Methods: Adult ALL patients who underwent allo-HSCT at our Institution were studied retrospectively. The patient cohort, according to serum IgG level on admission, was divided into 2 groups: patients with low (< 0.5 g/L) and high (≥0.5 g/L) IgG levels. Serum IgG level was compared with the percentage of following infectious complications: fever of unknown origin (FUO), CMV-reactivation, bacteremia, pneumonia, central venous catheter (CVC)-infection, number of infectious episodes (< 2 or ≥2). Moreover, the impact of IgG on transplant-outcome variables (overall survival [OS], relapse-free survival [RFS] and transplant-related mortality [TRM]) was evaluated by Kaplan-Meier analysis and compared to other variables, such as conditioning regimen, type of donor and disease status at HSCT.

Results: Between December 1st, 2000 and July 31st, 2017 forty-nine adult ALL patients (29 males and 20 females) underwent HSCT at our Institution. Median age was 33 years (range 14-63). Forty-four patients were diagnosed with B-cell ALL (including 14 Ph'+ ALL), while 5 patients had T-cell ALL. Twenty-three patients were in 1st CR at HSCT, whereas 26 patients were in 2nd or later CR, or had active disease. Twenty-seven patients had familiar HLA-identical donor (55%), 15 patients had matched-unrelated donor (UD) (30.5%), while 7 patients underwent mismatched-UD HSCT (14.5%). Stem-cell source was BM in 36 patients (73%), PBSC in 12 patients (25%) and 1 patient had cord blood transplantation (2%).

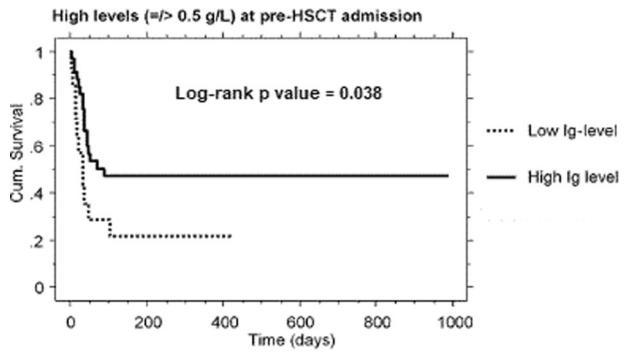
Median IgG serum level at admission was 0.6 g/L. It was significantly lower in patients with advanced disease (i.e. active disease or ≥2nd CR), compared to patients

transplanted in 1st CR (0.54 g/L vs 0.70 g/L, Mann-Whitney p-value: 0.03).

Splitting the cohort, according to IgG level < or ≥ 0.5 g/L, low IgG levels were significantly associated with both the incidence of pneumonia (15% vs 0%; Fisher p-value: 0.02) and ≥2 infectious episodes (45% vs 10%; Fisher p-value: 0.02). Univariate analysis of risk factors demonstrated reduced OS in patients with advanced disease at transplant (log-rank: 0.01), UD transplant (log-rank: 0.04) and low IgG-level at admission (log-rank: 0.038) [fig 1]. Multivariate analysis of IgG-level confirmed its impact on OS and it was independent of status of disease and donor type.

Conclusions: In the present study we found an association between low pre-transplant IgG levels and an increased risk of both higher number of infectious episodes and pneumonia during the early transplant phase. Moreover, hypogammaglobulinemia was associated with reduced overall survival after transplant.

Hypogammaglobulinemia has an unfavorable impact on HSCT outcome in ALL-patients. Well-designed future prospective studies should investigate whether the unfavorable impact could be overcome by IVIg-prophylaxis during the early HSCT phase.



[Overall survival in ALL patients with low (<0.5 g/L) and high IgG levels (≥0.5 g/L) pre-HSCT]

Disclosure: The authors declare. that there is no conflict of interest regarding the publication of this article.

P417

The use of Rifaximine in anti-bacterial Prophylaxis in Patient undergoing HSCT

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Background: Patients undergoing HSCT are at significantly higher risk of developing severe infections. Various methods of anti-bacterial prophylaxis are standard components of peri-transplant management procedure. In the most recent past, antibiotics, such as fluoroquinolones, has been widely used as a prophylaxis. Recently, new antibiotic, rifaximin, was proposed as a successor to previous approaches. Its minimal intestinal absorption allows for maintaining its activity limited to gastriintestinal tract.

Methods: Retrospective analysis of the characteristics of three major groups of patients, who underwent both autologous or allogeneic HSCT (N=247) between October 2015 and November 2019 was performed. Patients received different types of anti-bacterial prophylaxis according to current strategies, including use of ciprofloxacin (N=33), no prophylaxis (N=111) or use of rifaximin (N=103) The impact of type of prophylaxis on infectious complications during early post-transplantation period (100 days) including incidence and type of infections, in particular Clostridum difficile, incidence of septic shock, neutropenic fewer and need for broad-spectrum antibiotic treatment has been retrospectively analyzed and comparison between groups were made.

Results: The incidence of neutropenic fever was 81%, 65% and 81% in group without anti-bacterial prophylaxis, receiving rifaximin and ciprofloxacin, respectively. Infectious diarrhea has been noted in 3 patients receiving rifaximin and none of them had Clostridum difficile infection. In ciprofloxacin group diarrhea was observed in 8 patients (2 with Clostridium difficile) and in 8 patients without prophylaxis (2 Clostridum difficile). Need to use at least two lines of antibiotic (first line inefficiency) was noted in 73% patients without prophylaxis, 47% patients in rifaximin group and 66% patients in ciprofloxacin group. The incidence of septic shock, fungal infection was similar in all three groups.

Conclusions: The use of rifaximine is an effective method of antibacterial prophylaxis in patients undergoing HSCT. It reduces the incidence of neutropenic fever and limits the use of antibiotic therapy.

Disclosure: Nothing to declare.

P418

Risk Factors for CMV Reactivation and Disease Among Hematopoietic Stem Cell Transplant Recipients - Defining the Target Population for Letermovir Prophylaxis

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Background: CMV reactivation is one of the major infections occurring after allogeneic hematopoietic stem cell transplantation. With early detection and pre-emptive treatment the frequency of CMV disease has declined but was not eliminated and morbidity from CMV treatment still remains a clinical problem. We retrospectively analyzed CMV reactivation and disease as well as treatment efficacy and toxicity among 335 consecutive patients, who received alloHSCT within a 5 year period (2013-2017) at the UKD, Heinrich Heine University Düsseldorf.

Methods: CMV was monitored weekly for the first 100 days, every two weeks thereafter and once a month after day 200 after alloHSCT by a sensitive in-house real-time PCR and reported as number of copies per ug DNA.

Results: Reactivation, defined as viremia >10 copies per ug DNA in two consecutive PCRs,

occurred in 143 patients (42%) after a median of 33 days (-27-425) after alloHSCT. Patients with CMV reactivation were treated with antiviral therapy and CMV specific iv IgG. Median duration of 1st CMV reactivation was 29 days (2-254) and median peak of CMV viremia was 221 copies/ugDNA (12-1599988). A total of 40 patients (12%) had two and 9 (3%) had more than 2 reactivations. No reactivation occurred in CMV- patients with CMV- donors (P-D-). The risk for CMV reactivation was 75% in P+D+ with HLA-mismatch, 64% in P+D- and 58% in P+D+ with 10-of-10 HLA-match ($p< 0.05$). The risk for second and subsequent CMV reactivations was highest in P+D- and lowest in P+D + with 10-of-10 HLA-match (33% vs 12% and 13% vs 3%, $p< 0.05$). CMV disease occurred in 9 patients (3%). It involved the GI-tract in 8 patients (89%, 7 colitis, 1 gastritis) and one patient suffered from pneumonia. CMV disease was not associated with patient or donor CMV serostatus but with steroid treatment for (refractory) GvHD. Letermovir prophylaxis as introduced in 2018 for high-risk patients with P+D- and/or HLA-mismatch (n=12) was well tolerated and reduced CMV reactivation to 42%. However, 3 of 5 reactivations among these patients occurred after Letermovir cessation and the 2 reactivations seen on Letermovir prophylaxis were associated with steroid treatment for aGVHD.

Conclusions: The risk for 1st and recurrent CMV reactivation in CMV IgG+ patients is associated with donor CMV serostatus and HLA-match, defining seropositive patients with seronegative donors and/or HLA-mismatch as the high-risk population. Pre-emptive treatment with antivirals and CMV specific IgG is highly effective. CMV disease is rare and almost exclusively associated with severe GvHD. Letermovir prophylaxis reduces CMV morbidity among high-risk patients but reactivation after Letermovir cessation and during steroid treatment for aGvHD is still an unsolved problem.

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P419

Isavuconazole (ISA) use in Adult Allogeneic Hematopoietic Stem Cell Transplant (ALLO-HSCT) Recipients: A single-center Experience

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Background: Isavuconazole (ISA) is a second-generation triazole approved for the treatment of adults with invasive aspergillosis and mucormycosis. ISA is also an attractive candidate for primary mold-active prophylaxis in allogeneic hematopoietic stem cell transplant recipients. However, data supporting the use of ISA for primary prophylaxis in these patients is lacking. The most important adavantages of ISA are predictable pharmacokinetics, excellent bioavailability, no food effect with the oral formulation, potentially poor drug-drug interactions and its potential utility in renally impaired patients given the absence of cyclodextrin in the intravenous formulation. At present, it is unclear whether a therapeutic drug monitoring (TDM) of ISA would be necessary.

Methods: We conducted a retrospective review of the use of ISA as invasive fungal infections treatment or prophylaxis in allogeneic hematopoietic stem cell transplant recipients. We analyze the efficacy and safety of ISA. We also analyze in few patients the use of ISA TDM.

Results: A total of 24 allogeneic hematopoietic stem cell transplant recipients were included (M/F 9/15; median age 53 years). ISA was used as invasive fungal infections treatment in 22 cases and as prophylaxis in 2 patients. Donors were haploidentical in 23 patients and unrelated in 1 case. According to EORTC criteria, invasive fungal infections was proven in zero patients, probable in 4 e possible in 18 patients. Lungs were the main localization (18 cases); in 4 cases the paranasal sinuses were involved. The reason of the choice of ISA compared to other antifungal agents was: in 10 patients the less nephrotoxicity; in 9 the less hepatotoxicity; in 2 both the less nephrotoxicity and hepatotoxicity; in 2 the less nephrotoxicity and drug drug interactions; in 1 as rescue treatment for previous therapeutic failure of other antifungal agent. All the patients received 200 mg/die TID loading dose on days 1 and 2 and 200 mg/die manteinence, intravenous or oral. ISA was administered for a median of 80 days (range: 7-345). TDM was applied to 5 patients. The median ISA concentrations were 6.07 mcg/ml (range: 1.86-14.88). Invasive fungal infections complete remission was achieved in 20 cases; treatment failure was experienced by 2 patients. The prophylaxis was efficacy in the 2 patients. We didn't observe toxicity and drug-drug interactions.

Conclusions: ISA use appears efficacy and safe with a good tolerability and few drug-drug interactions.

In clinical practice may not require TDM.

Disclosure: Nothing to declare.

P420

Time- and therapy-dependent Bacteriuria in Children and Young Adults Following Allogeneic HSCT

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Background: Long-lasting bacteriuria and pathogenic species of urinary microbiota represent and important feature of immunocompromised conditions in the patients undergoing hematopoietic stem cell transplantation (HSCT). The aim of the present work was to evaluate detection rates of aerobic microbiota cultured by routine bacteriological techniques from urine samples taken before allogeneic HSCT and within 4 months after the treatment.

Methods: Aerobic bacterial cultures were made from 734 urine specimens taken from 50 patients aged from 1 to 21 years, subjected to allogeneic HSCT due to oncohematological or inborn diseases. All the patients received anti-infectious fluoroquinolone-based prophylaxis from D+1 to D+60 post-transplant, and peroral amoxycilline was administered later. Urinary bacterial cultures were seeded twice a week during hospitalization in BMT clinic, as well as in febrile neutropenia or haemorrhagic cystitis (5 to 34 bacterial cultures per patient). The data were analyzed for age groups of 1-5, 6-14, and 15-21 years. Statistical evaluation was performed with non-parametric tests using STATISTICA 5.0 software.

Results: : The bacterial cultures proved to be positive with 37.6% of urine samples. The following microbes were more common: K.pneumoniae, 95/734 (12.9%); E.faecalis, 90/734 (12.3%); E.coli, 65/734 (8.9%); E.faecium, 50/734 (6.8%), with only one microbial species revealed in 86% of positive samples. Prevalence of positive bacterial cultures was gender-independent, except of E.faecium, which was more common in girls following HSCT. We have shown that the frequency of positive tests for K.pneumoniae и E. coli in these samples were different for distinct age groups, i.e., the positivity rates were significantly higher in youngest children (up to 5 years old), being sufficiently increased 2-3 months after HSCT which may be an index of antibiotic resistance as well as a risk factor for infectious complications of other organs. The bacteriuria rates have shown distinct time dependence, with significantly increased detection rates of K.pneumoniae and E.coli at early terms (1^{st} month) after myeloablative conditioning, which could be explained by effective antibacterial prophylaxis over the time of conditioning and in early posttransplant period. Further, among these HSCT patients (n=50), we have discerned 16 cases with $\geq$3-time detection of K.pneumoniae in urine (a total of 298 samples). The clear time dynamics was observed during 4 months, i.e. a sufficient decrease of K. pneumoniae over 1^{st} month post-transplant (8%, compared to 22% pre-transplant, $p< 0.01$), followed by a peak of isolation rates at 3^{rd} month after HSCT (62%), thus nearly three-fold exceeding the initial levels ($p=0.006$). The K. pneumoniae strains isolated at these terms exhibited multiple resistance for antibiotics, as assessed by routine disc diffusion technique. Moreover, the increase of K.pneumoniae isolation rates at 2^{nd}-4^{th} months posttransplant was proven to be strongly associated with myeloablative conditioning regimens used for HSCT, thus reflecting a potential deficiency in local immunity due to intensive therapy.

Conclusions: Combined effects of bacteriostatic and anticancer therapy in HSCT cause pronounced time-dependent changes in urinary microbiota. They deserve more complete and detailed studies, by means of multiple PCR, or next-generation DNA sequencing. These results may be helpful for developing rational antibacterial therapy in HSCT.

P421

Phase 3 Randomized, double-blind Study of Maribavir Compared with Valganciclovir for Treatment of Cytomegalovirus (CMV) Infection in Hematopoietic stem-cell Transplant (HSCT) Recipients (Study Design)

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Background: CMV infection is associated with substantial morbidity and mortality in HSCT recipients, with current antivirals being limited by toxicities (e.g. valganciclovir is associated with myelosuppression); findings from a Phase 2 study of maribavir for the pre-emptive treatment of CMV (maribavir had similar efficacy for clearing CMV viremia as valganciclovir; serious adverse events were reported in 44% and 32% of patients, respectively; neutropenia was reported at Week 12 in 5% and 18% of patients, respectively; EudraCT: 2010-024247-32) led to the evaluation of maribavir in further Phase 3 studies.

Methods: This ongoing Phase 3 randomized, double-blind, double-dummy, active-controlled study (NCT02927067) in HSCT recipients (≥16 years) compares the efficacy and safety of maribavir (400 mg twice daily [BID]) with valganciclovir (900 mg BID, or 450 mg BID or daily as needed based on renal function) as treatment for asymptomatic CMV infection (a first episode of CMV infection, with no tissue-invasive CMV disease). Patients are stratified by CMV viral load and acute graft versus host disease status, and randomized 1:1 to double-blind treatment with maribavir or valganciclovir for 8 weeks. Patients are then followed for a further 12 weeks post-treatment. To be included in the study, patients must have a screening CMV DNA load ≥1365 to ≤273000 IU/mL in blood (≥455 to ≤91000 IU/mL, plasma) in two consecutive assessments. Patients with a lower CMV viral load (≥1365 to < 2730 IU/mL, blood [≥455 to < 910 IU/mL, plasma]) must also meet ≥1 criteria for a high risk of CMV infection. Key exclusion criteria include recurrent CMV infection and CMV infection genotypically resistant to anti-CMV drugs. The primary efficacy endpoint is confirmed CMV viremia clearance (plasma CMV DNA < 137 IU/mL in 2 consecutive post-baseline samples ≥5 days apart) at the end of Week 8. Noninferiority of maribavir to valganciclovir will be tested using a 7% noninferiority margin. Superiority testing will be performed only after establishing noninferiority. The key secondary efficacy endpoint is to compare maribavir and valganciclovir on maintenance of CMV viremia clearance and infection control, achieved at the end of Week 8 through Week 16 (8 weeks of post-treatment follow up). Other secondary endpoints include maintenance of CMV viremia clearance throughout the 12-week post-treatment follow-up period and recurrence of CMV viremia. Safety endpoints include adverse events and assessment of clinical laboratory data, including the incidence of treatment-emergent grade 3 or 4 neutropenia.

Results: Planned enrollment is 550 patients globally across ~105 sites (North America, Europe, and Asia Pacific). The study started in April 2017 and will be completed by ~August 2021.

Conclusions: This Phase 3 study will provide additional data on the efficacy and safety of maribavir compared with valganciclovir, for the treatment of CMV infection in HSCT recipients.

Clinical Trial Registry: Clinicaltrials.gov NCT02927067

Disclosure: This study was funded by Shire, a Takeda company.

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Robin Avery has received funding as a site principal investigator on studies for Shire/Takeda, Merck, Aicuris, Astellas, Chimerix, Qiagen, and Oxford Immunotec.

Per Ljungman has received funding as an Endpoint Adjudication Committee member for Shire/Takeda; as a scientific expert for AiCuris; as site principal investigator for Astellas, Oxford Immunotec and Merck; and as a speaker for Merck.

Johan Maertens has served as a consultant and on speaker bureaus for Amgen, Astellas Pharma, Merck, Basilea, Pfizer, Schering-Plough, Shire/Takeda, Gilead Sciences, Bio-Rad, F2G, Cidara, and Scynexis; and has received research grants from Merck, Pfizer, Gilead Sciences, and Bio-Rad.

Rose Ann Murray and Jingyang Wu are employees of Shire, a Takeda company.

P422

Incidence and Risk Factors of Viral Complications in Adult Patients undergoing Allogeneic Stem Cell Transplantation - A single-center Experience From Hungary

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Background: With the routine introduction of haploidentical stem cell transplantation and post-graft cyclophosphamide (PGCy) infusion for graft-versus-host (GvHD) prophylaxis, an increasing number of viral complications have been reported. Epidemiological data to support antiviral strategy have become increasingly important.

Methods: Incidence and risk factors of viral infections in adult patients undergoing allogeneic hematopoietic stem cell transplantation (alloHSCT) at our center in 2018 have been analyzed. Using real time polymerase chain reaction (rtPCR), copy numbers for cytomegalovirus (CMV), Epstein-Barr virus (EBV), adenovirus (ADV) and human herpesvirus-6 (HHV-6) have been monitored. Plasma samples were collected at least on a weekly basis for inpatients and as indicated by follow-up visits, afterwards. For high-risk patients, 90 mg/kg foscarnet has been administered from day +1 to engraftment or reactivation. In the standard risk cohort, routine acyclovir prophylaxis has been used. In case of clinically significant viral reactivation or disease, antiviral therapy has been instituted according to current guidelines. For refractory cases, when applicable, virus-specific T-cells were infused.

Results: Ninety-eight patients underwent alloHSCT. Four cases who had to be retransplanted due to rejection have been removed from analysis. The remaining cohort consisted of 55 males and 39 females, with a median age of 43 (19-66) years. Indications for alloHSCT were acute leukemia in 64, other hematologic tumors in 23, and another diagnosis in 7 cases. Median follow-up time was 170 (15-560) days. Clinically significant CMV infection occurred at median +33 [0-18] days in 38 (40%), EBV at median +72 [13-285] days in 32 (34%), an ADV infection at median +113 [6-320] days in 14 (15%), while HHV6 infection at a median +88 [5-121] days in 7 (7%) cases. In 71 patients receiving PGCy, a nonsignificant increase in the risk for EBV (RR: 1.40 [95% CI 0.66-2.98, p=0.38]), ADV (RR: 4.21 [95% CI 0.58-30.47, p=0.15]) infections, and for BK polyomavirus-related hemorrhagic cystitis (RR: 1.69 [95% CI 0.73-3.88, p=0.22]) was seen. ADV infection occurred more often in the younger age group (33 vs. 45 years, p=0.004), and in acute lymphoblastic leukemia (RR: 3.36 95% [CI 1.20-9.41, p=0.02]). With current strategies, viral infections did not seem to significantly influence nonrelapse mortality (RR: 1.04 [95% CI 0.49-2.23, p= 0.91]).

Conclusions: With present stem cell transplant modalities, a careful monitoring of viral infections is warranted. By using multimodal antiviral strategies, the majority of cases can be effectively managed. In the near future, more emphasis should be placed on antiviral prophylaxis and cellular therapies.

Disclosure: Nothing to declare.

P423

Unicentric Study: Prophylaxis Strategy against GVHD with post-transplant Cyclophosphamide (CPYT) and its Relationship with Cytomegalovirus

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Background: Cytomegalovirus (CMV) replication and disease was for decades the biggest cause of mortality in the allogeneic haematopoietic stem cell transplantation (alloHSCT). The consequence of the prophylaxis and monitoring by PCR and pre-emptive treatment is CMV´s disease reduction.

However, despite these measures the risk is not negligible. Both the type of transplant, conditioning and prophylaxis for graft versus host disease (GVHD) influence the incidence.

In recent years, post-transplant cyclophosphamide (CPYT) associated with other immunosuppressive agents is emerging as a promising pharmacological strategy in alloHSCT to reduce both acute and chronic GVDH. Widely used in haploidentical transplantation, its use is spreading in other types of allogeneic transplants such as the identical HLA and that of an unrelated donor. However, there are still doubts in its safety profile and especially in its relationship with CMV replication and disease. That is why we present the following work.

Methods: Unicentre, observational, analytical and retrospective study. From the 1st January 2015 to the 30th July 2018. AlloHCSTs performed, in the Public Health Group Quirón, were collected. Transplants were divided into two groups: Those who received a traditional GVHD prophylaxis, and those who received a post-transplant CFM strategy.

Results: Of 40 transplants, 53% were male (n = 21) and 47% were female (n = 19). The average age was 50 years, SD 11.22 years (19-68).

According to the donor employed: 17 HLA identical sibiling (42.5%), 17 haploidentical (42.5%), 4 (10%) HLA-

matched unrelated donor (MUD) and 2 mismatched related donor (5%).

18 transplants were performed using a non-myeloablative conditioning (45%), and 22 with myeloablative conditioning (55%). In 100% of cases the source of hematopoietic progenitors used was peripheral blood.

GVHD prophylaxis scheme: CYPT was used on days +3 and +4 (according to the Baltimore protocol) in 25 transplants (62.5%), of which 17 were haploidentical (100% of haploidentical), 3 in HLA Identical sibling (17.65% of transplants in this modality), 4 in MUD (100% of these) and 1 mismatch related donor (50% of this group).

50% of the transplants (n = 20) presented CMV reactivation, 15 of them (75%) with CYPT.

62.5% (n = 5) of patients undergoing non-haploidentical alloHSCT, receiving CYPT as a GVHD prophylaxis regimen (n = 8), presented CMV reactivation. 33.3% (n = 5) of patients not receive CYPT (n=15), did not present CMV reactivation.

The RR of CMV reactivation is 1.87 (95% CI 0.77-4.59) in prophylaxis with CYPT. Obviating patients undergoing haploidentical alloHSCT, and with a p=0. 17, there is no statistically significant relationship.

Conclusions: Our study shows that there is no evidence of CMV reactivation in an GVHD prophylaxis strategy with CYPT, however prospective studies should confirm our results, since the series is not very large.

Disclosure: Nothing to declare.

P424

Epidemiology and Clinical Features of Febrile Neutropenic Episodes: Three Years Experience at Hematology Wards

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Background: Severe neutropenia is one of the most significant and common side effects of chemotherapy and febrile neutropenic episodes (FNEs) are the major causes of morbidity and mortality in chemotherapy patients. The aim of this study was to evaluate the microbial epidemiology, resistance patterns, and outcomes in febrile neutropenic patients at our center.

Methods: In this longitudinal retrospective study, we evaluated FNEs in adult patients who received intensive chemotherapy or stem cell transplantation in our hematology department between December 2014 and December 2017.

Results: 400 FNEs in 195 patients (median age 50, range: 18-83 years, female 37%), who underwent chemotherapy (220, 55%), allogeneic hematopoietic stem cell transplantation (HSCT) (115, 29%), autologous HSCT (65, 16%) were evaluated in this study. Acute myelocytic leukemia (27%) was the most frequent primary diagnosis. The rate of infection (without documented infectious source or positive blood cultures) that resolved with empirical antibiotic treatments was 43%. Rates of bloodstream infection and clinically documented infection were found to be 31% and 33%, respectively. Gram-negative organisms such as Escherichia coli, Klebsiella pneumoniae were the most common (71%) pathogens isolated from blood cultures, followed by gram-positives (27%) such as methicillin-resistant coagulase-negative Staphylococcus. The rate of extended-spectrum beta-lactamase (ESBL) (+) Enterobacteriaceae and carbapenem-resistant Enterobacteriaceae (CRE) were 40% and 23%, respectively. Antifungal therapy was added to the treatment in 109 (27%) of FNEs, 82 of them had a positive response. A secondary infection occurred in 90 (22,5%) of 400 FNEs and 32 (35%) of them responded to the treatment. Mortality rate of the febrile neutopenic patients and secondary infections were 7% and 12%, respectively.

Conclusions: The most frequently isolated microorganisms in our patients were GNB (especially ESBL positive Enterobacteriaceae and CRE). The knowledge of resistance mechanisms and risk factors associated with CRE blood stream infections is very important for the management of neutropenic patients. Determining the current epidemiology of each center may be beneficial in improving survival rates.

Disclosure: nothing to declare.

P425

Toxoplasmosis Disease after allo-HSCT. What have we Learnt?

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Background: Toxoplasmosis disease is a rare but life-threatening complication after HSCT, in most cases due to the reactivation in a seropositive patient. Some predisponding factors are: allo-HSCT, mieloablative conditioning and inmunosuppressive theraphy, low T lymphocyte cell count, TBI, presence of GvHD, mismatched serological

status recipient-positive/donor-negative and absence of proper chemoprophylaxis.

Methods: We present a case of a disseminated toxoplasmosis in a 5-year-old girl with chemorefractory pre-B ALL, who achieved remission after treatment with inotuzumab and underwent allo-HSCT.

Results: The patient was first diagnosed with pre-B ALL at the age of 18 months in Honduras, genetic and molecular biology studies were not available (no infiltration of CNS). She received treatment according to the ALL-AHOPCA-2005 protocol, low risk group, with good response.

First medullar relapse happened 8 months after completing treatment. She was put under the ALL-AHOPCA-2014 protocol with good response. Fourteen months later, she presented a second medullar relapse, starting palliative chemotherapy in Honduras. Her family and she moved to Madrid. At our institution she was 5 years old, we confirmed the medullar relapse (99% blasts in BM, CSF not involved) with uterine and left ovary mass. Inmunophenotype: CD34+, CD38+, CD19+, CD10++, CD22+, KORSA+, no karyotype was obtain, amplification of EBF1 was detected. She received treatment similar to the IntReALL-2010 protocol, including bortezomib without response (MRD 75% after induction in BM). We decided to administer inotuzumab, achieving complete remission (MB and extramedullar disease) after 2 cycles of inotuzumab, LANSKY 100%. She underwent haploidentical HSCT from her father with myeloablative conditioning regimen (TT-FLU-BU), GvHD prophylaxis with CY on day +3, +4, tacrolimus plus mycophenolate since +5. Neutrophil engraftment on +17 and platelet on +22. She was in complete quimerism, no SVOD.

On day +39 she suddenly presented with respiratory symptoms (fever, hypoxia, distress), needing admission in PICU, mechanical ventilation and inotropic suppport. Cultures and a biopsy of a skin lesion (isolated papula on the back) were taken and broad spectrum antibiotic, antifungal, antiviral and TMP/SMX therapy was empirically initiated. At this time she was on mycafungin prophylaxis.

PCR was possitive for Toxoplasma gondii in all the samples, so we changed to first-line therapy with pyrimethamine/sulfadiazine. The patient showed favorable clinical evolution.

There was a mismatch in the serological status (recipient-positive/donor-negative).

Conclusions: Allo-HSCT is a predisponding factor for toxoplasmosis disease, an infectious complication with a mortality rate of 60-90%, in part due to delayed diagnosis. The incidence of toxoplasmosis after HSCT is low (average 0.8%) but can increased to 2-3% in seropositive patients. A consensus on the prophylaxis and treatment is still missing, although some measures are beneficial for an early diagnosis and treatment: serological screening receptor/donor before HSCT, weekly monitoring with PCR, early onset of chemoprophylaxis with TMP/SMX 3 times a week.

However, these measures do not eliminate the possibility of an infection, and it is vital to maintain a high index of suspicion, especially in seropositive patients coming from developing countries.

Disclosure: Nothing to declare.

P426

Tuberculosis in Patients Who receive an Allogeneic Hematopoietic Stem Cell Transplant. Two Case Report

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Background: Tuberculosis (TB) is one of the most relevant infections in immunocompromised patients because of its high morbidity and mortality. Numerous retrospective studies, like the EBMT study in which 29 centers were included, reveal how mycobacterial infection was diagnosed in 0.79% patients undergoing allogeneic stem cell transplant (allo-SCT).

Methods: We conducted a retrospective study in a series of patients diagnosed with TB after allo-SCT in our center.

Results: In the last two years we have diagnosed 2 cases of TB in the post-transplant period within a total of 66 allo-SCTs performed in our center (3.03%). The patients' characteristics are shown in table 1.

Clinical presentation: Patient 1 (P1) presented an acute condition with fever without focus and a rapid evolution, with initial respiratory failure and a subsequent disseminated form; with neurological and digestive involvement. Patient 2 (P2) was presented with a progressive and intense asthenia. It was accompanied by pleural effusion that appeared after allo-SCT which remained stable for months. This patient had suffered an episode of splenoportal thrombosis a year before SCT with secondary portal hypertension and ascites, so the effusion was justified in this context. However, the ascites improved and the pleural effusion and the asthenia worsened.

We investigated the time interval between symptom onset and diagnosis of TB: 12 days in P1 and 129 days in

P2. Microbiological confirmation after the samples were taken for culture, were 3 (P1) and 14 (P2) days.

Conclusions: It is estimated that TB diagnosis is made at a median 257.2 days after allo-SCT (range 21-1410 days). Symptoms may be confused with other pathologies or may appear as a long-standing disease. It is important to consider TB in the context of fever of unknown origin, progressive cachexia, asthenia and TB past infection or contact. P2 had a previous contact with TB which he did not remember, in addition to granulomas and calcified pulmonary adenopathies, which could be related to contracted TB. The lung is the most frequently affected organ (80%), although extrapulmonary involvement and disseminated forms can also become evident in almost a third of the cases.

TB is associated with high mortality after allo-SCT, up to 25% in the reviewed literature. In addition, there is usually an average delay of 46 days from the onset of symptoms until diagnosis. Differential diagnosis of infection after allo-SCT should include TB. Appropriate preventive/therapeutic strategies should be applied to reduce morbidity and mortality associated with this pathology.

	P1	P2
Sex / Age	Man / 60	Man / 69
Pathology / Previous treatment	Multiple myeloma / 7 lines	Myelofibrosis / Alpha Interferon, Busulfan, Ruxolitinib
Type of allogeneic transplant	Haploidentical	Unrelated donor
Risk factors for TB	GVHD, corticoesteroids	GVHD, corticoesteroids
Clinical start	Day +92 after allo-SCT	Day +149 after allo-SCT
Diagnosis	Bronchoalveolar and bronchoaspirate lavage culture (negative smear, positive PCR)	Microbiological culture of pleural effusion (negative smear and PCR)
Treatment	Isoniazide, Rifampicin, Pyrazinamide, Etambutol	Isoniazide, Rifampicin, Pyrazinamide (hepatotoxicity), Etambutol
Dead	Yes	No

[Table 1]

Disclosure: Nothing to declare.

P427

Polyomavirus BK Infection in Bone Marrow Transplantation Recipients. A Comparative Analysis on Children and Adults

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Background: Polyomavirus BK-associated hemorrhagic cystitis (BKPyV-HC) is a late-onset form of HC encountered in patients undergoing allogeneic hematopoietic stem cell transplantation (alloHSCT), impacting on morbidity and even mortality.

Methods: We retrospectively analyzed a number of 33 consecutive patients, 22 children and 11 adults, who received an alloHSCT at our institution over a period of 5 years, between 2014-2018, regarding BKPyV reactivation, with or without HC. The local ethics committee approval was obtained for the analysis of data.

Results: We observed a similar incidence of BKPyV viruria as well as of HC in children when compared to adults (18% versus 21% respectively). 12% of the children and 9% of the adults presented HC. The main risk factors with impact on the progression towards HC were: type of donor, with a higher incidence of HC in patients with unrelated donors, acute GvHD, concurrent CMV viremia, myeloablative conditioning regimen, high cyclosporine (CsA) concentration in blood, graft-versus-host disease prophylaxis with ATG. At the time of BKPyV detection in urine/BKPyV disease onset 85% of the adults and 66,66% of children presented high CsA levels in blood the rest of the patients presenting normal CsA levels. In 75% of children with significant viruria (7 log 10copies/mL) were asymptomatic as compared with adults (100% symptomatic). Hyperhydration and forced diuresis as well as reduction of immunosuppression was applied in all cases. Eight patients (25%) received high dose immunoglobuline (IvIg) as part of the treatment. Cidofovir was not administered because the medication was never available in a timely manner. The vast majority of the patients recovered from the infection. The mean time to resolution of HC was 21 days. In one patient who presented BKPyV-HC, high viruria and viremia, death was attributed to BKV post-renal acute kidney injury.

Conclusions: BKPyV-HC and especially BKPyV viruria are common in patients following alloHSCT. In the case of lack of cidofovir, a timely intervention with supportive measures and high-dose IvIg, together with reduction of immunosuppression (in patients without GvHD), may be efficient and safe for the majority of patients with BKPyV-HC, representing an argument for a weekly screening for this virus in urine samples.

Disclosure: No conflicts to declare.

P428

Leflunomide, Successful pre-emptive Therapy in Resistant Cytomegalovirus Reactivation in a Hematopoietic Cell Transplantation Recipient

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Background: Despite therapeutic advances, cytomegalovirus (CMV) infection remains a clinical significant complication in hematopoietic stem cell transplant (HCT) recipients (1). Valganciclovir, ganciclovir and foscarnet are effective as the first-line treatment for CMV infection. Second-line drugs, such as cidofovir, maribavir, brincidofovir, CMV-specific T cells, or CMV- hyperimmune globulin, are not available or are not easy obtainable in Colombia (South America). (2)

Leflunomide, an immunomodulatory agent approved for the treatment of rheumatoid arthritis, impedes virion assembly through inhibition of viral protein kinase activity and pyrimidine synthesis required in intracellular production. The addition of leflunomide could have a potential use in the treatment of CMV infections unresponsive to the standard medical care.

We hereby present the case of a successful pre-emptive therapy with leflunomide and valganciclovir in a HCT recipient with persistent detection of CMV viral load receiving therapy with ganciclovir/ valganciclovir and foscarnet.

Methods: A 33-year old CMV-seropositive man with AML received a matched unrelated CMV-seronegative donor HCT after a myeloablative conditioning regimen. As part of the standard immunosuppressive scheme to prevent graft versus host disease, he received antithymocyte globulin (6 mg/kg), tacrolimus, and metothrexate. For CMV prevention, the patient received ganciclovir from day -6 to day -3, and thereafter high dose of valacyclovir.

On day +20, the patient developed graft versus host disease (GVHD), which affected the skin (grade 3), with a global index of II and IBMT severity index C. He received prednisone (1mg/kg/day) plus topic corticoids with a satisfactory response.

On day +32, the patient had documented CMV reactivation with 7750 copies/ml, and valganciclovir was initiated (900 mg, BID). After receiving 1 month of pre-emptive induction treatment, CMV viral load remained in 7360 copies/ml. Treatment with foscarnet intravenously was initiated with a dose of 60mg/kg BID.

Three weeks after, the CMV was 4800 copies/ml, so the dose of foscarnet was raised to 90mg/kg BID.

Due to the further viral load increase after three weeks to 13700 copies/ml despite treatment with foscarnet, resistance was suspected. CMV genotypic analysis showed UL97 without mutations and UL54 with mutations without reported relevance (A885T and N898D). As salvage therapy for refractory CMV infection Leflunomide (20mg, QD) with high dose of valganciclovir (1800mg, BID) was administered without side effects.

After 3 months, the CMV viral load was undetectable.

Results: Our experience illustrates the use of leflunomide as an adjuvant pre-emptive therapy in refractory CMV reactivation. Leflunomide is an oral therapy that is feasible and available.

The optimal dosing of leflunomide for anti-CMV therapy is unknown; we used 20mg QD with successful results.

Conclusions: Given the limited number of drugs available for the treatment of resistant CMV infection, leflunomide can be considered for adjuvant therapy. Further prospective research is recommended.

Disclosure: Nothing to declare.

P429

Letermovir as Pre-emptive Therapy for Resistant Cytomegalovirus Infection after Allogeneic Stem Cell Transplantation

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Background: Cytomegalovirus (CMV) DNAemia is a well known cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT), increasing not only the risk of graft versus host desease (GvHD), but also the risk of non relapse mortality (NRM). Althought pre-emptive treatment reduces the development of CMV desease, it enteils to serious adverse events. Letermovir used as prophylaxis controls significantly the CMV DNAemia, but to date, it does not have marketing agreedment in Spain.

Methods: We present the case of a 55-year-old woman diagnosed with acute myelomonocytic leukemia. She underwent an allo-HSCT from HLA-matched sibling donor. Reduced intensity conditioning (RIC) regimen with fludarabine, busulfan and thiotepa was administrated, and prophylaxis for GvHD consisted in methotrexate and tacrolimus. Donor and recipient were seropositive for CMV.

Five months after the transplant, she was admitted due to diarrhea. Bowel biopsy was performed, with histological

findings of grade 1-2 intestinal GvHD and infectious ileitis due to Campylobacter jejuni. Inmunohistochemistry in the biopsy was negative for CMV. She received corticosteroids as a first line treatment, achieving a partial response. Second line treatment with 4 doses of infliximab was administrated, obtaining complete response.

CMV reactivation in the bloodstream was detected during corticosteroids treatment. Pre-emptive treatment with ganciclovir was initiated, but failed to achieve complete clearance of CMV DNAemia. Worsening of trombocythopenia and gram positive bacteriemia appeared during this period. Foscarnet was used as a second-line therapy with good response after three weeks. Electrolyte alterations related to the antiviral treatment were noticed.

One week after discontinuation of foscarnet, a new rise of the CMV DNAemia occurred. A complete sequencing of the UL54 (ADN polimerase) and UL97 (timidin kinase) was performed and showed no antiviral resistance related mutations. The patient started a third-line therapy with cidofovir, but the viral load increased dramatically within 5 days of treatment (peak of 12200 UI/mL). Waiting for the approval of letermovir, ganciclovir plus foscarnet was initiated as a new line. She completed ten days of combined therapy until letermovir was available. Electrolyte abnormalities and cytopenias appeared during this period.

Results: Seven months after the transplant, pre-emptive therapy with letermovir was initiated. Moderated neutropenia, hypokaliemia and hypomagnesemia occurred, possibly related to the prior combination therapy but were easily manageable. CMV DNAemia became undetectable after less than two months. Although the patient has had several episodes of GvHD that required inmunosupressive therapy, she has kept a negative CMV DNAemia after 1 year follow up.

Conclusions: Letermovir is a new agent approved for CMV prophylaxis in HSCT with a novel mechanism of action and a favorable adverse-effect profile compared to other conventional anti-CMV agents.

In the reported case, after trying all the approved therapeutic options, letermovir was the only antiviral that achieved an effective and long-lasting response despite multiple episodes of GvHD that needed adjustment of the inmunosupressive therapy. In the setting of clinical resistance or when the drug is not used as prophylaxis, letermovir can lead to an optimal control of CMV DNAemia with a safety profile.

Disclosure: Nothing to declare.

P430

Infectious Complications in Hematologic Patients with Hematopoietic Stem Cell Transplantation

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Background: Infections are serious life-threatening complications in patients during hematopoietic stem cell transplantation (HSCT). The number of possible pathogens is large and includes bacteria, micromycetes and viruses.

Methods: We studied twenty one patients (8 women and 13 men) aged 54 to 66 years who underwent hematopoietic stem cell transplantation (HSCT). In 18 patients multiple myeloma (MM) was diagnosed, in one non-Hodgkin´s lymphoma (NHL), in one primary myelofibrosis (PMF) and in one myelodysplastic syndrome (MDS). Nineteen patients underwent auto-HSCT and two - allo-HSCT. To detect the genomes of herpes viruses in the blood PCR-RT was used (Amplisens EBV/CMV/ HHV6-screen-FL", Inter-LabService, Russia). PCR-RT was performed every 3-5 days before and after HSCT, as well as during the course of antibiotic therapy. Antibacterial therapy was initiated in neutropenia or in the presence of fever. For blood culture, the BacT / Alert 3D automatic culture system was used. Blood cultures were taken regularly with an interval of 3-5 days for neutropenia and / or in the presence of fever.

Results: In 9 of the 21 examined patients (43%), genomes of herpes viruses were detected in the blood. In five cases were the genomes of EBV, in four HHV-6. In two cases, the genomes of 2 viruses were detected simultaneously (in first case - HHV-6 and CMV and in the second - EBV and HHV-6). When revealing the genomes of the herpes viruses, antiviral treatment (acyclovir)was performed. In two cases, bacteria were isolated from blood. In the first case, in a patient with a diagnosis of MM on the 7th day after autoTGSC, Enterobacter cloacae was isolated from the blood. On the same day, the CMV genomes was detected in the blood. A course of combined antibiotic therapy with antibiotics was carried out, as well as antiviral treatment with acyclovir + valacyclovir. The patient´s condition was regarded as septic shock, with episodes of loss of consciousness. Against the background of the combination therapy, an improvement was noted. In the second case (patient with a diagnosis of PMF), on the 27th day after allo-HSCT, the HHV-6 genomes were detected in the blood, which was demonstrated during four subsequent tests in spit of antiviral treatment. On day 41 after allo-HSCT, Candida albicans was isolated from sputum. The patient´s condition worsened sharply, severe shortness of breath at rest, lack of air. X-ray revealed 2-sided segmental pneumonia.

Conclusions: In the structure of infectious complications in oncohematological patients with HSCT, a significant role

is played by infectious complications caused by viruses. This requires their constant monitoring in the blood using PCR-RT. Due to the high risk of developing systemic bacterial infections, it is preferable to use broad-spectrum antibacterial drugs as part of the initial therapy, followed by correction of therapy according to the results of bacteriological studies.

Disclosure: No relevant conflicts reported.

P431

CMV Retinitis in a Stem Cell Transplant Recipient Treated with Foscarnet Intravitreal Injection and CMV Specific Immunoglobulin

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Background: CMV retinitis is a rare complication in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) which may lead to blindness.

Methods: We retrospectively analysed the clinical features of CMV retinitis in a HSCT recipient.

Results: A 32-year old man with Burkitt lymphoma received HSCT from a matched unrelated donor after conditioning including thiotepa, fludarabine and busulfan. Donor and recipient were both CMV positive. On day +35 CMV DNA in the whole blood was 37000 UI/ml and the patient was treated with Valganciclovir 900 mg bid. After 9 days of therapy, DNAemia raised up to 146800 UI/ml; a second line therapy with foscarnet 120 mg/Kg was started leading to a slow decrease of viral load (CMV DNA 25800 UI/ml after 2 weeks of treatment). Genotypic resistance for UL54 and UL97 gene resulted negative. Accordingly, a combination of foscarnet and valganciclovir was started leading to negative CMV DNA after 2 weeks of treatment. On day +180, the patient presented with eye hyperemia and moderate visual loss. Fundoscopy revealed papillary hyperemia, retinal necrosis, hemorrhage and vasculitis consistent with the diagnosis of CMV retinitis. The aqueous biopsy demonstrated the presence of CMV infection (230400 UI/ml), while CMV DNAemia on whole blood was negative; PCR for HSV, EBV, VZV were negative as well as the presence of underlying disease. Foscarnet 180 mg/kg i.v. and intravitreal injection at 1,2 mg were started along with anti CMV immunoglobulin (Cytomegatect) 0.5 ml/kg every two weeks for six doses. After 4 weeks of systemic therapy and 20 weekly doses of intravitreal foscarnet, a significant improvement of visual acuity was observed. Both i.v. Infusion and intravitreal injection were well tolerated with no side effects. Three months after the end of treatment, the patient experienced a blurry vision. Diffuse atrophic chorioretinitis and posterior hemorrhage were observed and subsequent retinal fluoroscopy demonstrate a diffuse retinal vasculitis with loss of capillary, macular edema, diffuse damage and steadily atrophic CMV lesions consistent with vasculitis requiring administration of steroids 1 mg/kg die. Two weeks later the fundoscopy evaluation suggested the reactivation of viral infection, however CMV DNA in the aqueous was negative. Maintenance therapy with Valganciclovir was started during treatment with steroids.

Conclusions: The characteristic lesions of fundus, the fluorescein angiographic evaluation and the CMV DNA load in the aqueous humor were consistent with the diagnosis of CMV retinitis. The use of systemic and intravitreal foscarnet combined with CMV Immunoglobulin led to a significant clinical improvement and negative CMV viral load.

Disclosure: Nothing to disclose

Lymphoma

P432

Efficacy and Safety of Donor Lymphocyte Infusions for Patients affected by Advanced Lymphoid Malignancies after Allogeneic Stem Cell Transplantation: A Retrospective Study

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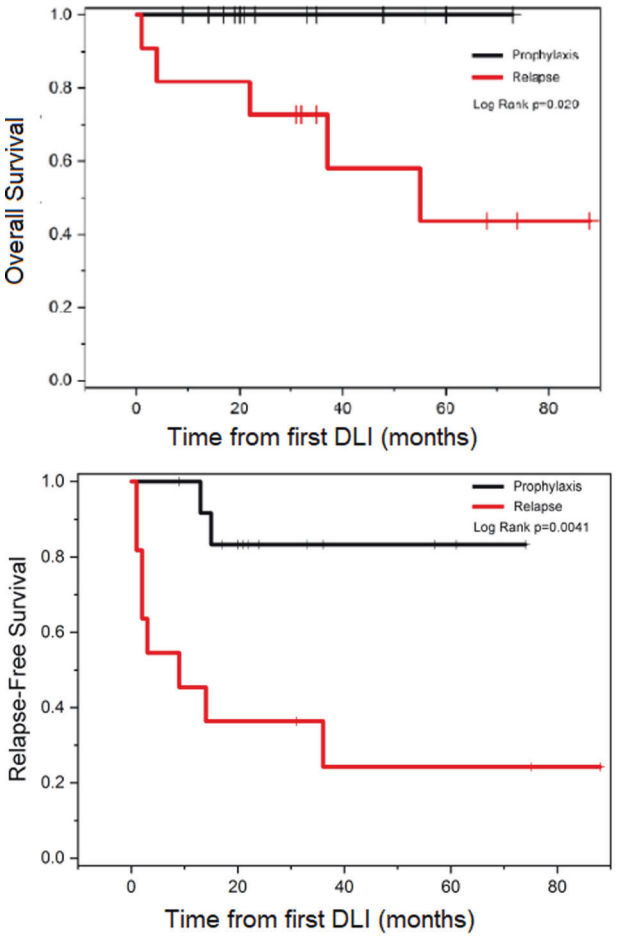
Background: Relapse after allogeneic stem cell transplantation (allo-SCT) is the major cause of treatment failure and data about DLIs in lymphomas are heterogeneous. The aim of this study is to explore the efficacy and toxicity of DLIs in relapsed/refactory (R/R) lymphoma for prophylaxis and treatment of relapse.

Methods: Between 2010 and 2018, 371 R/R lymphoma patients were transplanted in Marseille (Institut Paoli -

Calmettes) and Rozzano (Humanitas Cancer Center). Haplo familiar donors (haplo), unrelated donors (UD) and matched sibling donors (MSD) were used; conditioning regimens were non myeloablative (NMAC) or myeloablative; prophylaxis of GVHD consisted of MTX-CsA plus ATG for UD and MSD or PT-Cy-CsA-MMF for haplo. 27 patients (8% of evaluable patients) received DLIs for prophylaxis (proDLIs), as considered at high risk of relapse, or for treatment of relapse (tDLIs), with or without an associated treatment (chemo or radiotherapy).



[Figure 1: A - RFS according to DLI indication. B - OS according to DLI indication]

Results: Median age was 54 years. Patients were affected by NHL (n = 15), HL (n = 11) and CLL (n = 1). Disease status at allo-SCT was complete response (CR) in 56% and partial response (PR) in 44% of cases. Donors were MSD in 48%, UD in 11% and haplo in 41%. 96% of patients received a NMAC regimen. A total of 56 DLI infusions were administered, with a median number of 2 infusions per patient. 48% of patients (n = 13) received proDLIs and 52% (n = 14) received tDLIs, associated with chemotherapy or radiotherapy in 84% of cases. Median time from transplant to DLIs was significantly shorter for pro-DLIs compared to tDLIs (135 vs 444 days). For patients receiving proDLIs, the relapse rate was 15%. 46% of patients receiving tDLIs obtained CR. Median time of post-DLI relapse was 420 days (range 230-1073) from first DLI infusion. Regarding GVHD, 11% of patients experimented aGVHD (in all cases grade 1) and 30% of patients developed cGVHD (moderate-extensive in 50% of cases), without any case of GVHD-related death. At the end of follow-up (median time of 32 months from the first DLI), 78% of patients were alive; 86% of patients were in CR, 5% in PR and 9% with active disease; 95% of patients were free of immunosuppression. 2-year and 5-year relapse free survival (RFS) was 55% and 48%, respectively. When stratified according to DLI indication, RFS was 83% at 5 years for proDLIs and 38% and 25% at 2 years and 5 years for tDLIs ($p < 0.05$, figure 1A). The 2- and 5-year OS for the whole cohort was 83% and 65% respectively; divided according to DLI indication, 2-year and 5-year OS was 72.9% 43.8% respectively for tDLis and 100% for proDLIs (figure 1B).

Conclusions: DLIs are a feasible approach for both prophylaxis and treatment of post-transplant relapse in lymphoma patients, with acceptable rate of acute and chronic GVHD. DLIs seem to be especially effective in high risk patients to prevent relapse, but further investigations are needed to clarify their role.

Disclosure: Nothing to declare.

P433

Brentuximab-vedotin in Combination with Bendamustine as Salvage Therapy Prior Hematopoietic Stem Cell Transplantation for Patients with Hodgkin Lymphoma: Real-world Data from a Two Centers Study

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Background: Disease response to salvage treatment essentially determines the autologous stem cell trasplantation (autoSCT) outcome for patients with refractory/relapsed Hodgkin Lymphoma (RR-HL). So far, none of the proposed salvage regimens represents a standard approach

and therefore, an effective and minimally toxic regimen still remains a challenge. The combination of Brentuximab vedotin and Bendamustine (BvB) has demonstrated promising results as salvage treatment; however real-world data regarding its use are currently limited. In this study, we evaluated the efficacy, the safety and the impact on autoSCT of the BvB combination in 61 RR-HL patients

Methods: Thirty-nine patients with primary refractory and 22 with relapsed HL, aged of 24(16-69) years who received BvB in two different centers, were retrospectively analyzed. Fifty (82%) were assessed with advanced (≥IIB) stage, 36(60%) with B-symptoms, 23(38%) with extranodal involvement while 6(10%) had bulky disease. Thirty-two patients received BvB as 1st and 29 as ≥2nd salvage treatment. The treatment was given as previously described (La Casca et al. Blood 2018).

Results: The majority of patients (60/61) received the BvB combination in out-patient basis. Only 1 was treated as in-patient due to poor general condition. In 10(16%) patients toxicity WHO≥3 was observed (allergic reactions:3, seizures during the infusion:2, neutropenic fever: 5 and cardiotoxicity:1) All patients recovered after the appropriate management. Finally, 10(16%) patients required admission; 9 because of toxicity causes and 1 who received BvB as in-patient. Totally, 60 pts were able for evaluation. After a median of 3(2-6) cycles the overall response rate (ORR) was 80% (48/60 pts); 29(48%) achieved complete remission (CR), 19(32%) partial remission while 12(20%) failed to achieve efficient response. A superior ORR was observed for patients who received BvB as 1st salvage as compared to those who received BvB as ≥2nd salvage treatment, (87% vs. 72%, p=0,2). Noticeably, the CR achievement showed strong superiority trend for those patients who received BvB as 1st salvage (60% vs. 35%, p=0.06). The 45/48 responders were successfully mobilized either with additional chemotherapy plus GSCF (n=22) or with GCSF only (n=21) or with GCSF plus plerixafor (n=2). Two patients refused autoSCT while one allografted. The median collected CD34+ yield was 4,5(2,1-60)x10^6/kg. So far, 42 patients underwent transplantation (autoSCT: 41, alloSCT:1). Forty-one are currently alive and 29 are disease progression free. After a median follow-up of 15 months the 4-ys overall (OS) and progression free survival (PFS) post SCT are 96% and 35% respectively. Interestingly, for the 21 autografted patients who received BvB as 1st salvage regimen, the 4ys-OS and PFS were 100% and 89% respectively. In multivariate analysis the achievement of CR post BvB, the non-bulky disease and the early BvB administration, significantly favored a prolonged PFS.

Conclusions: Our data, in agreement with the already published studies, support the evidence that the BvB combination is safe and highly effective approach for maximizing responses prior SCT in patients with RRHL, especially if it is administered as 1st line regimen. More studies with larger series of patients are clearly indicated to clarify the BvB role as "salvage-bridge" to a successful SCT for patients with RR-HL

Disclosure: No disclosures of conflicts of interest

P434

Impact of Kir Ligand Mismatch after Allogeneic Hematopoietic Stem Cell Transplantation for Hodgkin Lymphoma: A Retrospective Study in 383 Patients from the SFGM-TC

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Background: Haploidentical transplants are particularly effective in Hodgkin lymphoma (HL), even after non myeloablative conditioning regimen, independently of GvHD. The alloreactivity of Natural Killer (NK) cells is increased in the case of KIR ligand mismatch between recipient and donor, especially in myeloid diseases. Killer cell Ig-like receptors (KIRs) ligands are major HLA class I antigens, predominately HLA- B and C, that inhibit lytic activity of NK cells. KIR ligands can be categorized into different families according to the KIR receptor that recognizes them: Family HLA-C C1 (KIR2DL2/3 ligand), HLA-C C2 (KIR2DL1 ligand) and HLA-Bw4 (KIR3DL1 ligand). No studies have evaluated the impact of mismatch

KIR ligand after allogeneic hematopoietic stem-cell transplantation (HSCT) for HL.

Methods: We conducted a retrospective multicentric analyze from the SFGM-TC and French Biomedicine agency registries. We extracted HSCT for HL between 2007 and 2017 whom recipient and donor HLA B and C typing was informative to determine KIR ligand family. Only patients with informative KIR ligand were included in this study.

Results: Based on the 668 patients identified, only 383 could be classified as followed : C1/C1 n=148 (38,64%), C2/C2 n=65, C1/C2 n=170 pts (44,39%), Bw4/Bw4 n= 66 (17,23%), Bw6/Bw6 n=171 pts (44,65%), Bw4/Bw6 n=146. Two hundred and seventeen patients were transplanted with a matched donor (MD) (siblings=56, matched unrelated donors=161) and 166 with a mismatched donor (MMD) (mismatched unrelated donor=47, haploidentical=62, unit cord blood= 57). Median follow up since HSCT was 25 months for MD and 22 months for MMD. There were no statistical differences between MD and MMD in overall survival (OS), progression free survival (PFS), acute GvHD (aGVHD), therapy related mortality (TRM). Chronic extensive GvHD (CextGvHD) was lower in MMD (p=0.012) with a two years cumulative incidence of 39.65% [32.91-46.39] in MD and 28.30 % [20.96-35.63] in MMD. In multivariate analysis in the MD population, complete response of HL at transplantation was associated with better OS (p=0,004), PFS (p < 0,001), less relapse (p=0,015) and GRFS (p=0,024. Administration of antithymocyte globulin was linked to reduced aGvHD II-IV, CextGVH and GRFS (p=0,023, p=0,02, p=0,004 respectively). aGvHD II-IV was higher in C1/C2 patients (p=0,018). In MMD HSCT, OS was better for Bw4/Bw4 or Bw6/Bw6 recipients transplanted with Bw4/Bw6 donor (p=0,057; p=0,058 respectively). Interestingly, even in small cohorts, no relapse was observed in bw6/bw4 patients transplanted with a bw4/bw4 donor whereas risk of aGvHD II-IV was increased (p< 0,001 and p=0,081 respectively). On the opposite, no aGVHD was observed in Bw6/Bw4 patients transplanted with Bw6/Bw6 donors. No differences were observed in HLA-group C recipients and donors in outcome for mismatch population.

Conclusions: Our study explores for the first time the impact of HLA-B and C group in Hodgkin lymphoma on transplantation outcomes. We observed that KIR-ligand incompatibility seems to be relevant for Bw6/Bw4 recipients in mismatch transplantation whereas homozygous recipients for C1 and C2 in matched transplants seem protected against aGvHD II-IV. Those results should be confirmed by larger studies.

Disclosure: Nothing to declare.

P435

The Impact and Challenges of Performing Beam Conditioned Autologous Transplants in 'older' Patients with Lymphoma

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Background: Autologous HSCT is an established treatment option for relapsed/refractory lymphoma patients who are chemo-sensitive to salvage. Although age alone should not prevent elderly or 'older' patients from undergoing HSCT, increased age correlates with more clinical risk which may include early non-relapse mortality (NRM) and potentially longer recuperation periods. We sought to determine whether older age correlated with increased morbidity or mortality in lymphoma patients undergoing HSCT in the South Wales Blood and Marrow Transplant (SWBMT) Programme.

Methods:

1. The SWBMT Programme database was interrogated to identify lymphoma patients undergoing autologous HSCT between January 1999 and August 2019. Day 100 NRM and length of stay (LOS) were calculated for age cohorts: 20-39, 40-59 and ≥60 years old.
2. Data was extracted from electronic/paper records.

Results: Results are summarised in Table 1.

LOS

The median LOS post Day 0 (D0) did not differ among the three cohorts but >20% of older patients had a LOS of ≥20 days (8.4% for 20-39, 21.2% for 40-59, 22.9% for ≥60). Some older patients experienced prolonged inpatient stays exceeding two months (>60 days) after transplant; 1% for 40-59 (2/179) and 2% for ≥60 (2/96).

NRM

D100 NRM was more than double for 60+ patients (10/98, 10.2%) compared to under 60 patients (11/274, 4%). However early NRM decreased over time for 60+ patients: 15% (7/48) for the early cohort transplanted before the median year to 6% (3/50) for 2013-2019 cohort. This could be related to improved patient selection and/or improvements in supportive care.

Infection was the main cause of early NRM for all cohorts, occurring in 86% (18/21) overall. No organism was identified in 44.4% (8/18) of cases and where one was

identified there was no trend towards any particular organism.

In 60+ patients with early NRM, almost all had Karnofsky Performance Status (KPS) scores ≥80% and they were not necessarily heavily pre-treated. Haematopoietic Cell Transplant-Co-morbidity Index (HCT-CI) scores were not available for most early NRM cases since routine HCT-CI assessments were introduced in 2011.

Conclusions: This data shows early NRM following HSCT for lymphoma increases with increasing age. However more recent older cohorts showed improving NRM approximating to but still greater than younger age cohorts. Infection was the main cause of early NRM for all age cohorts. Mucositis and gastrointestinal side-effects of conditioning are likely to be the main contributory factors for this increased infection risk.

More than a fifth of older patients aged 40 years and over experienced prolonged hospitalisation of 20 or more days. This is anticipated to result in increased financial and bed pressures. Given the increasing trend towards ambulatory transplantation, this increased LOS may prove challenging for this model.

The KPS and HCT-CI did not identify patients most 'at risk' of early NRM. We aim to introduce geriatric assessment tools to further improve our patient selection and decision making.

Disclosure: Nothing to declare.

P436

Allogeneic Hematopoietic Stem Cell Transplantation in Transformed Follicular Lymphoma (FL): Results from A Retrospective Multicenter Study From Gelth/geltamo Group

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Background: Follicular lymphoma (FL) is the most prevalent indolent lymphoma, usually with prolonged survival when achieving response with immunochemotherapy. However, transformation into an aggressive lymphoma (TrFL) is associated to a poor prognosis. Allogeneic hematopoietic stem cell transplantation (alloSCT) can be a curative therapy in this setting but its results have not been explored in large series. Within the GETH/GELTAMO group we have designed a retrospective multicenter study to analyze the long-term outcome of alloSCT in TrFL and potential independent prognostic factors.

Methods: We collected data from 43 patients diagnosed of TrFL who underwent alloSCT in 14 Spanish GELTAMO centers from January/2000 to January/2019.

Results: We included 26 male and 17 female patients with a median age of 51 years (31-67). Thirty-two patients (74.5%) had received ≥3 previous lines of treatment, including autologous stem cell transplant (ASCT) in 27 of them (63%). Donor was HLA identical in 66% and haploidentical in 6 (14%). Status pre-AlloSCT was complete response (CR) in 21 patients (49%), partial response (PR) in 14 (33%) and progression or stable disease (PD/SD) in 5 (12%).

After alloSCT, 28 out of 35 evaluable patients achieved CR (80%). Twenty-nine patients (67%) developed acute graft versus host disease (aGVHD); from them, in 73% it was grade 1-2. Chronic GVHD appeared in 13/35 patients alive at day +100 (37%).

After a median of follow-up of 60 months for surviving patients (1-123), 15 (35%) were alive in CR. Eleven patients relapsed (26%) at a median of 4.5 (3-27) months after alloSCT and 27 (64%) died, 17 (40%) of them due to transplant related mortality (TRM).

Estimated OS at 24 months was 48.5%. The only significant prognostic factor for OS in the univariate analysis was disease chemosensitivity at the time of alloSCT (62% for patients in CR vs 43% for patients in partial remission vs 0% for patients allografted in stable/progressive disease; p=0.037). Patients with a previous ASCT showed a trend to a better OS at 24m although it was not statistically significant (27% vs 60%, p=0.20). Previous ASCT was also associated to a lower risk of relapse (HR 0.16, 95% CI 0.03-0.75; p=0.021). We did not find any impact of aGVHD in OS, probably because only 7 patients had grade 3-4 aGVHD (OS at 24m: 50% absence of aGVHD, 54% grade 1-2, 29% grade 3-4); in a landmark analysis for patients alive at day +100, the development of cGVHD was

associated to a better OS (92% vs 32%; p=0.07). cGVHD demonstrated to have a protective effect in a Cox model (HR 0.26 (0.09-0.75); p=0.012).

Conclusions: Tr-FL can be potentially cured with alloSCT, especially when immune graft versus lymphoma effect is present, as the positive impact of cGVHD proves. However, relapse and transplant related mortality is still a handicap, so new strategies should be implemented to improve alloSCT results.

Disclosure: Nothing to declare.

P437

Allogeneic Hematopoietic Stem Cell Transplantation for Follicular Lymphoma Relapsing after Autologous Transplantation

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Background: Although allogeneic (allo-) stem cell transplantation (SCT) could be a promising treatment option for follicular lymphoma (FL) relapsing after an autologous (auto-) SCT, its efficacy and safety has not been fully evaluated.

Methods: FL patients receiving allo-SCT with a history of auto-SCT were retrospectively analyzed using the registry database of Japan Society for Hematopoietic Cell Transplantation (JSHCT). In total, 141 patients underwent allo-SCT between 2001 and 2017 were analyzed. Median age at allo-SCT was 53 years old (range, 32-76), and median duration from auto-SCT to allo-SCT was 26 months (range, 4-163). Fifty-nine (42%) patients had diseases in complete response (CR)/partial response (PR) at allo-SCT. Types of stem cell and donor were bone marrow (BM) or peripheral blood stem cell (PBSC) from matched related donor (N=30), from mismatched related donor (N=9), from unrelated donor (N=72) and cord blood (N=30). Reduced intensity conditioning (RIC) was used in 77% of patients.

Results: Except for 8 cases of early death, 129 of 133 (97%) patients achieved neutrophil engraftment at a median of 16 days (range, 8-45) after transplant. Two patients experienced secondary graft failure at 37 and 81 days after SCT resulting in fatal outcomes. With a median follow-up of 66 months in survivors, the cumulative incidence of non-relapse mortality (NRM) at 1 year and 5 years were 25.9% (95%CI, 18.9-33.5%) and 36.7% (95%CI, 28.4-44.9%), and that of relapse/progression was 15.9% (95%CI, 10.4-22.5%) at 5 years. There were no patients with relapse/progression 2 years after transplant. The 5-year progression-free survival (PFS) and overall survival (OS) were 47.4% (95%CI, 38.6-55.7%) and 49.1% (95%CI, 40.2-57.4%), respectively. The cumulative incidences of acute ($\geq$ grade II) and chronic graft-versus-host disease (GVHD) were 34.9% (95%CI, 27.1-42.8%) at day 100 and 29.5% (95%CI, 22.1-37.4%) at 1 year, respectively. In multivariate analyses, disease status of CR/PR at transplant (vs. others) and RIC (vs. myeloablative conditioning) were associated with better PFS, and performance status of 0-1 (vs. 2-4) was associated with better PFS and OS. In regard to secondary malignancies, five patients developed solid organ cancers (oral cancer, N=3; stomach cancer, N=1; thyroid cancer, N=1), and two patients developed myelodysplastic syndrome.

Conclusions: Despite high NRM, the results of our study suggest that allo-SCT is a curative treatment in patients with FL relapsing even after an auto-SCT.

Disclosure: Nothing to declare.

P438

Significant Role of Upfront Autologous Stem Cell Transplantation in Patients with High Risk Diffuse Large B-cell Lymphoma

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Background: The role of the upfront high dose therapy and autologous stem cell transplantation (ASCT) in patients with diffuse large B cell lymphoma (DLBCL) is still controversial. The purpose of this study is to confirm whether the role of upfront ASCT still remains in the era of novel agent.

Methods: We retrospectively analyzed 368 patients with newly diagnosed DLBCL who had achieved complete remission (CR) or partial remission (PR) after rituximab-based induction chemotherapy from 16 institutions in the Republic of Korea. One hundred ninety patients received ASCT as consolidation therapy and 178 patients had only induction chemotherapy.

Results: In comparison of baseline characteristics, the proportion of patients with high disease burden, such as Ann arbor stage IV (70% vs 60.7%, p=0.028), bulky disease (25.8% vs 14%, p=0.005), bone marrow involvement (33.3% vs 15.8%, p< 0.001) and extranodal involvement (46.3% vs 17%, p< 0.001) was higher in the ASCT group. After a median follow up of 34 months, progression or relapse had occurred in 39 patients (20.5%) of ASCT group and 46 patients (25.8%) of non-transplant group (p=0.227). Treatment related early mortality with ASCT occurred in 4 patients (2.3%). There was no difference between the two treatment groups in terms of overall survival (OS, p=0.884) and progression free survival (PFS, p=0.174). The 3-year OS and PFS rates were 78.8% and 70.9% in ASCT group and 81.3% and 66.3% in non-transplant group, respectively. However, upfront ASCT have been found to still have a significant role in some patients with high disease burden such as high LDH level, more than one extranodal involvement, bone marrow involvement. In subgroup analysis of the patients with high LDH level, OS (p=0.032) and PFS (p=0.001) of ASCT group were statistically significantly superior to that of the non-transplant group. Similar results were found in patients with more than one extranodal involvement (OS, p=0.028 and PFS, p=0.003). Finally, in patients with stage III or IV, high LDH levels and more than one extranational involvement, the difference of survival between ASCT group and non-transplant group was confirmed to be maximized.

Conclusions: The outcomes of upfront ASCT in patients with DLBCL at first CR or PR after induction therapy were acceptable. In particular, the role of the upfront ASCT is expected to be higher in patients with high tumor burden, such as high LDH level or extranodal involvement.

Disclosure: Nothing to declare.

P439

Autologous Stem Cell Transplantation in HIV+ and HIV- Lymphoma Patients: A Propensity Score Matched Analysis

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Background: ASCT has been demonstrated to be safe and is increasingly performed in HIV-associated Hodgkin and non-Hodgkin lymphoma (HIV-Ly). We analysed our single institution series of HIV-Ly receiving ASCT and compared their outcome with a matched cohort of HIV- patients.

Methods: We analysed all HIV+ patients with lymphoma who received ASCT at Spedali Civili di Brescia (Italy) since 2001. To compare their outcome with that of the HIV- population, we analysed all the HIV- patients with lymphoma who received ASCT at Spedali Civili di Brescia and Policlinico Rossi (Verona, Italy) between 2010 and 2017, and created an homogeneous matched cohort using the propensity score matching (PSM) analysis (ratio 1:1) (PSM1). The outcomes of the two groups in terms of OS and PFS were compared and assessed by Kaplan Meyer analyses. Multivariable Cox regression analysis (MVA) was used to assess predictors of relapse and mortality. To more accurately compare the two groups, a PSM analysis with a reduced distance of matching at one-tenth standard deviation was performed (PSM2).

Results: Between January 2001 and June 2019 66 consecutive patients with HIV-Ly underwent ASCT. Characteristics are reported in **Table 1**. Indications for ASCT were primary refractory (24%), first/subsequent relapse (39.5%), and consolidation after first line therapy for PR or high risk CR (36.5%). Median CD4+ count at ASCT was 208/mL (55-720), 8 patients had detectable HIV viral load. The most used conditioning regimen were BEAM (71%) and FEAM (26%). All patients received cART throughout ASCT; 3 patients temporarily suspended because of toxicity.

Median time to neutrophil and platelet engraftment was 10 days and 13 days, respectively. Thirty-nine% of patients experienced grade 3-4 non hematologic toxicity. An episode of FUO occurred in 48% of patients; 25% had a bacterial infection and 12% a viral reactivation (CMV, HZ, HHV6).

With PSM1 we identified 66 HIV- patients comparable for age, sex, histology, status at ASCT and number of prior lines of therapy (**Table 1**).

After median follow-up of 43 months, four years (4y)-PFS for HIV+ vs HIV- patients were 73% vs 65% (p=0.46) and 4y-OS 73% vs 74% (p=0.81) (**Fig. 1A**).

The relapse-rate in HIV+ vs HIV- patients was 27,3% vs 34,8% (p=0.45). In both groups 18 deaths (27,3%) were recorded. Lymphoma-specific mortality in HIV+ cohort was 22,7% vs 18.2% in HIV- population (p=0.51). HIV-infection was not associated with relapse or mortality risk at MVA.

With PSM2, we identified two 44-patients matched cohorts. 4y-PFS for HIV+ vs HIV- was 77% vs 60% (p=0.016) and 4y-OS 78% vs 69% (p=0.14) (**Fig. 1B**).

Conclusions: Long-term outcome of HIV+ patients with HL and NHL compare favourably with those of HIV- population. ASCT for HIV-Ly should be considered according to the standard transplant criteria.

	HIV- (%, n=66)	HIV+ (%, n=66)	p-value
Age Median Range	46 34-58	45 37-52	0.7
Sex M F	92.4 7.6	93.9 6.1	1
Histology Hodgkin DLBCL/ Plasmablastic Burkitt/Burkitt like T Cell Lymphoma Follicular Lymphoma PMBCL High grade transformed from low-grade	24.2 56.1 4.5 10.6 1.5 1.5 1.5	16.7 50 21.2 7.6 1.5 1.5 1.5	0.2
Status at ASCT 1st CR Chemo-Sensitive disease Chemo-Refractory disease	16.7 75.8 7.6	15.2 72.7 12.1	0.68
Prior therapies 1 2 ≥3	33.3 45.5 21.2	36.4 47 16.7	0.79

[Table 1. Characteristics of the HIV+ and HIV- cohorts matched according to PSM1]

Clinical Trial Registry: NA
Disclosure: None

P440

Allogeneic Stem Cell Transplantation can be Successfully Delivered Following BTKI Therapy Failure Following R-bac Re-induction Chemotherapy in Patients with Mantle Cell Lymphoma

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Background: Allogeneic haematopoietic stem cell transplant (alloHSCT) is a potentially curative treatment option for patients with mantle cell lymphoma (MCL). Bruton's Tyrosine Kinase inhibitors (BTKi) eg ibrutinib are highly effective in relapsed/refractory (R/R) MCL. The optimal timing of alloHSCT in this setting is not currently known. Here we report data on two groups of patients undergoing alloHSCT for R/R MCL following BTKi therapy. The first received BTKi as a bridge to alloHSCT, and a second underwent alloHSCT following BTKi failure and subsequent treatment with rituximab, bendamustine and cytarabine (R-BAC) chemotherapy

Methods: Twenty eligible patients were retrospectively collected across 13 centres (2016-2019). Follow-up was censored in 07/2019. Eleven patients received alloHSCT following ibrutinib as second-line treatment, 9 received alloHSCT after BTKi failure and subsequent salvage chemotherapy with R-BAC. Progression-free survival (PFS) and overall survival (OS) analyses were performed using Kaplan Meier methods and Cox regression with comparisons between categories using the log-rank test.

Results: Median OS of the whole group post alloHSCT was not reached (63% at 1 year). Median follow up post alloHSCT was 12 months.

AlloHSCT post BTKi alone Of patients transplanted following BTKi as bridging therapy, all received ibrutinib as second-line treatment (7/11 prior NORDIC protocol, 4/11 high dose cytarabine (HDAC)). Nine had undergone prior autologous stem cell transplantation. 1/11 was primary refractory to HDAC. Median time on treatment with ibrutinib was 6 (3-20) months. 5/11 achieved a complete response / complete response undetermined (CR/Cru) to ibrutinib, 5/11 had a partial response (PR) and one was transplanted after progressive disease (PD). 2/11 patients were transplanted from a sibling donor, 7/11 from an unrelated donor and 2/11 from a haploidentical donor. Conditioning regimen was fludarabine/melphalan in 8/11 patients. 1/11 received BEAM conditioning and 2/11 received fludarabine/cyclophosphamide/TBI. T-cell depletion with alemtuzumab was used in 8/11 patients. Median OS of patients was not reached (OS at 1 year 52%). All 4

deaths were due to transplant-related mortality (3/4 deaths were GvHD related).

AlloHSCT post BTKi and subsequent R-BAC Of patients transplanted following BTKi failure and subsequent R-BAC treatment. 8/9 had received prior ibrutinib, 1/9 had received M7583 (Merck BTKi). All patients had previously stopped BTKi due to PD/lack of response. 5/9 patients achieved a CR with R-BAC prior to alloHSCT, 1/9 PR and 2/9 had stable disease, best response was unknown in 1/9. Eight are alive with a median follow up of 4.3 months (median OS not reached, estimated 1 year OS 85.7%). 1/9 patient died due to PD.

There was no significant difference in OS between patients receiving alloHSCT following BTKi bridging, compared with patients undergoing alloHSCT following BTKi failure and subsequent R-BAC ($p = 0.39$, log-rank test).

Conclusions: We have recently reported that R-BAC is a highly efficacious regimen in the post BTKi setting. These data demonstrate that alloHSCT following BTKi failure and subsequent R-BAC salvage treatment represents a reasonable treatment option for a subset of patients. Thus, maximising the PFS on BTKi and reserving alloHSCT post BTKi failure and subsequent salvage with R-BAC may be a reasonable strategy for selected patients.

Disclosure: Nothing to declare.

P441

Clinical Outcomes of EBV$^+$ PTLD Patients Following HCT who Fail Rituximab: A Retrospective Chart Review Study from France

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Background: Post-transplant lymphoproliferative disease (PTLD) occurs as a consequence of immunosuppression following allogeneic hematopoietic stem cell transplantation (post-HCT). In most cases, PTLD is associated with Epstein-Barr Virus (EBV) infection of B cells, either due to reactivation of the virus after transplantation, or from primary EBV infection.[1,2,3] Clinical practice treatment guidelines recommend rituximab as preemptive therapy for EBV reactivation (based on EBV virus load) and for EBV$^+$ PTLD following HCT. Treatment options for EBV$^+$ PTLD patients (pts) who fail rituximab are not clearly defined and outcome is usually very poor.

Methods: This is a retrospective chart review study of pts diagnosed with EBV$^+$ PTLD following HCT who received rituximab or rituximab plus chemotherapy (CT) between 2000-2017 at 4 centers across France and who were refractory (failed to achieve complete [CR] or partial response [PR]) to rituximab or rituximab plus CT, or relapsed at any point after such therapy. Pts diagnosed with primary CNS PTLD were excluded. Medical charts were reviewed independently by a trained reviewer and an experienced physician. The Kaplan-Meier (KM) method was used to estimate the distribution of overall survival (OS) for pts who failed rituximab or rituximab plus CT post-HCT. The index date for rituximab failure was defined as the earliest date when pts became refractory to or relapsed after first line rituximab or rituximab plus CT.

Results: A total of 18 EBV$^+$ PTLD pts were included in the analysis. Median age at PTLD diagnosis was 55 years (yrs) (range 18-75) and median time to PTLD onset from transplant was 2 months (range 1-4). Median follow-up time was 2.6 months (range 0.7-58.3) from the date of PTLD diagnosis. Of all the PTLDs, 14 (78%) were Diffuse Large B Cell Lymphoma, 3 (17%) were polymorphic, and 1 (6%) was Burkitt lymphoma.

Fifteen pts received rituximab monotherapy and 3 pts received rituximab plus CT as first line of therapy. The three pts who received rituximab plus CT had received pre-emptive rituximab treatment for EBV viremia prior to PTLD treatment. Median OS was 1.7 months (95% CI: 0.7-2.9) for 18 pts who failed first line rituximab or rituximab plus CT. Median OS from PTLD diagnosis was 2.5 months (95% CI: 1.5-4.6).

Sixteen (89%) out of the 18 pts ultimately died. Causes of death were 10 (63%) related to PTLD and therapy, 1 (6%) from GvHD, 3 (19%) from sepsis/infection, 1 (6%) due to primary disease leading to HCT and 1 (6%) unknown.

Conclusions: The prognosis of EBV$^+$ PTLD pts following HCT who fail rituximab remains very poor with an estimated median OS of less than 2 months, highlighting the significant unmet need in this population.

Disclosure: Gérard Socié - Nothing to declare.

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P442

The Impact of Allogeneic Hematopoietic Cell Transplantation (ALLOHCT) on the Outcome of poor-risk Non-hodgkin Lymphoma (NHL): Update of a Retrospective intent-to-transplant (ITT) Analysis

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Background: AlloHCT is an accepted salvage treatment in high-risk relapsed/refractory NHL. The benefits of allo-transplantation in these indications, however, remain controversial, because published studies are mostly retrospective, uncontrolled and limited to patients that actually received transplantation. The present study was designed to assess the impact of alloHCT by ITT, i.e. calculating the outcome from the time of donor search indication and not from the time of transplant, thereby taking into account those patients who fail to proceed to allografting for any reason.

Methods: This single-centre retrospective analysis included consecutive patients with diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL) and peripheral T-cell lymphoma (PTCL) for whom a donor search was performed from 2004 through 2018. Primary endpoint was overall survival (OS) as measured from search initiation. A key secondary endpoint was OS from the 3-month landmark after search initiation.

Results: A donor search was initiated for 189 patients (DLBCL n=61 (32%), FL n=32 (17%), MCL n=43 (23%) and PTCL n=53 (28%)). Median age at donor search initiation was 54 (19-69) years, with the majority being male (74%). Within a median time from diagnosis to search initiation of 1.2 (0.1-19) years, a median of 4 (1-9) treatment lines had been administered, including an autoHCT in 52%. Of note, 133 of 176 patients (76%) with information available on this item had active disease at the time of search initiation (DLBCL: 97%). After a median follow-up 7.1 (0.1-15.8) years, OS at 5 years after search initiation for DLBCL, FL, MCL, and PTCL was 25%, 42%, 52%, and 49%, respectively (**Fig 1**). 173 patients (92%) were alive at the 3-month landmark. Of these, an MRD (20%), MUD (44%), MMUD (25%), or MMRD (7%) could be identified, whereas a donor was not found in only 4% of the cases. AlloHCT was performed in 72% of all 189 patients, and in 79% of the patients alive at the 3-month landmark, with a significantly lower rate in DLBCL (70%) compared to the other entities.

The 5-year survival after the 3-month landmark for patients actually undergoing alloHCT was 54% compared to 14% without transplantation, with DLBCL 32% vs. 18%, FL 60% vs. 0%, MCL 65% vs. 17% and PTCL 61% vs. 14%, respectively.

Conclusions: Despite a donor search success rate of >90%, >25% of those patients intended for alloHCT for NHL will never proceed to transplant. However, long-term OS by ITT does not seem substantially worse than alloHCT outcome observed in registry studies restricted to patients actually transplanted, with DLBCL appearing inferior to the other 3 entities. Patients surviving the 3-month landmark but not undergoing alloHCT for any reason have a poor outlook. These results could serve as a benchmark for new therapeutic approaches for the treatment of poor-risk NHL.

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P443

Comparison of Mitoxantrone - Melphalan and Beam Conditioning Regimens in Lymphoma Patients

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Background: High-dose chemotherapy in conjunction with auto-SCT is widely recognized as the preferred modality of treatment for patients with relapsed or refractory Hodgkin disease or non-Hodgkin lymphoma at the time of chemosensitive relapse. Despite different drug combinations and conditioning regimens before auto-SCT, the optimal choice is undetermined. Several studies have been made to identify a regimen with superior antitumor activity and acceptable toxicity. : In this retrospectical analysis, we compared the efficacy and the toxicity of the BEAM and Mitoxantrone/Melphalan conditioning regimens in relapsed NHL and relapsed Hodgkin Lymphoma patients.

Methods: A total of 101 patients with HL or NHL treated with Auto-SCT at our center between 2014-2019 are analyzed retrospectively. Patients were considered eligible for transplantation, if they met the following inclusion criteria: age between 16 and 65 years, ECOG performance status 0-2 (WHO (World Health Organization), left ventricular ejection fraction greater than 55%, creatinine clearance greater than 60 ml/min and adequate lung and liver function. Central nerve system involvement and chemorefractory disease were excluded. Mitoxantrone was given 60mg/m2 at day -5, and melphalan was given 180mg/m2 at day -2 of transplant.

Results: 60 patients (%59) received BEAM, 41 patients (%41) received Mito/Mel as conditioning regimen. There were no difference between two groups in terms of response status before SCT, histologic sub type, age, gender, received stem cell dose, received salvage regimen, bone marrow involvement and bulky disease at the time of diagnosis. After transplant median neutrophil (10 vs 11 days) and thrombocyte engrafment (12 vs 12 days) days were similar. Number of Febril neutropenic attack, and median febril neuropenic days were slightly more common in BEAM group but no statistical difference were observed. After 24 months of median follow up, median PFS and OS was not reached in both group. 5 year Progression free survival rate were %61 in BEAM arm while %74 in Mito/Mel arm (p=0,813). 5 year overall survival rate were %71 in BEAM arm while %75 in Mito/Mel arm (p=0,708). No significant difference was observed in two arms. First 100 day mortality was %3,3 in BEAM arm while %2,5 in Mito/Mel arm, son difference was observed. Nephrotoxicity and hepatotoxicity were in similar in two groups while mucositis was slightly more common in BEAM arm.

Conclusions: Despite the common use of BEAM as a conditioning regimen for auto-SCT in patients with lymphoma, there have been no reports comparing these two regimens. The Mito/mel conditioning regimen showed us a same neutrophil and platelet engraftment time, same hepatotoxicity and nephrotoxicity rate, same 5 year OS and PFS rate as BEAM regimen. According to our study analysis, Mito/Mel as a conditioning regimen for auto-SCT should be considered for countries which have a problem of BCNU (carmustin) provide. Prospective and randomized studies require defining the most efficient conditioning regimens for relapsed/refractory lymphoma patients.

	All Patients (101)	BEAM (60)	Mito-Mel (41)
Median Follow-up (months)	24	44	14
5 year PFS	%63	%61	%74
5 year OS	%70	%69	%75

[Patient Outcomes]

Disclosure: Nothing to declare.

P444

Nivolumab re-challenge in Patients with Relapsed/refractory Classical Hodgkin Lymphoma: Where is the Place for Allohsct?

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Background: Immune checkpoint inhibitors represent highly efficient treatment option for patients with relapsed/refractory classical Hodgkin lymphoma (r/r cHL). However, some patients require discontinuation of therapy due to various reasons. In this situation, the question of the effectiveness of nivolumab retreatment in patients with r/r cHL who achieved the response to initial PD-1 inhibitor therapy remains unresolved.

Methods: The analysis included 23 patients with r/r cHL who were treated with nivolumab (3 mg/kg every 14 days) and achieved complete remission (CR). After nivolumab

discontinuation the patients received no other treatment. In case of disease relapse patients were retreated with nivolumab monotherapy or in combination with chemotherapy. Response was assessed by PET/CT using LYRIC criteria every 3 month. Adverse events were evaluated by NCI CTCAE 4.03 criteria.

Results: The median follow-up after nivolumab discontinuation was 29 (14-32) months. The median age was 32 (20-48), the male/female ratio was 26/74%. The median number of nivolumab cycles was 24 (11-30), the median cycles before the best response - 6 (6-24). After the best response achievement, the therapy was continued with median time 7 (0-15) months.

The relapse of the disease was observed in 11 (48%) out of 23 patients. The median progression-free survival (PFS) was not reached, the 2-year PFS was 56,5% (95% CI, 23,18%-89,82%). The nivolumab retreatment was initiated in all 11 patients with relapse, the response was evaluated in 9 patients at the moment of analysis. The median follow-up after the retreatment initiation was 14,8 (2-25,4) months. The overall response rate was 67%: the CR was 33,3%, the partial remission (PR) - 33,3%. The median time before the best response achievement was 3,6 (2,8-8,1) months. At the moment of analysis all patients were alive. The median PFS was 16,5 months (95% CI, 16,291-16,709). The retreatment was discontinued in 5 patients due to different causes including the wish of patients. At the moment of therapy discontinuation 2 patients had the CR, 1 patient- the PR and 2 patients - the indeterminate remission. Four patients after the response achievement and nivolumab retreatment discontinuation had relapse of the disease and 1 patient had disease progression after 24 cycles of therapy.

The severe adverse events (AE) occurred in 4 (36%) patients during nivolumab retreatment. There was no deterioration in the course of complications during nivolumab re-challenge.

Conclusions: The nivolumab re-challenge is the effective option in patients with r/r cHL who achieved CR during initial PD-1 inhibitor treatment However, the stable response was not observed as a result of nivolumab retreatment. Thus, the issue of alloHSCT should be considered at the moment of disease relapse after initial nivolumab therapy in this patient group.

Disclosure: Nothing to declare.

P445

Outcome of Transplant Eligible Mantle Cell Lymphoma Patients with first-line Regimens in a real-world Setting - A Portuguese Multicenter Retrospective Analysis

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Background: Several chemoimmunotherapy (CIT) regimens containing rituximab (R) and cytarabine (Ara-C) followed by autologous stem cell transplant (ASCT) are currently used as first approach in the treatment of fit mantle cell lymphoma (MCL) patients. However, data comparing different induction regimens outside clinical trials is scarce.

Methods: Retrospective review of MCL patients, diagnosed between 01-2008 and 12-2017 in 6 Portuguese centers, treated with intention to consolidate with ASCT after first-line CIT induction. Data on patients at diagnosis and treatment characteristics were collected. Multivariate Cox regression analysis of variables with impact on 4 year (y) overall survival (4y-OS) and progression free survival (4y-PFS) was performed.

Results: A total of 116 patients was evaluated, with a median age of 58y (32-68y) and 75% were male. At diagnosis, 93% had ECOG performance status 0-1, 97% were stage III-IV, 40% had increased LDH and median leukocyte count was 8.55 $x10^9$/L. MIPI was low-risk in 38%, intermediate-risk in 40% and high-risk (HR) in 22%. CIT regimens had RCHOP backbone, with Ara-C and methotrexate (Ara-C/MTX) in 38%, Ara-C and platinum (Ara-C/PL) in 20%, Ara-C alone in 33% and RCHOP-only in 9%. Ara-C/MTX patients were older (median 60y) than Ara-C (median 57y) and RCHOP-only (median 53y) patients.

During induction, 1 patient each in Ara-C and RCHOP-only groups died, 2 patients in Ara-C/MTX and 3 in Ara-C stopped due to toxicity. Complete remission (CR) was 80% and partial remission was 11%, with no differences between CIT regimens. MCL progression before ASCT occurred in 14% of patients, with no differences between CIT groups.

Due to toxicity, 3 patients in Ara-C and 1 in Ara-C/MTX were ineligible to proceed to ASCT; 2 patients in Ara-C/MTX and 1 in Ara-C failed to collect stem cells and 2

patients in Ara-C/MTX refused the procedure. In total, 91 patients (78% of the population), received an ASCT, 78% of whom were conditioned with BEAM, 19% with FEAM and 3% with others; only 1 patient died. CR at day 100 was 97%, with no differences between regimens. Maintenance with R was offered to 7% of patients and with lenalidomide to 6% (clinical trial setting), more frequently in Ara-C group.

With a median follow-up of 43 months, 4y-PFS was 59% and 4y-OS was 70%, with no differences between CIT regimens. At 4y after CIT, 32 patients had died, 82% due to MCL, 6% each from CIT toxicity and secondary malignancies, 3% each from ASCT procedure and unrelated causes. In multivariate analysis, only HR MIPI impacted on 4y-PFS (hazard ratio (HR) 3.40 [95% confidence interval (CI) 1.75-6.37]; median 19 months) and 4y-OS (HR 4.15 [95% CI 2.02-8.53]; median 33 months).

Conclusions: Our data suggests that different first-line CIT induction regimens with Ara-C provide similar outcomes in MCL patients candidates to ASCT. RCHOP-only results should be interpreted with caution due to sample size. HR MIPI seems to be the most important adverse prognostic factor; these patients have an unmet need, where novel agents and different transplant modalities might improve outcome.

Disclosure: Nothing to declare.

P446

Evaluation of Fractionated Ice as an Alternative Outpatient Option for Relapsed/refractory Lymphomas

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Background: Administration of chemotherapy in inpatient setting is challenging due to limited availability of hospital beds and cost associated with hospital admission. Furthermore, it may negatively impact quality of life (QoL) of patients. Limited data is available on efficacy and safety of outpatient fractionated regimen of ifosfamide, carboplatin and etoposide (ICE) as salvage treatment prior to high dose chemotherapy and autologous stem cell transplantation (ASCT) in patients with relapsed and refractory lymphomas.

Methods: We retrospectively collected the data of patients who received outpatient fractionated ICE between August 2010 and September 2019 at a tertiary care center. The ICE protocol consisted of: ifosfamide 1500 mg/m2 infused over 2 h daily on days 1-3, carboplatin (mg dose = 5 · AUC) i.v. on day 1, and etoposide 100 mg/m2 i.v. daily on days 1-3, plus filgrastim 5 ug/kg/day s.c. for 5 days. Rituximab 375 mg/m2 on day 1 was added for patients with CD20 positive B cell Non-Hodgkin lymphoma. The Cycles of outpatient ICE were given every 21 days.

Results: The overall study sample included 89 patients (44% female and 56% male) with median age of 29.8 years (21.9-46.5). Majority of patients had HL (n=57), 24 DLBCL, 3 follicular, 2 mantle cell and 3 T-cell Non-Hodgkin lymphoma. 5% had transformed lymphoma. Over half of the study sample (55.1%) was initially categorized as stage 4 and just 23 (25.8%) patients achieved a complete response with initial therapy. The median time from the end of initial therapy to relapse was 4.2 months. 88% had stage III and IV with 49% having extranodal disease prior to ICE. Of patients who achieved a response qualifying for ASCT, stem cells were successfully collected with filgrastim alone and plerixafor plus filgrastim in 77.1% and 22.9% respectively. Upon completion of planed ICE cycles, overall response rate was 48,4% (21.4% achieved complete and 27% partial response) while 23.6% had progressive disease. Over half (53.9%) of the study participants proceeded to auto-SCT. Thirty-one of 59 patients were alive after a median observation time of 52.6 months (range, 5.8 to 202.9 months). The estimated median EFS for all patients was 14.5 months (95% CI, 7.7 to 28.0 months) and the estimated median OS was 88.7 months (95% CI, 48.1-NR). The factors significantly associated with hazard of death included age (≥40 years vs. < 40 years) (p=0.021), extranodal disease (p=0.003) and the response to ICE treatment (p=0.002).

Most common treatment related adverse events at any grade included mucositis (54.0%), vomiting (52.8%), lymphopenia (43.8%), neutropenia (28.1%), anemia (24.7%), thrombocytopenia (19.1%) and neuropathy (16.9%). Grade 3 neutropenia and thrombocytopenia was experienced in 10.1% and 9.0% of patients respectively. There were no grade 4 events related to ICE treatment in this study population.

Conclusions: In this, to our knowledge largest published experience with outpatient fractionated ICE, the results showed that this regimen is an interesting alternative to the classic ICE regimen with favorable safety profile. However, additional data from randomized clinical trials are warranted.

Disclosure: Nothing to declare.

P447

Efficacy of Haploidentical Stem Cell Transplantation for Patients with Relapsed/refractory Classical Hodgkin Lymphoma

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Background: Allogeneic hematopoietic stem cells transplantation (allo-HSCT) is a potentially curative option for patients with relapsed and refractory Hodgkin lymphoma (rrHL). For patients who lack an HLA-matched sibling, HLA-haploidentical related donors (haplo-HSCT) can be considered as alternative sources of donor grafts. The benefits of haplo-HSCT include immediate donor availability for patients who are in urgent need of the transplant. In addition, the greater HLA mismatch associated with haploidentical HSCT (haplo-HSCT) may potentiate graft-versus-tumor (GVT) effects. In recent years, evidence has emerged that the results of haplo-HSCT with post-transplant cyclophosphamide are comparable to the results of transplants performed from an HLA-matched related or unrelated donor. In addition, there is already data of the advantage of haplo-HSCT for patients with rrHL due to improved GVHD-free/relapse-free survival (GRFS). However, the use of an alternative donor is still not the standard of treatment for this group of patients. The aim of this study was to evaluate outcomes of haplo-HSCT for patients with rrHL.

Methods: We retrospectively evaluated the results of haplo-HSCT in 17 patients who had been transplanted at the R. Gorbacheva Memorial Research Institute of Children Oncology, Hematology and Transplantology at the First St. Petersburg State I. Pavlov Medical University (CIC 725). In this analysis, 16 patients received reduced-intensity conditioning regimen (fludarabine 30 mg/m2, bendamustine 130 mg /m2 per day for 3 days (FluBe)). GVHD prophylaxis based on post-transplant cyclophosphamide (PTCY-based GVHD prophylaxis) was employed in 16 patients. At the time of transplantation, 10 patients had an objective response -complete response (CR) and partial response (PR), 4 patients had an indetermined response (IR) according to the LYRIC and 3 patients in the general group received haplo-HSCT as salvage therapy. In order to achieve disease control, 10 patients received nivolumab therapy before haplo-HSCT.

Results: At the time of analysis, the median follow-up was 16 months (range,1-43.2).

The 1-year OS and EFS were 82,4% and 64,7% respectively, whereas the 2-year OS and EFS were 76,5% and 64,7% respectively.

Out of the 14 patients with engraftment, the cumulative incidence of acute GVHD grade II-IV and severe aGVHD grade III-IV was 23,5% and 17,6% respectively. The 1-year cumulative incidence of chronic GVHD (cGVHD) was 29%. There was no significant increase in the incidence of GVHD in the group of patients who received nivolumab before haplo-HSCT. The 1-year cumulative incidence of relapse and overall transplant-associated mortality was 17,6%/.

Conclusions: In summary, our results show that unmanipulated haplo-HSCT is a reasonable treatment option for adult patients with rrHL in the absence of an HLA-matched donor. However, the problematic issue is the higher rate of graft failure, increased non-relapse mortality (NRM) and post-transplant relapses. To improve the results of haplo-HSCT, the appropriate multicenter studies are required.

Disclosure: Nothing to declare.

P448

Risk Factors for Intensive Care Unit Admission in Patients with Non-hodgkin Lymphoma Undergoing Autologous Stem Cell Transplantation

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Background: High dose chemotherapy treatment (HDCT) following autologous stem cell transplantation (ASCT) in patients with non-Hodgkin B lymphomas (NHL) tries to decrease the risk of relapse, improving the progression free survival (PFS) and overall survival (OS).

ASCT safety has been improved over the past decades associating low rates of mortality, thanks to several advances in supportive care management in order to control side effects from the procedure.

Nonetheless, ASCT is associated with many early complications. Most of them, can be managed in a standard hospitalization area but the use of HDCT can also result in life-threatening complications requiring advance supportive therapy in intensive care units (ICU).

We try to describe which risk factors could be associated with ICU admission in patients with NHB lymphoma undergoing ASCT.

Methods: From 2016 to 2018, we have retrospectively reviewed 99 adult patients with NHL undergoing ASCT in a tertiary center in the Basque Country, Spain (median follow-up of 1.67 years). The most frequent diseases were: diffuse large B cell lymphoma (53.5%), mantle cell lymphoma (13.1%) and transformed lymphoma (10.1%). The median age was 53 years.

We compared 9 patients admitted to ICU versus 90 patients who didn't need it. We took into account the patients' basal characteristics, the pre-transplantation evaluation results, the comorbidities, the response status and the conditioning regimen and HCT-CI index (table 1).

PFS and OS (performed with Kapplan-Meyer estimator) were both calculated from the time of infusion to the time of relapse or death by any cause, respectively. The statistical program used was the "SPSS".

Results: No statistical differences were obtained in the studied parameters except in the ECOG scale. Patients with an ECOG ≥2 had more risk to be admitted in ICU compared with the ones with ECOG scale < 2 ($p < 0.001$). However, we observed that a Sorror index ≥ 3, a DLCO < 60%, a CrCl < 50 ml/min and ≥1 prior treatment line could remain significant risk factors due to an increase in ICU admission (p 0.143, p 0.192, p 0.181 and p 0.171, respectively). These alterations cannot be ruled out as potential risk factors.

The global mortality was 16.2%. The main cause of mortality was the disease progression (62.5%); there were 12.5% due to ASCT complications.

The mortality in ICU patients was 44.4% and the main cause of mortality was the ASCT complications (75%). The median length of stay in ICU was 6 days (4-54) and the main causes to admission were septic shock (77.7%) and respiratory complications (22.3%).

The median OS was 1.79 years for ICU patients; in the other group, it has not been reached yet ($p < 0.05$).

Conclusions: Patients with NHB lymphoma undergoing an ASCT with an ECOG scale ≥ 2, a Sorror index >2, with respiratory or renal disfunction as well as ≥1 prior quemotherapy treatment have a higher risk of admission into ICU. Pre-transplant evaluation with a correct patient selection becomes crucial to decrease the risk of complications.

Disclosure: Nothing to declare.

P449

Autologous Stem Cell Transplantation after Nivolumab Treatment for Patients with Relapsed/refractory Primary Mediastinal B-cell Lymphoma

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Background: Clinical outcomes of relapsed/refractory (r/r) primary mediastinal B-cell lymphoma (PMBCL) still remain dismal. Patients with chemosensitive disease may benefit from autologous hematopoietic cell transplantation (auto-HSCT) and disease status at the time of transplant influence on treatment efficacy. PMBCL frequently involves PD-1 ligand overexpression, potentially making PMBCL susceptible to PD-1 inhibitors, also there is evidence that nivolumab may restores sensitivity to chemotherapy in chemorefractory patients. Therefore, nivolumab may be therapeutic option as a bridge to auto-HCT in patients with r/r PMBCL

Methods: We retrospectively analyzed data of 6 patients with r/r PMBCL. Median age was 19 (range, 17 - 43) years. Most of the patients n6 (86%) had a primary chemoresistant disease and n1 (14%) patient had a relapse. The median of lines of prior therapy was 2 (range, 1 - 4) lines. Among this patients n2 received nivolumab as monotherapy, n1 - nivolumab in combination with brentuximab vedotin and n3 - nivolumab in combination with chemotherapy.

Results: Objective response (OR) was noted in n5 patients with complete response (CR) in n3 patients, and n1 patient as best response achieved stabilization. All n6 patients after nivolumab treatment underwent auto-HSCT with BeEAM conditioning regimen. After auto-HSCT - n2 patients with partial response and n1 patient with stabilization at the time of transplant, received nivolumab (monotherapy or combination with bendamustine) as post-transplant treatment and all n3 patients improved the response to CR. At the time of analysis, the median follow-up was 15 months (range,7-30). During the observation, only one patient developed relapse and this patient died of lymphoma progression. The 1-year OS and EFS were 83%.

Conclusions: nivolumab-based regimens as bridge to auto-HSCT after could be a promising option for r/r PMBCL. Additional studies are necessary to further assess the role of nivolumab in this group of patients

Disclosure: Nothing to declare.

P450

The Irish Experience of Thiotepa, Carmustine and Etoposide Conditioning Prior to ASCT for the Treatment of Central Nervous System Lymphomas

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Background: Primary CNS lymphoma (PCNSL) was initially treated with whole brain radiotherapy (WBRT) resulting in poor outcomes and severe neurotoxicity. High dose methotrexate (HDM) improved the median progression free survival (PFS) to 11.9 months and the overall survival (OS) to 37 months. Combining WBRT and HDM did not improve OS. The use of high dose thiotepa (TT) and carmustine (BCNU) supported by autologous stem cell transplantation (ASCT) resulted in a 3-year OS of 77%, without the associated neurotoxicity of WBRT.

We report the characteristics and outcome of patients with PCNSL and secondary CNS lymphoma (SCNSL) treated with TT, BCNU and etoposide (VP16) conditioning supported by ASCT in our institution over a 5-year period.

Methods: Patients with CNS lymphoma transplanted in St James's Hospital from 01/08/2014 to 01/08/2019 were included. Stem cells were mobilized with cytarabine (PCNSL) or cyclophosphamide (SCNSL). Patients were conditioned with BCNU (400mg/m2 on day -5), TT (5mg/Kg 12 hourly x 4) and VP16 (150mg/m2 x 3).

Results: Eight HIV negative patients were included: SCNSL (n=3) and PCNSL (n=5) which included 3 in CR1 and 2 in CR2. DLBCL with a MIB1 ≥70% was confirmed including 1 double hit lymphoma; all were CSF and bone marrow involvement negative. The median age at transplantation was 47 years (range 23-58) with the PCNSL versus 51 years in SCNSL.

A median of CD34+ 5.56 x 10^6 cells/Kg (range 3.42-7.2) were infused with average engraftment of 12 (range 10-13)days. Grade 3 diarrhoea, myelosuppression and febrile neutropenia occurred in all patients, and gut toxicity delayed discharge to a median of 22 (range 18-35) days, no toxic deaths occurred. The overall follow-up time for survivors was 339 days with no neurotoxicity observed.

PCNSL induction regimens pre-transplant: MATRix (n=2), Ferreri (n=2) and RMVP (n=1). The PCNSL patients consolidated with TT/BCNU/VP16 and ASCT in CR1 remain in CR. Two PCNSL patients were treated in CR2, they had previously relapsed at 13 and 32 months following HDM based induction and WBRT. Following ASCT, one relapsed within 100 days, the second remains in CR2 (797 days post-ASCT).

The SCNSL group (n=3) achieved CR1 with RCHOP and relapsed with isolated CNS disease between 119-1,031 days and were treated with the 'Ferreri' regimen. One patient with 'double hit' CNS lymphoma achieved a PR pre-ASCT, progressed by day 100 and died at day 231. Two patients were transplanted in CR including a primary testicular lymphoma patient who remained in CR at day 100, relapsed at day 365 and died at day 399. The final SCNSL patient remains in CR 1,626 days post-transplant.

Conclusions: Our study indicates that thiotepa, carmustine and etoposide-based conditioning followed by an ASCT is a safe and well tolerated regimen with no neurotoxicities observed. It appears that the PCNSL patients treated in CR1 have superior outcomes to those treated in CR2. Though longer follow-up and a larger patient cohort is needed to confirm this, we suggest that patients would benefit from referral for high dose therapy and ASCT as consolidation for primary therapy and avoid the neurotoxicity associate with WBRT.

Disclosure: nothing to declare.

P451

Allogeneic Hematopoietic Cell Transplantation as Treatment Option for Rare Transdifferentiation of Lymphoid Neoplasms into Histiocytic and Dendritic Cell Neoplasms to Achieve Long-term Survival

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Background: Histiocytic and dendritic cell (H/DC) neoplasms are very rare hematological disorders and constitute < 1% of lymphoid and soft tissue malignancies. Rare cases of secondarily derived H/DC neoplasms originating from lymphoid neoplasms have been described and provide evidence of clonal relationship of these two phenotypically different malignancies by demonstrating the same clonal immunoglobulin (Ig) or T-cell receptor gene rearrangement. This process of lineage conversion is termed transdifferentiation and results in a progressive disease course, even in the setting of an indolent underlying lymphoid neoplasm. There are no uniform treatment strategies available and the value of allogeneic hematopoietic cell transplantation (allo-HCT) is not clarified, due to limited existing data.

Methods: We present the clinical courses and survival data of 4 patients with secondarily derived H/DC neoplasms, including one patient successfully treated with allo-HCT. Moreover, we supplement this information with the existing published case reports.

Results: Between 2011 and 2017, 4 patients with the diagnosis of H/DC tumor with preceding lymphoid neoplasm were treated at the University Hospital Zurich. All 4 cases presented with a preserved IgH rearrangement in the lymphoid and the H/DC neoplasm, consistent with transdifferentiation. Basic characteristics, therapy regimens and survival data are summarized in Table 1. Of note, three patients showed a very aggressive disease course and died shortly after the diagnosis of H/DC neoplasm. One patient with refractory disease received allo-HCT from matched

Patient Nr.	Age (y)	Sex	Lymphoid neoplasm/ Type	Lymphoid neoplasm/ Treatment	Time to occurrence of H/DC neoplasm (y)	Treatment of H/DC neoplasm	Clonal IGH rearrangement by PCR	BRAF, Exon 15	Outcome/ time after diagnosed H/DC neoplasm
1	75	m	FL grade II	2 # BR	0.5	Prednisone	+	-	died during work-up/day 5
2	26	m	B-cell ALL	BMF-90 protocol	20	surgery/RT/ CTx -> allo-HCT	+	-	CR/ 6y
3	77	m	CLL	2 # ChP -> 6 # FCR -> Ofatumumab	12	1 # CHOP	+	na	died/ 12d
4	55	f	SMZL	splenectomie	2	1 # BR -> 2 # R-CHOP	+	-	died/ 6mo

[Patients with both lymphoid neoplasm and H/DC neoplasm treated at our institution.]

unrelated donor following reduced intensity conditioning (RIC; fludarabine, busulfan, ATG). 6 years post HCT the patient remains in complete remission with no evidence of chronic graft-versus-host disease or other long-term complications.

Reviewing the literature of reported cases of secondarily derived H/DC neoplasms, in 11 cases treatment and survival information was available (Table 2). The patients listed in Table 2 were given different chemotherapy regimens, most commonly lymphoma-based treatment protocols with one patient receiving allo-HCT. Strikingly, in line with the observation of our patient cohort, long-term survival (> 2y) was shown for the patient who underwent allo-HCT. Interestingly, in one recent report, one patient with trans-differentiated histiocytic sarcoma and mutation in MAP2K1 was successfully treated with MAK inhibitor.

Conclusions: The development of H/DC neoplasms out of prior lymphatic neoplasms is still incompletely understood. This fact is reflected in the lack of successful treatment options. Understanding the underlying pathological mechanisms will remain a major challenge in this rather heterogenic and rare disease. Our small patient cohort, as well as the cases reported in the literature, point towards the curative potential of allo-HCT and therefore this treatment approach should be considered in eligible patients.

Disclosure: Nothing to declare.

P452

Outcome of Allogeneic Hematopoietic Cell Transplantation for Patients with Peripheral T Cell Lymphomas: A Retrospective Analysis from the Polish Lymphoma Research Group (PLRG)

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Background: Peripheral T cell lymphomas (PTCLs) are often associated with a poor prognosis despite the use of conventional chemotherapy and autologous hematopoietic cell transplantation (autoHCT). In case of refractory or relapsed disease patients can benefit from allogenic HCT (alloHSCT).

Methods: We evaluated retrospectively data of 19 patients (pts) who underwent alloHCT due to refractory (10 pts) or relapsed (after autoHCT) PTCLs (9 pts) between year 2012 and 2019. They were treated in 6 transplantation departments of PLRG. The analysis included 15 men and 4 women. The histopathological type was: PTLC NOS - 13 pts (68%), other - 6 pts (32%). The median time from diagnosis to transplantation was 21, range 7-183 months. At the time of diagnosis 12 pts had the stage IV of the disease and general symptoms. The median age at alloHCT was 47 years (25-58) and the disease stage was CR - 7 pts, active disease - 12 pts.

The donor type was HLA-identical sibling in 9, unrelated in 9 and haploidentical in 1 case. The conditioning regimens were diverse: 84% regimens were myeloablative, 58% of them included TBI (dose 8 - 10 Gy). The immunosuppressive therapy consisted of cyclosporine + methotrexate in the vast majority of pts (84%). The median follow-up was 16 (1-95) months.

Results: All patients engrafted with median time of neutrophil and platelet recovery of 17 and 13 days,

respectively. Seven patients (37%) experienced acute GvHD (2 pts with grade 3-4). The incidence of chronic GvHD was 26% (5pts; mild - 2 pts, moderate - 2pts, severe - 1 pts).

The incidence of grade 4 infectious and non-infectious complications (CTCAE v. 5) was 16% and 21

%, respectively. Six patients died in the first year after transplantation. The cause of death was: relapse of the disease - 2 pts, infection complications - 2 pts, other complications - 2 pts (kidney failure and GvHD). The incidence of progression and TRM was 11% and 21%, respectively. The probability of PFS and OS at 36 months was 68% (+/-11%).

Conclusions: AlloHCT may offer a potential way of cure for patients with relapsed or refractory PTCLs. Further research is needed to improve outcomes in this population of patients.

Clinical Trial Registry: not applicable

Disclosure: nothing to declare.

P453

Treatment Outcome of Primary Mediastinal B Cell Lymphoma after High Dose Chemotherapy with Autologous Hematopoietic Cell Transplantation. A Study of The Polish Lymphoma Research Group

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Background: The optimal up front line therapy and strategy for relapsed/refractory (R/R) disease in patients (pts) with primary mediastinal B cell lymphoma (PMBL) is not established due to low incidence of the disease. High dose chemotherapy (HDT) and autologous hematopoietic cell transplantation (auto-HCT) is usually proceed in R/R disease but in high risk patients it is used for the consolidation of induction treatment.

Methods: We retrospectively collected data of pts diagnosed with PMBL between 1999-2018 and underwent auto-HCT at three hematooncology centers allied at Polish Lymphoma Research Group. We evaluated clinical features and the outcome of auto-HDT including adverse risk factors.

Results: Sixty nine patients with a diagnosis of PMBL were identified. Females were 40 (58%). Median age (range) was 28 (17- 62), only 1 patient was older than 60. Bulky disease was presented in 64 pts (94%). Clinical stage III/IV (CS), LDH and extranodal disease were found in 45 pts (65%), 62pts (89%) and 29 pts (42%), respectively. Sixty patients (87%) received rituximab: 58pts in first therapy and 2 in next regimen. As first therapy R-CHOP, DA-EPOCH-R, GMALL 2002 and CODOX-M/IVAC were given 44 pts (64%), 11pts (16%), 8pts (10.5%)and 7 pts (9.5%), respectively. Radiotherapy post first treatment was applied in 28 (40%) pts. Twenty five patients with high IPI underwent HDT with auto-HCT after first-line therapy. The probability of 3-year-overall survival (OS) and 3-year progression free survival (PFS) for these patients were 92% (95%C.I. 75%, 100%) and 92%(95%C.I. 75%, 100%) respectively. Rest of 44 pts with R/R PMBCL were treated with salvage therapy: median lines (range) 1 (1-5). Before transplant 18 of 44 pts R/R PMBCL (41%) achieved complete remission (CR). After median (range) follow up of 31 (1-233) months, the probability of 3-year OS and 3-year PFS were 65% (95%C.I. 50%, 80%), and 64% (95%C.I. 49%, 79%) respectively for R/R PMBCL. All failers were found within the first year after transplant. The lack of CR before transplant in R/R PMBCL pts increased significantly only the risk of progression HR=3.54 [95%C.I (1.01-12.43), p=0.01], but not the risk of death: HR 3.04[95%C.I (0.84-10.93), p=0.06]. 3-year PFS and 3-year OS for CR vs non-CR pts were 80% vs 49% (p=0.01), and 80% vs 53% (p=0.02) respectively. No other adverse factors for OS or PFS were found.

Conclusions: More than 60% of patients R/R PMBL had satisfactory outcome after HDT with auto-HCT, especially if they achieved complete remission before transplant. HDT and auto-HCT could also be a good option of the treatment in high risk PMBL in first remission.

Disclosure: No conflict of interest

P454

Place of Hematopoietic Stem Cell Transplantation in Patients with T-cell Lymphomas: Pavlov University Experience

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Background: T-cell lymphomas represent rare and heterogeneous group of aggressive non Hodgkin lymphomas. In 70% of patients undergoing first-line treatment, relapse develops or a refractory course is detected. There are currently no standards for the treatment of relapsed/refractory TCL. A number of novel therapy approaches are aimed for improvement of outcomes in patients with r/r TCL. This report summarizes the Pavlov University experience in the treatment of patients with TCL.

Methods: We analyzed data of 47 patients with r/r TCL treated in Raisa Gorbacheva Memorial Research Institute of Pediatric Oncology, Hematology and Transplantation of Pavlov University from 2005 to 2019. Among them n10 with anaplastic large cell lymphoma (ALK+), n5 with anaplastic large cell lymphoma (ALK-), n4 with angioimmunoblastic TCL, n4 with hepatosplenic TCL, n1 with γδ TCL, n20 with PTCL not otherwise specified, n1 with mycosis fungoides, n1 with primary cutaneous CD4+ TCL and n1 with subcutaneous panniculitis-like TCL. The median age was 45 years (range 1 - 72 years).

Median time from initial diagnosis to relapse or progression after primary therapy was 6.25 months (1-97). Among all patients n26 (55%) had a primary chemoresistant disease, while the rest n18 (38%) had a relapse after initial treatment. The treatment was tailored according to biological factors presented in patients. In 10 patients with CD30 + PTCL the brentuximab was used. One patient with ALK + anaplastic lymphoma received ALK inhibitor crizotinib. In 4 patients with PD-L1 hyperexpression was treatment with nivolumab. Overall 24 patients undergo SCT: high dose chemotherapy with autoHSCT was performed in 16 patients, 13 patients underwent alloHSCT (among them 5 patients with relapses after autoHSCT).

Results: At the time of analysis, 35 patients remain alive. The median follow up of alive patients was 35 months (6-122 mo). The median overall survival was not reached and 3-year survival rate was 65%. The disease status at the last follow up was CR in 22 patients, PR in 4 patients and PD in 21. Among factors significantly associated with adverse prognosis were lower ECOG performance status and B-symptoms at the time of diagnosis (p=0,06). Patients that had undergo HSCT showed significantly better disease status at the moment of last follow up: 17/19 (89%) were in CR, versus 5/16 (31%) in patients who did not undergo HSCT. One-year progression-free survival in patients with TCL after HSCT was 55%.

Conclusions: The results show that introduction of novel agents and consolidation with high dose chemotherapy and autoHSCT or alloHSCT in selected cases improve outcomes in patients with r/r TCL. Brentuximab based regimens may be successfully used as a bridge therapy before HSCT.

Disclosure: The authors report no conflicts of interest.

P455

Autologous Hematopoietic Stem Cell Transplantation for Diffuse Large B-cell Lymphoma: Toxicity and Survival Study

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Background: In patients with diffuse large B-cell lymphoma (DLBCL), rituximab-containing chemotherapy regimens can achieve superior long-term progression-free survival (PFS) and overall survival (OS) rates relative to regimens that do not contain rituximab. Consequently upfront autologous Hematopoietic Stem Cell Transplantation (auto-HSCT) was performed as a consolidation treatment following therapy with rituximab (R-CHOP) for high-risk DLBCL.

This study aimed to assess the toxicity, survival and associated factors with poor prognosis after auto-HSCT for DLBCL.

Methods: In this retrospective study, we analyzed the data of all consecutive patients with DLBCL who received frontline R-CHOP then high-dose chemotherapy followed by auto-HSCT at the Tunisian national center of stem cell transplantation between January 2012 and February 2018. Frontline auto-HSCT was indicated for DLBCL with aaIPI≥2. Second line auto-HSCT was indicated for refractory or relapsed DLBCL.

Results: A total of 49 patients underwent auto-HSCT in the period of study. The median age at transplantation was 47 years (19-62 years). At diagnosis, 78% of patients had stage IV lymphoma, 31% had more than one extra nodal involvement and 24% received more than one line of chemotherapy. Pre-transplant status was CR or PR in 26.5% and 73.5% respectively. The median duration until neutrophil recovery and of hospitalization was 11 days and 27 days respectively.

After a median follow up of 34.7 months (0.26-81.7 months), two years OS was 79.2%. The 100-days and 2-years non relapse mortality incidence was estimated at 4.1% and 10.2% respectively. Cumulative incidence of post-transplant relapse or progression (R/P) was 12.2%. R/P

occurred after a median time of 3 months (1-36 months). Gastric involvement (GI) and IPI=3 were associated with worse OS ($p< 0.05$) by univariate analysis. Multivariate Cox regression analysis revealed that patients with GI had significantly worse OS (2 years OS: 28.6% vs 87.8%, p=0.006).

Conclusions: In this retrospective analysis of patients with DLBCL, which underwent auto-HSCT, we found a favorable OS after auto-HSCT despite a high rate of non-relapse mortality. GI was identified as risk factor for inferior OS. This data is to be confirmed by larger studies.

Disclosure: Nothing to declare.

P456

Autologous Hematopoietic Stem Cell Transplantation for HIV-related Lymphoma

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Background: HIV infection is associated with an increased risk of cancer, including Hodgkin and non-Hodgkin lymphoma, even in patients treated successfully with modern combined Anti-Retroviral Therapy (cART). Nowadays, patients with HIV-related Lymphoma (HRL) receive standard chemoterapy and obtain responses comparable to those of seronegative patients. Also autologous stem cell transplantation (ASCT) is now safe and effective in patients with HRL. Here we report our experience in ASCT for HRL.

Methods: Between 2011 and 2019 we performed ASCT in 16 HRL patients. They underwent only one apheretic collection, with no failure in peripheral blood stem cell (PBSC) mobilisation. All patients received a conditioning regimen according to CEAM schedule: lomustina 200 mg/m^2 (day - 6), etoposide 200 mg/m^2 (from day -5 to -2), cytarabine 200 mg/m^2 twice daily (from day -5 to -2), and melphalan 140 mg/m^2 (day -1). The median stem cell dose infused was 4.5 x 10^6/Kg (2.5-9.8). Patients received PBSC rescue on day 0 and median CD34+ cell dose was 4.5x 10^6/kg (range 2.5 -9.8 x 10^6/kg). G-CSF was administered from day +1 to neutrophil engraftment and supportive care was given according to local institution.

Results: Median age of patients affected by HRL undergoing ASCT was 44 years (range 34-64). Underlying diagnoses were diffuse large B cell lymphoma in 10 patients (62,5%), plasmoblastic lymphoma in 4 patients (25%), Hodgkin and Burkitt lymphoma in 1 patient (6,25%). The pre-transplant HIV viral load was undetectable in all patients. Disease status at ASCT was complete remission in 11 patients (68,75%), and partial remission in 5 patients (31,25%). Median time to neutrophil and platelet recovery was 10 and 13 days respectively. After transplant, 12/16 patients (75%) developed mucositis in the gastrointestinal tract (G3 n=4; G2 n=8) but no patient stopped the cART. A total of 6 documented infectious events (37,5%) occurred, including 4 bacterial sepsis, 1 viral infection and 1 invasive aspergillosis; there were 7 fever of unknown origin and 2 pneumonia, without any case of Pneumocystis jiroveci pneumonia. 6/16 patients (37,5%) experienced at least 1 infectious event within 1 year after transplant, including 2 patients with severe infection. Immunological reconstitution studies were performed assessing recovery of CD4+ cells: median levels were 175 CD4/ml at 6 months and 305 CD4/ml at 1 year.

After a median follow-up of 39 months 14/16 patient are alive and free of lymphoma, 2 relapsed and one of them died for disease progression one year after AHCT. We also compared our cohort with 16 HIV negative patients affected by lymphoma and matched for age, performance status, primary disease, and disease status at transplant during the same period: no significant difference was seen in neutrophil and platelet recovery, incidence of mucositis and infections.

Conclusions: The results suggest that ASCT is safe and effective in patients with HRL and should be considered according to the same criteria adopted for HIV-negative patients. In conclusion, in the era of cART, the outcome of ASCT for HRL is driven more by lymphoma-dependent risk factors rather than by characteristics of HIV infection.

Disclosure: Nothing to disclose

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Allogeneic Hematopoietic Stem Cell Transplantation for Relapsed and Refractory Hodgkin Lymphoma: A Retrospective single-center Analysis of 23 Patients

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Background: Hodgkin lymphoma (HL) is considered a curable disease in approximately 70-80% of the cases with standard first-line chemotherapy regimens. However, relapsed/refractory (RR) HL patients (pts) have dismal prognosis. Allogeneic hematopoietic stem cell

transplantation (alloHSCT) using reduced intensity conditioning (RIC) is a salvage option, but its effectiveness is still unclear.

Methods: We performed a retrospective analysis of 23 RR-HL pts (16 males, 7 females) with a median age of 23 years (range, 15-41 years) who underwent alloHSCT in our center between August 2002 and February 2019. All patients received at least 3 lines of combined treatment (chemo- and radiotherapy), in 17 pts (74%) autoHSCT was performed, in 4 patients (17 %) immunotherapy with the use of brentuximab vedotin and/or nivolumab was applied. A median time from diagnosis to alloHSCT was 42 months (mts)(range, 15-119). Disease status at transplant was complete remission (CR) in 17%, partial remission in 31%, and stable/progressed disease in 52% of the pts. RIC regimens consisted of fladarabine/busulfane in 20 pts with additional alemtuzumab in 5 of them. In remaining 3 pts other nonmyeloablative conditioning regimens were used. Donor type was matched related in 40%, unrelated in 60% of the pts. A median of 5,38 $x10^6$ CD34+ cells/ kg of the body weight was transplanted (range, 1,37-7,58 $x10^6$).

Results: All pts except of 1 engrafted. In 19/23 pts complete donor chimerism was revealed at day 30. post alloHSCT. There were 2 early deaths (before day 30.) due to the infectious complications. 11 pts developed acute graft-versus-host disease (GvHD), among them 2 of grade ≥ III, in 3 pts chronic GvHD was observed. Median follow-up was 13 months (range, 0,1 -179). Five-year overall survival was 31% and progression-free survival (PFS) was 29%.

Conclusions: AlloHSCT using RIC represents a valid therapeutic option for pts with RR-HL. About one-third of the pts may achieve long-term disease-free survival following alloHSCT. The longest PFS was observed in pts transplanted in consecutive CR.

Disclosure: Nothing to declare.

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Autologous Stem Cell Transplant in a Seropositive a Patient with Plasmablastic Lymphoma (PBL)

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Background: Plasmablastic lymphoma (PBL) is aggressive subtype of non-Hodgkin lymphoma. initially described in patients with HIV infection, it has been identified in immune competent patients as well. PBL, characterized by CD20 negativity, is associated with Epstein-Barr virus infection.

The outcome with available therapy is poor, with median survival of less than 1 year.

Methods: Mr. A was 38 years old male, when he first presented in 2016 with obstructive uropathy secondary to enlarged retroperitoneal lymph nodes. He had pre-existing HIV infection since 3 years for which he was on ART. During this period, he was diagnosed with intestinal tuberculosis and took AKT for 6 months. LDH was (750 U/L). CT guided biopsy of retroperitoneal lymph node confirmed PBL, CD138 positive, CD20 negative. Bone marrow and CSF were uninvolved. After undergoing ureteral stenting, he received chemotherapy (EPOCH.) 6 cycles with Intrathecal Methotrexate. PET scan post 6 cycles showed CMR. He was continued on ART, while AKT stopped in 2018. He remained disease free for 2 years.

In April 2019, Mr. A presented with mild ascites. Cytological examination of ascitic fluid negative for malignant cells, ADA was very high (400 U/L). Gene Xpert for MTB was negative. CSF examination was normal. He underwent repeated high volume (1.5L) paracentesis for refractory ascites. With a suspicion of relapsed abdominal tuberculosis, he was restarted on AKT.

PET scan showed diffuse FDP uptake involving greater omentum and peritoneum. Laparoscopic omental and peritoneal biopsy revealed fatty tissue with infiltration of lymphoid and few plasmacytoid cells which were CD138 and CD 38 was positive. LCA, CD79a, CD20, CD3, PanCK, Calretinin were Negative, suggestive of relapsed PBL.

He received 2 cycles of ICE, 9 weekly Bortezomib and Daratumumab as salvage chemotherapy till July 2019.PET scan in August showed CMR. He was continued on ART by the HIV specialist.

He was counselled for high dose chemotherapy and autologous stem cell rescue.

Results: During pre BMT workup, he was detected with s Alloantibodies/Isoagglutinin's. These were identified and confirmed to be 's' Antibodies.

He underwent GCSF and plerixafor mobilized stem cell collection. Total CD 34 collected were 3.94 x 106 /kg.

He underwent conditioning with LACE (Lomustine, Cytarabine, Cyclophosphamide, Etoposide) regimen followed by autologous hematopoietic stem cell transplantation.

Post transplant period was unremarkable, WBC engrafted on day +9, Platelets engrafted by day +12. He developed grade 4 febrile neutropenia, managed with broad spectrum antibiotics.

He was given 2 units of Autologous irradiated PRBC, 5 PRBC units were group and antigen specific.

Patient was discharged on day +16 post transplantation.

Patient is asymptomatic and on regular follow up.

Conclusions: Autologous hematopoietic stem cell transplantation appears to be feasible and may produce better results than chemotherapy, but definitive data are sparse. Chemosensitivity before transplantation might be required to benefit from such therapy. Some data suggest a better outcome of PBL if consolidation with Auto HSCT is used in first-line setting, particularly for those with high-risk disease.

Our patient achieved a CR2, and we were able to offer him autologous stem cell transplantation.

Disclosure: No potential conflict of interest and source of funding

Minimal residual disease, tolerance, chimerism and immune reconstitution

P459

CMV Infection is Associated with Reduced Thymic Function and Less Regulatory T Cells after Pediatric Allogeneic HSCT

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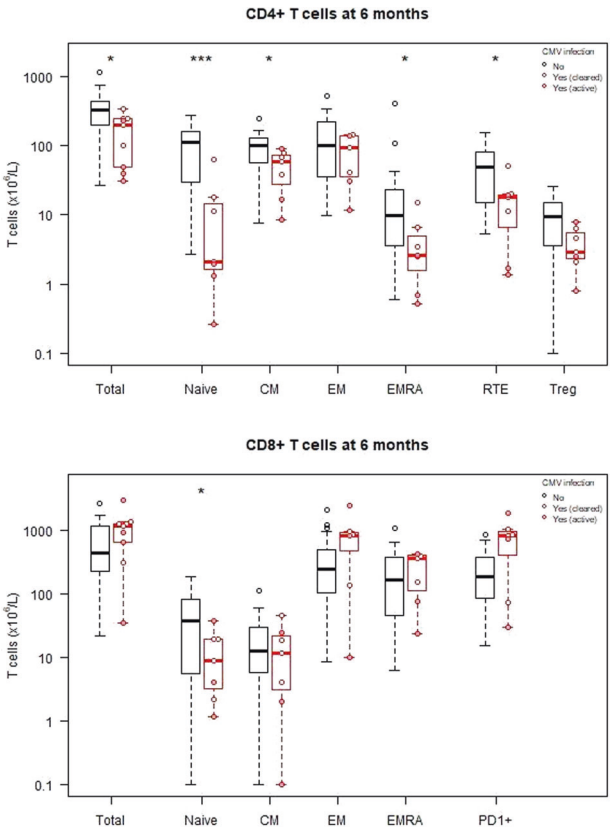
Background: Allogeneic HSCT is challenged by a delayed and imbalanced T-cell reconstitution hampering patients' longstanding immunity. Although the role of differentially and functionally distinct T-cell subsets has been addressed for development of complications, little is known about the factors controlling their long-term recovery.

In this study, we investigated the impact of early complications including CMV reactivation and aGvHD on thymopoiesis and T cell reconstitution.

Methods: We prospectively included 39 children undergoing allogeneic HSCT from 2015-2017 for ALL (n=11), AML (n=7), other malignancy (n=4) and benign disorders (n=17). Median age was 8.0 years (range: 1.5-17.2). Donors were either MSD (n=15), MUD (n=23) or MMUD (n=2), and grafts were either BM (n=37) or PB (n=2). Conditioning regimens were based on TBI (n=10) or high-dose chemotherapy alone (n=29) and included ATG in 28 patients.

T- and B-cell numbers were measured regularly within the first year after HSCT, and detailed characterization of T cell maturation and differentiation was performed by flow cytometry at 1, 3 and 6 months.



[T cell reconstitution at 6 months after HSCT in 35 children with and without CMV infection.]

Results: Acute GvHD grade II-IV was diagnosed in 11 patients (28%). Patients with aGvHD showed a strong trend towards higher amounts of circulating naïve CD4+ and CD8+ T cells at 3 months after HSCT (25.9 vs. 3.1 x10^6/L, P=0.064 and 31.5 vs. 1.2 x10^6/L, p=0.052, respectively). Additionally, these patients showed significantly increased numbers of CD25^{high}FOXP3+ Tregs (8.4 vs. 2.4 x10^6/L, p=0.023), including Tregs expressing CD39 and Helios that are both associated with higher suppressive capacity of Tregs (3.6 vs. 1.8 x10^6/L, p=0.037 and 6.1 vs. 2.9 x10^6/L, p=0.063, respectively). In contrast, patients with aGVHD had significantly lower B cell counts at 2- and 3-months post-transplant (p=0.0023 and p=0.031).

CMV reactivation requiring pre-emptive treatment occurred in 9 patients (23%) at median 34 days post-transplant (range: 5-55) and was completely cleared in 4 patients within 3 months. Patients with CMV reactivation showed inverted CD4/CD8 ratio and decreased levels of B cells at 6 and 12 months after HSCT. Furthermore, CMV

reactivation was associated with reduced numbers of CD31+ recent thymic emigrants and naïve CD4+ and CD8+ T cells after HSCT compared to patients without CMV reactivation (Figure). Within the CD4+ T cell population, $CD25^{high}$FOXP3+ Tregs tended to be reduced in patients with CMV reactivation at 6 months post-transplant (p=0.055, Figure), including a significant reduction in Tregs expressing the naivety marker CD45RA (0.1 vs. 0.65 $x10^6$/L, p=0.013) and Helios (3.2 vs. 8.1 $x10^6$/L, p=0.055). The CD8+ T cell population was dominated by EM and EMRA cells in patients with CMV reactivation with a significantly higher proportion of exhausted PD1-expressing cells (66% vs. 39%, p=0.023).

Conclusions: Our findings suggest that CMV reactivation reduces thymic output after pediatric HSCT, in line with findings from animal models, and may lead to a continued limitation in the T-cell repertoire. Interestingly, the impaired thymic function also seemed to affect production of regulatory T cells, providing a possible background for the association between early viral infections and development of alloreactivity. In contrast, only temporary changes in immune subsets were detected in patients following aGvHD.

Disclosure: Nothing to declare.

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Impact of Pre-transplant MRD Burden Measured by Multicolor Flow Cytometry on Relapse and Survival in AML Patients undergoing allo-SCT in CR

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Background: The outcomes for MRD+ AML patients undergoing allo-SCT in CR is poor due to increase relapses (Walter et al. JCO 2011). Here we reporting on outcomes for MRD+ patients focusing on impact of pre-transplant MRD burden on post-transplant survival outcomes.

Methods: A total of 108 patients who underwent an allo-SCT during 2016-2019 years at Hamburg University Medical Center were included. The MRD was assessed in bone marrow samples pre-transplant using multicolor flow cytometry approach by "different-to-normal" and leukemia-associated phenotype based methods according to ELN panel (n=21, Schuurhuis et al. Blood 2018) and to a 8-colored panel created in our clinic (n=87). The latter panel consisted of: (1) CD34-BV421, CD33-PE-Cy7, CD56-BV510, CD2-FITC, CD65-PE, CD14-PerCP, NG2-APC, CD45-APC-H7; (2) CD34-BV421, CD61-FITC, CD135-PE, CD14-PerCP, CD33-PE-Cy7; CD235a-APC, CD45-APC-H7; (3) CD34-PerCP, CD33-PE-Cy7, CD13-FITC, HLADR-PE, CD7-BV421, CD117-APC, CD45-APC-H7; (4) CD34-PerCP, CD33-PE-Cy7, CD19-APC, CD38-PE, CD15-FITC, CD123-BV421, CD45-APC-H7; (5) CD34-BV421, CD11b-FITC, CD65-PE, CD33-PE.Cy7, CD14-PerCP, CD117-APC, CD45-APC-H7. A number of 20 samples were assessed at same time using both panels and results were compared using lineal regression without significant difference. As a reference, samples from 60 healthy donors were assessed. There were 67 males; a median age was 69 years (21-78); 96 patients received MAC whereas 12 patients received RIC regimens; 14 patients (13%) had "favorable", 62 intermediate (57%) and 32 patients (30%) poor risk according to ELN criteria. A total of 51 patients (47%) were MRD- and 57 patients (53%) were MRD+.

Results: The 3y LFS and 3y OS were 75% (62-98%) and 83% (71-95%) for MRD- and 45% (28-62%, p=0.021) and 51% (33-69%, p=0.013) for MRD+ patients. Regarding the MRD+ patients (n=57), after the median follow up of 18 months (1-45), the cumulative incidences (CIs) of NRM and relapses at 3y were 11% (0-25%) and 55% (35-75%), respectively. There were more MRD+ patients in those with incomplete CR (CRi) comparing to CR patients (17/22, 77% vs. 39/84, 46%, p=0.02). In univariate analysis, only factor being associated with outcomes was percentage of aberrant blasts (≤1% vs. >1%). We observed improved survival for 37 patients with lower (≤1%) MRD burden (2y LFS: 54%, 34-74%, 2y OS: 60%, 40-80%) vs. that for 20 patients with higher (>1%) MRD burden (2y LFS 30%, 10-50%, p=0.009; 2y OS 38%, 13-63%, p=0.04). The CI of relapse was higher in patients with higher MRD burden: 65% (45-85%) vs. 30% (10-50%), p=0.008. The negative impact of higher MRD burden on LFS (HR 3.0, 1.2-7.5, p=0.016), OS (3.2, 1.1-9.0, p=0.029) and relapses (3.0, 1.2-8.0, p=0.024) was confirmed in multivariate analysis. Other covariates in the model were: patient's age, patient's sex, diagnose (de novo vs. s-/t-AML), CR vs. CRi, cytogenetics according to ELN (favorable vs. intermediate vs. poor), primary induction failure (yes vs.no), number of chemotherapy cycles prior to allo-SCT (≤2 vs. >2) and conditioning (MAC vs. RIC).

Conclusions: In conclusion, the MRD+ patients with high (>1%) MRD burden pre-transplant experience increased relapse incidence resulting in lower LFS and OS comparing with those with lower (≤1%) MRD burden. The former group of patients may need further pre- or/and post-transplant strategies to reduce relapses.

Clinical Trial Registry: not applicable

Disclosure: Nothing to declare.

P461

Flow-based Pre-transplant MRD Detection Strongly Impacts on the Outcome of Haploidentical Transplantation with AB T Cell Depletion in Pediatric Acute Lymphoblastic Leukemia

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Background: Detection of MRD before HSCT for pediatric ALL has been associated with relapse and poor survival.

Multiparameter flow cytometry is a commonly used method of MRD detection in clinical practice. This study aimed to evaluate the impact of flow-MRD status before HSCT on the outcome of children with ALL receiving allogeneic HSCT from haploidentical donors with αβ T depletion of the graft.

Methods: A total of 120 pts with ALL (T-ALL- 37, B-ALL-83, 45 female, 75 male, median age 8.7 years underwent HSCT between 2013 and 2019 y. All pts received Haplo graft. Disease status at transplant was CR1 in 35 pts, CR2 in 68 pts and CR>2 in 17 pts. Flow cytometry-based MRD detection in bone marrow prior to HSCT was performed in all pts. Eighty-six patients were MRD negative before HSCT, 34 were MRD-positive. Thirty pts received treosulfan-based preparative regimen, while TBI-based regimen was used in 90 pts. Two regimens of GvHD prophylaxis were used. Regimen 1 (n=27): thymoglobulin 5mg/kg, rituximab and bortezomib on day +2, +5; regimen 2 (n=93): tocilizumab at 8 mg/kg on day -1 and post-transplant bortezomib and abatacept at 10 mg/kg on day +2, +7, +14, +28.

TCR αβ+/CD19+ depletion of HSCT with CliniMACS technology was implemented in all cases. The median dose of CD34+ cells was 9.3 $x10^6$/kg, αβ T cells - $30x10^3$/kg. Median time of follow-up for survivors was 2 years.

Results: Primary engraftment was achieved in 116 of 120 pts. All engrafted pts had verified morphologic remission with complete donor chimerism by day +30. TRM was 5 % (95% CI: 2-11). CI of relapse was 23% (95%CI:16-32). Among patients, who had MRD-negative remission prior to HSCT, CI of relapse was 13 % (95%CI:7-23) with median time of relapse of 0.43 months, as compared to MRD-positive cohort, with CI of relapse of 47 % (95%CI:33-66) with median time of relapse 0.29 months, p=< 0,0001. CI of relapse in B-ALL pts, who were MRD(-) was 13% (95% CI:7-25), in MRD(+) group 52% (95%CI:35-79), p=0,000, in T-ALL pts in MRD (-) and MRD (+) groups CI of relapse was 15 % (95%CI:5-43) and 38% (95%CI:19-76), respectively, p=0.087. CI of relapse in MRD(+) group was lower among those who received TBI at 41% (95%CI:26-64), in contrast to those who did not receive TBI 71%(95% CI:45-100), p=0.2. Among patients of MRD(-) group use of TBI did not affect relapse incidence, CI of relapse being 13% (95%CI:7-26) in both groups. pEFS was 72% (95%CI: 63-80) for the whole cohort, in MRD (-) it was 80% (95% CI: 71-88), as compared to 52% (95%CI:35-69) in the MRD (+) group, p=0,003.

Conclusions: These results suggest that MRD detection by flow cytometry prior to HSCT is a significant prognostic factor in the setting of haploidentical HSCT on the platform of αβ T cell depletion. TBI regimen play a significant role only in MRD positive group in this cohort of patients. We expect that further improvement of the outcome can be achieved based on the combination of current safe haplo HSCT platform and novel targeted immunotherapy approaches.

Disclosure: Nothing to declare.

P462

CMV-specific T Cell Counts Early after Allogeneic Hematopoietic Stem Cell Transplantation Stratify the Risk of Subsequent CMV Reactivations: Results of a Prospective Observational Study

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Background: Cytomegalovirus (CMV) reactivations are important risk factors after allogeneic hematopoietic stem cell transplantation (allo-HSCT). CMV-specific immune reconstitution controls reactivations, but a protective level

of CMV-specific T cells or standardized method for its monitoring have not been yet determined.

Methods: We designed a prospective, single-center observational study to assess if the kinetic and quality of CMV-specific T-cell reconstitution impact the incidence of CMV reactivations. We enrolled 84 consecutive patients affected by hematological malignancies receiving allo-HSCT followed by Cyclophosphamide and Rapamycin. Polyclonal and CMV-specific T cells were quantified by flow cytometry using Dextramer®CMV-Kit (Immudex) in the graft and fresh whole blood (WB) at days -7, +30, +45, +60, +90, +120, +150, +180 and +365. Dextramer CMV-kit includes reagents for the identification of CMV-specific lymphocytes restricted for several HLA molecules: A*01:01/A*02:01/A*03:01/A*24:02/B*07:02/B*08:01/B*35:01. These alleles allowed the evaluation of 75 out of 84 (89%) patients. Donors were either HLA-matched (n=44) or HLA-mismatched (n=31). The CMV serostatus of host (H) and donor (D) pairs was: H^+/D^+(n=49, 65%), H^+/D^- (n=25, 33%) and H^-/D^+ (n=1, 2%); H^-/D^-(7% of the overall transplanted population at our center) were excluded. CMV DNAemia was assessed weekly in WB.

To further characterize the T-cell dynamics, we exploited polychromatic flow cytometry thanks to FACSymphony (BD) instrument. We designed a 20-color panel in order to simultaneously evaluate differentiation, activation and exhaustion markers on CMV-specific T cells.

Results: 38 (51%) patients experienced CMV-related clinically relevant events (CRE, median day +68). The incidence of CRE was influenced by H/D CMV serostatus (p=0.017) and by previous acute Graft-versus-Host Disease (aGvHD) requiring systemic immunosuppression (p=0.008).

Our data show that higher levels of CMV-specific $CD8^+$ T cells in the graft and at day +45 after allo-HSCT are associated with reduced risk of subsequent CRE ($p< 0.05$). Importantly, a threshold of 0.5 CMV-specific $CD8^+$T cells/mL at day +45 discriminates patients at higher risk of subsequent CRE. Conversely, absolute counts of polyclonal $CD3^+$, $CD3^+CD8^+$or $CD3^+CD4^+$T lymphocytes do not correlate with subsequent CRE.

Preliminary results showed that CMV-specific $CD8^+$T cells are detectable also on frozen PBMCs, with magnitude and kinetics that mirrors those observed on fresh WB. These cells were enriched in effector memory T lymphocytes compared to polyclonal $CD8^+$population.

Taking advantage of the HLA mismatched-HSCT setting, we then dissected CMV-specific T-cell response according to HLA restriction elements (H/D=shared n=64, D-restricted n=19, H-restricted n=13). In H^+/D^+pairs, we observed a fast and similar kinetic of reconstitution of H/D- and D-restricted CMV-specific lymphocytes. Conversely, in H^+/D^-pairs, we detected only H/D-restricted CMV-specific $CD8^+$T cells. H-restricted cells remained undetectable for the first year after allo-HSCT.

Conclusions: A threshold of 0.5 CMV-specific $CD8^+$T cells/ml at day +45 after allo-HSCT stratifies patients for the risk of subsequent CRE. Protective CD8+ T cells can also be detected and deeply characterized in frozen PBMCs. Furthermore, our findings indicate that CMV reactivations can stimulate memory H/D- and D-restricted T cells educated and primed in the donor and can efficiently prime H/D restricted, but not D- nor H-restricted donor-derived lymphocytes in the first year after allo-HSCT.

Disclosure: Liselotte Brix is an employee of Immudex.

Fabio Ciceri is a consultant of San Raffaele Telethon Institute for Gene Therapy (SR-TIGET), a joint venture between Fondazione Telethon and Ospedale San Raffaele (OSR) (Type of relationship: Wiskott-Aldrich Syndrome (WAS) gene therapies was licensed to GlaxoSmithKline (GSK) in 2014. WAS was licensed to Orchard Therapeutics (OTL) in April 2018 and Research Funding).

Chiara Bonini received research founding by Intellia Therapeutics, is owner of patents in the field of adoptive T-cell therapy and is a consultant of Molmed Spa, Intellia therapeutics, TxCell, Novartis, GSK, Allogene and Kite/Gilead.

The other authors declare. no conflict of interest.

P463

Improved Relapse-free-survival in Patients with High Natural Killer Cell Doses in Grafts and during Early Immune Reconstitution after Allogeneic Transplantation with Peripheral Blood Stem Cells

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Background: Mature immunocompetent cells from the stem cell graft as well as early robust immune reconstitution are essential for the graft-versus-tumor effect to eliminate residual malignant cells after hematopoietic stem cell transplantation.

Methods: We performed a prospective study to characterize graft composition and immune reconstitution in peripheral blood of T cells and natural killer (NK) cells at days 28, 56, 91, 180, 365 post-transplant in 88 recipients of peripheral blood stem cell grafts, table 1. Transplanted cell doses and early immune reconstitution of T and NK cells were analyzed for associations to clinical outcomes. Multicolor flowcytometry stained for anti-TCRαβ, TCRγδ, CD3, CD4, CD8, CD45RA, CD45RO, CD197, HLA-DR, TCRVδ2, TCRVδ1, CD16, CD56, CD314 and CD337 was used.

Results: Patients transplanted with graft NK cell doses above the median value of $27x10^6$/kg had significantly increased relapse-free-survival (RFS) compared to patients transplanted with grafts containing NK cell doses below that value, HR 2.12 (95% CI 1.01-4.45), p=0.04. The dose of transplanted NK cells/kg correlated significantly with NK cell concentrations in patients early after transplantation (Spearman's ρ 0.26, p=0.02, and ρ=0.35, p=0.001 for days 28 and 56, respectively). Early immune reconstitution above median values (285 and $200x10^6$/L day 28 and 56, respectively) of NK cells was significantly associated with improved RFS (HR 2.84 [95%CI 1.29-6.28], p=0.01, and HR 4.19[95% CI 1.68-10.4], p=0.002, for day 28 and 56, respectively). Correlations between NK cell doses and RFS remained significant in multivariate analyses adjusted for pre-transplant factors and other cell subsets. Early concentrations above the median value of the mature effector CD56dim NK cell subset were significantly associated with decreased relapse incidences at 1 year, 7 % (95% CI 1.8-17) versus 28 % (95% CI 15-42), p=0.04, and 7 % (95% CI 1.8-18) versus 26 % (95% CI 14-40), p=0.03, for days 28 and 56, respectively. Cumulative incidence of acute or chronic graft-versus-host disease (GVHD) was not associated to NK cell doses in stem cell grafts or peripheral blood concentrations during immune reconstitution. The expression of the activating receptor NKG2D was highest on the immature CD56bright NK cell subset in both stem cell grafts and during immune reconstitution but was not associated with RFS or GVHD.

Conclusions: The results suggest a favorable effect of high doses of NK cells in grafts and during early immune reconstitution and support the perception of NK cells as innate effector cells with anti-tumor effects in the setting of allogeneic hematopietic stem cell transplantation.

N	88
Follow-up time, days, median, min-max	667 (386-884)
Age, years, median, min-max	60 (23-74)
Disease, n, percent AML ALL MDS Myelofibrosis NHL Chronic leukemia Other	34 (39%) 9 (10%) 25 (28%) 8 (9%) 5 (6%) 3 (3%) 4 (5%)
Disease Risk Index Low Intermediate High	7 (8%) 72 (82%) 9 (10%)
Donor, n, percent MRD MUD	23 (26%) 65 (74%)
Donor HLA match, n, percent 10/10 or 9/10 allele match 1 Ag mismatch	81 (92%) 7 (8%)
Donor-recipient sex, n, percent M/M M/F F/F F/M	43 (49%) 20 (23%) 16 (18%) 9 (10%)
Conditioning intensity, n, percent Myeloablative Non-myeloablative	36 (41%) 52 (59%)
Conditioning regimen, n, percent TBI-Flu Flu-Treo TBI-Cy TBI-Etopophos Other	50 (57%) 25 (29%) 10 (11%) 2 (2%) 1 (1%)

[Table 1. Patient and transplant characteristics.]

Disclosure: Nothing to declare.

P464

Potential Influence of Immunodeficiency-related Hereditary Predisposition Gene Variants on Relapse after Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Hematological Malignancies

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Background: Hereditary predisposition genes may play a certain role in the development of complications after allogeneic hematopoietic stem cell transplantation (allo-HSCT). In present clinical study, the influence of immunodeficiency-related hereditary predisposition gene variants of the recipients on relapse after allo-HSCT was investigated.

Methods: Between January 2018 and July 2019, total 109 patients with hematological malignancies who underwent allo-HSCT with the same protocols in our hospital were enrolled. The median age was 30 (2 to 66) years old. Male to female was 1.60:1. The diagnosis included AML (n=52, 47.7%), ALL (n=36, 33.0%) and NHL (n=21, 19.3%). The disease status before transplants was CR1 in 36 cases (35.8%), CR2 in 50 cases (45.9%), PR in 9 cases (8.3%), and NR in 14 cases (12.8%). Hematological and immunological hereditary predisposition genes of the patients, their parents and potential related donors were prospectively detected before transplant with whole exon sequencing and validation by sanger sequencing. Donors were from haploidentical family members (n=82, 75.3%) or identical siblings (n=19, 17.4%) or unrelated volunteers (n=8, 7.3%). Myeloablative conditioning regimens with either total body irradiation/Fludarabine-based or Busulfan/Fludarabine-based were applied. Anti-thymocyte globulin was used in haploidentical and unrelated transplants. Graft-versus-host disease prophylaxis was with cyclosporine, short-term methotrexate and mycophenolate mofetil.

Prevention of fungal, pneumocystis carinii and herpes virus infections was routinely administrated. Chi-square test was used to analyze whether hereditary predisposition genes were associated with relapse after allo-HSCT. The study was analyzed with the IBM SPSS Statistics software. P value <0.05 was considered to be statistically significant.

Results: The immunodeficiency-related hereditary predisposition gene variants with higher frequency which were recurrent more than 5 times in this cohort were IFIH1, LRBA, TYK2, ATM, IL7R, CARD14, NOD2, POLE, RNF31, TNFRSF13B, TTC7A, CBLB, CFTR, CHD7, NLRP12, C6, C8A, CFHR2, IGLL1, NFAT5, and TCF3. The functions of these genes include immune deficiency, T-cell dysfunction, antibody deficiency, and complement deficiency. Total 107 patients (98.17%) carried immunodeficiency-related hereditary predisposition gene variations, with an average number of 3.52 per patient (range 1-9). The patients with more than 3 immunodeficiency-related hereditary predisposition gene variants had significantly higher relapse rate within 6 months after transplants than that with less than 3 immunodeficiency-related hereditary predisposition gene variants (P <0.05). Hemophagocytic lymphohistiocytosis-related gene variants and fanconi anemia-related gene variants had no significant impact on relapse.

Conclusions: Our preliminary results have shown that the patients of hematological malignancies with multiple immunodeficiency-related hereditary predisposition gene variants increased relapse rate after allo-HSCT. A larger cohort and longer follow-up are needed to address this issue.

Clinical Trial Registry: no

Disclosure: Nothing to declare.

P465

Abstract already published.

P466

Impact of Residual Circulating Tumor DNA Status Post Allogeneic SCT in Patients with Acute Myeloid Leukemia and Myelodysplastic Syndromes: Interim Results of a Prospective Study

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Background: We previously reported the utility of residual circulating tumor DNA (ctDNA) status for identifying patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) at high risk for relapse post myeloablative allogeneic hematopoietic stem cell transplantation (alloSCT) in the retrospective setting (Nakamura and Yokoyama et al, Blood 2019). However, it remains to be elucidated whether this approach could be useful in the prospective setting as well. Here, we report the interim results from a Japanese multicenter prospective observational study, examining the clinical utility of this approach (KSGCT1702, conducted on behalf of Kanto Study Group for Cell Therapy).

Methods: Since June 2018, we've enrolled patients with AML and MDS planning to undergo myeloablative alloSCT. We collected tumor and matched serum samples at diagnosis and serum samples every month until the fourth month post alloSCT. We subjected tumor DNA (bone marrow or peripheral blood), and buccal swab DNA, to next-generation sequencing, identifying candidate driver mutations. We designed representative one or two allele specific droplet digital PCR (ddPCR) assays for each patient to monitor ctDNA, the median detection limit of which was 0.04% as previously described. The primary endpoint was to compare the cumulative incidence of relapse rate (CIR) within 1 year post alloSCT according to residual ctDNA status.

Results: As of November 2019, a total of 38 patients were enrolled and 28 patients (26 AML and 2 MDS) of

whom received alloSCT. The median follow up period post alloSCT was 119.5 (1-365) days. The median age was 54 years (25-66 years) including 15 males (53.6%). The conventional risk category was adverse or high risk in 42.9% of patients. To date, we've finished sequencing in 24 (85.7%) patients. A total of 33 somatic driver mutations/fusion genes were detected in all 24 patients, with one, two and three mutations found in 17, 5, and 2 individuals, respectively. These mutations included: single nucleotide variants, DNMT3A, CEBPA, NRAS, CEBPA, TET2, PTPN11, NPM1, IDH2, TP53, SMC3, RUNX1, JAK2, and FLT3; structural variants, CBFB/MYH11, KMT2A/MLLT3, and KMT2A/AFDN. We could construct ddPCR assays for 20 of 24 (83.3%) patients. Notably, there was a clear correlation of VAF between diagnostic ctDNA and matched tumor DNA from BM in available patients (r^2 =0.86; p=0.0009). Of these 24 patients, one patient died without relapse, with six in clinical relapse with a median of 4 months (range, 1 to 10 months), and with the remaining 17 in remission. Of 20 patients available for personalized assays, fourteen patients were available for ctDNA status 3 months post alloSCT, and 4 of whom were positive ctDNA status with the average allele frequency of 1.52 (0.12 to 5.0) %. Most importantly, when we compared CIR according to residual ctDNA status, positive ctDNA status at 3 months post alloSCT was associated with higher CIR at 10 months: 100% in positive patients vs. 0% in negative patients (p=0.0259 by Log-rank test).

Conclusions: Our ctDNA monitoring could identify patients who were more likely to relapse. Additional enrollment and further follow-up are needed to confirm this promising result.

Clinical Trial Registry: KSGCT1702 is registered at Japanese Trial Registry # UMIN000033003

Disclosure: Nothing to declare.

P467

Pattern of Reconstitution of Recent Thymic Emigrants after Reduced Intensity Conditioning Based on Targeted Busulfan in Paediatric Recipients of Allogeneic Haematopoetic Stem Cell Transplantation

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Background: CD4+ T-cell reconstitution including the subpopulation of recent thymic emigrants (RTE) is considered critical for a beneficial outcome after allogeneic Haematopoietic Stem Cell Transplantation (allo-HSCT). RTE are endowed with a broad repertoire of T-cell receptor specificities after purging of autoreactive cells as part of selection processes in thymus. In comparison to Myelo-Ablative Conditioning (MAC), Reduced Intensity Conditioning (RIC) is substantially less damaging on most organ systems including thymic epithelial cells. Yet, it is uncertain whether RIC is superior with respect to thymic T-cell production.

Methods: We performed a retrospective clinical study with data used form electronic patient records. We analysed longitudinally assessed CD31+-CD45RA+CD4+-RTE data from paediatric patients with malignant (MD) and non-malignant diseases (NMD), who had received an allo-HSCT at the Division of Stem Cell Transplant in University Children's Hospital in Zürich from 2008 to 2018. These longitudinal data were compared with age-specific RTE-percentiles. We used statistical software R with RStudio, including models suitable for longitudinal data. The Ethics Committee of the Canton Zürich (2017-02040) granted ethical approval.

Results: Overall 80 children with a mean age of 7 years (3 months to 17 years), comprising n=24 (30%) females were included for analysis. N=53 patients (53%) were transplanted for NMD (including N=23 with Chronic Granulomatous Disease, N=15 with Haemophagocytic Lymphohistiocytosis, N=3 with Wiskott Aldrich Syndrome, N=6 with Beta-thalassaemia and N= 6 with Sickle cell disease). All patients with NMD received a clearly defined RIC based on targeted Busulfan (median cumulative AUC 65 mg/Lxh) and Fludarabine. N=27 patients with MD (including N=19 with acute lymphoblastic leukaemia, N=6 with acute myeloid leukaemia and N=2 with juvenile monomyelocytic leukaemia) were transplanted with MAC-regimens based on myeloablative targeted Busulfan, Treosulfan or 12 Gy Total Body Irradiation.

Acute GvHD occurred in 49 (61%) patients. In a multivariate longitudinal data analysis (including age, gender, indication, donor, source, secondary procedure, serotherapy) occurrence of GvHD was associated with a slower RTE-reconstitution (coefficient -0.19, 95% CI -0.35 to -0.04, p-value < 0.01). However, time to reach the first percentile for RTE was not significantly longer in patients with GvHD after correcting for differences in age, gender, indication, type of donor, source, secondary procedures and serotherapy (Event Time Ratio 1.14, 95% CI 0.90 to 1.44, p-value = 0.27).

In a multivariate longitudinal data analysis (including age and gender) patients with NMD with RIC showed a faster RTE-reconstitution (coefficient 0.20, 95% CI 0.02 to 0.39, p-value = 0.032) compared to MAC-patients transplanted for MD. However, time to reach the first percentile for RTE was not significantly faster in patients with NMD and RIC after correcting for differences in age and gender

(Event Time Ratio 0.88, 95% CI 0.64 to 1.22, p-value = 0.45).

Conclusions: Reconstitution of appropriately selected naïve RTE is critical for recipients of allo-HSCT. The cohort assessed here is exceptional with respect to the homogeneity of the RIC-regimen administered including the accuracy of the measurement of its intensity. This allowed us to better correlate conditioning intensity, occurrence of GvHD and re-emergence of thymic function after adjustment for other important factors.

Disclosure: Nothing to declare.

P468

A Risk Score System Based on Post-transplantation Minimal Residual Disease for Stratification of Relapse in B-ALL Patients after Allogenic Stem Cell Transplantation

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Background: Relapse remains the major cause of treatment failure in patients with acute lymphoblastic leukemia (ALL) after allogeneic stem cell transplantation (allo-SCT). Although the association of post-transplantation minimal residual disease (post-MRD) with relapse has been reported, however, more precisely prediction of relapse is still needed.

Methods: In this study, we analyzed 477 patients with B-ALL to evaluate the effect of post-MRD on outcomes after allo-SCT, and attempt to establish a risk score to identify patients with different probability of relapse. MRD were determined using multiparameter flow cytometry.

Results: All patients achieved neutrophil engraftment. The 100-day cumulative incidence of platelet engraftment was 94.0% (95% CI, 91.2%-96.8%). The 100-day cumulative incidence of acute graft-versus-host disease (GVHD) was 52.8% (95% CI, 48.3%-57.3%). After a median follow up of 1816 days (range, 1277-3107days), the 3-year cumulative incidence of chronic GVHD, relapse, and non-relapse mortality (NRM) was 48.0% (95% CI, 43.1%-52.9%), 19.8% (95% CI, 16.3%-23.3%) and 13.4% (95% CI, 10.5%-23.3%), respectively. The 3-year probability of leukemia-free survival (LFS) and overall survival (OS) was 67.9% (95% CI, 63.8%-72.0%) and 72.1% (95% CI, 68.0%-76.2%), respectively. We found that patients with post-MRD^{pos} had higher incidence of relapse (69.7% vs. 13.4%, P <0.001) and worse leukemia-free survival (LFS) (28.2% vs. 73.3%, P <0.001) as well as overall survival (OS) (41.5% vs. 76.0%, P <0.001) compared to post-MRD^{neg}. And for patients with post-MRD < 0.01%, < 1% and ≧0.01%, and ≧1%; the cumulative incidences of relapse (CIR) were 13.8%, 65.7%, and 82.0%, respectively. Moreover, multivariate analysis also showed that patients transplanted beyond the first complete remission (≥CR2) and without chronic GVHD had higher CIR and worse LFS as well as OS. A risk score for predicting relapse was established based on post-MRD, disease status, and chronic GVHD. The 5-years relapse rates were 6.7%, 19.5%, 62.2%, and 81.8% for patients with scores 0, 1, 2, and 3, respectively; 5-years LFS were 84.4%, 66.6%, 31.8%, and 18.2%, respectively; while 5-years OS were 86.9%, 71.7%, 39.7% and 27.3%, respectively.

Conclusions: The results indicate that a risk score based on post-MRD^{pos} could predict relapse and survival more precisely after allo-SCT.

Disclosure: Nothing to declare.

P469

Outcome of Children with Hematological Malignancies who Develop Mixed Donor Chimersim after Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Mixed donor chimerism is a condition in which recipient blood cells persist side by side with donor cells after hematopoietic stem cell transplantation (HSCT). Mixed donor chimerism (MC) can be an indicator of subsequent graft loss or relapse and often prompts physicians to intervene by adjusting immune suppression if the clinical condition of the patient allows. The goal of our study was to assess the outcome of children with hematological malignancies who develop MC after HSCT and the impact of adjusting the immune suppression (IS) on overall survival (OS) and relapse-free survival (RFS).

Methods: Clinical data including patient demographics, degree and timing of mixed donor chimerism, donor lymphocyte infusions (DLI), RFS and OS was collected retrospectively from children who underwent allogeneic HSCT for hematological malignancies between 2008 and 2018 at the Hospital for Sick Children, Canada. Patients were grouped in four groups depending on occurrence of first MC (1-3 months, 3-6 months, 6-12 months and above 12 months after HSCT) and action taken by physician at time of first MC was assessed (reduction, increase or no change of immune suppression) and correlated to RFS and OS. Statistical analysis was done utilizing R Statistical software (http://www.r-project.org). Survival curves were calculated using Kaplan Meier estimate and cohorts were compared using the log rank test. A p value of less than < 0.05 was considered statistically significant.

Results: A total of 121 Children with hematological malignancies developed mixed donor chimerism. The majority of patients (78%, 95/121) developed MC during the first 3 months, 55% (67/121) during the first 4 weeks. 10% (12/121) developed MC at 3-6 months, 5% (6/121) at 6-12 months and 7% (8/121) after one year from HSCT. Patients who developed MC in the first three months, had a significant better RFS 68% vs 32% [95% CI: 58-78%, 18-55%, p=0.0002] compared to patients who developed MC at later time points; OS was 71% vs 48% [95% CI: 62-82%, 32-72%, p=0.1]. Patients who developed MC at 3-6 months post HSCT had a significantly inferior RFS of 14% vs 65% [95% CI: 4-52%, 56-75%, p< 0.0001] and inferior OS of 25% vs 71% [95% CI: 9-67%, 62-81%, p< 0.001]. Patients who developed MC at 6-12 months or later also had a significant decreased RFS, OS was not significantly different. The better prognosis for patients who develop MC < 3 months was further investigated by assessing physicians response to MC. For 45% of patients who developed MC < 3 months post HSCT IS was reduced, 55% were continued on the same dose; however, neither RFS nor OS were significantly different between both groups suggesting that early MC may rather be an expression of incomplete engraftment rather than a prognosticator of disease recurrence.

Conclusions: Mixed donor chimerism most commonly occurs early in the first 3 months after HSCT. Early mixed donor chimerism carries a more favorable prognosis than occurrence of MC at later time points and reduction of IS in these patients does not influence outcome.

Disclosure: Nothing to declare.

P470

Prophylactic high-dose Donor CD45RO+ Memory T-cells Infusion after Allogeneic Transplantation: Safety and Outcome

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Background: Immune Reconstitution (IR) is essential to control severe infections after Hematopoietic Stem Cell Transplantation (HSCT). Reconstitution of adaptive immunity is delayed and it may take up to 2 years to recover T-Lymphocytes (LT). Adoptive transfer of selected T cell subset with low alloreactivity is a strategy to improve IR. Depletion of CD45RA+ naive T cells, preserving CD45RO+ memory T cells provide functional lymphocytes to protect against infection and leukemia relapse with low risk of graft versus host disease (GvHD).

We present our experience with **high-dose donor CD45RO+ memory T cell** as donor lymphocyte Infusions (DLI) on a **prophylactic regimen on days +30, +60 and +90 post-HCST** to assess outcome and safety.

Methods: A total of 26 DLI of CD45RO+ after HSCT were performed on a prophylactic regimen on days +30, +60 and +90. DLI product was obtained performing a CD45RA depletion on donor leukapheresis product using the CliniMACS® device.

Results: Nine pediatric patients (median age 5 years (range 1-13)), with ALL (n=4), AML (n=3), MDS (n=1) and aplasia (n=1) received HSCT with CD45RA+ (n=8) and TCR alpha/beta (n=1) depletion from haploidentical (n=6), match unrelated (n=1) and match related (n=2) donors. Three patients had received a previous HSCT. Six patients received NK cell infusion on day +7 to boost innate immunity.

DLI product was infused on days +30, +60 and +90 post-HSCT. DLI contained a median of **CD45RO+** cells of $1.35x10^7$/Kg (range $3.5x10^6$/Kg-$5.9x10^7$/Kg), **CD3+CD45RO+** cells $1x10^7$/Kg (range $1x10^6$/Kg-$1x10^7$/Kg) and **CD3+CD45RA+** cells $2.65x10^4$/Kg (range $1.8x10^2$/Kg-2.6 $x10^5$/Kg). Four patients were receiving immunosuppression at moment of DLI infusion (6 infusions). All infusions were well-tolerated.

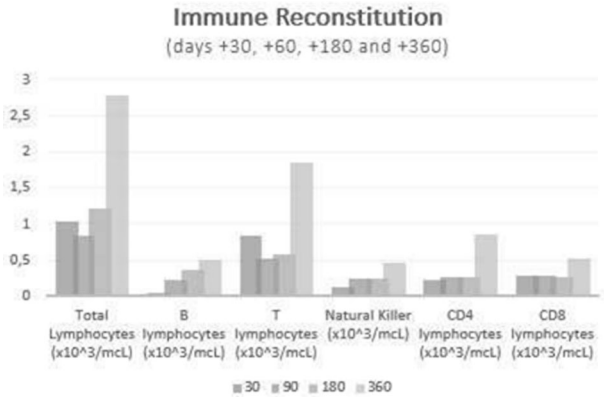
2 patients presented acute GVHD grade 2, and 4 patients skin grade 1. No chronic GVHD was seen. Only 1 patient presented CMV reactivation. Other virus detected were Adenovirus in 1 patient, parainfluenza 3 in 2, HHV-6 reactivation in 2, and parvovirus in 1. One patient relapsed and died on day +169. The remaining patients are in complete remission with full donor chimerism after median follow up of 289 days (92-545). Immune reconstitution is showed in Table 1.

Conclusions: Our preliminary data suggest that **prophylactic DLI of high dose CD45RO+ memory T cells**

are a safe adoptive immunotherapy strategy. No CMV, HHV6, ADV disease and very low rate of viral reactivations was seen with a fast lymphocyte count recovery at day +30 and low rates of GVHD. However, to determine the real efficacy of high dose memory T cells DLI, prospective studies are required.

	Total Lymphocytes (x10^3/mcL)	B lymphocytes (x10^3/mcL)	T lymphocytes (x10^3/mcL)	Natural Killer (x10^3/mcL)	CD4 lymphocytes (x10^3/mcL)	CD8 lymphocytes (x10^3/mcL)
+30	1,045	0,038	0,835	0,135	0,22	0,285
+90	0,83	0,23	0,53	0,25	0,27	0,28
+180	1,22	0,36	0,585	0,24	0,275	0,26
+360	2,79	0,51	1,85	0,46	0,855	0,52

[Table 1. Immune reconstitution of lymphocytic populations (median values)]



[Figure 1. Evolution of Immune reconstitution]

Disclosure: Nothing to declare.

P471

Multicolor Flow Cytometry Panel with CCD79A Gating to Detect Minimal Residual Disease in Patients with B-lymphoblastic Leukemia/lymphoma Post Anti-CD19 Car-t Therapy Bridging to allo-HSCT

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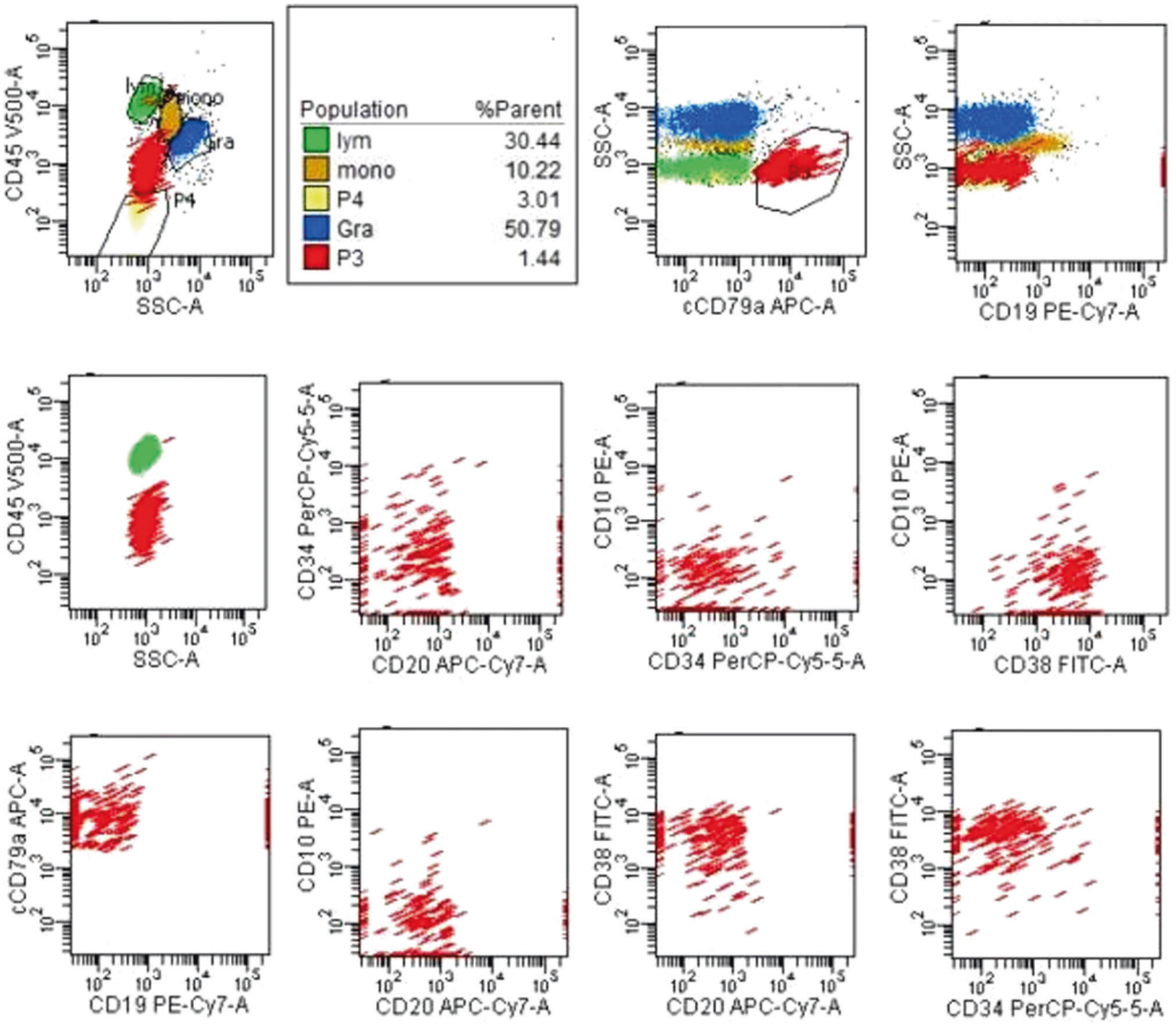
Background: Minimal Residual Disease(MRD) detection is an important prognostic parameter in patients after therapy in B-lymphoblastic leukemia (B-ALL). Anti-CD19 CAR-T Therapy Bridging to allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is an effective and safe treatment for patients with relapsed/refractory B-cell acute lymphoblastic leukemia (r/r B-ALL). However, it has been testified by literature and our data(unpublished) that in more than 60% of relapsed or MRD cases after CD19-CAR-T treatment the expression of CD19 will lose or partially lose. Some alternative rough B gating panels are needed for MRD detection by flow cytometry(FCM).

Methods: A different rough B gating method with cytoplasmatic CD79a(cCD79a) instead of CD19 is applied, as well as panel changing from the classical one (CD38 FITC/CD10 PE/CD34 PerCP/CD19 PE CY7/CD13+33 APC/CD20 APC CY7/CD45 V500) to the new one (CD38 FITC/CD10 PE/CD34 PerCP/CD19 PE CY7/cCD79a APC/CD20 APC CY7/CD45 V500). To test the efficiency of two panels, 10 normal control bone marrow(BM) samples and 10 B-ALL MRD positive BM samples were parallelly stained and detected. To evaluate our new MRD panel in prognosing and guiding treatment, we assessed 59 patients' BM MRD by FCM who treated with Anti-CD19 CAR-T Therapy Bridging to Allo-HSCT from June 2016 to March 2017.

Results: The two panels were highly correlated in normal control and MRD positive arms ($R2=0.992$, $y=1.021x+0.1027$, and $R2=0.9975$, $y=1.0376x+0.0374$, respectively). Before and after treatment by CD19 CAR-T Therapy, all 59 cases were detected using the new panel with cCD79a gating. Before treatment by CD19 CAR-T Therapy, the percentages of MRD were 0.48% to 93.28% (median 8.31%). 51 patients remained MRD negative CR after CAR-T therapy, and received allo-HSCT from day 40 to day 122 (median 64d). 8 patients MRD positive or relapsed after CAR-T therapy, and received allo-HSCT from day 15 to day 211 (median 31d). The percentages of MRD were 2.95% to 45.3% (median 6.35%). As to CD19 recovery time, no B cells was observed after 30 days of Anti-CD19 CAR-T Therapy. Partial CD19 recovered after 2 months. In CR patients CD19 almost totally recovered after 3 months, but CD19 negative B subset still could be found in 1 case after 2 years of CAR-T. New panel can effectively predict the prognosis of Anti-CD19 CAR-T Therapy Bridging to Allo-HSCT. Follow-up 18 to 30 months (median 24 m) after Allo-HSCT, 42/51 cases (82.35%) was MRD negative-CR. 3/51 patients (5.88%) were detected MRD-positive with percentage 0.05% to 43.02% (median 20.07%) in 90d to 450d (median 120d) and died of relapse. 6/51 cases (11.76%) couldn't be evaluated because 2 case (3.92%) lost to follow-up after 6m in MRD negative-CR period, and 4 patients (7.84%) died of GVHD in MRD negative-CR period. In 8 patients who



[Fig 1. CD19 neg MRD after CD19-CART Therapy]

received allo-HSCT with MRD-positive after Anti-CD19 CAR-T Therapy, 3/8 patients(37.5%) were MRD negative-CR in 24 months, 1/8 patients(12.5%) were MRD negative-CR in 5 months, but lost to follow-up of GVHD.4/8 patients(50%) MRD-positive in 25 d to 66d (median 30d) with percentage 0.0031% to 1.93% (median 0.025%), and 2/4 died of relapse.

Conclusions: The multi-color FCM ALL-B MRD panel with cCD79a gating can effectively monitor MRD after CD19-CART and predict the prognosis of bridging Allo-HSCT.

Clinical Trial Registry:
ClinicalTrials#: ChiCTR-IIh-16008711, NCT03173417
https://www.globalclinicaltrialsdata.com/

Disclosure: There are no conflicts of interest

P472

Non-invasive Monitoring of Minimal Residual Disease and graft-versus-host Disease By Circulating cell-free Nucleic Acids after Allogeneic Hematopoietic Cell Transplantation

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Background: Relapse of the underlying disease and acute Graft-versus-Host Disease (aGvHD) are frequent

complications after allogeneic hematopoietic cell transplantation (allo-HCT). Current standard diagnostic procedures are not sensitive and specific enough to detect subtle relapse and subclinical aGvHD in order to prompt early therapeutic interventions. We hypothesize that detection of circulating cell-free nucleic acids (cfNA) might result in early diagnosis of relapse and subclinical aGvHD. We developed a digital PCR (dPCR)-based platform of cfNA analysis, including chimerism, frequent mutations and tissue-specific microRNAs (miRNA) to assess the risk of complications after allo-HCT.

Methods: To assess chimerism after allo-HCT, a panel of twelve insertion/deletion polymorphisms was amplified by dPCR both in peripheral blood mononuclear cells (PBMCs) and cfNA obtained from plasma. Mutations frequently detected in acute myeloid leukemia (AML) and used for minimal residual disease assessment (NPM1, JAK2, IDH1/2, NRAS, KRAS, DNMT3A, U2AF1) were also investigated in PBMCs and cfNA by dPCR. To identify differentially miRNA expression in plasma in patients with GvHD and relapse, we performed a discovery phase using a high-throughput miRNA array that contains specific primers for 185 miRNAs. We assessed the assay perfomance of the differentially expressed miRNA using the area under the curve (AUC) of a ROC curve.

Results: We detected a significant higher recipient derived cfNA (mixed chimerism) in relapsing patients (39,5% vs 6,4% $p< 0.01$) and those with GvHD (52% vs 6,4% $p=0,0118$) compared to control patients without relapse/GvHD. To identify, which patients were at risk for relapse or GvHD, we analyzed for the presence of mutations and tissue-specific miRNAs in cfNA, respectively. The mutation load, calculated as mutation percentage or normalized copy number, for all the tested molecular markers was significantly higher in plasma when compared with PBMCs in patients at relapse ($p=0.015$). Hence, in those patients with AML relapse isolated in the central nervous system ($n=5$), mutations found in the initial diagnosis (FLT3-ITD, NPM1) were detected in cerebrospinal fluid and the cfNA fraction but were not detected in PBMCs. Plasma miRNA profiling revealed a set of 18 and 4 differentially expressed miRNAs in patients with aGvHD or relapse compared to control patients, respectively. Using a cut off value of 2.5 fold change, we assessed the assay perfomance of the differentially expressed miRNA using the area under the curve (AUC) of a ROC curve. We identify three (miR590-5p, miR127, miR223) and two (miR505-3p, miR200c-3p) miRNA with AUC ≥ 0.8 in the case of patients with GvHD and relapse respectively. The differentially expressed miRNA, found in the discovery phase, in relapsing patients was used to identify potential gene targets. Using an integrated platform that links the identified miRNA with their targets and predicted functions (miRNET), three genes were identified: TUBB, DNAJB9 and IKZF2.

Conclusions: Our dPCR platform for cfNA analysis represent a useful tool for chimerism analysis, mutation detection and miRNA to assess the risk of frequent complications after alloHCT.

Disclosure: Nothing to declare.

P473

Torque Teno Virus as Biomarker to Predict Complications and Outcome after Allogeneic Hematopoietic Stem Cell Transplantation

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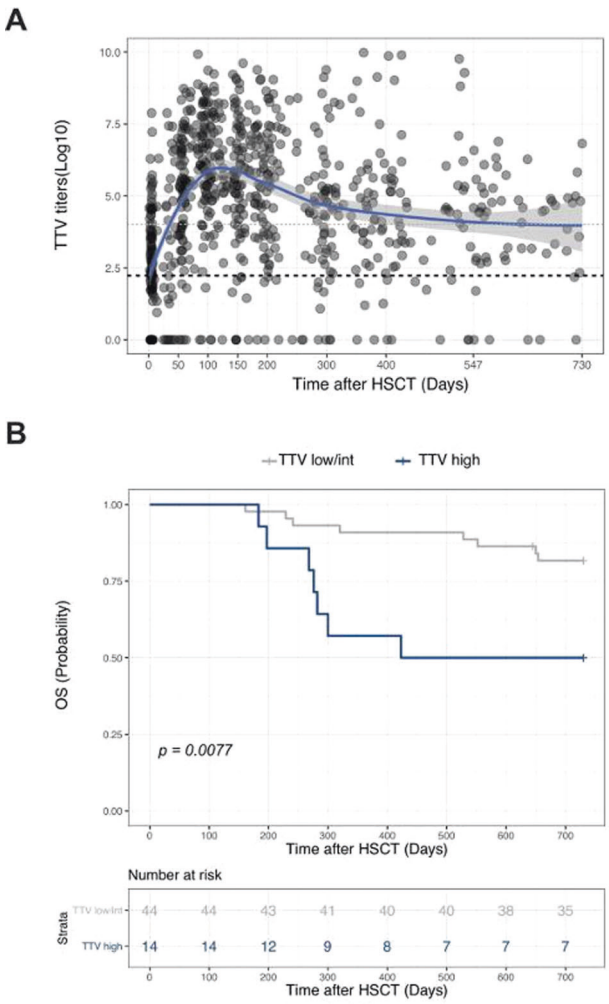
Background: Impaired immune reconstitution after allogeneic hematopoietic stem cell transplantation (HSCT) contributes to increased risk of cancer relapse and infection resulting in significant morbidity and mortality. Unfortunately, effective strategies to functionally assess the quality of immune reconstitution are still missing. Quantification of in vivo replication of the ubiquitous, non-pathogenic virus Torque Teno Virus (TTV) may represent a test to functionally evaluate the quality of post-transplant immune reconstitution.

Methods: In the present prospective study, we analyzed TTV titers in plasma samples by quantitative PCR from a large cohort of 132 HSCT recipients up to 2 years post-HSCT. In parallel, numbers of CD3, CD4, CD8 and NK cells were determined by flow cytometry.

Results: TTV titers peaked at 100 days post-transplant (median 6.4 log copies/ml, IQR 5.1-7.7), followed by progressive normalization thereafter (figure 1A). A negative correlation of TTV titers with CD4 T cells absolute numbers was observed during the first year post-transplant, pointing to the restoration of an active anti-TTV immunity. Multivariable linear regression analysis performed between d100 and 730 demonstrated that donor CMV positive serostatus ($p< 0.0211$) and donor type (MUD: $p< 0.0001$ and MMUD $p< 0.0001$) were associated with higher TTV load. Immune suppression resulting from GVHD treatment also affected the restoration of anti-TTV immunity with TTV titers

significantly higher at day 100 in patients with GVHD (median 6.9 log copies/ml, IQR 5.4-7.9) compared to patients not experiencing the complication (5.6 log copies/ml, IQR 4.4-6.6; p=0.013). This association was confirmed in the multivariable analysis (p=0.0247). Importantly, patients with higher TTV titers (upper quartile) at 100 days post-HSCT displayed a significantly worse 2-year OS (50%, 95%CI 30-84%) compared to patients with lower TTV titers (82%, 95%CI 71-94%; Figure 1B). This difference was confirmed in a multivariable analysis performed taking into account transplant and disease characteristics (HR 3.5, 95%CI 1.1-11; p=0.03). In addition, cumulative incidence analysis revealed that patients with high TTV titers were at higher risk of developing GVHD (p=0.026) and infections (p=0.025). These results were confirmed by multivariable analysis.



[Figure 1. TTV viral load post-HSCT and as a predictive biomarker of OS.]

Conclusions: To date, this is the largest study investigating TTV as a marker of immune reconstitution after HSCT. Our results provide new insights into the factors affecting the dynamics of TTV replication and indicate that TTV is a potentially useful biomarker to assess immune reconstitution and to predict complications and outcomes after allogeneic HSCT.

Disclosure: Nothing to declare.

P474

Preemptive Interferon-α Treatment Could Protect against Relapse and Improve Survival of Acute Lymphoblastic Leukemia Patients after Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Preemptive interferon-α (IFN-α) treatment is known to help clear the minimal residual disease (MRD) after allogeneic hematopoietic stem cell transplantation (allo-HSCT), and we aimed to identify the efficacy and safety of preemptive IFN-α treatment in acute lymphoblastic leukemia (ALL) patients who had MRD after allo-HSCT.

Methods: MRD was monitored by multiparameter flow cytometry (MFC) and polymerase chain reaction (PCR), and a patient was considered to have an MRD-positive status when a single bone marrow sample tested positive by PCR or MFC. Recombinant human IFN-α-2b injections were administered subcutaneously for 6 cycles. The study was registered at http://clinicaltrials.gov as #NCT02185261. This work was supported by National Key Research and Development Program of China (grant number. 2017YFA0104500), the Foundation for Innovative Research Groups of the National Natural Science Foundation of China (grant number 81621001), the Key Program of the National Natural Science Foundation of China (grant number 81530046, 81930004), CAMS Innovation Fund for Medical Sciences (CIFMS) (grant number: 2019-I2M-5-034).

Results: The median cycles of IFN-α treatment was 2 (range, 0.5-14 cycles), and 3 patients received IFN-α treatment for more than 6 cycles. The reasons for discontinuing IFN-α treatment included MRD turned negative

(n=21), grade ≥3 toxicity (n=7), graft-versus-host disease (GVHD. n = 28), and relapse (n = 12). The 4-year cumulative incidence of total acute and chronic GVHD after IFN-α treatment was 14.7% and 40.0%, respectively. Twenty-four (35.3%), 5 (7.4%), 6 (8.8%), and 13 (19.1%) patients achieved MRD negativity at 1, 2, 3, and >3 months, respectively, after IFN-α treatment. The 4-year cumulative incidences of relapse and non-relapse mortality after IFN-α treatment were 31.9% and 6.0%, respectively. The 4-year probabilities of disease-free survival and overall survival after IFN-α treatment were 62.1% and 71.1%, respectively.

Conclusions: Our data confirmed that preemptive IFN-α treatment could protect against relapse and improved survival of ALL patients who had MRD after allo-HSCT. Because IFN-α may preferably be started in patients with relatively low tumor burden, this strategy was giving the right treatment to the right patients at the right time, which could both unlock the therapeutic potential of IFN-α in ALL and spare the patients in remission from further therapy. Importantly, IFN-α treatment could also be performed conveniently on an outpatient basis without severe toxicity. Future randomized clinical trials can further compare the efficacy of preemptive IFN-α treatment and cryotherapy in ALL patients who had MRD after allo-HSCT.

Clinical Trial Registry: The study was registered at http://clinicaltrials.gov as #NCT02185261.

Disclosure: Nothing to declare.

P475

A New Multivariate Model to Describe Impact of Immune Reconstitution on the Development of Relapse in Children undergoing allo-HSCT for Hematologic Malignancies at Day +100

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Background: The speed and quality of immune reconstitution are of paramount importance in outcomes after allo-HSCT. Given the complex network of interactions characterizing this phenomenon, new mathematical models are needed for his description. In this manuscript, we exploited the use of Principal Component Analysis (PCA) to identify a low-dimensional multivariate model to describe how impaired immune reconstitution at day +100 post allo-HSCT is related to relapse in children with hematological malignancies.

Methods: We considered 92 patients (49M, 43F), mean age 9.1 (range 10.7 mo-24.9 y.o.) undergoing allo-HSCT between January 2012 and December 2017, excluding patients with graft failure or death within 100 days. All patients (n=28 AML; n=61 ALL; n=3 MDS) but 4 were in complete morphologic remission at the time of HSCT.

Patients received first allo-HSCT from sibling (n=15), unrelated (n=40), haploidentical family (n=19), mismatched unrelated donors (n=18). Graft sources were BM (n=79), PBSC (n=4), CB (n=6). Conditioning regimen was TBI-based for 60 patients. GvHD prophylaxis included cyclosporine +/- short course methotrexate +/- ATG (added in n=60 patients) or tacrolimus + MMF. PT-CY was used in 17 patients.

Lymphocyte subsets were measured by flow cytometry on day 100 +/-20. In order to compensate for age-dependency of immune-reconstitution we normalized each absolute cell count with its corresponding age-specific expected mean value.

To generate the model, the dataset included: disease type; disease status; HLA-matching; TBI y/n; ATG y/n; PT-CY y/n; aGvHD y/n; viral infections; bacterial infections; fungal infections; steroid therapy; $CD3^+$ cells/ul; $CD3^+CD4^+$ cells/ul, $CD3^+CD8^+$cells/ul, $CD3^+CD56^+$cells/ul; $CD19^+$cells/ul.

To compensate for different range of variation of the considered parameters, we pre-processed the data to give each variable a zero mean and unit variance.

Results: Successful engraftment was observed in all children with a follow-up period of at least 2 years. Thirty-two patients developed aGvHD, including 5 with grade III-IV. Steroids were administered in 51(55%) patients. Viral, bacterial and fungal infections occurred in 62 (67%), 35 (38%), 6(6%) patients respectively. Twenty-six patients relapsed after transplantation. The median time to relapse was 7.3 months (range 1.8 to 33.2 months). The results of PCA on the 16 variables are presented graphically in a combined plot with scores and vectors showing that CD3 count at day +100, the use of ATG or PT-CY or steroid therapy and the occurrence of viral infections contribute to the major variability in our population. Among these, only CD3 count at day +100 seems to be the related to the relapse event.

Conclusions: Thanks to our PCA-model we could comprehensively visualize immune reconstitution and its influencing factors in a selected pediatric population at a given time point. We observed a correlation between lower CD3 count and relapse, even months before the events. We strongly believe that, implementing this model with functional immune variables, MRD measure at multiple time points, this approach could lead toward a great predictor and guide for prophylactic administration of cellular therapy in high risk pediatric patients.

Clinical Trial Registry: No Clinical Trial
Disclosure: Nothing to declare.

P476

Acquisition of Complete Chimerism in Bone Marrow, Peripheral Blood and Leukocyte Subsets Depends on the Transplant Setting and Correlates with the Clinical Outcome

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Background: Chimerism analysis is a useful tool to assess the adequate evolution of allogeneic hematopoietic stem cell transplantation (allo-HSCT), and it is crucial for the diagnosis and management of several complications. The objective of our study was to analyse and compare chimerism dynamics in peripheral blood (PB), bone marrow (BM) and leukocyte linages in various allo-HSCT settings as well as to study the relationship between chimerism dynamics and the development of complications.

Methods: We included 199 consecutive allo-HSCT recipients transplanted at our institution between 2010 and 2015. Patients that had received a previous allo-HSCT (n=17) were excluded from the analysis. The different transplant settings performed were matched-identical sibling transplant (n=57), matched-unrelated donor (n=39), cord blood donor (n=25), or haploidentical donor (n=72). Chimerism analysis was performed using microsatellite PCR (AmpFISTR SGM Plus, Life Technologies) in PB, BM and in different leukocyte subsets, obtained by immunomagnetic separation (AutoMACS, Miltenyi Biotec). Chimerism analysis were done in PB on days 15, 30, 60, 90, 180 and 365; in BM and BM CD34+ cells on days 30, 90, 180 and 365; and on PB lineages (myeloid cells [MyC], NK cells, B cells, T cells [TC], activated leukocytes, regulatory T cells) every other week from day 15 until complete donor chimerism (CC) was achieved in each particular lineage.

Results: Significant differences in chimerism dynamics among leukocyte lineages were found, with an early achievement of CC in MyC, NK cells and B cells, and a later achievement of CC in PB and TC. Chimerism dynamics was found to be influenced by transplant and pretransplant factors, with early CC in haploidentical allo-HSCT, in patients diagnosed with lymphoma, myeloma or acute lymphoid leukemia (ALL, when compared with acute myeloid leukemia), intensity of prior chemotherapy, and pre-transplant complete remission. Late CC was found in cord blood allo-HCST, older patients and diagnosis of myelodysplastic/myeloproliferative neoplasia. Regarding post-transplant complications, no relationship was found between chimerism dynamics and the development of acute or chronic graft versus host disease; a larger study analysing chimerism and changes in immunosuppression would be needed in order to further investigate this association. All patients presenting graft failure (n=8) showed donor T cells below 40% on day 30 (primary graft failure) or at graft failure diagnosis (secondary graft failure). Higher relapse incidence was found in matched related donor allo-HCST recipients with persistent BM mixed chimerism (MC) at day 30, as well as in patients with diagnosis of AML and MC at day 30 in BM-isolated CD34+ cells. Early CC achievement in PB, TC and BM was correlated with better overall survival.

Conclusions: Different chimerism dynamics is observed in each type of sample analysed (BM, PB and leukocyte subsets), which depends on different patient and procedure characteristics. Studying chimerism dynamics can help us better understand the biologic mechanisms underlying the success or failure of each allo-HCST. Therefore, chimerism analysis is a mandatory diagnostic tool in clinical practice to monitor engraftment or to establish graft failure diagnosis, and it provides important complementary information in clinical diagnosis and management of other transplant-derived complications.

Disclosure: Nothing to declare.

P477

Early Lymphoid Subsets Reconstitution after Allogeneic Haematopoietic Stem Cell Transplantation (HSCT) as Predictor of Relapse and Survival in Acute Leukemias

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Background: Acute Leukemias are the most frequent haematological disease undergoing allogeneic Haematopoietic Stem Cell Transplantation (HSCT), although the outcome remains poor, mostly due to high relapse rate. Different donor

lymphoid subsets belonging to either innate or acquired immunity, play a key role on preventing disease relapse after HSCT. The majority of them are represented by CD3+CD8+ T-cells and CD3-CD56+ Natural Killer lymphocytes, while CD3+CD4+ cells act mainly as modulatory and regulatory cells. The early post-HSCT ratio among these subsets could be an indicator of Graft vs-Leukemia (GvL) effect.

Methods: We retrospectively revised the immune recovery of 101 allogeneic HSCT performed at our Institution from 2012 to 2018 for Acute Leukemias, analysed on peripheral blood by multiparametric flow cytometry lymphocyte subpopulations panel. Seventy-three patients were affected by Acute Myeloid Leukemia (72%), 28 by Acute Lymphoblastic Leukemia (28%). We analysed the ratio of CD3+CD8+ *CD3-CD56+ /CD3+CD4+ cells (ER) and the patients main characteristics 2 months after HSCT.

Results: Median ER at + 60 days was of 0,2667. Patients displaying ER higher than the median had a better Leukemia Free Survival (LFS) (median LFS time not reached vs 8 months; p = 0,013) and Overall Survival (OS) (median OS time not reached vs 11 months; p = 0,013). This survival advantage was independent on both the CR achievement (p =0,015) or the onset of chronic Graft vs-Host Disease (cGVHD; p = 0,011). Multivariate analysis confirmed the prognostic role, both on OS (HR 2,544 95% CI 1,184 - 5,468; p = 0,017) and LFS (HR 2,581 95% CI 1,257 - 5,298; p = 0,01).

Conclusions: Our data show that ER ratio represent a component of donor immune recovery which can predict both survival and leukemia recurrence after HSCT. Patients experiencing a delayed recovery are at higher risk of relapse and disease -related death and therefore represent a population which may benefit of early therapeutic interventions such as prophylactic use of donor lymphocyte infusions (DLI).

Disclosure: Nothing to declare.

P478

Comparison of Immune Reconstitution Between 30Mg/kg and 60Mg/kg Anti-T-lymphocyte Globuline (ATLG) as Graft versus Host Disease Prophylaxis after Allogeneic Myeloablative Peripheral Blood Stem Cell Transplantation

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Background: The use of anti-T-lymphocyte globulin (ATLG) in allogeneic hematopoietic stem cell transplantation (allo-SCT) to prevent rejection and Graft versus Host Disease (GVHD) has been extensively studied. However, data on the influence of ATLG dose on immune reconstitution (IR) post allo-SCT is limited. In this study, we compared the influence of different ATLG doses (30mg/kg vs 60 mg/kg) on IR and transplant outcomes.

Methods: We included in this retrospective study conducted at University Medical Center Hamburg-Eppendorf (UKE) between the years 2005 and 2019 476 patients who received allo-SCT from a Matched related donor (n=74), Matched unrelated donor (n=303), Mismatched related donor (n=3) and Mismatched unrelated donor (n=96) with ATLG as GVHD prophylaxis. One hundred and sixty-two patients received 30mg/kg ATLG and 314 Patients received 60mg/kg ATLG, all patients had ATLG doses fractionated between days -4 to -1 and received Calcineurin inhibitor and mycophenylatmofetil. To render groups comparable, we included in the study only patients that received peripheral-blood-stem-cells and myeloablative-conditioning allo-SCT. All patients were transplanted for hematological malignancies, and both groups were comparable in terms of patients and donor age, gender, CMV serology, blood group mismatch and type of hematological malignancy. Blood samples were collected on days +30, +100 and +180 and analyzed by multiparametric flow cytometry for the following cells: T-Lymphocytes (CD3+), activated T-Lymphocytes (CD3+HLADR+), T-helper cells (CD3+/CD4+), Cytotoxic T-cells (CD3+/CD8+), B-Lymphocytes (CD19+), B-Lymphocytes subpopulations (CD19+CD5+CD1d+)(CD19+CD27+), Naïve B-cells (CD19+CD27-CD10+), NK-cells (CD56+CD3-), NKT-cells (CD56+CD3+), Naïve helper-T-cells (CD4+CD45RA+), Memory helper-T-cells (CD4+CD45R0+), Naïve cytotoxic T-cells (CD8+CD45RA+), memory cytotoxic T-cells (CD8+CD45R0+), γδT-cells (γδTCR+, CD3+), regulatory T-cells (CD4+CD25+CD127+).

Results: Neutrophil engraftment was significantly delayed in the 60mg/kg group; with a median of 11 days (range, 8-36) and 12 days (8-30) (p< 0.001) in the 30mg/kg and 60mg/kg ATLG respectively, while we observed no significant differences in time to platelet engraftment. We observed a higher incidence of EBV reactivation within the first 100 days in the 60mg/kg group, with an incidence of 35% and 21% in the 60mg/kg and 30mg/kg groups respectively (p=0.003). Immune cell reconstitution differed significantly between the two groups. The use of 30mg/kg ATLG was associated with a higher percentage of memory helper T-cell percentage at day 30 (p=0.001), naïve helper T-cell at day 180 (p=0.043) and a higher mean count and percentage naïve B cells at day 30 (p=0.001). While the use of 60mg/kg ATLG was associated with significantly higher count of activated T-cells at days 30 (p=0.032) and 100 (p=0.038) and a higher Memory cytotoxic T-cells at day 100 (p< 0.001). We observed no

significant differences in CMV reactivation, infections and Grade II-IV aGVHD. After a median follow up of 42 months (range, 2-169) there were no significant differences in overall survival, progression free survival, non-relapse mortality, relapse incidence and incidence of chronic GVHD between the two groups.

Conclusions: Our results suggest that choice of ATLG dose has no impact on the innate immune system reconstitution post allo-SCT, however it significantly affects the adaptive immune system reconstitution. However, these differences do not affect disease control or mortality post allo-SCT.

Clinical Trial Registry: not applicable

Disclosure: nothing to disclose

P479

Functional Immune Reconstitution after Allogeneic Hematopoietic Stem Cell Transplantation: A Comparison of Pre- and post-transplantation Cytokine Responses in Stimulated whole-blood

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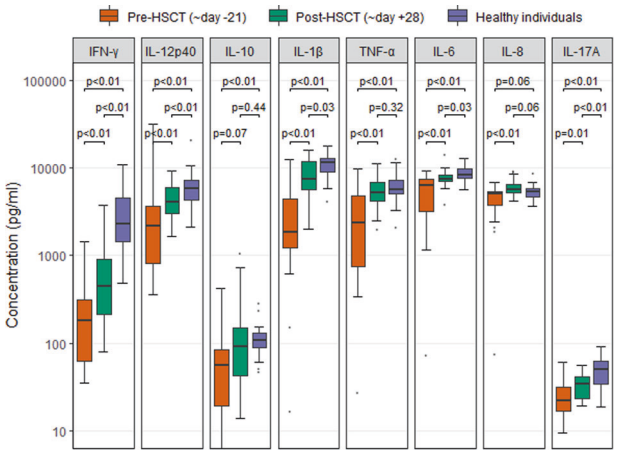
Background: The quantitative reconstitution of immune cells after allogeneic hematopoietic stem cell transplantation (HSCT) is well characterized, but the degree of functional reconstitution is less known.

Methods: We investigated the cytokine response to four stimuli—lipopolysaccharide (LPS, mimicking bacteria), resiquimod (R848, mimicking single stranded-RNA virus), heat-killed Candida albicans (HKCA, mimicking fungus) and polyinosinic:polycytidylic acid (Poly-I:C, mimicking double stranded-RNA virus)—in 24 patients who underwent HSCT between April and September 2018. Whole-blood samples were collected pre- (around day -21) and post-HSCT (around day +28) and stimulated for 22 hours using TruCulture assays (Myriad RBM), after which we measured the concentrations of interferon-gamma (IFN-γ), interleukin-12p40 (IL-12p40), interleukin-10 (IL-10), interleukin-1-beta (IL-1β), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-17A (IL-17A) and interleukin-8 (IL-8) by Luminex (LX200, R&D Systems). For each stimulus, we compared pre- and post-HSCT cytokine responses to each other and to healthy individuals using Mann-Whitney U tests. Log-transformed linear models were used to adjust for leukocyte differential counts (monocytes, neutrophils and lymphocytes).



[Cytokine response in lipopolysaccharide-stimulated whole-blood in patients pre- and post-HSCT (n = 24) and in healthy individuals (n = 31)]

Results: The 24 study patients (54% females) had a median age of 63 years (range 21 to 78 years) and were mainly transplanted for MDS (46%) and AML (25%) with a matched unrelated donor (67%) after non-myeloablative conditioning (75%). At the time of post-HSCT blood sampling, all patients received immunosuppressants as graft-versus-host disease (GvHD) prophylaxis, had neutrophil engraftment and were free of acute GvHD. Patients' median monocyte, neutrophil and lymphocyte count were 0.4, 2.0 and 1.1 (10^9/L) pre-HSCT, and 1.1, 4.0 and 0.7 (10^9/L) post-HSCT, at the day of the respective blood sampling. The cytokine responses to LPS stimulation were significantly decreased in patients pre-HSCT compared with healthy individuals. Post-HSCT, the response to LPS stimulation increased for all cytokines (except for IL-10), and all increases (except for IL-17A) remained significant after adjustment for leukocyte differential counts. However, only TNF-α and IL-8 increased to concentrations comparable to healthy individuals. For R848, we similarly observed that the cytokine responses (except for IL-10) increased significantly from pre- to post-HSCT, also after adjustment for leukocyte differential counts (except for IL-17A), but here, post-HSCT concentrations were significantly higher than in healthy controls. For HKCA, the post-HSCT responses were significantly higher than pre-HSCT responses (except for IFN-γ and IL-17A), also after adjustment for leukocyte differential counts, and post-HSCT responses were generally higher than in healthy controls. For Poly-I:C, the responses were generally weak, but pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and IFN-γ were significantly reduced in patients pre-HSCT when compared with healthy individuals, and they remained reduced post-HSCT.

Conclusions: Our study revealed a significant functional immune dysfunction in patients pre-HSCT. Post-HSCT, the

functional immune reconstitution was heterogenous: the cytokine responses to LPS, R848 and HCKA (but not Poly-I:C) were generally improved, despite that patients received immunosuppressive prophylaxis post-HSCT. R848 and HKCA elicited a greater cytokine response in patients post-HSCT than in healthy individuals, whereas the post-HSCT responses to LPS and Poly-I:C remained less than normal for most cytokines. We are currently investigating if post-HSCT cytokine response patterns can predict infections and acute GvHD.

Disclosure: Nothing to declare.

P480

Measurable Residual Disease (MRD) Testing for Acute Leukemia in EBMT Transplant Centers: A Survey on Behalf of The ALWP of the EBMT

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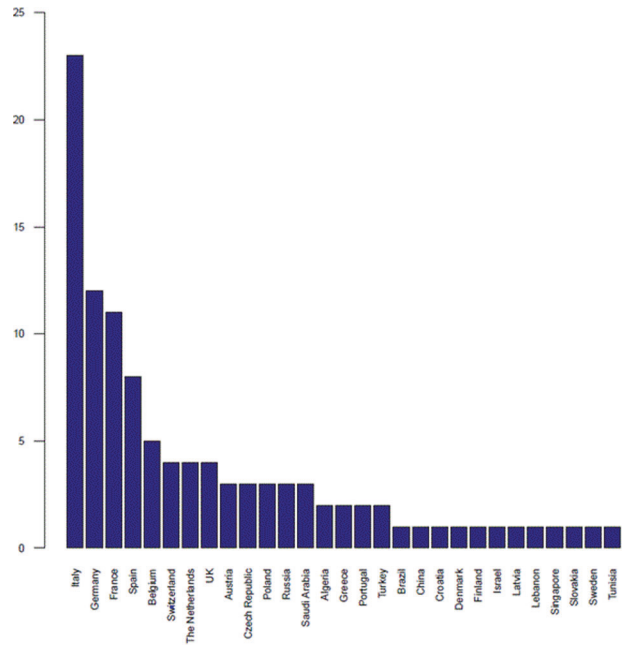
Background: MRD is key prognostic factor in both adult ALL and AML. Peri -transplant MRD status is of particular importance in predicting alloSCT outcome (Czyz A, Int J Mol Sci. 2019). MRD is assessed by either multiparameter flow cytometry (MFC) and/or molecular techniques including RQ-PCR, NGS and digital droplet PCR with sensitivity ranging from 10^{-4} to 10^{-6}. Thus, incorporating MRD as an additional parameter in large transplant registry data bases, though challenging, is of special importance.

Methods: We conducted a survey in EBMT transplant centers focusing on post alloSCT MRD for both ALL and AML. Data assessed included center policy, MRD testing technique, starting day, ability to perform MRD measurement, sensitivity, and measurement schedule (time-points and length of MRD measurement).

Results: 106 centers responded with Italy-23, Germany-12, France-11, Spain -8, and Belgium-5 being the most frequent (Fig). 100 centers routinely assessed MRD, 91 in both ALL and AML while 4 only in ALL. In 95 centers MRD for ALL started as standard practice since 2010 (range, 1990-2019). Of these, 48 (50%) do it in house, 20 (21%) outsource and 27 (28%) use both options. MRD is assessed by PCR in 79 centers (83%) and using MFC in 66 (69%), including 50 centers using both techniques: molecular techniques include NGS (9%), in addition to MFC and/or PCR in 9 centers. By PCR (n=79) the threshold for MRD negativity is 10^{-4} in 18, 10^{-5} in 40, and 10^{-6} in 7 centers, respectively. As for MFC sensitivity (n=66), MRD negative cut-off is 10^{-4} in 37, 10^{-5} in 13 and 10^{-6} in 4 centers, respectively. The majority of centers assess MRD every 2-3 months for 2 (range, 1-5) years following alloSCT or until relapse. For AML, assessing MRD was routine in 92 centers since 2010 (range 1990-2019). It is performed in-house in 67 (74%), outsourced in 9 (10%) and by both strategies in 15 (16%) of centers. Assessment of MRD was performed by molecular techniques in 68 (74%) and MFC in 59 (60%), including 39 centers performing both techniques. In addition to MFC and/or RQ-PCR, NGS was also used in 17 of these centers. Using PCR (n=79) MRD negativity is regarded as 10^{-4}, 10^{-5}, and 10^{-6} in 22, 28 and 6 centers, respectively. While by MFC (n=66) MRD negativity is regarded as 10^{-3}, 10^{-4}, 10^{-5} and 10^{-6} in 20, 29, 7 and 4 centers, respectively. The majority assess MRD for AML every 2-3 months for 2 (range, 1-5) years or until relapse.

Conclusions: Assessing MRD for both ALL and AML is a routine practice in close to 100 EBMT transplant centers, with 50-74% of them establishing the assay in house. The laboratory technique and thresholds varied between centers, but achieves a minimum sensitivity of 10-4 in the vast majority of cases. MRD status is assessed every 2-3 months for a median of 2 years, or until relapse. This survey is the first step in the aim to include MRD status as a routine registry capture parameter predicting transplantation outcome in acute leukemia.



[Figure Legend: Number of centers responding to the MRD survey per country]

Disclosure: Maria Gilleece, Kiadis - scientific advisory board chair (September 2019)

P481

TBF Regimen Induces Full Donor Chimerism after Allografts in Myelofibrosis

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Background: The conditioning regimen for patients with myelofibrosis undergoing an allogeneic HSCT is usually composed of a combination of fludarabine (FLU) with one alkylating agent, busulkfan (BU), thiotepa (THIO) or melphalan. In a recent prospective randomized study comparing BU-FLU versus THIO-FLU, the proportion of patients with full donor chimerism at 6 months, was respectively 63% and 65% (Patriarca et al, BBMT 2019).

Assess the rate of full donor chimerism in patients with myelofibrosis, after conditioning with one or two alkylating agents.

Methods: We analyzed 113 patients with myelofibrosis, for whom chimerism data were available on day +30. There were two groups: 35 patients were conditioned with either thiotepa-cyclophosphamide, thiotepa-fludarabine or busulfan-fludarabine (ONE-ALK), (Tab.1) whereas 78 patients were prepared with thiotepa, busulfan, fludarabine (TBF). Patients receiving TBF were older (57 vs 52 years, p=0.008), were less frequently splenectomized pre-HSCT (30% vs 54%, p=0.03), had more frequently intermediate-2/high DIPSS scores (89% vs 74%, p=0.04), and had comparable transfusion burden pre-HSCT (p=0.7).

Results:

Complete chimerism day+30 When looking at whether patients had (n=84) or not (n=29) full donor chimerism on day +30, the CI of relapse was respectively 44% vs 15% (p=0.002), the CI of TRM 18% vs 15% (p=0.5), and the 5 year DFS 65% vs 32% (p=0.001).

GvHD

Acute GvHD grade II-IV occurred in 27% vs 37% of patients in the two groups (p=0.7), and moderate severe chronic GvHD in 20% and 21% (p=0.8).

Conclusions: Early full donor chimerism is a pre-requisite for long term control of disease in patients with myelofibrosis undergoing an allogeneic HSCT. The combination of 2 alkylating agents in the conditioning regimen, provides a significantly higher chance of achieving full donor chimerism on day+30, and thus long term disease control.

N	One alkilating agent 35	TBF 78	P
Age	51 (24-65)	57 (31-72)	0.008
DIPSS int2-high	74%	89%	0.04
Spleen (cm)	22.8	22.5	0.9
Splenectomy	54%	30%	0.03
RBC trasf >20	20%	24%	0.7
Alternative donor	34%	83%	0.001
PB source	40%	24%	0.09
Year of tx	2008	2015	0.001
Median follow up (days)	1642	714	0.001

[Patients' characteristics into the two conditioning regimen groups]

Disclosure: Nothing to disclose

P482

Real World Utility of Treating Minimal Residual Disease after Allogeneic Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

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Background: Post-HCT MRD confers poor prognosis but the value of MRD-directed therapy is debated. We sought to describe practice patterns in detection and treatment of post-HCT MRD vs. morphologic relapse of AML, asking which approach may prolong OS.

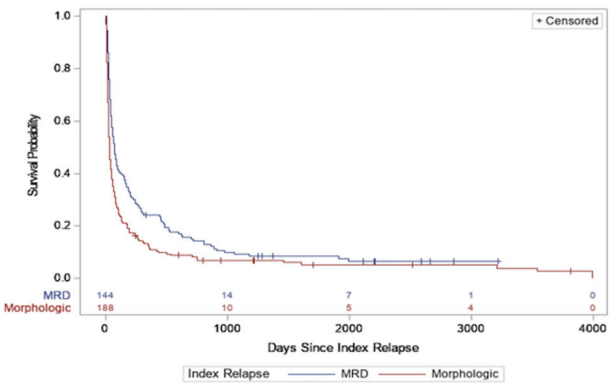
Methods: Patients whose first alloHCT for AML was followed by persistent/relapsed AML detected between 1/2005-3/2018 were included. OS was measured from first post-HCT disease detection ("t0") to death or last follow-up as of 7/2019. In one analysis, we assessed the impact of the timing of treatment among t0-MRD+ patients by modeling treatment as a time-dependent covariate (values: "no treatment", "treatment for MRD", "treatment for morphologic disease"). In a second analysis, the impact of first treatment type on outcome among all patients was assessed from first treatment ("Rx0"), regardless of t0 stage. Failure-free survival (FFS) from Rx0 was defined as survival without progression to morphologic disease (among t0-MRD+ patients) or morphologic disease at post-treatment restaging (among t0-morphologic patients). Treatments included hypomethylator (HMT), chemotherapy (CT), DLI, second HCT, and other. Combined modalities given concurrently or sequentially without restaging between were collapsed, e.g., HMT+CT counted as CT; CT+DLI as DLI. Multivariable Cox regression for OS and FFS was adjusted for conditioning intensity, stage at HCT1, relapse year, age, ELN risk, time from HCT1 to t0, and t0 stage. "CR" denotes morphologic remission without MRD, regardless of blood count recovery.

Results: From t0, median OS was 208 days (95% CI, 174-280) for t0-MRD+ pts (n=144) and 135 (95% CI, 98-209) days for t0-morphologic patients (n=188) (adjusted HR=0.53, 95% CI: 0.40-0.69, p< 0.0001). Restricting to t0-MRD+ patients, modeling treatment as a time-dependent covariate, treatment for MRD (n=75) yielded a hazard of death similar to no treatment (HR=0.96, 95% CI: 0.55-1.67, p=0.88). However, if first treatment was for morphologic disease, such patients had a higher hazard of death compared to treatment for MRD (HR=4.76, 95% CI: 2.59-7.76, p< 0.00001).

Of 62 t0-MRD+ patients who were not immediately treated, 14 (23%) subsequently registered MRD-negative CR without any treatment, but 12/14 later relapsed or died. The 2/14 long-term survivors received maintenance after CR.

The most common first treatments used post-HCT were CT (n=123) and HMT (n=112). The HMT-first cohort was older, started treatment earlier after HCT, and 59% were treated for MRD (vs. 3% in the CT-first cohort). After adjustment for these factors, the hazard of death (starting at Rx0) was higher for CT-first compared to HMT-first, but not statistically significant (HR=1.33, 95% CI: 0.88-2.02, p=0.18). FFS was similar (HR=1.10, 95% CI: 0.71-1.69, p=0.67). As a first treatment, CT and HMT were similarly likely to induce MRD-negative CR (43% and 42%).

Conclusions: After post-HCT MRD detection, delaying AML treatment until overt relapse increases the hazard of death substantially, although ~23% may have temporary MRD disappearance without treatment. Limitations: a) survival estimates associated with first treatment also reflect subsequent lines of therapy; b) confounding-by-indication (more aggressive AML may be treated more aggressively); c) unmeasured confounding, e.g., immunosuppression is ignored.



[Overall survival]

Clinical Trial Registry: Not applicable (retrospective chart review)

Disclosure: Nothing to declare.

P483

Comparison of Immune Recovery in Cord Blood and T and B Depleted Haploidentical Grafts Recipients

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Background: The use of either cord blood (CB) and T- and B-cell depleted PB grafts is associated with delayed immune recovery in comparison to other stem cell sources In the former case, this is due to the lower stem cell content of the graft and the "naïve" properties of lymphocytes; in the latter, it is related to the selective ex-vivo removal of committed T-cell precursors.

Both hematopoietic cell transplant (HCT) modalities are widely used in the paediatric setting and suitable to any urgent procedure given the prompt availability of the graft. It is unclear whether one should be preferred to the other in specific clinical situations. To address this issue, we performed a retrospective study comparing immune recovery in two cohorts of patients who underwent HCT at our Institution.

Methods: Between March 2011 and July 2019, 13 patients received CB HCT (CBT), while 49 haplo-HCT procedures were performed in 45 patients. Patients' characteristics are detailed in Table 1.

	CB	HAPLO
Age (median, years)	3.9 (0.32-13.2)	10 (0.3-36.3)
Underlying disease (n°)	Malignant 11/13 (84.6%); Non-malignant 2/13 (15.4%)	Malignant 34/45 (75.5%); Non-malignant 11/45 (24.5%)
Donor (n°)	UCB 11/13 (84.6%); Related CB (sibling) 2/13 (15.4%)	Mother 20/49 (40.8%); Father 26/49 (53.1%); Other 3/49 (6.1%)
Graft failure (n°)	3/13 (23.1%)	4/49 (8.1%)
Early viral reactivation (CMV, EBV, Adenovirus) (n°)	6/13 (46.1%)	24/49 (48.9%)
Early onset bacterial/Fungal infection (n°)	2/13 (15.4%)	8/49 (16.3%)

[Table 1]

Conditioning regimen was myeloablative in all cases, and serotherapy was administered in 11 out of 13 patients in the CB cohort and in all patients in the haplo cohort.

Immune recovery was evaluated quantitatively through enumeration of the following lymphocyte subsets:

-CD3+ T-lymphocytes
-CD3+CD4+ positive cells (T-helper lymphocytes)
-CD3+CD8+ positive cells (cytotoxic T-lymphocytes)
-CD19+ positive cells (B-lymphocytes)
-CD16CD56+ positive cells (NK cells).

Assessment was performed monthly from engraftment to day +360 (+12 months) post-HCT. Data were compared by mean of 2 way Anova test, considering time from HCT and stem cell source as factors influencing cell count trend.

Results: With the exception of the CD16CD56+ subset, regardless of the stem cell source, all cell counts tended to increase over time. Stem cell source had a statistical significant effect on the following populations: total lymphocytes, CD3CD4+ and CD19+ cells that were more abundant in the patients of the CB cohort than in the haplo one. Trends and p values are detailed in figure 1. Interestingly, rate of viral reactivation and invasive bacterial and fungal infection in the same time period was similar in the two groups.

Conclusions: We observed higher absolute counts of different lymphocyte subsets in a cohort who underwent CBT as compared to a T and B depleted haploidentical cohort, within the first year after transplant.

Our study needs to be prospectively integrated with more specific phenotypical and functional data to accurately assess the quality of immune recovery; however, our experience suggests non-inferiority and possible better immune recovery with the use of cord blood as stem cell source in comparison to T and B depleted haplo grafts, confirming CBT as an appealing approach to HCT.

Disclosure: Nothing to declare.

P484

The BCR-ABL P210 Chimeric Transcript in Vitro Transfer into Bone Marrow Mesenchymal Stromal Cells Via Exosomes

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Background: The key challenge of molecular genetics in oncohematology is the determination of molecular markers, which can be applied to malignant cells in diagnostics of the disease is the analysis of molecular markers, which can be applied to malignant cells in diagnostics of the disease, its progression, and relapse risks. One of the most promising test subjects to approach this might be exosomes,

extracellular membrane vesicles of 30-150 nm in size, that potentially contain such oncogenic markers. Exosomes are among important players in intercellular communication and are able to transfer a variety of biopolymers, which can potentially affect the results of minimal residual disease (MRD) determination. Since the main role in the regulation of hematopoiesis belongs to mesenchymal stromal cells (MSCs) of the bone marrow, we suggest that the source of the detectable transcript can be as exosomes that are persisting in the bone marrow, and their migration into stromal microenvironment cells.

Methods: Exosome isolation was performed by differential ultracentrifugation of K562 cell line (Chronic Myeloid Leukemia) conditional media. The isolated exosomal particles were analyzed using laser correlation spectroscopy approach including zeta-potential assessment to ensure electrokinetic capability to interact with biological systems. Transfer of BCR-ABL p210 transcript was performed in a 24-well plate. After that, 300 μl of serum-free growth medium with exosomes (isolated from about 70 millions cells per well) was added. Co-cultivation of K562 and MSC was performed in a 24-well plate with inserts of semi-permeable membrane (pore diameter 0,4 μm).

Results: The largest number of vesicles in the sample corresponded to a presumed size of exosomes with average diameters in the range of 52÷107 nm and a mean value of79 ±20 nm. The results of the study showed that the

distribution of the average sample size in diameter is in the range of 51,8÷107,0 nm and a mean value of 78,96 ±20,03 nm. The zeta potential corresponds to stable particles and is on mean equal to 29,3±7,4 mV. According to Real-Time PCR, the relative representation of the BCR-ABL p210 chimeric transcript in exosomes ranged between 44÷864 copies/ml of conditioned medium with a median value of 154 copies. After MSCs co-cultivation with K562, the relative content of BCR-ABL p210 mRNA in recipient mesenchymal cells was between 0,03 to 11,4% of ABL1 level, with a median of 0.29%. As a result of exosome-mediated transfection, the relative content of the chimeric transcript in the MSCs of healthy donors ranged from 0,01 to 15,88%, with a median value of 0,11%.

Conclusions: Exosomal fraction of microvesicules of K562 contain the chimeric BCR-ABL p210 mRNA transcript, a marker of CML, and are able to its transfer to the bone marrow MSCs of healthy donors. It has been confirmed during as experiments of co-cultivation, and direct transfection with exosomes. The amount of transcript transferred to stromal cells is comparable to the one in CML patients with a minimal residual disease, which proves the potential role of exosomes in contribution to the results of MRD determination.

Disclosure: Nothing to declare.

P485

Prognostic Significance of donor-specific Isoagglutinin re-appearance in abo-mismatched Stem Cell Transplant Recipients

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Background: Following ABO-incompatible hematopoietic stem cell transplants (HCT), recipient anti-A/anti-B isoagglutinins are expected to eventually become undetectable during the engraftment period. In some patients, after initial clearance, these isoagglutinins re-appear and cause hemolytic anemia, pure red cell aplasia, and even experience disease relapse. However, natural history and clinical significance of donor-specific isoagglutinins not well characterized. A retrospective chart review was therefore performed.

Methods: The transfusion records and clinical outcome of all major-side or bidirectional ABO-incompatible HCT performed between May 2009 and July 2018 were reviewed. Patients with no detectable anti-donor isoagglutinin at time of transplant, or within 28 days post-transplant were excluded from the analysis. Isoagglutinin clearance was defined as loss of reactivity of recipient plasma against donor-type reverse grouping cells after HCT. Re-appearance was defined as a 2+ or stronger serologic reaction after one or more non-reactive results. Clinical outcome including overall (OS), relapse free survival (RFS) and non-relapse mortality (NRM) were compared.

Results: 236 patients with major or bidirectional ABO-mismatched HCT were included in the analysis; 125 patients (53%) showed sustained clearance of isoagglutinin (median 49 days from HCT to clearance, range: 6-1565 days), while 56 patients (23.7%) showed reappearance of isoagglutinin after initial clearance (median 97 days from HCT to re-appearance, range: 10-1646). The remaining 55 patients (23.3%) demonstrated persistently detectable anti-donor antibodies. Our study was mostly focused on the first 2 groups; There was not a statistically difference in time to isoagglutinin clearance, age, sex, recipient blood group, and initial diagnosis between those with sustained clearance vs whose isoagglutinins later re-appeared, however, there was a statistically significant difference in relapse free survival (RFS) rate between the 2 groups: The reappearance group showed 26.2% RFS rate at 3 years vs 47.1% in complete

clearance group (p=0.0214). With respect to OS, there was a trend of lower OS rate in the reappearance group (33.4% at 3 years) compared to those in the sustained clearance group (48.5%; p=0.093), without any difference in cumulative incidence of NRM between the two mentioned groups (43.3% vs 41.3% NRM rate at 3 years, respectively, P=0.807). A higher proportion of isoagglutinin reappearance was observed in patients received reduced intensity (RIC) compared to myeloablative (MA) conditioning regimen (38.14% vs 22.62% respectively, p=0.0242). When analysis was restricted to the group receiving RIC, OS in the reappearance group was inferior, but not significantly different compared to the sustained clearance group (25.3% vs 47% at 3 years; p=0.1573), also, in RIC subgroup, a higher relapse rate was noted in the reappearance group (83.1%) vs complete clearance group (56.2%, p=0.1461).

Conclusions: Most of ABO-incompatible HCT recipients lose detectable donor-specific isoagglutinin within 2 months of transplant. However, this does not guarantee against later reappearance of the isoagglutinin, which is associated with disease relapse, especially in the patients received RIC, therefore, warrants notification of the clinical team by the blood transfusion laboratory.

Disclosure: Nothing to declare.

P486

Immune-reconstitution of Lymphocyte Subpopulations with Respect to Msc-treatment for Steroid Refractory GVHD following HSCT

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Background: Mesenchymal stromal cells (MSCs) are a promising immunotherapeutic tool in the treatment of steroid refractory GvHD following hematopoietic stem cell transplantation (HSCT) by inhibiting the proliferation and cytotoxic potential of GvHD mediating cells. We sought to describe the effect of MSC-FFM therapy on immune reconstitution of patients with steroid refractory GvHD.

Methods: Peripheral blood samples of pediatric patients (n=20) receiving MSC-FFM for the treatment of life-threatening GvHD were periodically collected and monitored. T cells including T-helper (T4) and cytotoxic (T8) subsets, NK cells and monocyte counts were assessed by flow cytometry. Data were analyzed with R statistical environment applying a B-spline mixed linear model.

Results: A major question of MSC application is whether MSC-induced suppression of immune cells carries a risk for cellular aplasia. Therefore, we analyzed the effect of MSC-FFM application on the immune-reconstitution in patients suffering from GvHD grade II (n=1, 5%), grade III (n=7, 35%) and grade IV (n=12, 60%). Patients were divided into those reaching complete GvHD remission (CR, n=8), those showing partial response with a GvHD relief of at least one grade (PR, n=10) and those without response to MSC treatment (NR, n=2). The immune-reconstitution was examined before and after MSC-FFM infusion. Variations in the cell counts were evaluated with respect to the absolute counts measured before MSC-FFM application. Independent of the GvHD status, T4 cell counts were constitutively increasing whereas monocyte levels were stable in all patients. However, a significant difference in the development of T8 cells was detected showing delayed reconstitution in PR patients versus boosting T8 cells in CR patients ($p < 0.042$). Interestingly, an opposed trend in NK cell development was detected, showing increasing levels in PR patients vs. a short period of NK cell count increase followed by a decrease towards stable NK cell counts until approximately 150 days post MSC-FFM infusion in CR patients (p=0.081).

Conclusions: Treatment of life-threatening steroid refractory GvHD with MSC-FFM influences the immune-reconstitution by selectively affecting lymphocyte subpopulations like T8 and NK cells, and not but by impairing the entire immune system.

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Zyrafete Kuci: Nothing to declare.

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Donor Factors Influence Outcomes of Patients Receiving Donor Lymphocyte Infusion for Mixed Chimerism after Reduced Intensity Conditioning Allogeneic Stem Cell Transplantation

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Background: Donor lymphocyte infusion (DLI) is an effective treatment for mixed chimerism (MC) but little is known of factors affecting outcomes in reduced intensity conditioning (RIC) stem cell transplantation (SCT).

Methods: We performed a retrospective study with 61 adult patients who received DLI for MC after RIC SCT according to our institutional protocol, from 2005 to 2016. The aim was to find prognostic factors for response to treatment (achievement of T-cell full donor chimerism (T-FDC)), and outcomes post-DLI. Chimerism was monitored by Short Tandem Repeats analysis.

The chi-square test was used to determine categorical variables between groups (responders vs non-responders to DLI). Univariate comparisons to test significant predictors of treatment response were made using logistic regression, and those significant ($p< 0.05$) were entered into a multivariate analysis (results below). Survival curves were estimated with the Kaplan-Meier method. DLI-related mortality was calculated by competing-risk analysis using Fine and Gray method.

Results: Median follow-up was 45 months (3-160). The median number of DLI doses was 1 (1-3). The median cumulative dose was 1.0 CD3x10^6/kg (0.1-61).

Following DLI, 65.6% patients achieved T-FDC. Patients with female donors were more likely to achieve it compared to those with male donors (81.5% vs 52.9%, $p=0.004$). Also, patients whose donors were CMV negative were more likely to attain T-FDC than those with CMV positive donors (76.5% vs 52%, $p=0.004$). No other patient/donor factors impacted on T-FDC.

One-hundred-day DLI-related mortality was 1.6%. One-year overall survival (OS) from the date of first DLI was 85%. Patients with younger donors (≤45 years) compared to those with older donors (>45 years) (80.6% vs 50%, $p=0.011$) and patients who achieved unfractionated whole blood (UWB) FDC compared to those who did not (76.6% vs 28.6%, $p< 0.001$) had better OS. Graft-versus-host disease-free/relapse-free survival (GRFS) at 1-year post-DLI was 71%.

Relapse occurred in 24.6% of patients and was more prevalent in patients whose donors were older compared to their younger counterpart (36.7% vs 13%, $p=0.024$), and in patients who remained on UWB MC compared to those with UWB FDC post-DLI (50% vs 17%, $p= 0.001$).

Acute graft-versus-host disease (aGvHD) post-DLI occurred in 29.5% patients: 39% grade I, 33% grade II, 17% grade III and 11% grade IV. No patient/donor factors were found to contribute to aGvHD.

Twenty-three percent of patients developed chronic GvHD (cGvHD) post-DLI: 43% mild, 50% moderate and 7% severe. The incidence of cGvHD was higher in patients whose donors were females compared to their male counterpart (37% vs 11.8%) ($p=0.026$).

Conclusions: Despite female donors influenced on T immune-reconstitution post-DLI, it entailed higher cGvHD rate. In addition, achieving T-FDC did not impact on relapse or OS, but attaining UWB FDC did. Moreover, patients with younger donors had lower incidence of relapse, contributing to a better OS.

These results support the recruitment of younger donors, as they have proved to impact favourably not only in outcomes post-RIC SCT but also following DLI.

Disclosure: Nothing to declare.

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Determine Patients at Risk of Relapse and Death in Acute Leukemia and Myelodysplasic Syndrome using Chimerism on Bone Marrow Samples at Day 28 after HSCT

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Background: Non myeloablative allogeneic stem cell transplantation (HSCT) by limiting toxicity, can be proposed to elderly patients. However, risk of relapse seems to be more important than myeloablative regimen. Some studies have evaluated this risk around 25% to 45%. Some markers, as chimerism, could potentially predict the risk of relapse. The purpose of our study is to determine whether

the results of chimerism analysis performed after allogenic HSCT can be predictive of the outcome of the patients in patient with acute leukemia or myelodysplasic syndromes.

Methods: We retrospectively studied all consecutive patients who received a non-myeloablativ allogeneic stem cell transplantation at Limoges University Hospital from June 2009 to August 2018 for acute myeloid leukemia (AML), acute lymphoid leukemia (ALL) and myelodysplasic syndromes (MDS). Treatment consisted in conditionning by Fludarabine 30 mg/m2/day between D-6 and D-2 before allograft and Busulfan 3.2 mg/kg/day at D-4 and D-3. GvH prophylaxis consisted in rabbit anti-lymphocyte serum dose of 2.5 mg/kg at D-2 and D-1, and ciclosporin at the beginning dose of 3mg/kg per os twice a day. Mycophenolate mofetil was adding for patients with HLA-matched or mismatched unrelated donors. All patients received a peripheral stem cell transplant.

For each patient, chimerism was tested at day 28 and day 100 post-transplant on DNA isolated from whole blood, CD3 sorting cells, and bone marrow sample. Two techniques were used: PCR-STR (Promega kits) for all samples and PCRq (GendX kits) retrospectively for all available samples. Full Chimerism (FC) is defined for a donor percentage> 95% in PCR-STR and> 99% in PCRq.

Results: We included 68 patients (45 AML, 17 MDS, 6 ALL), with a median [min-max] age of 59 [47-71] years. 19% of patients received an HLA-identical related donor, 74% an HLA-matched related donor and 7% an HLA-mismatched unrelated donor. The two years overall survival (OS) and relapse free survival (RFS) were estimated at 77.5% IC95 [67%-88%] and 73.6% respectively IC 95 [63%-84%]. There was no significant difference in survival at two years between FC patients and patients with mixed chimerism (MC) in whole blood ($p = 0.35$) or in CD3 sorted cells ($p = 0.87$) at day 28. In contrast, patients with FC (> 95% donor) at day 28 on bone marrow samples had a significantly higher probability of survival at two years than those with MC which is estimated at 85.4% and 53.3% respectively ($p < 0.0001$). Similar results were observed for the risk of relapse at two years which is estimated at 8,3% and 53.3% respectively with a statistically significant difference between patients with FC and MC on bone marrow samples ($p < 0.0001$). The same trend was observed at day 100 but without significant statistical difference.

Conclusions: In a strategy to prevent post-transplant relapse in non myeloablativ stem cell transplantation, our study shows the interest of the chimerism performed on bone marrow samples at day 28 after HSCT to determine patients at risk of relapse and death in acute leukemia and myelodysplasic syndrome.

Disclosure: Nothing to declare.

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Concurrent- Synergistic Assessment of Two Techniques in Monitoring Minimal Residual Disease for Ph(-) Acute Lymphoblastic Leukemia Post Allogeneic Transplantation Leads to Favorable Clinical Outcomes

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Background: Monitoring of Minimal Residual Disease (MRD) in Ph(-)ALL patients post allogeneic hematopoetic cell transplantation (allo-HCT) defines patients in risk for imminent relapse who further benefit from immunotherapeutic interventions. Six-color Flow Cytometry (FC) and unmanipulated bone marrow chimerism with STR-PCR by fragment analysis (STR-PCR) have been easily applied.

Methods: We evaluated the prognostic value of these techniques in monitoring MRD for Ph(-) ALL patients post allo-HCT. Fifty-one patients aged 32 (13-57) years who underwent allo-HCT for B- (27), T- (20) ALL or MPAL(4) mainly after myeloablative conditioning (47/51) were evaluated. Twenty-six out of 51 transplants were matched unrelated, 22 sibling and three alternative ones. Monitoring of MRD with both methods was available for all patients, performed on days +30, +60, +90 and every 3 months for 2 years.

Results: Median follow-up was 38 (2-123) months and 264 samples were analyzed with both methods. Overall, only 6/51 patients relapsed. FC and STR-PCR showed concordant results in 216/264 samples (82%). Discordant results were as follows: i) 9 patients in 12 samples had positive FC-MRD and complete donor chimerism in STR-PCR (FC+/ STR-). According to our protocol, immunosupression was reduced promptly and no patient relapsed. Interestingly, in this cohort, 3 patients experienced later concurrent FC+/STR+ MRD detection, and 2 patients showed subsequent low level mixed chimerism (LLMC)/ FC-, reflecting the increased sensitivity of both methods, ii) 17 patients in 19 samples >+3 months post-alloHC, experienced mixed chimerism with negative FC-MRD (FC-/STR+). Among them no intervention was applied in 12 patients due to chimerism >=97.5%. The rest 5 had previously been FC+/STR-, and immunomodulation was successfully performed. Subsequently two FC-/STR+

patients relapsed, showing greater sensitivity of STR vs FC in these cases, iii) the remaining discordant samples were FC-/STR+ during first trimester, before full engraftment had occurred. Progression Free Survival (PFS) did not differ in the two groups (FC+/ STR-, FC-/ STR+) compared to the entire cohort. Similarly, no differences were found in PFS when each method was assessed separately. However, patients experiencing concurrently FC and STR-PCR positive MRD showed a trend for shorter PFS [PFS: mean 71(95% CI: 33-108) vs 107(98-115) months, p=0.052 for FC+/STR+ vs other, respectively]. Interestingly, survival post transplantation was better among FC+/ STR- patients, [mean 62(95% CI: 18-106) vs 30(20-39) months, p=0.045, for FC+/ STR- vs other], probably due to successful immunotherapeutic interventions.

Conclusions: In conclusion: i) positive MRD by FC is frequently followed by low level mixed chimerism (LLMC) by STR-PCR, reflecting the high sensitivity of both methods and leading to prompt therapeutic interventions ii) concurrent detection of MRD by FC and STR-PCR indicates a worse prognosis. In this cohort of patients, 6-color FC was not superior to STR-PCR in terms of PFS and OS. This could be explained by the low incidence of relapse in our population following our immunotherapeutic interventions. Larger scale studies are warranted to evaluate the prognostic value of each method and answer the arising question of the benefit from the concurrent diagnostic approach.

Clinical Trial Registry: N/a

Disclosure: Nothing to declare.

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Donor Chimerism Evaluation of MRD-suspected Cells Isolated by flow Cell Sorting is an Accessible Tool for MRD Verification in Patients After Allogeneic HSCT

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Background: In the setting of hematopoietic stem cell transplantation (HSCT), minimal residual disease (MRD) assessment is crucial for early relapse recognition and for selecting appropriate additional treatment. The use of multicolor flow cytometry (MFC) remains indispensable for MRD testing. However, some cases demonstrate rather ambiguous immunophenotypic features of normal and leukemic cells, especially after targeted treatment. This unfortunate aspect complicates MFC MRD monitoring. Flow cell sorting of the suspicious cell subsets followed by chimerism testing may assist in confirming of MRD presence. This study aimed to determine the ability of flow cell sorting with further chimerism evaluation to verify MFC MRD detection results in children underwent allogeneic HSCT.

Methods: We analyzed 43 bone marrow (BM) samples from 31 patients diagnosed with various hematological malignancies (10 with T-lineage neoplasms, 15 with B-cell precursor ALL (BCP-ALL), and 6 with AML) after allo-HSCT. MFC-based follow-up MRD studies of these samples revealed questionable testing results. In 36 cases, we sorted MRD-suspected cells, while in the remaining 7 ones we isolated normal hematogones with slight immunophenotypic differences from BM regeneration patterns. Sorted cells were then analyzed for donor chimerism by RQ-PCR. In order to define a lower limit of cells needed for a successful chimerism evaluation, we also prepared multiple aliquots with various number of sorted cells: from 100 to 1000.

Results: The chimerism distribution in sorted cells was evaluated in 41 samples (95.3%). The lower limit set for a successful RQ-PCR was 400 sorted cells. All cell populations originally interpreted as MRD demonstrated up to 99% of recipient chimerism, while the cells considered as normal precursors demonstrated complete donor origin. In one case of BCP-ALL, sorted cell populations with an ambiguous immunophenotype turned out to be normal immature BCPs of donor origin. This finding helped to disprove relapse development. In one case, two tumor populations (CD19+ and CD19-), as well as early BCPs, were sorted after the blinatumomab treatment. The chimerism analysis showed that almost all of the CD19+ cells were normal precursors of donor origin with just slight immunophenotypic deviations. This finding allowed to terminate CD19-directed therapy.

Conclusions: When MFC MRD testing of post-HSCT samples is difficult due to an ambiguous immunophenotypic profile, doubtful cells can be isolated by flow cell sorting and analyzed for donor chimerism. This procedure proved to be a beneficial tool for MRD verification in almost all complicated cases.

Disclosure: Nothing to declare.

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Donor Lymphocyte Infusions Augment Graft versus Malignancy Effect following alemtuzumab-based Reduced Intensity Allografts: Reflections on a Single Centre Study

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Background: Reduced-intensity, Alemtuzumab-based conditioning decreases graft-vs-host disease after allogeneic hematopoietic stem-cell transplantation but it can delay the establishment of full donor chimerism and attenuate graft versus malignancy phenomenon. Donor lymphocyte infusions (DLI) are deployed to offset these complications but their clinical and biological effects remain partially unfathomable and open to study.

Methods: This is a retrospective analysis of clinical data obtained from patients who received DLI between 2016 and 2019 in our institution. Indications for DLI were either mixed chimerism (pre-emptive, p-DLI), or disease relapse post-transplant (therapeutic, t-DLI). DLI were administered 2-3 monthly according to the escalating schedule: 0.5x 10^6 CD3+ per kg (starting dose for unrelated donors) and 1x 10^6 CD3+ per kg (starting dose for sibling donors), 5x10^6 CD3+ per kg 1x 10^7 CD3+ per kg, 5x 10^7 CD3+ per kg until 1x 10^8 CD3+ per kg.

Results: Between January 2016 and November 2019, 42 patients received DLI, comprising 26 p-DLI and 16 t-DLI. Patients showed a male predominance (n=25, 60%), median age was 60.5 years (range 20-73). A range of underlying diagnoses were represented: most common being AML/high-risk MDS in 20 patients (48%), myelofibrosis in 5 (12%), and high-grade NHL in 4 (n=2 DLBCL, n=1 MCL, n=1 ALL) (10%).

Concurrent chemotherapy was given to all 16 patients with relapsed disease. The median number of DLI received was 2 (range 1-6). Median time to first DLI was 5 months post-transplant (range 2-114 months). With a median follow-up of 19 months (95% CI 15 to 23 months) post-DLI, the estimated median overall survival (OS) for all patients was 24 months. Median OS for t-DLI was 19 months, whereas for p-DLI median OS was not reached (p=0.47 log-rank). T-cell chimerism increased with p-DLI from median 16% donor (range 3%-85%) pre-treatment, to 95% donor (74%-100%) at 6 months, with 10/15 (67%) surviving patients achieving full or stable mixed donor chimerism. At 6 months, 7/9 (78%) surviving patients achieved full or stable mixed donor whole blood chimerism after t-DLI. Post DLI GvHD was diagnosed in 23/42 patients (55%), including 8 (19%) grade 3-4. The most commonly affected organ was the skin (45%), followed by gut (21%) and liver (12%). Non-relapse mortality post-DLI was 8/42 (4 were due to GvHD or its complications, and 4 were unrelated) whereas cumulative incidence of death due to relapse was 10/42 (24%). After a median follow-up of 25 months from transplant, the median overall survival of this cohort of patients is 28 months.

Conclusions: Our data suggest that repeat, escalating dose DLI combined with epigenetic treatment, immunotherapy or chemotherapy turned around disease relapse in more than 50% of patients. Pre-emptive DLI was effective in instating full donor chimerism. Grade III/IV GVHD affected 19% of patients but NRM directly associated with DLI was less than 10%. Prospective studies are needed to define state of the art DLI use.

Disclosure: Nothing to declare.

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Myeloid-derived Suppressor Cells Recover Quickly Following Autologous Hematopoietic Stem Cell Transplantation in Multiple Myeloma Patients

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Background: Myeloid-derived suppressor cells (MDSCs) inhibit anti-tumor immune response and may promote the expansion of multiple myeloma (MM) cells. The aim of the study was to evaluate MDSC recovery and functional activity following autologous hematopoietic stem cell transplantation (AHSCT) in MM patients.

Methods: Counts of circulating $Lin^-HLA\text{-}DR^-CD33^+CD66b^-$ "early" MDSCS (E-MDSCs), $Lin^-HLA\text{-}DR^-CD33^+CD66b^+$ polymorphonuclear MDSCs (PMN-MDSCs) and $CD14^+HLA\text{-}DR^{low/-}$ monocytic MDSCs (M-MDSCs) in 33 MM patients before conditioning and at the day of engraftment were assessed using flow cytometry. Surface expression of PD-L1 molecule and intracellular production of arginase-1 (Arg-1) and indolamine 2,3-dioxygenase (IDO) enzymes were measured to evaluate suppressive potential of studied cell subsets

Results: Relative counts of circulating PMN-MDSCs and M-MDSCs in MM patients were significantly higher compared with healthy donor values, while E-MDSC counts did not significantly differ (Table). Absolute counts of studied subsets in both patients and donors were nearly equal due to decreased absolute MNC

quantity (Table). Percentages of all evaluated MDSC populations restored rapidly following AHSCT, and reached pre-transplant levels at the day of engraftment. Notably, relative and absolute counts of PMN-MDSCs after AHSCT were higher compared with pre-transplant. The post-transplant percentage of M-MDSCs was increased as a trend. Post-transplant E-MDSC counts did not significantly differ from pre-transplant values. E-MDSCs and M-MDSCs realized the suppressive effect by expression of PD-L1 molecule (51.85 % of E-MDSCs (9.77—68.48 %) and 58.62 % of M-MDSCs (26.17—85.59), respectively). The production of Arg-1 was the main factor of the suppression in PMN-MDSCs: 81.08 % of PMN-MDSCs (75.75-86.32 %). After high-dose chemotherapy with AHSCT, the described suppressive factors retained in the respective cell populations.

Conclusions: Relative counts of circulating PMN-MDSCs and M-MDSCs in MM patients were significantly higher compared with healthy donor values. MDSC populations restored rapidly following AHSCT, and reached pre-transplant levels at the day of engraftment.

Disclosure: Conflict of interest. Nothing to declare.

Multiple myeloma

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Uninterrupted Mobilization and Transplantation Procedure with Non-cryopreserved Yield is Feasible without Increasement of Complication Risk in Multiple Myeloma Patients

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Background: High dose conditioning regimen and autologous hematopoietic stem cell transplantation (ASCT) is standart care after induction regimen in eligible patients with multiple myeloma (MM). We aimed to compare standart ASCT procedure with cryopreserved graft and uninterrupted procedure used with non-cryopreserved graft in patients mobilized with G-CSF.

Methods: This is a retrospective analysis of consecutive myeloma patients undergoing first ASCT using G-CSF mobilized 62 patients (34 patients uninterrupted procedure and 28 patients standart procedure). Peripheral blood stem cells were harvested enough for two ASCTs over 1-2 days after mobilization with G-CSF± plerixofar. After apheresis; 1. stem cell yields were cryopreserved with DMSO, ASCT was perform after at least 2-4 week or 2. non-cryopreserveds yield were stored at +4°C refrigerator for up to 72 hours and was continued reinfusion after conditioning regimen. Stem cell yields obtained for second ASCT were cryopreserved. High dose melphelan± bortezomib was used as conditioning regimen.

Results: Uninterrupted and standart procedure groups were similar according to age [63(32-74) vs 59(40-68)], gender (12 female/16 male vs 21 female/13 male), prior treatment line [(1-6) vs 2(1-8)], (p>0.05). Neutrophil and platelet engraftmant days, erythrocyte and platelet transfusion requirement, number of neuthropenic days after ASCT were not different between uninterrupted and standart procedure groups (p>0.05). Frequency of early complication including catheter infection, febril neutropeni, engraftment syndrome and graft dysfunction were similar between two groups (p>0.05). Patient's characteristics and comparing results of two group as shown in Table 1. Progression free survival (%73.7 vs %49.2) and transplantation-related mortality (%3.6 vs %2.9) results were not significantly different between uninterrupted and standart procedure groups (p>0.05)

Conclusions: Uninterrupted mobilization and high dose conditioning-transplantation procedure with non-cryopreserved yield is feasible without increasement of complication risk in multiple myeloma patients. Uninterrupted procedure may have advantage due to no DMSO toxicity and low cost, lack of risk of yield loss during dissolution, and without twice catheter application in most of patients.

	Uninterrupted procedure (n=34)	Standart procedure (n=28)	p
Mobilization n(%) G-CSF G-CSF+Plerixofar	19 (67.9) 9(32.1)	19(55.9) 15(44.1)	NS
İnfused CD34+ cell (medianx10e6/kg)	4.5 (3.3-6.2)	4(3.0-5.4)	NS
Day of neuthrophil engraftment (median day)	12(8-17)	12(11-18)	NS
Day of platelet engraftment (median day)	13(8-22)	12(10-20)	NS
Transfusion requirement (median U) Erytrocyte Platelet	1(1-8) 3(1-8)	1(0-7) 2(0-9)	NS
Catheter infection n(%)	2(5.8)	2(7.1)	NS
Febril neuthropenia n(%)	13(38.2)	13(46.4)	NS
Engraftment syndrome n (%)	4(11.7)	8(28.5)	NS
Graft dysfunction n(%)	2 (5.8)	3 (10.7)	NS

[Patient's characteristics and comparing results of two group; NS:not significant]

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Conditioning with Bortezomib-MEL200 in Comparison to MEL200 Improves Survival Among Myeloma Patients IN≤PR Prior to Auto-HCT: A Study from the CMWP of the EBMT

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Background: Attempts to improve outcomes by intensifying chemotherapy conditioning regimens have, in general, only worsened toxicity without appreciably improving efficacy. A recent randomised comparison of Bortezomib-Melphalan (Vel-Mel) and single-agent Melphalan (Mel-200) found no significant difference (Roussel et al. Blood 2017). In this retrospective study, we have compared the outcomes of patients who received Vel-Mel as conditioning for either first or second auto-HCT with the outcomes of those who received standard Mel-200.

Methods: A total of 4125 patients who had a first auto-HCT (3832 Mel-200 and 293 Vel-Mel) between 2010 and 2016 were eligible. The study was limited to centres which had treated at least one patient with Vel-Mel. We also analysed data from 256 salvage, 318 tandem (194 within 6 months and 124 later than 6 months without prior relapse) and 579 second Auto-HCT (436 Mel-200 and 143 Vel-Mel). Response, treatment related mortality (TRM), Progression-Free Survival (PFS) and Overall Survival (OS) data were captured from Med-A and Med-B forms. The impact of confounding risk factors such as ISS, Karnofsky, age and FISH results was assessed in the multivariable analysis.

Results: Pre-transplant patient characteristics (ISS, Gender, Ig type, depth of response to induction) did not significantly differ (Table-1). TRM by day 100 was similar: 0.7% (0.6-0.7%) in the Mel-200 and 1.0% (0-2%) in the Vel-Mel groups. Two year PFS was better in the Mel-200 than in the Vel-Mel group (65% (63-67%) vs 59% (51-67%), p=0.015). Regardless of conditioning, those patients who were in CR/VGPR pre-transplant had better PFS than those in PR (67% (65-70%) vs 62% (59-66%), p=0.01). However, Vel-Mel patients in PR at the time of transplant were more likely to reach CR/VGPR at day 100 and had a superior median PFS when compared to Mel-200 patients (OR=2.2 (1.1-4.4), p=0.02) (Fig. 1). Patients in ≥VGPR at transplant were more likely to relapse/die if treated with Vel-Mel (1.7 (1 - 3); p=0.05), but this was not the case for patients in PR (0.6 (0.3 - 1.3); p=0.19). At a median follow-up of 17.8 (16.6-19.3) months, two year OS was though slightly but significantly better with Mel-200: 90% (88-91%) vs 82% (76-88%) (p=0.003).

The interval between transplants was longer for Vel-Mel (29.2 vs. 12.7 months, $p < 0.001$). Overall, 256 patients received a salvage transplant (66% Mel200, 34% Vel-Mel) compared to 318 those transplanted without a prior relapse (83% Mel-200, 17% Vel-Mel). HR for PFS comparing the effect of a salvage vs non-salvage transplant in Mel200 and in Vel-Mel were 2.3 (1.4-3.8) (p=0.0012) and 1.24 (0.66-2.35) (p=0.5) suggesting patients who receive Mel-200 as salvage have worse outcomes than who receive Mel-200 as tandem. Patients who receive Vel-Mel as salvage have similar outcomes to tandem Vel-Mel. OS was not influenced by conditioning type during Auto-HCT-2.

Conclusions: This study is the first to analyze the impact of Vel-Mel in Auto-HCT-1&-2. Prolonged survival following Auto-HCT-1 was only seen in patients in PR pre-transplant. PFS salvage AutoHCT-2 was inferior to tandem AutoHCT-2 when the conditioning was Mel-200 but not when Vel-Mel was used.

Disclosure: Nothing to declare.

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Abstract already published.

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In Vitro Stimulation with CD40l/il-21 Can Retrieve B-cell Dysfunction in Multiple Myeloma Patients Suffering from Secondary Immunodeficiency

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Background: Secondary immunodeficiency (SID) due to malignancy and cancer treatment increases the susceptibility for infections. In multiple myeloma patients these infections are a major cause for morbidity and mortality. In particular patients treated with standard high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (autoHSCT) have been shown to present with hypogammaglobulinemia and an impaired immune response upon stimulation with Staphylococcus aureus cowen (SAC) in vitro. This study aimed to analyse and compare B-cell immune defects at different treatment time points by quantitatively characterising B-cell subsets as well as analysing B-cell functionality.

Methods: The distribution of specific B-cell subsets was analysed ex vivo using flow cytometry. Samples were taken from patients undergoing autoHSCT, before high-dose chemotherapy and in early reconstitution within one month after HSCT. An additional group represented patients newly diagnosed with multiple myeloma. During a seven-day culture, PBMCs were stimulated with either SAC or CD40L and IL-21. Differentiation and antibody secretion of memory B-cells and plasmablasts were subsequently assessed by flow cytometry and B-cell ELISpot.

Results: Results were compared between three different patient groups and healthy controls. All patients presented with a diminished frequency of CD19+ cells, memory B-cells and plasmablasts, which was most prominent in patients after HSCT with a reduction of 98%. In accordance to previously published results, patients' B-cell differentiation and antibody production were impeded upon SAC stimulation in patients after HSCT. However, stimulation with exogenous CD40L/IL-21 restored the differentiation capacity of remaining memory B-cells and the functionality of antibody secreting cells (ASC). First results indicate that secreted immunoglobulin levels per numbers of total B-cells are comparable to those of healthy controls. Immunofixation of the stimulated samples detected no proliferation of myeloma cells. CD4+ T-cells, which are known to activate B-cells via CD40L and IL-21, were also reduced in patients after HSCTHSCT.

Conclusions: B-cell related secondary immunodeficiency in multiple myeloma patients showed to be caused by lower B-cell counts and an impeded differentiation capacity to SAC stimulation. However, reconstitution of B-cell functionality upon CD40L/IL-21 stimulation suggests an extrinsic B-cell dysfunction due to an in vivo lack of CD40L and IL-21, resulting from low numbers of CD4+ T-cells, which are known to restore last in myeloma patients undergoing HSCT.

Disclosure: Nothing to declare.

P497

Allogeneic Stem Cell Transplantation for Multiple Myeloma; Excellent Outcomes for Early Transplantation

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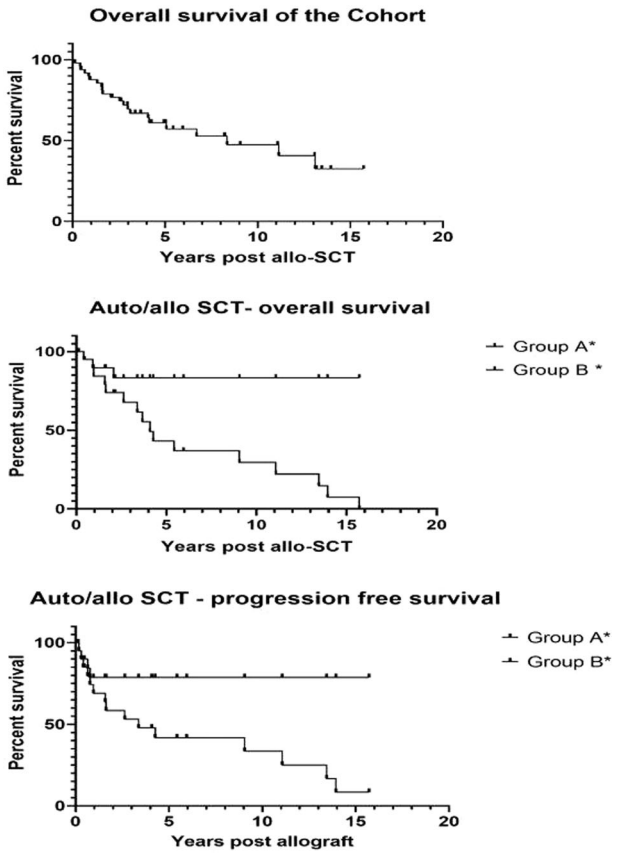
Background: Advances in drug therapy for multiple myeloma (MM) have shown significant improvements in survival. However none provide sustained responses and MM remains incurable. Data from our center suggest that early 'first intention' autologous/allogeneic stem cell transplantation (auto/alloSCT) can result in long-term disease control.

Methods: Transplant outcomes for all patients who received an allogeneic stem cell transplant (alloSCT) for myeloma within the University Hospital Southampton transplant program over the period 2002 - 2019 were analysed. For patients transplanted since 2015 results of minimum residual disease (MRD) by flow cytometry were used to further define response status. Data were locked in October 2019. Disease responses post auto and alloSCT were defined using EBMT criteria. Survival and disease progression data were analysed by Kaplan-Meier statistical analysis using Prism statistical software.



[Outcomes of allogeneic stem cell transplantation for multiple myeloma]

Results: A total of 49 patients received an auto/allo SCT in the period 2002 - 2019. Median age at transplant was 52 years. 26 patients had a sibling donor, 21 patients had a 10/10 fully matched volunteer unrelated Donor (VUD) and 2 patients had 9/10 matched VUD. Conditioning regimens; Fludarabine, melphalan, anti-CD66 targeted radiotherapy and Campath(21/49), fludarabine, melphalan and Campath (15/49), TBI, melphalan and Campath(4/49), TBI and melphalan (3/49), TBI/cyclophosphamide and Campath(3/49), Melphalan, Bortezomib and Fludarabine (1/49), TBI/fludarabine and Campath (2/49).21(43%) patients received an alloSCT within 180 days post autoSCT in the first line setting as 'first intention'(group A); median time between autoSCT and alloSCT in this group was 159 days.28(57%) patients received an alloSCT later in their disease course, after relapse and further lines of treatment including a second autologous SCT(group B). Median follow-up 4.89 years, range 2 months - 15 years. Median Overall Survival (OS) for group A was not reached versus 4.3 years in group B, p= 0.0017. At 15 years post transplant OS for group A was 83.3%, progression free survival 78.7% versus 8.4% for Group B. Non relapse mortality for group A was 4.6%, vs14.8% for group B. Grade 1-2 acute graft versus host disease (aGVHD) was observed in 45% and 66%of patients respectively, grade 3-4 aGVHD was observed in 9% and 14% respectively. Limited chronic graft versus host disease (cGVHD) was observed in 13.6% and 25%, extensive cGVHD was observed in 4.5% and 11.1% respectively. Disease status at last follow up; group A,11 patients are in stringent Complete Remission (sCR), 5 patients are in Complete remission (CR) but MRD not tested, 1 patient not in CR,1 patient not yet assessed (not yet at D+100). In group B, current disease status: 3 patients in sCR, 3 patients in CR, and 4 patients with active disease.

Conclusions: Our data suggest that there is a role for auto/alloSCT in selected myeloma patients, however for maximal benefit the allogeneic transplant must be performed prior to disease progression, early in the course of the disease. Early allogeneic SCT results in lower non-relapse mortality and lower disease recurrence post transplant, these two factors combine to produce excellent PFS and OS.

Disclosure: None

P498

Results of Autologous Stem Cell Transplantation in Patients with Monoclonal Immunoglobulin Deposition Disease

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Background: Conventional chemotherapy, previously used in patients with multiple myeloma (MM), has shown suboptimal results in the setting of light chain deposition disease (LCDD). In recent years, treatment of younger patients with a bortezomib-based regimen, followed by high dose intravenous melphalan and autologous stem cell transplantation (HDM/ASCT) has been increasingly used. Also, if complete response is achieved and patients are on dialysis, kidney transplantation should be considered.

Methods: To update and extend our experience in the treatment approach with bortezomib-based regimes in patients with newly diagnosed LCDD and candidates to HDM/ASCT we reviewed the medical records of all patients with a biopsy proved diagnosis of LCDD who had undergone HDM/ASCT between January 2007 and June

2019. Clinical and laboratory test results were analyzed to study the characteristics at diagnosis, during treatment, and at relapse, including their outcomes and subsequent lines of treatment received overtime.

Results: Fourteen patients were diagnosed with LCDD through the biopsy of an affected organ (12 kidney, 2 heart). Median age of the series was 54 years old (9 men and 5 women). The organ more frequently involved was kidney (85.7 %). Median values of involved FLC was 4695mg/L (range 37200-299) and median value of bone marrow plasma cell infiltration was 36.4% (range 60-5). All of them were initially treated with bortezomib based regimes (10 VD, 2 CyborD, 2 VTD) followed by HDM/ASCT, with no major complications. At least a partial response (PR) was obtained after induction therapy in 11 patients (78.5 %), including complete response (CR) in 3 patients (21.4 %). All hematologic responses improved after the HDM/ASCT (10 CR, 1 VGPR, 1PR). In six cases, given the sustained complete hematologic response but persistence of renal impairment requiring dialysis, kidney transplantation was successfully performed.

Conclusions: Our results confirm and expand on the use of bortezomib based regimes followed by ASCT as a safe and well tolerated treatment for patients with LCDD. In consequence, induction treatment with bortezomib, followed by ASCT, should be considered the treatment of choice in younger patients with LCDD. Additionally, renal transplant should be taken into consideration in those patients still requiring dialysis and who have achieved a sustained hematologic CR.

Disclosure: Nothing to declare.

P499

Abstract already published.

P500

Aberrant Phenotype Plasma Cell Multiparametric Flow Cytometry (MFC) Detection in Autograft Products of Newly Diagnosed Multiple Myeloma (NDMM)

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Background: Over the last decades the incorporation of novel agents such as proteasome inihibitor (PI) and immunomodulatory drug (IMID) prior of autologous stem cell transplantation (ASCT) resulted in high response rate after induction therapy in newly diagnosed Multiple Myeloma (NDMM). Nevertheless the relapse occurs in virtually all MM patients. Many authors suggested that the presence of myeloma plasma cells (PC) in the graft may contribute to the recurrence of myeloma after ASCT. Recent techniques of multiparameter flow cytometry (MFC) can be applied to detect such contamination.

Methods: From December 2017 to September 2019 the apheresis products of 51 NDMM were collected before cryopreservation in order to assess the presence of myeloma PC by 8-colour MFC. Fourty-nine patients (96%) received bortezomib/thalidomide/dexamethasone (VTD) regimen for a medin of 4 cycles as induction and high doses cyclophosphamide plus G-CSF for mobilization; the other two patients (4%) received lenalidome instead of thalidomide (VRD regimen). 300 mcl of the cell suspension was forwarded to the flow cytometry laboratory for PC assessment by MFC analysis in order to evaluate 3000000 events. According to the current guidelines, limit of detection (LOD) was set at 30 aberrant phenotype PC. Fourty-three out of 51 patients were also evaluated for bone marrow MFC minimal residual disease (MRD) after induction. Bone marrow MFC-MRD performed 3 months after ASCT was available for 34 patients.

Results: After induction, 36 (70,6%) patients achieved a high quality response (21 VGPR, 8 CR), while 14 (27,4%) patients were in PR and 1 patient had a progressive disease. Thirty out of 43 (69,7%) had a detectable MFC-MRD in the bone marrow. Aberrant phenotype PC over the LOD were found in 9 (17,6%) apheresis products, whereas further 3 (5,8%) samples were below the LOD. Apheresis positivity was not significantly influenced by MRD status (8 vs 23 % for negative and positive MRD status respectively, $p = 0,236$) post induction and also post ASCT ($p=0,220$). Only achieving both a CR and a MRD negativity post-iduction was found to be significant protective factor for MRD apheresis positivity (OR 0,875, 95% CI: 0,778 - 0,984; $p = 0,044$). Other factors known to have a prognostic significance on survival of NDMM, such as International Staging System (ISS) subgroup and cytogenetic risk, were not found to be predictive for the apheresis contamination. No aberrant phenotype PC were found in the graft of 2 poor mobilizer patients treated with plerixafor.

Conclusions: Eight-colour MFC is a reproducible and reliable method to detect myeloma PC in autograft products. Notewhorty, no aberrant phenotype PC was found in patients who achieved a CR MFC-MRD. A too short follow-up time doesn´t allow to evaluate the impact of this

analysis on ASCT outcome, particularly on progression free survival.

Disclosure: Nothing to declare.

P501

Retrospective Multi-center Study of Adolescent and Young Adult (AYA) Multiple Myeloma in Kansai Myeloma Forum Registry

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Background: Multiple myeloma (MM) is considered as a disease of the elderly patients with reported median age of 60 to 70 years. However, it is rarely seen in adolescent and young adult (AYA) generation; age between 16 and 39 years. We retrospectively analyzed their clinical features and outcomes of the real-world cohort of AYA generation with symptomatic MM (sMM) registered in the Kansai Myeloma Forum (KMF).

Methods: By March 2018, KMF had registered the clinical data of 3284 patients with plasma cell dyscrasias. Of whom 44 were AYA generation. 26 patients had been diagnosed as sMM (59%), following monoclonal gammopathy of undetermined significance (MGUS) (32%, n=14), plasma cell leukemia (5%, n=2), smoldering MM (2%, n=1), and plasmacytoma (2%, n=1). We retrospectively analyzed 26 sMM in AYA generation, diagnosed from April 1998 to March 2018.

Results: The prevalence of AYA-sMM was 0.8 %. Among 26 patients, the median age was 36 (range; 20-39) years old. The M-proteins consisted of IgG (45%), Bence Jones Protein (BJP) (33%), IgA (11%), non-secretory (7%), and IgD (4%). According to ISS, Stage I was 43%, Stage II was 38 %, and stage III was 19 %. 20% of the patients were in poor PS (ECOG≥2). Kappa and lambda ratio was 18 to 7. High risk chromosomal abnormalities were seen in five patients. Del(17) was seen in three patients, t(4;14) was in 2 patients, however, t(14; 16) was not seen in any patients. Other chromosomal abnormalities were del(13) in 4 patients and t(11;14) in one patient. Median follow-up period was 6.5 (0.5- 16) years. The most frequent CRAB symptom was bone lesion(n=18), following renal insufficiency(n=11), anemia(n=6), and hypercalcemia(n=1). 39% of patients were treated with autologous stem cell transplantation (auto-SCT), following combination of autologous and allogeneic SCT (auto/allo-SCT) (23%), chemotherapy without SCT (19%) and allo-SCT (19%). 5-year OS with all the patients was 71.0 %. 5-year OS according to the treatment was 83.3% with auto/allo-SCT, following 77.8% with auto SCT, 75.5% with chemotherapy without SCT, and 40.0% with allo-SCT (p=0.846). 5-year OS according to ISS was 46% with stage I, 100% with stage II, and 80% with stage III(p=0.015). Anemia and hypercalcemia are associated with poor prognosis in univariate analysis (HR: 6.62 (95%CI: 1.80-24.32), p = 0.004/HR: 11.14 (95%CI: 1.01-123), p = 0.049), whereas, other factors; male sex, renal insufficiency, bone lesion, high risk chromosomal abnormality had no significant influence on OS. Late-onset adverse events were seen in five patients; secondary breast cancer (n=1), amyloidosis (n=2), cardiovascular events (CVE) (n=2). 12 patients were fatal. 9 patients died of MM progression. Two patients died of transplant related complication and one patient died of infection.

Conclusions: The prevalence of AYA-sMM was 0.8 % in our cohort. 81% of the patients was received SCT, which may improve outcome. Anemia and hypercalcemia might be prognostic factors, however ISS failed to predict OS. Five patients developed late-onset adverse events which were serious and life-threatening. 5-year OS is 71.0%. We need to develop the new strategy to overcome AYA-sMM.

Clinical Trial Registry: Kansai Medical University #2018216

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Pharmaceuticals corporation. JKU, HS, AT received honoraria from Janssen Pharmaceuticals. JKU, AT, IM received honoraria from Bristol-Myers Squibb. JKU, HS, IM received honoraria from Takeda Pharmaceutical Company. HS received honoraria from Kyowa Hakko Kirin Co. HS received honoraria from Chugai Pharmaceutical Co. MH, IM received honoraria from Pfizer, Inc. MH received honoraria from Merck & Co. IM received honoraria from AbbVie GK.

P502

Autologous Stem Cell Trasplantation Candidacy in Patients with Newly Diagnosed Systemic Light-chain Amyloidosis

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Background: Immunoglobulin light chain (AL) amyloidosis is a plasma-cell disorder characterized by organ deposition of monoclonal light chain-derived amyloid fibrils. High-dose melphalan (HDM) followed by autologous stem cell transplantation (ASCT) has shown its potential to obtain deep and durable hematologic responses, a high organ response rate and prolonged overall survival in this disease. However, the procedure portends an elevated transplant-related mortality (TRM). Although TRM has decreased over time based on the acquisition of experience in transplanting centers, patient's selection remains critical and limits the applicability of this effective therapy.

Methods: The aim of our study was to investigate the real proportion of patients able to receive HDM in our center as well the reasons for being considered a non-transplant candidate. Therefore, we analyzed a series of patients consecutively diagnosed with a systemic AL amyloidosis and evaluated for therapy at our institution from January 2008 to March 2019.

Results: In the study period, 130 patients with a newly diagnosed systemic AL amyloidosis (median age: 65 years; 53% women) were evaluated to receive therapy at our institution. Light-chain isotype was lambda in 76% of them, with a median involved serum free light chain (FLC) of 340 mg/L and bone marrow plasma cell infiltration of 10%. Heart involvement was present in 72% of patients and 38% were classified as revised Mayo stage III-IV. In our series, 35 patients (27%) received an ASCT while 95 (73%) were considered as non-transplant candidates. Among the latest, 41 were not selected for HDM because of their age over 70 years. In the remaining 54 patients, reasons for exclusion from the transplant program were: advanced amyloid cardiac disease in 36 (67%), severe renal failure or gastrointestinal involvement in 6 and 3 respectively, age over 65 and clinical trial availability in 3, patient's decision in 3, severe macroglossia in 2 and lung involvement in one. These patients were treated with combinations of bortezomib, alkylating agent and corticosteroid in most of the cases (CyBorD regimen in 65% of them) and, in an intention-to-treat analysis, the overall hematologic response rate (partial or better) was 72%. Mortality rate during first year after diagnosis was 24% in this population (13/54), resulting in an event-free survival and overall survival of 15 and 37 months, respectively, as compared to 48 and 116 months, respectively, in the 35 patients who received an ASCT in the same period of time.

Conclusions: In our series, 27% of patients with newly diagnosed AL amyloidosis received an ASCT and had a favorable outcome. Among the remaining patients, 57% were potential transplant candidates based on their age but did not receive HDM mainly due to an advanced amyloid cardiac disease. Most of these patients received bortezomib-based therapies and had poor survival outcomes due to an elevated early mortality.

Disclosure: Nothing to declare.

P503

Novel Protocol for Autologous HSCT in Multiple Myeloma Achieves "Zero" Central Line associated Blood Stream Infections (CLABSI)

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Background: The standard protocols of autologous HSCT include application of frozen stem cells through the central venous catheter. In an attempt to reduce the risk of catheter related infections we have redesigned the process of

AHSCT in multiple myeloma and other patients so it could be performed without the central lines in most of the patients targeting "ZERO" central line associated blood stream infections (CLABSI) in an autologous HSCT.

Methods: We analysed the medical data of consecutive patients who underwent AHSCT with new protocol from October 2017 and October 2019. Patients underwent ambulatory mobilization when possible - low dose Ara-C plus tailored G-CSF as previously described. The collected cells were split in parts:1) for use as fresh transplant 2) frozen for possible 2nd transplant and/or as backup. The checklist with bundle of interventions aiming at unifying the procedures and at prevention of possible complications was introduced. In accordance with internal AHSCT protocol - the central venous catheters (CVC) and peripherally inserted central catheters (PICC) were not used when possible in patients planned for AHSCT with fresh cells. The AHSCT were performed first in closed haematology ward (first 50 patients), and then in open haematology ward during extensive construction work at the department (last 25 patients).

Results: There were 108 autologous transplantations in studied period: 75 patients treated with new protocol with fresh cells (56 without and 19 with central line) and 33 transplantations with frozen cells. The novel protocol group included subgroup of 25 (30%) high risk patients (dialysis, amyloidosis and organ involvement). All mobilized patients immediately proceeded to transplantation (100% of successful mobilizations after first line of chemotherapy in multiple myeloma).

The WBC engraftment time was 10 days, median time of neutropenia 6 days, PLT 20 engraftment time 12 days. The total combined time of in-patient treatment for mobilization and AHSCT was reduced from around 48 days to 20 days.

INFECTIONS: Neutropenic fever was present only in 15 patients (20%). Five patients had pneumonia during AHSCT (6.7%) (0% (0/50) patients in closed ward, and 20% (5/25) in open ward). There were 5 patients with positive blood cultures in novel protocol group (6%). Each episode was analysed with CDC criteria for blood stream infections. 4 episodes did not fulfil LCBI criteria (2 patients without central venous catheters and one positive commensal, 1 patient with one positive commensal and no fever, 1 patient with positive blood culture assessed as contamination by laboratory). One patient with probable MBI-LCBI-1 was consulted with National Healthcare Safety Network and episode was qualified by NHSN as BSI not related to central line. There were no CLABSI in studied population for two consecutive years.

Conclusions: We present here a novel approach to autologous HSCT with extremely low rates of infectious complications. In the studied cohort of 75 patients undergoing AHSCT with 1500 days of hospitalization "ZERO" CLABSI was achieved for two consecutive years.

Disclosure: Nothing to declare.

P504

Outcomes of Non-cryopreserved Versus Cryopreserved Peripheral Blood Stem Cells for Autologous Stem Cell Transplantation in Multiple Myeloma

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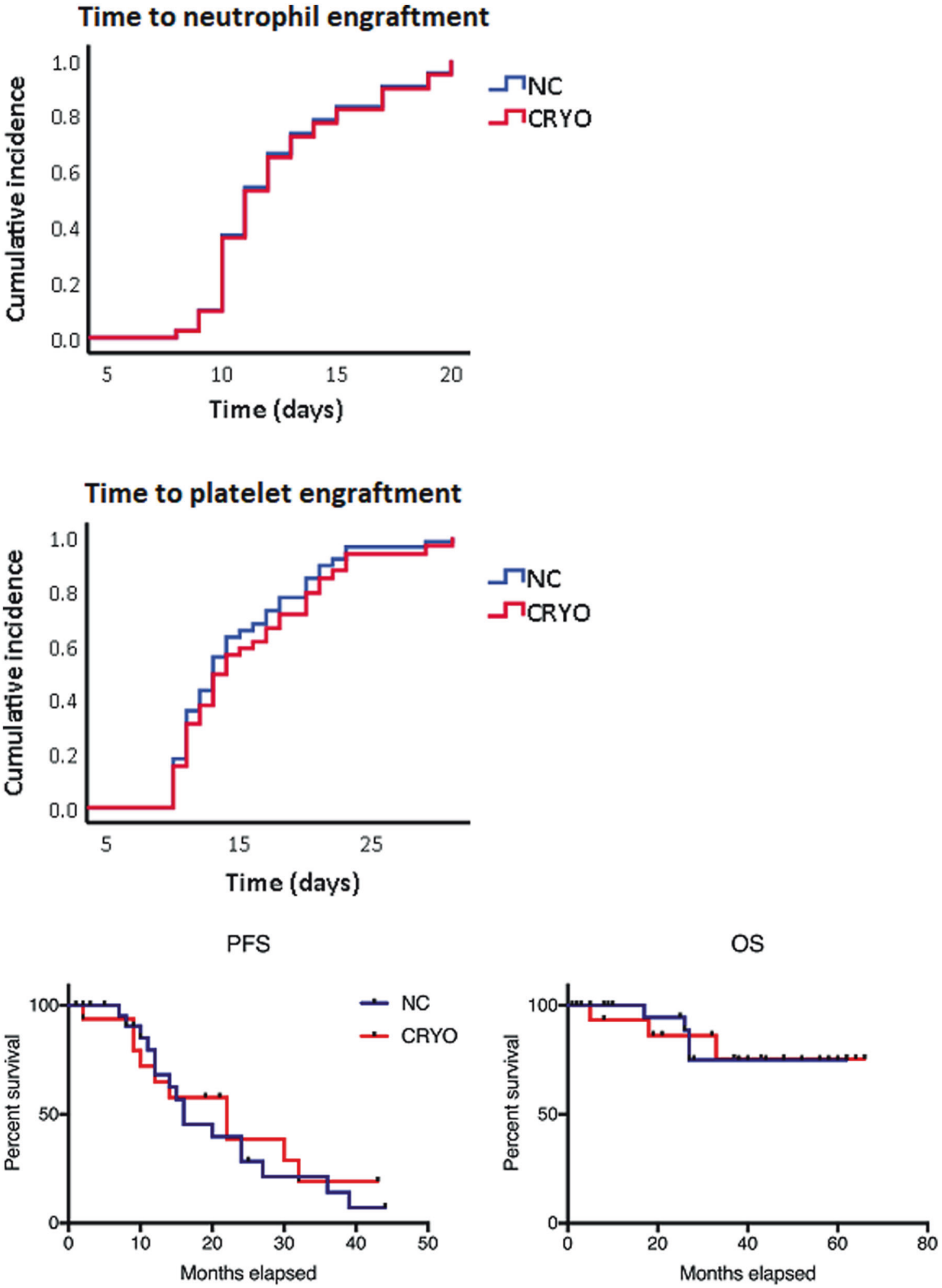
Background: Autologous stem cell transplantation (ASCT) becomes current standard procedure in young multiple myeloma (MM) patients responding to treatment. Cryopreservation (CRYO) of stem cells using dimethyl sulfoxide (DMSO) is a conventional standard method but can be associated with some adverse reactions of DMSO and the cost of the procedure. Previous studies showed that stem cells storage at 4 centigrade, a non-cryopreserved (NC) method, is possible and may have some advantages such as faster engraftment. This analysis will focus on comparing the efficacy in transplant-related outcomes and the cost effectiveness of the two stem cells preservation methods.

Methods: This is a cohort study of consecutive MM patients received ASCT at Division of Hematology, Faculty of Medicine, Chiang Mai University from March 2014 to October 2019. Primary outcome is time to neutrophil and platelet engraftment. Key secondary outcomes are incidence of infusion reactions, duration of hospitalization, cost, and survival.

Results: There were a total of 42 MM patients underwent ASCT, 26 patients using NC and 16 patients using CRYO method. The mean age was 55 years. There was no difference in pretransplant disease characteristics except there were 6 patients (37.5%) in CRYO group, but none in NC group, receiving second ASCT. Total $CD34^+$ cell dose in CRYO tended to be higher than NC group (4.7 vs 3.8 $x10^6$/kg, p=0.062). After adjusted for total $CD34^+$ cell dose, there was no difference in time to neutrophil engraftment (HR 1.03; 95%CI 0.50-2.12) or time to platelet engraftment (HR 1.19; 95%CI 0.58-2.45) between groups (graph 1). Infusion reactions occurred 19.2% in NC and 37.5% in CRYO group (p=0.172). The median length of hospital stay was shorter in NC group (25.5 vs 33 days, p=0.002). Average cost of ASCT was lower in NC group (340,500 vs 377,700 THB [approx. 10,000 vs 11,000



[Graph 1. Time to neutrophil engraftment, time to platelet engraftment, PFS, and OS]

EUR]). At the median follow-up time of 37.5 months, there was no difference in progression-free survival (PFS) in NC group (16 months; 95%CI 13.2-18.7) and CRYO group (22 months; 95%CI 10.4-33.5) (p=0.601 by log-rank test) or overall survival (not reached in both groups; p=0.835).

Conclusions: NC is comparable to CRYO method in both short-term and long-term safety and efficacy outcomes. Moreover, it leads to shorter length of hospital stay and a 10% average cost reduction.

Outcomes	Non-cryopreserved (n=26)	Cryopreserved (n=16)	P value
Time to neutrophil engraftment (days) -- median (range)	12 (10-19)	10.5 (8-20)	0.203
Time to platelet engraftment (days) -- median (range)	14 (10-23)	12 (10-31)	0.809
Incidence of graft failure -- no. (%)	0	0	1.000
Transplant-related mortality -- no. (%)	1 (3.8)	0	0.619
CD34+ cell dose (x10^6 cells/kg) -- median (range)	3.8 (2.0-16.5)	4.7 (2.3-29.1)	0.062
CD34+ cell viability (%) -- median (range)	98.5 (94-99)	93.5 (70-98)	**<0.001**
Stem cells infusion reactions -- no. (%)	5 (19.2)	6 (37.5)	0.172
Total days of hospitalization -- median (range)	25.5 (18-30)	33 (17-55)	**0.002**
Total cost of ASCT (in 1,000 THB) -- mean ± SD	340.5 ± 75.8	377.7 ± 159.8	0.394

[Table 1. Transplant-related outcomes]

Disclosure: Nothing to declare.

P505

Favorable Long-term Outcomes with Autologous Stem Cell Transplantation for High Risk Patients with Multiple Myeloma Who are Positive at FDG-PET/CT

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Background: The imaging studies are becoming more important for patients with multiple myeloma (MM) to predict prognosis and to find out extramedullary lesions. Several previous studies demonstrated the usefulness of FDG-PET/CT to identify high risk groups for newly diagnosed MM (NDMM) patients. Patients having focal lesions (FLs) more than three (>3) or extramedullary disease (EMD) on PET/CT scan at initial diagnosis frequently showed inferior survival outcomes. PET/CT was especially useful for determining the outcomes of MM patients with Revised International Stratification System (R-ISS) stage II and III. This study evaluated the role of autologous stem cell transplantation for NDMM patients with PET/CT positivity at baseline.

Methods: We retrospectively reviewed medical records of 210 transplant eligible patients with NDMM who performed PET/CT at initial diagnosis between June 2011 and November 2018. The PET/CT positivity was defined as having hypermetabolic FLs more than three (>3) within bones or FDG-avid soft tissue lesions outside bone marrow. All the patients were classified as the R-ISS and treated with frontline therapy containing at least PIs or IMiDs in combination with alkylating agents or steroids.

Results: Among 210 patients, 115 patients (54.8%) were defined as PET/CT positive at baseline, and 54 (25.7%) proceeded frontline ASCT. According to the R-ISS, PET/CT could define high risk group in the R-ISS II and III, while PET/CT positivity was not related with poor outcomes in R-ISS stage I. Among 185 patients with R-ISS stage II and III, median follow-up duration was 21.1 months (range 1.4-66.6) and 2-year progression free survival (PFS) and overall survival (OS) were 44.1% and 78.0%, respectively. Patients with PET/CT positivity showed significantly shorter 2-year PFS (29.7% vs. 59.8%, p< 0.001) and 2-year OS (67.6% vs. 89.6%, p=0.003) than those with PET/CT negativity. Frontline ASCT significantly improved survival outcomes: median PFS (30.5 vs. 18.7 months, p=0.006) and OS (not reached vs. 48.0 months, p=0.012). Among the patients with PET/CT positivity, the survival benefit of ASCT was also observed: median PFS (27.6 vs. 12.6 months, p=0.002) and OS (not reached vs. 34.5 months, p=0.007). However, the patients with PET/CT negativity did not demonstrate significant survival differences by undergoing ASCT (p=0.640 for PFS; p=0.326 for OS). In the multivariate analysis, PET/CT positivity was an independent adverse prognostic factor for PFS (HR 2.85, 95% CI 1.85-4.39, p< 0.001) and OS (HR 2.73, 95% CI 1.42-5.24, p=0.003). Meanwhile, frontline ASCT was independent favorable prognostic factor for PFS (HR 0.45, 95% CI 0.27-0.76, p=0.003) and OS (HR 0.37, 95% CI 0.16-0.85, p=0.020).

Conclusions: PET/CT positivity affected adversely long-term outcomes for NDMM patients. However, frontline ASCT improved PFS and OS for the patients with PET/CT positivity. Therefore, the patients having PET/CT positivity at baseline should consider frontline ASCT to improved long-term outcomes.

Disclosure: Nothing to declare.

P506

Long Term Survival of Multiple Myeloma Patients after Autologous Stem Cell Transplantation (ASCT) in Relation to Availability of Novel Drugs

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Background: Autologous hematopoietic stem cell transplantation (ASCT) after conditioning with high doses of melphalan (Mel200) has indispensible place in the treatment of younger patients with newly diagnosed multiple myeloma (NDMM), especially one's with high risk disease. Until recently, tandem ASCT has been considered as a standard treatment for all patients. Given the relatively low toxicity, having more than one ASCT is feasible and it has been shown that tandem ASCT as the initial part of treatment can significantly deepen the response and prolong survival in certain patient populations.

In the era of new drugs, with the new options for consolidation and maintainance, there is a tendency to abandon this approach, and single or delayed second transplants are increasingly being considered. In the Republic of Croatia, given the availability and financing of new drugs, ASCT (single and tandem) plays a significant role. Although available for 3rd and 2nd line treatment since 2006 bortezomib was approved for reimbursement in first line only recently (2/2018) while lenalidomide was on the market/reimbursed from 10/2014 for 3rd line, and from 2/2018 for 2nd. Other novel agents (pomalidomide, carfilzomib, ixazomib and daratumumab) are reimbursed also recently.

Methods: All patients with multiple myeloma transplanted between 7/2007 and 12/2019 were included in the analysis. In total, 101 patients with MM, 54 men and 47 women were transplanted. Given the availability of new drugs for consolidation and maintenance, our approach during the stated period was to plan, if feasible, a tandem transplant (within 6months).

Results: We performed a total of 165 transplants, that is, 61 tandem, 38 single, 1 double and 1 triple (so-called delayed - in relapse) with 4 patients planned for 2nd ASCT. The median age of patients at 1st ASCT was 58 years (range 28 to 69). Total 69 (60%) patients received bortezomib as treatment before ASCT either as 1st line (29) or 2nd or later (40). The median follow-up of all transplant patients is 36 months (0-133 months). The median overall survival of all patients after the 1st transplant was 89 months. The total transplant-related mortality was < 3%, while the overall response after the last transplant was >90%. No significant differences were found in survival with respect to sex, age, ISS, Ig type, SLC type, renal function, initial treatment or posttransplant maintenance. In patients who have successfully undergone a tandem transplant, there is a trend for better survival than other patients (p=0.05%), but with a correction for early mortality that excluded the possibility of 2nd ASCT, this trend is lost. There is also no difference in survival between patients transplanted before 10/2014 and after (different availability of novel drugs).

Conclusions: In our experience, both single and tandem ASCT represents efficacious and safe procedure in the treatment of MM. Tandem ASCT was not associated with better outcome comparing to single ASCT after excluding the patients with early mortality. Increased availability and prolonged treatment with novel agents will probably lead to further improvement, thus counterbalancing the role of tandem ASCT even in high risk patients.

Disclosure: Nothing to declare.

P507

Multiple Myeloma (MM) in First Relapse Patients. Role of the Second Autologous stem-cell Trasplant (ASCT) in Real Life. Experience of Two Spanish Centers

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Background: The 2nd ASCT is considered as a salvage therapy in the 2016 IMWG guidelines for patients with MM in the 1st relapse, provided that the duration of the response to the 1st ASTC is ≥ 18 months. When is available, the 2nd ASCT source are cryopreserved hematopoietic stem cells (HSC) obtained and stored from 1st ASCT aphaeresis.

The objective is to evaluate the results of the 2nd ASCT as a salvage therapy in patients with MM at their 1st relapse, and to evaluate the impact of new aphaeresis versus cryopreserved HSC infused at 2nd ASCT.

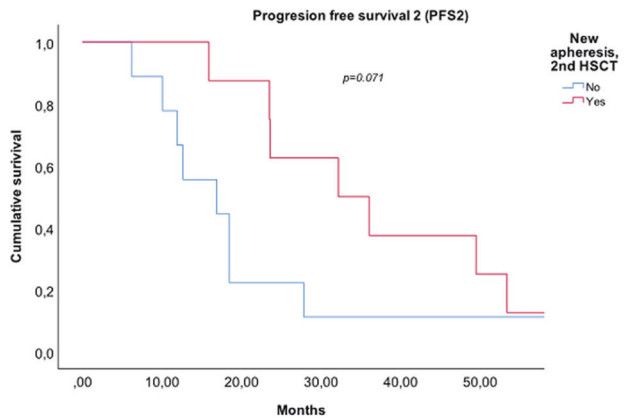
Methods: This is a retrospective observational study involving patients with MM treated with a 2nd ASCT in 1st relapse from January 2000 to November 2019 (last transplant included was performed in February 2018), in the Mútua de Terrassa University Hospital and at the San Llàtzer University Hospital. Patient information has been collected retrospectively

by consulting the medical records. Demographic variables, date of diagnosis, type of MM, previous response to the first and second ASCT, date of first and second ASCT, data related to aphaeresis and adverse events, date of progression, date of last visit and mortality have been included in the database. Descriptive and survival analysis with the Kaplan-Meier method were performed.

Results: 24 double ASCT were included. 70,8% were male, median age was 57,7 years and most frequent type of MM was IgG (58,3%). 33,3% were International Staging System (ISS) stage I, 37,5% ISS stage II and 29,2% ISS stage III. The median follow-up since the diagnosis is 102 months. The overall survival was not reached. The median PFS after the 1st ASCT was 42 months and the median PFS after the 2nd ASCT was 23.8 months.

One half of patients, 12 (50%), were infused cryopreservation HSC and the other half cells obtained by new aphaeresis. Median of CD34x10^6/Kg cells infused was 2.58 (1.7-7.5), being higher in cryopreservation CD34 cells group (3.9 (1.77-7.5) vs 2.1 (1.72-2.67)). Median days of neutrophils and platelets recovery was 7, being a little lower on cryopreserved CD34 cells group (media of 6.5 days). All patients had fever after procedure, but with only 4 positive microbiological isolations (2 E. coli, 1 Staphylococcus sp. and 1 C. difficile). There was not statistically significant difference (p 0.071) in PFS between sources used at 2nd ASCT (Graph 1).

Conclusions: in our series, the 2nd ASCT as a salvage therapy in 1st relapse, allows to achieve a treatment-free time and a prolonged PFS. If we consider the rates of PFS obtained in 1st relapse in the pivotal studies with the new therapeutic combinations (CASTOR DVd 27m, POLLUX DRd 44.5m, ENDEAVOR Kd 22.2m, ASPIRE KRd 29.6m), the 2nd ASCT is still a good treatment option. No statistically significant difference in PFS between the source used at 2nd ASCT are seen, but both median of CD34 cells infused and median days of hemoperiferic recovery was higher in patients infused with cryopreserved HSC from 1st ASCT aphaeresis versus new HSC aphaeresis.



[Graph 1]

Disclosure: Nothing to declare.

P508

Allogeneic Hematopoietic Stem Cell Transplant in Multiple Myeloma: Single Center Experience

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Background: Prognosis of patients with multiple myeloma (MM) has improved in last years due to the important advances in knowledge of biology of the disease and implementation of new drugs. The role of allogeneic hematopoietic stem cell transplant (alloHSCT) is controversial and still reserved for selected young patients with high risk features.

Methods: We retrospectively analyzed 21 patients with MM who received an alloHSCT between 1996-2018. All cases with identical sibling donor, except one haploidentical and another with unrelated matched donor. Most of them received reduced-intensity conditioning (76.2%). Three patients received bone marrow as source of stem cells. The majority of patients were transplanted relapsing after an autologous transplant or as part of a sequential transplant protocol in patients with high risk disease. Only one patient had no previous autotransplant. Patient's characteristics are shown on table 1.

Results: The procedure was, in general, well tolerated. Transplant related mortality (TRM) before day 100th was of one case due to a thromboembolic event. The total TRM was 14.9% (3 cases).

The incidence of acute graft versus host disease (aGVHD) is 23.8%, controlled on most cases with steroids. More than half of the patients developed chronic graft versus host disease (cGVHD).

With a median follow up of 8.2 years, median overall survival (OS) was 37% [IC 95% 24.3-49.6] and estimated progression-free survival (PFS) was 16 months [IC 95% 11.8-20.1]. A total of 6 patients are still alive, 3 of them in long-term complete remission. From the six patients alive, three relapsed and were treated with new drugs: one patient with monoclonal antibody (MoAb) against CD38, one with immunomodulatory drugs (IMiDs) and the other one with combination of MoAb and IMiDs.

Conclusions: There is a need to redefine the role of alloHSCT in the era of the new drugs. Our results are similar to published on literature. In our patients, the morbidity and mortality was acceptable with the limitation of a high rate of cGVHD. Despite the improvements of outcome

because of novel therapies, alloHSCT can be an option for carefully selected patients.

Characteristics	N (%)
Gender Male / Female Age Median age (range), years	10 (47.7%) / 11 (52.3%) 49 (42-56)
Secreted Protein IgG κ IgG λ IgA κ BJ Plasmocitoma	10 (47.6%) 6 (28.6%) 1 (4.8%) 3 (14.2%) 1 (4.8%)
Debut D-S stage I-A II-A II-B III-A III-B Plasmocitoma	1 (4.8%) 6 (28.6%) 2 (9.5%) 8 (38%) 3 (14.3%) 1 (4.8%)
Previous lines of treatment ≤2 3-4 ≥5	7 (33.3%) 12 (57.1%) 2 (9.5%)
Disease status Complete remission Very good partial response Partial remission Relapse	5 (23.8%) 3 (14.2%) 11 (52.4%) 2 (9.52%)
Conditioning regimen Myeloablative Reduced-intensity	5 (23.8%) 16 (76.2%)
GVHD prophylaxis CsA+MTX CsA+CS CsA+MMF	13 (61.9%) 3 (14.3%) 5 (23.8%)
Acute GVHD Yes No	5 (23.8%) 16 (76.2%)
Chronic GVHD Yes No	9 (42.9%) 12 (57.1%)

[Table 1. Patient and transplant characteristics.]

Disclosure: Nothing to declare.

P509

Allogeneic Hematopoietic Stem Cell Transplant in Multiple Myeloma: Single Center Experience

Analys Ruiz, Isabel Iturrate, Isabel Vicuña, Yisele Paz, Ángela Figuera, Adrián Alegre, Beatriz Aguado

Hospital Universitario La Princesa, Madrid, Spain

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Conclusions: There is a need to redefine the role of alloHSCT in the era of the new drugs. Our results are similar to published on literature. In our patients, the morbidity and mortality was acceptable with the limitation of a high rate of cGVHD. Despite the improvements of outcome because of novel therapies, alloHSCT can be an option for carefully selected patients.

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[Table 1. Patient and transplant characteristics.]

Disclosure: Nothing to declare.

P510

Use of Netupitrant/palonosetron in Multiple Myeloma Patients Receiving High-dose Melphalan and Autologous Stem Cell Transplantation: A Single Centre Experience

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Background: Chemotherapy-induced nausea and vomiting (CINV) is one of the most significant non-hematologic adverse effects that often compromises the quality of life in patients receiving high-dose chemotherapy. This single-centre, open-label, prospective, observational study was designed to assess the efficacy of Netupitant / Palonosetron (NEPA) in the prevention of acute and delayed CINV in Multiple Myeloma (MM) patients receiving high-dose melphalan at dosage of 200 mg/mq (HDM) and autologous stem cell transplantation (ASCT).

Methods: All patients received antiemetic prophylaxis with multiple dose of NEPA at a dose of 1 capsule (300 mg netupitant; 0.5 mg palonosetron) 1 h before the start of HDM and repeated administration after 72 h and after 120 h. All patient underwent oral cryotherapy for the prevention of mucositis during the administration of the HDM. The primary endpoint for the study was to evaluate the efficacy of NEPA in terms of rate of complete response (defined as no emetic episodes and no-need for rescue therapy) during the HDM administration and within 15 days after the end of the chemotherapy. The secondary endpoints were: the rate of complete control (defined as no emetic episodes, no need for rescue therapy and no significant nausea); the incidence of nausea and vomiting of any grade during the HDM administration and within 15 days after the end of the chemotherapy; the efficacy of a second and third dose of NEPA to prevent breakthrough emesis. The occurrence of breakthrough emesis after 72 hours was considered as treatment failure. The safety of NEPA was also evaluated. The number of vomiting episodes, the grade of nausea, adverse events, and need for rescue therapy were recorded in patient diaries according to standard policy for data management. 81 consecutive patients were enrolled.

Results: A complete response was observed in 67.7% of patients. The percentage of patients who attained a complete control was 18.3%. Grade 1 nausea and vomiting were experienced by 81.8% and 11.9% of patients, respectively; grade 2 nausea and vomiting were reported in 18.2% and 9.6% of patients, respectively. No patients had grade 3-4 nausea and vomiting. For 86.36% of patients, a rescue therapy was not necessary. Indeed, breakthrough emesis occurred in 13.6% of patients, who received Levosulpiride as a salvage treatment.

Conclusions: In this study, NEPA emerged as a safe, innovative and effective antiemetic option for MM patients receiving HDM treatment followed by ASCT.

Disclosure: Nothing to declare.

P511

Safety and Effectiveness of Autologous Stem Cell Transplantation in Patients with Multiple Myeloma in First Line

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Background: Despite availability of new treatments, multiple myeloma (MM) is still an incurable disease. Autologous Hematopoietic Stem Cell Transplantation (AHSCT) as consolidation treatment after intensive chemotherapy is nowadays considered first-line standard in "fit" patients". The role of AHSCT as consolidation treatment has been disputed due to new induction regimes with better responses results, better progression-free survival (PFS) and new rescue regimes today available. Our aim is to analyze results of patients undergoing AHSCT in our center.

Methods: Retrospective analysis of patients with MM who received AHSCT between 2015 and 2018 in a single center using "IBM SPSS Statistics 20". Our aim is to classify achieved responses after induction and achieved responses after AHSCT. We used GEM (Spanish Myeloma Group) response criteria adapted from the International Myeloma Working Group (IMWG).

Results: 27 AHSCT of patients with MM were performed. Associated factors with worse prognosis were non-IgG MM subtype (34%) and ISS III at diagnosis (30%). 17.7% of patients had poor prognosis cytogenetics. 11.11% of patients received immunomodulator with proteasome inhibitor as first induction line and 18.5% of patients required a second line to improve response before TAPH. 62.9% of patients presented optimal response prior to TAPH. 96.3% of patients improved or didn´t worsen their response after transplantation. 44.5% patients were reported being 7.4% of them exitus due to disease progression. 75% of relapsed patients had received TAPH in suboptimal response. PFS was 25.8 months (range 19.9-31.7) and OS was 43.2 months (range 39.8-46.6).

Conclusions: Our results in terms of PFS and OS are similar to larger published series in literature. Larger and comparative studies, clinical trials which are already being carried out, and longer follow-up studies are necessary to clarify the role of TAPH. In our experience it is a safe procedure which improves patient responses and probably PFS, so it seems to be still a very good option in first line treatment.

Disclosure: Nothing to declare.

P512

Plasmapheresis Assisted the Treatment of 1 Case of Hyperglobulinemia after Cart Therapy

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Background: Multiple myeloma (MM) is a plasma cells cancer, more common in elderly people and can't be cured by drugs. Once relapse, the prognosis is extremely poor. B cell maturation antigen(BCMA) has shown a higher complete remission(CR)rate in r/r MM patients, but cytokine release syndrome(CRS) and neurotoxicity can be life-threatening in these patients.

We analyzed the effect of therapeutic plasma exchange (TPE) in adjuvant therapy of hyperglobulinemia during CRS for a r/r MM patient who had central nervous system leukemia(CNSL) after BCMA-CART therapy.

Methods: A 66-year-old male patient was diagnosed MM 4 years and had the second relapse. After bone marrow examination, abnormal plasma cells expression of BCMA was confirmed by flow cytometry(FCM). So BCMA-CART cell therapy was started, and before CART infusion, fludarabine with cyclophosphamide were gaven,

D4 after BCMA-CART cells infusion, he complained the heart rate(HR) was slightly increased. D7, HR was up to 140 beats/min. D8, the patient developed fever above 38°C, the body temperature could be temporarily reduced to normal after oral administration of ibuprofen suspension. D9, the patient developed persistent high fever above 40°C and no response to antipyretic drugs. His HR reached 170 beats/min, dyspnea and obvious hypourocrinia occurred. Biochemical examination indicated that globulin and creatinine elevated, and the increase of cytokines in patients, it was worried that fatal complications might be occurred by CRS, so high-dose methylprednisolone(MP) combined with TPE therapy was given! COBE Splectra 6.1 blood cell separator and TPE model was used. Red blood cells and platelets were injected before replacement to prevent hypovolemic response and potential bleeding risk. Femoral vein hemorrhage and venous return of the arm were selected and replaced once a day for three consecutive days, and sodium citrate was given for anticoagulation. During the replacement process, ecg monitoring was continued, and oral calcium gluconate oral solution was used to prevent low calcium reaction. The replacement process was smooth and the vital signs were stable. The plasma volume of each exchange was 4000ml, 3000ml and 2000ml, and the exchange rate was 25-30ml/ min. Changes in globulin and creatinine before and after replacement were monitored.

Results: This case, globulin was elevated and renal function was impaired. After MP combined with TPEt, the clinical symptoms were improved. Globulin was significantly reduced. Before replacement, globulin was detected at 96g/L, which was reduced to 35.5g/L after three times of replacement, with an effective clearance rate of 62.6%. However, the removal effect of creatinine was not obvious, and the creatinine level returned to normal after treatment with glucocorticoid.搜索

Conclusions: TPE can significantly reduce globulin and improve patients´ clinical symptoms. Combined with other therapy, it is effective and safe for hyperglobulinemia caused by CART. In addition, TPE can create conditions for simultaneous or follow-up treatment, prolong the time, and help more patients pass through the CRS after BCMA-CART.

Disclosure: Nothing to declare.

Myelodysplastic syndromes

P513

Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) in Patients with Therapy-related Myeloid Neoplasm: A Study from The Chronic Malignancies Working Party of the EBMT

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Background: Patients with t-MN have a poor prognosis and HSCT represents the only curative treatment. We here report the outcomes of patients who received HSCT for a t-MN (excluding post MDS, MPN and CMML) with the hypothesis that the primary cancer impacts the outcome.

Methods: From the EBMT registry, patients with MDS or AML occurring after a primary cancer who then received a HSCT between 2006 and 2016 were included. OS and RFS were analyzed using Kaplan Meier curves and log-rank test. Relapse and NRM were analyzed as competing risks with cumulative incidence curves and Gray´s test.

Results: 2334 patients were identified. Primary cancers were CLL in 102, non-Hodgkin lymphoma (NHL) in 668, Hodgkin lymphoma (HL) in 235, plasma cell disease (PCD) in 111, breast cancer in 643 and other solid tumor (ST) in 575. 981 patients had MDS and 1353 had AML at the time of transplantation. Performance status by Karnofsky score was 90 or higher in 1376 (59%) patients. 722 (31%) patients were transplanted from HLA matched sibling donor (SIB) and 843 (36%) received a MAC. 1307 patients were in remission at the time of transplantation: 29% of MDS and 76% of AML patients.

Three-year OS and RFS were 34%(32-36) and 32%(30-34) respectively. OS and RFS were impacted by the primary cancer: post NHL (30% and 27%), post HL (29% and 28%), post ST (34% for both), post breast cancer (41% and 37%), post CLL (34% and 31%) and post PCD (32% and 25%) ($p< 0.001$). CR status at HSCT did not affect outcomes in MDS patients (30%). NRM was lower in patients with breast cancer (24% post breast cancer, 36% post NHL, 33% post HL, 29% post ST, 34% post CLL, 26% post PCD $p< 0.001$). Relapse rate was higher after RIC (33% vs. 28%, $p=0.014$) but was not influenced by the primary type of cancer.

The multi-variables Cox models included age, regimen intensity, donor type, Karnofsky score, t-MN category (AML in CR, AML not in CR, MDS) and the primary type of cancer. Patients with HL (HR:1.36, $p=0.005$) or NHL (HR:1.31, $p=0.001$) had a higher adjusted risk of death than patients with other primary diseases. Other risk factors for OS were t-MN type (AML not in CR, HR:1.45, AML in CR, HR:0.76, MDS = reference, $p< 0.001$), type of donor (no SIB, HR:1.20, $p=0.004$) and performance status (HR:1.34, $p< 0.001$). Patients with HL (HR:1.24, $p=0.05$) or NHL (HR:1.21, $p=0.01$) had also a higher adjusted risk for RFS than patients with other diseases. Adjusted t-MN relapse risk was not influenced by the primary cancer. NRM risk was significantly higher in patients with NHL (HR: 1.52, $p< 0.001$), HL (HR:1.58, $p=0.007$) and CLL (HR:1.55, $p=0.039$) than in patients with primary solid tumor or PCD. Other risk factors for NRM were age (HR:1.15, $p=0.01$), MAC (1.29, $p=0.006$), t-MN (AML in CR, HR: 0.76, $p=0.005$; AML not in CR, HR:1.29, $p=0.05$), performance status (HR:1.22, $p=0.03$).

Conclusions: The type of primary cancer influenced outcomes with lower mortality, especially NRM in patients with prior solid tumor or PCD as compared to patients with a history of lymphoma.

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P514

Impact of Mutation Profile in Chronic Myelomonocytic Leukemia undergoing Allogeneic Hematopoietic Cell Transplantation

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Background: Current risk stratification for newly diagnosed chronic myelomonocytic leukemia (CMML) includes clinical and genetic features. We aimed to investigate the molecular profile of CMML patients

undergoing hematopoietic cell transplantation (HCT) and its role on outcome.

Methods: Next-generation sequencing was performed on samples collected prior to HCT. Patients with transformation to acute leukemia were excluded. Top predictors of overall survival (OS) outcome were identified using Cox regression resulting in hazard ratios (HR).

Results: The total cohort consisted of 192 patients (8 with CMML-0, 105 with CMML-1, and 79 with CMML-2) with a median age of 60 years. The median follow-up was 64 months and median OS was 34 months for the total cohort and differed for CMML-0 (not reached), CMML-1 (51 months), and CMML-2 (15 months). 5-year incidence of relapse and non-relapse mortality (NRM) were 27% and 37% for the total cohort.

Frequencies according to risk groups using the molecular CMML-specific prognostic scoring system (CPSS-mol) were 6% (low risk), 18% (intermediate-1 risk), 40% (intermediate-2 risk), and 36% (high risk). Transplants were mostly received from matched unrelated donors (51%). Conditioning intensity was reduced (49%), myeloablative (43%), or non-myeloablative (8%).

Most frequently mutated genes were: TET2 (63%), ASXL1 (47%), SF3B1 (42%), SRSF2 (33%), DNMT3A (27%), NRAS (23%), EZH2 (21%), RUNX1 (19%), ZRSR2 (19%), and SETBP1 (17%). Ninety-two percent of patients showed at least one somatic mutation and >3 mutations were present in 55% of all patients.

In the first step, we identified ASXL1, KRAS, SF3B1, and ZRSR2 as high-risk mutations (HRM) predicting worse OS. In addition, the number of the HRMs influenced outcome and accounted for most of the outcome variance of the number of all mutations. Thus, we identified 3 distinct molecular risk groups: the absence of HRMs (reference; low risk), presence of 1-2 HRMs (HR, 1.92; intermediate-risk), and 3-4 HRMs (HR, 3.11; high-risk). Corresponding median OS was not reached for the low-risk group, 33 months for the intermediate-risk group, and 13 months for the high-risk group ($P< 0.001$). Notably, HRMs showed distinct NRM being 16% for low risk, 38% for intermediate risk, and 51% for high risk ($P=0.02$). In contrast, the CPSS-mol genetic risk classification including ASXL1, RUNX1, NRAS, and SETBP1 mutations as well as current cytogenetic categories showed no distinct OS nor NRM. Other clinical variables in univariable analyses were increasing percentages of peripheral and bone marrow blasts, worse performance status and comorbidity index, higher leukocyte counts, and male sex. Donor relation and conditioning intensity were not associated with outcome.

Last, independent predictors for worse OS in multivariable analysis were molecular risk, increasing percentages of circulating and bone marrow blasts, and higher comorbidity index. This multivariable model showed a concordance index of 0.701 suggesting improved prognostic ability compared with all currently existing models such as CPSS-mol (0.597), CPSS (0.572), molecular Mayo model (0.580), and GFM score (0.579).

Conclusions: In conclusion, mutations in ASXL1, KRAS, SF3B1, ZRSR2, and the number of these mutations predict OS and NRM in CMML undergoing HCT. Accounting for these lesions may improve the prognostic precision and facilitate patient counseling.

Disclosure: Nothing to declare.

P515

Outcome and Mutational Profile in MDS Patients undergoing Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Myelodysplastic syndrome (MDS) is heterogeneous group of clonal hematological malignancies with highly variable clinical course. We analyzed the mutational profile in patients with MDS undergoing allogeneic hematopoietic stem cell transplantation (alloHSCT) which is currently the only treatment option with curative potential in this disease category.

Methods: Twenty-six patients were included in the study with median age 45 (18-65) years. Among them 10 patients were classified as MDS-RAEB 1, 14 - RAEB 2, 1 - MDS-MLD, 1 - 5q-syndrome. Six patients belonged to very high IPSS-R risk, 14 - high, 5 - intermediate, 1 - low. Four patients were diagnosed with secondary MDS, 22 - with primary MDS. The majority of patients (22) were treated with hypomethylating agents before alloHSCT. Reduced intensity conditioning was performed in 19 patients, myeloablative - in 7 patients. Graft versus host disease (GVHD) prophylaxis consisted of tacrolimus/mophethyl-mycophenolate and antithymocytic globulin (ATGAM 60 mg/kg or thymoglobuline 5 mg/kg) (11) or posttransplantation cyclophosphamide 50 mg/kg D+3,+4 (15). AlloHSCT was performed from unrelated (21), related (3) and haploidentical (1) donor. Stem cell source was granulocyte colony-stimulating factor mobilized peripheral blood progenitor cells (17) and bone marrow (9). Median number of CD34+cells/kg was 4,4 x 10^9 (1,4-8,5). Next generation sequencing was performed to analyze mutations in epigenetic regulators TET2, IDH1,2,

ASXL1, DNMT3A, SF3B1, and TP53 genes. Also we analyzed mutations in T cell inhibitory receptor genes: CD274, CD276, CTLA4, LAG3.

Results: Median follow up was 24 months (3-98). Engraftment was documented in 23 (89%) patients. Median time to neutrophil, platelet, leukocyte engraftment was 21 (14-43), 20 (11-49), 21 (12-43) days, respectively. Acute GVHD grade 2-4, grade 3-4 and chronic moderate/severe GVHD were documented in 26%, 17% and 26%, respectively. Three-year relapse rate was 38%, 1-year non-relapse mortality - 15%, 3-year overall and progression free survival was 58% (95%CI 35-75%) and 36% (95%CI 17-25%). Pathogenic mutations in ASXL1 were detected in 42% of cases. The incidence of mutations in TET2 was 30%, IDH1,2 - 15%, DNMT3A -4%. Twenty-six percent carried 2 or more mutations simultaneously. Thirty percent of patients had pathogenic mutations in SF3B1 - 30%, TP53 - 8%. Mutations in T cell inhibitory receptor genes were identified only in a small proportion of patients: CD274 - 4%, CD276 - 8%, CTLA4 - 8%, LAG3 - 4%.

Conclusions: Expression of various molecular markers differs substantially among MDS patients. The further researches in the field of immunotherapy susceptibility and mutational status of immune checkpoint genes are necessary for discovering of new therapeutic approaches in MDS and developing more fine-tuned prognostic models.

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New drugs- and cell-based immune therapies

P516

Nivolumab Increases Antigen Specific Immune Responses Against Leukemic Progenitor and Stem Cells (LSC/LPC)

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Background: The efficacy of immunotherapies in cancer treatment has become more important in recent years in different solid tumors, but also in hematological malignancies. The potency of immune therapeutic approaches such as chimeric antigen receptor T cells, immune-checkpoint inhibitors, or bi-specific T cell activating antibodies is becoming increasingly obvious. Leukemia-associated-antigens (LAA) might be relevant for the elimination of malignant cells by cytotoxic T cells (CTL), since they represent immunogenic structures to target malignant cells.

At the same time, mechanisms of immune responses involved and responsible antigen structures have to be further elucidated.

Methods: We investigated the influence of the anti-programmed-death 1 antibody (anti-PD-1) Nivolumab on antigen-specific immune responses by CTL against leukemic myeloid progenitor and stem cells (LPC/LSC) in functional T cell assays using ELISpot, Tetramer-analysis and Colony Forming Immunoassays (CFI). Expression of different LAA, such as PRAME (P300), RHAMM (R3), Wilms' Tumor 1 (WT1) and Proteinase 3, was correlated to functional T cell assays.

Results: CFI showed a significant inhibition of colony forming units in 50 AML patient samples when adding LAA-specific CTL. In all patient samples, T cells activated against at least one LAA were successful to decrease the colony number significantly. The intensity of immunogenic reactions using the LAA P300 as target ranged from 14-86% (mean: 44 %), for WT1 from 0-85% (mean: 40%), and for R3 from 0-90% (mean: 48%). Specific immune responses were detected by ELISpot assays and correlated to results detected in CFI. Immune effects increased considerably when Nivolumab was added to CTL for several days before starting CFI. Notably, no effect was measured when CTL were incubated with Ipilimumab only. The combination of Nivolumab and Ipilimumab showed no additional effect of immune responses compared to Nivolumab alone.

Conclusions: Taken together, the immune checkpoint inhibitor Nivolumab increases specific T cell responses of LAA-stimulated cytotoxic T cells and the cytotoxic effect of T cells against LPC/LSC. No additional effect was detected with Ipilimumab. These data suggest that anti-PD-1 antibodies could be an immunotherapeutic approach in AML and combination with LAA-directed vaccination strategies might open interesting application possibilities.

Disclosure: JG only has poteial conflict of interest to declare. with BMS (Bristol-Myers Squibb).

P517

Eltrombopag for the Treatment of Poor Graft Function following Allogeneic Stem Cell Transplants : A Multicenter Survey Update

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Background: The occurrence of cytopenia following an HSCT has been reported to occur in 25% of patients within day +100. Infections and/or GvHD have been reported as predictive factors. Treatment with CD34 selected cells from the same donor, has been reported as an effective form of therapy. This implies the availability for a second donation from the same donor; The median interval between CD34 boost infusion and trilineage recovery is over 3 months. Eltrombopag (EPAG) has been recently shown to be effective in the management of patients with SAA. The hypothesis is that EPAG would be effective to treat poor graft function (PGF): it was defined as cytopenia requiring transfusions, in the presence of complete donor chimerism.

Methods: Forty eight patients were retrospectively collected among 5 Centers and they received EPAG for uni, bi or trilineage cytopenia, after HSCT from January 2012 until May 2019

Results: The diagnoses were acute myeloid leukemia (n=17); acute lymphoblastic leukemia (n=6), mielodysplastic syndrome (n=6); myelofibrosis (n=9); chronic myeloid leukemia (n=1); lymphoproliferative disorders (n=7); severe aplastic anemia (n=2); there were 22 male and 26 female with a median age of 55 years (rang: 24-71). Disease phase at transplant was CR (n=29), PR (n=8) and stable disease (9). Conditioning regimen was: fludarabine and busulfan in 11 patients; thiotepa, fludarabine and busulfan in 25 patients; TBI and cyclophosphamide in 2 patients and reduced intensity conditioning in 5 patients and others in the remaining 5 patients. GvHD prophylaxis was cyclosporine (CSA) mycophenolic acid (MMF) in 28 patients, CSA and methotrexate in 14 patients, CSA alone in 1 patient and other in 5 patients.

Three donor were identical siblings; seven were mismatched related donors; twenty were haploidentical family donor and sixteen were matched unrelated donors. Stem cell source was bone marrow in 21 patients, peripheral blood in 22 patients and unknown for the remaining 5 patients. Major ABO mismatch was present in 11 pts; minor was in 10 pts, while 22 pts were matched for ABO

Median CD34 cell dose infused was 4.6 x10^6/kg (range 0.6-7.7). Neutrophil engraftment (>0.5x10^9/L) was achieved in all patients, with a median interval of 19 days (12-37) and platelets engraftment (>20x10^9/L) was 28 days (11-89). Platelet recovery was not reached in 23 patients.

Partial response (PR) was defined as transfusion independency; complete response (CR) was defined as normalization of peripheral blood counts.

EPAG was started at a median interval from HSCT, on day + 95 (range 17-877) and was given for a median time of 120 days (range 10-591), at a dose of 25-100 mg/day. Transfusion independence was reached at a median interval of 2 months after initiation of EPAG treatment (range 1-10) Two patients also received EPO and GCSF together with EPAG, for trilinear cytopenia.

Twenty-four patients (50%) had a complete response, 10 patients had a partial response (21%), reaching transfusions independence, while 12 patients (25%) had no response. Six patients still continue treatment wit EPAG.

Conclusions: EPAG is effective in patients with PGF, following an allogeneic HSCT. These data warrant a prospective trial

Disclosure: No disclosure to declare.

P518

Donor NK Cells Infusion as a Strategy of Immunotherapy to Prevent HHV6 Reactivation in Pediatric Patients after CD45RA-depleted Transplantation

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Background: HHV-6 reactivation has been reported in 30-70% of patients after hematopoietic stem cell transplantation (HSCT) especially during the first month. Delayed immune reconstitution (IR) is a risk factor to develop HHV-6 encephalitis. The incidence of this complication is low (0.95 to 11.6%). Our group has reported a 34% cumulative incidence of HHV-6 encephalitis in pediatric patients receiving haploidentical HSCT with CD45RA-depletion. NK cells act against infected and transformed cells as part of innate immunity. When infection occurs, NK cells control virus dissemination acting against HHV-6-infected peripheral blood mononuclear cells.

NK cells infusion could provide functional cells to protect against infections and to control HHV-6-infected cells in peripheral blood. We present our experience with NK cells infusion at day +7 post-HSCT after CD45RA-depleted transplantation to assess safety and infections rate focusing on HHV-6 reactivations and encephalitis.

Methods: A total of 14 patients received NK cells infusion on day +7 after CD45RA-depleted HSCT following non-myeloablative conditioning. NK product was obtained performing CD3 depletion on donor non-mobilized leukapheresis product followed by CD56 enrichment using the CliniMACS® device. Protocol also included donor CD3+CD45RO+ lymphocyte infusion on a prophylactic regime on days +30, +60 and +90 ($1x10^7$/Kg) to boost immune reconstitution.

Results: Fourteen pediatric patients median age 8,5 years (range 1-16), 13 with malignant diseases (8 ALL, 4 AML, 1 MDS) and 1 aplasia, received CD45RA-depleted grafts from haploidentical (11) and match related donor (3).

NK cells were infused on day +7 post-HSCT with a median dose of $7,3x10^6$/Kg (range $7,3x10^5$/Kg-$2x10^7$/Kg). There was only one infusion reaction in a patient. Two of 14 patients died, one patient with refractory disease died on +8 due to abdominal sepsis, the other patient died at day +135 due to respiratory sepsis due to multiresistant Serratia. One patient presented a hyperacute graft failure during a haemophagocytic syndrome. The remaining patients presented full donor chimerism and were on complete remission at last follow up.

Five patients presented acute GvHD≥grade II (35,7%) non-related with NK infusion. There were 3 CMV and 2 Adenovirus reactivations. Two patients presented mild Parvovirus infection. HHV-6 reactivation occurred in 2 patients, one of them was complicated with enteritis. No HHV-6 encephalitis was seen after a median follow up of 221 days (range 8-575 days).

Conclusions: Our preliminary data suggest that infusions of NK in the early post-HSCT (day +7) are a safe adoptive immunotherapy strategy to prevent HHV-6 encephalitis and other viral reactivations after CD45RA-depleted transplantation. In our series there were less viral reactivations observed, and no patient presented HHV-6, CMV nor EVB disease. However, to determine the real efficacy of this strategy, a larger number of patients and prospective studies are required.

Disclosure: Nothing to declare.

P519

Development of Cell Vaccine Based on Autologous Dendritic Cells Loaded with Lipid Nanoparticles Containing CMV PP65 Messenger RNA

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Background: Infection with human cytomegalovirus (CMV) is a significant cause of morbidity and mortality in solid organ and hematopoietic stem cell transplant (HSCT) recipients. After transplantation, an active cytomegalovirus infection usually develops in the first four months. The source of infection can be the reactivation of own CMV or re-infection of the recipient through donor cells, transfusion of blood and its components. Immunosuppressive therapy leads to conditions that contribute to development of CMV diseases due to a lack of cells that could fight the infection. Therefore, it might be beneficial to induce the immune response before meeting a real infection.

Methods: We tested mononuclear cells from 5 CMV seronegative healthy volunteers. All volunteers did not have neither CMV-specific IgM nor IgG. Part of the cells was used for the creation of monocyte-derived dendritic cells (DCs), and the other part - for $CD3^+CD45RA^+$ cells isolation. DCs were generated from monocytes in the presence of IL-4 and granulocyte-macrophage colony-stimulating factor. Maturation was induced at day 7 through addition of tumor necrosis factor-α for 48 hr. After dendritic cells maturation, lipid nanoparticles (LNPs) containing CMV pp65 messenger RNA (mRNA) were added. Dendritic cells were analyzed by flow cytometry with antibodies to CD83, CD86, HLA-ABC and HLA-DR 1 day after the addition of LNP. DCs loaded with LNPs CMV pp65 mRNA (DC^+) were cultured with CD3 cells from the same donor for 1 day. Control DCs were generated using the same method without incubation with LNPs containing CMV pp65 mRNA (DCs^-). The ratio of DCs to $CD3^+CD45RA^+$ cells was 1 to 10 ($20*10^3$ DC to $200*10^3$ $CD3^+CD45RA^+$ cells). Detection of CMV pp65-specific T cells was performed by IFNγ ELISpot assay. Frequencies of CMV pp65-specific IFNγ-secreting cells were calculated by ImmunoSpotâ MultiPlate AutoCount™. The result is considered positive if the value of antigen-specific spot count was more than 10 per well.

Results: Mature dendritic cells exhibited high expression of CD83, CD86, HLA-ABC and HLA-DR. No CMV-specific T cells were detected after incubation of $CD3^+CD45RA^+$ with a CMV pp65 peptides pool (without DCs). The value of IFNγ-producing cells did not exceed 10 after incubation of DCs^- with $CD3^+CD45RA^+$ cells and these values were subtracted from the values that were in the wells with DCs^+ and $CD3^+CD45RA^+$. Induction of CMV-specific T-cell responses was detected in all cases after incubation of DCs^+

and $CD3^+CD45RA^+$ cells. The median frequency of CMV pp65-specific T cells after cultivation with DCs loaded with NLP containing CMV pp65 mRNA was 27 (from 10 to 38) per $200*10^3$ $CD3^+CD45RA^+$ cells.

Conclusions: DC vaccines induced a CMV-specific cellular response in all healthy CMV-seronegative volunteers, that providing a base for its further exploration in larger cohorts. We have also shown that lipid nanoparticles are a good way to deliver CMV mRNA to cells. We suggest this strategy of development of cell vaccine based on autologous dendritic cells loaded with LNPs containing CMV pp65 mRNA may reduce the risk of developing CMV infection in patients after HSCT.

Disclosure: Nothing to declare.

P520

Smac Mimetics (SM) and Natural Killer (NK) Cells - A Promising Combination to Overcome Cell Death Resistance of Rhabdomyosarcoma (RMS) Cells

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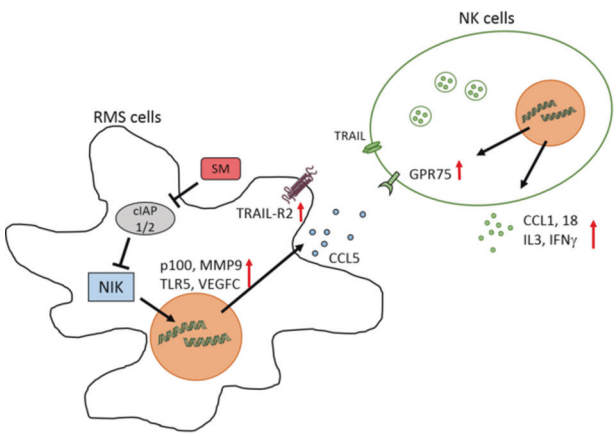
Background: Dysregulation of inhibitor of apoptosis proteins (IAPs) is one underlying mechanism causing cell death resistance of rhabdomyosarcoma (RMS) cells. Smac mimetics (SM) mimic the endogenous antagonist of IAPs called Second mitochondria-derived activator of caspases (Smac) and can counteract IAP mediated cell death resistance and restore the pro-apoptotic machinery (Fulda & Vucic 2012). Former studies showed that SM sensitize RMS cells to a pro-death commitment. This sensitization can be exploited by co-cultivation with NK cells, leading to an increased NK cell-mediated killing of RMS cells (Fischer et al. 2017).

Methods: The molecular mechanism of this sensitizing effect of SM was investigated by an exploratory transcriptome analysis using RNA sequencing. Hypothesized and newly discovered signaling pathways were validated by qPCR, Western blot and ELISA. Analysis of surface expressing receptors or ligands was performed by flow cytometry. Cell death induction of RMS and NK cells was measured by PI/Hoechst staining on a high throughput fluorescence microscope. To model a more in vivo situation, a three-dimensional RMS spheroid was formed and assessed using the IncuCyte® platform.

Results: On RMS cells, SM sensitize towards TRAIL mediated cell death. Further, SM lead to an upregulation of the respective death receptor TRAIL-R2 on the cell surface. A direct impact of the SM is the degradation of cIAPs, leading to the activation of the non-canonical, NIK dependent NF-κB signaling pathway. The explorative RNA sequencing approach led to the discovery of the SM mediated transcriptional upregulation of genes regarding calcium and PLC signaling functions (i.e. GDPD5, CCL5, PLCH2, CAMK1G, CAMK2A) followed by a transcriptionally induced putative bimodal feedback mechanism of the canonical and non-canonical NF-κB signaling pathways.

On the NK cell side, pretreatment of RMS cells with SM can increase the NK-mediated specific lysis of RMS cell. This increase of specific lysis is also true in a more complex spheroid model, were RMS spheroids pre-treated with SM showed a faster killing kinetic. RNA sequencing revealed a transcriptional change in NK cells after contact with RMS cells. This includes the upregulation of several biological processes, e.g. cell differentiation (NR4A3), response to cytokines (IL3, PLAU) and chemotaxis (CXCL8, NR4A1, CCL1, CCL18, IFNg).



[Smac mimetic mediated interaction of rhabdomyosarcoma and NK cells]

Conclusions: Aforementioned experiments provide evidence for a complex sensitizing effect of SM on RMS cells. The transcriptional activation might facilitate a shift of immunological cold tumor cells towards a more immunological hot phenotype, i.e. secretion of immunostimulatory

chemokines. RNA sequencing could identify CCL5 as highly upregulated by SM treatment of RMS cells. In NK cells upon contact with SM treated RMS cells, the transcription of GPR75, a non-canonical CCL5 receptor, is upregulated. This axis and the mentioned molecular mechanisms require comprehensive study, which will aid the development of a novel SM - NK cell based immunotherapy.

The graphical abstract displays the transcriptional upregulation of selected target genes within SM treated RMS cells and NK cells. Further, it depicts the CCL5-GPR75 axis induced by a RMS-NK cell-cell contact upon SM pretreatment.

Disclosure: Nothing to declare.

P521

Role of Exosomes as Promotors or Biomarkers To Study Activation of Leukemia-derived Dendritic Cells (DCLEU)-mediated Antileukemic Activation of Adaptive and Innate Immune-reactive Cells against AML-blasts

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Background: Antileukemic responses of immune reactive cells in AML-patients need to be improved. Combinations of blast-modulatory kitM (GM-CSF+PGE1) (vs control) convert myeloid blasts into dendritic cells of leukemic origin (DCleu), that effectively activate immune-cells against leukemic blasts.

Exosomes are small (30-150 nm) membranous vesicles of endocytic origin produced by all cells under physiological and pathological conditions. Their involvement in nearly all aspects of malignant transformation has generated much interest in their biology, mechanisms responsible for information transfer and their role in immune-surveillance as well as -escape.

Exosomes secreted by dendritic cells (DCs) have been shown to allow efficient activation of T lymphocytes, displaying potential as promoters of adaptive immune responses.

Methods: 1)DC/DCleu-culture of blast containing AML patients' whole blood (WB) (n=10) and of healthy volunteers(n=8) with kits, T-cell enriched mixed lymphocyte culture (MLC) with kit- vs un-treated WB, functional blast-cytotoxicity and, leukemia-specificity assays (Degranulation/intracellular cytokine-assays), Flowcytometric evaluation of blast-, DC- and lymphocyte composition before or after cultures.

2)Exosomes were isolated by immunoaffinity from serum, DC- and MLC-culture supernatants of 3 AML patients and 3 healthy volunteers. Exosomes were negatively stained and characterized by transmission electron microscopy (TEM). Fluorescence nanoparticle tracking analysis (fNTA) was performed to determine exosomal size and -concentration. Obtained results were compared in AML and healthy volunteers.

Results: Addition of kitM to blast-containing WB significantly increased frequencies of mature DC/DCleu and their subtypes compared to untreated WB without induction of blasts' proliferation. Immune monitoring showed a continuous increase ofactivated/ proliferating cells of the adaptive and innate immune system after Tcell-enriched MLC using kitM pretreated vs -untreated WB, suggesting a production/activation of (potentially leukemia-specific) cells after kit-stimulation. Moreover kit-pretreated WB regularly and significantly improved provision, activation as well as antileukemic and leukemia-specifically directed immune reactive cells after MLC.

TEM showed exosome-like structures with a typically cup-shaped appearance without any differences between healthy and AML samples. fNTA revealed average vesicle sizes of 177±23 nm (healthy) and 178±17 nm (AML). Higher levels of EVs were detectable in AML samples compared to healthy controls in serum and after DC-culture, but lower levels after MLC independent of culture conditions. Interestingly, the number of EVs increased during cultivation of DC of AML and healthy samples, but not in AML-derived MLC samples.

Conclusions: We will provide data in AML patients and healthy volunteers about a potential role of DCs- and MLC-derived exosomes as biomarkers in immune responses, malignant progression or as potential therapeutic targets for AML patients.

Disclosure: Nothing to declare.

P522

Blinatumomab for the Treatment of Relapsed/refractory B-acute Lymphoblastic Leukemia: Report from a Single Center

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Background: Blinatumomab is a bispecific T-cell engager (BiTE) antibody construct with dual specificity for CD19 and CD3, approved by FDA for the treatment of relapsed or refractory (R/R) precursor B-cell ALL, on the basis of results from two clinical trials, TOWER and ALCANTARA. We collected data about 10 patients, treated at our Institution from September 2015 until now.

Methods: There were 5 male and 5 female, with a median age of 49 years (range 28-70); 6 pts were positive for Philadelphia chromosome, 4 negative, with a normal karyotype, except one with trisomy 21, affected by Down syndrome; status disease was: morphological relapse in 4 pts; molecular relapse in 3 pts, refractory disease in 3 pts. All pts, except 1, received Blinatumomab as compassionate use. In each cycle, pts received treatment for 4 weeks. During cycle one, dose was 9 μg/day for 1 week, then 28 μg/day for 3 weeks to reduce risk of cytokine release syndrome. For subsequent 4 week cycles dose was 28 μg/day, followed by two treatment-free weeks. Two out 6 pts who relapsed after HSCT, received DLI during the two treatment-free weeks and after the end of treatment and another one before. All pts were submitted to central nervous system (CNS) chemotherapy prophylaxis. All 6 pts with bcr-abl transcript were treated with tyrosin-kinasi inhibitors (TKI), but in particular 2 patients continued ponatinib during Blinatumomab infusion.

Results: Four out ten pts (40%) completed all 4 cycle, without complications; treatment was interrupted during first cycle in two pts (20%) for onset of neurological symptoms, such as confusion, seizures, tremor and in other 3 patients (30%) for progressive disease, one for extramedullary disease. One patient completed two cycle, obtaining second molecular remission and he was submitted to alloHSCT from MUD. Among 6 pts relapsed after HSCT, DLI was performed in 2 pts during Blinatumomab treatment. After 6 infusion, DLI was stopped because of GVHD onset, which required steroid therapy with complete resolution. Six patients obtained CR with MRD negativity detected by flow cytometry and by PCR; in particular 3 pts relapsed after HSCT, restored full donor chimerism. The remaining 4 pts died because of progression disease. One patients relapsed after one years from the end of treatment with Blinatumomab, and he started therapy with Inotuzumab which is still ongoing.

Conclusions: Blinatumomab represent a valid therapeutic option for pts with R/R B-ALL, with a good tolerability and efficacy. It is necessary to train medical staff, nurses and patient in the management of infusional pump kit and about prompt recognition of side effects.

Disclosure: No disclosure

P523

IFNY Secretion of Adaptive and Innate Immune Cells as a Parameter to Display Leukaemia Derived Dendritic Cell (DC_{Leu}) Mediated Immune Responses in AML

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Background: Myeloid leukaemic blasts can be converted into leukaemia derived dendritic cells (DC_{leu}) with blastmodulatory Kit-I and Kit-M, which have the competence to regularly activate T and immunoreactive cells to gain anti-leukaemic activity or rather cytotoxicity. As innate and adaptive immune responses are notably promoted by the cytokine interferon gamma (IFNy), we hypothesised that the IFNy secretion could be a suitable parameter to display DC/DC_{leu} mediated immunologic activity and even anti-leukaemic cytotoxicity.

Methods: DC/DC_{leu} were generated from leukaemic WB with Kit-I (GM-CSF + OK-432) and Kit-M (GM-CSF + PGE_1) and used to stimulate T cell enriched immunoreactive cells. Initiated anti-leukaemic cytotoxicity was investigated with a cytotoxicity fluorolysis assay (CTX). Initiated IFNy secretion of innate and adaptive immune cells (T cells, T^{CD4+} cells, T^{CD8+} cells, NK^{CD56+} cells, NK^{CD161+} cells, CIK^{CD56+} cells, CIK^{CD161+} cells and iNKT) was investigated with a cytokine secretion assay (CSA). In some cases IFNy production was additionally evaluated with an intracellular cytokine assay (ICA). Conclusively, the IFNy secretion of immunoreactive cells was correlated with the anti-leukaemic cytotoxicity.

Results: Significant amounts of DC and DC_{leu} as well as migratory DC and DC_{leu} could be generated with Kit-I and Kit-M without induction of blast proliferation. T cell enriched immunoreactive cells stimulated with DC/DC_{leu} showed an increased anti-leukaemic cytotoxicity and an increased IFNy secretion of T, NK and CIK cells compared to control. Both the CSA and ICA yielded comparable amounts of IFNy positive innate and adaptive immune cells. The correlation between the IFNy secretion of immunoreactive cells and the anti-leukaemic cytotoxicity showed a positive relationship in T cells, T^{CD4+} cells, T^{CD8+} cells and NK^{CD56+} cells.

Conclusions: We found blastmodulatory Kit-I and Kit-M competent to generate DC/DC_{leu} from leukaemic WB. Stimulation of T cell enriched immunoreactive cells with DC/DC_{leu} regularly resulted in an increased anti-leukaemic cytotoxicity and an increased IFNy dependent immunological activity of T, NK and CIK cells compared to control. Moreover the anti-leukaemic cytotoxicity positively correlated with the IFNy secretion in T cells, T^{CD4+} cells, T^{CD8+} cells, NK^{CD56+} cells. We therefore consider the IFNy secretion of innate and adaptive immune cells to be a suitable parameter to assess the efficacy of in vitro and potentially in vivo AML immunotherapy. The CSA in this regard proved to be a convenient and reproducible technique to detect and phenotypically characterise IFNy secreting cells of the innate and adaptive immune system.

Disclosure: Nothing to declare.

P524

Treatment of Severe Hematopoietic Stem Cell transplant-associated Thrombotic Microangiopathy (HCT-TMA) with the masp-2 Inhibitor Narsoplimab (OMS721)

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Background: HCT-TMA is a rare and serious complication of HSCT. Patients with mild forms respond to adjustments/withdrawal of calcineurin-inhibitors and to the treatment of triggering events. However, patients with severe HCT-TMA who do not respond to such measures have a dismal prognosis. There are not specific drugs approved for HCT-TMA treatment. Since its main pathogenic mechanism is an endothelial dysfunction with complement activation, eculizumab has been used off-label, but in allogeneic HSCT recipients, full complement blocking may increase infection-related mortality. Narsoplimab (OMS721; www.omeros.com), a human monoclonal antibody against MASP-2, offers a more selective inhibition of the complement lectin pathway and a may be less immunosuppressive in HCT-TMA, for which it has received breakthrough therapy designation by FDA.

Methods: We describe our experience with narsoplimab (4 mg/kg, once to twice weekly depending on severity and response) as compassionate use in two patients with severe HCT-TMA who did not respond to general measures.

Results: Case 1: A 19-year-old female recipient of a matched sibling allogeneic HSCT for B-ALL in CR1 who developed late-onset acute GVHD 5 months after transplant (MAGIC III, gastrointestinal grade II, skin grade II). Despite rapid response of skin GVHD, the gastrointestinal symptoms required multiple lines (steroids, mesenchymal stromal cells and extracorporeal photopheresis). At 6.5 months post-transplant, an episode of lower gastrointestinal bleeding, colonoscopy with ischemic ulcers and additional features in histology and blood tests confirmed a diagnosis of severe HCT-TMA. In the context of heavy immunosuppression to treat GVHD and multiple previous infective complications, she received a single dose of eculizumab while compassionate use of narsoplimab was organized. The patient received a total of 18 doses of narsoplimab, showing a favourable response with resolution of the gastrointestinal bleeding and micro-angiopathic hemolytic anemia, and reaching transfusion independence with platelets $>100x10^9$/L. Following discontinuation of narsoplimab, the patient is now alive, in complete remission of her B-ALL and with no signs of HCT-TMA 21 months posttransplant.

Case 2: A 48-year-old HIV+ man with Hodgkin's disease in third CR underwent a cord-blood HSCT. He suffered a very early HCT-TMA on day 0, which did not respond to CNI withdrawal and rapidly developed severe renal failure requiring hemodialysis. Narsoplimab started on day +6 with a twice weekly administration for a total of eight doses. LDH, bilirubin and schistocyte counts improved rapidly with treatment. However, despite partial improvement in renal function and fluid management, he remained in dialysis. At this early phase after HSCT, the patient continued with transfusion requirements, had infectious complications and experienced sudden death on day +31. Clinical autopsy was not granted.

Conclusions: Narsoplimab is a novel selective inhibitor of the complement lectin pathway with FDA breakthrough therapy designation for HCT-TMA. In patients with severe HCT-TMA that do not respond to conventional measures, our experience is very encouraging, both in terms of safety and efficacy on laboratory and clinical parameters, including full and sustained resolution with prolonged survival in cases that otherwise have a dismal prognosis of survival of only a few weeks.

Disclosure: Rafael Duarte: Omeros Corporation advisor

Non-haematopoietic stem cells

P525

Factors Influencing the Presence of Bone Marrow Mesenchymal Stem Cells after Allogeneic Stem Cell Transplantation

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Background: The success of allogeneic stem cell transplantation (SCT) is limited by complications of impaired hematopoiesis and recurrence of neoplasia. Critical for both the engraftment of the donor hematopoietic stem cells (HSC) and the persistence of malignant stem cells of the neoplasia is the niche function of the bone marrow (BM). Mesenchymal stem cells (MSC) are an essential part of the BM niche. MSC are fibroblast-like cells within the BM stroma and therefore play an essential role in the regulation of healthy hematopoiesis as well as the emergence and maintenance of hematopoietic neoplasms. After allogeneic SCT, MSC originate from the recipient. We hypothesize that the recipient BM niche is altered by allogeneic SCT, therefore influencing treatment outcome.

Methods: In a retrospective single center study, we analyzed the MSC presence in bone marrow aspirates from patients who underwent a routine bone marrow biopsy during the course of their treatment. To obtain total MSC, BM mononuclear cells (MNCs) were isolated by density gradient separation and subsequently cultivated. Results were correlated with the clinical data of the patients, including intensity and type of conditioning, donor characteristics and complications of SCT. Both univariate analysis and multiple regression were performed.

Results: Our cohort consisted of 963 bone marrow biopsies from 637 patients with various hematological diseases, 145 of these patients received an allogeneic SCT. Presence of MSC was significantly reduced after allogeneic SCT in both overall (84.2 % vs. 69.8 %, p=0.002) and matched pair analysis (84.8 % vs. 62.1 %, p=0.003). In multivariate regression, a history of previous allogeneic SCT remained an independent factor (OR 0.52, p=0.006). In patients with multiple BM biopsies after SCT, the reduced presence of MSC did not recover within the first 8 months after transplant. Type and intensity of conditioning had an effect on MSC presence after allogeneic SCT with total body irradiation (TBI) and myeloablative conditioning regimens (MAC) leading to significantly reduced presence of MSC. Furthermore, in patients with poor engraftment of the transplant, MSC presence was significantly reduced.

Conclusions: Allogeneic SCT leads to a significant and sustained reduction of BM MSC presence. The extent of this reduction depends on type and intensity of conditioning and is associated with the graft function. We conclude that allogeneic SCT leads to alterations in the BM niche that impact the outcome of SCT and may therefore provide new information to improve the results of allogeneic SCT.

Disclosure: Nothing to declare.

P526

Analysis of the Genetic Stability of Donors` Bone Marrow Stroma Mesenchymal Cells during Cultivation

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Background: Currently, research and application of bone marrow mesenchymal stromal cells (MSCs) are promising directions of the development of transplantology. Expansion of cell cultures in vitro is the necessary step to obtain MSCs at the amounts required for clinical use. In this regard, verification of the genetic stability of MSCs is relevant.

Methods: The selection of nuclear cells from the bone marrow was carried out by fractionation on a density gradient ($\rho = 1{,}077$ at 22°C). MSCs were cultured according to a common protocol using donors` platelet-rich plasma. As methodological approaches for assessing the MSCs` genetic stability a standard cytogenetic study and analysis of short tandem repeats (STR) were used. For determination of MSCs` karyotype ($n = 23$), colcemid at a final concentration of 0.1 μg / ml was introduced into the cell culture at the exponential phase of growth and incubated for 24 h at 37°C. The procedure of chromosome preparations` obtaining included hypotonic treatment with a solution of potassium chloride, prefixing with glacial acetic acid, fixation with a mixture of chilled carbinol and glacial acetic acid, and differential coloring. DNA preparations from MSCs were isolated by column filtration using the QIAamp Blood Mini Kit reagent kit (Qiagen, Germany). STR profiles of MSCs were determined during multiplex polymerase chain reaction of 20 loci located on different chromosomes (COrDIS Plus, Russia).

Results: Studying of the karyotypes of MSCs obtained by 4 passages, chromosomal aberrations were not detected in any sample. During the expansion of cell lines, the STR profile of MSCs remained stable throughout the entire culture cycle and corresponded to the STR profile of the genetic material of the bone marrow donor. The probability of individuals` matching by the indicated STR loci in the

population is 1 for $4*10^{22}$, so the STR-profile of the cell line obtained from a certain donor may be used to assess the authenticity of medication based on MSCs.

Conclusions: MSCs obtained by cultivation are characterized by genetic stability both at the chromosomal and individual genes` levels. The STR analysis may be used to identify donor affiliation of the cell line (according to the recommendations of the American National Standards Institute, 2012).

Disclosure: The authors declare. no conflict of interest.

P527

The Polish Experience of Wharton´s Jelly-derived Mesenchymal Stem Cell Treatment of Paediatric Patients

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Background: Human mesenchymal stem cells (MSCs) have wide therapeutic potential. Wharton's jelly from the umbilical cord is a noncontroversial and accessible source

of these cells (WJ-MSCs). These pluripotent cells are easy to culture and have the ability to proliferate into cartilage, bone and fatty tissue, among others. Furthermore, they present anti-inflammatory and immunoregulatory properties and can therefore be used for treating many diseases and injuries. WJ-MSCs are immunoprivileged, and so are easy to use in allogenic administration. In this paper, we present a review of WJ-MSC medicinal products prepared by Polski Bank Komórek Macierzystych S. A. (FamiCord Group), Warsaw, for paediatric patients.

Methods: Products based on WJ-MSCs manufactured by the PBKM S. A. have been used in medical therapeutic experiments between 2011 and 2019. A total of 613 children have participated in these procedures. The WJ-MSCs were of third-party donor origin and cultured in the PBKM laboratory. Cells were collected from healthy new-borns, then processed, screened for bacterial contamination and endotoxin content, and finally frozen in liquid nitrogen vapours. The immunophenotype of the cells was confirmed by flow cytometry. The WJ-MSCs were administered mainly by intravenous and intrathecal injections. As these administrations were given during medical therapeutic experiments, for each patient, there was the approval of the relevant Bioethical Commission. Depending on the treatment, patients received up to 10 separate WJ-MSC injections. Adverse event (AE) monitoring was conducted during the whole procedure. The age of the patients ranged from 10 months to 17 years, 11 months with a median age of 6 years, 2 months. The average cell dose per infusion was 1,091 x 10^6/kg of body weight.

Results: In Poland, over 50 diseases have been treated in paediatric patients, mainly in neurology

(91,31% of all patients) and haematology (4,94%), as well as orthopaedics (1,12%) and ophthalmology (1,12%). The most common indications were cerebral palsy (237 patients), autism spectrum disorder (116 patients), epilepsy (62 patients), spina bifida (51 patients) and graft versus host disease (28 patients). During the first 24 hours after stem cell injection, 11 adverse events (AE) occurred and another 5 AE at least 24 hours after WJ-MSC administration were observed. Most reported AE were mild to moderate, e.g. the most frequent were nausea, fever or headache, which were easily managed with medications. Severe AEs (4 occurrences) consisted of epileptic seizures. All AEs were transient.

Conclusions: The use of PBKM-manufactured, WJ-MSC-based products shows promising results. During almost ten years of administering WJ-MSCs, no severe adverse events related to paediatric cell administration were registered. They have proven to be effective in improving the clinical condition of patients with many diseases. This is a strong argument for using WJ-MSCs in the standard therapy for many paediatric diseases.

Disclosure: Authors are employees of Polski Bank Komórek Macierzystych S. A. (FamiCord Group), Warsaw

P528

The Polish Experience of Wharton´s jelly-derived Mesenchymal Stem Cell Treatment of Adult Patients

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Background: Wharton's jelly is a reliable and easy to obtain source of mesenchymal stem cells (MSCs).

WJ-MSCs have a great expansion potential. These cells are easily cultured and have the ability to differentiate into many cell types. Furthermore, they are immunologically privileged, present anti-inflammatory and immunomodulating properties, so they can be used in treating many diseases and injuries. Here we present current (as of 2019) therapeutic, WJ-MSC-based, hospital-exempt, advanced therapy medicinal products prepared by the Polski Bank Komórek Macierzystych S. A. (FamiCord Group), Warsaw.

Methods: Between 2011 and 2019, PBKM S.A. manufactured and delivered WJ-MSCs medical products for 737 adult patients. WJ-MSCs have been used in Poland in therapeutic experimental procedures. Based on physicians' requirements and following Bioethics Committee approval, third party donor WJ-MSCs were administered to the patients intrathecally, intraocularly or intravenously. Cells were collected from donated umbilical cords of healthy new-borns, then processed, screened for bacterial contamination and endotoxin content and finally frozen in liquid nitrogen vapours. The immunophenotype of the WJ-MSCs was confirmed using flow cytometric assay. Depending on the chosen optimal treatment regimen, patients received from 1 up to 15 injections. Adverse events were monitored during the whole therapy. The age of the patients ranged from 18 years to 86 years, 11 months, with a median age of 47 years, 3 months. The average cell dose per infusion was 0.426 x 10^6/kg of body weight. All patients were monitored for any procedure related adverse events.

Results: Adult patients in Poland have been treated for over 50 diseases, mainly in neurology

(54.5% of all patients), ophthalmology (28.8%), orthopaedics (12.3%) and endocrinology (2.4%), as well as with other recipients including those in haematology (5 patients), gynaecology (5 patients) and dermatology (3 patients). The most common indications were amyotrophic lateral sclerosis (225 patients), optic atrophy (96 patients), retinitis pigmentosa (84 patients), muscular dystrophies (46 patients), spinal cord injury (41 patients), multiple sclerosis (39 patients), spinocerebellar ataxia (30 patients) and osteoarthritis (28 patients). After the injection of WJ-MSCs 8 adverse events (AE) were observed; 6 AEs were classified as severe - tractional retinal detachment (3 cases) and conglomerate in the vitreous body (3 cases). Severe AEs were assessed as not related to cell therapy.

Conclusions: During nearly 10 years of our WJ-MSC therapeutic use, no severe adverse events related to cell administration have been observed. They have proven to be effective in improving the clinical condition of patients with many diseases. The results of the treatment provide hope for new, effective medical procedures for adult patients.

Disclosure: Authors are employees of Polski Bank Komórek Macierzystych S. A. (FamiCord Group), Warsaw

Non-infectious early complications

P529

Bacterial and Metabolic Profiling of the Saliva Identifies Unique Patterns of Microbiota Injury in Hematopoietic Stem Cell Transplantation Recipient with Severe Oral Mucositis

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Background: Inflammation and apoptosis result in disruption of the mucosal barrier and development of oral mucositis (OM), a common debilitating complication of hematopoietic stem cell transplantation (HSCT). We hypothesized the commensal bacteria and their metabolites facilitate OM phenotype.

Methods: In this single-center prospective study, we serially collected saliva samples and documented OM using the Common Terminology Criteria for Adverse Events (CTCAE; v4.0) system in 184 adult recipients of allogeneic-HSCT. A total of 625 samples underwent 16S rRNA gene sequencing. In addition, 60 samples underwent metabolic profiling using Ultrahigh Performance Liquid Chromatography-Tandem Mass Spectroscopy (UPLC-MS/MS) (Metabolone).

Results: The majority of patients received high-intensity conditioning regimens (myeloablative [41.3%] and reduced-toxicity [28.8%]). Methotrexate was administered to 135 patients (73.4%). A total of 79 (42.9%) patients developed grade 3-4 (defined as severe) OM, while 78 patients (42.4%) had no/minimal OM (grade 0-1). OM appeared at a median of 7 days after transplantation. At baseline (days -7 to -1), salivary alpha diversity, a measure of sample richness, was similar between patients and healthy controls (n=19). Alpha diversity decreased over time, reaching a nadir on day 14, and in contrast to the gut (Taur, Blood 2014) was not correlated with survival. In patients treated with methotrexate, using two independent methods (XGBoost machine learning algorithm and LEFSE analysis), pre-transplantation colonization with Kingella and Atopobium were predictive of later development of severe OM. In a pair-wise comparison of pre and post-transplant samples, severe OM was associated with a reduction in alpha diversity ($q < 0.01$) and an increase in beta diversity ($q=0.054$), which were not observed in the grade 0-1 OM group. Notably, genera associated with infections and inflammation, including Mycoplasma, Methylobacterium, Campylobacter, and Staphylococcus, increased in the grade 3-4 OM group.

Since metabolites generated by the microbial consortium regulate immune activation, we studied the

salivary metabolic profile of patients with and without severe OM at baseline, and on days 7 to 13 post-transplant. We discovered 846 metabolites of known identity. Within the severe OM group, 101 metabolites significantly ($q < 0.05$) changed between the two time points, while only seven compounds changed in the grade 0-1 group. Metabolites with shifting abundances were involved in a variety of metabolic pathways, including amino acid, xenobiotics, and lipid metabolism. In the grade 3-4 OM group, four metabolites (Urea, 5-Amino-valerate, N-Acetylputrescine, Agmatine) that had a significant fold-change between the pre and post-transplant samples were considered well explained by the microbiota. Both N-Acetylputrescine and Agmatine are part of the polyamine pathway, and conversion of the later from Arginine is exogenous to the host and bacterially mediated. Importantly, polyamines are required for mucosal homeostasis and contribute to the preservation of mucosal barrier integrity and post-injury recovery in the gut (Timmons. J Gastrointest Dig Syst 2012).

Conclusions: In this largest study of oral microbiome among allogeneic-HSCT recipients, we identify pro-inflammatory bacteria, as well as bacterial metabolites involved in epithelial integrity among patients developing oral mucositis. These findings open new avenues for prevention and mitigation of oral mucositis, which is amongst the most common complications of high-intensity cancer treatments.

Disclosure: Nothing to declare.

P530

Diagnosis and Management of Secondary HLH/MAS following HSCT and CAR-t Cell Therapy in Adults; An EBMT-wide Survey on Behalf of the ADWP and TCWP

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Background: Secondary haemophagocytic lymphohistiocytosis (sHLH) is a life-threatening hyperinflammatory syndrome associated with infection and malignancy and termed macrophage activation syndrome (MAS) when triggered by autoimmune disease. Secondary HLH is a rare complication of haematopoietic stem cell transplantation (HSCT), with a high mortality and may be associated with graft versus host disease in the allogeneic HSCT setting. Incidence estimates are 3%-9%. Secondary HLH is also reported in 1% of cases following CAR-T cell therapy, but differentiation from cytokine release syndrome (CRS) is challenging. The clinical features of sHLH are non-specific and can mimic more common conditions, including sepsis, delaying identification and leading to under recognition of this heterogenous syndrome of hyperinflammation. Recent advances in diagnosis and treatment for sHLH in non-HSCT patients with cytokine blockade has revolutionised outcomes. Since there are currently no approved guidelines for screening, diagnosis or treatment of sHLH in patients following HSCT and CAR-T cell therapy we surveyed European Society for Blood and Marrow Transplantation (EBMT) centres to understand current practice.

Methods: An online questionnaire was sent to the Principal Investigators of all EBMT member transplant centres treating adult patients (18 years and over) inviting them to provide information regarding: number of cases of sHLH seen in their centre over 3 years (2016-2018 inclusive); screening strategies; use of existing diagnostic/classification criteria and treatment protocols.

Results: 114/472 centres responded from 24 different countries giving a response rate of 24%. Prevalence of sHLH is estimated at 1.09% (95% CI=0.89-1.30) following allogeneic HSCT, 0.15% (95% CI=0.09-5.89) following autologous HSCT and 3.48% (95% CI=0.95-6.01) following CAR-T cell therapy. A majority of centres (70%) did not use a standard protocol to screen for sHLH in this setting. Serum ferritin was the most commonly used screening marker, at 78% of centres, followed by soluble IL-2 receptor, triglycerides and fibrinogen. There was significant variation in definition of "clinically significant" serum ferritin levels ranging from 500 to 10,000µg/mL. The most commonly reported published criteria in use to support diagnosis of sHLH/MAS were HLH-2004 (43%) and the H

score (15%). 80% of responders reported using no standard protocol to guide management, though reported using corticosteroids, chemotherapeutic agents, cytokine blockade and monoclonal antibodies.

Conclusions: This is the largest survey of sHLH/MAS following HSCT/CAR-T cell therapy to date. We report a lower perceived incidence of sHLH/MAS following HSCT than previous, smaller reports, which may reflect under-recognition. We did however find a slightly higher incidence following CAR-T cell therapy than previously reported. There is a remarkable lack of consistency between EBMT centres in the approach to screening, diagnosis and management. There are clear trends in terms of use of serum ferritin in screening, use of the HLH-2004 criteria and H score in diagnosis, and management with corticosteroids with chemotherapy, cytokine blockade and monoclonal antibodies, which form the cornerstone of treatment in other settings. Further research in this field is needed to raise awareness of and inform harmonised, evidence bases approaches to the recognition and treatment of sHLH.

Disclosure: Nothing to declare.

P531

Impact of Abo Incompatibility on Complications of Allogeneic Hematopoietic Cell Transplantation-Retrospective, International, Multicenter Analysis by the Transplant Complications Working Party EBMT

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Background: Blood groups and the human leukocyte antigen (HLA) system are inherited independently. As a result, up to 50% of allogeneic hematopoietic stem cell transplantations (allo-SCT) are performed despite ABO incompatibility. Although it is considered that ABO mismatching negatively affects outcomes of allo-SCT, available data is ambiguous.

Methods: We performed a retrospective analysis using data from the EBMT registry. Eligibility criteria included adult patients with diagnosis of hematological malignancies receiving a first allo-SCT using mobilized peripheral blood (PB) or bone marrow (BM) between 2005 - 2017 and availability of ABO compatibility information between donor and recipient. Data on donor/recipient sex, disease status at transplantation time, type of donor, conditioning regimen, graft-versus-host disease (GvHD) prevention were analysed. The primary endpoint of the study was non-relapse mortality at two years after allo-SCT. Overall survival, relapse incidence, chronic (c) GvHD incidence at two years, acute (a) GVHD incidence, non-engraftment at day 30 after allo-SCT were selected as secondary endpoints. Cause-specific hazard model was used in the multivariate analysis for whole study population and specific subgroup analysis by cell source and type of the donor.

Results: Study included 28577 patients, of whom 57% underwent ABO-matched and 43% ABO-mismatched transplantation. Among patients with ABO incompatibility, minor incompatibility was the most prevalent 20%, followed by major incompatibility 18% and bidirectional incompatibility 5%. Most patients were transplanted for acute myeloid leukemia (43%). 44% of transplantations were from identical sibling donors, 37% from HLA-matched unrelated donors (MUD, 10/10), 11% from HLA-mismatched unrelated donors (mMUD, 9/10) and 8% from haploidentical donors. The primary source of stem cells was peripheral blood (83%). Reduced-intensity conditioning regimens were used in the majority of cases (57%). The most frequently used GvHD prevention regimen was a calcineurin inhibitor with methotrexate (41%).

In multivariate analyses, we found no significant differences between patients with different settings of ABO-incompatibility compared to ABO-compatible in terms of non-relapse mortality, overall survival, relapse incidence. Sub-group analysis according to type of the donor and stem cells source also did not show statistically significant differences in these outcomes except for increased relapse incidence rate in patients transplanted with bidirectional ABO - incompatibility compared to compatible (HR 1.51; p=0.048). However, non-engraftment incidence was higher in patients transplanted with major ABO-incompatibility compared to compatible (HR 1.04; p=0.015) and this effect was mainly observed in BM recipients (HR 1.17; p=0.0008) and patients transplanted from MUD (HR 1.10; p=0.001). The occurrence of aGvHD, especially severe aGvHD, was lower in patients transplanted with major ABO-incompatibility compared to compatible (HR 0.87; p=0.005). This observation was particularly seen in patients

transplanted with PB (HR 0.85; p=0.002). The occurrence of extensive cGvHD was higher in patients transplanted with minor ABO-incompatibility compared to compatible in mMUD transplants (HR 1.29; p=0.019). However the occurrence of extensive cGvHD was lower in patients transplanted with major ABO-incompatibility compared to compatible in haplo group (HR 0.63; p= 0.039).

Conclusions: In our study, stem cell transplantation across major blood group barrier did not have influence on non-relapse mortality. However, ABO incompatibility had moderate impact on engraftment and GvHD occurrence.

Disclosure: Nothing to declare.

P532

Hypoalbuminemia Prior AlloHCT is a Relevant Negative Predictor for Survival

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Background: Albumin serum levels decline in relation to malnutrition, decrease in muscle mass and function, and inflammation. Hypoalbuminemia in alloHCT patients has been described as a negative prognostic factor for survival in elderly patients undergoing transplantation. We aim to explore the impact of hypoalbuminemia in post-transplant outcomes in a large and heterogeneous cohort of alloHCT patients.

Methods: Between October 2015 to September 2019, 368 adults underwent RIC alloHCT combined with ATG-PTCY and cyclosporine for GVHD prophylaxis. Serum albumin level prior alloHCT (between day -30 to -10) was retrospectively collected. The main explanatory variable of interest was albumin level prior alloHCT (ALB-PRE). The main outcome variables were overall survival (OS), and non-relapse mortality (NRM). The effect of the main explanatory variable in OS, and NRM was explored using Cox proportional hazards regression model. Albumin level was transformed using log 2 for the statistical analysis. Because regression models report on a linear scale, we used log 2 transformed index values for modelling. Those variables found to be significant in the univariate Cox Regression model were included in the multivariable analysis. Based on the binary partitioning method, an optimal serum albumin level cut-off point of OS was defined.

Results: Baseline characteristics and main post-transplant information are reported in the Figure 1. Median age was 59 (range: 18.3-74.5) years. Median ALB-PRE was 40g/L (range: 21-49). The probability of presenting an albumin serum level lower than 38 g/L prior transplantation was independent from patient's age (P=0.3275).

Results from the multivariate analysis are shown in Figure 1. Decreased level of albumin prior transplantation was a significant predictor for worse OS (HR 4.34 (95% CI 1.58-12.5); P=0.004) as well as NRM (HR 7.69 (05% CI 2.43-25); P< 0.001) in the multivariable analysis.

Increasing age prior to alloHSCT, KPS between 70-80%, high DRI, grafts from 9/10 MUD or haploidentical donors were significant risk factors for worse OS. Developing grade I and II acute GVHD was found to be a protective factor for OS [HR 0.4 (95% CI 0.2-0.6)]; P< 0.001) and NRM [HR 0.28 (95 CI 0.15-0.54); P< 0.001].

The optimal serum albumin level cut-off point of overall survival was 38 g/L. Those patients with an albumin serum level ≥38 g/L had better OS in comparison with those patients with an albumin serum level < 38g/L (P=0.013).

Conclusions: Albumin serum level is a relevant prognostic marker for OS and NRM in alloHSCT recipients across all ages.

This study identifies an at risk population in which pre-transplant interventions may be instituted prior alloHCT to increase albumin serum levels in order to pre-habilitate patients candidates prior alloHCT.

Albumin serum levels could be incorporated in future prognostic tools built to improve the estimation of post-transplant outcomes.

Clinical Trial Registry: No applicable

Disclosure: Nothing to declare.

P533

Incidence and Clinical Impact of Atrial Fibrillation Diagnosed during Hospital Stay for Allogeneic Stem Cell Transplantation

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Background: Atrial fibrillation (AFib) is a pre-transplant risk factor for allogeneic stem cell transplantation (SCT) included in risk-assessment by the hematopoietic cell transplantation comorbidity index (HCTCI). We retrospectively analyzed

incidence and clinical impact of AFib-diagnosis during SCT-hospital stay.

Methods: Records of all consecutive allogeneic SCTs for adult patients between 01/2013 and 10/2019 at Hannover Medical School were analyzed for inpatient AFib-occurrence. Admission to intensive care unit (ICU), duration of ICU stay, ICU-survival, overall survival (OS), disease-free survival (DFS), non-relapse mortality (NRM) and aGvHD-incidence were analyzed. The impact of AFib was compared to a matched non-AFib control cohort.

Results: 553 patients underwent 568 allogeneic SCTs between 01/2013 and 10/2019. During pre-SCT risk assessment 26 patients were scored positive for arrhythmia according to the HCTCI (4.7%) including 16 AFib patients (2.9%). AFib occurred during SCT-hospital stay in 43 patients (7.8%, 7.6% of all SCT-procedures) with 35 of these diagnosed with AFib for the first time. Paroxysmal and persistent AFib had been previously diagnosed in 6 and 2 patients, respectively. AFib occurred before and after SCT in n=15 and n=28 cases, respectively, and in 16 patients during infections/septicemia. The remaining patients had no signs of infection at AFib onset. To analyze the impact of inpatient AFib onset we compared the 43 AFib patients with a cohort of non-AFib patients (n=70) matched for HCTCI, EBMT-score, conditioning (MAC 21%, RIC 79%) and disease (AML 65-67%, MDS 13-14%, ALL 12-13%, other 7-9%). Median follow-up was 233 days in the AFib and 394 days in the non-AFib cohort. ICU admission during the SCT-hospital stay was necessary for 19 AFib patients (44.2%; 68.8% for patients with infections and 26.1% for non-infected patients at AFib diagnosis ($p< 0.05$)). Reasons for ICU admission in patients with AFib were cardiac decompensation (31.6%), septic shock (57.9%), and impaired consciousness (10.5%). Median duration of ICU stay was 5 (1-7.5) days with an ICU survival rate of 68%. In contrast, only 5 patients in the non-AFib cohort were admitted to the ICU (7.1%, $p< 0.01$) with a median duration of ICU stay of 14.5 (5.3-24.8) days (n.s.). Only one of these patients survived ICU- and hospital stay (20%, n.s.). OS was superior in the non-AFib group (one year: 61.8 % vs. 42.3 %, five year: 41.9 % vs 19.5 %, p=0.01). DFS in non-AFib and AFib patients was 52.8% and 35.9% (one year) and 42.3% and 17.8% (five years) (p=0.01), respectively. NRM was 27.5% and 43.6% at one year and 23.1% and 69.6% at five years for the non-AFib and AFib patients ($p< 0.01$). Incidence of grade II-IV° GvHD at day +100 was not significantly different with 47.8% and 39.9% for the non AFib and the AFib group (n.s.).

Conclusions: In this single center analysis onset of AFib during SCT hospital stay led directly or indirectly to increased ICU admission rates and worse OS, DFS and NRM with no negative impact on ICU survival and incidence of II-IV° aGvHD.

Disclosure: nothing to disclose

P534

Transplantation-associated Microangiopathy (TAM) in Recipients of Unmanipulated HLA-haploidentical Hematopoietic Stem Cell Transplants using Ptcy for GVHD Prophylaxis: Incidence and Outcome

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Background: Transplant-associated microangiopathy (TAM) is a life-threatening endothelial damage syndrome that is increasingly identified as complication after hematopoietic stem cell transplantation (HSCT), comprising severe thrombocytopenia, microangiopathic hemolysis and organ dysfunction (e.g. renal, neurological) in the absence of disseminated intravascular coagulation. Etiological factors include conditioning, immunosuppressive drugs, infections and GvHD. The reported incidence of TAM after allogeneic HSCT varies between 0,5 to 70%. Data for TAM occurrence and outcome in the context of HLA-haploidentical transplantation (haplo-HSCT) are rare. Here, we report our experience on TAM incidence, disease manifestation, treatment and outcome in patients undergoing a first T-cell-replete haplo-HSCT using PTCY, CNI and MMF as GvHD prophylaxis.

Methods: We retrospectively analyzed the treatment course of 172 patients undergoing a first T-cell replete haplo-HSCT for malignant and non-malignant hematologic disease at our center from January 2009 to March 2019. All patients were followed for early complications, acute GvHD, infections, survival, as well as for TAM incidence, risk factors, treatment and outcome. The diagnosis of TAM required the fulfillment of the criteria as defined by Ruutu et al., Haematologica 2007.

Results: Median age of the entire cohort was 54 years (23-74). Post-grafting immunosuppression consisted of PTCY, CNI and MMF in all patients. Bone marrow was used as graft source in 55% of the patients. Haplo-donors were predominantly first-degree relatives (94%) and male in 52% of HSCTs. Median follow-up time upon survivors was 4,4 years (4 months - 9,5 years).

Twenty-two of 172 patients developed TAM, with a cumulative incidence of 9,6% at day +100.

Median platelet count at diagnosis was 20 x 10^9/L (range: 6-146). Median LDH level was 411 IU/L (305-1445 IU/L). Serum haptoglobin levels were decreased in 86% of the TAM

patients. 14/22 patients had active infection at the time of TAM diagnosis, mostly viral (12/14). All but three patients presented with concurrent active aGvHD requiring systemic steroid treatment in 18 patients. Renal function abnormalities were diagnosed in 68% of the patients affected by TAM, with 4 patients requiring hemodialysis. Nine patients developed ° III hypertension and three showed neurologic dysfunction. Upon diagnosis of TAM, CNI dose was reduced (9 patients) or temporarily discontinued (7 patients). No switch to another CNI was performed. FFPs were transfused in eleven patients, three underwent plasma exchange therapy without any effect. In four patient rituximab was applied.

With a CI of 18% vs 2% ($p< 0.001$) using a PBSC graft was a risk factor for TAM development when compared to BM. Neither origin of disease (myeloid/lymphoid) nor sex of patient/donor or conditioning intensity influenced the incidence significantly.

Estimated one-year and three-year overall survival did not differ between the TAM and the non-TAM cohort (59% vs 62% and 48% vs 52%, $p=0.75$). Only one patient died because of TAM.

Conclusions: Our haplo-cohort showed a TAM incidence of 9,6% at day +100, thus we conclude that TAM quite rarely occurs in the haplo setting using PTCY, CNI and MMF as GvHD prophylaxis, however disease course was moderate with low TAM-associated mortality. PBSCs as graft source could be identified as risk factor.

Disclosure: nothing to declare.

P535

IGF-1 and IGFBP-3 Gene Polymorphisms Predict Circulating IGF Levels and Systemic Inflammation in Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Allo-HSCT is challenged by significant toxicities that are propagated by systemic inflammation induced due to damage of epithelial barriers. Insulin-like growth factor-1 (IGF-1) is key in growth and repair of most tissues including epithelium and have an anti-inflammatory effect. To assess the impact of polymorphisms in genes encoding IGF-1 and its binding protein (IGFBP-3) on circulating levels of IGF-1 and IGFBP-3, systemic inflammation and clinical outcomes after allo-HSCT we investigated ten single nucleotide polymorphisms (SNP) in IGF1 and IGFBP3 in allo-HSCT patients in a retrospective study.

Methods: We included 551 patients (age range: 0.3 - 66.1, mean: 26.3 years) undergoing HSCT at the University Hospital Rigshospitalet, Denmark between January 2004 and December 2016. Diagnoses included malignancies ($n = 446$) and non-malignant disorders ($n = 105$). Donors were either matched siblings ($n = 165$), matched unrelated donors ($n = 311$) or mismatched unrelated donors ($n = 75$) and grafts included marrow ($n = 385$) or peripheral stem cells ($n = 166$). Ten SNPs in or near IGF1 and IGFBP3 were systematically selected based on previously validated and consistent findings of association with circulating IGF-1 and IGFBP-3.

Due to the clinical routine at our institution scheduled measurements of serum IGF-1 and IGFBP-3 were available only for pediatric patients pre-HSCT and at regular intervals until several years post-HSCT. IGF-1 and IGFBP-3 serum levels were converted into age- and sex-adjusted SD-scores based on healthy Danish children.

Results: Overall, IGF-1 and IGFBP-3 levels were significantly reduced in pediatric patients compared with healthy children (mean IGF-1 SD-score: -1.1, 95% CI -1.3 - -0.8, $P < .001$ and mean IGFBP-3 SD-score: -1.2, 95% CI -1.5 - -1.0, $P < 0.001$) from before transplantation and until two years post-HSCT. Patients being homozygous for the minor alleles of rs1520220 or rs978458 in IGF1 and rs2854744 in IGFBP3 had significantly higher circulating IGF-1 and IGFBP-3 levels, respectively, both pre- and post-HSCT. Those with the homozygous minor allele genotype for rs1520220 or rs978458 had significantly lower levels of systemic inflammation evaluated by peak C-reactive protein (CRP) levels in the early toxic phase post-HSCT (median: 66 vs 102 mg/L, $P = 0.005$ and 53 vs 104 mg/L, $P < 0.001$, respectively) as well as when comparing daily CRP through the first three weeks.

Conclusions: This study is the first to investigate genetic variation in the IGF1 gene and impact on outcome after HSCT. We found that three SNPs in the IGF-1 axis, known to affect protein levels, were associated with circulating IGF-1/BP-3 levels in the setting of HSCT. For the two IGF1 SNPs this translated into lower systemic inflammation most likely reflecting less tissue damage. These findings are important because they provide new insights into mechanisms that may explain individual variability in sensitivity to toxic tissue damage seen during HSCT. Accordingly, genetic variation in the IGF-1 axis possibly protect against toxic effects of the myeloablative regimen.

Disclosure: Nothing to declare.

P536

Low Risk of Early Toxicity and Unplanned 100-day Readmissions after Matched and Mismatched Related

and Unrelated Donor Allogeneic Hematopoietic Stem Cell Transplantation with post-transplantation Cyclophosphamide

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Background: Post-transplant high dose cyclophosphamide (PTCy) represents a major advance in the field of GvHD prophylaxis after HCT. Nevertheless, few studies have investigated the impact of PTCy on early events and organ toxicities after transplant and their impact on early hospital readmission.

Methods: We retrospectively investigated 64 patients with hematologic malignancies who received a non-haploidentical HCT with single agent GvHD prophylaxis and PTCy between 2016 and 2019. Patient characteristics are summarized in Table 1.

Results: One-year overall survival and progression-free-survival were 78% and 68%, respectively. Median times of neutrophil (w/o G-CSF) and platelet (>20,000/mL) recovery were 22 (range: 16-36) and 24 days (range: 10-249). Graft failure occurred in 6 patients (9%) and 4 of them had a successful second HCT using a different conditioning platform also including PTCy.

Grade 3-4 CTCAE extrahematologic toxicities within 100 days were: Pulmonary: 0%; Cardiac: 1.6%; Liver: 1.6%; renal: 6.5%. There was only 1 case of veno-occlusive disease (1.6%) and no cases of transplant-associated thrombotic microangiopathy. The rate of grade 3-4 mucositis was 28%, mostly affecting patients treated with myeloablative conditioning regimens (53 vs. 19 %), while hemorrhagic cystitis grade >2 occurred in 6 patients (9%). Thirty-one patients (48%) developed pre-engraftment bacteremia. By day +100 CMV, reactivation occurred in 24 (37%) patients, without cases of end-organ disease (details on early toxicity shown in Figure 1). Median length of stay was 36 days (range: 24-121) and hospital mortality was 3% (n=2). A total of 15 100-day re-admissions (23% of patients) were identified. Infections (n=6), gastrointestinal symptoms (n=4) and neutropenic fever (n=2) were the most common reasons for readmission. Four patients (6%) died within 100 days at a median of 60 (25-100) days. Causes of 100-day NRM were: infection (n=2) and acute GvHD (n=2). There was a trend toward worse 1 year-overall survival in the group of patients who were readmitted before day 100 post HCT (66% vs. 82%; p 0.1).

Conclusions: Our study found low rates of organ toxicity after PTCy-based GvHD prophylaxis. Delayed engraftment may explain longer hospitalization compared to classical allo-SCT platforms. We also observed low rates of early-readmission, which may be associated with long term outcomes.

Age, median (range) ≥ 50 years	55 (19-72) 39 (61)
Sex, male	34 (53)
Underlying disease AL and MDS NHL/Hodgkin Myelofibrosis or other MPN Others	33 (51) 15 (23) 9 (14) 7 (11)
Advanced disease at transplant	27 (42)
Sex mismatch: female to male	8 (12)
Donor type HLA Identical Sibling 10/10 matched URD / 1-allele mismatched URD	19 (30) 20/25(31/39)
Disease risk index: High/Very high	12 (41)
Conditioning Fludarabine-Busulphan (RIC) Fludarabine-Melphalan (RIC) MiniTiothepa-modified RICs Fludarabine- TBI or Busulphan (MAC)	11 (17) 13 (20) 23 (36) 17 (26)
Stem cell source (PBSC)	62 (97)
Second immunosuppressive agent: Single-agent Tacrolimus/Sirolimus	61/3(95/5)

[Patient characteristics (n=64)]

Disclosure: Nothing to declare.

P537

Keratinocyte Growth Factor Decreases Hospital Readmission and Regimen-related Toxicities after Autologous Stem Cell Transplantation for Lymphoma

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Background: Patients undergoing consolidative high dose chemotherapy followed by autologous stem cell transplantation (ASCT) experience considerable regimen-related toxicities leading to significant morbidity and high readmission rates. Palifermin is a recombinant keratinocyte growth factor (KGF) that is FDA approved to ameliorate oral mucositis and other gastrointestinal toxicities associated with myelotoxic therapy, yet used in < 1% of lymphoma patients undergoing ASCT per CIBMTR data. We examined the impact of adding palifermin to standard BEAM (busulfan, etoposide, cytosine arabinoside, melphalan) conditioning on hospital readmissions and gastrointestinal toxicities in patients with relapsed lymphoma.

Methods: We prospectively incorporated palifermin as a supportive care measure to the University of Minnesota ASCT protocol and enrolled all lymphoma patients undergoing ASCT with BEAM conditioning between November 2018 and October 2019. Palifermin was given per standard schedule at 60 mcg/kg/dose IV on days -9,-8,-7 and on days 0, +1,+2. We compared outcomes of this cohort with historical cohort of ASCT recipients treated between October 2017- November 2018 having at least 30 days follow up. All patients received identical conditioning regimen (BEAM) in inpatient setting with discharge at day +1 and supportive care including G-CSF starting at day +5 and standard anti-infective prophylaxis.

Results: We analyzed 73 patients, 35 received palifermin. Patients had a median age of 62 years (range 18-74), were predominantly male (n=50, 68%) with a diagnosis of Hodgkin (n=14, 19%) or non-Hodgkin lymphoma (n=59, 81%). Age, disease status, KPS and comorbidity score, CD34 cell dose, rate of neutrophil engraftment, actual or ideal body weight were similar. Most patients received all 6 doses of palifermin (n=27, 74%).

Initial hospital admission length was the same in both groups. The median number of hospital readmission days was lower in the palifermin group (4 days vs 7 days, $p< 0.01$). The total number of days in the hospital through day +30 was lower in the palifermin group (median 13 days vs 15 days, p=0.1). Patients who received palifermin were less likely to be readmitted (57% vs 82%, p=0.04).

Regimen related toxicities particularly oropharyngeal mucositis and requirement for total parenteral nutrition were 2-fold lower in palifermin treated patients. However, this difference did not reach statistical significance. Rates for diarrhea and vomiting were similar (Table 1).

Conclusions: The addition of palifermin as a supportive care measure to BEAM conditioning offsets regimen related toxicities, decreasing likelihood of readmission and duration of hospital stay. More analysis is underway to determine if adding palifermin is a cost effective measure to decrease regimen related toxicities and healthcare cost in this patient population.

Clinical Trial Registry: Not applicable

Disclosure: No relevant conflict of interest to declare.

P538

Systemic Corticosteroid Therapy is Unlikely to be the Primary Cause of Hyperglycemia following Treatment of Acute Graft-versus-host Disease

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Background: Metabolic disorders, including diabetes mellitus (DM) are well defined in long-term survivors of allogeneic hematopoietic stem cell transplantation (alloHSCT), but information is limited on hyperglycemia occurring during the early post-transplant period. The etiology of hyperglycemia in alloHSCT recipients is also not well established. Recent data suggest that pre-existing insulin resistance, rather than the use of immunosuppressive agents (ISA) for treatment of acute graft-versus host disease (aGVHD), drives the development of hyperglycemia post-transplant. We evaluated the incidence of hyperglycemia and the relative contribution of ISA in its development in a group of alloHSCT recipients who had grade I-IV aGVHD and received systemic corticosteroid therapy.

Methods: All patients ≥18 years who underwent alloHSCT at MD Anderson between January 2010 and December 2014 and were diagnosed with aGVHD requiring treatment with systemic steroids were eligible for the study. Patients who had a pre-transplant diabetes diagnosis other than type II or had Minnesota high-risk aGVHD score were excluded. Hyperglycemia was diagnosed retrospectively based on at least two independent readings of fasting plasma glucose level ≥126 mg/dL or random plasma glucose level ≥200 mg/dL. The cumulative incidence (CumInc) of post-steroids hyperglycemia was estimated starting on the day of initiation of steroid therapy for aGVHD and was compared considering death as a competing risk.

Results: A total of 348 patients met the eligibility criteria. Median age was 53 years. At initiation of systemic therapy, 58 (17%) patients had grade I, 275 (79%) grade II, and 15 (4%) grade III-IV aGVHD. Systemic therapy was initiated at a median of 37 (range 2-98) days since aGVHD diagnosis. Before steroid initiation, 188 (54%) patients had been diagnosed with hyperglycemia, including 59 with DM history pre-transplant and 129 with documented hyperglycemia after transplant before the initiation of steroids. After steroids initiation, hyperglycemia was documented for 298 of 348 patients at a median of 3 days [inter-quartiles: 2-9] since initiation of steroids. The majority (57%) of cases occurred in patients with pre-transplant DM or patients who developed hyperglycemia post-transplant before the initiation of steroids. The 6 months CumInc of post-steroid hyperglycemia was 86% (95% Confidence Interval (CI) 82-89) overall, and differed significantly based on pre-steroid hyperglycemia history. It was highest in patients (n=59, 98% (95% CI 92-100, reference) with pre-transplant DM, followed by those (n=129, 87% (95% CI 81-93), p=0.001) who developed hyperglycemia post-transplant before

steroids, and finally those (n=160, 81% (95% CI (75-87), p< 0.01) who did not have any DM or hyperglycemia diagnosis before initiation of steroids. The difference between the last 2 groups was statistically significant (p=0.003). The median steroid starting dose was 1.5, 1.5, and 1.6 mg/kg in the 3 respective groups. Systematic evaluation of independent predictors of post-steroid hyperglycemia will be presented.

Conclusions: Our results show a high incidence of hyperglycemia in aGVHD patients after receiving systemic steroid therapy. The majority of cases occurred in patients with history of hyperglycemia before initiation of steroid therapy. These findings support a role for ISA dependent and independent mechanisms in the etiology of hyperglycemia in patients who develop aGVHD after alloHSCT.

Disclosure: Nothing to declare.

P539

Cost-effectiveness Analysis of Defibrotide for the Treatment of Severe Veno-occlusive Disease/sinusoidal Obstruction Syndrome in Spain

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Background: Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially fatal complication of haematopoietic cell transplantation (HCT). The most severe form of VOD/SOS is associated with multi-organ failure, extremely poor outcomes, and >80% mortality when left untreated. Defibrotide is the only approved intervention for these patients. This study aimed to determine cost-effectiveness of defibrotide versus best supportive care (BSC) as a treatment for severe VOD/SOS post-HCT in Spain.

Methods: A Markov model composed of 2 phases was adapted to Spanish settings. A 1-year acute phase with 1-day cycles and a lifetime long-term phase with 1-year cycles were considered. A cohort of patients who successfully underwent HCT and subsequently developed severe VOD/SOS were included in the model. Efficacy data for the acute phase of the model and length of stay related to VOD/SOS were obtained from Study 2005-01 (NCT00358501). Specifically, hospital stays associated with VOD/SOS were 15.7 days longer with BSC than with defibrotide. Moreover, patients treated with defibrotide spent fewer days in the intensive care unit than those treated with BSC (30% vs 60% of the duration of the stay for defibrotide and BSC, respectively). Assumptions for the long-term phase and utility values were obtained from the literature. Costs were from the Spanish Health System perspective (€ 2019). Cost of defibrotide was calculated considering a dose of 25 mg/kg/day and a treatment duration of 17.5 days, based on local expert opinion. Life years (LYs), quality-adjusted life years (QALYs), and costs were estimated over a lifetime horizon, and a 3% discount rate for both costs and outcomes was applied. Sensitivity analyses were performed to assess robustness of the results.

Results: Defibrotide produced an additional 1.214 QALYs and 1.348 LYs versus BSC. Regarding costs, defibrotide was associated with a total cost of €58,409 versus €24,701 for BSC (**Table**). Although defibrotide generated an additional cost, it resulted in savings associated with cost of hospital stay of up to €16,644 per patient. Difference between costs and effective measures led to ratios of €27,757/QALY gained and €25,007/LY gained. When a sensitivity analysis was performed, variables related to additional hospital stays showed the greatest influence on the base-case results. Probabilistic analysis confirmed the robustness of the deterministic results.

Conclusions: The results obtained from this cost-effectiveness model, adapted to Spanish settings, show that treatment with defibrotide in patients with severe VOD/SOS after HCT is a cost-effective alternative compared with only BSC in those patients.

Disclosure: David Carcedo Rodriguez: employee of Hygeia Consulting SL; Hygeia received funding from Jazz Pharmaceuticals to conduct the analysis

Teresa Artola Urain: no conflicts of interest to disclose

Anabelle Chinea Rodriguez: has served in an advisory role for Jazz Pharmaceuticals

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P540

Neurologic Complications IIN 169 Consecutive Allogeneic Stem Cell Transplants: Etiology, Clinical Syndromes and Outcome

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Background: Hematopoietic Stem Cell Transplantation (HSCT) is the only curative option for many haematologic malignancies, but post-transplantation complications are frequent and vary widely in severity and in organ involvement.

Neurologic complications incidence after HSCT, ranges from 8% to 42%, mostly within 100 days from transplant.

Methods: We conducted a retrospective analysis in 169 consecutive allogeneic HSCT, from 1 January 2010 to 31 December 2017, in order to evaluate incidence, and risk factors for neurologic complications, and to find correlations between the etiology, the clinical syndromes, the outcome and GVHD incidence.

Results: We recorded 60 neurologic events in 169 patients (35%), involving both Central Nervous System (CNS) and Peripheral Nervous System (PNS); 49 (81%) occurred early, during the first 100 days after HSCT, 11 (18%) later (late complications).

As for the early events 63% have been classified as toxic etiology (conditioning-related or drug-related), 24% of metabolic origin, 6% caused by infections, 4% recognizing cerebrovascular etiology, 2% immune-mediated. As for the 11 late complications, 54% were represented by infections, 18% were toxicity-related, 18% recognized cerebrovascular etiology and 9% were immune-mediated.

Most toxic complications have been attributed to calcineurin inhibitors (CNI) used for GVHD prophylaxis. Among the metabolic complications we identified 5 sepsis related, 2 cases of thiamine deficiency, 3 of hypernatriemia and 2 cases of Veno Occlusive Disease. Among the documented infections we identified 3 IFI by Scedosporium (2 patients) and Aspergillus (1) amd one Toxoplasma Gondii infection, while in 3 patients we could not identify any microbiological agents although large spectrum antimicrobial therapy was used successfully. Among the cerebrovascular events 2 were ischemic and 1 hemorrhagic. Finally 2 patients had diagnosis of neurological GVHD, but only after exclusion of all other possible causes.

Complete neurologic events resolution was recorded in 70% (42 patients), partial resolution/sequelae in 18% (6 patients), death in 6% (4 patients) due to Thrombotic Microangiopatia (2), Scedosporium infection (1), encephalitis of unknown origin (1); 5 more patients died for sepsis related causes.

Outcome was significantly different between patients with or without neurologic events, also in those neurologic event resolved.

One year and two year Overall Survival was 47% and 34% in patients with neurologic complications, and 62% and 56% in patients without neurologic events.

We found also a significant correlation ($p< 0.0001$) between neurologic events and concomitant acute graft versus host disease (GVHD).

Conclusions: Neurologic complications affect the HSCT outcome with different syndromes. Even in the case of positive evolution of the neurologic events, the final outcome remains poor and deaths frequently occur, mainly for acute GVHD and sepsis.

In our study most of neurologic events were ascribed to CNI toxicity but further data will be necessary to confirm.

Disclosure: nothing to declare.

P541

Venetoclax, Hypomethylating Agents and Dli for Salvage Treatment of Myeloid Malignancies Relapsing after Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Treatment of relapse after allogeneic hematopoietic stem cell transplantation (alloHSCT) remains a great challenge.

Methods: Aiming to evaluate the combination of venetoclax and hypomethylating agents (HMAClax) for the treatment of relapse of myeloid malignancies after alloHSCT, we retrospectively collected data from 32 patients treated at 11 German centers and analysed response, survival, treatment schedules and adverse events.

Results: Venetoclax was given in combination with azacitidine (n=13) or decitabine (n=19), 11 patients also received DLI. For 19 patients a 28day and for 13 patients a 21day administration with a 7day venetoclax free period was scheduled. Starting daily dose (DD) varied between 20 and 400mg and final DD was 200-1600mg. The highest continuous DD was 800mg. Median number of cycles per patient was 2 (1-19). Altogether 90 cycles were given, median cycle duration was 33days (17-92), median number of days with venetoclax was 21 (5-92). The median DD of the mean DD dose per cycle was 346mg (84-1500). A run-in period was planned in 15 patients for the first cycle. Three patients had non-fatal tumor lysis syndrome.

All but one patient had grade 3/4 neutropenia and 26 patients (81%) had grade 3/4 thrombocytopenia. Median duration of neutropenia was 13 days (0-60) in 49 cycles and no recovery was observed in 29 cycles.

Hospital admission for grade 3/4 infections was necessary in 23 patients (72%), 5 were fatal. One patient experienced new onset of cGVHD and mild aGVHD occurred in two patients.

In 30 evaluable patients overall response rate (ORR) was 47% (14/30, 3 CR MRD-, 5 CR, 2 CRi, 1 MLFS, 3 PR). Two patients died of infection before response evaluation. HMAClax was first salvage therapy in 8 patients (3 molecular (MR); 5 hematologic (HR) relapses). Six (86%) of 7 evaluable patients responded, vs 35% of patients receiving HMAClax as later salvage therapy (p=0.03). In total 6 patients had MR and 4 (67%) of these responded, ORR in patients with HR (n=24) was 42% (p=n.s.). Time to best response was 1.5 months (0.7-4.2). Seven patients lost best response after a median of 2 months (0.4-3.6.), 2 underwent second transplant in remission, 5 have ongoing responses. There was neither a difference regarding ORR between patients who received AZA or DAC, nor between DLI or no DLI, nor between the 21 or 28 day schedule.

On November 20th 2019, 25 patients (78%) had died and 7 were alive (median follow up 8.4months). Four were continuing HMAClax. Estimated median overall survival was 3.7ms. Median survival of patients with HMAClax first versus later salvage therapy was 5.7 and 3.4months (p=n.s.) and of patients with MR versus HR not reached and 3.4months (p=0.024).

Conclusions: This retrospective series shows that venetoclax is utilized in various different combinations, schedules and doses for treatment of relapse of myeloid malignancies after alloHSCT. Toxicity is substantial and patients who receive venetoclax/HMA combinations for MR or as first salvage therapy had the greatest benefit. Controlled prospective studies are needed to define the best partner, dose and schedule of venetoclax in this particular situation.

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P542

Evaluation of TGF-beta Level After Supplementation with Whey Protein Concentrate for Oral Mucositis Prophylaxis

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Background: Transforming growth factor beta (TGF-β) present in whey is associated with the control of intestinal inflammation and mucositis. It was previously published by our research group that whey protein concentrate (WPC) reduces the severity and duration of oral mucositis (OM). Therefore, we conducted a randomized trial with WPC supplementation in patients undergoing hematopoietic stem cell transplantation (HSCT) to assess whether these findings are related to serum TGF-β level.

Methods: A blind randomized study was conducted with patients undergoing HSCT at the UFJF University Hospital between January 2018 and June 2019. Patients received WPC (treatment group) or milk powder (control group) daily starting on the first day of conditioning chemotherapy until the end of neutropenia. Blood samples were collected on the first day of chemotherapy (sample 1) and on the first day of neutropenia (sample 2) in order to determine TGF-β levels, and the analysis was performed by ELISA with the Human TGF beta1 ELISA Kit (BMS249- 4) from the company INVITROGEN. Samples with undetectable value were excluded. The World Health Organization oral toxicity scale was used to assess the degree of oral mucositis, and adverse events were graded according to the National Cancer Institute criteria. All patients underwent mucositis prevention protocols using low-intensity laser therapy (1J / cm2).

Results: Forty patients were randomized, with no difference between treatment and control groups for the main factors that may influence the occurrence of mucositis. The overall incidence of OM was 57.5% (n = 23). Of these 23 patients 43.5% (n = 10) were supplemented with WPC, and 56.5% (n = 13) were not (p = 0.523). Although without significant statistical difference (p = 0.669), there was twice as much severe oral mucositis in the control group (66.6%, n = 6) in comparison to the patients receiving WPC (33.3%, n = 3). A reduction in TGF-β levels was observed at neutropenia compared to pre-supplementation in both groups. There was a trend towards higher TGF-β in sample 2 of the WPC-supplemented group (p = 0.079) compared to the control group, which was confirmed by the fact that the reduction in TGF-β variation between the pre- supplementation and onset of neutropenia samples was thirteen times greater in the control group, with a mean reduction of 35.38 ng ± 202.38 in the WPC group and 417.70 ng ± 377.05 in the control (p = 0.005).

Conclusions: Patients supplemented with WPC had a significantly lower reduction in TGF-β than the control group at the onset of neutropenia, which probably resulted in twice as much severe OM in patients who did not receive WPC.

Clinical Trial Registry: CAAE:15456513.5.1001.5133 http://plataformabrasil.saude.gov.br/login.jsf

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P543

Treosulfan-induced Myalgia in Pediatric Hematopoietic Stem Cell Transplantation

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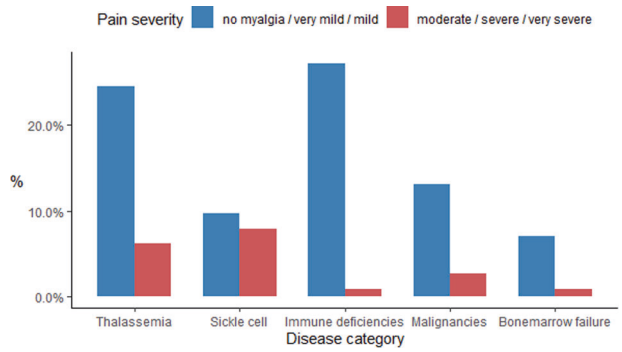
Background: Treosulfan (Trecondi®) is recently registered as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation (alloHSCT) in adult and pediatric patients. Treosulfan is increasingly used, particularly in children with non-malignant diseases because of its favorable toxicity profile. Common side effects of treosulfan are gastrointestinal, mucosal, skin disorders and elevation of liver enzymes. In our pediatric HSCT program, some patients experienced myalgia after conditioning with treosulfan. Since this is a relatively unknown side-effect of treosulfan in pediatric patients, we investigated the incidence, duration, severity and treatment of myalgia after treosulfan-based conditioning in a large cohort of pediatric patients and compared this data with a cohort of patients that received busulfan-based conditioning.

Methods: Patients transplanted in the pediatric transplant unit in the Leiden University Medical Center between May 2011 and May 2019 with a treosulfan-based (TreoFlu and TreoFluThiotepa) or busulfan-based (BuFlu, BuFluClo and BuFluThiotepa) conditioning regimen were included. Electronic Medical Records until 28 days after HSCT were screened for myalgia and 22 synonyms. Time to myalgia, location of pain, duration, severity and drug treatment were collected. Creatine kinase (CK) was collected if available. Pain severity was deduced from drug treatment: paracetamol (PCM) alone (very mild), PCM and tramadol (mild), PCM + tramadol + opiate (moderate), PCM + tramadol + opiate + other drug (e.g. NSAID, clonidine) (severe), PCM + tramadol + opiate + neuropathic drug or PCM + tramadol + opiate + duration >3 weeks (very severe).

Results: In this study, 206 patients were included. 114 patients received treosulfan and 92 patients busulfan. Myalgia was reported in 37 patients; 34 patients (30%) in the treosulfan group and 3 patients (3%) in the busulfan group (p< 0.001). The 3 patients who received busulfan, experienced this myalgia during or directly after infusion of clofarabine. In the treosulfan group, median time to myalgia was 7 days (0-12) and median duration of pain was 19 days (4-73). Most reported locations of pain were legs (97%) and arms (82%), more specifically the knees (47%) and elbows (26%). CK levels were not elevated. In the treosulfan cohort, myalgia occurred in both TreoFlu and TreoFluThiotepa regimens, however the incidence was significantly higher in patients with hemoglobinopathy (43% in beta thalassemia and 65% in sickle cell disease), as compared to other underlying diseases (immunodeficiencies, bone marrow failure and malignancies (9%), p< 0.001). Pain severity in the treosulfan cohort according to disease category is shown in Figure 1.

Conclusions: Myalgia appears to be a common adverse effect of treosulfan-based conditioning in pediatric HSCT, especially in patients transplanted for hemoglobinopathies (particularly sickle cell disease). A majority of patients required opiates to manage the pain. Although myalgia might be classified as a 'minor' side effect, it is a frequent cause of comorbidity in the early post-HSCT period. Recognition of treosulfan-induced myalgia is important for timely pain management strategies and improving quality of hospital stay. Exploration of other risk factors (e.g. genetic predisposition) is warranted to possibly prevent or manage this side effect.



[Pain severity according to disease category.]

Disclosure: Nothing to declare.

P544

Validation of Early Increase of SC5B-9 as a Predictive Marker for Later Transplantation Associated Thrombotic Microangiopathy

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Background: Hematopoietic stem cell transplantation (HSCT)- associated thrombotic microangiopathy (TA-TMA) is a multifactorial complication. Complement pathway dysregulation may play an important role in the pathogenesis of TA-TMA. Our recent observations suggested that early (i.e. from baseline to day 28 after HSCT) increase of soluble C5b-9 (sC5b-9), before the development of other markers, can predict later TA-TMA. Our aim was to identify pediatric patients with TA-TMA during two study periods, and to validate early increase of sC5b-9 as a predictive marker for later TA-TMA.

Methods: We enrolled 33 pediatric patients in the first (2013-September 2015) and 68 pediatric patients in the second (October 2015-January 2019) study period who underwent allogeneic HSCT. Five different TA-TMA diagnostic criteria were applied, and all important clinical and laboratory parameters of TA-TMA activity were registered. Complement pathway activities, components and sC5b-9 levels were systematically measured before transplantation and on day 28, 56 and 100 after HSCT.

Results: Overall 10/33 and 10/68 subjects met at least one of the different TA-TMA diagnostic criteria according to the five classification systems, typically on day 61 and 62 (median, range: 16-98 and 35-90). After some modifications in our institutional conditioning therapy and prophylactic immmunosuppression protocol, fewer patients (10/33 vs. 10/68; p=0.05) fulfilled the definition of TA-TMA. However, a strong and remarkable association still have been found between early increase of sC5b-9 (10 of 10 patients with TA-TMA vs. 28 of 58 without TA-TMA; p= 0.0017) and later development of TA-TMA. An increase in sC5b-9 concentration had 100% sensitivity and 54% specificity for TA-TMA in the whole pediatric cohort. All TA-TMA cases have been observed during cyclosporine immunosuppression (N=20/85), no TA-TMA was diagnosed during tacrolimus (N=0/11) or mycophenolat mofetil (N=0/4) therapy, a patient with an identical twin donor received no immunosuppression. After reduced toxicity conditioning regimen, in majority of patients (N=15/20) TA-TMA was mild and self-limiting, without any signs of organ damage. No additional complement parameters were closely associated with the development of TA-TMA.

Conclusions: Early raise of the sC5b-9 activation marker was predictive for later development of TA-TMA throughout the whole study period. In patients with a marked increase, early and frequent monitoring of TA-TMA activity markers should be attempted, to facilitate subsequent therapy decisions in time. However, patients with TA-TMA were only identified during or after cyclosporine immunosuppression. Further studies enrolling higher number of patients are necessary to determine the role of immunosuppression in the pathogenesis of TA-TMA.

Clinical Trial Registry: Our study was approved and registered by the National Committee of Science and Research Ethics (under number 41/EB/2014, Hungary). This work was supported by the Hungarian Pediatric Oncology Network, the Hungarian Scientific Research Fund (KH_18_130355), EFOP-3.6.3-VEKOP-16-2017-00009 and the Ministry of Human Capacities in Hungary.

Disclosure: Nothing to declare.

P545

Early Transjugular Intrahepatic Portosystemic Shunt (TIPS) Insertion Improves Outcome of Very Severe Hepatic Veno-occlusive Disease/sinusoidal Obstruction Syndrome (VOD/SOS) after Unmanipulated Haploidentical HSCT with Post-transplantation Cyclophosphamide

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Background: The use of unmanipulated Haploidentical HSCT (Haplo-HSCT) with post-transplantation Cyclophosphamide (PT-Cy) has widely extended. Hepatic veno-occlusive disease or sinusoidal obstruction syndrome (VOD/SOS) is a threatening complication after both autologous and allogeneic HSCT, with high mortality rates despite early medical treatment, including the use of defibrotide (DF). The objective of this study was to describe characteristics and outcomes of patients with VOD/SOS after Haplo-HSCT with PT-Cy, and particularly those with very severe VOD/SOS treated with transjugular intrahepatic portosystemic shunt (TIPS) as salvage procedure.

Methods: We retrospectively analyzed 185 unmanipulated Haplo-HSCT with PT-Cy consecutively performed between 2011 and June 2019 in a single centre. VOD/SOS diagnosis was defined using the Baltimore, modified Seattle or revised EBMT criteria. Severity was retrospectively graded according to revised EBMT severity criteria into four categories: mild, moderate, severe and very severe. Complete response (CR) was defined as a normal total bilirubin level (< 2 mg/dL) or, in patients with normal bilirubin or alternative causes of hyperbilirubinemia, as normalized renal function, reduction of elevated transaminase level < 50%, tense ascites resolution, and no need for oxygen supplement in the absence of alternative hypoxemia causes.

Results: Seventeen patients (9.2%) were diagnosed from VOD/SOS. Based on revised EBMT severity criteria, there were 2 mild (11.7%), 2 moderate (11.7%), 2 severe (11.7%) and 11 very severe (64.9%) grade VOD/SOS. Thirteen patients (76%) were treated with DF, including all patients with severe or very severe VOD/SOS, except one with CNS haemorrhage (Patient 1). Sixteen patients (94%) were alive at day-100 after HSCT. Seven patients (41%) with very severe VOD/SOS, were treated with TIPS due to rapid clinical or analytical deterioration or refractory hepatorenal syndrome, despite medical treatment including DF except Patient 1 (Table 1). TIPS insertion was performed on a median time since VOD/SOS diagnosis of 4 days (range 1-28) without technical complications in any case. Median hepatic venous pressure gradient (HVPG) prior to and after TIPS was 24 (range 14-29) and 7 (range 2-11) mmHg respectively, with a median drop of 16 mmHg (range 9-19). Following TIPS, all patients showed clinical improvement with hepatomegaly, ascites and renal failure resolution, and all showed analytical improvement with ALT, creatinine and INR values reduction, except for patient 2, whose TIPS indication was refractory hepatorenal syndrome with normal ALT levels. The 6 patients who had initiated DF before TIPS, completed 21 days of treatment. All patients met criteria for CR in a median of 8 days after TIPS insertion (range 2-82). The 100-day overall survival (OS) for these patients was 100%.

Conclusions: Incidence of VOD/SOS after Haplo-HSCT with PT-Cy is comparable to those reported after HLA-identical HSCT series. For patients with rapid progressive VOD/SOS, early TIPS insertion allowed completion of DF therapy. The use of TIPS together with DF resulted in CR and no associated complications with a 0% of VOD/SOS associated mortality despite high severity. In our experience, timely and individualized use of TIPS significantly improves outcome of very severe VOD/SOS after Haplo-HSCT. Therefore, TIPS should be promptly considered in rapid progressive cases.

Disclosure: Nothing to declare.

P546

Neurological Complicantions in Adult Allogeneic Hematopoietic Stem Cell Transplant Patients: Results from a Retrospective Multicenter Study

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Background: Allogeneic hematopoietic stem cell transplant (HSCT) is a potentially life-saving procedure that can be associated with severe complications with possible long-term, even fatal, effects. Neurological complications are relatively uncommon, of different etiology and difficult to diagnose. Existing data are obtained from relatively small series of patients and are extremely variable in terms of incidence, severity and prognosis. Aim of this study is to analyze, in a large sample of HSCT patients, neurological complications in respect to etiology, time of onset and outcome.

Methods: Data were collected from medical records of 1748 adult patients who underwent HSCT from 01/01/2007 to 30/09/2019 in 5 Italian Bone Marrow Units. Neurological complications were considered from the time of HSCT conditioning until the last follow-up or death and classified according to etiology and time of onset.

Results: Sixty-five (3,72%) of the 1748 patients analyzed developed a neurological complication. Patients median age was 53 (19-70) years, F/M ratio was 20/45. Conditioning regimen was myeloablative in 39/65 (60%) patients and of reduced intensity in the remaining. Fourteen (21,5%) patients had a matched-related donor, 9 (13,9%) a haploidentical, 14 (21,5%) a matched-unrelated, and 28 (43,1%) a mismatched-unrelated. At neurological complication onset 21/65 (32,3%) patients were presenting a Cytomegalovirus reactivation and 19/65 (29,2%) a non-neurological Graft vs Host Disease (GVHD), with 16/19 (84,2%) being under immune-suppressive treatment. Diagnostic tools were NMR in 49/65 (75,4%) cases, CT-scan in 46 (71%), lumbar puncture in 46 (71%) and electroencephalography in 21 (32,3%). Table 1 resumes neurological complications according to etiology and time of onset. Neurological complications were mostly infectious with 26/65 (40%) cases, for the most part of viral origin (46%), and occurred independently of the time from HSCT. Immune-mediated complications, starting from day +30, were 14/65 (21,5%), thus constituting the second most represented (with the majority being neurological GVHD). Disease relapse was found in 10/65 cases (15,4%), with median time of onset of 244 (180-530) days. Drug-related toxicity occurred in 8/65 cases (12,3%) and was mainly due to cyclosporine. Neurological complications occurred after a median time of 119 (0-1006) days from HSCT, with 50,8% developing within the first 120 days. Overall, 25/65 (38,5%) patients died of neurological complication (infectious 11, central nervous system relapse 5, immune-mediated 3, drug toxicity 2, cerebral neoplasia 1), while 7 (11%) suffered from long-term consequences (immune-mediated 4, infectious 1, cerebrovascular 1).

Conclusions: Our study suggests that, although quite rare, neurological complications are associated with significant mortality and long-term disabilities in HSCT patients. In our series neurological complications were mostly infection-related and immune-mediated and occurred through a wide range of time after HSCT, thus suggesting the need of a careful surveillance of neurological symptoms, rapid diagnosis and prompt intervention in all patients regardless of the time from HSCT.

Disclosure: Nothing to declare.

P547

Allogeneic Stem Cell Transplantation Recipients Admitted to the Intensive Care Unit - Reappraisal of Prognosis and Prognostic Factors - A Single Center Study

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Background: More patients with hematological malignancies (HM) are referred to the intensive care unit (ICU) and their mortality has dropped sharply. Among them, recipients of allogeneic stem cell transplantation (ASCTR) remain a specific subgroup with dismal prognosis.

Methods: This is a retro-prospective descriptive single-center study from Grenoble University Hospital (France). All ASCTR admitted in ICU from hematology ward between January 2012 and June 2019 were included as a subgroup of ongoing CARE-HEMA study (NCT 03399149).

Results: 57 ASCTR (15.7% of the 363 ASCT performed over the period) were included : 35 males and 22 females, with a median age of 51 years (IQR [41-68]).

Their HM were 65% myeloid, 30% lymphoid and 5% were aplastic anemias.

35% had undergone a myeloablative and 65% a reduced intensity conditioning regimen.

Stem cells source was bone marrow in 17.5%, peripheral blood in 77.2% and cord blood in 5.3% of cases.

Donors were sibling genoidentical in 23%, familial haploidentical in 17% and unrelated in 60% (10/10, n=21; 9/10, n=10, cord blood, n=3) of cases.

At time of transplant, 47% of patients were in complete remission, 8.8% had a stable disease, and 43.2% were in a relapse/refractory situation.

These 57 patients accounted for 65 ICU admissions (26% of the 250 ICU admissions of HM patients over the period), with a median delay of 23 days (IQR [6.5-83]) after ASCT.

At time of admission, specific complications were ongoing GVHD (24.6%), a history of invasive pulmonary aspergillosis (30.8%), ongoing CMV reactivation (15.8%), other virus reactivation (26%), thrombotic microangiopathy (4.6%) and veno-occlusive disease (9.2%).

Main reasons for ICU admission were acute respiratory distress (44%) and sepsis (44%).

Median Sepsis-related Organ Failure Assessment (SOFA) score at admission was 7 (IQR [5-9]) and improved over the first 72h in 65% cases.

70% of the cases required ventilation support (31 invasive mechanical ventilation (MV), 4 non-invasive ventilation and 5 high flow nasal oxygen), 74% required vasopressors and 38.5% requested renal replacement therapy (RRT). Several organ replacement strategies were required in 35 cases (2 in 16 cases and 3 in 19 cases).

Median length of stay (LOS) was 7 days in ICU (IQR [2-23]), 48 days in hospital (IQR [30-64]). Death rate was 32% in ICU, 51% in hospital and 75% 1 year after ICU admission.

None of demographic and hematologic/transplant factors influenced ICU survival.

In univariate analysis, ICU survival was impaired by the requirement of any organ support and their accumulation, severity at ICU admission, deterioration in the first 72h of ICU stay, and ICU LOS. Multivariate analysis showed a pejorative impact of several organ supports requirement. ICU/hospital death rate were 90%/100% when MV, vasopressors and RRT were required.

One year survival was impaired by a relapse/refractory status of HM at time of ASCT, severity at ICU admission, requirement of several organ supports, and hospital LOS.

Conclusions: The prognosis of ASCTR requiring ICU admission remains poor. The impact of severity at ICU admission and cumulative need of organ support techniques suggests that an early admission might be beneficial.

Clinical Trial Registry: NCT 03399149

Disclosure: Nothing to declare.

P548

Enteral Versus Parenteral Nutrition in Adult Hematopoietic Cell Transplantation Recipients Suffering from Gastrointestinal Mucositis

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Background: Gastrointestinal (GI) mucositis is a severe side effect of intensive chemotherapy (ICT) and/or radiotherapy and is associated with nutrient maldigestion and malabsorption. Total parenteral nutrition (TPN) is predominantly used in adults treated with ICT and hematopoietic cell transplantation (HCT) albeit without evidence indicating superiority of TPN over enteral nutrition (EN). We performed a prospective randomized single centre clinical trial (RCT), comparing two feeding strategies (TPN or EN) in HCT adults.

Methods: Adult patients (³ 18 years), admitted to the Radboud University Medical Center Nijmegen for treatment with an autologous (a)HCT following conditioning with high-dose melphalan (HDM) or carmustine, etoposide, cytarabine and melphalan (BEAM), were eligible for inclusion. Exclusion criteria were pre-existing bowel diseases, BMI < 18 (kg/cm2), serum albumin < 20 g/l and creatinine clearance < 50 ml/min.

Patients were randomized to receive either EN or TPN. An elementary tube diet was administered by continuous enteral drip through a naso-gastric tube (EN group).

Primary endpoints were changes in nutritional status (Dbodyweight and Dmid-upper arm circumference (DMUAC) on day +28 post-HCT, and severity of GI mucositis (nadir citrulline levels). Secondary endpoints include treatment-related complications (FN, bacteraemia, inflammation).

Results: Between September 2014 and January 2018 the planned 34 adult patients were included. Six patients were not evaluable because they did not tolerate EN or lost their naso-gastric tube within 48 hours of placement, but as defined in the protocol they were replaced by 6 additional patients although 3 of them also proved unevaluable. Finally 31 patients were evaluable, 11 patients received EN and 20 patients received TPN. Median age was 59 (44-69) years, and most patients were male (77.4%). All received an aHCT with HDM (18 patients) or BEAM (13 patients). The Dbodyweight on day +28 was -4.02 kg in the EN and -3.68 kg in the TPN group (absolute difference -0.34 kg; CI 95% -2.6 - 1.99, p=0.77). The DMUAC on day +28 was -1.41

cm in the EN and -1.02 cm in the TPN group (absolute difference -0.39 cm; CI 95% -1.38 - 0.60, p=0.43). The course of citrulline levels was comparable.

The mean duration of neutropenia was 15.36 days in EN and 16.35 days in TPN (p = 0.77). Incidence of FN was 10 in the EN group and 14 in the TPN group (p=0.18).

There were no differences in patients with a bacteraemia between the EN (3 patients) and the TPN group (7 patients) (p=0.67).

Conclusions: Although preclinical studies suggest a beneficial role of EN in patients with GI mucositis in this RCT with adult HCT recipients tolerability and feasibility was poor and efficacy could not be established (although underpowered).

Disclosure: Nothing to declare.

P549

Delayed Engraftment and Prolonged Hospital Stay Following Omission of Folinic Acid after Methotrexate for GVHD Prophylaxis in Allogeneic Transplant Recipients

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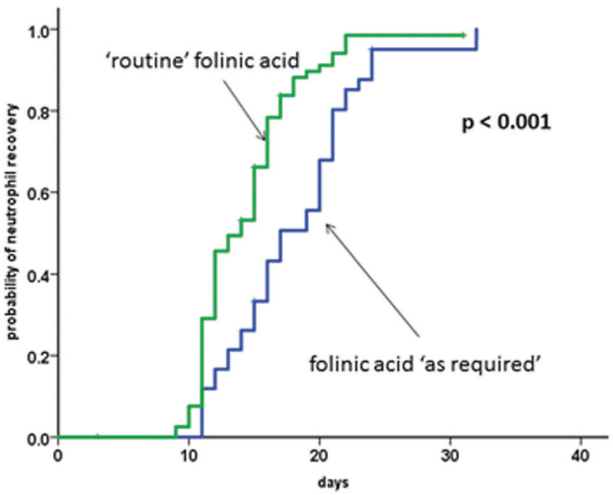
Background: Methotrexate (MTX) has an established role in the prevention of graft versus host disease (GVHD) but may contribute to delayed engraftment, hepatotoxicity and mucositis. While folinic acid administered after each dose of methotrexate may reduce this toxicity, it is not universally used. In 2017 our centre stopped routinely prescribing folinic acid after MTX. We compared patient outcomes before and after this change in practice.

Methods: We collected data on consecutive patients who received myeloablative conditioning and ciclosporine + MTX GVHD prophylaxis following allogeneic peripheral blood haemopoetic progenitor cell transplant (HPCT) for haematological malignancy from 2015 to 2018. Methotrexate was administered at 15mg/m^2 on day 1 and 10mg/m^2 on days 3, 6, 11 in all patients. Where prescribed, folinic acid 12.5mg IV was administered q6 hourly starting 12 hours after day 1 MTX (total 3 doses) and 24 hours after subsequent methotrexate doses (6-8 doses per MTX).

Results: A total of 122 patients were included, with a median age of 51 years (16-66yrs). Conditioning regimens were busulphan + cyclophosphamide (Cy), TBI + Cy or fludarabine + melphalan, and 83 (68%) had an unrelated donor. Eighty patients (66%) received routine folinic acid rescue after each methotrexate dose ('routine folinic group'). Forty-two patients (34%) received folinic acid only if creatinine was elevated >25% from baseline at the time of methotrexate dose ('as required folinic group'). Age, conditioning regimen intensity and donor type was similar between groups. Both time to neutrophil engraftment (mean 14 versus 18 days, see Figure) and length of hospital stay post infusion of HPC (mean 18 versus 25 days, p< 0.001) were significantly shorter in the 'routine' compared with the 'as required' folinic group. There was no difference in the incidences of grade II-IV acute GVHD (34% [95% confidence interval (CI) 23-45%] versus 30% [95%CI 16-44%]), 12-month chronic GVHD (51% [95%CI 40-63%] versus 52% [95%CI 35-69%]) nor 12-month overall survival (71% [95%CI 61-81%] versus 74% [95%CI 60-88%]) in the routine versus as required folinic groups, respectively. Cumulative incidences of relapse and non-relapse mortality were also similar. Finally, MTX levels were measured in 10 patients in the 'as required' group and ranged from 0.04-0.14 umol/L at 12 hours post day 1 MTX and 0.04-0.99 umol/L at 24 hours after subsequent doses (median=0.04 umol/L). The patient with MTX level 0.99 umol/L had developed acute kidney injury (eGFR 34ml/min) at the time of methotrexate dosing.

Conclusions: We observed a significant increase in time to neutrophil recovery and length of stay after omitting routine folinic acid in peripheral blood HPC recipients given MTX GVHD prophylaxis, with no associated change in acute or chronic GVHD, mortality or relapse. We postulate that despite low plasma MTX levels at time of administration, folinic acid rescue ameliorates MTX-induced suppression of neutrophil recovery. Based on these results our programme has returned to routine folinic acid rescue after MTX. These results may be applicable to other centres seeking to reduce short-term morbidity and length of stay after allogeneic HPCT.



[Figure: neutrophil recovery by folinic acid group]

Disclosure: Nothing to declare.

P550

The Usefulness of Liver Stiffness Measurement before Hematopoietic Stem Cell Transplantation to Predict Sinusoidal Obstruction Syndrome

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Background: Sinusoidal obstruction syndrome (SOS) is a potentially life-threatening complication affecting patients undergoing hematopoietic stem cell transplantation (HSCT). Several risk factors have been identified for the development of SOS: pre-existing hepatic disease, prior HSCT and previous therapy with Inotuzumab ozogamicin. Liver stiffness measurement (LSM) is a physical parameter that reflects structural and vascular changes of the liver; recently, LSM has been demonstrated as a promising non-invasive ultrasound-based technique for early SOS diagnosis after HSCT.

Methods: We report pre-HSCT evaluation of liver stiffness in 10 patients (table 1) aged between 23 and 70 years with hematologic clonal disorders (3 myelofibrosis, 2 acute myeloid leukemia, 4 acute lymphoblastic leukemia, 1 mantle cell lymphoma) who underwent HSCT from different donors (4 matched unrelated, 3 haploidentical, 2 HLA identical siblings) and stem cell sources (1 umbilical cord blood and 9 peripheral blood). All patients had several risk factors for developing SOS: advanced disease, heavy pre-treatment (previous allogeneic HSCT in 2 patients e autologous HSCT in 1 patient), conditioning regimens based on alkylating agents at reduced doses in 8 patients and at full myeloablative doses in the other 2 cases. Moreover, 4 patients received 2 or 3 cycles of Inotuzumab as salvage treatment for refractory disease and "bridge to" HSCT. LSMs before HSCT were assessed by a point shear wave elastography technique (Siemens' ARFI).

Results: Three out of 10 patients developed severe hepatic SOS at day +15, day +3, day +4 after HSCT, respectively, that were treated precociously with defibrotide. In 1 out of 3 cases, SOS recovered without sequelae (pt.8), while the other two patients showed a fatal course due to multi-organ failure at day +22 (pt.4) and +14 (pt.7) respectively, despite defibrotide treatment. The median pre-HSCT shear wave velocity was higher in patients who subsequently developed SOS versus those without SOS (1.8 m/s vs 1.6 m/s). Moreover, LSM values were increased in patients previously treated with Inotuzumab (median 1.99 m/s vs 1.49 m/s).

Conclusions: Even if the small sample of patients examined did not allow us to detect significant differences in pre-HSCT LSM values between the groups examined, our study observed higher LSM values in patients treated with Inotuzumab and in those who further developed SOS, suggesting that liver elastography before conditioning could predict liver complications after HSCT. Taking in account the fact that defibrotide treatment initiated at SOS diagnosis could be unsuccessful in some patients with multiple risk factors of SOS, knowledge of pretransplantation LSM values before HSCT can be useful to select cases for using defibrotide prophylaxis in patients with persisting risk factors for SOS and urgent need of HSCT.

Disclosure: Nothing to declare.

Pt 1: Myelofibrosis	Pt 2: Acute Myeloid Leukemia	Pt 3: Myelofibrosis	Pt 4: Acute Lymphoblastic leukemia B Ph neg	Pt 5: Myelofibrosis	Pt 6: Mantle Cell Lymphoma	Pt 7: Acute Lymphoblastic leukemia B Ph neg	Pt 8: Acute Lymphoblastic leukemia B Ph pos	Pt 9:Acute Lymphoblastic leukemia B Ph neg	Pt 10: Acute Myeloid Leukemia
No prior stem cell therapy	No prior stem cell therapy	No prior stem cell therapy	**Prior ASCT**	No prior stem cell therapy	No prior stem cell therapy	**Prior HAPLO HSCT**	No prior stem cell therapy	No prior stem cell therapy	**Prior MUD HSCT**
MUD (Treo-Bu-Flu)	MUD (Treo-Flu)	UCB (Treo-Bu-Flu)	HLA-ID (Treo-Flu)	MUD (Treo-Bu-Flu)	HAPLO (EDX-Flu-TBI)	HAPLO (Treo-Bu-Flu)	MUD (Treo-Flu)	HLA-ID (Bu-EDX)	HAPLO (Treo-Flu)
No inotuzumab	No inotuzumab	No inotuzumab	**2 cycles of inotuzumb administered**	No inotuzumab	No inotuzumab	**2 cycles of inotuzumb administered**	**2 cycles of inotuzumb administered**	**3 cycles of inotuzumb administered**	No inotuzumab
LSM pre-HSCT= 2,15 m/s	LSM pre-HSCT= 1,15 m/s	LSM pre-HSCT= 2,27 m/s	LSM pre-HSCT= 2,27 m/s	LSM pre-HSCT= 0,88 m/s	LSM pre-HSCT= 1,1 m/s	LSM pre-HSCT= 1,33 m/s	LSM pre-HSCT= 2,03 m/s	LSM pre-HSCT= 2,36 m/s	LSM pre-HSCT= 1,4 m/s
No SOS	No SOS	No SOS	**SOS DIAGNOSIS (+15)**	No SOS	No SOS	**SOS DIAGNOSIS (+3)**	**SOS DIAGNOSIS (+4)**	No SOS	No SOS

[Table 1. Characteristics of patients]

P551

Endothelial Cell Complications after Allogeneic Stem Cell Transplantation, A Single Centre Analysis on 99 Consecutive Patients undergoing allo-sct

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Background: Allogeneic transplant (allo-SCT) is still associated with significant morbidity and mortality, which is not only attributable to infections or GVHD, but also to endothelial damage. Veno-Occlusive disease, Capillary leak syndrome, engraftment syndrome, transplant-associated microangiopathy, diffuse alveolar hemorrhage, and idiopathic pneumonia syndrome represent the main nosological entities, but a growing interest focused on the relationship between endothelial damage and refractory GVHD.

Methods: We analyzed 99 patients undergoing allo-SCT between January 2015 and December 2018 at our institution for different haematological malignancies: AML/ALL (65% of patients); MDS (6%); PMF/LMC (10 %); NHL (10%) and MM (4%), with a median age of 55 yrs. The donor was identical sibling in 30%, 10/10 UD in 28%, < 10/10 UD in 17% and haplo in 25% of cases, respectively; stem cell source was BM in 43%, PBSC in 54%, PBSC+BM in 3% respectively; conditioning was MAC (61%), RIC (36%), nMAC (3%); GVHD prophylaxis was CSA/MTX (63%) and ptCY/CSA/MMF (37%). Median follow up was 26 months.

Seven clinical pattern of endothelial cell complication (ECc) have been identified, according to EBMT standards: Transplant-associated thrombotic microangiopathy (TA-TMA), capillary leak syndrome (CLS), engraftment syndrome (ES), idiopathic pneumonia syndrome (IPS), Sinusoidal obstruction syndrome (SOS) of the liver, Diffuse alveolar hemorrhage (DAH), Posterior reversible leukoencephalopathy syndrome (PRES).

Results: In 39/99 patients an ECc has been documented. In 20 patients different entities overlapped: 8 patients developed TA-TMA and PRES, 5 patients SOS and PRES; the remaining 7 patients developed variable combination of PRES, TA-TMA, DAH, ES and SOS. Median time to the clinical onset differ according to the kind of ECc: 16 days (2-123) for TA-TMA, 9 days (1-114) for PRES, 16 days (6-55) for DAH, 24 days (2-161) for SOS, 10 days (9-11) for ES. Overall the incidence of acute GVHD (aGVHD) was 53% in the 99 patients, while incidence of grade 2-4 aGVHD was 26%. Among those patients developing grade 2-4 aGVHD the ECc incidence was 54%, significantly higher than reported (4%) in patiens who did not develop aGVHD.

In 9 patients ECc preceded aGVHD, in 2 patients ECc and aGVHD developed together while in 3 ECc developed after aGVHD. A statistically significant association has been observed between ECc and aGVHD (p=0.04), although it was not possible to establish a chronological time line.

Cumulative incidence of NRM at one year was 22%, significantly higher in patient developing any ECc (34%) as compared to patients who did not develop such complications (18%, p=0.02).

Main causes of death were infections and GVHD associated with ECc, but 10 patients died directly for ECc. Overall survival at 2 years was 56%. OS was higher in the group of patients who did not develop ECc (59%) as compared to patients who experienced ECc (40%, p< 0.24)

Conclusions: These results suggest that the endothelial complications are an emergent issue after allo-SCT; indeed the real-life incidence of ECc is far higher than reported in past surveys and represents a real challenge in order to reduce both the GVHD incidence and the overall NRM.

Disclosure: Nothing to declare.

P552

Influence of Abo-incompatibility on the Outcome of Stem Cell Transplantation - A Retrospective Study on Children and Young Adults

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Background: In hematopoietic stem cell transplantation (HSCT) hematopoietic stem cells of variable donors and sources are administered to patients with the aim of repopulating or replacing the hematopoietic system. The main criteria of finding a suitable donor is whether they have matching HLA-antigens with the patient. Other factors such as age, sex, number of parities, CMV-serostatus and ABO-compatibility are only secondary. ABO-incompatibility is present in approximately 50% of all HSCTs but it is vastly unclear to what extent it affects the outcome.

Methods: In this study 573 cases of allogenic HSCTs performed at the St. Anna Kinderspital in Vienna between 1980 and 2016 were retrospectively analyzed to check if ABO-incompatibility has an influence the outcome. A wide range of patients differing in age (mean age 8,9 years, range

0-26 years), underlying disease (leukemia, non-malignant disease, solid tumor and lymphoproliferative disease), stem cell graft source (bone marrow, peripheral blood stem cells and umbilical blood) and the type of donor were included. 294 (51,3%) of the analyzed cases were ABO-compatible whereas 113 (19,7%) were major-, 114 (19,9%) minor- and 52 (9,1%) bidirectionally incompatible.

Results: In univariate as well as multivariate analysis ABO-incompatibility had no influence on the overall survival. A significant effect on the non-relapse mortality (NRM), the rate of successful engraftment, the rate of rejections, the overall transfusion requirements, the engraftment of thrombocytes, the incidence of acute or chronic graft-versus-host disease (GvHD) or the risk of having a positive antiglobulin test post-HSCT could not be observed either. However, some of the analyses (NRM, engraftment, transfusion requirements) showed a trend towards a possible influence. Therefore, it cannot be excluded that an actual influence was underestimated due to an insufficient number of included cases or the applied statistical methods. Additional larger multicenter studies and meta-analysis are required to further investigate if ABO-incompatibility leads to an increased mortality or morbidity.

Conclusions: This study is including solely pediatric patients. Children are different from adults in several aspects. Thus, it is important that particular attention is paid to this group of patients in future studies.

Disclosure: no disclosure to declare.

P553

Abstract already published.

P554

Veno-occlusive Disease: Online, Interprofessional, Case-based Education Significantly Improves Knowledge and Skills of the Entire Care Team

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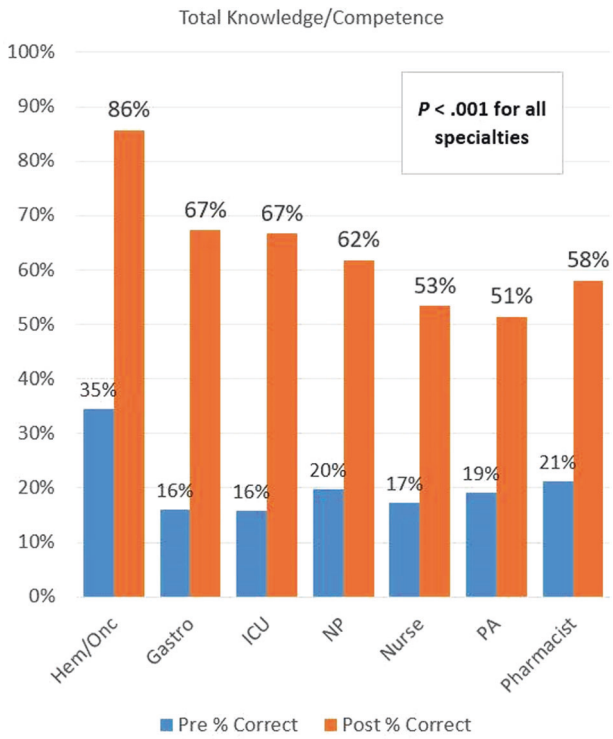
Background: Veno-occlusive disease (VOD) is a potentially devastating complication that can occur after hematopoietic stem cell transplant (HSCT) and in severe cases can lead to multi-organ failure. (Mohty 2016) Defibrotide has been proven to be effective to prevent and treat VOD, and it is critical that clinicians are aware of how to diagnose and treat this serious complication of HSCT. This study was conducted to determine if an online, interprofessional, case-based continuing medical education (CME) intervention could improve skills of the oncology care team in the diagnosis and treatment of patients with VOD.



[Figure 1. Total Knowledge and Competence Gains from Pre- to Post-Education]

Methods: The format was an online CME-certified text-based activity composed of 2 patient cases with interactive questions on the diagnosis and treatment of VOD. Evidence-based educational feedback was provided following each response. Three multiple-choice knowledge/competence questions and 1 self-efficacy question were selected from the set of intra-activity questions to be repeated immediately after activity participation. These questions assessed the impact of the education in the form of a repeated pairs pre-assessment/post-assessment study design in which each participant served as his/her own control. Using data from the assessment completers, percentages of

correct responses to pre- and post-assessment questions were compared. A McNemar's test was then used to assess statistical significance of the educational impact, where $P < .05$ was considered statistically significant. The activity launched online on October 31, 2019 and data reported were collected through December 11, 2019.

Results: At the time of the data pull there were 28 hem/oncs, 56 gastroenterologists (gastro), 19 critical care physicians (ICU), 2,672 nurses, 177 nurse practitioners (NP), 103 physician's assistants (PA), and 486 pharmacists. Three questions were repeated (Figure 1), while some questions were only asked once during the activity (Table 1).

	Hem/Onc	Gastro	ICU	Nurse	NP	PA	Pharmacist
Due to her induction therapy, Angela is at greater risk for which of the following post-transplant complications?	54%	11%	37%	18%	15%	18%	17%
Increased busulfan exposure can increase the risk of developing VOD. What medication increases busulfan exposure and should be avoided while Angela is receiving busulfan to reduce this risk?	18%	36%	11%	31%	36%	34%	32%
Which of the following would you recommend stopping during the transplant period (until at least 30 days after transplant) to reduce the risk of VOD?	61%	34%	32%	33%	35%	36%	46%
Approximately what proportion of pediatric patients with VOD develop hyperbilirubinemia?	36%	52%	42%	46%	46%	44%	47%
What would you recommend doing, if anything, with the defibrotide, leading up to the biopsy?	43%	45%	47%	33%	37%	37%	36%

[Table 1. Percentage of Clinicians Who Answered Each Intra-Activity Question Correctly]

Conclusions: This online, interactive, interprofessional, case-based CME-certified educational activity led to statistically significant improvements in the knowledge and clinical competence of the entire clinical team regarding diagnosis and management of patients with VOD. The results indicate that unique educational methodologies and platforms, which are available on-demand, can be effective tools for advancing clinical decision making. Additional studies are needed to assess whether improved aptitude translates to improved performance during clinical practice.

Reference: Mohty M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. Bone Marrow Transplant. 2016 Jul;51(7):906-912.

Acknowledgements: Sameer Bhagavatula contributed to data analysis for this research.

Disclosure: Nothing to declare.

P555

Hyperhemolysis Syndrome is a Novel Cause of Severe Hemolytic Anemia after Allogeneic Transplantation with Very Poor Response to Treatment and Outcome

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Background: Hyperhemolysis syndrome (HHS) is a serious and potentially life-threatening type of hemolysis defined by: 1) severe intravascular hemolysis with hemoglobinemia, hemoglobinuria, undetectable haptoglobin and increased bilirubin and LDH after transfusion of compatible red cells; 2) bystander hemolysis of the patient´s red cells, with hemoglobin reduced to levels below pretransfusion, and 3) reticulocytopenia. HHS has been primarily described, albeit with an unclear mechanism, in patients with sickle cell disease. Here we present evidence of HHS as a novel cause of severe hemolysis in allogeneic transplant recipients.

Methods: We describe three female recipients of allogeneic cord-blood transplantation (dual protocol with third-party CD34+ cell; Bautista et al. https://doi.org/10.1038/bmt.2008.329) who developed HHS that shared clinical and analytical features of a common pathophysiologic mechanism.

Results: From a previous full erythroid recovery, patients presented at approximately 5 months after transplant, following tacrolimus withdrawal, with very severe acute anemia and low reticulocyte counts (see attached). Transfusion of compatible red cells triggered HHS, as defined above. In the following days, patients developed positive direct antiglobulin test (DAT) for Ig-G an C3d, and an anti-E Rh antigen IgG auto(allo)-antibody was identified in the elution product from DAT positive cells in two of the three cases. Recipient´s pre-transplant Rh phenotype were E-positive. Although donor (i.e. cord blood) Rh E genotype

was not studied (not normally studied as part of donor assessments), our results suggest that cord blood genotype in these cases was E-negative, and following engraftment, cord-chimerism and immunosuppression withdrawal, they developed an auto(allo)-antibody with anti-E specificity triggered by Rh antigen E-positive in the recipient (or the third-party donor in this transplant modality). Hemolysis was refractory to all treatments, including corticosteroids, immunoglobulins, erythropoietin, rituximab, plasmapheresis with red cells exchange, cyclophosphamide, eculizumab, bortezomib and splenectomy. Also, transfusion of compatible E-negative red cells precipitated additional HHS crises and worsened the anemia further (bystander effect). One patient received a bovine-derived hemoglobin substitute (HGB-250; Hemopure®). All three patients died from severe anemia unresponsive to treatment.

Conclusions: These unfortunate cases highlight the potential occurrence and poor outcome of HHS after allogeneic transplantation. Severe hemolysis and low reticulocyte counts after stable erythroid engraftment should raise a suspicion of life-threatening HHS and differentiate it from other recognized entities such as autoimmune hemolytic anemia or AB0 incompatibility, where hemolytic episodes are usually milder and associate with increased reticulocytes. Although the mechanism will require further elucidation, these cases showed an association of HHS with the generation of anti-E auto(allo)-antibodies. In the absence of an effective treatment to control this complication, and given that the mathematical probability of a donor E-negative and recipient E-positive mismatch is around 20% in caucasians, a potential alternative would be to study (phenotyping and/or genotyping) recipient and donor Rh antigens to avoid E negative donors for E positive patients. Assessing Rh E-mismatch appears more important than AB0 compatibility, which is standard practice. We have already implemented Rh E-testing in cord blood transplants. Awareness of this complication in allogeneic transplantation and further analysis of its pathophysiology and treatment are warranted.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare.

P556

Easix as a Predictive Biomarker of Complications and Outcome in Allogeneic Hematopoietic Cell Transplantation

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Background: Penack and Luft developed EASIX (Endothelial Activation and Stress Index; (LDH × creatinine) / thrombocytes) as a biomarker based on simple laboratory tests to assess endothelial dysfunction and stress signals that underlie many potential complications of allogeneic HSCT (alloHSCT) and predict outcomes. Other simple laboratory tests such as ferritin and uric acid are also danger and inflammation signals that may associate with alloHSCT outcomes. Here, we analyse the impact of these measurements in alloHSCT outcomes in an independent series in our center.

Methods: EASIX was measured at several time-points (pre-conditioning, day 0, +14 and +28 after alloHSCT), and ferritine and uric acid levels were measure only pre-conditioning, and the results analysed with regards to major complications and outcome in all consecutive alloHCT recipients between 2009 and 2018.

Results: 237 alloHCT in 224 recipients were included: 138 men (58.2%); median age 45 years (16-69); 56.5% acute myeloid leukemia/myelodysplastic syndromes, 16% acute lymphoblastic leukemia, 15.6% chronic lymphoproliferative disorders, 6.3% myeloma and 5.5% other; 43.5% matched-related, 30% cord-blood, 18.1% unrelated and 8.4% haploidentical donors; 52.3% myeloablative conditioning; 74 (31.2%) had acute graft-versus-host disease (GVHD) grades II-IV, 24 (10.1%) had transplant associated thrombotic microangiopathy, 15 (6.3%) had veno-occlusive disease and 108 (45.6%) had at least one episode of sepsis during the first year after alloHCT. Increased EASIX levels (all defined as above the median) prior to conditioning associated in our series with higher rates of sepsis (52.5% vs 39%, p=0.037), and increased EASIX levels at day +14 associated with higher rates of TMA (14.4% vs 6.1%, p=0.037) and sepsis (54.6% vs 37.4%, p=0.008). In addition, raised uric acid levels above median associated with higher rates of acute GVHD (37.9% vs 25.2%, p=0.036) and sepsis (51.7% vs 39.5%, p=0.06), and increased ferritin levels were also associated with higher rates of acute GVHD (36.8% vs 22.4%, p=0.09). Of particular relevance, EASIX levels above median were associated with lower overall survival at every timepoint assessed (pre-conditioning: 55.9% vs 73.7%, p=0.038; day 0: 59% vs 72%, p=0.029; day +14: 52.9% vs 78.3%, p< 0.001; day +28: 60% vs 72.4%, p=0.005) and with higher non-relapse mortality at day 14 and 28 (day +14: 36% vs 13.2%, p< 0.001; day +28: 29.4% vs 17.9%, p=0.004).

Conclusions: Laboratory tests that measure endothelial dysfunction and danger signals, such as EASIX, uric acid and ferritin, have been proposed as simple tools to predict alloHSCT complications and outcome. Specific associations of these measurements with particular complications may

depend on patient and transplant characteristics that vary among centers. However, our independent series confirms a sound association between these biomarkers, specifically EASIX, and hard endpoints such as patient overall survival and non-relapse mortality. Broader implementation of the use of these test and analysis of their performance to predict alloHSCT outcomes in the real-world is warranted.

Disclosure: Nothing to declare.

P557

Survival with Normal Pulmonary Function is Possible Despite Significant and Prolonged Respiratory Support, Including Prolonged High Frequency Oscillatory Ventilation (HFOV) in Children

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Background: Acute respiratory failure (ARF) contributes significantly to non-relapse mortality among allogeneic hematopoietic stem cell transplant (HSCT) recipients. Lung injury may be classified as non-infectious or infectious. Non-infectious lung injury may be acute idiopathic pneumonia syndrome (IPS) or chronic, leading to either obstructive lung disease or restrictive lung disease. Management includes mechanical ventilation in pediatric intensive care unit (PICU) and this may itself, if protracted, be damaging to the lung. The longer term prognosis for pulmonary function of ventilated patients is discussed frequently, and in this study we report excellent long-term pulmonary outcome of patients ventilated following HSCT and who recovered from ARF.

Methods: Retrospective cohort study of the data collected from ventilated patients who survived to discharge over a 7 years period from 2012 to 2019 at a single tertiary care paediatric BMT unit.

Results: Eight children were eligible to be included having undergone HSCT and recovered from ARF to discharge. The age of the patients ranged from 8 months to 44 months. The underlying aetiology needing HSCT was 3-Hurler's syndrome, 1 - CGD, 1- Idiopathic anemia, 2 - AML/MDS and 1 JMML. The time post HSCT when they had ARF was 12 days to 30 days and one patient was on HFOV pre transplant for pulmonary involvement of JMML.

The clinical and pathological causes of ARF were IPS/ARDS/Pulmonary haemorrhage or Bronchiolitis obliterans/GVHD.

The duration of invasive ventilation ranged from 15 days to 60 days, and the duration of HFOV specifically ranged from 5 to 28 days. There were other organ dysfunctions: Acute renal failure requiring renal replacement therapy in 1/8, cardiovascular compromise needing inotrope support in 4/8.

7/8 received systemic steroids and 6/8 received Etanercept during their PICU stay for their pulmonary disease. A 2 year old case of MDS needed two more PICU admissions for respiratory compromise at 9 and 14 months after HSCT. None of the 8 who survived need home oxygen therapy and only 1/8 is on any long-term respiratory medication with inhaled bronchodilator, inhaled steroids and Montelukast.

Conclusions: Adverse pulmonary events can significantly complicate the hospital course of HSCT patients. Steroids and Etanercept are beneficial in managing such illness. Critically even ARF requiring prolonged ventilation and HFOV does not preclude long term survival without clinically relevant sequalae and these data should inform prognostic discussions in the PICU setting with children suffering ARF after HSCT.

Disclosure: "Nothing to declare."

P558

Use of Intravesical Hyaluronic Acid to Treat Hemorrhagic Cystitis after Hematopoietic Cell Transplantation

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Background: Hemorrhagic cytitis (HC) is a significant complication following hematopoietic cell transplantation (HCT). The reported incidence ranges from 7 to 70% and the clinical presentation is diverse. Early onset is attributed to direct toxicity of the conditioning regimen, whilst late cases are associated with BK polyomavirus replication and immunosuppression. Beyond conventional support measures, treatment options remain limited. Hyaluronic acid (HA), with protective effects on bladder mucosa, has been successfully used in HC and other forms of urothelial

damage, yet data on its application in HCT recipients is scarce.

Methods: We present a retrospective review of the characteristics and outcome of HCT-related macroscopic HC cases that occurred from 2007 to 2018 in our center.

Results: We identified 32 episodes of grade ≥2 HC in 29 alloHCT (10% of 282 alloHCT in this period) performed in 28 patients: 20 men; median age 41 years (19-63); AML (11), ALL (9), MDS (4), NHL (3), AA (1) and immunodeficiency (1); 15 single-cord blood plus third-party donor cells [Bautista G, 2009], 7 haploidentical HCT, 5 HLA-identical siblings and 2 unrelated donors; myeloablative conditioning regimen in 20 cases, 10 with total body irradiation, and cyclophosphamide in all but 1 cases. Most HC episodes (87%) had a late onset (≥ 8 days post-HCT), median 33 days (1-122), and were BK virus related (81%), with a grade II severity in 15 cases, III in 8 and IV in 9 others. Patients who did not respond to conventional measures consisting of hyperhydration and transfusion support, with or without continuous vesical irrigation, received HA bladder instillations (n=26 episodes; 81%). These were performed at a median of 2 days (0-59) after the symptoms arised, with a variable frequency based on the clinical course and a median of 5 doses (1-16). HA administration was well tolerated. Overall response rate to HA administration was 88% (69% complete responses and 19% partial responses). HA treatment was used in combination with other agents in 5 cases: cidofovir in 3 cases and mesenchymal stromal cells, immunoglobulins and leflunomide in 1 episode each. Clinical improvement occurred at a median of 3 days (1-22) following HA instillation and best response was obtained at a median of 8 days (2-42). Median time to best response was 15 days (6-63). Twelve patients died (43%) from alloHCT complications, only two deaths were attributed to HC, both non-responders with grade IV HC.

Conclusions: HC is a potentially severe complication of alloHCT. Patients who do not respond to support treatment have poorer outcomes and limited treatment options. Our experience suggests that HA bladder instillation is an effective and safe procedure in patients who had failed conservative treatment, leading to marked overall and complete response rates, especially when introduced promptly after diagnosis. Validation of single-center experience in prospective controlled studies should be warranted.

Disclosure: Nothing to declare.

P559

Current Practice in Nutrition after Allogeneic Hematopoietic Stem Cell Transplantation in Austria, Germany and Switzerland

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Background: Malnutrition is associated with an adverse prognosis after allogeneic stem cell transplantation (alloHSCT). Therefore, nutrition is one of the major challenges in the post-transplant period. To document the current clinical approach in nutritional support, we designed a questionnaire concerning the current practice in nutrition after alloHSCT and distributed it to centres performing alloHSCT in Germany, Austria and Switzerland.

Methods: This survey was conducted from November 2018 to October 2019. We invited all centres in Germany, Switzerland and Austria performing alloHSCT to participate. The questionnaire consisted of 30 questions regarding nutrition during the peritransplant period including restrictions of oral nutrition of patients during the neutropenic phase, nutrition in intestinal graft-versus-host disease (GvHD) including the use of special diets and/or food supplements. In addition, we addressed questions towards special laboratory testing and the experience with food associated infections.

Results: Responses from 23 centres (37%) were received, 20 from Germany, 2 from Austria and one from Switzerland. All centres reported having nutritional guidelines for patients undergoing alloHSCT, whereby only 36% offering special nutrition during the neutropenic phase. The criteria to start parenteral nutrition directly after alloHSCT seem to be consistent. Parenteral nutrition is usually started if the oral nutritional intake or the bodyweight falls below a certain limit. About 80% of the centres document the daily nutritional intake of the patients in their clinical routine and the majority of the centres recommend special nutritional guidelines for the patients during 3 to 12 months after discharge. In the setting of intestinal GVHD the current practice appears to be more heterogenous. About 70% of

the centres follow a special diet, adding food stepwise according to GvHD symptoms, while only 5 centres regularly stop oral intake completely. The majority of centres (65%) apply a lactose-free diet, followed by 52% providing fat- and 26% gluten-free food in patients with gastrointestinal GvHD. Additionally, there is a high variety concerning food supplements: all responding centres provide oral nutritional supplements, primarily energy-dense (100%) or rich in protein content (56%). General supplementation of micronutrients is performed in 65% of the centres, whereas 78% additionally add Vitamin D and 70% add Vitamin B12 regularly. Fibre is part of the regular diet in 47% of the centres. Only 4 participating centres have ever observed a food-associated infection during hospitalization, whereas food-associated infections were reported to occur more often in the outpatient setting.

Conclusions: The survey documents a general consensus about the need for nutritional guidelines for patients undergoing alloHSCT; this includes rules after discharge and nutritional guidelines for intestinal GvHD. However, the nutritional support in clinical practice (i.e. lactose-, gluten- or fat-free in intestinal GvHD) as well as the use of food supplements still are very heterogeneous. In line with current general recommendation less than 50% of the centres provide a special neutropenic diet and seem to rather focus on save food handling practice instead. In conclusion, the majority of the participating centres adjusted their nutritional guidelines to the latest findings, however more high-quality data are required to provide evidence-based nutrition to patients after alloHSCT.

Disclosure: Nothing to declare.

P560

Incidence and Severity of Cytokine Release Syndrome Following Haploidentical Peripheral Blood Stem Cell Infusion

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Background: Cytokine release syndrome (CRS) following the infusion of HLA Haploidentical (haplo) peripheral blood stem cells (PBSCs), but prior to the administration of post-transplant cyclophosphamide (PTCy) on day +3 and +4 is a well-described phenomenon with an incidence approaching 90%. Severe CRS (grades 3 to 5) has been reported in up to 17% of patients and has been associated with clinically significant morbidity and mortality. We report our single center experience of the incidence and severity of CRS following infusion of haplo PBSC.

Methods: We retrospectively reviewed the records of all patients who received haplo PBSCs at NYU Langone Health from September 2017 to December 2019. Patients received variable intensity conditioning regimens followed by graft-versus-host disease prophylaxis with PTCy 50 mg/kg on day +3 and +4 followed by tacrolimus or sirolimus and mycophenolate mofetil starting on day +5. Per institutional protocol, patients received forced hydration at 250 mL/hr starting on day +3 and continued through day +5 for hemorrhagic cystitis prophylaxis during PTCy. CRS was graded according to Lee and colleagues (Blood 2014) from day zero to +5 for each patient.

Results: Thirty-one patients were included in this analysis. Baseline characteristics are in Table 1. CRS (any grade) occurred in 30/31 (97%) patients most commonly as fever (29/30; 97%). CRS onset was typically on day 0 or day +1 (25/30; 83%). All CRS was considered mild -no patients experienced severe CRS (grades 3 to 5). There were no ICU admissions or grade 3 or higher acute kidney injury. Most episodes of hypotension were responsive to IV fluids. Only one patient was placed on a low-dose vasopressor for hypotension lasting only a few hours. This patient had known adrenal insufficiency prior to transplant and thus received prophylactic anti-IL-6 therapy with tocilizumab on day -1. Supplemental oxygen was given to 13% of patients. Eighty-seven percent of patients required loop diuretics for fluid management. No deaths related to CRS occurred.

Characteristic	Study Population (n=31)
Age, years, median (range)	44 (20 - 75)
Conditioning intensity, n (%)	
Non-myeloablative	17 (55)
Myeloablative	11 (35)
Reduced-intensity	3 (10)
Disease, n (%)	
AML	10 (32)
ALL	10 (32)
Other	11 (36)
Hematopoietic cell transplantation-specific comorbidity index (HCT-CI) score, n (%)	
0	11 (36)
1-2	5 (16)
3+	15 (48)
$CD34^+$ cells/kg infused, median (range)	6.58×10^6 ($2.8 - 9.16 \times 10^6$)
Tacrolimus use, n (%)	30 (97)

[Table 1]

Conclusions: We report a high incidence of CRS using haplo PBSCs, but no severe CRS. Our data is in contradiction with other reports in term of lack of life-threatening CRS requiring mechanical ventilation or hemodialysis. No patient died due to CRS. It is conceivable that forced hydration prevented more severe hypotension and the need for the use of vasopressors and renal support.

Disclosure: Nothing to declare.

P561

Engraftment Syndrome Following Autologous Hematopoietic Stem Cell Transplantation: Retrospective Study from a Single Center

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Background: Engraftment syndrome (ES) is an early complication following hematopoeitic stem cell transplant (HSCT), characterized by the occurrence of a new non-infectious fever during the 72 hours surrounding neutrophil engraftment. Skin rash, weight gain, diarrhea, pulmonary infiltrates, renal or hepatic dysfunction may be associated to fever.

Methods: We retrospectively reviewed all autologous HSCT performed in our HSCT center from January 2016 to December 2018, for multiple myeloma or lymphoma, in order to analyse the frequency, the clinico-biological features and the risk factors for ES.

Results: A total of 176 autolougous HSCT were performed in our center in the past 3 years. Patient's median age was 51 years [8- 66] and the sex ratio was 1,5. Most common diagnosis was multiple myeloma (60%), followed by non-Hodgkin´s lymphoma (26%), and Hodgkin´s lymphoma (14%). Median dose of CD34+ cells infused was $5{,}18.10^6$ CD34/ kg [2,4 - $23{,}6.10^6$]. Median neutrophil recovery was on day +11 [day+9 - day+21]. Median duration of antimicrobial use was 14 days [3 - 61]. Patients (pts) discharged from hospital with a median of 17 days after HSCT [Day+11 - Day+61].

A total of 27/176 (15.3%) pts developed an ES. In all, 27 (12.5%) fulfilled the Maiolino criteria and 22 (15.3%) the Spitzer criteria.

Late onset fever (after Day+9) was noticed in 128/176 pts (72%). In 21% of cases, this late onset fever was due to ES (27/128).

C-reactive protein (CRP) values were significantly higher in the group of ES pts. (p=0,031).

66% (18/27) of pts in the ES group developped non-infectious pulmonary infiltrates. Serious forms with hypoxemia were noticed in 39% of cases (7/18).

Corticosteroids were prescribed for 25/27 pts.

92.5% of pts with ES (25/27) had a favorable outcome and two patients died from multiple organ failure despite the early initiation of corticosteroids. Global non relapse mortality in autologous HSCT is of 2% (4/176) (2 deaths due to septic shock and 2 deaths due to ES)

There was a significant difference in number of days of hospitalisation (p=0,003), days of antimicrobial use (p=0,005), scanner prescriptions (p=0,023) and transfusional needs (p=0,04) between the ES and non ES groups.

In multivariate analysis, renal clearance MDRD inferior to 90 ml/min (p= 0,03) and age superior to 50 years (p=0,049) were significantly associated with the occurrence of ES. None of the factors including comorbidities, number of chemotherapy cycles, underlying diagnosis, disease status, dose of CD34 infused, type of growth factors were statistically significant.

Conclusions: ES is a common complication following autologous HSCT. Developing an ES diagnosis score including clinical features and biomarkers such as CRP and procalcitonin may be highly useful to avoid unnecessary investigations and additional antimicrobial therapy.

Disclosure: no disclosure

P562

Wernicke's Encephalopathy in a Child with B Lymphoblastic Lymphoma after HAPLO-HSCT

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Background: Wernicke's encephalopathy (WE) is the severe neurological complication due to thiamine deficiency. This condition was known primary as part of beriberi disease and alcoholic Korsakoff syndrome. In the modern time WE was reported as possible complication in certain conditions with malnutrition including post-HSCT patients. Modern pediatric morbidity of WE is unknown and according to autopsy studies is underestimated. Diagnostic criteria include triad of symptoms: mental confusion, oculomotor dysfunction and gait ataxia. Nevertheless only part of symptoms is evident in more than half of cases. The diagnosis can be proven by Radiology assessment or activity of transketolase in RBC. The estimation of serum thiamine level is generally not relevant. Typical radiological findings include symmetrical lesions in medial thalamus,

mammillary bodies, hypothalamus, colliculi and gray matter around aqueduct and floor of the forth ventricle.

Methods: Clinical, MRI imaging, blood chemistry testing

Results: The 14 year old boy was treated for B-lymphoblastic lymphoma. After 2.5 years late relapse with bone marrow and testicular involvement occurred. The orchiectomy and subsequent 4 courses of chemotherapy were carried out and followed by one blinatumomab course. After achievement of negative MRD in bone marrow we performed HSCT from hapoloidentical mother. Conditioning included thiothepa, treosulfan 4 and fludarabine, GVHD prophylactic consisted of post-transplant cyclophosphamide and tacrolimus/sirolimus. The engraftment was late and occurred on day 33 with 100% donor chimerism. No signs of acute GVHD or infection were noticed. During 1.5 months period since the beginning of conditioning we oversaw severe vomiting resistant to combination therapy and loss of 15% of body weight. Ataxia, gradual reduction of tendon reflexes and muscular strength (to 4.5 grade in both left extremities) were revealed in neurological status. Later vegetative dysfunction (subfebrile evening temperatures and supraventricular tachycardia) occurred. We oversaw little mental disability with Glasgow Outcome Scale score 13 and progression of ataxia and muscular strength loss. Lansky index was 60%. Brain CT imaging was normal. MRI with gadobutrol load showed symmetrical enhancement of MR signal in T2-weighted and FLAIR sequences in mammillary bodies and on the anterior edge of midbrain with contrast accumulation. We considered these radiological findings and clinical status as WE and began treatment with intravenous thiamine 250 mg thrice a day with dose enhancement from day 2 up to 500 mg thrice a day. After 7 days we noticed gradual improvement of clinical condition - gain in physical activity, restoration of full consciousness, gradual reduction of ataxia. Lansky index became 80%. In MRI imaging the improvement was evident (see image 2). We continued thiamine substitution in dose 100 mg thrice a day up to 2 months without clinical worsening.

Conclusions: WE is a rare and potentially lethal neurological complication of chronic thiamine deficiency. Children after HSCT and with severe oncological diseases are at major risk of WE. Early clinical signs of WE may be not specific and evident. Clinical and MRI imaging matching can be useful for early and efficient diagnostics of this severe condition. Neurological deficit can be reversible with use of early and sufficient thiamine substitution therapy.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare.

P563

Eculizumab for the Treatment of Severe Transplant-associated Thrombotic Microangiopathy: Multicenter Experience

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Background: Transplant-associated thrombotic microangiopathy (TA-TMA) is a multisystem disorder that usually presents 20-100 days after hematopoietic stem cell transplantation (HSCT) with hemolytic anemia, renal and neurologic dysfunction, hypertension and complement activation. Its incidence is reported to vary between 0.5%-76%, amounting to 10-35% in the severe forms. The condition is associated with a high mortality rate, reaching 80%-90%.

The TA-TMA pathogenesis resembles that of atypical hemolytic uremic syndrome, involving endothelial damage and complement activation, secondary to multiple possible factors such as conditioning regimens, use of calcineurin inhibitors (CNI), infections and others. Several TA-TMA diagnostic criteria systems are currently available. Severe cases are associated with proteinuria and increased levels of the terminal complement complex (sC5b-9) in the serum.

Given the paucity of data on the use of eculizumab in TA-TMA, particularly in adults, and the suggested efficacy of this drug, we herein present results of TA-TMA treatment with eculizumab in Israeli centers.

Methods: Data on transplanted adult patients treated with eculizumab for TA-TMA were retrieved from the databases of all SCT centers in Israel.

Results: Results of an overall of four patients were reported, with a median age of 55 (52-60) years; all the four were females, the baseline diagnosis was non-Hodgkin lymphoma in two patients and acute leukemia in the other two patients. Matched related donors were used in two patients and matched unrelated donors (MUD) - in the other two patients. Myeloablative conditioning regimens were given to two patients; the rest two individuals received reduced-intensity conditioning. Graft-versus-host disease

(GVHD) prophylaxis consisted of CNI and methotrexate in two and CNI with mycophenolate in the rest. ATG was added to GVHD prophylaxis in patients receiving MUD grafts. The stem cell source was peripheral blood in all the patients.

TA-TMA was diagnosed at a median of 55 (21-210) days post-transplant. All the patients fulfilled the criteria of TA-TMA diagnosis, including thrombocytopenia, anemia, presence of schistocytes in the peripheral blood smear, increased lactate dehydrogenase, decreased haptoglobin levels as well as elevated creatinine and blood pressure. The number of eculizumab doses ranged between 1-4. Three patients received eculizumab as first-line therapy. The forth patient underwent plasmapheresis for TA-TMA prior to eculizumab administration. Following eculizumab treatment, two patients recovered from TA-TMA.

Conclusions: The diagnosis of TA-TMA is challenging due to insufficient awareness and overlapping manifestations mimicking TA-TMA that may delay the diagnosis and prompt treatment initiation. Moreover, the availability of complement analysis is limited, further delaying targeted therapy. A high index of suspicion is warranted to facilitate early administration of eculizumab. Randomized control studies are required to establish the precise role of this drug in this clinical setting.

Clinical Trial Registry: N/A

Disclosure: Nothing to declare.

P564

Impact of Post-transplant Cyclophosphamide (CYPT) as Graft-versus-host Disease (GVHD) Prophylaxis in Terms of Sinusoidal Obstruction Syndrome (SOS)

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Background: SOS is a potentially life-threatening complication observed after hematopoietic stem cell transplantation (HSCT). In this syndrome, sinusoidal endothelial cells are damaged by toxic metabolites generated during the conditioning regimen. Some risk factors are directly transplant-related, such as the stem cell source, the conditioning regimen and the GVHD prophylaxis. Our aim is to evaluate the incidence of SOS in patients receiving alloHSCT using CYPT as GVHD prophylaxis, regardless the kind of donor, compared to those who received a traditional GVHD prophylaxis scheme.

Methods: This is a retrospective, unicentric and observational study of 40 patients from a group of 4 public hospitals in Madrid (Spain) who underwent alloHSCT from January 1st 2015 until July 30th 2018. We have studied the incidence of different events associated to HSCT: acute and chronic GVHD, hemorrhagic cistitis or veno-oclusive disease. We applied Kaplan-Meier test to analyze the overall survival (OS) and analysis of Cox in variables that interfere in the OS.

Results: 53% of patients were male (n = 21) and 47% were female (n = 19). The average age was 50 years, SD 11.22 years (19-68).

According to the donor employed, 17 were matched sibling donor (MSD) (42.5%), 17 haploidentical (42.5%), 4 HLA-matched unrelated donor (MUD) (10%) and 2 mismatched related donor (5%).

18 transplants were performed using a non-myeloablative conditioning (45%) and 22 myeloablative conditioning (55%). In 100% the source of hematopoietic progenitors used was peripheral blood.

In terms of GVHD prophylaxis, CYPT was used in days +3 and +4 according to the Baltimore protocol in 25 transplants (62.5%), of which 17 were haploidentical (100% of haploidentical), 3 in MSD (17.65% of transplants in this modality), 4 in MUD (100% of these) and 1 mismatch related donor (50% of this group).

Sinusoidal Obstruction Syndrome (SOS) occurred in 6 patients (15%) and 5 of them (83,3%) had received CYPT. 37,5% of patients who underwent to a non haploidentical SCT using CYPT as GVHD prophylaxis presented SOS. Nevertheless, it only appeared in a 6,7% of whom had not received CYPT. So, relative risk (RR) of SOS is 5.62 (IC 95% 0.70-45.7) for CYPT prophylaxis, beyond the haploidentical SCT, with p 0.06. So, it showed trend to statistical significance.

Conclusions: CYPT is an intensive GVHD prophylaxis scheme and sometimes, it can be translated into a higher risk of toxicities. SOS is a severe complication after alloHSCT, so more date is required in prospective studies in order to define the best GVHD prophylaxis based on type of donor and conditioning regimen, because toxicity is relevant as well.

Disclosure: No disclosures

P565

Ischemic Stroke in Children and Young Adults with Malignant Hematological and Oncological Diseases in Allogeneic Hematopoietic Stem Cell Transplantation

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Background: The amount of ischemic stroke of the child population is 2-13 per 100000 per year. Patients with cancer and hematological diseases have additional risks of stroke, which can be associated with both the underlying disease and the toxic effects of the treatments used.

Methods: On the basis of data register R. Gorbacheva memorial Research Institute for Pediatric Oncology, Hematology and Transplantation we analyzed the catamnesis of 371 patients younger than 21 years, who underwent hematopoietic stem cell transplantation (HSCT) for the period 01.01.2016-01.07.2018 (autologous-148, allogeneic-223) with a median follow-up of 365 days.

Results: Ischemic stroke was detected in 6 patients in the group of allo-HSCT (2.69%; in auto-HSCT stroke was not diagnosed). In the group of the first year of life (4 patients) ischemic stroke was diagnosed in 1 patient with malignant infantile autosomal recessive osteopetrosis (25%) in the early posttransplantation period after allo-HSCT from identical sibling after non-myeloablative (NMA) conditioning. In the group of 1-14 years, stroke was detected in 5 patients (3.5% of patients of this age allogenic-group). This group was represented by the following nosologies: 1) MPS-I H/S - 1 patient after allogeneic unrelated HSCT with myeloablative (MA) conditioning on the background of infectious process, endotheliopathy, deep vein thrombosis of the lower extremities; 2) aplastic anemia PNG(+) - 1 in the early stages after allogeneic unrelated HSCT after NMA regimen; 3) AML and MDS in a patient with Down syndrome - 1 patient after haplo-HSCT with NMA regimen on the background of primary graft failure and sepsis of bacterial and fungal etiology; 4) juvenile myelomonocytic leukemia - 1 patient after haplo-HSCT with myeloablative regimen on the background of severe AGVHD; 5) congenital hemolytic anemia +beta-thalassemia - 1 patient after haplo-HSCT with non-MA regimen on the background of sepsis.

In patients 15-21 years - stroke was not detected.

All strokes were diagnosed in patients with HSCT in terms of D+8 to +137.

The analysis of mortality in the early posttransplantation period showed that the lethal outcome in patients with stroke was observed in 66.6% (4 patients of 6 died in the nearest terms after diagnosis of stroke), which is significantly more often than in the absence of this complication. The risk of adverse outcome in the group of patients with stroke was associated with more than 8-fold increase in the risk of death compared to patients without stroke (OR 8,42; 95% - CI 2,046-42,12; p< 0,005).

Conclusions: Ischemic stroke in HSCT-patients younger than 21 years is a relatively rare complication (1.62% in the study group, 2.69% among allo-HSCT). This type of complication was found exclusively in recipients of allo-HSCT younger than 10 years, mainly in patients with congenital diseases affecting the development of the CNS on the background of severe posttransplantation complications of infectious and immunological nature.

The development of ischemic stroke may be an independent risk factor for the adverse outcome of allo-HSCT in children younger than 14 years. The influence of the degree of myeloablative conditioning regimens on the development of stroke in children was not revealed.

Disclosure: Nothing to declare.

P566

Melphalan Dose Adjustment and Cryotherapy Reduce Oral Mucositis after Autologous Hematopoietic Stem Cell Transplantation

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Background: The oral mucositis is one of the most common complications after hematopoietic stem cell transplantation. To reduce the rates of mucositis we applied different additional strategies - including adjusting the dose of melphalan in selected patients and using cryotherapy with ice-cream for prevention of mucositis. The reduction of melphalan dose based on response to treatment in multiple myeloma (VGPR of better) was shown to correlate with improvement of OS after AHSCT (EBMT CALM study). The cryotherapy can be effective especially when chemotherapeutics with short half-life are used. Both strategies are quite often overlooked as means to reduce the oral mucositis after AHSCT when melphalan is used in conditioning. We aimed to analyze possible impact of those strategies on occurrence of mucositis after AHSCT.

Methods: We retrospectively analyzed the data of 75 consecutive patients that were treated with AHSCT with fresh cells after the melphalan conditioning. The patients were given melphalan dose 200 mg/m2 or 140 mg/m2 based on their body surface, renal function, general

condition, disease type and response to previous therapies - in accordance with EBMT CALM study results. Oral mucositis was assessed following the WHO Oral Mucositis Grading Scale (0-IV). The patients received cryotherapy on demand or as requested by physician as a prevention of oral mucositis which was given during the melphalan infusion.

Results: Twenty one patients (28%) developed oral mucositis (defined as grades I-IV). Higher dose of melphalan (200 mg/m2) was more frequently associated with oral mucositis compared with lower dose (140 mg/m2) ($p< 0.001$). There were significantly less cases of oral mucositis in patients who received cryotherapy during melphalan infusion ($p< 0.025$). Furthermore, we observed a correlation of diarrhea and oral mucositis after autologous HSCT ($p< 0.02$). The higher dose of melphalan correlated with diarrhea ($p< 0.02$) and earlier cryotherapy did not prevent diarrhea. Neutropenic fever correlated with diarrhea ($p< 0.01$). Further analysis did not show any correlation between the grade of oral mucositis and weight, age, gender, anti-infectious prophylaxis (ciprofloxacin or levofloxacin), neutropenic fever and dialysis. There was no sepsis in studied population that was qualified as mucosal injury related.

Conclusions: The prevention of mucositis reduces the burden of transplantation for the patients. The reduction of melphalan is indicated in some patients due to the comorbidities. Moreover, the CALM study of EBMT has shown that reduction of melphalan dose depending on treatment response increases overall survival time. As we show in this work - the real life application of this strategy also possibly reduces the burden of short term complications. The use of cryotherapy is another important step in prevention of mucositis - it is cheap and effective in preventing this common complication. Interestingly it is the diarrhea not the mucositis that correlates with neutropenic fever - and this points to gut damage as a possible cause of neutropenic fevers.

We conclude that the melphalan dose adjustment and cryotherapy could be explored as simple means to reduce the short term complications in patients undergoing AHSCT conditioned with melphalan.

Disclosure: Nothing to declare.

P567

Clinical Features and Risk Factors of Engraftment Syndrome in Patients Undergoing Autologous Hematopoietic Stem Cell Transplantation

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Background: Engraftment syndrome (ES) is a practically exclusive complication of autologous hematopoietic stem cell transplantation (auto-HSCT), which frequency differs from one series to another, due to the variability of risk factors and diagnostic criteria. The objective of this single-center retrospective study is to clarify the relationship between risk factors described in the literature, and the development of ES as well as to establish its incidence.

Methods: We have studied the incidence of ES, according to Maiolino criteria (2003), in 134 patients undergoing auto-HSCT from 2014 to 2018. Baseline characteristics are described in Table 1. We analyzed the association of patients demographic variables, disease characteristics, and the use of granulocytic colony stimulating factor (G-CSF) (prescribed in case of serious infections or fever of more than three days), with the development of ES.

Results: Twenty three patients (27%) developed ES. The median time until the onset of symptoms following transplantation was 12 days (8-23) with a median neutrophil count of 510 / μL (110-3180). The most frequent symptoms were fever (100%), respiratory failure (69.5%), skin rash (39.1%), diarrhea (17.4%), acute renal failure (13%) and weight gain (13%). The length of hospital stay was significantly longer ($p=0.01$) in patients with ES [25 days (18-110) vs 22 days (16-120)], and five patients (21.7%) required admission to intensive care unit, without any case of death due to this complication.

The onset of ES was significantly related to sex (25% among females vs 10.8% among males, $p=0.03$), age (30.3% vs 12.9% for patients >65 years vs < 65 years respectively, $p=0.02$), and the use of G-CSF (28% in treated patients vs 10.7%, $p=0.01$), without differences in the number of doses. No significant differences were observed with respect to previous lines of therapy ($p=0.35$), conditioning regimen ($p=0.38$) or pre-transplant response ($p=0.53$), as well as the time elapsed after mobilization of hematopoietic progenitors with G-CSF ($p=0.68$). A greater tendency ($p=0.07$) to the development of ES was observed in patients with multiple myeloma (18.6%), amyloidosis (66.3%) and lymphoma (15.1%), and in those treated with immunomodulatory agents ($p=0.05$).

Most patients (95.7%) recovered after treatment with corticosteroids (methylprednisolone), without significant differences between the daily administration of 1mg/kg or 2mg/kg. The response could not be assessed in one patient (4.3%) due to early mortality not related to ES.

Variable	Age	Sex	Underlying disease	Previous lines of therapy	Immunomodulatory agents	Pre-trasplant response	Previous radiotherapy	Conditioning regimen	G-CSF
n	<65 (101) >65(33) Median (57) Range (18-73)	Male (74) Female (60)	MM(86) NHL(25) HL(8) AM (3) AD(6) ST(5) AML (1)	One(78) Two(42) Three(8) Four(3) Five(1) Seven(1) Nine(1)	YES(85) NO(49)	Complete response (79) Partial response (48) Refractory (6) Relapse (1)	YES(15) NO(119)	Melphalan (83) BEAM (29) BUMEL(7) Cyclophosphamide +ATG(6) Carmustine +Thiotepa(4) Carboplatin +Etoposide(4) BEA(1)	YES (50) NO (84)
%	<65 (75,4) >65 (24,6)	Male (55,2) Female (44,8)	MM(64,2) NHL(18,7) HL(6) AM (2,2) AD (4,4) ST (3,8) AML (0,7)	One(58,3) Two(31,4) Three(6) Four(2,2) Five(0,7) Seven(0,7) Nine(0,7)	YES(63,4) NO(36,6)	Complete response (59) Partial response (35,9) Refractory (4,4) Relapse(0,7)	YES(11,2) NO(88,8)	Melphalan(62) BEAM (21,6) BUMEL(5,3) Cyclophosphamide +ATG(4,4) Carmustine+Thiotepa (3) Carboplatin +Etoposide(3) BEA (0,7)	YES (37,3) NO (62,7)

[TABLE1 MM:Multiple myeloma NHL:Non-Hodgkin lymphoma HL:Hodgkin lymphoma AM:Amyloidosis AD:Autoimmune disease ST:Solid tumor AML:Acute myeloid leukemia]

Conclusions: Engraftment syndrome is a relatively frequent complication in patients undergoing auto-HSCT, with good prognostic when early identified. Age, sex and the use of G-CSF are risk factors for its development. Unlike other series, we have not found a relationship between the incidence of ES and the underlying disease, although the sample size of the study may have been insufficient to determine this association.

Disclosure: Nothing to declare.

P568

Real-life Experience of Two Italian Hematolgy Centres on Efficacy and Safety of Oral Nepa (Netupitant/palonosetron) in Patients with Multiple Myeloma Undergoing Hematopoietice Stem Cell Transplantation

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Background: Chemotherapy induced nausea and vomiting (CINV) is the most frequent side effect in high dose conditioning regimen (HD-CR) prior stem cell transplantation (SCT). International guidelines recommend a combination of dexamethasone with a second generation serotonin receptor antagonist (5-HT3RA) and neurokinin 1 receptor antagonist (NK-1RA) in preventing acute and delayed CINV in patients undergoing SCT.

Methods: We retrospectively analyzed 62 Multiple Myeloma patients undergoing High Dose Melphalan conditioning regimen for Autologous SCT and receiving CINV prophylaxis with NEPA and dexamethasone. The primary end-point was the rate of Complete Response (CR), defined as no emesis and no nausea without rescue medications, for both acute (CR-24) and delayed (CR 25-120) CINV and rate of post-transplant complications until discharge. In our series, 34 patients (55%) were female. The median age of patients was 57 years (35-72). Patients received one day HD-CR with Melphalan (77% Mel200/23% Mel140) (schedule and patient characteristics shown in fig.1).

Results: The incidence of CR-24 and CR 25-120 observed was 77% (48/62) and 55% (34/62) respectively. More than grade 1 CINV (according to CTCAE-4), was reported in 19% (9/48) and 9% (3/34) of patients reached CR-24 and CR 25-120, respectively. The rate of CINV greater than grade 1 was 57% (8/14) and 54% (15/28) in patients who did not reach RC-24 and RC 25-120 respectively. An increased risk of developing more than grade 1 CINV was reported in patients who did not reach an RC-24 (HR 2,84; p 0,0067 95% CI 1.336-6.055) and an RC 25-120 (HR 6,07; p 0,0018 95% CI 1.953-18.875). Female sex, Melphalan dosage, disease status and Body Mass Index were not associated with an increased risk of both acute and delayed CINV. Median leinght of stay was 20 days (15-29). No case of cardiotoxicity and no exitus was observed from recovery to discharge. The incidence of febrile neutropenia was 37% (83% FUO; 13% sepsis; 4% pneumonia).

Neutrophil (>1000/mcL) and Platelet (>50000/mcL) recovery occurred in median on day 10 (10-15) and on day 14 (4-45) respectively.

Conclusions: NEPA is safe and effective in preventing acute and delayed CINV in Myeloma patients undergoing Melphalan HD-CR for Autologous SCT. Female sex, traditionally considered a major risk factor for CINV, has not statistical significance in our series, but remains unclear if it is attributable to NEPA prophylaxis.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare.

P569

Early Treatment with Daratumumab for Refractory Post-Allogeneic Stem Cell Transplant Pure Red Cell Aplasia

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Background: Pure red cell aplasia (PRCA) is a potential complication after allogeneic stem cell transplantation (allo-SCT) associated with ABO blood group incompatibility. Although some cases of PRCA spontaneously resolve, others do not and optimal management remains unclear. Preliminary data are showing promising responses with Daratumumab, an antiCD8 monoclonal antibody targeting plasma cells, in refractory cases. We describe our successful experience with this therapy.

Methods: In March 2014, a 75-year-old female was diagnosed with myelodysplastic syndrome with refractory anaemia with excess blast 1. Cytogenetic analysis revealed 46, XX,+8[13]/46, XX[7]. She received erythropoietin until 2016, then azacytidine 75mg/m2 due to increased transfusion requirements. Several months later, she developed a secondary acute myeloid leukaemia (s-AML). She achieved complete remission after one cycle of idarubicin-cytarabine-etoposide and was referred for allo-SCT from a matched, unrelated donor with major ABO incompatibility (recipient O+/donor A+).

She received a conditioning regimen consisting of fludarabine and busulfan. Sirolimus and tacrolimus were used as GvHD prophylaxis. A total of 6x10^6/kg CD34+ cells with less than 30ml of red cells was infused the 25th of July,2018. While engraftment of neutrophils and platelets occurred on time (on +13 and +18, respectively), the patient remained anaemic requiring RBC transfusions.

Bone marrow aspirate on day 30, showed no evidence of disease but absence of erythroid precursors (less than 1% of total cellularity). Chimerism studies showed a high level of donor chimerism (100% leukocytes with 75% T-cell subset). The extensive workup of her persistent anaemia showed reticulocytopenia with absence of type A erythrocytes and anti-A-IgG titer of 1:1024 (Table 1) leading to the diagnosis of PCRA.

The first clinical approach was immunosuppression tapering, which was started on day 90 and finally stopped on day 120, however, this was uneffective.

High-dose steroids was started on day +160 due to development of moderate chronic GVHD, with no effect on the haemoglobin levels, reticulocyte count nor iso-hemaglutinin titers.

Compassionate treatment with daratumumab was considered, requested and approved. On day +190 post-transplantation Daratumumab was initiated at a dose of 16mg/kg (days +1, +8, +22).

Results: After the first 2 doses of daratumumab with no infusion related toxicity nor side effects, a brisk reticulocytosis developed, the isohemaglutinin titers reduced and the patient became transfusion independent.

At +18 months, the patient has a normal haemoglobin (13,3g/dL), reticulocyte count and her blood group type converted to A+ with no titers of anti-A. Recent bone marrow aspirate showed complete remision and normal erythroid precursors. Immunoglobulin replacement therapy has been initiated due to persistent hypogammaglobulinemia after daratumumab administration.

Conclusions:

· Our experience supports the early use of daratumumab since its effective, safe and may help avoid side effects of other less effective interventions.

· Daratumumab administration may contribute to hypogammaglobulinemia in stem cell recipients.

Post allo-HSCT	Anti-A IgM titers	Anti-A IgG titers
+180	266	1024
+266	0	1/32
+308	0	0

[Table 1]

Disclosure: Nothing to declare.

P570

Prognostic Factors for Early Mortality of Hematological Patients Admitted to the Intensive Care Unit: Preliminary Results of A Prospective Multicenter Study

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Background: Nowadays, haematological patients are frequently admitted to the Intensive Care Unit. Many of them are receiving sophisticated biological or cellular therapy. Nevertheless, up-to-date data on short and long-term survival, along with risk factors for mortality are lacking. We present preliminary results of risk factors for early mortality of a prospective multidisciplinary multicenter study.

Methods: Prospective study of every consecutive haematological patients admitted to the Intensive Care Unit (ICU) of seven tertiary hospitals, between January 1 and October 31 of 2019. Demographic, laboratory, clinical parameters and scales, such as, Glasgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA) and APACHE IV (Acute Physiology and Chronic Health Evaluation) were prospectively recorded. Early mortality was defined as exitus occurring during ICU admission. Risk factors for early mortality were analized. Mean values were compared using an unpaired two-sample two-tailed Student's t-test. SPSS (version 24.0) and R Core Team (version 3.4.1) software were used. P-values < 0,05 were considered statistically significant.

Results: The haematologic condition was diagnosed at ICU in 10% of patients. The 13,5% were allogeneic hematopoietic transplant recipients (34,5% of them had grade $\geq$2 graft versus host disease at ICU admission) and 5% were patients receiving advanced cell therapy or therapy against biological targets. Global ICU mortality rate was 35%. For the whole cohort, the association between age and mortality (r=0,27) did not reach statistical significance (p=0,08), although transplant recipients over 50 years had a higher mortality rate (37%) than patients under 50 (21%), (p=0.02). Graft versus host disease grade $\geq$2 was also associated to mortality (41% vs. 19%) (p=0,02). The diagnosis debut of the hematological disease at ICU was associated with higher rates of mortality (p= 0.04). Finally, SOFA $\geq$ 5 (32% vs. 16%), (p=0,02) and APACHE IV $\geq$ 18 (29% vs. 11%), (p=0,03) also correlated with increased risk for early mortality.

Conclusions: Early mortality was clinically associated to increased age, especially in hematopoietic transplant recipients, de novo diagnosis of the haematological disease made at the Intensive Care Unit and graft versus host disease in the sub-group of hematopoietic transplant recipients. SOFA and APACHE scales also predicted increased risk for early mortality.

Disclosure: This study was partially funded by a grant from Astellas.

P571

T-PA/Urokinase in Combination with TPE as a Substitutional Therapy for Treatment of TA-TMA

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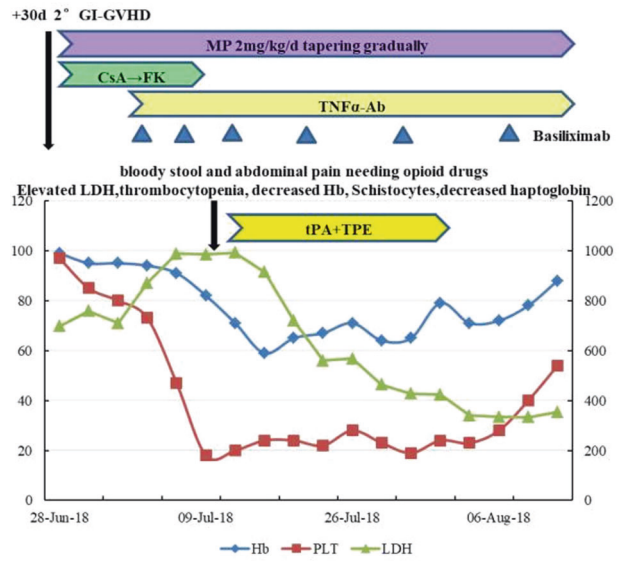
Background: Transplant-associated thrombotic microangiopathy(TA-TMA) is an early complication of hematopoietic stem cell transplantation(HSCT). The main treatments for TA-TMA include calcineurin inhibitors(CNI) cessation, therapeutic plasma exchange(TPE), defibrotide, eculizumab and so on. Since defibrotide and eculizumab has not been approved or available in some countries, it is important to find certain substitution therapy. The aim of this study is to explore application of tissue plasminogen activator(t-PA) and urokinase(UK) in treatment of TA-TMA in combination with TPE.

Methods: This study enrolled two patients who were diagnosed with malignant hematologic diseases and underwent allogeneic HSCT. The first patient developed TA-TMA following gastro-intestinal aGVHD 40 days after transplant. She received Treatment including discontinuation of tacrolimus, TPE every other day(7 within 16 days), t-PA(10mg/d). The second patient developed TA-TMA with no apparent cause 2 months after transplantation, and he received treatment including discontinuation of cyclosporin, frequent TPE (6 within 14 days) and t-PA (10mg/d).

Results: For the first patient, she was diagnosed with TA-TMA 40 days after HSCT for the first time. Hb and platelet count started elevating while LDH started decreasing after 2 weeks of therapy(see Figure 1). Meanwhile the patient's abdominal pain and diarrhea was relieved. The patient recovered and was discharged from hospital 78 days after HSCT. No significant bleeding was observed during the course of the thrombolysis treatment. However, the patient developed gastro-intestinal GVHD 5 months after HSCT again, and subsequently developed TA-TMA for the second time. The patient gave up treatment because of financial problems. For the seconde patient, serum creatinine decreased to baseline level and polyserous effusions improved dramatically within 9 days after thrombolysis started. Almost all the clinical manifestation and laboratory indicators improved significantly and went back to normal after 3 weeks of therapy. During thrombolysis treatment, the patient presented blurred vision in the left eye accompanied by visual field defect, which was considered as fundus hemorrhage. In addition, prolonged slight bleeding was observed at the site of femoral vein catheterization. Unfortunately just like the first patient, he developed TA-TMA for the second time 8 months after HSCT. Since the patient's insurance cannot cover t-PA, he was treated with TPE and UK(100000-200000U/d, discontinued when PLT< 10*10E9/L) instead and recovered after 2 weeks of therapy. No active bleeding occurred this time.



[Figure 1. Clinical manifestation, laboratory results and key treatments of the first patient.]

Conclusions: In this study, the clinical manifestations and laboratory results related to TA-TMA were alleviated after treatment of t-PA/UK in combination with TPE in both patients, proving the effectiveness of this treatment regimen. Therefore, TPE in combination with t-PA/UK might be considered substitution therapy for TA-TMA patients who do not have access to defibrotide, eculizumab or other recommended medication. More efforts should be made to prevent TA-TMA relapse and decrease major bleeding. In addition, the use of t-PA/UK for preventive intervention to reduce the incidence and mortality of TA-TMA is well worth trying especially in HSCT patients with high risks for TA-TMA.

Disclosure: Nothing to declare.

P572

Hemophagocytic Syndrome after Ex-vivo Lymphodepleted Hematopoietic Transplantation

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Background: Post-transplant hemophagocytic syndrome is a severe complication, probably underestimated, characterized by hyperinflammation caused by uncontrolled proliferation of activated macrophages and lymphocytes that secrete high amounts of inflammatory cytokines. Here we present 2 cases of pediatric patients that showed hyperacute graft rejection in the context of post-transplant hemophagocytic syndrome.

Methods: Patient 1st: 2 years old male affected by ALL Ph+ in CR1, submitted to allo-HSCT from unrelated donor (HLA 9/10). Ex-vivo lymphodepletion of peripheral blood was performed to minimize GvHD risk and was based on TCR alpha/beta manipulation by CliniMacs® device. Here reported the composition of the graft (cells/Kg): TNC 5.64 x10^8, CD34+ 6x10^6, CD3 5.4 x10^7, Alpha/Beta 0.8 x10^4, Gamma/Delta 4.28 x10^7, CD19 0.56 x10^5.

Patient 2nd: 10 years old male affected by AML related to MDS in CR1, submitted to Haplo-HSCT from the father. Ex-vivo lymphodepletion of peripheral blood was based on CD45RA+ manipulation by CliniMacs® device. Here reported the composition of the graft (cells/Kg): CD34+ 11.15 x10^6, TNC CD45RO+ 3.2x10^6, CD3/CD45RO+ 1.39x10^6, CD3/CD45RA+ 1x10^4. NK cell infusion was performed on day +7 (56 x10^6/Kg).

Both patients received reduced intensity conditioning based on Total Lymphoid irradiation 8 Gy, Fludarabine 150mg/m2, Thiotepa 10mg/Kg and Melphalan 140mg/m2. No serotherapy was administered. GvHD prophylaxis was based on MMF 15mg/Kg/8h since day +1. G-SCF 5ug/Kg was started since day +8.

Results: Both patients started engraftment early showing > 500 neutrophils at day + 11 and total donor chimerism was

confirmed. In the meanwhile, a state of inflammation characterized by high fever, liquid retention and light erythematous rash appeared. Steroids 2mg/Kg/day was started for possible engraftment syndrome. Due to persistent fever Tocilizumab was administered (12mg/Kg in the first patient and 8mg/Kg in the second one, for a total of 1 and 3 doses respectively). Nevertheless, both patients showed persistent fever, coagulopathy with hypofibrinogenemia, hepatitis, increase of triglycerides and splenomegaly accompanied by a sudden decrease of leucocyte count. Dexamethasone 10mg/m2 and Cyclosporine were added. Unfortunately bone marrow aspirate confirmed graft rejection. Both patients showed complete solution of symptoms after 10 days and they have been submitted to a second haploidentical transplant including serotherapy and Cyclosporine as GvHD prophylaxis.

Conclusions: In our experience post-transplant hemophagocytic syndrome is a severe complication responsible of hyperacute rejection. The absence of serotherapy, that was substituted by TLI, could have promoted the activation of the autologous lymphocytes. It will be important in the future to know the incidence of this syndrome in particular in case of ex-vivo lymphodepletion.

Disclosure: Nothing to declare.

P573

Immunoadsorption in Hematopoietic Stem Cell Transplantation with Major ABO Incompatibility

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Background: In allogeneic stem cell transplantation (HCT), ABO incompatibility between donor and recipient occurs in about 40 % of the patients. Major incompatibility consists of the presence of antibodies, so called isohemagglutinins (IHA) against the red blood cells (RBC) of the donor in the recipient blood, while minor mismatch is the presence of IHA against the RBC of the recipient in the blood of the donor. In major ABO incompatibility, IHA can induce hemolysis at infusion of the stem cell product, a delay of engraftment with a higher need for transfusion during the first weeks after transplantation as well as the occurrence of a pure red cell aplasia (PRCA) weeks or months after HCT. Different strategies have been described to reduce IHA before HCT. Here we describe the effect of immunoadsorption (IA) in patients with a high IHA titer on transfusion need and incidence of PRCA post HCT in comparison to patients with a low IHA titer. Until now, no study for IA as a prophylactic procedure before HCT has been described.

Methods: Patients with a major ABO incompatibility and IHA titer equal or higher than 1:128 were treated by IA before the start of conditioning. We analyzed retrospectively the occurrence of PRCA and the need for transfusion and compared them to a population of patients with a major ABO incompatibility but a IHA titer < 1:64 without any treatment to reduce IHA. Statistical analysis was made by Fisher's exact test.

Results:

9 patients were treated by IA and in all but one, the titer of IHA could be deceased to < 1:128 by 2-3 IA procedures. No relevant side effects related to the IA were observed. One patient had a decrease of 1:1024 to 1:256. PRCA occurred in one of the 9 patients and treatment with rituximab was successfully administered. The mean number of erythrocyte transfusion from d0 to d100 was 10.1 (0 - 36).

In the group of patients with a low IHA titer, the need for RBC transfusion between d0 and d100 was 10.2 (1 - 35). None of these 15 patients developed PRCA, however, however, four patients had received Rituximab before 6 months after transplantation, three for EBV reactivation and one for immune thrombocytopenia. Rituximab could masque a PRCA.

The difference in incidence of PRCA was statistically not significant (p=0,375).

Conclusions: Unexpectedly, there was no higher rate of transfusion in patients with high IHA titer, an effect potentially induced by the IA. PRCA occurred only in one patients with a high anti A titer before transplantation despite an effective lowering of IHA titer of 256 before to 64 after IA. IA is an effective procedure to decrease IHA before HCT. It can safely be applied before HCT and may also be an alternative to plasmapheresis to eliminate e.g. HLA antibodies in case of HLA mismatched HCT. Direct comparison of plasmapheresis and IA on a higher number of patients to compare safety and efficacy for elimination of IHA or HLA antibodies is necessary.

Disclosure: Nothing to declare.

P574

Immune-mediated Fever after T-cell Replete Haploidentical HSCT using Peripheral Blood Stem Cell Grafts and Post-transplantation Cyclophosphamide

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Background: Acute GVHD can present as a culture-negative, immune-mediated fever (IMF) post-HSCT. The incidence of IMF post-haploidentical T cell replete transplants using peripheral blood stem cell (PBSC) grafts has not been described. Also, as there is a bi-directional relationship between acute GVHD and viral reactivation, immune-mediated fever if not treated and recognised in time may become a source of significant morbidity, diagnostic dilemma and mortality. With the above background we retrospectively analysed immune-mediated fever in our patient population to understand its impact on CMV reactivation, as well as risk factors associated with its occurrence in the setting of T-cell replete haploidentical transplantation using post-transplantation cyclophosphamide (PTCy) and PBSC grafts.

Methods: 16 patients underwent T cell replete haploidentical transplants using PBSC grafts from April 2017 to August 2019 for various hematological disorders and malignancies, 3 ALL, 6 AML, 4 CML-BC, 1 MPAL, 1 PNH, 1 SAA. All patients as well as donors were CMV IgG positive. These patients were included in this study. All patients received post-transplant cyclophosphamide (50 mg/kg on day+3 and +4), intravenous cyclosporine to target levels of 200-300 μg/L and mycophenolate moefetil starting 24 hours after PTCy completion. The association of IMF within 100 days of transplant with type of conditioning (TBI based vs Non-TBI based), occurrence of acute skin, liver or gut GVHD, CD34 dose infused and CMV reactivation was analysed using Fisher exact test. Immune-mediated fever (IMF) was defined for the purpose of this study as persistent, moderate to high grade fever (lasting > 72 hours) post-engraftment and whithin 100 days of HSCT, in a stable patient, with absent localizing signs, no other symptoms, normal CT scan of chest, with negative serum biomarkers (galactomannan, C-reactive protein and procalcitonin), negative blood and urine culture and prompt defervescence (within 24 hours) with steroids (methylprednisone equivalent) at 0.5 -1 mg/kg/day. Before initiation of steroids consensus of two transplant physicians in the treating team was mandatory. Steroids were tapered over 2-4 weeks.

Results: 7/16 (43.6%) patients experienced IMF in the first 100 days of transplant. There was no association of IMF with occurrence of subsequent acute GVHD, with 2/9 in non-IMF subgroup vs 2/7 in IMF subgroup experiencing acute GVHD. There was no grade ¾ acute GVHD. CMV reactivation occurred in 5/7 (71%) patients with IMF vs 3/9 (33.3) patients without IMF (p=0.13). TBI based conditioning was utilized in 8/16 patients (50 %). We found a significant association of TBI based conditioning with subsequent development of IMF, 0/8 without TBI vs 7/8 (87.5 %) patients who underwent TBI based conditioning (p=0.001). There was also a higher incidence of CMV reactivation in patients who underwent TBI based conditioning (75 % vs 20 %, p=0.13).

Conclusions: IMF can be common post T-cell replete haploidentical HSCT and may be associated with TBI based conditioning. Early identification of IMF is important and can prevent subsequent morbidity, diagnostic dilemma and mortality. Larger studies and a longer follow-up is required to confirm this hypothesis and further understand the clinical implications of the above finding.

Disclosure: Nothing to declare.

Non-infectious late effects, quality of life and fertility

P575

Bronchiolitis Obliterans Syndrome in the Changing Landscape of Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Bronchiolitis obliterans syndrome (BOS) remains a serious complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT) with a high incidence of disability and mortality. **The aim** of this study was to characterize the cumulative incidence, risk factors, clinical manifestation and prognosis of BOS in the modern landscape of allo-HSCT with the increased use of non-myeloablative conditioning, haploidentical donors and the post-transplant cyclophosphamide (PTCy) as GVHD prophylaxis.

Methods: The study included adult patients who received allo-HSCT between 2008 and 2019. BOS was diagnosed according to the NIH criteria (2014). We analyzed cumulative incidence and risk factors of BOS in the Fine-Gray regression model for competing events, the nature of the clinical manifestation, results of pulmonary function tests and pulmonary changes on chest computed tomography (CT). The overall survival (OS) was calculated according to the Kaplan-Meier method since the diagnosis of BOS.

Results: As a December 1, 2019, a total of 42 patients (22 males and 20 females) developed BOS in a whole cohort of 1189 patients. Median age at the moment of allo-HSCT and BOS diagnosis was 34 (18-58) and 35 (20-60)

years respectively. Cumulative incidence of BOS was 1.9% (95% CI, 1.2-2.8), 4.2 (95% CI, 3.0-5.7) and 5.3% (95% CI, 3.7-7.4) at 1, 3 and 5 years after allo-HSCT, respectively. The median time from allo-HSCT to the development of symptoms and BOS diagnosis was 321 (86-1771) and 371 (161-2134) days, respectively. Cumulative incidence of BOS was associated with haploidentical and mismatched unrelated donor (MMUD) (HR 2.211, 95% CI, 1.167-4.190, p=0.015), myeloablative conditioning (HR 2.343, 95% CI, 1.254-4.377, p=0.008) and GVHD prophylaxis other than PTCy (HR 2.187, 95% CI, 1.145-4.175, p=0.018). The history of chronic obstructive pulmonary disease before HSCT had a borderline significance. Other manifestations of cGVHD preceded the onset of BOS in 41 cases. In 1 patient, BOS was the first manifestation of cGVHD. In 44% of the patients the onset of BOS was associated with current infection which required confirmation of the diagnosis by re-evaluating the criteria after its resolving. Clinical manifestation of BOS onset was presented by cough (88%) and dyspnea 0 (10%), 1 (5%), 2 (33%), 3 (47%), 4 (5%) degrees according to modified Medical Research Council scale. Three patients (7%) didn't have any pulmonary complaints. The median forced expiratory volume in the first second, Tiffeneau index and residual volume at the moment of BOS diagnosis were 36.9%, 47.1% and 196.7%, respectively. The most frequent CT findings were bronchial wall thickening (95%) and expiratory air trapping (78%). With a median follow-up of 2.0 (0.2-7.7) years, 29 patients were alive (69%), the 5-years probability of OS was 58.2% (95% CI, 36.9-74.6).

Conclusions: This large cohort study allowed to detail the key clinical characteristics of BOS as a rare pulmonary complication of allo-HSCT. The current trend is a decrease in the cumulative incidence of BOS due to the use of non-myeloablative conditioning and PTCy, while maintaining an increased risk in the context of haploidentical and MMUD allo-HSCT.

Disclosure: Nothing to declare.

P576

Current Status and Needs of Long-term Follow-up Clinics for Hematopoietic Cell Transplant Survivors: Results of a Nationwide Survey in Japan

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Background: With increasing attention being paid to the importance of long-term survivorship care after allogeneic hematopoietic cell transplantation (allo-HCT), more institutions have been establishing long-term follow-up (LTFU) clinics. Currently, however, with various volumes of HCT numbers and resources, HCT centers do not have a standardized way of operating these clinics.

Methods: We conducted a nationwide questionnaire survey to characterize the current operation of LTFU clinics in Japan. We targeted 271 HCT centers (189 adult and 82 pediatric) that registered allo-HCT cases to the national transplant registry database. A paper-and-pencil questionnaire was sent to the targeted centers in March 2018, and they were asked to respond by June 2018. Transplant centers that had established a LTFU clinic were asked to answer all questions in the survey, including target patients; time points for follow-up; staffing model including paramedical staff and roles of each medical staff; standard institutional practices for late-phase follow-up; and current utilization of LTFU tools and needs related to these tools. Other centers that did not operate a LTFU clinic were asked to provide freeform comments regarding reasons or barriers for not operating a LTFU clinic.

Results: The response rate was 69%, and 117 (62%) of the 188 participating centers had an established LTFU clinic. In 71 centers without a LTFU clinic, the most frequent reason for not operating LTFU clinics was a "lack of human resources" (47%), especially nurses, while 24% of centers stated that they were "planning" to start a HCT-specific LTFU clinic. Most centers with a LTFU clinic targeted allo-HCT patients, although autologous HCT survivors were followed up at 18% of adult and 48% of pediatric centers. Ninety-two percent of centers did not terminate LTFU at a specific time point, and 56% recommended that patients visit the LTFU clinic beyond 5 years after HCT. Fifteen of 20 pediatric centers indicated that they did not routinely refer survivors who received HCT at a young age to adult HCT centers for their adulthood LTFU. The other five centers that did make referrals to adult HCT centers reported that such

transitions occurred mainly when patients moved to other areas to start college or employment. Currently, the most frequently used tool at LTFU clinics was a patient medical questionnaire (82% of adult centers, 86% of pediatric centers). When asked about the needs for standardized nationwide tools for LTFU clinics (e.g. patient medical questionnaire, and patient education materials regarding vaccination or secondary cancer screening), medians of respectively 68% and 27% of centers replied "definitely necessary" and "desirable" for each tool. The need for standardized tools was generally perceived as high, even for tools not frequently used at each institution at the time of this study.

Conclusions: We found that staffing and standard practices varied widely among centers, and that most centers continued to see long-term HCT survivors at their own outpatient clinics. The need for standardized tools was generally high. The development and utilization of common LTFU tools may be helpful in facilitating standardized interventions and efficient transitions, and reducing the burden on healthcare staff.

Disclosure: Nothing to declare.

P577

Survivorship Care for Allogeneic Transplant Patients in The UK: Current Service Provision and Barriers to Implementation

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Background: Survivorship care for allogeneic transplant recipients is variable despite international guidelines. A survey was undertaken in the UK in 2014 which identified barriers to implementation of long-term follow-up services (Hamblin et al, BMT, 2017, 52:889-894). A repeat survey was undertaken in 2018/19 to assess whether the service provided by the National Health Service for this group of patients had changed over time and to identify key barriers to implementation.

Methods: A web-based survey was designed based on the previous survey to allow for data comparison and assessment of progress. The questionnaire was piloted by senior physicians prior to circulation. The survey was designed so that responders selected one item from a list of multiple choices with the addition of free text for certain questions. The link was sent by the Head of the British Society of Blood and Marrow Transplantation and Cellular Therapy data registry and two reminders were sent to non-responders. Additional questions were added regarding screening for second cancers and access to vaccinations. Vaccination questions were based on a previous study (Miller et al, BMT, 2017: 52, 775-777).

Results: The response rate was 25/31 (81%) with 21/25 (84%) of responses from English centres. Improvements were seen in the number of centres having a dedicated long-term follow up clinic for allogeneic transplant recipients (52% versus 33%) and an SOP (88% versus 69%). Some centres (44%) adopted a shared care policy where care was also undertaken by primary care or local hospital. Forty-five percent of responders had to refer to another trust or community for access to key specialists.

Only 20% of centres had undertaken an audit against the SOP. The inclusion of psychological assessment in SOPs remained low at both time points (32% versus 28%). Twenty-three out of 25 centres reported a vaccination programme (two centres did not respond). Difficulty in implementing the vaccination protocol was reported by five centres. The main difficulties reported were primary care staff refusing to give vaccines (5) or being reluctant to administer vaccinations which were usually given to children (2) as well as shortage of vaccinations (2). The main difficulty highlighted in relation to screening for second cancers was access to early breast cancer screening for patients who had received TBI with 36% of centres reporting that this was difficult.

The main barriers to implementation of long-term follow up clinics were the same in 2019 and were mainly financial. The biggest of these was funding for clinical staff (ranked highest by 19% of centres) followed by funding for psychological support (ranked highest by 18%). Only 12% of centres thought geography was the biggest barrier and only 9% of centres thought that lack of motivation of patients was the biggest barrier.

Conclusions: Some improvement has been made in the provision of survivorship care for allogeneic transplant patients in the UK since 2014 but key barriers to implementation remain. These barriers are mainly financial/resource related and predominantly relate to funding for clinical staff and psychological support. In addition, access

to breast cancer screening and vaccinations requires improvement.

Disclosure: Nothing to declare.

P578

Whole Body Vibration Training during Allogeneic Hematopoietic Cell Transplantation - The Effects on Patients´ Physical Capacity, Fatigue, Body Compsition and Quality of Life

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Background: Patients undergoing alloHCT experience a considerable decline in physical and psycho-social capacity. Since whole body vibration (WBV) is known to efficiently stimulate the neuromuscular system and enhance cardiorespiratory fitness and muscle strength in frail individuals, we hypothesized that WBV would maintain various physical and psychological capacities in patients during alloHCT.

Methods: Seventy-one patients were randomly allocated to either an intervention group doing WBV (IG) or an active control group doing mobilization (CG) exercises five times per week. We determined peak oxygen consumption (VO_{2peak}) and maximum power, maximum strength, functional performance, body composition, quality of life (QoL), and fatigue. Tests were carried out before conditioning therapy, at hospital discharge and at day ±180 (follow-up).

Results: As 18 patients did not participate in post-intervention assessment and follow-up data from 9 patients was not collectible, per-protocol (PP) analysis of 44 patients is presented. During hospitalization, WBV maintained maximum strength, height and power output during jumping, as well as reported QoL, physical functioning, and fatigue level compared to mobilization (CG). At follow-up, relative VO_{2peak} ($p=0.035$) and maximum power ($p=0.011$), time and power performing chair-rising-test ($p=0.022$; $p=0.009$) and reported physical functioning ($p=0.035$) significantly increased in the IG, while fatigue decreased ($p=0.005$). CG´s body cell mass and phase angle had significantly decreased at follow-up ($p=0.002$; $p=0.004$).

Conclusions: Thus, WBV might maintain maximum strength, functional performance, QoL, and fatigue during alloHCT, while cardiorespiratory fitness might benefit from accelerated recovery afterwards.

Disclosure: Nothing to declare.

P579

Multi-morbidity in Adult Survivors of Stem Cell Transplantation (SCT)

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Background: As the number of long-term survivors increases, systems for follow-up assume greater importance. The ideal model of care is not established: in particular where the follow up should occur (hospital services or in the community) and by whom (hospital physician, GP or nurse). The cumulative incidence of a chronic health condition after HCT has been estimated as 59% at 10 years[1]. The burden of morbidity accumulated by individuals surviving beyond 10 years is less clear. The National Institute of Clinical Excellence (NICE) in the UK highlights specific needs of patients with multi-morbidity (2 or more long-term health conditions) which include establishing patient values and priorities in follow up and attention to co-ordination of their care services[2]. In this study we have collected data on the morbidity of patients surviving a minimum of 15 years after transplant.

Methods: Data was collected on consecutive patients attending a dedicated long-term follow up clinic over a 6-month period. We included data on prescribed medication, potentially curable conditions (e.g. cancer, reduced bone density), treatable conditions (e.g. dyslipidaemia, hypertension) as well as those associated with chronic debility e.g. diabetes, asthma. A history of successful cataract removal, premature menopause/infertility or treated vitamin D deficiency was not included. Mental health conditions, sensory impairment, chronic pain and alcohol abuse were included as per the NICE definition of multi-morbidity[2].

Results: Data were collected on 67 patients, median age 51y (range 26-74) a median of 24y (range 15-39) after transplant. The median age at transplant was 28y (range 6-55). Underlying conditions were as follows: CML (51), ALL (5), AML (4), Aplastic anaemia (3), thalassemia (3) and juvenile CML (1). The majority of patients with malignant disease had TBI conditioning regimens. The most frequent physical or mental health diagnoses were dyslipidaemia (26/67), low bone mineral density (18/67), cancer (17/67 including 4 non-melanoma skin cancer), hypertension (13/67), chronic GVHD in at least one site (11/67: skin n=7, ocular n=4, lung n=2), hypothyroid (10/67), ischaemic heart disease (7/67), depression/anxiety (7/67), asthma

(5/67), gout (5/67), testosterone deficiency (5/67). In addition, 8 patients had chronic pain, 4 had sensory impairment (visual n=2, auditory n=2) and two excessive alcohol intake. The median number of conditions per patients was 3 (range 0-10). Two patients had more than 6 physical conditions and were > 37 years post- transplant. 2/3 patients who had no underlying health conditions 23y post HCT received non-TBI transplants for beta-thalassaemia aged 7 and 11. The median number of medications per patient was 4 (range 0-14), with five taking 10 or more. The most frequently prescribed were vitamin D/Ca-vit D (n=34), prophylactic antibiotics (n=28), statins (n=27) and antihypertensives (n= 22).

Conclusions: Long-term survivors of transplant have multiple medical conditions requiring treatment and this is reflected in the high median number of tablets prescribed per patient. It is important that evolving strategies for following up this group of patients take into account the potential complexity of patients surviving more than 15 years after transplant.

Clinical Trial Registry: Not Applicable

Disclosure:

Authors:

Nothing to declare.

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P580

Gonadotoxicity after Treosulfan-based Myeloablative Conditioning Regimen for Allogeneic HSCT in Girls with Leukemia

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Background: Treosulfan is well known as myelo- and immunoablative agent in conditioning regimens with potential to reduce early toxicity of allogeneic hematopoietic stem cell transplantation (allo-HSCT), but there are no evident data about long-term effects, especially gonadotoxicity and possible fertility preservation

Methods: We performed a retrospective analysis of gonadotoxicity in 55 girls, who got allo-HSCT at BMT Departments of Dmitry Rogachev National Research Center of Pediatric Hematology, Oncology and Immunology between January 2012 and June 2019 with treosulfan-based conditioning regimen, and who are now not younger than 14 years (for appropriate gonadal function estimation). Minimum follow-up period was 6 months, maximum - 7 years.

Results: Fifty-five girls, median age 14,6 (range 9-18,5) years with acute leukemia (17 lymphoid and 38 myeloid, 42% in CR1, 31% in ≥CR2, 27% in advanced disease) underwent allogeneic-HSCT in our center. Transplants were from MFD in 14 (25,5%, two of them with TCRαβ/CD19-depletion), MUD in 16 (29%, all but one with TCRαβ/CD19-depletion), haploidentical with TCRαβ/CD19-depletion in 25 (45,5%). Median age of last follow-up was 17,5 years (range 12-22). All received treosulfan-based myeloablative conditioning, in 32 (58%) HD melphalan 140 mg/m2 was added, in 22 cases (40%) thiotepa 300 mg/m2 was used and one had posttransplant cyclophosphamide 100 mg/kg. All patients engrafted, but 16 relapsed (29%). Twenty girls died, 13 due to progression of the disease, 7 had TRM. At a median follow-up of 3 years overall survival was 60% (CI 47.2, 76.4), relapse-free survival - 50,9% (CI 37.6, 68,8). Acute GVHD developed in 26 (47%), grade 3-4 in 8 (14,5%). Chronic GVHD incidence was 25,4%. Various gynecological disfunctions have been reported in 33 patients, hypergonadotropic hypogonadism (HH) was confirmed in 16 (48,5%). Two girls with HH had spontaneous gonadal recovery, 7 needed replacement hormonal therapy (RHT) and 7 did not receive RHT. Among patients on RHT 4 responded to it and 3 were lost to follow-up. One case of pregnancy and birth giving was registered. Cumulative incidence of HH at 3 years was 27,4% (CI 17.5, 42.9), with no difference between incidence in girls with lymphoid or myeloid leukemia (31,7% vs 26,8%, p=0,875). Recipients of treosulfan/melphalan regimen showed slightly higher, but not statistically significant rates of HH (29,3% vs 23,8%, p=0,708), compared with recipients of treosulfan/thiotepa or treosulfan/cyclophosphamide. Six of 16 girls with HH (37,5%) showed recovery of gonadal function including menstrual recovery.

Conclusions: Treosulfan-based conditioning allows to preserve gonadal function in about 70% of girls after allo-HSCT. Further studies are needed to evaluate gonadal

function recovery and its persistence in allo-HSCT with treosulfan-based conditioning in larger groups with longer follow-up.

Disclosure: Nothing to declare.

P581

Reduced-intensity Transplantation in Patients Older than 65 Years with High-risk or Advanced Hematological Malignancies in Last 10 Years - Single Centre Experience

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Background: in recent years, the number of elderly patients treated with hematological malignancies has increased. However, in some of them, despite the inclusion of new targeted drugs, this treatment fails. Increasing data supports the utility of allogeneic hematopoietic stem cell transplantation after reduced-intensity conditioning (RIT) in such older pts resulting in improvement of their outcomes. But in a large proportion of elderly patients, RIT is not performed due to concerns about high toxicity, morbidity and mortality. Therefore, the outcomes of RIT in elderly pts remain still poorly defined. To evaluate the current results of RIT in elderly pts with "high-risk" hematological malignancies we retrospectively analysed the outcomes of pts older than 65 years transplanted in our centre during last 10 years.

Methods: from 9/2009 to 9/2019 60 consecutive pts with median of age 66 years (range: 65-74 years) with high-risk or advanced hematological malignancies (77% AML, 8% CLL, 5% MDS-EB2, 5% NHL, 3% OMF, 2% ALL) underwent RIT (13% HLA identical related, 28% HLA haploidentical related, 42% HLA matched unrelated, 17% HLA mismatched unrelated). HCT-CI ≥ 3 was in 38% of pts. Source of stem cells was peripheral blood in 87% and bone marrow in 13% of pts. The median of infused CD 34+ cells was 6,38x10^6/kg (range: 2,46-16,9x10^6/kg). The conditioning regimen consisted of fludarabine and melphalan (+ATG in unrelated donor). GVHD prophylaxis was cyclosporine and methotrexate in 67% of pts and cyclosporine or tacrolimus and MMF, in case of haploID RIT also with post-transplant CPA, in 33% of pts.

Results: 97% of pts engrafted and among 57 evaluable pts 41 (68%) of them developed acute GVHD (6 pts grade III-IV). Among 44 evaluable pts 16 (36%) of them developed chronic GVHD (8 mild, 5 moderate, 3 severe). With median follow-up of living pts 24 months (range 6-120 months) 27 pts (45%) are alive in CR. 11 pts (18%) relapsed or progressed with median time to progression 5 months (range 3-27 months) and all of them died. 22 pts (37%) died due to NRM. NRM till day +100 after RIT was 15%. The estimated probabilities of 2 and 5-years GRFS is 48% and 33%, PFS 55% and 37% and OS 58% and 38%.

Conclusions: our results suggest that RIT is a promising treatment option for selected group of elderly pts with high-risk or advanced hematological malignancies with a 2-year and 5-year OS 58% and 38% and with relatively good quality of life (2-years and 5-years GRFS 48% and 33%). Somewhat higher TRM and relapse incidence in our cohort of elderly pts could be positively influenced in the future by correct selection of pts who would benefit from RIT and their earlier indication for RIT. In our opinion age alone should not be criterion against RIT and RIT should be considered as potential standard treatment option among suitable elderly pts with hematological malignancies.

Disclosure: Nothing to declare.

P582

Fatherhood after a Myeloablative Treosulfan Based Allogeneic Stem Cell Transplantation: Analysis on 453 Patients

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Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is increasingly used as curative option in treatment of malignant and non-malignant diseases.

Eighty percent of those who survive the first 2-years are expected to become long-term survivors. Preservation of fertility is becoming a crucial issue for quality of life after HSCT.

In the past years both EBMT and CIBMTR addressed this topic, unveiling that only few patients preserved fertility

and eventually underwent a pregnancy. The Pediatric WP published an interesting survey across EBMT showing how with the advent of less toxic conditioning regimen (notably with treosulfan) the gonadal toxicity was likely to be reduced.

How this will allow to preserve fertility and afford a pregnancy will be object of further studies.

Our study seeks to describe the event of fatherhood across the male patients that underwent a first HSCT at our Institute in the past 20 years.

Methods: This is a prospective cohort analysis of data collected at our Long-Term Follow-Up clinic including 453 consecutive adult patients (273 male - median age at HSCT 49y, range 17-76y) - with at least 24-months follow-up (median follow-up 7y, range 2-25y) - transplanted between 1996 and 2017. Last update Nov 2019.

A written consent was given by patients allowing the use of medical records for research in accordance with the Declaration of Helsinki.

An all-comprehensive standardized life-time follow-up of HSCT-survivors is applied at our Center, according to Jacie Standards and international guidelines.

Results: Twelve patients fathered a child - median age at transplant 31y (range 25-48y), median follow-up 10y (range 2,5-10y). Patients features are reported on table 1.

Of note, all but 1 patients received the transplant after diagnosis of a malignant disease and all but 2 were affected by GvHD. Ten patients received a treosulfan based conditioning regimen.

At last follow-up we reported 15 pregnancies in female partners of 12 male HSCT recipients: the pregnancies resulted in successful deliveries of 15 live-born singletons (9 boys and 6 girls). The pregnancy outcome was uncomplicated in all cases. There was no delivery-related complication in the mothers.

Ten pregnancies were achieved with spontaneous conception. Five men reported use of cryopreserved sperm. One pregnancy is actually ongoing.

Conclusions: Fertility preservation is a major issue after transplantation, it is related not only to transplant procedure but - of course - also to all the treatment (chemotherapy, targeted therapy, radiometabolic treatment) administered before transplant.

An adequate patient's counseling and the pursuit of strategies to preserve fertility after transplantation are essential. Treosulfan seems to be associated with a lower gonadal damage: further longitudinal cohort studies are essential for improving the care and assistance of our patients.

Our experience underscores the importance of dedicated program.

	Age at HSCT - median (range)				Conditioning Treosulfan based	Donor			GvHD
	<20y	20y-40y	40y-50y	>50		MRD	MMRD	UD	
All (273	6	66	52	149	238	81	96	96	173
Patients who fathered a child (12)	0	8	4	0	10	7	2	3	10

[Patients features]

Disclosure: "Nothing to declare."

P583

Older Age and Peripheral Blood as a Stem Cell Source are the Major Negative Predictors of Survival Long Term

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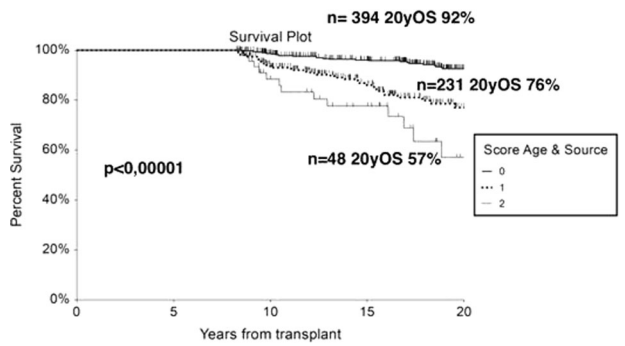
Background: Allogeneic hemopoietic stem cell transplantation (HSCT) has been widely used in hematologic malignancies for over 4 decades. One important question is the assessment of risk factors for long term survival.

Methods: We used our transplant relational database, in which patients' clinical and laboratory data are prospectively recorded during each outpatient visit or during admission. We selected 673 patients who were still alive at 3000 days post transplant. Patients underwent transplantation between 1978 and 2011. The median follow up was 17.5 years (range 8.2-36.6), median age was 34 years (range1-65) The diagnosis were acute leukemias (n=316), chronic leukemias (n=238), mds (n=39), lymphoma (n=45), myeloma (n=18). The stem cell source was bone marrow (BM)(n= 568), peripheral blood (PB) (n=74), cord blood (CB) (n=31). Patients received grafts from sibling, mud, haploidentical and UCB donors in number of 470, 135, 37 and 31 respectively. 97.33% of patients received GVHD prophylaxis with cyclosporin and methotrexate and only 2.67% with post transplant cyclophosphamide.

Results: The overall actuarial survival at 20 years was 86% (95%CI 83%-89%). Leading causes of death were second tumours (31.88%), chronic GvHD (27.54%) relapse

(27.54%). In univariate analysis pre-transplant negative predictors of survival were the following : Conditioning without TBI (HR 2 p=0.0006) compared to conditioning including TBI, Donor Age over 40 yo (HR 2.35 p< 0.0005), Active disease at transplant (HR 2.06 p=0.005), Time from diagnosis to transplant over 245 days (HR 1.9 p=0,005), diagnosis of acute leukemia (HR 1.89 p=0,0039), recipient age >= 39 (HR 3.66 p< 0,0001) and peripheral blood as stem cell source (HR 3.18 p< 0.0001). in multivariate Cox analysis, negative predictors for survival were only recipient age over 40 (RR3.14 p< 0.0001) and PB versus BM (RR 1.94 p=0.02). We so attributed 1 point for age>39 and peripheral blood as stem cell source respectively to obtain a simple clinical score. As shown in figure 1 patients with a score of 0,1 and 2 have a 20 year overall survival of 92%, 76% and 57 % respectively. Hazard Ratio 1/0 was 3.49 and 2/0 was 6,38 (p< 0.0001). We also found that 48% of patients grafted with peripheral blood stem cells (PBSC) developed grade 2-3 cGVHD vs 33% of patients grafted with bone marrow stem cells (BMSC) (p< 0.005). Chronic GVHD was a cause of death in 33% and 25% of patients grafted with PBSC and BMSC respectively although this result do not reach statistical significance (p=0,6).

Conclusions: Age over 39 years old and peripheral blood as stem cell source are negative predictors of long term overall survival. Higher incidence of grade 2-3 Chronic GvHD is seen in long term survivors grafted with peripheral blood stem cells. A simple score that uses age and source type could be, if validated prospectically, an useful tool for prediction of long term survival.



[Figure 1]

Disclosure: Nothing to declare.

P584

Prevalence of Bronchiolitis Obliterans Syndrome (BOS) Following Allogeneic Hematopoietic Stem Cell Transplant (ALLOHSCT) in The US, Europe and Japan

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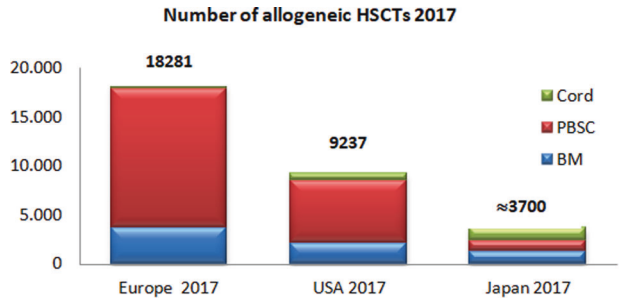
Background: Bronchiolitis obliterans syndrome (BOS) is a fatal obstructive airway disease most commonly associated with lung transplantation or alloHSCT. Regardless of preceeding injury, BOS is characterized by T-cell mediated inflammation and fibrosis of bronchiolar walls that reduces the diameter of the bronchioles resulting in progressive and irreversible airflow obstruction. BOS is a well described complication following lung transplant with a 5-year prevalence rate of 50%, but is less well described following alloHSCT. The aims of this study were to describe the prevalence of BOS following alloHSCT in the US, Europe, and Japan.

Methods: First, to evaluate the total number of alloHSCT performed, a review and analysis of the following data sources was performed: AlloHSCT activity reports from the European Society for Blood and Marrow Transplant 2017, the Center for International Blood and Marrow Transplant Research 2017, Health Resources and Service Administration report 2017, and the Japanese Data Center Hematopoeitic Stem Cell Transplantation 2017. Further, a PubMED literature search was conducted and identified publications with >100 patients using the key terms "bronchiolitis obliterans and haematopoietic stem cell", "bronchiolitis obliterans after stem cell transplant", and "prevalence" from 2011 to 2017. Case reports, reviews, and redundant publications were excluded.

Results: Approximately 31.200 alloHSCTs were performed in 2017 according to published regional reports (US: 9.237; Europe+Affiliates: 18.281; Japan: ~3.700). In Europe and the US, peripheral blood stem cells (PBSC) are the major source for alloHSCTs, respectively 77% and 69%, followed by bone marrow. In both regions, cord blood represents less than 10% of total alloHSCTs. In Japan, each cell source accounts for approximately one third of total alloHSCTs. Based on eligible studies identified by literature search, the reported prevalence of BOS in patients who underwent alloHSCT ranged from 3.4% to 10%. Median time to diagnosis of BOS following alloHSCT was 273 to 547 days post-transplant. Several risk factors for developing BOS were identified but were not consistent across studies.

Conclusions: Based on number of procedures and estimated prevalence, up to 3.000 patients could be diagnosed with BOS following alloHSCT every year. Source for alloHSCT varied per region. In the identified studies, BOS was most likely to be diagnosed 1-2 years post alloHSCT.



[Number of allogeneic HSCTs 2017]

Disclosure: Emilie Hofstetter is a consultant to Breath Therapeutics and received consultancy fees. Dominik Kappeler and Noreen Roth Henig are employees of Breath Therapeutics, a Zambon company. Anne Bergeron has nothing to disclose.

P585

Netupitant-palonosetron (NEPA) to Prevent Chemotherapy-induced Nausea and Vomiting (CINV) in Multiple Mieloma (MM) Patients Receiving High-Dose (HD) Melphalan and Autologous Stem Cell Transplantation (ASCT)

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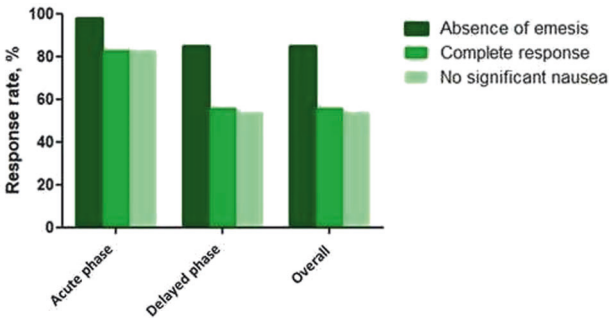
Background: In MM patients receiving HD melphalan followed by ASCT, the addition of a Neurokinin-1 (NK1)-receptor antagonist (RA) to a 5-hydroxytryptamine-3 (5HT3)-RA and corticosteroids combination significantly reduced CINV. NEPA is an oral, fixed combination of a NK1-RA and a 5HT3-RA largely tested in solid cancer patients and approved for highly and moderate emetogenic chemotherapy. To our knowledge, no data exist on the use of NEPA before HD melphalan and ASCT.

Methods: This is a single institution, prospective, observational study aiming to assess the efficacy and safety of NEPA before HD melphalan followed by ASCT in MM patients. Patients received NEPA on day 1, together with a single dose of oral dexamethasone, one hour before melphalan infusion. Dexamethasone was reduced to 10 mg due to the known interaction with netupitant and infectious risk concerns. ASCT was performed on day 3. Patients received a daily questionnaire from day 1 to 5 to assess nausea and emesis. Nausea was graduated by patients on a 100-mm visual analog scale (VAS). Significant nausea was defined as VAS > 25 mm. The primary endpoint was the absence of emesis and rescue medication requirement (complete response, CR) during the first 120h after chemotherapy infusion. Secondary endpoints were CR rate during the acute (0-24h) and delayed phase (24-120h), the rate of emesis and significant nausea and safety.

Results: We analyzed the outcome of 70 consecutive patients undergoing 80 ASCT, between May 2017 and November 2019. 33 patients were male (47%) and median age at ASCT was 59 years (range 42-69). Melphalan dose was 200 mg/mq and 100 mg/mq in 70 and 10 cases, respectively. CR rate during the 120h observation period was 56% (45/80), without any episode of emesis in 68 cases (85%). No significant nausea was reported in 43 (54%) cases. During the acute phase, CR rate was 83% (66/80), with 78 cases (98%) reporting no emesis and 66 (83%) no significant nausea. Data during the delayed phase were comparable to the 120h period, figure 1. 120h CR rate tended to be higher in males (67% vs. 46%, p=0.076), but it did not differ according to melphalan dose (p=0.5) or age (p=0.1). No significant side effects likely related to NEPA were recorded, except one case of headache (G2) and one of hiccup (G1). Finally, we further evaluated the subgroup of 33 patients receiving a second ASCT: excluding those (10/33) who received NEPA during both ASCT, 65% of the patients (15/23) reported a reduced level of nausea compared to their previous transplant, in which a different NK1-RA/5HT3-RA/corticosteroids combination was employed, while in 35% of the cases it was comparable; no one reported a worse level of nausea.

Conclusions: Oral NEPA was effective and safe in MM patients receiving HD melphalan and ASCT. CR rate was comparable to published studies combining intravenous formulation of a 5HT3-RA and a NK1-RA, without increasing costs (at currently selling prices in Italy) and with an easier administration schedule. Additional efforts are required to further reduce CNIV in this setting.



[Figure 1]

Clinical Trial Registry: Not applicable
Disclosure: Nothing to declare.

P586

Most Frequent Late Effects after Allogeneic Hematopoietic Stem Cell Transplantation iIn Adult Acute Lymphoblastic Leukemia does not seem to Worsen Performance Status

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Background: The sequence of chemotherapy treatment for high risk adult acute lymphoblastic leukemia (ALL) followed by myeloablative conditioning for hematopoietic stem cell transplant (HSCT) supposes a high degree of toxic exposure specially from prolongued steroid use and TBI. The aim of this report is to identify common late effects in this population and analyze its impact on patients' performance status.

Methods: From a cohort of 139 HSCT performed in 128 ALL patients (11 double HSCT) between 1990 and 2018, 65 patients (46,7%) surviving longer than 12 months, were evaluable for late effects. Patients and HSCT characteristics are in table1. Chemotherapy protocols were the habitual for this disease and Cyclophosphamide +TBI was the most employed conditioning regimen (n=56; 86%). Patients' performance status was evaluated with Karnfosky score.

Results: With a median follow up of 84 months (36-730) 51 patients (78,5%) were identified to have at least one late sequalae or effect. The most common, in order of frequency, were cardiovascular (hypertension and dyslipidemia) in 20 patients (39,2%), ovarian failure/infertility in 16 patients (31,4%), hypothyroidism in 12 patients (23,5%), cataracts in 11 patients (21,6%), osteopenia or osteoporosis in 7 patients (13,7%) and secondary malignancies (all cases were cutaneous squamous cell carcinoma) in 6 patients (11,8%).

Thirty nine patients with late effects reported a score of ≥80% by Karnofsky scale. Moreover, most of them (n=35; 90%) had a score of 90-100% and only one 60%. Data was unavailable in 6 patients. All 14 patients free of late sequelae reported a Karnofsky score of ≥80%.

Conclusions: In our cohort of 65 prolongued survivors of HSCT in high risk adult ALL, where TBI was broadly employed, cardiovascular risk factors, ovarian failure/infertility, hypothyroidism and cataract were frequent late effects (20-40%) but patients' performance status seemed to be relatively unaffected by them.

Characteristics	Late effects YES N=51	Late effects NO N=14	Total N=65 (%)
Sex (female/male)	24 / 27	10 / 4	34 (52%) / 31 (48%)
Age (<40/≥40 years)	33 / 18	10 / 4	43 (66%) / 22 (33%)
Ph cr (negative/positive)	32 / 19	8 / 6	40 (62%) / 25 (38)
Bone marrow/peripheral blood	29 / 22	4 / 10	33 (51%)/32 (49%)
Donor (sibling/unrelated/haplo)	33 / 18 / 0	9 / 3 / 2	42 (65%) / 21 (32%)/ 2 (3%)
HLA disparity (no/yes)	2 / 49	3 / 11	5 (8%) /60 (92%)
Conditioning (CyTBI/other)	46 / 5	10 / 4	56 (86%) /9 (14%)

[Table 1]

Disclosure: Nothing to declare.

P587

Involving Stem Cell Transplant Patients and Their Families to Improve The Anthony Nolan my Transplant Tracker App

Jonathan Kay[1], Julia Laflin[2], Vasileios Karageorgos[2], David Hoskins[2], Hayley Leonard[1], Tom Bishop[1], Clare Cooper-Hammond[2], Laura Phillips[1], Chiara Di Biase[1]

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Background: In 2018 Anthony Nolan launched My Transplant Tracker, the first app that allows stem cell transplant patients to track and record aspects of their recovery. Over 1500 users have now downloaded the app to track their blood test results, medical appointments, medication and personalised goals. The app also features post-transplant recovery health information and advice to give

patients a much-needed sense of control over their recovery and ultimately improve their quality of life.

As part of Anthony Nolan's commitment to using the voice of our patients to develop the services we provide, we reviewed the app after its first year to identify how it could be improved.

Methods: Stem cell transplant recipients and family members attending a patient information day were invited to take part in a focus group for the app. Two groups of ten attendees were each shown a list of possible functions or topics of interest that could be included in their ideal app. No indication was given as to whether they already featured in My Transplant Tracker.

Through discussion, each group also generated their own ideas and ranked the options in order of importance. All feedback was recorded and analysed to identify the functions to be incorporated into the new version of the app.

Results: Three key areas of improvement were identified as a result of the focus group.

1. The option to store and track a wider range of transplant related topics including:

user's mental health/mood
scanned hospital letters
pictures of visible side-effects such as skin GvHD.

'Being able to actually see your improvement is a big deal.'

2. While some patients were interested in tracking their diet, exercise and sleep, they saw no benefit in setting recovery related goals they could work towards. They felt the idea of failing would have a negative impact on their mental health.

   'It's difficult to set goals because you don't know how you will feel from day to day'
3. To connect with other stem cell transplant patients and to share their experiences. Patients also wanted improved access to online forums and the ability to ask questions directly to other app users.

'I had trouble finding trusted community groups and often ended up on completely irrelevant online forums'

Conclusions: Exploring the needs of our patients and their families has provided valuable insight into the improvements needed to better meet their physical and mental needs. The app is now being updated to give patients more options to personalise the information they store, which can be recalled later, within a diary format. Better integration with the Anthony Nolan Patient Forum and ways to communicate with other users will also be included.

Disclosure: Nothing to declare.

P588

Early Menopause and Risk Factors after Allogeneic Hematopoietic Stem Cell Transplantation in Premenopausal Adult Women

Yoo Jin Lee, Jeong Sook Kim, Jae-Cheol Jo, Jaekyoung Cheon, SuJin Koh, Young Joo Min, Kukju Kweon, Sang-Hyuk Park, Jun-Woo Ahn, Yunsuk Choi

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Background: Allogeneic hematopoietic stem-cell transplantation (HSCT) is only curative option for most hematologic malignancies and bone marrow failure syndromes. In premenopausal women, however, HSCT can cause early menopause and various complications. Therefore, we aimed to investigate risk factors predicting early menopause and its clinical implications among survivors post HSCT.

Methods: We retrospectively analyzed 30 adult women with hematologic malignancies (n=22) or aplastic anemia (n=8) who had received HSCT at premenopausal status between 2015 and 2018 at Ulsan University Hospital, Ulsan, Korea. We excluded patients who had received autologous hematopoietic stem cell transplantation or those who had a relapse or died of any cuauses within 2 years after HSCT. The survey data including quality of life assessment (FACT-BMT), Hospital Anxiety and Depression Scale, and NCCN Distress Thermometer were collected as patient reported outcomes during routine practice of survivorship clinic.

Results: The median age at HSCT was 41.6 years (range, 22-53). Of all included patients, 20 patients (66.5%) showed menopause at 2 years after HSCT. Older ages tended to be more associated with post HSCT menopause (50% in 20-< 30 years, 60% in 30-< 40, 70% in 40-50 years and 100% in ≥50 years, P=0.813). According to disease types, there were significant differences in the rate of early menopause post HSCT which was more frequently found in 91.7% (11/12) of acute myeloid leukemia (AML), in 66.5% (4/6) of acute lymphoblastic leukemia (ALL), and in 100% (2/2) of lymphoma than in 50% (1/2) of myelodysplastic syndrome (MDS) and in 25.0% (2/8) of aplastic anemia (P=0.018). In addition, conditioning regimens containing higher doses of busulfan were significant adverse factors affecting the early menopause after HSCT (P=0.023). Among patients who had received myeloablative conditioning including 4 days of busulfan plus 2 days of cyclophosphamide, 90% (9/10) of patients showed early menopause at 2 years after HSCT. Of patients who were treated with two or three days of busulfan plus fludarabine regimen, 80% (8/10) had post HSCT menopause. In non-

busulfan based conditioning regimens, however, early menopause following HSCT was found only in 30% (3/10) of patients. According to donor types, the use of anti-thymocyte globulin, graft versus host disease, and immunosuppressant use, there were no significant differences in the incidence of early menopause after HSCT. In early menopausal women after HSCT, more frequently observed symptoms were hot flush (100% vs. 0%, $P < 0.001$) and weight gain (40% vs. 20%, $P < 0.041$), compared to those in premenopausal status even after HSCT. However, early menopause post HSCT did not influence on quality of life as well as insomnia, fatigue, pain, anxiety, depression, and distress among survivors post HSCT.

Conclusions: Acute leukemia, lymphoma, and busulfan based conditioning regimens were significant risk factors affecting post HSCT menopause. Considering our data, we need to make therapeutic plan of HSCT and do individualized fertility counseling before HSCT for premenopausal women.

Disclosure: Noting to declare.

P589

Clinical Characteristics and Management of Late Relapse of Acute Myeloid Leukaemia more than Five Years after Allogeneic Stem Cell Transplantation

Shafqat Inam, Shu Wong, Michelle Kenyon, Victoria Potter, Austin Kulasekararaj

Kings College Hospital NHS Foundation Trust, London, United Kingdom

Background: Disease relapse is after allogeneic haemopoietic stem cell transplantation (HSCT) of acute myeloid leukaemia (AML) remains a major challenge. The biological mechanisms of relapse include clonal evolution and immune escape, though remain incompletely understood. A majority of relapses happen within the first 12 months after transplantation, and CIBMTR data shows that less than 20% occur after 2 years. The occurrence of relapse after 5 years of transplantation is extremely uncommon and there is limited literature on the clinical and biological features of these cases.

Methods: We compiled our single centre's relapses after allogeneic HSCT for AML over the period January 2008 to August 2019. We characterised the clinical and pathological features of very late relapse defined as occurring 5 years after first documentation of morphologic complete remission (< 5% bone marrow blasts) after HSCT, or at least 5 years after the last therapeutic intervention for mixed chimerism with donor lymphocyte infusion (DLI).

Results: We identified 10 patients who relapsed more than 5 years following remission with allogeneic HSCT for AML. 7 had matched unrelated and 3 matched sibling donors. As the date of transplantation ranged from a period of 1999 to 2013, there was heterogeneity in the conditioning regimens and use of in vivo T cell depletion. Myeloablative conditioning was used for 5 patients [Busulfan and Cyclophosphamide (BU/CY) for 4, and BU/CY/TBI for 1] and reduced intensity conditioning for the remainder [Fludarabine and Busulphan 6.4 mg/kg (FB2) for 5]. 7 of 10 patients had in vivo T cell depletion: 5 UD transplants alemtuzumab, and 2 matched sibling transplants had alemtuzumab and ATG respectively.

The mean time to relapse was 3381 days (9 years and 3 months), with range 5 to 16 years. The donor chimerism was tested in the year preceding relapse for 5 patients with full unfractionated and CD3 donor chimerism in all. Relapse of disease rather than donor derived leukaemia was supported by a marked drop in unfractionated bone marrow chimerism at time of relapse in 6 patients, or cytogenetic abnormalities consistent with return of the original clone in 4. The site of relapse was the bone marrow for 9 patients and extramedullary for one.

One patient died soon after relapse, and the other 9 received some form of treatment. 6 patients received hypomethylating agent (5 azacitidine, 1 decitabine) all in combination with DLI (median 2 doses), and 3 had intensive chemotherapy. 2 patients who received azacitidine later had intensive chemotherapy with one proceeding to a second HSCT. Of all patients, two remain in complete remission, one transfusion dependent after reversion to an MDS phenotype, and active treatment and response assessment ongoing for 4 others.

Conclusions: We present the largest series to date of very late AML relapse after HSCT. Salvage treatment was feasible for most patients, with a combination of chemotherapy, hypomethylating agents and DLI achieving durable remissions in some. Although rare the potential for very late relapse has implications for disease monitoring and the length of follow up after HSCT, and long term storage policies for DLI.

Disclosure: Nothing to declare.

P590

Following up with Adult Patients with Acute Lymphoblastic Leukemia Following 5+ Years of Allogeneic Hematopoietic Stem Cell Transplantation: A Single Center Experience

Yuta Katayama, Ryouta Imanaka, Koji Iwato, Tatsuya Terasaki, Takuya Nunomura, Fumiaki Jinnouchi,

Takeshi Okatani, Kohei Kyo, Mitsuhiro Itagaki, Shinya Katsutani, Tsuyoshi Muta, Hideki Asaoku

Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital, Hiroshima, Japan

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective treatment for acute lymphoblastic leukemia (ALL). An important problem has been highlighted in data related to follow ups with survivors following long-term allo-HSCT. We performed a retrospective survey of adult patients with ALL who underwent transplantation for more than 5 years in our institution.

Methods: We retrospectively analyzed the records of 43 adult patients with ALL who underwent their first allo-HSCT in our hospital between January 2007 and December 2014. We defined the observation period as January 2007 to December 2019. Disease, transplant, outcome related data were collected from clinical files and telephone interviews.

Results: The underlying diseases in the patients surveyed were Philadelphia chromosome-positive B-cell ALL (Ph+ B-ALL) in 21 of the patients, Philadelphia chromosome-negative B-cell ALL (Ph- B-ALL) in 15, and T-cell ALL (T-ALL) in 7. The age range was 17 to 65 years (median: 37). The status of the disease was 1st CR in 34 of the patients, 2nd CR in 3, and NR in 6. The conditioning regimen was myeloablative regimen in 37 of the patients and non-myeloablative in 6. Graft-versus-host disease (GvHD) prophylaxis was performed on all the patients using tacrolimus and short-term methotrexate or mini methotrexate. Eight of the patients received Anti-human Thymocyte Immunoglobulin (ATG). The donor source was bone marrow (BM) from a sibling in 13 of the patients, peripheral blood stem cell (PBSC) from a sibling in 5, unrelated BM in 21 and unrelated cord blood in 4. The median observation period was 2462 days (3-4554 days). Relapse-free survival (RFS) and overall survival (OS) were 65.1% (95% confidence interval (CI): 49.0-77.3%) and 67.4% (95%CI: 51.3-79.3%) at 7 years, and 60.1% (95%CI: 42.2-74.1%) and 62.6% (95%CI: 44.7-76.2%) at 10 years respectively. Non relapse mortality at day 100 was 11.6%, and the causes of death were early treatment-related complications (4 patients. The ages of all patients were over 50 years) and acute GvHD (1 patient). Five patients relapsed after allo-HSCT. Twenty patients developed chronic GvHD (limited in 1 patient and extensive in 19). Three patients developed a secondary solid tumor following allo-HSCT. In this study, 15 patients died, and the causes of death were disease relapse and complications during 2nd allo-HSCT (4 patients), early treatment-related complications (4 patients), acute GvHD (1 patient), chronic GvHD (4 patients), and infection (2 patients developed chronic GvHD). Twenty-one patients (75.0% of survivors) continued living their lives and started working again, and 13 patients (46.4% of survivors) have chronic GvHD in social life.

Conclusions: Early death of patients after allo-HSCT was mostly due to treatment-related complications among those over the age of 50, but they were already in poor condition at the time of transplantation. All late deaths were associated with chronic GvHD. Currently, we control the onset of GvHD by administering ATG to older patients, and further improvement in the treatment of chronic GvHD is necessary.

Disclosure: Nothing to declare.

P591

Low Back Pain and Laser Acupuncture in Patients Undergoing Haematopoietic Stem Cells Transplantation

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Background: Low back pain is a limiting factor in the functional activities of patients undergoing haematopoietic stem cells transplantation [HTCT]. The Acupuncture Laser [LA] technique is a noninvasive method that has similar effects to traditional acupuncture and seems to provide pain desensitization. The aim of this study is to describe a [LA] approach in patients with low back pain after hematopoietic stem cell infusion.

Methods: This is a cross-sectional study with quantitative data analysis of 12 patients who underwent laser LA technique after HSCT. This study was approved by the University Ethics Committee under number 89910618.8.0000.5283. Patients were assessed using the Karnofsky Performance Scale, Quality of Life Questionnaire (EORTC QLQ-C30) and Visual Analogue Scale (VAS) at admission and discharge from the hospital´s HSCT sector. LA was applied from the moment the patient had severe low back pain (VAS> 8) with regular analgesic use, until the patient had no low back pain or VAS < 3 with Karnofsky performance scale between 80% -90 %. For the application, distal points (upper and lower limbs) were used based on the diagnostic pattern of the eight principles of traditional Chinese medicine and points in the lower back, with the DMCTherapy XT 3 Joules Laser for 30 seconds at each point. Mann-Whitney test was performed for comparative analysis using Statistica®, the significance level adopted was $p < 0.05$. This study was approved by the

Ethics Committee of the Unigranrio University, Rio de Janeiro, under number 89910618.8.0000.5283.

Results: Participants (n = 12, men n = 8), transplants (autologous n = 8, allogeneic n = 4), mean age 53.9 ± 13.2 years, time of aplasia 11.7 ± 2.9 days, hospitalization time 41.8 ± 34.7, showed Karnofsky at admission: 97.5 ± 4.5% and at discharge 88.3 ± 12.6% p = 0.16, EORTC QLQ-C30 (Functional Scale) at admission: 81.4 ± 15 and at discharge: 72.2 ± 16.5, p = 0.75 and Admission Symptom Scale: 14.3 ± 13.9, at discharge 28.2 ± 14.4 p = 0.14 and initial VAS 8.0 ± 0, 8 and final 0.8 ± 0.5, p = 0.001.

Conclusions: Due to the clinical conditions of the patient, conventional needle treatment may not be the most appropriate; the use of LA seems effective and safe in the control of low back pain in patients undergoing HSCT, with maintenance of functional performance and quality of life of these individuals.

Disclosure: Nothing to declare.

P592

Effects of Controlled Exercise on Patients Undergoing Hematopoietic Stem Cell Transplantation

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Background: In Hematopoietic stem cell transplantation [HSCT], high doses of chemotherapy followed by rescue with hematopoietic stem cells are often indicated. These treatments have side effects which may impact physically, psychologically and upon the quality of life of these patients, as well as prolong hospital stay. Thus, the aim of the study is to observe the effect of a controlled exercise program on the recovery of patients undergoing HSCT.

Methods: This is a cross-sectional study with quantitative data analysis of 50 patients undergoing HSCT who participated in a program of strength, coordination and resistance exercises daily from hospitalization until discharge, according to indication and clinical stability. Biceps strength was measured by the number of repetitions performed in 30 seconds with a 2kg dumbbell and steady walking by the number of right knee flexions for 2 minutes. This study was approved by the Ethics Committee of the Unigranrio University, Rio de Janeiro, under number 89910618.8.0000.5283. Student's t-test was performed for comparative analysis using Statistica®, the significance level adopted was $p < 0.05$.

Results: Participants (n = 50, men n = 27), transplant (autologous n = 35 and allogeneic n = 15), mean age 47.9 ± 11.1 years, aplasia time 12.2 ± 4.2 days, hospitalization time 43.1 ± 33.5, EORTC QLQ-C30 (Functional Scale) at admission: 79, 1 ± 17.6 and at discharge: 73.2 ± 17.3, p = 0.09, biceps strength at admission: 21.8 ± 5.5 and at discharge 22.4 ± 5.39 repetitions / 30 seconds p = 0.59, steady gait admission: 75.2 ± 18.5 and at discharge 75.2 ± 18.3 right knee flexions / 2 minutes p = 0.99.

Conclusions: Controlled physical exercise in patients undergoing HSCT did not present any additional risks to patients and seems to promote maintenance of functional capacity and quality of life.

Disclosure: Nothing to declare.

P593

Development of Guillain-barré-like Syndrome in a Patient with Acute Lymphoblastic Leukemia after Haploidentical Hematopoietic Stem Cells Transplantation

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Background: Neurological complications of allogeneic hematopoietic stem cell transplantation occur with a frequency of 3% to 44% and vary widely in severity. Causes of their development can be neurotoxic drugs, infections, metabolic disorders, immune-mediated disorders and cerebrovascular diseases. The most common immuno-mediated neurological complications are Guillain-Barré-like syndrome, myasthenia gravis, myositis and chronic graft-versus-host disease (GVHD).

Methods: A 37-year-old patient with acute lymphoblastic leukemia, pro-T variant, with multiple karyotype abnormalities and refractory early relapse without remission recieved haploidentical HSCT from his father (63 years). Prevention of GVHD included CsA 3 mg/kg/day, Cph 50 mg/kg/day + 3, + 5 days, MMF 3 g/day. Conditioning regimen was Thiotepa 5 mg/kg/day -15, -14 days, Cph 400 mg/m^2/day, Etoposide 100 mg/m^2/day -13, -12, -11, -10 days, Busulfan 3,2 mg/ kg/day -6, -5 days, Fludarabine 30 mg/m^2/day from -6 to -2 days.

Results: On day +105, the patient had clinical and hematological remission II, transplant normofunction,

MRD (-), complete donor linear chimerism in the absence of infectious complications and signs of GVHD. For prophylactic purposes to prevent relapse of the underlying disease on day + 134, donor lymphocytes, total of $1x10^4$/kg were infused (DLI). On day +160, acute GVHD skin form 3 grade developed. Due to steroid refractoriness, the patient was switched to therapy with ruxolitinib 20 mg/day and sirolimus 1 mg/day. On day +176 the patient developed Guillain-Barré-like syndrome in the form of flaccid tetraparesis, moderate sensitive ataxia, neuropathic pain syndrome, bulbar syndrome. Results of cerebrospinal fluid for infectious agents by PCR and bacteriological crops were negative. Tests for creatine kinase, myoglobin level, neuron-specific enolase were normal. MRI data revealed mixed encephalopathy, atrophic changes in the cortex and white matter of the brain. Electromyography confirmed acute polyradiculoneuropathy with severe axonal-demyelinating sensorimotor neuropathy. Sessions of plasmapheresis № 7 (PCS-2, Specra Optia), the introduction of intravenous immunoglobulin at dose 0,4 g/kg № 5, Rituximab 375 mg/m2 № 4 weekly, pulse therapy with methylprednisolone 1000 mg/day №5 along with symptomatic therapy, as well as continued therapy with ruxolithinib led to a regression of GVHD and neurological symptoms.

Conclusions: Successful treatment of neurological symptoms with immunosuppressive therapy suggests an immune-mediated damage mechanism. The presence of a temporary relationship between neurological manifestations and the prophylactic infusion of donor lymphocytes, as well as their combination with skin GVHD, does not exclude damage to the central and peripheral nervous system both in the framework of GVHD and the independent nature of the complication.

Clinical Trial Registry: no.

Disclosure: authors declare. no conflict of interests.

Paediatric issues

P594

Haploidentical Donor or Unrelated Donor for Infants with Severe Combined Immunodeficiency?

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Background: Severe combined immunodeficiency (SCID) is a paediatric emergency and early haematopoeitic cell transplantation is the only curative therapy. Whilst international donor registries and cord blood banking provide an increased availability of alternative donors and new stem cell sources, some patients, particularly for ethnic minorities, do not have suitable HLA-matched donors. An alternative is to use a haploidentical related donor and deplete the T-lymphocytes in the graft prior to infusion.

Methods: We study transplant outcomes in 39 infants with SCID who were transplanted at our centre from 2013 to 2019. Three patients who received add-back T cells were excluded. Outcomes of interest included overall survival, acute GvHD, days of inpatient stay, days of parenteral nutrition, cost analysis, immune reconstitution and latest donor chimerism.

Results: Transplantation characteristics and outcomes according to donor types are summarized in the table. Stem cell sources were: Haploidentical donor (HID) (TCR ab/CD19 depleted PBSC, n=9), matched family donor (MFD) (marrow, 9; PBSC 4), matched unrelated donor (MUD) (marrow, 3; cord, 10; PBSC, 4). Fludarabine and Treosulfan were used for patients who received conditioned transplant. There were no significant differences in pre-transplant PCP infection (p=0.68) disseminated BCG (p=1.0) between donor types. Total nucleated cell dose (p=0.049) and CD34 cell dose (p=0.004) were significantly higher in haploidentical donor with TCR ab/CD19 depleted PBSC. The neutrophil engraftment kinetics was significantly different between stem cell sources (p=0.03). 5-year overall survival was 100% for HID, 81% (43-95%) for MSD and 85% (53-96%) for MUD. CD4 immune reconstitution was significant faster at month 2 post-transplant in CB recipients. TCR ab/CD19 depleted PBSC recipients had comparable CD4 reconstitution kinetics compared MFD/MUD marrow and PBSC recipients. Duration of hospital stay, PN support and cost were compared between donor types.

Conclusions: Our findings emphasize that HID performed in an experienced immunology transplant center is a safe alternative donor source for infants with SCID.

Immune reconstitution kinetics and donor chimerism after HID were comparable with MFD and MUD. In our center, haploidentical donor is preferred than MUD in patients without MFD.

	MFD (n=13)	MUD (n=17)	Haploid (n=19	p-value
Newborn SCID, n	4	3	4	0.73
Median age at diagnosis (range), months	1.9 (at birth-5.7)	2.3 (at birth-13.8)	2.8 (at birth - 12.7)	0.54
Median age at transplant (range), months	4.3 (1.0-7.2)	5.4 (0.8-16.6)	6.1 (1.7-16.4)	0.36
		2.3 (0.3-14.6)	2.3 (0.6-9.9)	0.49

	MFD (n=13)	MUD (n=17)	Haploid (n=19	p-value
Median interval between diagnosis and transplant (range), months	1.8 (1.0-3.89)			
Median day to neutrophil engraftment (range)	14.5 (6-32)	21 (11-33)	19 (13-27)	0.04

[Transplantation characteristics according to donor types]

Clinical Trial Registry: Not applicable
Disclosure: Nothing to declare.

P595

Use of Ruxolitinib in Pediatric Patients with Steroid-Refractory Graft-versus-host Disease (GVHD)

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Background: GvHD remains a cause of significant morbidity and mortality in patients receiving allo-HSCT. JAK/STAT signaling is a target to treat steroid-refractory GvHD (SRGvHD). Herein, we report efficacy and safety of Ruxolitinib in pediatric patients with SRGvHD.

Methods: We retrospectively analyzed 18 pediatric patients with malignant/non-malignant diseases treated at our Department for SRaGvHD (n. 7)/SRcGvHD (n. 11) between June 2018 and November 2019. Response was assessed at 1 and 3 months from the beginning of Ruxolitinib, and at the last follow-up. CR was defined as resolution of all manifestations GvHD-related; PR as improvement in at least 1 organ/site without progression in any other organ. Monitoring of toxicity (peripheral blood cytopenia, as well as viral reactivation, bacterial and fungal infections) was performed throughout the treatment period. Steroid tapering was started after improvement of GvHD features. At CR Ruxolitinib was discontinued. Median follow-up from the start of Ruxolitinib was 241 days.

Results: Characteristics of patients are included in Table 1. Seven children had grade 3-4 SRaGvHD (5 patients with skin involvement stage 3, 6 with gut involvement stage 2-4; 1 patient had stage 4 gut-only aGvHD; 3 patients had liver aGvHD, 1 of which isolated, and 2 in combination with skin/gut involvement). Eleven patients had SRcGvHD (mild, n.1; moderate, n. 4; severe, n. 6). cGvHD affected more frequently skin with sclerosis, joint/fascia, lung, gut and liver. A median of 2 previous lines of immunosuppressive therapy (range: 1-4) were used before Ruxolitinib. Median initial dose was 12 mg/mq/die achieving a maximum dose of 10 mg twice daily. Steroid therapy was discontinued in thirteen patients at a median of 31 days (range: 19-46) in SRaGvHD and of 36 days (range: 11-70) in SRcGvHD after Ruxolitinib initiation. The ORR at last follow-up was 100% for SRaGvHD and 63.6% for SRcGvHD. Median duration of treatment was of 107 days (range: 89-174). Among patients treated for SRaGvHD, 29% achieved a CR (n. 2) and 71% a PR (n. 5) after 1 month, while 80% achieved a CR (n. 4) and 20% a PR (n. 1) after 3 months. At last follow-up, 86% of patients with SRaGvHD had a CR (n. 6) and 14% a PR (n. 1). Among patients treated for SRcGvHD, 9% achieved a CR (n. 1) and 27% a PR (n. 3) after 1 month, while 22% achieved a CR (n. 2) and 56% a PR (n. 5) after 3 months. At last follow-up, 18% of patients with SRcGvHD had a CR (n. 2) and 45% a PR (n. 5). Two patients, one each with gut and pulmonary SRcGvHD, did not respond to treatment. At last follow-up 3 patients have died: 1 of refractory cGvHD, 2 of relapsed disease (AML FLT3-ITD, ALL). Overall Ruxolitinib was well tolerated without severe adverse events. 5/18 patients experienced grade 3-4 cytopenia. CMV/EBV reactivations were observed in 22% of patients (n. 4).

Conclusions: Our data show that Ruxolitinib is an effective and well-tolerated therapeutic option for pediatric patients with SRaGvHD/cGvHD. Rapid steroid-tapering until discontinuation is feasible in most patients, without further flares of GvHD.

Disclosure: Nothing to declare.

P596

Hematopoietic Stem Cell Transplantation (HSCT) in Refractory Cytopenia of Childhood (RCC): Improved Engraftment Following a Treosulfan Based Conditioning Regimen

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Background: Refractory cytopenia of childhood (RCC) is the most common subtype of myelodysplastic syndrome (MDS) in childhood. Most patients have a hypocellular bone marrow and no cytogenetic aberrations. HSCT with a reduced intensity regimen consisting of thiotepa and fludarabine has resulted in excellent outcomes with a probability of overall survival of 94% in our previous study. However, there was a considerable rate of graft failure and poor graft function, resulting in second HSCT or additional cellular therapies in about 15% of the patients. We therefore investigated whether a more intensive regimen consisting of treosulfan and fludarabine resulted in improved engraftment rates.

Methods: Between 2004 and 2019, 41 patients (21 males/20 females) with RCC and normal karyotype were transplanted from a matched sibling donor (MSD) (n=12), an HLA-phenotypically identical family donor (MFD) (n=1), a matched (n=14) or mismatched (HLA 9/10 (n=14)/HLA 8/10 (N=1)) unrelated donor at a median age of 9.6 years (range 1.6-17.6). Four patients had previously failed immunosuppressive therapy with cyclosporine and anti-T-lymphocyte globuline (ATGAM®) and the median time from diagnosis to HSCT was 149 (14-3233) days. The conditioning regimen consisted of treosulfan (42 g/m^2 over 3 days) and fludarabine (160 mg/ m^2 over 4 days). Graft-versus-Host Disease (GvHD) prophylaxis was CSA and MTX for MSD-HSCT and CSA, MTX and anti-T-lymphocyte globuline (Grafalon®) for unrelated donor HSCT in the majority of cases. Stem Cell source was bone marrow (n=39) or peripheral blood (n=2).

Results: All patients engrafted. Median time to neutrophil and platelet engraftment was 18 (8-35) days and 26 (12-79) days, respectively. Engraftment was sustained over time and none of the patients received additional cellular therapy to ensure engraftment. One patient experienced late secondary graft failure on day + 496 after matched unrelated donor HSCT in the presence of 95% donor chimerism and is currently scheduled for 2nd HSCT. At last follow up, 32 (78%) patients had a complete donor chimerism, whereas 8 patients (22%) had a low level mixed chimerism (95-99%) with good hematological recovery. Grade II-IV acute GVHD occurred in 4 patients (aGVHD°II (n=3), aGVHD °IV (n=1)) and one patient was diagnosed with severe chronic GvHD. Two patients developed Epstein-Barr Virus related lymphoproliferative disease and were successfully treated with rituximab and in one case with additional chemotherapy. No patient died of transplant-related complications and after a median follow up of 1.0 year (range 0.3 -9.1 years) all patients are alive.

Conclusions: The reduced toxicity conditioning regimen consisting of treosulfan and fludarabine resulted in an excellent outcome with sustained engraftment and low incidence of GvHD in this cohort of patients with RCC. Long term follow up is needed to investigate the incidence of late effects, including the risk of infertility.

Disclosure: Nothing to declare.

P597

Pharmacokinetics of Active ATG Impacts T-cell Recovery after TCRαβ/CD19-Depleted HSCT in Paediatric Patients

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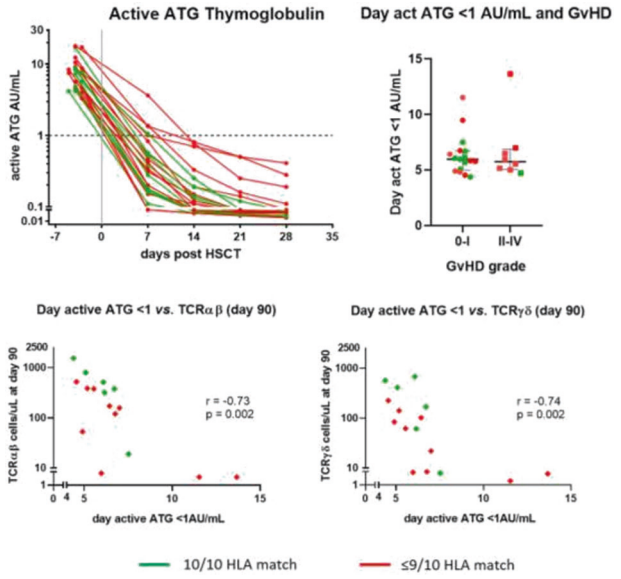
Background: Previous studies have shown that the removal of TCRαβ+ T-cells and CD19+ B-cells is an effective strategy to reduce the risk of GvHD after (mis) matched donor HSCT. To further prevent graft rejection and GvHD, serotherapy treatment with ATG is often given in combination with this strategy. In this study, we investigated the impact of active (the T-lymphocyte binding component) ATG-Thymoglobulin® clearance on immune recovery and clinical outcome after TCRαβ/CD19-depleted HSCT in a cohort of paediatric patients with non-malignant disorders.

Methods: Twenty-five children with primary immunodeficiencies or hemoglobinopathies, who received a TCRαβ+/CD19+ depleted graft (Clinimacs®) from either a matched-(un)related donor (10/10, n=9) or a mismatched-(un)related donor (≤9/10, n=16) at the Dmitry Rogachev National Medical Center of Pediatric Hematology, Oncology and Immunology between March 2018 and September 2019 were included. Stem cell source was

peripheral blood. Pretransplant conditioning was fludarabine/treosulfan (n=18) or fludarabine/cyclophosphamide (n=6) based, in 21 patients melphalan or thiotepa was added. One patient was treated with a fludarabine/thiotepa based regimen. ATG-Thymoglobulin® was given to all patients in a median total dose of 5 mg/kg (range 4-10mg/kg; median day start ATG day -5). Serum samples (pre-conditioning; +1; +2; +3 and +4 weeks post-HSCT) were analysed by quantitative flowcytometry on HUT78 cells for the presence of active ATG. For all patients, lymphocyte subsets were measured by flowcytometry until +12 months after transplantation or until death, graft failure or last follow-up.



[Active ATG clearance influences T-cell recovery]

Results: No significant difference was found between patients with a 10/10 HLA-matched and patients with a ≤9/10 matched donor in median day that active ATG reached < 1AU/mL, the lympholytic level of ATG (day +6.0 vs. day +5.9 post-HSCT, p=0.57). However, the day that active ATG fell < 1AU/mL varied between patients from day +4 to +14 after transplantation and significantly correlated with CD3 T-cell recovery even until 3 months post-HSCT (day +28; n=23, Spearman correlation r=-0.49, p=0.017; day +90, n=17, r=-0.66, p=0.005). When analysing the TCRαβ+ and TCRγδ+ subsets separately, similar results were obtained (day +90, n=16, TCRαβ+ r=-0.73, p=0.002; TCRγδ+ r=-0.74, p=0.002, see graph). For NK- and B-cell recovery no correlation with ATG clearance was found. Acute GvHD (grade II and III) occurred in 7 patients of the ≤9/10 HLA-matched group and in 1 patients of the 10/10 matched group (p=0.15) and was not influenced by ATG pharmacokinetics (see graph). No significant differences were observed for CMV reactivation, graft failure and OS between the two groups and median day active ATG reached < 1AU/mL was similar for these clinical outcome parameters in patients affected vs. non-affected.

Conclusions: Within this cohort of paediatric patients, the difference in ATG-Thymoglobulin® pharmacokinetics has an impact on T-cell immune recovery. Although this did not affect the clinical outcome in our study, we believe that ATG clearance and, therefore, the timing of T-cell recovery may be critically important especially for patients treated with a mismatched donor. Future studies, with clinical cohorts of non-malignant hematologic diseases and the TCRαβ/CD19-depleted HSCT setting, are necessary to increase our knowledge on ATG pharmacokinetics and dynamics, eventually leading to further optimization of ATG treatment.

Disclosure: The work described in this study performed in the Leiden University Medical Centre is funded in part by Neovii Biotech (Rapperswil, Switzerland).

P598

Haploidentical Hematopoietic Stem Cell Transplantation in Pediatric Patients: A Multicentre Study from India

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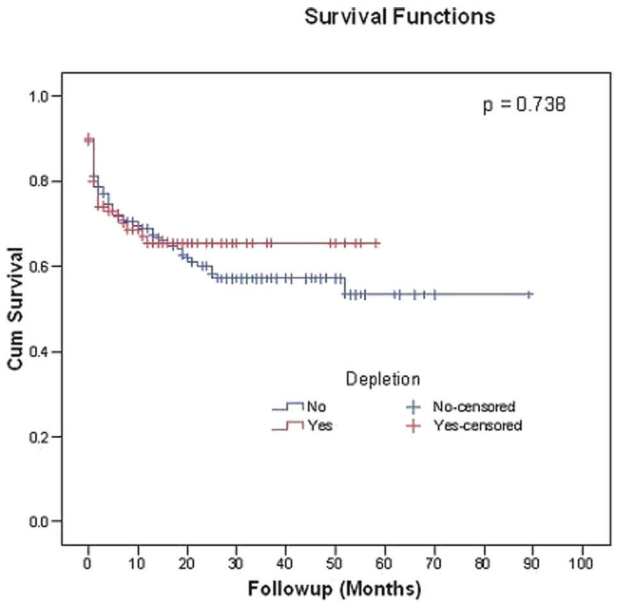
Background: Transplantation from a mismatched family donor has seen a striking growth in the last 20 years, but mostly for adults with hematological malignancies. Related HLA haplotype-mismatched ('haploidentical') hematopoietic stem cell transplantation (HSCT) is an alternative method to expand the donor pool for children especially in India due to lack of unrelated donor registries. Here we describe outcome of children undergoing haploidentical HSCT for both haematological malignancies and non-malignant conditions in India.

Methods: This was a retrospective study in children from five bone marrow transplant centers across India who underwent haploidentical HSCT from year 2012 to 2019. A

common data entry format with study parameters was shared between centers.



[Survival curves comparing T cell replete and T cell depleted HSCT]

Results: A total of 491 children underwent 517 haploidentical HSCT (from parent/sibling). The median age at transplantation was 747.5 months (interquartile range, 46- 130 months) in which 322 were males and 169 were females. Diagnoses included; acute leukemia (n=154), hemoglobinopathies (n=119), severe aplastic anemia (n=56), primary immunodeficiency (n=56), Fanconi anemia (n=38), myelo-proliferative neoplasms (n=20) and others (n=48). In this cohort, 119 patients underwent T-cell depleted (TCD) HSCT while another 398 underwent T-cell replete haploidentical HSCT with post-transplant cyclophosphamide (PTCy). Majority of patients received myeloablative conditioning (n= 327) while 185 patients received reduced intensity conditioning (RIC) and 5 patients no conditioning. Predominant graft source was peripheral blood stem cell (PBSC) in 95.4%. Median CD34+ cell dose was 9.0 × 106/kg. Eighty three percent patients engrafted and mean time to neutrophil and platelet engraftment was 15.35 (+/- 4.67) and 16.11 (+/- 7.37) days, respectively.

Acute GvHD was seen in 171/491 (34.8%) children of which 98/491 (19.9%) had grade I/II GvHD where as grade III/IV GvHD was seen in 73/348 (14.8%). Acute GvHD rate was similar in T cell deplete and T deplete group (35 % vs 37 %: P =0.780). Chronic GVHD was seen in 44/491 (9%) patients. Chronic GVHD rate was significantly less in T cell deplete vs. T cell replete group (5 vs 39; P value =0.49).

Day 100 post-transplant survival of this cohort is 73%. The overall survival of this heterogenous patient cohort is 68%. There was a trend towards better OS in T depleted group but didn't reach statistical significance (figure 1). There were a total of 164 deaths. Infection (48%), GVHD (11.5%), and graft failure (14.3%) were the main causes of death. Other causes of death included veno-occlusive disease (N=3), interstitial pneumonitis (N=5), hemorrhage (N=5) and rest other causes.

Conclusions: Haploidentical HSCT is a curative option for children with both malignant & non-malignant conditions. Outcomes were acceptable and comparable in terms of engraftment, aGVHD, relapse and OS in T-deplete and T-replete groups. Chronic GVHD was significantly higher in the PT-Cy approach. This is the largest series of haploidentical HSCT from India.

Disclosure: Nothing to disclose

P599

Immune Recovery and long-term Survival Following Haploidentical T And B Cell Depleted Stem Cell Transplantation - Influence of Various ATG Doses

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Background: Challenges of haploidentical stem cell transplantation, e.g. engraftment failure and a higher incidence of GvHD, can effectively be met by combining ATG-based lympho-depletion with ex vivo depleted grafts. Otherwise, ATG itself may prolong immune recovery, harm coinfused donor NK cells and possibly enhance relapse rate. Thus, optimal dosing and scheduling of ATG application remain controversial.

Here, we retrospectively analyzed the influence of different doses of Grafalon (ATG) on long-term immune reconstitution, GvHD, and overall survival (OS).

Methods: 51 pediatric patients (ALL/AML n=10; relapsed solid tumors n=34; nonmalignant diseases n=7) received either 3x5 (n=8), 3x10 (n=34) or 3x20 mg/kg (n=9) ATG (d-12 to -9), followed by fludarabine (160 mg/m^2, d -8 to -5), thiotepa (10 mg/m^2 d -4) and melphalan (140 mg/m^2 d -3 to -2). Grafts consisted in the mean of 17,32 x10^6 CD34/kg and 61,65 x10^6 NK cells/kg. MMF was added until d +30 depending on the residual T cells in the graft (> 2,5x 10^4/kg). ATG serum levels were determined by flow cytometry (T cell specific rabbit IgG).

Results: Grafts were rejected in 3/8 (37,5%) patients receiving 15 mg, in 7/34 (20%) patients with 30 mg and in 1/9 (11%) patients with 60 mg ATG. Acute GvHD of any grade occurred in 50% (4/8) of patients with 15 mg ATG, in 56% (19/34) of patients with 30 mg, and in only 22% (2/9) of patients with 60 mg, whereas 14% (1/7), 26% (8/31), and 0% (0/8) of patients developed cGvHD in the corresponding groups. Only 2 cases of aGvHD III-IV° were observed, both of them received < 60 mg/kg ATG.

3-year-OS varied from 37% (15 mg/kg ATG), 57% (30 mg/kg ATG) to 65% (60 mg/kg ATG). 1-year TRM of the whole cohort was 12%, 3-year TRM 16%, respectively.

Various ATG dosing resulted in different kinetics of immune reconstitution: at day +30, mean CD3+ T cell count was 4 vs 112 vs 97/µl (60 vs 30 vs 15 mg/kg ATG), but increased to 247 vs 289 vs 83 cells/µl at day +180, to 726 vs 784 vs 1657 cells/µl after 1 year. CD56+ NK cells recovered promptly to 192 vs 314 vs 425 cells/µl at day +30 (60 vs 30 vs 15 mg/kg ATG), then decreased to 117 vs 183 vs 125 cells/µl at day +180, to 155 vs 201 vs 172 cells/µl after 1 year.

Conclusions: The 15 mg ATG regimen offers a quick CD3+ T cell recovery early after transplant, whereas CD3+ cell counts rest < 10 cells/µl till d+90 in the 60 mg/kg subgroup. CD56+ cell counts varied less between the three ATG subgroups, even in the early posttransplant phase, indicating that a 12-day interval between ATG start and transplant prevents hampering donor CD56+ cells. Lower ATG dosing resulted in higher aGvHD incidence, but did not evoke severe aGvHD. Nevertheless, the 15 mg ATG regimen does not seem to be feasible due to a rejection rate of 37%. Administration of 30 mg/kg ATG, even before d-12, should be further evaluated in the haploidentical setting.

Disclosure: Nothing to declare.

P600

Outcomes of Haploidentical vs Matched Unrelated Hematopoietic Stem Cell Transplantation with Post-Transplant Cyclophosphamide (PTCY) in Pediatric High-Risk ALL and AML in 1st and 2nd CR

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Background: Transplantation from a full haplotype mismatch family donor (Haplo-HCT) is a suitable option for children with acute leukemia (AL) either relapsed or at high-risk of treatment failure and has been studied for several decades, initially with T-cell depletion. However, comparable efficacy is now confirm after unmanipulated graft Haplo-HSCT, which has become of favor over the past years. First of all, this is due the use of PTCy GVHD prophylaxis. Haplo-HSCT using PTCy has improved donor availability. In spite of this, a matched sibling donor is still considered the optimal donor, but the benefits of MUD are being specified. The primary end point was to compare 6-year OS after allo-HSCT with Haplo vs MUD in patients with AML and ALL in 1st-2nd CR. Secondary end points-to estimate hematopoietic recovery, incidence of relapse, acute and chronic GVHD.

Methods: We included children (n=211) with high-risk ALL (n=116) and AML (n=95) in CR, who underwent Haplo-HSCT (n=51) or MUD allo-HSCT (n=160). In haplo-HSCT group MAC obtained 30 pts (58,8%), RIC - 21 pts (41,2%), GVHD prophylaxis based on PTCy±calcineurin inhibitor (CNI) and m-TOR inhibitor (m-TOR) received 45 pts (88,2%), seroprophylaxis were in 6 pts (11,8%). MUD allo-HSCT patients received MAC in 97 cases (60,6%), RIC - 63 pts (39,4%). GVHD prophylaxis was PTCy±CNI and m-TOR in 70 pts (44%), seroprophylaxis-90 pts (56%). Kaplan-Meier curves were used to estimate the probability of OS. Hematopoietic recovery was assessment by Mann-Whitney U-test. Cumulative incidence was used to estimate the probability of GVHD and relapse.

Results: Neutrophil engraftment with full donor chimerism achieved on D+21 in haplo-HSCT group in 80,4% (41pts), with PTCy in 82,2% (37pts). Unrelated HSCT group is fixed neutrophil recovery with full donor chimerism on D+19 in 88,1% (141pts), with PTCy in 94,3% (66pts) (p>0,05). Relapse developed in 35% (13pts) after haplo-HSCT with PTCy versus 27,3% (18pts) in unrelated HSCT with PTCy pts (p>0,05). Haplo-HSCT with PTCy group had 13% (5pts) of severe III-IV^0 aGVHD vs 8% (5pts) in unrelated HSCT with PTCy pts (p>0,05); lower

rates of extensive cGVHD was observed 8% vs 26% respectively (p=0,01). Haplo-HSCT with PTCy and MUD with PTCy groups were not different with regard to 6 years OS: 75% vs 72,9% (p>0,05).

Conclusions: Our results indicate a lower rate of extensive cGVHD after PTCy-based Haplo-HSCT vs MUD and similar 6,5 years OS in pediatric high-risk ALL and AML in 1st and 2nd CR. Chronic GVHD and its complications are primary determinants of long-term quality of life after allogeneic HSCT. The lower incidence of cGVHD after Haplo-HSCT is likely due to PTCy. Haplo-HSCT with PTCy is a viable alternative to MUD HSCT in this category of patients.

Disclosure: Nothing to declare.

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Abstract already published.

P602

Abstract already published.

P603

Landmark Analysis in High Risk Childhood Acute Leukemia Patients Undergoing Allogenic Hematopoietic Stem Cell Transplantation. A Retrospective Study

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Background: Allogeneic hematopoietic stem cell transplantation is the only curative option for some high-risk childhood malignant hematological diseases. The greatest risk of complications occurs during the first year and decreases progressively. There is not much information about those patients who survive beyond the first year after transplantation. We retrospectively analyzed prognostic factors associated with long-term survival.

Methods: A total of 162 patients alive one year after transplantation who undergoing an allogeneic transplant in our center between 1991 and 2016 were included in this study, 97 men and 65 women, with a median age of 7 years. Half of the patients were transplanted in an advanced phase. The most frequent diagnosis was ALL (n = 90), followed by AML / MDS (n = 59) and CML (n = 13). Graft source was mostly peripheral blood (n = 133) and 105 patients with ex vivo graft manipulation. Regarding the type of donor, there were 72 patients transplanted from match related donor, 48 from haploidentical donors and 42 from a match/mismatch unrelated donor (including cord blood).

Results: With a median follow-up of 10 years (range: 2 - 27) the overal survival rate was 89 ± 2%. The cumulative incidence of relapse and toxic mortality (MRT) were 10 ± 2% and 8 ± 2% respectively. In the univariate analysis, the factors associated with better survival were: transplant in an early phase (87 ± 3% vs 74 ± 5%, p = 0.04), the absence of acute GVHD, (87 ± 3% vs 73 ± 5%, p = 0.038), not having severe chronic GVHD (85 ± 3% vs 41 ± 10%, p = 0.0001), having total B lymphocytes per year above the median of 421 / mcL (89 ± 4% vs 73 ± 6 %, p = 0.04) and having total CD4 lymphocytes at 2 years above the median of 837 / mcL (98 ± 2% vs 82 ± 6%, p = 0.026). However, in the multivariate analysis the only factor that impacts negatively is the presence of severe chronic GVHD (HR: 6.85, 95% CI: 1.35-34.48, p = 0.02). We have analyzed the role of immune reconstitution in MRT, determining the number of total T lymphocytes (median of 1246 / mcL in survivors versus 242 / mcL in not survivors, p = 0,0029) and their subpopulations, as well as the number of B lymphocytes at one year after transplantation (median of 456 / mcL in the survivors versus 12 / mcL in not survivors, p = 0.0005), as factors that affect statistically significantly.

Conclusions: The presence of severe chronic GVHD is the only factor that negatively impacts the survival of those patients who are alive one year after transplantation. Immune reconstitution has an important prognostic role in toxic mortality, not only in the first months after transplantation, but also in the long term survivors.

Disclosure: Nothing to declare.

P604

Defibrotide in Hematopoietic Stem Cell Transplant: An Study of Grupo Español De Trasplante Hematopoyetico (GETH) And Grupo Español De Trasplante De Medula En NiñOS (GETMON)

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Background: Sinusoidal obstruction syndrome (SOS) is a hematopoietic stem cell transplant (HSCT) complication with high morbidity and mortality. Diagnosis was traditionally based on Baltimore or modified Seattle criteria, but EBMT recently published new diagnostic criteria for adults and children and reviewed treatment mainly based on defibrotide. Defibrotide is now approved in EU for treating severe hepatic SOS post-HSCT in adults and children. However, it also has been used in SOS prophylaxis, treatment of moderate SOS and in other cases of endothelial damage, such as post-transplant thrombotic microangiopathy (TMA).

The objective of this study is to evaluate current uses, effectiveness and safety profile of defibrotide in different complications of HSCT caused by endothelial damage.

Methods: This is a multicenter, retrospective study that includes patients treated with defibrotide for any indication from 28 HSCT centers from GETH and GETMON in Spain. SOS was diagnosed using Baltimore or modified Seattle criteria.

Results: A total of 388 patients treated with defibrotide were included between January 2011 and December 2018. Median age was 11 years (2 months-70 years) with 240 males. 253 patients were children and 135 were adults. Primary disease was predominantly acute leukemia and most patients received myeloablative conditioning. 333 transplants were allogeneic, and the remainder were autologous. Patients characteristics are shown in Table 1.

Main indications for defibrotide use was severe/very severe SOS in 173, SOS prophylaxis in 133 patients, moderate SOS in 44, TMA in 6 patients and other causes in 32 patients. Main adverse effects were hemorrhage in 19%, thromboembolic events in 11%, hypotension in 10%, and allergy in 0.8% of cases. Complete remission rate in severe/very severe SOS was 64%.

Overall in the 173 severe/very severe SOS patients, Kaplan-Meier (KM) estimated day +100 survival was 62 (95% CI, 59%-65%). If we analyze it according to age, KM estimated day+100 survival was 77% (95% CI, 72%-82%) in children vs 52% (95% CI, 47%-57%) in adults. KM estimate survival in prophylaxis group was 63 (95% CI, 59%-67%). Only 8/133 patients developed SOS while undergoing in prophylaxis with defibrotide. Moderate and severe acute GVHD cumulative incidence with death as a competing event in this high-risk group of patients was 16% (95% CI, 12%-20%).

58 patients relapsed from their underlying disease. 190 patients have died. SOS was main cause of death in 25 patients (13%).

Conclusions: Defibrotide has an acceptable safety profile with improved response of severe/very severe SOS compared with historical controls. The use of defibrotide in prophylaxis could improve the prognosis in patients at high risk of complications due to endothelial damage.

	N=388
Age	11 years (2 months-70 years)
Gender: Male/Female	240/148
Weight (Kg)	39 (4-136)
Diagnosis: - AML/MDS/MPS - ALL - Non-malignant diseases - Solid tumour - Lymphoma - Mieloma - Others	114 85 56 46 37 8 42
Conditioning: - MAC - RIC	292 96
Number of transplant: - First - Second or more	292 94
Type of transplant: - Autologous - Allogeneic: • Unrelated donor • Haploidentical • HLA Identical sibling • Cord blood	56 122 92 85 33

[PATIENT´S CHARACTERISTICS]

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P605

Nivolumab-based Therapy Prior to Hematopoietic Stem Cell Transplantation in Pediatric Hodgkin´s Lymphoma

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Background: Immune checkpoint inhibitors (ICIs) allow to achieve remission and precede to hematopoietic stem cell transplantation (HSCT) in the majority of patients with relapsed or refractory (R-R) Hodgkin´s lymphoma (HL). The role of nivolumab (nivo) prior to HSCT in pediatric HL is only to be elucidated. The aim of the study was to assess the role of nivo-based therapy in pediatric R-R HL as a bridge to HSCT.

Methods: Eight pediatric patients with R-R HL received nivo prior to HSCT in Raisa Gorbacheva Memorial Research Institute of Children Oncology, Hematology and Transplantation, Pavlov First St. Petersburg State Medical University. Median age was 15.5 years (11 to 17). Histological forms of HL were as follows: nodular sclerosis was diagnosed in 5 patients (62.5%); mixed cellularity HL, 2 cases (25%), lymphocyte-rich HL, 1 (12.5%). At the onset of the disease, the early-stage favorable status was diagnosed in 2 patients (25%); early-stage unfavorable or advanced disease was diagnosed in 6 cases (75%). B-symptoms were documented in 6 patients (75%). Bulky disease (>7 cm) and extranodal lesions were registered in 5 (62.5%) and 6 (75%) children, respectively. The disease was refractory in 3 cases (37.5%), whereas resistant or multiple relapses occurred in 5 patients (62.5%). Median number of previous therapy lines was 4 (2-5) with radiation therapy in 3 patients (37.5%). Prior to nivo therapy, 4 children (50%) had progression; 2 (25%), stabilization, and 2 (25%), partial remission according to Lugano criteria. Monotherapy was used in 3 (37.5%) and combination with other drugs in 5 (62.5%). Treatment schedule consisted of 3 mg/kg of nivo biweekly in 3 (37.5%) or 40 mg of nivo biweekly in 5 (62.5%). Combinations of nivo with following drugs were used: brentuximab vedotin 1,8 mg/kg triweekly (n=2) with median of 5 cycles (4-7), bendamustine 180 mg/m2 triweekly (n=2) with median of 5 cycles (5-7) and gemcitabine 1000 mg/m2 №5 weekly (n=1). Median number of nivo cycles was 7 (3-12). Response to treatment was evaluated by the LYRIC criteria. After nivo-based treatment, 8 patients (38%) received auto- or allogeneic HSCT. Conditioning regimen in autologous HSCT (n=4) was BeEAM (bendamustine, etoposide, cytarabine and melphalan). Haploidentical donors were employed in two allo-HSCTs, and two matched related siblings were used in two other cases. The conditioning regimen in allogeneic HSCT consisted of bendamustine 360 mg/m2 and fludarabine 150 mg/m2. Graft-versus-host disease prophylaxis was based on posttransplant cyclophosphamide and calcineurin inhibitors.

Results: Overall response to nivo-based therapy was registered in 7 children (87.5%); complete response, in 4 cases (50%); partial response, in 3 patients (37.5%) and indeterminate response, in 1 case (12.5%). Consolidation with HSCT (auto- or allo-) after nivo-based therapy resulted in 2-year overall and progression free survival of 87.5% and 75%, respectively. Only 1 patient died in early post-transplant period due to infectious complications (pneumonitis). There were no clinically significant side effects of nivo-based therapy.

Conclusions: The presented limited data hypothesizes that consolidation with HSCT after nivo-based therapy may result in high cure rates in pediatric R-R HL. Further research is needed to clarify this proposal.

Disclosure: Nothing to declare.

P606

School during and after Allogeneic HSCT : A Survey of Practices in Three European Countries

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Background: Allogeneic haematopoietic stem cell transplantation (HSCT) patients experience very long periods of non-attendance to school. This has a major impact on their quality of life and could impact their academic performance and their future. Yet, literature is extremely poor on this topic.

Methods: We conducted a survey of practices and policies regarding school during and after allogeneic HSCT in 3 different countries in Europe. Online questionnaires were sent to physicians in all paediatric transplant centres in Switzerland, France and United Kingdom (UK) and included questions on procedures, return to school, school in hospital and after discharge. Chi-2 tests were used to compare practices according to country, centre size (< 30 transplants per year vs >30) and type of transplant centre (paediatric only vs joint adult-paediatric).

Results: 20 centres completed our questionnaire : 13/15 French centres, 4/12 UK centres and 3/3 Swiss centres (one only partially). 90% of the centres were JACIE-accredited but only 4 (20%) had a Standard Operating Procedure (SOP) about school issues. This did not vary according to countries, centre size or type of centre. Only 2 of these 4 SOPs included criteria for return to school. Criteria used for return to school included CD4+ counts in 75% of centres. 84% would also apply a minimum length of time from transplant. Another 12 clinical or biological parameters were cited as criteria for return to school with a total of 13 different combinations of criteria among the 20 centres. Thresholds for CD4+ counts varied from 0.2 to 0.4 x 10^9/L or were undefined. Minimal time from HSCT to allow return to school was 6 months in 45 % of centres, and ranged from 3 to 12 months in others. When comparing centres practising short or no minimal time length vs 6 months or more, there was no statistical difference in country, centre size or type of centre. 15 centres (75%) admitted that the length applied could also vary according to pre-transplant characteristics (donor type, source of cells, intensity of conditioning regimen and GVHD prophylaxis). 11 centres (all French) would also modulate this length according to the patient age and school grade. In all centres, an hospital teacher was responsible to ensure continuity in education. 95% and 82% of centres respectively estimated that more than 80% of their patients could benefit from teaching given by hospital teachers during their stay and from homeschooling after discharge. 95% estimated that their patients were enabled to sit their exams as inpatients and 100% after discharge. 80% of centres prepared school staff for the patient's return, and 50% prepared other pupils. Only 2 centres proceeded to monitoring or quality assessment on school issues.

Conclusions: This is to our knowledge the first survey on practices regarding school in allogeneic HSCT patients. HSCT patients seem to benefit from policies to promote continuity in education common to all severely ill children and long-established in paediatric units. However, on transplant-specific issues, our study revealed an important need for consensus, standardisation and quality assessment.

Disclosure: nothing to declare.

P607

Haematopoietic Stem Cell Transplantation in Patients with Fanconi Anaemia: Experience of the Spanish Working Group for Bone Marrow Transplantation in Children (GETMON)

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Background: Haematopoietic stem cell transplantation (HSCT) is currently the only curative option for bone marrow failure (BMF), myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) in patients with Fanconi Anaemia (FA). However, it does not prevent the development of solid tumours in these patients.

Methods: We conducted a multicentre national study to collect the experience based on recommendations of Spanish Working Group for Bone Marrow Transplantation in Children (GETMON). Conditioning regimen consisted of fludarabine (FLU) + cyclophosphamide (CY) + antithymocyte globulin (ATG) in matched siblings donors (MSD) transplants and total body irradiation (TBI) 3 Gy + FLU + CY + ATG in matched unrelated donors (MUD) transplants. An ex-vivo T-cell depletion with CD34+ cell positive selection and adjustment of CD3+ was made when peripheral blood was the source of hematopoietic progenitors.

Results: We transplanted 34 patients with FA (16 boys, 18 girls, median age at transplant 8 years; range: 4-26) of

seven Spanish centres between 2009 and 2016. Before transplant, 90% of patients had received transfusions (23% >20 transfusions) and 37% had been treated with androgens. Disease status before HSCT was severe aplastic anaemia (SAA) in 30 patients (88%) and advanced MDS/AML in four. Donors were MSD in 18, MUD in 15 and a mismatched related donor in one. Bone marrow was the main source of progenitors in MSD transplants (11 of 18; 61%) and peripheral blood in MUD transplants (11 of 15; 73%). All except one patient engrafted. The median time for neutrophils >$0.5x10^9$/L was 11 days (range 8-29) and for platelets >$20x10^9$/L was 26 days (range 7-100). Early post-transplant toxicities and infections were frequent. Cumulative incidence of grades II to IV acute graft-versus-host disease (aGvHD) were 29% (95% CI, 16-48%) and for grades III to IV was 8% (95% CI, 2-28%). Cumulative incidence of chronic graft-versus-host disease (cGvHD) was 11% (95% CI, 4-30%). Median follow-up after HSCT was 6.5 years (range 0.1-11.15). Ten patients died. Causes of death were graft failure and infection in 1, toxicity in 2, infection in 3, relapse/progression of MDS/AML in 2 and subsequent malignancies in 2 [one EBV PTLD and one squamous cell carcinoma (SCC)]. Overall survival (OS) was 74% at 5 years post-transplant (95% CI, 55-85%), with no differences between MSD and MUD transplants. Results for patients with MDS/AML were poor (OS 25%; 95% CI 0.9-66%) with higher mortality risk when indication of HSCT was MDS/AML comparing to BMF (hazard ratio [HR], 8.60; p 0.0010). One patient with cGvHD developed a head and neck SCC 6.5 years post-transplant and died.

Conclusions: Our data suggest HSCT from a matched related or unrelated donor can cure hematologic disorders of most FA patients with BMF. Follow-up of patients with FA will reveal the long-term results of HSCT.

Disclosure: Nothing to declare.

P608

The Role of Donor KIR Genotyping in Pediatric Hematopoietic Stem Cell Transplantation For Non-Malignant Disorders

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Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative treatment option for several non-malignant diseases in children. Few studies have addressed the impact of donor KIR genotype in clinical outcomes after HSCT for benign disorders, showing that activating genes could favorably impact survival outcomes. Therefore, our aim is to evaluate the impact of donor KIR genotyping in clinical outcomes after allo-HSCT in a cohort of non-malignant disorders.

Methods: We evaluated 80 patients with non-malignant disorders transplanted between January 1999 to December 2016 at Lucile Packard Children's Hospital, Stanford, CA. Donor KIR genotyping were typing using sequence specific typing (SSP).

Results: Median age at transplant was 6.9 years (0.3-21 years) and 53.7% were male. Underlying disease were classified into five groups: severe aplastic anemia (SAA, n=28, 35%), primary immunodeficiency (PID, n=18, 22.5%), hemoglobinopathies (HP, n=13, 16.2%), metabolic disorders (MD, n=11, 13.8%) and Fanconi anemia (FA, n=10, 12.5%). Bone marrow was the graft source in 73.7%. Unrelated donors were employed in 41 (51%) cases, 61% of whom had one mismatch. Non-myeloablative conditioning regimen was administered in 50% of patients. Acute [AB1] and chronic GvHD occurred in 38.7% and 28.7% of patients, respectively. For five patients we didn't have enough donor DNA for KIR analysis while in two cases KIR typing failed. Donor KIR haplotype B/x were found in 63% (n=46) and KIR centromeric B/x in 37% (n=27). Although not statistically significant, donor KIR genotyping B/x showed higher relative risk for overall survival (RR 1.89, CI: 0.61-5.88, p=0.3), grade I-IV acute GVHD (RR 2.09, CI: 0.75-5.82, p=0.16) and chronic GVHD (RR 2.38, CI: 0.88-0.45, p=0.06). No difference was seen in the risk of graft failure.

Conclusions: Our preliminary data show that donor KIR genotyping A/A can be associated with better overall survival in patients with non-malignant disorders with a reduced risk of chronic GVHD. Donor KIR typing should be explored in a larger cohort of patients to validate these results.

Disclosure: Nothing to declare.

P609

Single-center Experience of TCRαβ/CD19 Depleted Stem Cell Transplantation in Children with Fanconi Anemia

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Background: TCRαβ+/CD19+ graft depletion is a modern technology with proven efficiency in preventing graft-versus host disease (GVHD) and favorable transplant related mortality after HSCT from haploidentical related donor and matched unrelated donors (MUD). Herein, we share the results of this technology in patients with Fanconi anemia (FA).

Methods: 20 patients with FA (M:F=3:1, median age 9.3 years; range 3.7-11.9) were transplanted from April 2012 to May 2019. All patients were transplanted with TCRαβ+/CD19+ depletion of the graft: 19 from MUD (10/10, n=14, 9/10, n=5) and 1 from haploidentical donor. Nineteen patients with bone marrow failure were preconditioned with TLI 2-4 Gy, FLU 150 mg/m^2 and CY 40 mg/kg; 1 patient with secondary AML received BU 6 mg/kg, FLU 150 mg/m^2 and ARA-C 900 mg/m^2. All patients received rabbit ATG 5 mg/kg (n=11) or horse ATG 90 mg/kg (n=9) as serotherapy. We used rituximab (100 mg/m2 on day -1) to decrease the risk of EBV-PTLD in 16 patients. TCRαβ+/CD19+ depletion of PBSC with CliniMACS technology was implemented in all cases. The median dose of CD34+ cells in transplant was 10,95 x10^6/kg (range 4.9-13.7), TCRαβ+ cells - 9.17x10^3/kg (range 0.027-345). 11 patients received CNI-based posttransplant GVHD prophylaxis (6 - monotherapy; 4 - with short course of MTX, 1-with MMF, 4 - with abatacept). In other 5 cases GVHD prophylaxis consists of abatacept (n=2), abatacept + MTX (n=2) or abatacept + MMF (n=1).

Results: 19 patients achieved engraftment with a median time of 11 days (9-15) for WBC and 12 days (9-30) for PLT. Graft failure occurred in 2 patients (non-engraftment, n=1; rejection in 2 months after HSCT, n=1). Severe toxicity was observed in 15 patients: mucositis (n=15), hemorrhagic cystitis (n=5; 3 of them in combination with BK-viruria), PRES (n=1), VOD (n=1), pancreatitis (n=2), TMA (n=1), severe drug-associated kidney injury (n=2). CMV reactivation was observed in 7 patients, ADV viremia occurred in 2 cases. There were no cases of CMV or ADV diseases. 5 of 19 engrafted patients (26.3%) developed acute GVHD grade (grade II, n=4; grade III, n=1) and 4 patients had chronic GVHD (limited, n=1; extensive, n= 3). With median follow-up of 19 months (3-83 months), OS was 73.5% (95%CI 54.2-93.6%). The causes of death were bacterial sepsis in non-engrafted patient (n=1), GVHD and associated infections (n=3), progression of primary tumor (n=1, pigmented epithelioid melanocytoma).

Conclusions: We observed a high incidence of toxic complications, which is most likely related to high sensitivity of FA cells to radiation and alkylating agents. In addition, GVHD and associated infections were relevant morbidity and mortality factors. Though, we believe that HSCT with TCRαβ+/CD19+ graft depletion is an appropriate technology for HSCT from alternative donor in patients with FA. However, a longer follow-up and a larger cohort are needed for better understanding the relevance of TCRαβ +/CD19+ graft manipulation during HSCT for FA patients.

Disclosure: no conflict of interest

P610

Detection of Recipient-specific α/β-T-cells during the Pre-engraftment Phase Does not Predict Graft Rejection in Patients after Haplosct: Preliminary Results of Single Centre Prospective Trial

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Background: Flow cytometry-based monitoring of hematopoietic chimerism in distinct subsets of immunocompetent cells early after HLA-haploidentical stem cell transplantation (haploSCT) may increase understanding of the dynamics of immunological recovery and identify patients at risk of graft rejection, possibly allowing timely intervention.

Methods: We present early results of a prospective, single-centre study evaluating feasibility and clinical significance of flow cytometry-based monitoring of hematopoietic chimerism in subpopulations of T and NK lymphocytes. Inclusions criteria were transplantation of hematopoietic stem cell from an HLA-haploidentical donor and signed informed consent. Each recipient-donor pair was tested before transplantation to identify the most informative HLA disparity. Peripheral blood was collected during the pre-engraftment (day +7), early (days +14, +21, +28), intermediate (days +42, +56, +70, +84, +100) and late (days +180, +365) phase of recovery. Chimerism was assessed separately in α/β-T-cells, γ/δ-T-cells and NK lymphocytes by flow cytometry only, and in CD3+ and CD3- cell populations by both flow cytometry and standard STR/PCR-based assay. Agreement between assays was assessed by calculating Kappa coefficient.

Results: The study included 11 patients (6 males and 5 females) who underwent 12 haploSCT in University

Hospital in Scania between 2018 and 2019 at the median age of 25.8 (1.1-61.1) years. Indication for haploSCT was AML in 4, ALL in 3, MDS/MPN in 2, bone marrow failure in 1 and CGD in 1 case. All patients received Fludarabine and Thiotepa in conditioning regimen, combined with either Melphalan (4), 12 Gy TBI (4), Treosulfan (2) or Busulfan (1). Ex-vivo α/β-T-cell depletion (10) or post-TX Cy (1) was used as GvHD prophylaxis. All patients but one received Grafalon to prevent graft rejection. One patient died prior to engraftment, one rejected and was successfully re-transplanted. Of 10 patients who achieved definitive engraftment, one died due to multi-organ failure, two relapsed and died due to the disease. In the pre-engraftment phase, recipient-specific α/β-T-cells were detectable in 9/11 patients. The proportion of autologous α/β-T-cells was 100% in 7, 50% in 1 and 13% in 1 case. α/β-T-cells converted to 100% donor at the end of follow up in 8/11 patients. γ/δ+-T-cells were detectable on day +7 in 9/11 patients. In all but one case, γ/δ-T-cells were exclusively of donor origin and remained allogeneic until the end of follow up. Low percentage (≤5%) of autologous NK cells was detected on day +7 in 2 patients and on day +21 in one. All the remaining analyses revealed 100% donor origin of NK lymphocytes. Comparison of flow-cytometry and PCR-STR assays revealed substantial agreement while analysing CD3+ cells (Kappa = 0.78, 95%CI: 0.62 - 0.95) and moderate agreement in case of CD3- population (Kappa = 0.53, 95%CI: 0.17 - 0.89). Only one out of 9 patients with detectable autologous α/β-T-cells on day +7 experienced graft rejection.

Conclusions: Flow-cytometry based analysis of hematopietic chimerism in different cell populations is reliable and characterised by moderate to substantial agreement with standard STR-PCR. Despite limited sample size, the early results indicate that detection of up to 100% autologous α/β-T-cells in pre-engraftment phase does not predict graft rejection.

Disclosure: Supported by grant no. TJ2018-0090 from Barncancerfonden.

P611

Improved Survival after MIBG Therapy in Combination with Megachemotherapy than after Stand-Alone Therapy in Children with Neuroblastoma - Polish Nation-wide Retrospective Study

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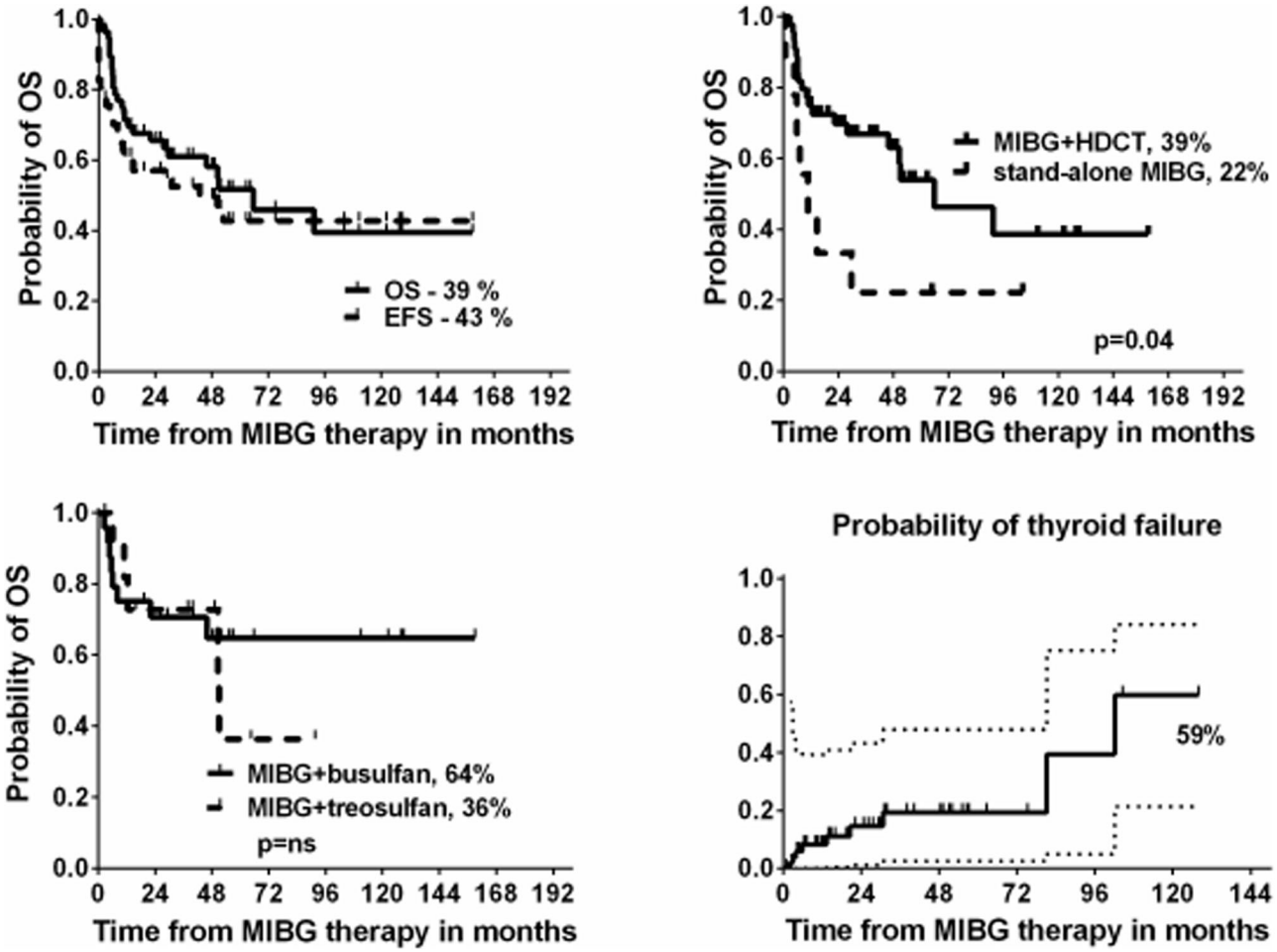
Background: The MIBG I-131 therapy is a promising targeted treatment in refractory and relapsed neuroblastoma with or without stem cell transplantation (SCT). We performed a retrospective analysis of the MIBG I-131 therapy outcomes in children (pts) treated in Poland in years 2006-2019.

Methods: 58 pts (34 M:24 F) with median age of 6.7 years (range 1.5-18.5) with neuroblastoma underwent one or more courses of MIBG I-131 therapy. The pre-requirement for therapy was an avid MIBG disease, and unfavourable prognostic factors like relapse (18 pts), primary chemoresistance (19 pts) or progressing disease (8 pts). Patients received MIBG at a dose of 100-500 mCi. Among 14 patients left without additional chemotherapy, 7 required SCT due to prolonged cytopenia. Four children received standard dose chemotherapy with autologous (auto-)SCT. In 36 patients after MIBG therapy the megachemotherapy (HDCT) was performed (busulfan-melfalan in 24 pts, treosulfan-based in 11 pts, and other in 1 pt). In 5 cases, the MIBG therapy was administered as a part of tandem transplantation (MIBG/ auto-SCT/ HDCT/auto-SCT). Grafting material was autologous in 36 children, haploidentical from a parent in 5, matched allogeneic in 4, and syngeneic in 1 patient. Average time from MIBG to SCT was 21 days (ranged 8-102).

Results: The probability of 5- and 10-year OS was 52% and 39%, respectively. Addition of HDCT with SCT irrespectively of the donor type (autologous, allogeneic or haploidentical) versus no chemotherapy was associated with superior 5-year OS (54% vs 22%, p=0.04). The 5-year OS after allogeneic, haploidentical and autologous SCT was 37%, 40% and 57%, respectively. The overall incidence of venoocclusive disease (VOD) was 8.6%, but all VOD cases were seen in the busulfan-melphalan HDCT cohort, with an incidence of 21%. In this retrospective study, patients with progressing, refractory or relapsed disease showed no significant differences in OS probability. The choice of busulfan or



[Survival and the risk of thyroid failure after MIBG therapy]

treosulfan did not affect OS probability (65% vs 36%, p=ns). In 20% of treated children a hypothyroidism was diagnosed within a period of 24 months after MIBG therapy, but at 10 years the cumulative incidence of thyroid failure increased to 59%. In 2 patients the second malignancies were diagnosed - myelodysplastic syndromes.

Conclusions: The MIBG therapy can be incorporated into the therapy of neuroblastoma patients, but most advantage is achieved when combined with HDCT. The VOD incidence did not seem to be affected by the MIBG megatherapy. The thyroid gland failure showed increasing incidence trend over the follow-up time. Further prospective studies are needed to optimize the role of MIBG therapy in neuroblastoma patients.

Disclosure: Nothing to declare.

P612

Use of RIC Regimens Combined with Tcrab Depletion and Posttransplant Cyclophosphamide in Pediatric Mismatched SCT

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Background: Two strategies to prevent GvHD are used in haploidentical transplantation: ex-vivo depletion of TcRa/b-cells or tolerizing donor T-cells of unmanipulated grafts by post-transplant cyclophosphamide (pCy). Moreover, major

obstacle for engraftment is the persistence of patients' T-cells. We hypothesized that both methods could be combined in a setting of Reduced Conditioning (RIC). Ex-vivo T-cell depletion would allow to omit post-transplant immunosuppression and the pCy at day +3 and +4 could induce in-vivo tolerance of residual patients' T-cells not eliminated by RIC.

Methods: We report on a cohort of 6 patients who were not eligible for myeloablative condition regimens due to preexisting organ dysfunctions (lungs, gut or liver) but were in urgent need of an SCT from matched unrelated (n=2) or haploidentical donors (n=4). Diagnoses were: immune deficiencies (n =4; CARMIL 2, STAT 1, ICF 2, 1 not classified), relapsed metastatic ependymoma, refractory Burkitt´s lymphoma. All patients received a non-myeloablative conditioning regimen (ATG (Thymoglobin) 2mg/kg d-9 to d-7, fludarabine 30mg/m² d-6 to d-2, TBI 4Gy d-1, cyclophosphamide 50mg/kg d+3, d+4; adapted from Aversa, Reisner et al. Blood Adv. 2017. One patient additionally received thiotepa 2x5mg/kg on d-2. The CliniMACS® device was used for TCRab/CD19 depletion of peripheral stem cells; a median number of 14x10E6 CD34+ cells/kg bw with 6.4x10E3/kg bw residual TCRa/b T-cells was infused without any further posttransplant immune suppression. Four patients received a single add back of CD45 RA depleted donor T-cells at d+7. Dosages of 1x10E5/kg, 1x10E6/kg or 5x10E6/kg were administered. Two patients received an additional T-cell depleted stem cell boost after pCy

Results: Engraftment occurred in 4/6 patients; 2 patients rejected their haploidentical grafts and showed complete autologous reconstitution. Median time to reach ANC>500 was 19 days. Four patients had no signs of GvHD; 1 patient had grade I; the patient who had received the highest dose of CD45RA depleted DLI developed grade III but could be treated successfully. No cGvHD occurred. Immune recovery was rapid. Median numbers of CD3+ T-cells, CD3/CD4+ T-cells, CD19+ B cells and CD56+ NK cells at d30 and d100 were 120/µl, 9/µl, 0/µl, 140/µl and 205/µl, 60/µl, 67/µl and 206/µl, respectively.

3 patients are alive and well with a median follow up of 824 days. Last observed donor chimerisms were 80-100%. Causes of death in 3 other patients were: MAS/sepsis (STAT 1 deficiency, d 264) and progression in both patients with malignancies (d282 and d73). The ependymoma patient showed a transient tumor regression for 3 months whereas the lymphoma patient had only a short response for 4 weeks.

Conclusions: The combination of TCRa/b depletion and pCy allowed to use a very reduced conditioning regimen which could be administered even with preexisting significant organ dysfunctions without severe side effects. GvHD could be effectively prevented together with an acceptable engraftment rate provided by pCy. Thus, this method might offer the possibility to establish a donor-derived hematopoiesis without using pharmacological myeloablation and with minimal toxicity and might be the basis for future strategies to further reduce the conditioning regimen, especially for patients with non-malignant diseases.

Disclosure: Nothing to declare.

P613

The Role of HLA-DP Matching in Donor Selection for MUD-HSCT in Children with Hematologic Malignant Diseases

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Background: HLA compatibility is a crucial determinant of GvHD and GvL. The impact of HLA-A/B/C/DR/DQ-mismatches in HSCT recipients is clearly defined, whereas data about the effects of HLA-DP mismatches are controversial. Studies on pediatric populations are lacking.

Methods: We aimed at studying the effect of HLA-DP mismatches on the outcome of pediatric MUD-HSCT for hematologic malignancies in terms of risk of GvHD/relapse and survival.

We retrospectively studied 87 children who underwent MUD-HSCT for leukemia or myelodysplasia between January 2005 and February 2019 in the Pediatric Hematology, Oncology and Stem Cell Transplant Unit of Padua University Hospital. HLA-DP typing was performed at high resolution for all recipients and donors. HLA-DP mismatch permissiveness was classified according to the "TCE" algorithm. To assessed whether viral reactivations represent a risk factor for GvHD we considered only the episodes diagnosed before or at most 7 days after GvHD occurrence.

Results: Of 87 donor-recipient pairs, 88.5% were HLA-DPB1-mismatched. In particular, in 40.2% of the pairs the mismatch was isolated, while in 48.2% multiple mismatches were present. According to the TCE algorithm, 44.2% of HLA-DP mismatches were permissive and 55.8% not permissive.

The incidence and severity of acute GvHD were not influenced by HLA-DPB1 matching status or permissiveness. The frequency of chronic GvHD, on the contrary, was higher in patients with an HLA-DPB1 mismatch plus other HLA differences than in those with an isolated HLA-DPB1

mismatch. Notably, no cGvHD cases were diagnosed in HLA-DPB1-matched patients (p=0.0125). Moreover, the type of mismatch influenced the risk of cGvHD since not permissive mismatches were associated with the highest frequency of cGvHD, confronted to permissive mismatches and HLA-DPB1 matched patients (p=0.0289). The rate of moderate severe forms of cGvHD appeared similar in permissive and not permissive mismatches. However, interestingly, in patients with a not permissive HLA-DPB1 mismatch a history of viral reactivation resulted in a statistically significant increase in the risk of moderate-severe forms of cGvHD. The frequency of relapse, on the other hand, showed a tendency to be higher in patients with 12/12 HLA compatibility (50% of 6 patients) than in patients with HLA-DPB1 mismatches (isolated or combined with other ones), although not reaching statistical significance.

Lastly, by analyzing the impact of HLA-DPB1 mismatch on outcomes, we identified a clear trend towards better overall survival in patients with isolated HLA-DPB1 mismatch when compared to those with multiple mismatches or HLA-DPB1 match. In particular, HLA-DPB1 mismatches correlated with higher relapse-free survival in comparison to HLA-DPB1 identity. Of note, patients with not permissive mismatches showed a clear trend towards better overall and relapse-free survival. Neither HLA-DPB1 mismatch nor its non-permissiveness resulted in an increased risk of TRM.

Conclusions: Our results, which need to be confirmed in larger case series, suggest the importance of a careful consideration of HLA-DPB1 matching status during donor selection for MUD-HSCT in children with hematologic malignancies. Non permissive HLA-DP mismatches, while increasing cGvHD incidence without rising TRM, could contribute to a better outcome through protection against relapse, especially in patients with high risk of disease recurrence.

Disclosure: Nothing to declare.

P614

Early Initiation of Cyclosporine-mycophenolate Plus Antithymocyte Globulin in HAPLO Transplant with Post-transplant Cyclophosphamide in Children: Low Incidence of Severe Acute GVHD with Encouraging Survival

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Background: Several reports have showed that unmanipulated haploidentical stem cell transplantation with post-transplantation cyclophosphamide (Haplo SCT-PTCy) is feasible and achieves good results in children with hematologic malignancies; however acute graft versus host disease (aGVHD) remains a problem especially in very young children. With the idea to decrease it, we modified the time of starting the immunosuppression, from day +5, as in the Baltimore protocol, to zero and +1, and added low doses of antithymocyte globulin (ATG).

Methods: Patients received melphalan 140 mg/m2 on day -7, fludarabine 40 mgs/m2/d from days -6 to -3 and total body irradiation 200 cGy on day -2. All patients were given cyclosporine, at usual dose, from day 0 to +180 and mycophenolate 45 mg/kg/d from day +1 to +60. ATG 2 mg/kg/d was administered on days -8 to -7 in 14 cases.

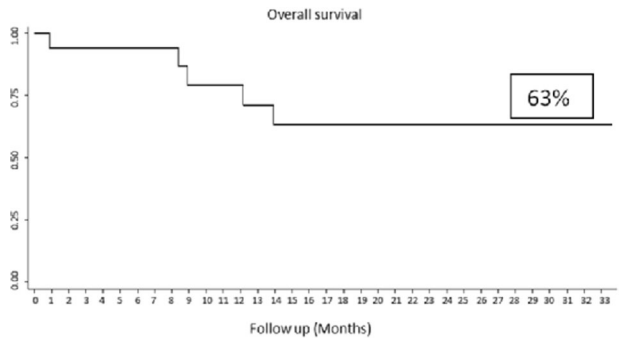
After a signed informed consent, 17 patients were transplanted, median age was 9 years (range 3-17), 14 had acute lymphoblastic leukemia and 3 acute myeloid leukemia. Eleven were in first remission, 2 in second and 4 in third or with refractory disease

Results: All donors shared 4 out of 8 alleles with the recipient, median age was 30 years (range 11-47); in 82% of the cases was a parent and in 18% a sibling. Five male patients received cells from female donors. In 7 cases the cellular source was bone marrow (BM) and in 10 was peripheral blood (PBSC). A median of 3 million CD34+ cells/kg were infused (range 1-5) in recipients of BM and 9 million (range 4-11) in PBSC.

Engraftment rate for neutrophils at day +30 was 100%, median 14 days (range 11-20), and 94% for platelets, median 13 days (range 8-20). Chimerism at D+100 was available in 75% of cases; all had full donor hematopoiesis. Median follow-up of surviving patients was 19 months (range 3-33). The cumulative incidence of aGVHD II-IV and III-IV for the whole group was 41% and 12% (based on MAGIC criteria). In 7 patients who had BM as cellular source the incidence of aGVHD III-IV was 0%, while in those who received PBSC was 20%. The incidence of extensive chronic GVHD (based on NIH 2014 criteria) was 19% for the entire group, 14% for recipients of BM and 22% for PBSC. Tolerance and anti-leukemic activity of the protocol was good, non-relapse mortality at 1 year was only 12% while the relapse rate was 18%. The overall and disease-free survival (Kaplan-Meier) at 33 months were the same; 63% (CI: 0.34-0.83). Fig 1.

Conclusions: Early initiation of cyclosporine and mycophenolate plus low doses of ATG in children who underwent Haplo SCT-PTCy is feasible and can decrease the incidence of severe aGVHD, especially when cellular source is BM. Furthermore, it doesn´t seem that this modification decreases the anti-leukemic effect of the

conditioning. We will continue recruiting patients with the scope to confirm these results.



[Fig. 1]

Disclosure: Nothing to declare.

P615

Veno-occlusive Disease with Emphasis on Renal Manifestations in Pediatric Hematopoietic Stem Cell Transplantations: A Single Center Experience

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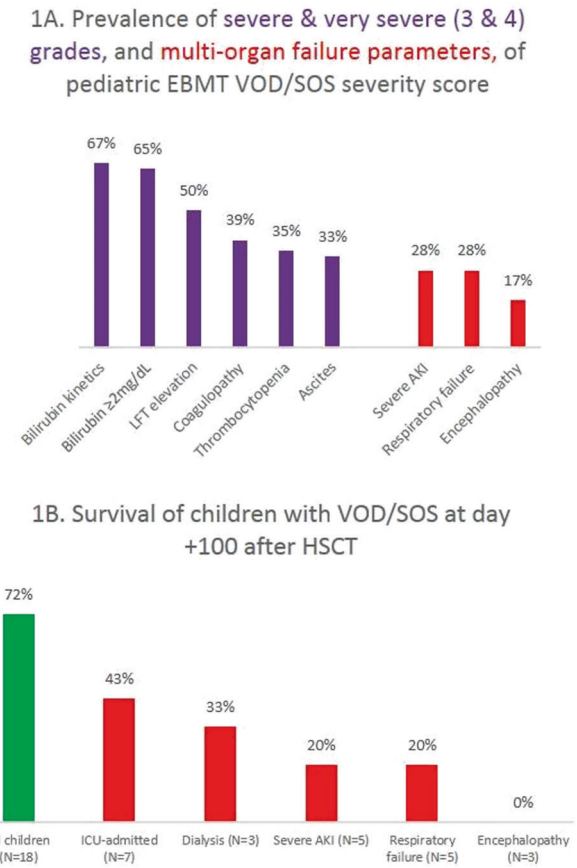
Background: Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) of the liver is a potentially fatal complication of hematopoietic stem cell transplantation (HSCT). As such, it may deteriorate to multi-organ failure (MOF), including renal failure, which independently predicts inferior prognosis in HSCT recipients. The differences between children and adults, including delayed- and anicteric-presentations, have led to revision of diagnostic criteria for children. We present a single-center experience in pediatric VOD/SOS, focusing on renal manifestations and management.

Methods: All pediatric patients who underwent HSCT and developed VOD/SOS, between 2005 and 2019, were included in this single-center retrospective analysis. VOD/SOS diagnosis was based on the European society for blood and marrow transplantation (EBMT) 2018 criteria, and all data were obtained from electronic patient records.

Results: Of 312 transplanted children, 18 (6%) were diagnosed with VOD/SOS. Median age at HSCT was 5 years (range: 0.4-18); 59% were males. Fourteen patients (78%) had a malignant indication for HSCT, mostly acute leukemia and neuroblastoma. Nine patients (50%) developed VOD/SOS following an allogeneic HSCT, and the other 9 following an autologous HSCT. Risk factors for VOD/SOS were Busulfan or total body irradiation in the conditioning regimen in 16 patients (89%), and neuroblastoma in 5 (28%). Median time between HSCT and VOD/SOS diagnosis was 13.5 days (range: 1-27); 5 cases (28%) were diagnosed beyond day 21, in 6 (35%) the bilirubin value never reached 2 mg/dL (34μmol/L).

Most children fulfilled criteria for severe, or very severe VOD as per EBMT criteria; 5 patients progressed to MOF, defined by either severe acute kidney injury (AKI) in 5 cases (28%), respiratory failure in 5 (28%), or encephalopathy in 3 (17%), as shown in figure 1A.



[Figure 1: Severity parameters (1A) and survival (1B) of children with VOD/SOS]

All patients were treated with supportive care and corticosteroids; 14 patients (78%). received Defibrotide. Median duration of Defibrotide treatment was 11 days (range: 5-21). Seven patients (41%) were admitted to the intensive care unit. Three patients (17%) required renal replacement therapy (RRT), 1 child due to renal failure, and 2 due to metabolic indications (ammonia removal due to encephalopathy). The mode of RRT was intermittent

hemodialysis in 2 of 3 children (66%). Median duration of dialysis therapy was 2 days (range: 2-3).

Thirteen patients (72%) were alive without VOD/SOS on HSCT day +100. The survival rate of ICU-admitted, dialyzed-patients, and severe AKI were 43%, 33%, and 20%, respectively; figure 1B presents the survival data.

Conclusions: The incidence of VOD/SOS in this cohort was lower than previously reported; which could be attributed to the retrospective nature of this study, or to misdiagnosis. Despite high prevalence of severe VOD/SOS, outcome for most patients was favorable. Progress to MOF, including severe AKI and need for dialysis, and ICU hospitalization, were unfavorable prognostic factors. Our results emphasize the need for high awareness (especially for less typical forms of childhood VOD/SOS), multidisciplinary approach, and the benefit of early treatment strategies, including early initiation of RRT. Prospective studies are needed.

Disclosure: Nothing to declare.

P616

Outcome after HSCT in Children with JMML from a Historical Point of View

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Background: Hematopoietic stem cell transplantation (HSCT) is still the only curative option for the vast majority of children diagnosed with Juvenile Myelomonocitic Leukemia (JMML). Relapse remains the major cause of treatment failure.

Methods: Between 1989 and 2018, 50 children with JMML was retrospectively registered among the Spanish National Transplantation Group (GETMON). The median follow-up in survivors was 77,4 months. Cumulative Incidence Relapse (CIR) and Transplant related mortality (TRM) were estimated using Fine-Gray regression whereas Kaplan Meier curves were used for Overall Survival (OS).

Results: The male:female ratio was 37:13. Median age at diagnosis was 1,5 years (IQR 0,6-2,9). Cytogenetic analysis revealed monosomy 7 in 15 patients (30%) and molecular analysis results are available in eighteen patients. Foetal hemoglobin elevated levels were detected in 13 (43,3%). Four patients had a congenital disorder.

Median age at HSCT was 2,2 years (IQR 1,0-3,5). Most of the patients (39 patients) received therapy prior to HSCT. Median interval between diagnosis and transplantation was 5,8 months (IQR 3,7-9,5).

Donors were HLA-matched unrelated in 20 cases, matched siblings in 11 and Haploidentical in 5 cases. Stem cell source was 14 umbilical core blood in (28%), peripheral blood in 17 (34%) and bone marrow in 18 (38%). GVHD prophylaxis was based on Cyclosporin and a short course MTX in half of the patients. Thymoglobulin was added in 24 (65%) patients, and Bu-CY-MEL was the most commom regimen condition in 19 (51%) children.

Patients who engrafted reaching 500 neutrophils between days 4 to 45 days (20d median). Grade III to IV aGVHD was observed in 11 (22%) patients. Three patients (6.0%) developed limited or extended cGVHD.

The OS was 50.6% (95CI 35.7-63.8) at 10 years follow-up (64.1% from 2005 onwards). The overall TRM was 14.0 % at 1st year (95CI 6.2 - 25.0), 13.2 % since 2005.

20 (40%) children had relapse of JMML at a median time of 2,2 months (IQR 1,2 - 3,8) after HSCT. The CIR is 34,1% (95CI 21,4 - 47,1) at 1 year (21,1% from 2005). 12 patients received a second HSCT (3 of them Haploidentical), 4 of them are still alive and in remission after a median observation time of 43 months.

Conclusions: Although the results are improving in the last 10 years, graft failure and early relpase continue to be a problem. After relapse, second HSCT should be considered the treatment of choice although the best strategy has to be designed.

Disclosure: Nothing to declare.

P617

The Impact Recovery Absolute Lymphocyte Count at Days +21 on Outcome Allogeneic Stem Cell Transplantation in Pediatric ALL

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Background: Allogenic hematopoietic stem cell transplantation (allo-HSCT) is curative option for children with high risk disease and relapse ALL. Despite the existence of a number of factors determining OS, according to some studies one of important factor prognosis allo-HSCT is absolute lymphocyte count recovery (ALCR) at Days +21 and +30 more than 30 x 10^9/l [J.Morando et al.,2012], [M K Ishaqi et al, 2008]. At the same time, there are no data regarding ALC recovering at the various conditioning regiments and GVHD prophylaxis.

Purpose: Estimate overall survival (OS); evaluated the influence recovery ALC on Days +21 on relapse incidence (RI) in MAC vs RIC, incidence of infectious complications (IC) up to Days +100, acute and chronic graft versus host disease (GVHD), early transplant related mortality (TRM), relapse free survival (RFS), GVHD-free/relapse-free survival (GRFS) in children with ALL.

Methods: We included 112 of children with ALL, who underwent the first allo-HSCT and had engraftment. The median age was 10 years (range 0-18). Remission of disease at allo-HCST was in 92 of pts (82%). Allo-HSCT was performed from HLA compatible donor (n=52 pts, 46%), haplo-donor (n=51, 46%). Seventy-seven (69%) pts received Bu-based MAC. RIC was Flu/Mel in 34 pts (30%). Source of stem cells was bone marrow (BM) in 89 (71%) pts, peripheral blood (PB) in 22 (20%), one child (1%) had both source. One hundred and six children (95%) received PT-Cy prophylaxis GVHD, 6 pts (5%) - antithymocyte globulin (ATG). ALC analyzed at Days +21 and determined as lymphocyte count =>0.3 x 10^9/l in PB. The Kaplan Meier method was used for calculation the OS, RFS, GRFS and TRM. RI, incidence IC and factors associated with early LR was assessment by Mann-Whitney U-test.

Results: ALC at Days +21 was achieved in 27 (24%) pts. Two years OS was higher in pts with ALCR at Days +21 (82% vs 52% p=0.021. There was no different in ALCR and status of disease (p=0.3), source of stem cells (p=0.3). ALCR was earlier in HLA compatible (n=17, 32%), than incompatible (n=8, 13%), p=0.049. ALC at Days +21 in MAC+Cy (30%) vs MAC+ATG (50%) were no different, p=0.3. ALC at Days +21 in MAC+Cy (29%) was higher vs RIC+Cy (9%), p=0.02. RI, acute and chronic GVHD were similar in children with early ALC and without (RI 33% vs 47%, p=0.2; a GVHD 41% vs 42%, p=0.8; chronic GVHD 27% vs 35% p=0.3, respectively). Incidence IC up to Days +100 was significant lower in pts with ALCR at Days +21 (44% vs 66%), p=0.048. TRM up to Day + 100, RFS and GRFS were no different; TRM was 7% in pts with ALCR vs 12%, without at Days +21, p=0.5; RFS 67% vs 54%, p =0.34, GRFS 26% vs 14%, p=0.6 respectively.

Conclusions: ALCR at Days +21 predicts low incidence IC at Days+100 and better OS in pediatric ALL. ALCR did not depend on GVHD prophylaxis in MAC (ATG vs PT-Cy), but depended on intensity of the conditioning regimen using PT-Cy prophylaxis and donor compatibility.

Disclosure: Nothing to declare.

P618

T-cell-rich Haploidentical Stem Cell Transplantation Improves Survival in Children with Acute Leukemia Relapsed after Allogeneic Transplantation

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Background: Recurrent acute leukemia after allogeneic hematopoietic stem-cell transplantation (allo-HSCT) entails a dismal prognosis and further therapeutic options are limited. One potential curative approach is a second allo-HSCT. Our institution has been performing T-cell-rich haploidentical HSCT (TCR-haplo-HSCT) with low-dose anti-thymocyte globulin (ATG 2.5 mg/kg) that allow for powerful graft-versus-leukemia (GVL) effects in high-risk leukemias as an immune therapy. In this study, we performed a retrospective analysis of pediatric patients with leukemias who underwent a TCR-haplo-HSCT as the second allo-HSCT for relapse after their first allo-HSCT in our institution. The aim of this study is to verify the safety and efficacy of TCR-haplo-SCT for preventing GVHD through the combination of low-dose rabbit ATG, tacrolimus, methotrexate (MTX), and prednisolone (PSL) in children with acute leukemia relapsed after allo-HSCT.

Methods: From Aug 2009 to April 2019, consecutive 30 patients (pts) underwent TCR-haplo-HSCT were included. The median age of pts was 8 (1-19) years old. The diagnosis included ALL (n=17), AML (n=13). The disease status at TCR-haplo-HSCT were 15 in CR (positive MRD: 5 pts), 15 in non-CR. Donors included fathers (n=17), mothers (n=7), siblings (n=2), uncles (n=3), aunt (n=1). 25 pts received myeloablative conditioning (TBI based: 4 pts, Bu based: 21

pts). The GVHD prophylaxis post transplantation was conducted with tacrolimus, MTX and PSL. To prevent GVHD, all pts received ATG (anti-thymocyte globulin 1.25 mg/kg/day) intravenously for 2 consecutive days, on days − 2 to − 1. 29 pts received peripheral blood stem cells.

Results: Neutrophil engraftment (defined as >0.5x10^9/L) was 90% with a median day of 13 (range, 10-15). With a median follow up of 614 (18-3312) days for survivors after TCR-haplo-HSCT, the estimated 2 years leukemia-free survival (LFS) was 47.9% and the 2 years overall survival (OS) was 61.1%. The day 100 cumulative incidence of non-relapse mortality rate was 13.3%, and the cumulative incidence of acute GVHD and chronic GVHD were 70.0% and 66.7% respectively at 1 year after TCR-haplo-HSCT. Younger age (10 years or less), morphological CR at the TCR-haplo-HSCT, Karnofsky performance status (≥90%) prior to TCR-haplo-HSCT, CD3 cell dose (≥5.0×10^8/kg), and acute GVHD were found to be related to longer survival. In multivariate analysis, favorable prognostic factors (P< 0.05) for OS included CR before TCR-haplo-HSCT.

Conclusions: Our analysis suggests that TCR-haplo-HSCT with low-dose ATG (2.5 mg/kg) hold promise to improve outcome in children relapsed after allo-HSCT. We propose TCR-haplo-SCT as a new immune cell therapy for improving survival rate in patients with relapsed/refractory acute leukemia, for which no effective treatment is currently available.

Disclosure: Nothing to declare.

P619

High Prevalence of Vitamin C Deficiency in a Large Paediatric Cohort Undergoing Hematopoietic Stem Cell Transplantation: A Single Centre Experience from 2003-2019

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Background: Vitamin C or L-Ascorbic Acid (ASA) has an essential role in numerous cellular processes such as collagen synthesis, cellular oxidation, and various hydroxylation reactions. ASA derivatives exhibit strong and selective antitumor and antiviral activity. Deficiency is more common in patients with cancer and undergoing hematopoietic stem cell transplant (HSCT) due to poor intake, nausea, vomiting, mucositis and other gastrointestinal complications. Deficiency may result in delayed healing, increased infections and may lead to poorer outcome in patients undergoing HSCT. Monitoring was introduced in the unit after cases of scurvy were diagnosed in this population.

Methods: Vitamin C blood levels were measured in patients undergoing HSCT at The Children's Hospital at Westmead, pre transplant and monitored regularly post transplant. A level more than 40umol/L was defined as normal and levels of 25-40umol/L, 11-24umol/L and < 11umol/L were classified as mild, moderate and severe deficiency.

Results: 356 transplants involving 326 patients with age range 0.25 to 19 years (Mean: 7 yrs) (Males=211, Females=115) undergoing HSCT had vitamin C levels monitored from January 2003 to October 2019. Seventy three (20.5%) of all transplants were autologous and 283 (79.5%) allogeneic HSCT respectively for malignant (n=232) and non-malignant (n=124) indications. Low vitamin C levels were found in 257 (72.2%) of all transplants at some time point (pre or post-HSCT), with 54 (15%), 80 (22%) and 123 (36%) of all transplants having patients with mild, moderate and severe deficiency. Pre-transplant levels were available for 285 transplants (not tested in 62) and out of these, 171 (60%) had low levels (30% mild, 35% moderate and 35% with severe deficiency). 76% of the low vitamin C levels were from patients with malignant disease with 57% of malignant transplants having mild deficiency, 65% of malignant transplants having moderate deficiency and 80% of all malignant transplants having severe vitamin C deficiency.

Conclusions: Vitamin C deficiency is highly prevalent in children undergoing HSCT. As would be expected, vitamin C deficiency was more common in patients with malignant disease. Early recognition and management, well before HSCT, and monitoring in post-transplant period until adequate dietary intake is established is recommended. With such a high prevalence of vitamin C deficiency we now plan to analyse its impact on clinical outcomes including survival and transplant related morbidity and mortality.

Disclosure: Nothing to declare.

P620

Ex Vivo T Cell-depleted Haploidentical Hematopoietic Cell Transplantation for Pediatric Patients with Non-malignant Disease

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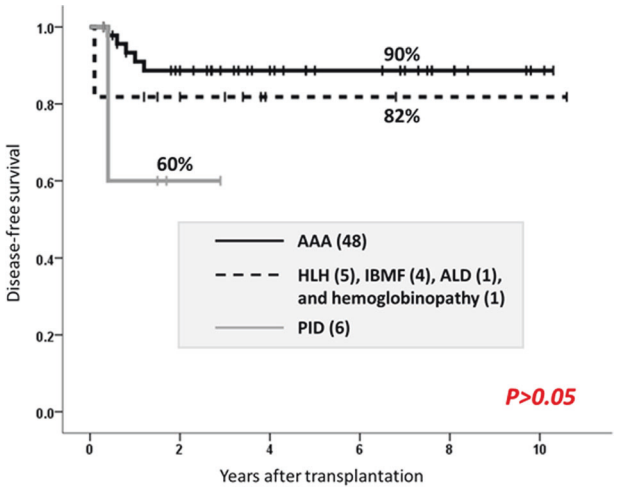
Background: We evaluated the outcome of haploidentical HSCT (haplo-HSCT) using ex vivo T cell-depleted grafts in pediatric patients with non-malignant disease.

Methods: Between April 2009 and August 2019, 65 patients with non-malignant disease (48 with acquired aplastic anemia (AAA), 6 with primary immunodeficiency (PID), 5

with HLH, 4 with inherited BMF (IBMF), 1 with adrenoleukodystrophy, and 1 with hemoglobinopathy) received haplo-HSCT using ex vivo T cell-depleted grafts (18 from CD3-depleted PBSC and 47 from TCRαβ-depleted graft) at Asan Medical Center Children's Hospital. The conditioning regimens are shown in Table 1.

Conditioning regimens	Number
Low-dose TBI/fludarabine/Cy/ATG	47
Treosulfan/fludarabine/thiotepa/ATG	10
Fludarabine/Cy/ATG	7
None	1

[Table 1. Conditioning regimens]



[Figure 1. Outcomes of haploidentical HSCT for pediatric patients with non-malignant disease.]

Results: Sixty-two of 65 patients achieved neutrophil engraftment at a median of +10 days (range, 8-13 days). Three patients experienced primary graft failure (GF) and additional 7 patients developed graft rejection within 30 days post-transplant. One more patient with AAA developed late GF at +81 days. Therefore, a total of 11 patients experienced GF, leading to cumulative incidence (CI) of 17%. All the 11 patients received rescue transplantations and 9 of them achieved neutrophil engraftment. The remaining two patients did not obtain engraftment and they are alive with disease. The CI of acute GVHD ≥ grade 2 and ≥ grade 3 were 31% and 17%, respectively. No patient developed grade 4. The CI of extensive chronic GVHD was 4%. As of November 2019, seven out of 65 patients died at a median of 6.7 months after haplo-HSCT (CMV disease in 2, and pure red cell aplasia with autoimmune hemolytic anemia, TMA, pneumonia, Infection and GVHD in 1 each). The TRM at 2 years was 12%. With a median follow-up of 41 months (range, 4-129), the overall survival (OS) and disease-free survival (DFS) of total patients were 88% ± 4.1% and 85% ± 4.5, respectively. The DFS for AAA, PID and the remaining patients were 90%, 60%, and 82%, respectively (figure 1).

Conclusions: Our study demonstrated that our current haploidentical HSCT using ex vivo T cell-depleted graft is a feasible approach for pediatric patients with life-threatening non-malignant disease.

Clinical Trial Registry: NCT01759732
NCT02014506

Disclosure: Nothing to declare.

P621

Long-term Erythropoietic Recovery after Allogeneic Stem Cell Transplantation in Pediatric Patients: Host Determines Result

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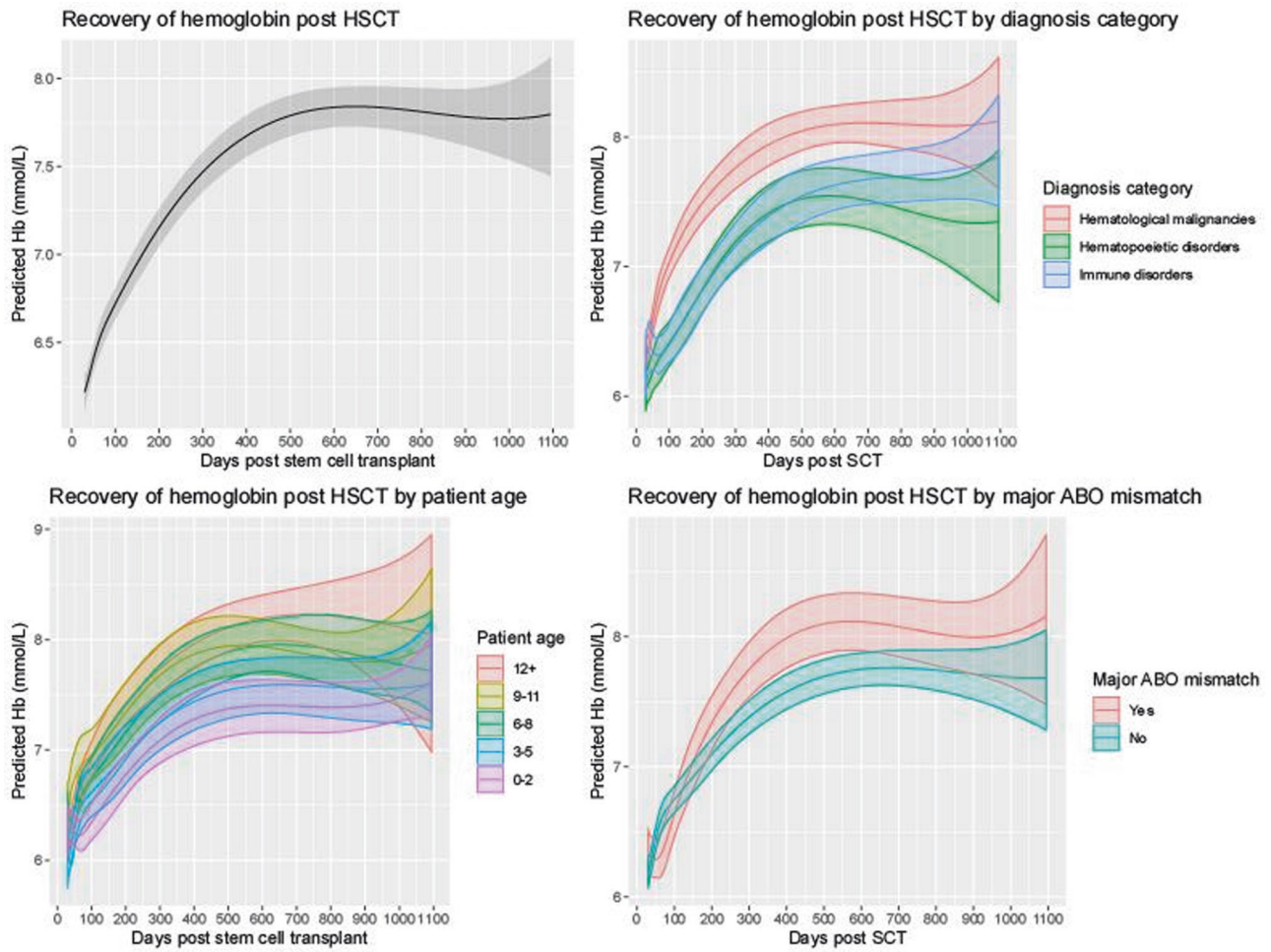
Background: Multiple factors, such as conditioning regimen and ABO mismatch, have been related to short-term erythropoietic recovery and red cell transfusion requirement after hematopoietic stem cell transplantation (HSCT). However, long-term effects of these factors on erythropoietic recovery have not been investigated. In this study, we aimed to identify the most important factors influencing erythropoietic recovery in pediatric patients up to three years post HSCT to tailor future treatment regimens supporting effective erythropoiesis.

Methods: We retrospectively included 414 patients and 11957 hemoglobin measurements from pediatric patients undergoing HSCT in our center between July 2004 and July 2018. Hemoglobin measurements between day 30 and day 1095 were analyzed using linear mixed models and B-splines. To assess reticulocyte recovery for ABO mismatched patients, we included reticulocyte measurements and analyzed time to reticulocyte engraftment, defined as a level above $30*10^9$/l using survival analysis.

Results: Hemoglobin levels increased most rapidly around the first 100 days post HSCT. In the following weeks this growth slowed down and reached a plateau phase at day 648 with an average hemoglobin level of 7.48 mmol/L. Patients transplanted for hematological malignancies showed faster hemoglobin recovery as compared to patients transplanted for non-malignant diseases ($p< 0.0001$). Reduced intensity conditioning was followed by slightly higher hemoglobin values than myeloablative



[Recovery of hemoglobin overall, by diagnosis category, patient age and major ABO mismatch]

conditioning, and this difference was increasing over time (p=0.0075). Increasing patient age correlated with faster recovery (p< 0.0001), while donor age had no influence. Donor type and graft type also did not influence erythropoietic recovery significantly. Patient hemoglobin levels after HSCT correlated better to reference values based on patient age and gender as compared to donor age and gender. In patients receiving grafts with a major ABO mismatch, hemoglobin levels seemed lower initially and reticulocyte recovery was 2 days slower (21 vs 19, p=0.012). However, hemoglobin levels reached higher levels between day 263 and day 629 post HSCT. The overall p-value for the effect of a major ABO mismatch was less than 0.0001.

Conclusions: Hemoglobin levels reached steady state at day 648 after HSCT in pediatric patients. Recovery is strongly determined by host factors, such as age, conditioning regimen and primary disease, and less by donor factors. ABO mismatch has a small impact on reticulocyte recovery initially, but does not have a negative long-term impact on hemoglobin levels. This indicates that in the pediatric setting, donor selection has no relevant impact on long-term hemoglobin recovery

Disclosure: Nothing to declare.

P622

Boost with CD34+ Cells for Poor Graft Function Treatment after HSCT in Paediatric Patients. A Multicenter Study

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Background: Poor graft function (PGF) after HSCT is a severe complication with high mortality. There are different options for PGF management and one of the most widely used is the infusion of a boost of selected CD34+ donor cells without previous conditioning; but so far, specific data in the paediatric population are limited. Here we report the outcome of 16 children with PGF treated by infusion of CD34+selected cells from the same allogeneic donor used for the previous HSCT.

Methods: Sixteen patients (male=9, female=7) with a median age of 12 years (range 1-17) underwent HSCT between 2002 and 2018 at 3 different paediatric centers for both malignat and non-malignat diseases (ALL=5, NHL=3, SAA=2, Mucopolisaccaridosis=2, AML=1, Fanconi Anaemia=1, Dykeratosis Congenita=1, Sickle Cell Disease=1). HSCT donors were: siblings=4, unrelated=11 and haplo=1. Among the unrelated donors 6 were 1 antigen HLA mismatch, while the haplo donor displayed a 3 loci HLA mismatched. The HSCT source was bone marrow and peripheral blood stem cells for 12 and 4 patients, respectively. The median donor age was 28 years (range 10-44) and the donor gender was male=11 and female=5. The conditioning regimen was TBI-based for 7 patients, Treosulfan-based for 3 patients and Busulfan-based for 1. Others (5) received alternative conditioning according to disease and comorbidities. Overall survival (OS) was calculated according according to the Kaplan-Meier method by using NCSS software (Hintze, 2001; NCSS PASS, Number Crunched Statistical System, Kaysville, UT, USA)

Results: At CD34+ boost infusion 11 patients had neutrophils below 1x10^9/L and 14 patients were platelets transfusion-dependent. Before CD34+ boost 14 patients showed a full-donor chimerism, while 2 patients had mixed chimerism. Median time between HSCT and CD34+ boost was 194 days (range: 48-607).

In all the cases CD34+ boost was infused without any conditioning regimen. Donors were stimulated by subcutaneous G-CSF 10 mcg/kg/d for 5 days and CD34 +selection was performed by immunomagnetic separation using the CliniMACS Device (Miltenyi Biotec). Median infused cell dose was 10.5 x 10^6 CD34+ cells/kg (range: 18.4-4.5). After the infusion 13 patients receveid immunesuppressive drugs for GvHD prophilaxis while 3 patients did not. Neutrohils engraftment was achieved in all the patients who underwent to CD34+ boost for neutropenia, while transfusion-dependent thrombocytopenia was resolved only in few cases. At 2 years from CD34+ boost OS was 56% (95%CI 32-80). After CD34+ boost 2 out of 8 patients affected by malignancies relapsed and 2 of 16 patients developed GvHD symptoms. Cause of death was infections in 4 cases.

Conclusions: Our data suggest that CD34+ boost may improve cytopenia in a significant proportion of patients. However, this approach seems to be able to rescue only approximately one half of patients developing PGF in the long term

Clinical Trial Registry: NA

Disclosure: The authors have no commercial, proprietary or financial interests in the products or companies described in this article.

P623

Allogenic Stem Cell Transplantation for Fanconi Anemia: A Single Center Experience

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Background: Fanconi anemia (FA) is a rare heterogeneous disorder characterized by congenital malformations, progressive marrow failure, and predisposition to leukemia and epithelial malignancies. Allogeneic stem cell transplantation (allo-HSCT) is the only therapy that can correct the hematological manifestations of FA patients.

Methods: Retrospective analysis of all FA patients, who underwent matched-family donor (MFD), unrelated cord blood (UCB) or haploidentical allogeneic HSCT (Haplo-HSCT) at King Hussein Cancer Center (KHCC) from Jan2005 until Oct2019.

Results: Thirty patients underwent allo-HSCT (median age, 8.5yrs; range, 4-23). Donors were MFD (N=24, 80%: 14 siblings, 6 parents and 4 other family members; one antigen mismatch in 3 patients), UCD (N=3, 10%), and Haplo-HSCT (N=3, 10%). The source of stem cells for MFD were bone marrow (N=17), peripheral blood stem cells (PBSC, N=6). All MFD and UCB patients received fludarabine-based conditioning, cyclophosphamide and ATG (29 received Rabbit ATG, thymoglobulin® and 4 horse ATG). Single fraction TBI (300cGy) was added to 2 MFD and 1 UCB recipients with Myelodysplastic syndrome (MDS). T-cell repleted Haplo-HSCT recipients received fludarabine 150 mg/m2 and single fraction TBI (200cGy). Cyclophosphamide (14.5mg/kgX2days) was given for one patient, and omitted due to regimen-related toxicity. T-cell-repleted PBSC was used for one patient and 2 received BM cells. Cyclophosphamide (25 mg/kg on day +3 and +4) was used for T-cell depletion in all Haplo-HSCT recipients. The median time for neutrophil engraftment was 13days

(range,9-27), and for platelet engraftment was 17 days (range, 12-93). Patients were followed for a median of 5.68yrs (range, 0.9-13.84). Four patients underwent second allo-HSCT (3 due to primary graft failure and 1 developed donor-type aplasia 2 years post-transplant). There were 5 deaths in our cohort: Two patients developed metastatic squamous cell carcinoma; both died 5.5 and 12 years post allo-HSCT; a patient died due to chemotherapy toxicity before engraftment, a patient died on day 31 post-transplant due to pulmonary and intracranial hemorrhage, and the last patient died one year post-transplant due to encephalopathy. The probability of 5 years-overall-survival was 90%.

Conclusions:

	MFD	UCB	Haploidentical	Second transplant	Persentage
number of patients	24 patients	3 patients	3 patients	4 patients	30 patients
Graft failure	1	2	0	0	10%
Death	2	1	1	1	16%
CMV reactivation	22	0	2	4	80%
aGVHD(gradeII-III)/overlap syndrome	5	0	2	2	23%
cGVHD	9	0	2	2	43%
Bactermia	14	0	3	0	56%
Fungal infection	1	0	0	1	7%

[Post-transplant Followup]

Most of our transplants for FA were from MFD. We had manageable toxicity and we noticed better results for patients who did not have MDS. In our region, extended family search should be done to identify potential donors. CMV reactivation and cGVHD are still challenges to overcome. These patients need long-term follow-up.

Disclosure: no conflict of interest

P624

Abstract already published.

P625

First Allogeneic Hematopoietic Stem Cell Transplantation in RASGRP1 Deficieny

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Background: RAS guanyl-releasing protein 1 (RASGRP1) is a guanine-nucleotide-exchange factor that is involved in lymphocyte development and function. The present case was the first patient in whom RASGRP1 deficiency was shown to cause primary immunodeficiency in 2016. Eight more RASGRP1 deficiency cases are defined in literature until today. The main characteristics of the disease include combined T and B cell deficiency including life-threatening infections and EBV-associated lymphoproliferation. Here we present the results of first allogeneic hematopoietic stem cell transplantation in RASGRP1 deficiency

Methods: Clinical and transplantation characteristics of the patient were recorded from his files.

Results: A 4-year-old boy admitted to our hospital with the history of recurrent infections, especially pneumonia leading to bronchiectasis. He was the ninth child of consanguineous parents and three older siblings had died in the first 2 years of life possibly due to immunodeficiency related infections. Over time, severe failure to thrive, with height and weight below the third percentile and finger clubbing became evident. At the age of 8 years, the patient underwent right middle and upper pulmonary lobectomy due to severe bronchiectasis and collapse. Monthly intravenous immunoglobulin therapy was started as he had idiopathic $CD4^+$ lymphopenia at the age of 12 years. Routine adenoidectomy was performed at the age of 15 years and the pathological examination revealed an unpexpected low-grade Epstein-Barr virus (EBV)-associated B cell lymphoma. Remission was achieved after chemotherapy for lymphoma. After detailed immunological analysis of the patient (Kaan Boztuğ, CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences), RASGRP1 deficiency, causing immunodeficiency with impaired cytoskeletal dynamics, was defined in this patient.

At the age of 16 years the patient underwent HSCT from his HLA identical cousin. Reduced intensity conditioning regimen, including busulfan (2.8 mg/kg, intravenously), fludarabine (180 mg/m^2), anti thymocyte globulin (30 mg/kg; fresenius) is preferred due to severe comorbidity. Cyclosporine A and methotrexate were used as graft versus host disease (GVHD) prophylaxis. Bone marrow was used as the stem cells source. Neutrophil and thrombocyte engraftment was achieved on day +20 and on day +21 respectively. Chimerism analysis showed 96% donor profile at the third month and 100% at the sixth month of HSCT. Acute/chronic GVHD or venoocclussive disease were not observed. The patient developed pulmonary infection on day +8 and treated with broad spectrum antibacterial and antifungal agents. The patient had been hospitalized (for 3 to 14 days) for pneumonia five times within 18 months after HSCT. Afterwards he did not have any infections requiring hospitalization. The patient is still in good clinical condition

with full donor chimerism 43 months after HSCT. He is now well in the last follow-up, and IVIG therapy is stopped.

Conclusions: In view of the life-threatening infections and malignancy risk, and as a form of combined immunodeficiency, HSCT is the curative treatment in RASGRP1 deficiency. Two cases with RASGRP1 deficiency who underwent autologous HSCT due to EBV positive lymphoma were reported in the literature. The present case is the first allogeneic HSCT in RASGRP1 deficiency.

Disclosure: There is no conflict of interest

P626

Successful HSCT In Immune Disregolatory Diseases

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Background: To date, many diseases of hematological/immunological interest are known with a controversial indication to HSCT.

The latest generation manipulation techniques, the new GVHD prophylaxis strategies and the prompt prevention of complications have greatly improved the outcome of transplants in recent years. We present 4 "successful" transplants in patients with pathology without clear indication to HSCT

Methods: Case1

3-month-old girl with specific defect of type 2 granules (SMARCD2). History of recurrent invasive infections with destabilizing perineal disease. MSD-BMT. Subject to MAC with Busulfan, Fludarabine, Tiothepa. GVHD-prophylaxis with ATG (15mg/kg), cyclosporine and mycophenolate. Neutrophil engraftment at D+18 and Platelets at D+29. Recorded GVHD skin grade I. Chimerism 100% PMN, 96% PBL.6-months after transplantation, she is in good conditions with persistent low intestinal inflammation.

Case2

18-month-old child with TRNT1 deficiency, characterized by sideroblastic anemia hypogammaglobulinemia, periodic fevers and developmental delay, bilateral sensorineural hearing-loss and recurrent arthritis, partially responsive to anti-TNF-alpha therapy, for which he was subjected to HSCT-MUD, after conditioning with treosulfan, fludarabine and tiothepa (5mg/kg), GVHD prophylaxis with ATG (30mg/kg), cyclosporine and mycophenolate. Neutrophil engraftment occurred at D+13, PLT at D+14. Post-transplantation course complicated by adenovirus infection that responded to Cidofovir, with no signs of GVHD. Chimerism was 100%.

In post-transplantation he has no longer presented arthritis with resolution of anemia.

Results: Case3

2-year-old girl with IL10-R deficiency with crohn-like VEO-IBD and history of recurrent folliculitis and fever. The girl didn't respond to conventional treatments. Because of this, she underwent CBU-HSCT, after conditioning with treosulfan, fludarabine and tiothepa. Prophylaxis for GVHD was performed with ATG (15mg / kg) and ciclosporine. PMN's engraftment at G+14 and PLT at D+36. Chimerism was 100%. She showed no signs of GVHD, the intestinal pattern regressed and never showed signs of secondary infection except for CMV-reactivation responding to ganciclovir.

Case4

8-year-old girl with LRBA deficiency, history of hypogammaglobulinemia, recurrent invasive infections, autoimmunity and enteropathy treated with abatacept and sirolimus. Because of the severity of the disease, it was therefore decided to proceed with HSCT. Therefore, MUD-BMT was performed after conditioning with treosulfan, fludarabine and thiotepa. Prophylaxis for GVHD was performed with ATG (15 mg/kg), sirolimus and mycophenolate mofetil. Due to an autoimmune hepatitis, we also performed prophylaxis for VOD with defibrotide. Engraftment of PMN at D+13 and PLT at D+11. The post-transplantation course was characterized by cutaneous GVHD grade I. Sirolimus-therapy was resumed with optimal control of enteropathy. Immunological reconstitution is almost complete one-year-after transplantation.

Conclusions: The increasing control of post-transplant complications with the reduction of TRM also allows us to submit to HCST also pathologies that do not have an explicit indication. The outcome is one of better quality of life with the resolution of disabling symptoms.

Disclosure: Nothing to declare.

P627

Levofloxacin Based Prophylaxis in Children Receiving Allogeneic Hematopoietic Stem Cell Transplantation Does not Affect the Incidence of Acute GVHD and Bloodstream Infections

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Background: The impact of a quinolone-containing regimen for bacterial infection prophylaxis on allogeneic hematopoietic stem cell transplantation (allo-HSCT) outcomes is still debated. Evidences are lacking particularly in children undergoing allo-HSCT, as numbers are limited, and data mainly based on retrospective studies. Although pioneering studies demonstrated a favorable effect of germ-free conditions on GvHD and survival, more recent data suggest that the antibiotic-mediated perturbation of the microbiota could conversely increase the risk of acute GvHD (aGvHD) and bloodstream infections (BSI).

Methods: We retrospectively evaluated the incidence of aGvHD and BSI together with related rate of antibiotic resistance in children undergoing allo-HSCT c/o our Institution from 2010 to 2019. Patients admitted before May 2016 received antibiotic prophylaxis using levofloxacin 10 mg/kg/day from the beginning of conditioning to the engraftment. Patient and transplantation characteristics were comparable between the two groups. GvHD prophylaxis was CSA and MTX for matched sibling donor HSCT and CSA, MTX and anti-thymocyte globulins for unrelated donor HSCT in the majority of cases. We considered bacteria as antibiotic resistant if presenting more than three antibiotic resistance. The BSI and GvHD incidences were calculated as a cumulative incidence.

Results: 121 children between 2010 and 2019 were analyzed, 74 (61.2%) patients receiving levofloxacin in prophylaxis. The median age at transplant was 9.25 years (range 0-23). There were no significant differences in the incidence of aGVHD (40.0% vs 42.2%; p= .84), and severe grade III/IV acute GVHD (14.1% vs 8.9%; p= .37). The grade III/IV gut aGvHD occurred in 9.3% and 6.7% in patients receiving or not levofloxacin, respectively (p=.60). Similarly, the incidence of BSI was 29.3% and 37.0% in patients receiving and not receiving levofloxacin, respectively (p= .42). The analysis of the isolated bacteria showed an increase of the antibiotic resistance in the levofloxacin group (45.5% vs 12.5%; p= .03), particularly an increase of bacteria resistant to fluoroquinolones (51.4% vs 6.6%; p= .004). At a median follow up of 28 months (range 1 months - 8 years) the OS, EFS, and transplant related mortality of patients receiving and not receiving levofloxacin were 62.6% vs 60.9% (p= 0.75) and 59.4 vs 55.8% (p= 0.80) and 19.1% vs 11.0% (p= 0.12), respectively.

Conclusions: In this retrospectively analyzed pediatric cohort the levofloxacin based bacterial prophylaxis did not reduce the rate of aGvHD and BSI. Bacteria isolated from patients receiving levofloxacin presented more antibiotic resistances. Further large-scale based prospective studies are warranted to determine the impact of a broad antibiotic management before HSCT on transplant outcomes.

Disclosure: Nothing to declare.

P628

Rituximab-induced Secondary Hypogammaglobulinemia; Memorial Sloan Kettering's 10-year Experience in Pediatric Allogeneic Hematopoietic Stem Cell Transplant Patients

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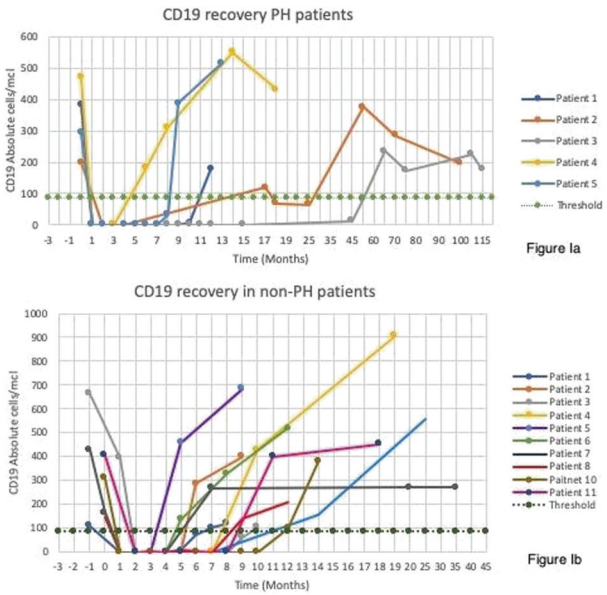
Background: Rituximab, a chimeric monoclonal anti-CD20 antibody has been employed as a strategy to induce transient B cell aplasia in allogenic stem cell transplant (HCT) recipients with autoimmune cytopenias (AI) or evidence of reactivation of the Epstein Barr Virus (EBV) by rising PCR, or lymphoproliferative disease (LPD). The effects include peripheral B cell depletion 24-48 hours after the initial dose, with phenotypic recovery within 6-12 months. We report a subset of pediatric and young adult recipients of HCT who develop persistent hypogammaglobulinemia (PH), defined as IgG< 600mg/dL beyond 12 months, relying on intravenous immunoglobulin (IVIG) replacement despite recovery of peripheral CD19+ B cell population (>85 cells/mcl)

Methods: A retrospective chart review was performed on 46 patients who underwent HCT on the pediatric service between 2008-2018 and received rituximab for prophylaxis, or documented EBV viremia, or LPD. Patients transplanted for a primary immunodeficiency, requiring CD19+ or CD22+ directed therapy as a bridge to transplant, or with poor engraftment were excluded. Five patients with PH after rituximab were compared to 11 who received rituximab with recovery of circulating IgG >600mg/dL. We compared recovery of circulating B cells, immunophenotype of peripheral B cells, and immunoglobulins in patients with and without PH.

Results:

	Persistent hypogammaglobulinemia (n=5)	No persistent hypogammaglobulinemia (n=11)
M:F	4:1	10:1
Malignant/Non-malignant	5/0	6/5
HLA Matched/Mismatch	4/1	7/4
T cell depleted/ Unmodified	4/1	11/0
Median time frame from HCT to rituximab in days (range)	82 (33-193)	84 (57-117)
Median number of doses of rituximab (range)	6 (2-6)	4 (2-6)

[Comparison of PH vs without PH]



[Figure 1- CD19+ recovery in PH versus non-PH cohort]

Five patients developed PH after rituximab; 4 of whom still require IVIG replacement 7 years later. Additionally, the patients with PH, despite recovery of B cells have low serum levels of IgM, median < 5mg/dl (< 5-358mg/dl), in addition to IgG deficiency versus a median of 95mg/dl (20-311mg/dl) in the non-PH cohort. The HCT recipients who recover IgG levels and respond to vaccination after rituximab, recovery of CD19+ B cells is rapid and occurs at median of 9 months (5-12 months) post treatment. In contrast, those with PH demonstrate recovery of B cells at a median of 12 months (6-50 months). Comparing B cell immunophenotype in 4/5 PH patients versus 7/11 without PH, both cohorts have overall reduction in switched memory B cells, median of 0.4% (0-1%) versus 2% (0.5-8.0%).

Conclusions: We report, 5/16 (31%) recipients post-HCT rituximab with a persistent antibody production defect despite recovery of CD19+ B cells. Both groups recover naive CD19+ B cell population, but are deficient in switched memory B cells. However, the PH patients have reduced levels of IgM, thus implying an overall B lymphocyte dysregulation, not solely an isolated defect in class switching. We will perform in vitro class switching analysis and further immunophenotype the B cells from patients with and without PH after rituximab. Aberrations may identify effects of rituximab on B cell niches in the bone marrow and the germinal center, which required for normal development.

Disclosure: Richard, O´Reilly- Atara Biotherapeutics Nancy, Kernan- Amgen, Merck, Johnson & Johnson, and Pfizer

P629

Effect of Serum Panel Reactive Antibodies on Allogeneic Hematopoietic Stem Cell Transplantation in Pediatric Patients: A Single-center Experience

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Background: Some of the studies suggest that in highly sensitized patients who have antibodies against human leukocyte antigens (HLA) before allogeneic hematopoietic stem cell transplantation (AHSCT), primary graft failure risk increases. These HLA antibodies which are called as panel-reactive antibody (PRA) may be caused because of previous blood transfusions or AHSCT. In this study, we aimed to determine the association of PRA with engraftment, chimerism and graft versus host disease (GVHD) in pediatric hematopoietic stem cell transplant patients.

Methods: In this study, 43 patients who had PRA positivity and went to AHSCT between October 2014 and November 2019 are investigated retrospectively. Fourty-two patients who were matched for diseases and PRA negative were taken as control group. Class I and Class II PRAs directed to HLA antigens were detected by Luminex System. In PRA-positive group, three types of treatment modalities were used. Methylprednisolone was administered at a dose of 0.5 mg/kg/day for 28 days starting from day -1. Rituximab was given at a dose of 375 mg/m2/day, at day -1. Plasmapheresis (PP) was performed two times, before conditioning regimen and at day -1. Both groups were compared in terms of graft failure, chimerism and GVHD.

Results: Median age of patients was 89.7 in months. Fourty-three (50.6%) of them were female. Both of the

groups were homogenous in terms of diagnosis, donor type, HLA match, stem cells source and ABO mismatch. The most frequent diagnosis was hemoglobinopathies (n=:36, 42.3%). In PRA-positive group, PRA Class I, II or both were detected in 14 (32.5%), 11 (25.5%) or 18 (42%) patients, respectively. Median value of PRA Class I±SD was 51.5±33.9% and PRA Class II±SD was 46±28.8%.

Thirty-eight patients received at least one of treatment modalities. Treatment strategy was decided according to the patient's underlying disease, donor type, level of PRA positivity and PRA class. Eighteen patients received only methylprednisolone, 3 patients received only rituximab, 2 patients underwent PP, 5 patients received methylprednisolone plus rituximab, 7 patients underwent PP plus methylprednisolone and 3 patients received all of three treatment modalities. Five patients who had low titer of PRA in Class II didn't take any treatment.

Poor graft function occurred in 6 (13.9%) patients in PRA-positive group and 5 (11.9%) patients in control group. There was no statistically significant difference in both groups in terms of myeloid engraftment, thrombocyte engraftment, chimerism, acute GVHD and viral infection frequency. The 100-day overall survival (OS) was 96.7% for the PRA-positive group and 90.4% for control group (p>0.05). The 1-year OS was 85% for the PRA-positive group and 83% for the PRA-negative group (p>0.05). The 5-year OS was 66% and 83% for PRA-positive and negative groups, respectively (p>0.05).

Conclusions: In conclusion, our experience suggests that PRA positivity does not influence the engraftment and survival. Further more comprehensive studies aimed at the influence of PRA on AHSCT in pediatric patients are needed.

Disclosure: The authors declare. that there is no conflict of interest.

P630

Single Centre Experience with Stem Cell Transplantation for Inherited Bone Marrow Failure Syndromes

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Background: Inherited bone marrow failure syndromes (IBMFS) are rare hematological disorders that associate physical abnormalities ineffective hematopoiesis and predisposition to cancer, accompanied by a range of congenital abnormalities. The most common are Fanconi Anemia (FA), dyskeratosis congenita (DC), Diamond Blackfan anemia (DBA), Shwachman-Diamond syndrome (SDS). Hematopoietic stem cell transplantation (HSCT) using related or unrelated donors is the only curative approach when severe marrow failure has established. The aim of the study was to analyze the results of HSCT in patients with IBMFS in a single center.

Methods: We performed retrospective study in pediatric patients with IBMFS admitted in Fundeni Clinical Institute between January 2000 and November 2019. Diagnosis and severity of IBMFS were based on hematological results, bone marrow biopsy and clinical findings. HSCT indication was established when patients developed moderate/severe aplastic anemia and became transfusion dependent. In case of DBA, SCT indication was established for steroid resistant disease. The donors were selected from family members or unrelated donors, 10/10 matched or haplo. Cconditioning regimens used: Fludarabine 120-150mg/m^2, Cy 20mg/kg, F-ATG 40mg/kg for with AF and DC receiving 10/10 graft from MUD/MSD, Fludarabine 140mg/m^2-Busulfan 1.2mg/kg x 2-Cy10 mg/kg x 4-F-ATG 40mg/kg for AF and haplo-TCR α/β depletion, F-ATG 30mg/kg, Thiotepa 10mg/kg, Fludarabine 160mg/m^2, Melphalan 70mg/m^2 for AF and haplo TCR α/β depletion and Busulfan 4.8mg/kg x 4, Fludarabine 150mg/m^2, Thiotepa 10mg/kg x 2, F-ATG 30mg/kg for DBA. GvHD prophylaxis : standard Methotrexate and CSA/Tacrolimus for MSD/MUD, and for haplo-TCR CSA and MMF, respectively. All parents signed informed consent forms.

Results: In our center, between 2000 and 2019, we had 30 patients with IBMFS: 17(56.7%) with FA, 9(30%) with DBA, 2(6.65%) patients with DC, and 2(6.65%) patients with IBMFS. We performed HSCT to 11 patients(36.66%): MSD 3 patients(2 with AF, 1 with DC), MUD 6 patients(5 with AF, 1 with DBA) and haplo TCR α/β depletion(2 with AF). Median infused cell dose was 6.75x10^6 CD34/kg. All patients(100%) engrafted for PMN(median=19.5, range: 10-29 days) and platelet (median 21.5, range: 11-46 days). 5/11 presented CMV reactivation: 4/11-Valganciclovir and Ganciclovir, 1/11-Valganciclovir and Foscavir, 3/11-BKV cystitis and required extensive hydration and Levofloxacin, 2/11-grade II-III acute skin GvHD, responded to topical treatment and low dose of corticosteroids. 2/11 developed grade III-IV intestinal acute GvHD, responded to high-dose corticosteroids.1/11 developed grade IV intestinal chronic GvHD(day +160), without response to high-dose

corticosteroids, MMF and later died on day221, due to infectious complications(severe pulmonary and cerebral aspergillosis). 1/11 patient had concomitant CMV disease and BKV reactivation, and received T-cell specific lymphocytes for both CMV and BKV, but died due brain haemorrhage. 1/11 presented severe CMV reactivation resistant to Ganciclovir associated with tuberculosis, followed by graft-failure and death. 8/11 patients(73%) are alive, with 100% donor chimerism. Median follow-up for HSCT patients was 515 days(31 days-8y 2mo).

Conclusions: We observed a low incidence of severe complications associated with low mortality rate in our study. If no compatible donor is available, other options should be considered. Close monitoring for viral reactivation of CMV and BKV should be performed, and also resistant disease should be considered.

Clinical Trial Registry: NA

Disclosure: nothing to disclose

P631

Time Course and Impact of Body Weight Change Early after Allogeneic Stem Cell Transplantation in Children and Adolescents

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Background: There has been little information on body weight (BW) change and its role in children and adolescents who received hematopoietic stem cell transplantation (SCT). The aim of this hospital-based retrospective study was to describe the time course of BW change early after allogeneic SCT and to evaluate its association with the clinical outcomes in children and adolescents.

Methods: A total of consecutive 130 allogeneic SCT recipients (median follow-up period, 86 months; median age at SCT, 7 years; 57% female; median baseline BW, 20.3 kg) who underwent transplantation between January 2004 and December 2018 at Kobe Children´s Hospital were included in this study. Patients who died within four weeks posttransplant were excluded. Baseline (TP-1), BW at day 0 (TP0), at two weeks (TP1), and at four weeks (TP2) posttransplant were obtained from the medical records.

Patients were analyzed in three groups determined by the BW gain between TP0 and TP2: group A (n = 43), BW gain less than -5%; group B (n = 60), BW gain within the range of -5 to 0%; group C (n=27), BW gain more than 0%. There were no significant differences between the groups in baseline characteristics of the patients.

Results: During the first four weeks posttransplant, BW loss was found in 104 of 130 (80%) patients. A significant BW decrease was observed between TP-1 and TP2 (TP-1 25.2±14.6 kg vs. TP2 23.7±13.5 kg, $P < 0.001$). There was also a significant reduction in BW between TP0 and TP2 (TP0 24.7±14.3 kg vs. TP2 23.7±13.5 kg, $P < 0.001$). A moderate negative correlation was detected between TP0-TP1 change and TP1-TP2 change ($r = -0.417$, $P < 0.001$). Overall, the probability of 5-year overall survival (OS) after SCT was 70.7%. The probability of 5-year OS was 74.4% in patients of group A, 75.0% in group B, and 55.3% in group C ($P = 0.086$). Subgroup analysis of patients with SCT from related donors (n = 75) confirmed a remarkable difference between the groups in the probability of 5-year OS (group A 85.7%, group B 67.3%, group C 56.2%, $P = 0.047$). Among the patients with reduced-intensity conditioning (n = 62), patients of group C had a lower probability of 5-year OS (group A 81.8%, group B 100%, group C 54.5%, $P = 0.003$). The overall cumulative incidence of 5-year transplant-related mortality and relapse of malignancy was 7.7% and 32.4%, respectively. The cumulative incidence of 5-year relapse was 20.0% in group A, 26.5% in group B, and 61.0% in group C ($P = 0.002$). There were no significant difference between the groups in the incidence of graft failure, hepatic sinusoidal obstructive syndrome, and acute and chronic graft-versus-host disease.

Conclusions: Early posttransplant BW loss was common in pediatric and adolescent allogeneic SCT recipients. Our results suggest that BW gain during the first four weeks after allogeneic SCT may be associated with an increased risk of posttransplant relapse and a reduced survival.

Disclosure: Nothing to declare.

P632

Autologous Hematopoietic Stem Cell Transplantation for Pediatric High Risk Ewing Sarcoma, A Single Center Experience

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Background: Ewing sarcoma (ES) is the second most frequent bone tumor of childhood and adolescence. It is a highly aggressive with survival of 70-80% for local disease and 30% for metastatic disease. Approximately 30-40% of patients with localized primary ES who initially achieve

remission experience disease relapses and have dismal prognosis using conventional chemotherapy (CC) only. Several studies reported the survival benefit of high dose chemotherapy with hematopoietic stem cell transplantation (HSCT) as consolidation treatment after CC in high risk ES patients.

Methods: Between 2011- 2018, 18 pediatric patients (14 males, 4 females) with median age of 14.7 years (range 7.75-22) suffering from metastasis to lungs (12) less than 90% necrosis (2) or relapsed (4) ES underwent autologous HSCT. Primary sites of disease were pelvis (5) spine (4) femur (3), scapula (2), tibia (1) ethmoidal and frontal sinuses (1) humerus (1) and fibula (1). Fifteen patients received conditioning regimen consisted of busulfan and melphalan with area under the curve monitoring of busulfan levels. Three patients who had contraindication for busulfan received treosulfan (2) or etoposide (1). Sixteen patients (88.8%) were in complete remission prior to transplantation. Two patients had a very good partial response with minimal residua in bones.

Results: Median number of CD34 positive cells per kg infused was $4.8x10^6$ (range 2.93-8.11). All patients engrafted with median time for neutrophil engraftment of 10 days (range 8-11) and for platelets engraftment of 13.5 days (range 9-26). All patients suffered from mucositis, 15 required total parenteral nutrition. None of the patients developed sinusoidal obstruction syndrome. Fifteen patients suffered from at least one episode of neutropenic fever treated with broad spectrum antibiotics. Five documented bacteremia occurred in 5 patients. (1 Pseudomonas aeruginosa, 2 Staphylococcus epidermidis,1 aeromonas hidrophila and 1 carbapenem-resistant enterobacteriaceae). Median hospitalization time was 20.5 days (range 15-47). All patients were alive 100 days following transplantation. Nine patients (50%) relapsed after transplantation (5 transplanted due to lung metastasis, and 4 due to relapsed ES). Median time from transplantation to relapse was 15 months (range 4-55). Three patients had local relapse and were successfully treated using radio chemotherapy, and the remaining six had relapse in multiple sites and could not be salvaged. Overall survival was 66% for a median time of 3.2 years (range 1-9), (75% for patients transplanted due to lung metastasis, 100% for those transplanted due to less than 90% necrosis and 25% for relapsed ES).

Conclusions: Autologous HSCT is a feasible treatment for pediatric high risk ES with acceptable toxicity using busulfan and melphalan as conditioning regimen, with overall survival of 100% on day 100 and 66% at a median of 3.2 years after transplantation. Patients who experience local relapse following HSCT could be salvaged as opposed to patients who relapsed in multiple sites. The efficacy of HSCT in pediatric patients with ES should be evaluated in larger randomized control studies.

Disclosure: Nothing to declare.

P633

Conditioning for Retransplantation from the same Donor after Partial Autologous Reconstitution in Patients with PID: Immunosuppression is not Required

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Background: Autologous reconstitution of myeloid cells after allogeneic hematopoietic stem cell transplantation (HSCT) in patients with primary immunodeficiencies (PID) is associated with incomplete immunological reconstitution or recurrence of the primary disease. T cells can remain- at least in part- of donor origin. Conditioning before a second HSCT from the same donor in this situation is supposed to preserve established donor t-cell function, cause limited toxicity but to allow stable myeloid engraftment.

Methods: In a retrospective analysis we reviewed data of seven consecutive pediatric patients with different PIDs (SCID n=3, CGD, Griscelli syndrome, Reticular Dysgenesis, Leukocyte Adhesion Deficiency I), who underwent allogenic stem cell transplantation between 2005 and 2016. After initial myeloid engraftment, all patients experienced partial or complete autologous reconstitution of myeloid cells with remaining donor t-cells.

Results: Second stem cell grafts were administered at 5 to 38 months after the initial transplantation. Patients received a conditioning regimen containing predominantly myelosuppressive drugs (Busulfan, Treosulfan, Thiothepa or Melphalan) or radioimmunotherapy avoiding additional immunosuppression by serotherapy before the administration of T-cell replete (n=2) or T-cell depleted (n=5) grafts from the same donor. Myeloid engraftment between day +13 to +22 was noted and associated with reduced toxicity. No acute (>II°) or chronic GvHD occurred. All patients survived with complete (n=5) or stable mixed (n=2) chimerism.

Conclusions: In summary these data demonstrate that a selective myelosuppressive conditioning regimen for retransplantation from the same donor after autologous myeloid reconsititution is a feasible approach to achieve stable myeloid engraftment with low toxicity, reduced treatment related mortality or infectious complications. In summary these data demonstrate that a selective myelosuppressive conditioning regimen for retransplantation from the same donor after autologous myeloid reconsititution is a

feasible approach to achieve stable myeloid engraftment with low toxicity or treatment related mortality.

Disclosure: Nothing to declare.

P634

Tocilizumab Treatment for CRS in Haploidentical Stem Cell Transplantation: A Single Center Experience

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Background: Tocilizumab is a monoclonal antibody directed against the IL6 receptor, and has recently been used in the treatment of acute GVHD and CRS in the context of haploidentical transplantation.

Methods: We present retrospective data of 4 pediatric haploidentical HSCT receiving therapy with tocilizumab between January and November 2019 in our Unit.

Results: All patients were diagnosed with hematological malignancies in 1st complete remission (3 ALL and 1 AML), and were submitted to haploidentical SCT (donors: mother in 2 cases, father in 1, and 1 sibling), with ages at the time of SCT between 2 and 15 years. All of them received a reduced intensity conditioning, with CD34+ positive selection and CD45RA+ depleted grafts. Only 1 of them developed acute GVHD (grade III), being the indication for treatment with tocilizumab, while in the other 3 cases tocilizumab was administered as a treatment of CRS/engraftment syndrome with persistent fever. The first dose was administered between 11 and 64 days after infusion (2 patients received a single dose, and the others received 2 doses). In all CRS cases the treatment was effective, while in the case of the patient with GVHD the treatment was interrupted due to toxicity. 3 patients presented hematological toxicity, two of them with a minimum number of neutrophils of 130 and 670 on the seventh and eighth day of treatment respectively, while the third patient presented a secondary graft failure (not completely attributable to tocilizumab). These 3 same patients presented liver toxicity, with a maximum number of AST/ALT 121/168, 130/312 and 1007/520 U/L respectively, between the third and fifth day after tocilizumab first dose, with no increased bilirubin or coagulation failure. The patient with GVHD died due to complications related to SCT (GVHD, infection, TA-TMA), while the other 3 patients remain alive in complete remission, with a follow-up ranging between 7 and 11 months after SCT. The patient suffering from graft failure is currently under conditioning for a 2nd TPH.

Conclusions: Tocilizumab is an effective treatment against cytokine release syndrome in haploidentical SCT, but special attention should be paid to its possible hepatic and hematological toxicities. Future prospective studies are warranted to assess its safety and efficacy.

Disclosure: Nothing to declare.

P635

Idiopathic Pneumonia Syndrome (IPS) After Peripheral Blood Stem Cell Transplantation from Unrelated Donor for Hurler Syndrome (Mucopolysaccharidosis Type 1) Successfully Treated with Etanercept and Steroids

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Background: A 16 months old girl with MPS1 with typical facial and skeletal deformities, macrocephaly with mild hydrocephalus, mild mitral insufficiency, corneal opacities, hearing loss and hepatosplenomegaly, on enzyme replacement therapy for 4 months received a transplant from a 9/10 HLA-matched unrelated female donor (February 2019). The graft comprised PBSC with CD34 positive selection and CD3/CD19 depletion (27 x10^6 CD34+/kg, 1.27 x10^5 CD3/kg). CMV serostatus donor positive/recipient negative. Conditioning was administered according MPS-HCT2005 Protocol: fludarabine/busulfan/ melphalan/ATG. GvHD prophylaxis: MMF. Post-transplant complications: Adenovirus PCR in stool on day 10 treated with 2x Cidofovir. Engraftment: day +12 neutrophils, day +18 platelets. MMF was stopped on day +19 by 90% chimerism. No GvHD. She was discharged on day +30. She regularly received PCJ-prophylaxis. On day +37 post-HSCT, she presented in good clinical condition with low-grade fever, rhinitis and normal auscultation of lungs. CRP was 6 mg/dl; nasopharyngeal swab multiplex PCR was positive for Rhinovirus. PCR-negative for Mycoplasma. Blood PCR for Adenovirus, EBV, CMV and HHV-6 were negative. Blood culture, Galactomannan in blood, as well as urine antigen Legionella tests were negative. Empiric antibiotic therapy with piperacillin/tobramycin/azithromycin was started. On day+41 fluconazole was changed to ambisome. On day +43 she progressed rapidly to acute respiratory insufficiency requiring high flow 02 therapy with nCPAP (90% Fi02, 15 L/Min) and became transfusion-dependent (red cells/platelets). High-resolution chest-CT (HRCT) revealed diffuse interstitial lung disease with ground-glass opacities

and cardiomegaly. Antibiotic treatment was switched to meropenem/vancomycin. Echocardiography on day +45 showed elevated pulmonary artery pressure 70 mmHg (N 8-20 mmHg), right atrial and ventricle dilation, tricuspid insufficiency, normal left ventricular function. She developed arterial hypertension, requiring clonidine, enalapril and low dose of furosemide 2 mg/kg/day. She had no clinical signs of GvHD, normal kidney function, no proteinuria. Normal plasma levels of D-dimer, fibrinogen and soluble terminal complement complex activity (sC5b-9), LDH was 1.5 folds increased. IPS was suspected at day +47.

Methods: High dose prednisolone 10 mg/kg/day was started. As the Patient was critically ill, we refrained from bronchoscopy with BAL, wich would have been desirable in case of lung disease after HSCT. After three days, no significant reduction of ventilation parameters was observed. Prednisolone dose was decreased to 2 mg/kg/day; etanercept s.c (0.4 mg 2x/week) was initiated on day +51.

Results: After three days, she rapidly improved with no residual signs of pulmonary hypertension in echocardiography and normalized platelets count. One week later, supplemental oxygen could be stopped. She received in total six doses of etanercept while steroids could be rapidly tapered. HRCT on day +70 showed normal lungs. Currently, 10 months after HSCT she is alive and well without pulmonary compromise.

Conclusions: Mortality from IPS ranges from 60-80% despite treatment with high-dose steroids. TNF-α is crucially involved in inflammation and immune responses in the lungs post-HSCT. Etanercept, a TNF-α inhibitor, has been postulated to improve the Overall survival in IPS patients. Here we present a pediatric case, where IPS resolved after Treatment with etanercept and Steroids, suggesting that this combination therapy contributed to it s Resolution in this case.

Disclosure: Nothing to declare.

P636

Effect of Desensitization Protocol on Transplantation Success in Children with Anti-HLA Antibodies

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Background: Anti- HLA immunization is a severe complication of allogeneic hematopoietic stem cell transplantation (Allo-HSCT) that increase the risk of primary graft failure (PGF). For this reason, it is now strongly recommended to screen recipients for anti-HLA antibodies (AntiHLA-Ab) prior to Allo-HSCT. We aimed to report effect of desensitization treatment on engraftment and chimerism in patients who had antiHLA-Abs before allo-HSCT.

Methods: Anti-HLA antibodies test were studied (LifeCodes, Immucor Transplant Diagnostics Inc) according to the manufacturers instructions and analysed by Luminex and XY platform (LabPlus Fluoro Analyser, Luminex Corporation, USA). Treatment regimen was a combination of plasmapheresis, rituximab, antibody adsorption with buffy coat suspansion, total body irradiation (TBI) and bortezomib according to the Consensus Guideline of EBMT (MD Anderson Cancer Center protocol). Following desensitization, a myeloablative conditioning regimen consistent with the diagnosis was given to the patients. For graft versus host disease (GVHD) prophylaxis tacrolimus and mycophenolate mofetil were used.

Results: Five children who had high-titer antiHLA-Ab (MFI>1000) included in the study. The clinical features and transplant results patients are presented in Table 1. Four

Patient No	Age (year)	Gender	Primary diagnosis /HSCT type	Anti-HLA class 1 MFI before/ after HSCT (HLA loci)	Anti-HLA class 2 MFI before/ after HSCT (HLA loci)	CD34 count (x 106/ kg)	Myeloid Engrafman (day)	Platelet Engrafman (day)	1. month chımerısm (%)
1	11,5	M	FAA/MSD	Negative/ Negative	4577/2404 (HLA DQB1)	7,42	13	33	99,1
2	6	M	FAA/MSD	15478/3267 (HLAB48)	19247/4342 (HLA DQ9)	10	14	32	97,1
3	3,8	M	JMML/ HAPLO	Negative/ Negative	8349/2020 (HLA DQ7)	11,27	13	50	99,9
4	3,5	F	CEP/MSD	3562 /Negative (HLA B62)	Negative/ Negative	8,02	Failure	Failure	Graft failure
5	6,5	F	TM/MSD	5074 /1788 (HLAB27:08)	Negative/1366 (DQB1 03:02)	5,11	14	19	NA

[Table1. Clinical features and transplant results of patients]

transplantations were from HLA-matched siblings (MSD) and 1 from his haploidentic mother. Out of 5 patients, 3 had second transplantation due to PGF. Indications for HSCT were Fanconi aplastic anemia, congenital erytropoetic porfiria, Pesaro Class 2 thalassemia major in MSD transplantations and juvenil myelomonocytic leukemia in haploidentic transplantation. Two patients had class 1, two patients had class 2, and one patient had both class 1 and 2 antibodies. None of the patients had donor specific AntiHLA-Abs. Although MFI of antibodies decreased in all patients, MFI values < 1000 has been achieved in only one patient. However, engrafment could not achieved only in this patient whose MFI values decreased to < 1000.

Conclusions: There is no consensus regarding the appropriate approach for children who had high titer AntiHLA-Abs prior to Allo-HSCT. In this study, we adjusted EBMT regimen for haplo-HSCT for our patients who had high-titer AntiHLA-Abs. The regimen has been successful in 4 patients. We believe, drawing a strong conclusion could be possible by including more patients in the study.

Disclosure: Nothing to declare.

P637

Outcome of Allogeneic Stem Cell Transplantation (ALLOHSCT) with Different Intensity Conditioning Regimens in Infant AML

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Background: AML in children aged 0-2 years (i.e., infants) is different both in prognosis and treatment strategy. AlloHCST is a potentially curative option for these patients however indications are under discussion due to the high risk of transplant-related mortality (TRM) which is especially associated with myeloablative conditioning (MAC). Reduce intensity conditioning (RIC) is probably an option to avoid severe complications but there is no sufficient data about RIC efficacy. **Aim:** to evaluate outcomes of alloHCST in infant AML depending on intensity conditioning regimen (MAC vs RIC)

Methods: The data of 40 children with infant AML underwent alloHSCT between 2004 and 2018 were analyzed. Overall, 28 pts. had the 1st or 2nd remission (CR), 12 pts had an active disease (AD). Median age at the moment of diagnosis 1 yo (2 month-2 yo), at the moment of alloHCST - 2 yo (11 month - 4 yo). MAC based on busulfan (Bu) (10-16 mg/b.w.) received 16 (57%) patients in CR, 7 (58%) with AD, on treosulfan - 4 (14%) pts in CR. RIC based on melphalan received 8 (28%) pts in CR, 5 (42%) pts with AD, based on Bu (8 mg/b.w.) - 1 (3%) pts in CR. Prophylaxis of aGVHD was: ATG 16 (40%) or PTCy - 22 (55%) pts plus CsA - 19 (47%) or tacrolimus ± sirolimus - 21 (53%) pts that depended on donor [related - 4 (10%), unrelated - 22 (55%), haplo - 14 (35%)]

Results: At the median follow up 3,5 years OS in all pts is 70%. In the cohort of CR pts after MAC OS is 80% vs 87% after RIC (p>0,05), in patients with AD OS is 42,9% vs 40% accordingly (p>0,05). RFS in CR pts after MAC is 80% vs 87% after RIC, in pts with AD is 57% vs 40% accordingly (p>0,05). Graft-versus-host-disease free/relapse free survival (GRFS) in CR after MAC 36% vs 62% after RIC, in pts with AD is 42% vs 40% accordingly (p>0,05). Cumulative relapse incidence (CRI) in CR pts after MAC is 22% vs 12,5% after RIC, in pts with AD is 54% vs 62% accordingly (p>0,05). TRM in CR pts after MAC is 22% vs 12,5% after RIC, in pts with AD is 28% vs 0% accordingly (p>0,05).

Conclusions: RIC efficacy is equal to MAC in infant AML on the basis of OS, RFS, GRFS, CRI and TRM and especially has to be considered in CR1. Potentially RIC may reduce long-term severe side effects of alloHSCT correlated with toxic effect of conditioning regimen intensity.

Disclosure: Nothing to declare.

P638

Higher Incidence of CMV and BKV Reactivation in Haploidentical Transplants Comparative to MUD or MSD Transplants - Single Centre Retrospective Analysis

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Background: Viral infections (CMV, BKV, EBV) in allotransplant patients are frequent complications. We evaluated CMV and BKV reactivation after allogeneic HSCT in order to compare the incidence, severity, risk

factors and outcome in patients receiving MUD vs MSD vs Haplo, in a single center.

Methods: We performed retrospective analysis of paediatric patients with viral reactivation admitted at Fundeni Clinical Institute between January 2013 - November 2019. Viral reactivation was based on PCR from plasma (CMV, EBV, BKV) and urine (BKV), clinical signs, imaging. Conditioning regimens were used according to disease. GvHD prophylaxis were standard methotrexate + CSA/tacrolimus +/- ATG, posttransplant cyclophosphamide and MMF + tacrolimus or MMF/CSA/tacrolimus in haplo recipients. All parents signed informed consent forms.

Results: We performed 71 procedures of allogeneic HSCT to 69 patients: MUD (52%), MSD (27%), Haplo (21%). Patients diagnosis were: ALL-16 patients(23.2%), AML-18 patients (26.1%), JMML-4 patients(5.8%), Hodgkin lymphoma-4 patients(5.8%), SAA-12 patients (17.4%), MDS-3 patients(4.4%), Diamond Blackfan Anemia-1 patient(1.4%), Fanconi Anemia-9 patients (13.1 %), Wiskott-Aldrich Syndrome-1 patient(1.4%), Congenital dyserythropoietic anemia-1 patient(1.4%). We excluded 2 patients due to early death. 27/67 (40.29 %) presented BKV reactivation, 22/67 (32.83%) had CMV reactivation, 6/67 had EBV (8.9%) reactivation. 10/67 had concomitant CMV + BKV, 2/67 had concomitant CMV + EBV, and 4/67 presented concomitant CMV, BKV and EBV. BKV reactivation incidence was 53.33% in haplotransplants, 37.83% in MUD and 21.05% in MSD. BKV symptoms were: hematuria 12/27(3/27 severe), dysuria(18/27), polakyuria(11/27), CNS symptoms(2/27), 7/27 had no symptoms, but with BKV in urine. Symptoms appeared between d10 to d197(median 28.5 days), lasted 4 to 43 days(median 12.5 days). 2/27 patients presented severe cytokine release syndrome (CRS). BKV PCR levels in urine at onset ranged from 100 to 21.49 $x10^9$ copies/ml (median 284 $x10^6$), plasma levels ranged from 0 to 6546 copies/ml(median 915.5). 1/27 had concomitant severe intestinal GvHD, 3/27 had grade 2-3 skin GvHD before BKV reactivation, 2/27 had severe skin and intestinal GvHD after BKV reactivation, 1/27 developed mild chronic GvHD afterwards.12/27 patients had US(thick bladder mucosa), 6/27 patients presented bladder clots. Treatment were: extensive hydration(22/27 patients), Levofloxacin(25/27 patients), Cidofovir(1/27 patients), r-FVII(3/27 patients), supportive treatment(7/27 patients), 2/27-continuous bladder irrigation, 1/27-emergency bladder electro-cauterization, 3/27-acute kidney injury. CMV incidence was 46.66% in haplotransplants, 35.13 % in MUD and 9.09 % in MSD. 6/22 patients with CMV donor incompatibility. CMV appeared from d1 to d69(median d27), PCR levels-from 20 to 945000 copies(median 255.5), became negative from d26 to 202(median d61) in 17/22 patients. 5/22 patients-digestive symptoms, 4/22-neurological symptoms, 13/22-no symptoms. Treatment: 8/22 patients-Valganciclovir, 3/22-Valganciclovir+Ganciclovir, 3/22-Valganciclovir+Foscavir, 5/22-Ganciclovir, 2/22-Foscavir, 1/22-no treatment. 2/5-Foscavir toxicity (electrolyte disorders), 3/22 patients died due to CMV encephalitis, 2/22 died due to other infections but with concomitant CMV.

Conclusions: BKV and CMV reactivation are common complications of HSCT, with higher incidence in haplotransplants. BKV incidence in our study was 40.29%, HC appeared in 60% of patients. CMV incidence was 32.83% in our study, with 9.09% in MSD. 16/22 patients responded to treatment and became CMV negative. Further studies are needed in order to completely understand the pathophysiology and mechanisms of viral reactivation in HSCT recipients.

Disclosure: Nothing to disclose

P639

Use of Polyclonal Igm-enriched Immunoglobulins for the Treatment of Septic Episodes in Children with Oncohematological Diseases

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Background: Children with oncohematological diseases are at high risk of infections. Fever represents infection's typical sign and it appears often during neutropenic periods. The use of IVIg with high titer of IgM (Pentaglobin) in addition to antibiotics could be indicated in these patients but there is a lack of studies on its potential benefit. The primary goal of our study was therefore analysing the characteristics and outcome of febrile episodes treated with Pentaglobin. The secondary goals were analysing possible survival risk factors and frequency of bacteremia due to drug-resistant strains.

Methods: Data were retrospectively analysed. Inclusion's criteria were presence of fever (T >38°C) and administration of Pentaglobin within 72 hours from fever onset. Study period goes from January 2011 to March 2019 and two Italian sites participated.

Results: 70 febrile episodes (in 63 patients) were identified. In 66% of cases children had an acute leukaemia or non-Hodgkin lymphoma and in 37% patients had received an HSCT. 57% of episodes occurred after chemotherapy for a first diagnosis of malignancy, whereas 33% occurred after

HSCT. The median duration of fever was 5 days. In 89% of cases patients had a severe neutropenia (ANC < 500/mm^3) at fever presentation. Hypotension and hypoxemia arose in 26% and 21% of episodes, respectively; moreover, 20% of episodes required the admission of patient to ICU and 20% necessitated the administration of inotropes. Signs of localized infection, mostly pulmonary, was found in 44% of episodes. Blood cultures were positive in 40% of cases and the most frequent isolated agents were Gram negative bacteria. The frequency of antibiotic resistance within Gram negative strains was 26%. In 69% and 30% of episodes a first line antibiotic therapy for Gram negative non ESBL-producers and ESBL-producers was respectively used. Only in 2 cases a monotherapy was initially set up, whereas in 68 (97%) episodes a broad-spectrum antibiotic combination was administered. An escalation of empiric antibiotic therapy within five days from its start was made in 37% of cases and a de-escalation within seven days in 7%. An antifungal therapy was set up in 54% of episodes. Pentaglobin was started within 24 hours from fever onset in 57% of episodes, between 24 and 48 hours in 34% and between 48 and 72 hours in 9%, mainly (83%) at the standard dosage of 5 mL(250 mg)/kg/die for three consecutive days. Pentaglobin-related allergic reactions occurred in 3 (4%) episodes. Overall, 30-day and 90-day mortality was 6% (n=4; OS 94%) and 13% (n=9; OS 87%), respectively. Infection-attributable mortality resulted 8.6% (n=6). Risk factors for 90-day mortality ($p< 0.05$) were: hypotension and hypoxemia at fever presentation, admission to ICU, use of inotropes, presence of localized-organ-infection signs and escalation of antibiotic therapy within five days.

Conclusions: Treatment of febrile episodes with Pentaglobin in oncohematological children has been shown feasible and well tolerated. The outcome, both in terms of overall and infection-related mortality, seemed to be more favourable compared with other studies. These data show that adjuvant therapy with Pentaglobin deserves further assessment of efficacy by prospective randomized studies.

Disclosure: Nothing to declare.

P640

Paediatric Bone Marrow Transplant Care on BMT versus NON-BMT Paediatric Wards

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Background: Growing demands on Paediatric Bone Marrow Transplant (BMT) services require patients to move to general wards to make space on BMT wards. Inappropriate environment and poor communication are problems when caring for patients on inappropriate or non-BMT wards. BMT is well researched in the literature, but there is no information relating to BMT care in non-specialist areas.

A service evaluation reviewed the Paediatric BMT service at our centre.

Methods: The standard hospital satisfaction questionnaire was modified. A parent and staff questionnaire was compiled, split into 3:

1. Ward environment (privacy, noise, time taken to answer call bell, comfort)

2. Communication and interaction from the team (condition clearly explained, consistent advice, daily ward rounds, sufficient time for questions, team knows child, get advice quickly)

3. Pharmacist's involvement in care.

Questionnaires were anonymous. Staff questionnaires were distributed to nurses, pharmacists, healthcare assistance, play specialists, social workers, physiotherapists and teachers.

Results: Twenty parent, and seventy staff questionnaires were distributed. Response rate was 70% and 62% respectively.

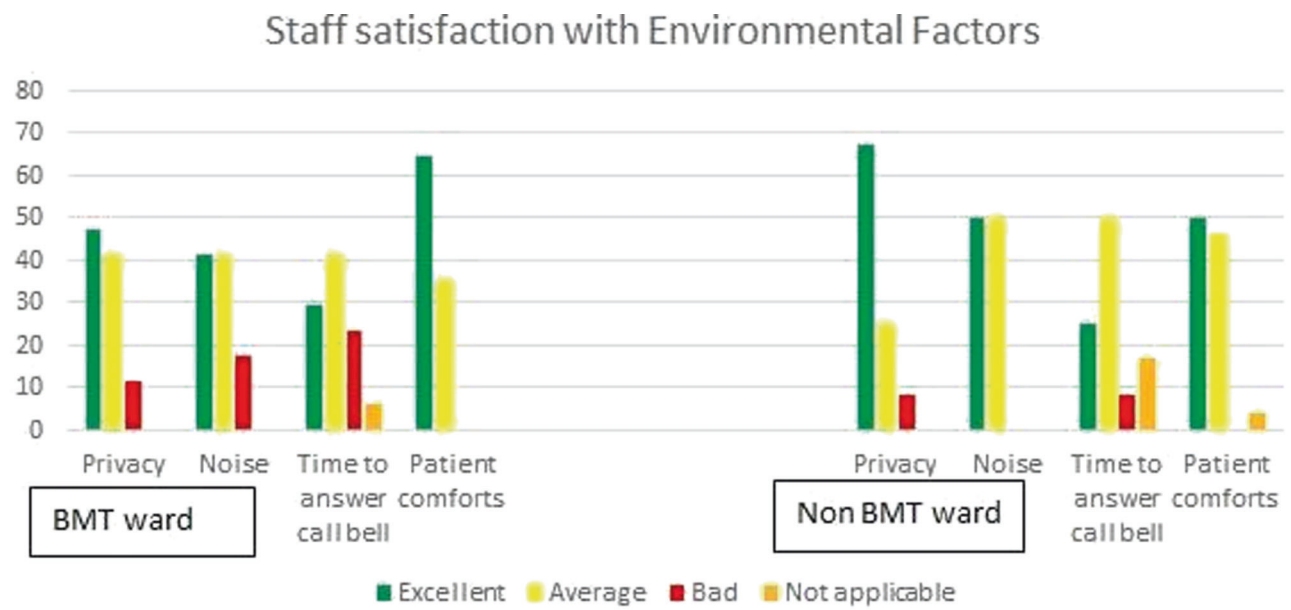
Parent's satisfaction: Environmental factors were rated excellent or average on BMT and non-BMT wards. No one was dissatisfied. All parents were satisfied with communication and interaction on the non-BMT ward. Most parents on the BMT ward were satisfied with communication, 14% felt there was not enough time to ask questions to doctors.

38% of parents on the BMT vs 29% on non-BMT wards said there was enough pharmacist involvement in their child´s care. 12% on BMT vs 29% on non-BMT wards said there was not enough involvement and 50% on BMT vs 42% on non-BMT wards said pharmacist's involvement was irrelevant to care.

Staff satisfaction: Environmental factors, especially noise, privacy and time to answer call bell, were considered by staff on the BMT ward to be bad in some cases, and worse on the BMT than the non-BMT ward (Figure 1). More staff on BMT ward considered patient comforts to be excellent but staff on non-BMT wards considered patient comfort excellent or average.

Staff ranked each aspect of communication higher on the BMT than the non-BMT ward, however, the staff on non-BMT wards were more than 50% satisfied with all aspects.

Staff on the BMT ward were 100% satisfied that pharmacists had enough involvement. On non-BMT wards 60%



[Figure 1: Staff satisfaction with environmental factors]

felt pharmacist's involvement was adequate, 6% felt there was not enough pharmacist's involvement. 34% felt that pharmacist's involvement was irrelevant.

Conclusions: Staff were less satisfied with environmental factors on the BMT ward, but more satisfied with communication than on non-BMT wards. Further studies are required to determine and address issues causing dissatisfaction, and investigate parental opinion that pharmacists are not involved enough and where increased involvement would be valued. Additionally, many parents and staff do not view pharmacy involvement in care as relevant. Further studies are required to determine reasons for this, including lack of understanding of role, and poor visibility on the ward.

Disclosure: Nothing to declare.

P641

Non-white Hispanic Ethnicity as a Risk Factor for Sinusoidal Obstruction Syndrome after Hematopoietic Transplant

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Background: Sinusoidal obstruction syndrome (SOS) is a hematopoietic stem cell transplant (HSCT) complication with high morbidity and mortality. It is important to identify risk factors to facilitate prophylaxis and early treatment.

Methods: We assessed the incidence of moderate-severe SOS in 126 pediatric patients diagnosed with hematologic malignancies that underwent haploidentical HSCT between 2007 and 2017, to establish the main SOS risk factors.

The median age in our sample was 9 years (1-19) with 85 males. In recent years, an increase of patients from Latin America has been observed in our unit, so that 31 children were non-white Hispanics. Sixty-nine patients had acute lymphoblastic leukemia (ALL) or lymphoma and sixty-five acute myeloblastic leukemia (AML) or myelodysplasic syndrome (MDS). Thirty-four were in 1st complete remission (CR), 51 in 2nd CR and 49 in advanced disease.

SOS was diagnosed using modified Seattle criteria and it was retrospectively validated using the new system proposed by the EBMT.

Results: Seven out of 134 evaluated transplants met the SOS criteria with a cumulative incidence of 5.22%. All of them were treated with defibrotide and six patients responded. There was only one death due to multisystem organ failure by SOS.

SOS risk factors we analyzed in this fairly homogeneous population showing that ethnicity had become in the main risk factor (17.52% in non-white Hispanic vs 2% in Caucasians, p=0.029) beside donor KIR genotype which difference is almost the statistical significance level(12.5% in A genotype vs 3.6% in B genotype, p=0.078).

In the logistic regression analysis, non-white Hispanic origin increases SOS risk nearly five times (HR: 4.94, 95% CI: 1.1-23.41, p = 0.04). When we compared the Caucasian

and Hispanic population, the only difference was an increase in A genotype donors in the Hispanic group (p=0.0035).

Day +100 transplant related mortality (TRM) was 8% in patients without SOS versus 57% in patients with SOS (p = 0.0001). With a mean follow-up of 4 years, overall survival was 53±5%.

Conclusions: SOS is an important cause of morbimortality after HSCT. We analyzed the incidence of moderate-severe SOS in children that underwent haploidentical HSCT finding that non-white Hispanic origin increases SOS risk nearly five times.

About hepatic CYP2B6 expression, striking differences among different ethnic groups were observed. This inter-ethnic variability in genetic polymorphisms frequencies for metabolizing enzymes could influence transplant toxicity, such as SOS. Although the Latin America population is continuously growing, they are underrepresented in pharmacogenetic studies.

We have also found an increase of KIR A genotype in donors of patients with SOS. The role of the donor KIR genotype in post-transplant toxicity, including SOS, should be analyzed.

In conclusion, pharmacogenetic studies in HSCT setting should include Hispanic population which is underrepresented. In our experience, Hispanic ethnicity is a main risk factor of SOS and it could be considered as an indication for defibrotide prophylaxis. More studies would be necessary to analyze ethnicity role in SOS.

Disclosure: Marta Gonzalez Vicent and Miguel Angel Diaz served as consultants to Jazz Pharmaceuticals.

P642

Pneumatosis Intestinalis as a Rare Post-transplant Complication in Pediatric Patients

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Background: Pneumatosis intestinalis (PI) has been described as a rare but severe complication following bone marrow transplantation. Therapeutic management is mostly conservative, but remains a challenge in cases of acute abdomen.

Methods: In a retrospective analysis, we reviewed data of two pediatric patients with chronic granulomatous disease (CGD) who developed PI following allogeneic bone marrow transplantation.

Results: Patient 1 was diagnosed with an X-linked CGD at age four years, following recurrent episodes of fever and colitis. At age fourteen, he underwent bone marrow transplantation after myeloablative conditioning (MAC) with busulfan, fludarabine and thiotepa from a 9/10 matched unrelated donor, resulting in complete donor chimerism. Nine months post-transplantation, he presented with severe upper abdominal pain and haemorrhagic diarrhea. A thoracic X-ray led to the incidental finding of free abdominal air. An emergency diagnostic laparotomy showed PI of the entire colon, but no perforation. The patient received intravenous antibiotic treatment and was kept on total parenteral nutrition for 20 days, which led to a resolution of clinical symptoms. Stool samples were negative for any pathogens and a colonoscopy showed no evidence of intestinal GvHD. At the time of diagnosis of PI, the patient was treated with prednisolone (1mg/kg), mycophenolic acid, tacrolimus and ruxolitinib for GvHD of the skin. Ruxolitinib was stopped subsequently. Unfortunately, the patient died at age seventeen due to respiratory failure following a systemic adenovirus infection with pneumonia.

Patient 2 was diagnosed with a sporadic form of CGD at age two years, following an episode of fever, cervical lymphadenopathy with abscess formation and recurrent respiratory infections suspicious of Aspergillus. Subsequently, he underwent bone marrow transplantation from a 10/10 matched unrelated donor after MAC with with busulfan, treosulfan and thiotepa, resulting in complete donor chimerism. On day +125 post-transplantation, a follow-up chest CT scan detected PI and free abdominal air as an incidental finding. Clinically, the patient remained well without any abdominal symptoms. He was kept on total parenteral nutrition for few days, and received oral metronidazole and colistine. Stool samples were negative for any pathogens. At the time of diagnosis, the patient was treated with tacrolimus and ruxolitinib for GvHD of the skin; prednisolone had been applied at 1 mg/kg and stopped after reduction two days before. Rixulitinib was discontinued following PI. A CT scan 2 months later showed a complete resolution of the previous findings. Currently, the patient remains well 12 months post-transplantation without any relapse of PI.

Conclusions: We present two pediatric patients with CGD who developed PI following allogeneic bone marrow transplantation. Both cases confirm the previously described association of PI with GvHD and intense immunosuppression. While conservative management was successful in one asymptomatic patient, an emergency diagnostic laparotomy could not be avoided in the other patient due to acute abdominal pain. In conclusion PI is a rare, potentially life-threatening but mostly benign complication after HSCT. Due to unclear pathogenesis and rare appearance, therapeutic guidelines do not exist but microbial decontamination, intravenous antibiotic therapy and intermittent total

parenteral nutrition should be considered for conservative management.

Disclosure: Nothing to declare.

P643

The Challenges and Outcomes Surrounding Intravesicular Cidofovir Administration - A Paediatric Pharmacy Perspective

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Background: Intravesicular cidofovir (IC) is a treatment option that may be considered to treat BK virus (BKV) associated haemorrhagic cystitis (BKHC) in paediatric patients post allogeneic haematopoietic stem cell transplantation (HSCT). Symptoms such as persistent dysuria accompanied by haematuria are not only debilitating for the patient but are also associated with an increase in long-term morbidity. Patient X, a 9-year-old female who underwent an 11/12 matched unrelated donor HSCT for Fanconi Anaemia with Myeloid Transformation. On day 19, she developed BKHC with 1.4 billion BKV copies/mL in urine. She was consequently started on renal dose intravenous (IV) cidofovir as per local guidance as her creatinine had risen a third from her baseline - another common symptom of BKV. Despite IV therapy which in itself is renally toxic the patient's renal function continued to decline and symptoms worsened. It was decided on day +44 to initiate IC.

Methods: There is very limited information on paediatric dosing in this indication via this route as well as administration challenges. The first step was to conduct a literature review to find evidence for an appropriate dose for this indication and to see if there was any information to determine that this route would indeed be safer for the kidneys. Information was also extrapolated from adult studies but for a paediatric patient as parameters such as bladder size and the amount of drug in millilitres will vary for a smaller bladder size. After a dose was determined, the next challenge was to ensure this could be administered safely and effectively. This had not been administered before on the inpatient ward and our cross-site aseptic unit had not formulated this before. Therefore, the procedure had to be locally risk assessed and working procedures such as label changes, stability in a syringe instead of a bag and the transfer across site of a medication treated as a cytotoxic within the trust had to be considered in order to formulate cidofovir for the intravesicular route. Consequently, the administration risks were discussed with the nurses and they were given administration instructions. In addition to this, the drug was appropriately prescribed on the electronic prescribing system.

Results: Five days after administering IC the patient no longer complained of pain, discomfort or dysuria. Although there was a degree of haematuria, this had improved with minimal blood clots. The patient's symptoms continued to improve until BK cytotoxic T-Lymphocytes (CTLs) were administered on day +77.

Conclusions: IC proved to be a useful holding measure whilst obtaining BK CTLs, alleviating the severe symptoms experienced by this patient. This case was an apt example of the challenges faced by paediatric pharmacy to ensure novel therapies are safely and effectively administered for a complex cohort of patients. The multi-disciplinary approach and effective communication between health care professionals ensured the best treatment outcomes for this patient.

Clinical Trial Registry: N/A

Disclosure: Nothing to declare.

P644

Haploidentical Stem Cell Transplantation (HAPLO-SCT) with Post-transplant-HD-Cyclophosphamide for Relapsed B-lymphoblastic Lymphoma (B-LBL) with MLL-rearrangement in 1 Y.O. Child: Clinical Case

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Background: We observed child of 6 month with an atypical manifestation and course of B-LBL: with soft tissues infiltration in parietal region. According to the literature, this manifestation of V-LBL (extranodal and extramedullary) as also in this age is very rare.

This was reason for difficulties on diagnostic stage in another center: the case was diagnosed as B-cell NHL by histology and treated according to Protocol NHL-BFM 2003 (AA-BB-AA-BB). After short time of remission (5 months) patient relapsed and came for further treatment to BMT-department of Pediatric Oncolohematological Center of National Children's Hospital.

Methods: A 1 y 3 months old girl was diagnosed as relapsed in primary region B-LBL but also with bone marrow and thymus involvement and spread to the roots of the lungs, tumor mass in the subphrenic space, retroperitoneal space at

the level of the pancreas infiltrating mesentery of the small intestine, small pelvis (uterus, left ovary).

Diagnostic signs included:

- blast cells in PB

- blast cells in BM: the leukemic cells population (18%) carried an immunophenotype corresponding to the common-ALL type (CD45+(100%); CD38+(94%); HLA-Dr+(82%); CD10+(52%); Anti-TdT+(43%); CD19 +(100%); CD22+(81%); cCD79a+(93%); CD58+(91%) CD20-.

- Molecular cytogenetic study of BM: revealed MLL-gene rearrangement

The patient received treatment by ALL-Rez-BFM-2001 Protocol (F1, F2, protocol II-IDA) and achieved 2nd CR BM FC=MRD negativity; as also MLL-rearrangement negativity in BM by FISH.

Then patient had haplo-SCT with post-transplant-HD-Cyclophosphamide while she had no HLA-identical family donor.

Results: The patient received haplo-SCT in November 2017 from mother as donor SC with BM was used for collection: TNC $2.4x10^8$/kg, CD34+ $2,9x10^6$/kg, CD3 $5.4x10^7$/kg, CD56+ $0.053x10^8$/kg.

We used conditioning regimen FLAME-Flu 150mg/m^2 +CCNU 300mg/m^2 (p.o.) + ARA- C 4000mg/m^2+ VP-16 1000mg/m^2+Mel 140mg/m^2 with post-transplant-HD-cyclophosphamide (Cy (50mg/kg) on days +3 and +4). Cyclosporine A (CyA; 3mg/kg/d i.v., then 6 mg/kg/d p.o. adjusting for blood levels 200-400 ng/ml) and mycophenolate mofetil (MMF; 15mg/kg two times daily per os) were started on day+5. MMF was discontinued on day+35.

Pt achieved full engraftment; neutrophil up to D+17; RBC up to D+19; platelet up to D+34.

The patient had complete donor chimerism in PB and BM and CR (MRD negative) in Days +30, +60, +100, +180, +365.

Pt received anti-microbial prophylaxis according to institutional practices.

Post-transplant complications:

Toxicity - intestinal IIIgr, infectious - IVgr (paraproctitis, pneumonia), dermal - IIIgr.

D+56 aGVHD gr.3: skin, gastrointestinal tract, BM (full resolution on therapy with methylprednisolone 2mg/kg, after the withdrawal of methylprednisolone there was a reversal, in therapy - MMF, Basiliximab; full resolution D +100). Immunosuppressive therapy canceled for a D+110. D+343 chronic GVHD: skin, BM, febrile, gastrointestinal, treated with methylprednisolone and Rituximab#4.

At the moment (2y1mo) girl is alive, in CR and had complete donor chimerism in PB and BM. She has extensive cGVHD, receives immunosuppressive therapy CsA and taking a photophesis course.

Conclusions: HLA-haploidentical HSCT with post-transplant high-dose cyclophosphamide is feasible and effective in children with relapse B-lymphoblastic Lymphoma.

Reason for a-GVHD and cGVHD in this case was connected with high numbers of transfusions in first line of therapy (not always with leukodepleted products).

Disclosure: Nothing to declare.

Regenerative medicine

P645

Marrow Derived Cells Bring a Long Lasting Relief When Injected Intraarticularly to the Joints with Degenerative Arthritis

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Background: Bone marrow cells enriched in the mononuclear population improves the function of the hip and knee with degeneration and cartilage damage.

Methods: In continuation of our study on the potential of marrow cells in regeneration of worn-out joints we are presenting the new data based on examination of a cohort (n=56 patients, F/M 34/22, age 16 to 84 median 57 yrs) of patients which received marrow cells after centrifugation in a gradient of own plasma (3300 g for 3 minutes in the AutoStemCells kit tubes). The clinical outcome was verified with the use of appropriate standard questionnaires. The cell suspension profiling was made by cytometry analysis of cells labelled with CD45, CD34, CD 235a, CD73, CD105, CD90, CD133 (Becton Dickinson) and ALDH (Merck Millipore) MoAbs. The marrow (40 mLs) was collected from the posterior iliac crest then centrifuged as above and finally in a small portion (median 4.8 mL) injected intraarticularly. The procedure was side-effects free.

Results: 1. The injected cell suspensions contained from 4.6E+04 to 1.1 E+07 (median 2.4 E+06) cells with a contribution of CD45-CD34- in 14.9%, and that of CD45-CD34+:in 0.05%.

2. Population of cells lacking both CD45 and CD34 epitopes included (proportions) the cells as follow: CD90+: 0.52%, CD105+: 4.3%, CD73+:0.22%.

3. The whole population of cells injected had: CD133+ cells: 0.75%, ALDH+ cells:0.67%, Oct3/4+ cells: 0.38, CD309+ cells: 0.56%.

4. The patients filled the questionnaires reflecting the feel of pain and functional ability which depended on the affected joints at 6 time points. Bringing all the information together only 6 patients did not report any relief, in all other patients the improvement started as soon as 2 weeks after intra-articular injection and usually lasted for the whole year.

5. The improvement being observed in a majority of cases was not associated either with the total number of injected cells or with the participation of cells having epitopes attributed to MSC or ESC. Also there was no association with age of the patients. Notably, the improvement was clearly seen only in the patients with rather severe dysfunction of the affected joints.

6. Of note, the patients for which the injection was the most advantageous had the highest proportions of ALDH+ cells in the injected population.

Conclusions: In conclusion the procedure of the intra-articular injection of marrow derived cell employed in the patients suffering from degenerative joint diseases was safe and clinically effective especially in the patients with rather severe joint affection.

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Clinical Trial Registry: no applicable

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Solid tumours

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Successful KIR Alloreactive HSCT in a Child with Resistant Ewing Sarcoma

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Background: Ewing´s sarcoma is a primitive tumor of bone or soft tissue location, with a peak incidence in the second decade of life, defined by the presence of a combination of morphological and immunophenotypic elements. It is a chemo-radiosensitive cancer with a high risk of recurrence and 5-year survival between 70-80% which is significantly reduced in case of metastatic disease at diagnosis or relapse.

At the age of 5 years (March 2014) our patient presented with swollen left foot which was suspected for cancer. He performed total mass removal surgery with histological diagnosis of Ewing´s Sarcoma (confirmed by positivity of the transcript EWSR1).

In July 2014 he started therapy according to Euro Ewing 99 protocol. Doubtful imaging evidence of pulmonary metastasis.

In March 2015 surgery was performed to remove nodulary lesions of the right lung with no histological evidence of disease and in April he perform surgery to amputate the left leg and then he was treated with high-dose chemotherapy followed by reinfusion of autologous bone marrow stem cells.

In June 2016, he relapsed with lung metastasis and performed pulmonary radiotherapy, thoracic metastatectomy and chemotherapy with temozolomide and irinotecan.

Despite these treatments, persistence of lung metastasis were detected.

Methods: Given the absence of other therapeutic strategies, the patient was enrolled in an institutional hematopoietic stem cell transplant protocol based on the potential antineoplastic effect of NK alloreactivity in the context of haploidentical donor.

After conditioning therapy with TBI 200rds, fludarabine (160 mg/m2), thiotepa (10 mg/kg), melphalan (110 mg/m2) ATG (10 mg/kg), the patient received haploidentical BMT with KIR-alloreactive PBSC (GB/kg $1{,}6x10^9$, CD34/kg $19x10^6$) from his mother. Cyclophosphamide was administered after the transplant according to Baltimore protocol and immunosuppressive therapy was undertaken with sirolimus (suspended in August 2018) and MMF.

Results: No major side effects were reported after infusion. Engraftment of neutrophil was reached at G+16 and platelets at G+30 without evidence of GVHD. Immunological studies documented complete recovery of hematopoietic cell counts and immune function with evidence of total PBL and PMN donor chimerism.

In addition, imaging studies carried out in June 2019 were negative for recurrence of disease.

Conclusions: We describe the case of a patient with lung relapsed Ewing sarcoma. Relapsed patients remain chemoresponsive but the chances of long-term survival are low. In particular, current studies of patients who have a recurrence of the disease within the first two years of diagnosis display a survival of less than 10%.

Despite the ongoing studies focused on the Ewing biology, given the difficulty in performing clinical trials in paediatric setting, it seems important to emphasize this positive result in the contest of bone marrow transplant of patients with solid tumor.

Alloreactive NK-cell mediated anti-tumor effects might provide useful perspective with the aim to design innovative new cell therapy approaches against Ewing sarcoma or other solid tumors in children.

Disclosure: Nothing to declare.

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Abstract already published.

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Abstract already published.

Stem cell donor

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Impact of KIR on Patients with Lymphoid Diseases after T-cell Replete Haploidentical Hematopoietic Stem Cell Transplantation

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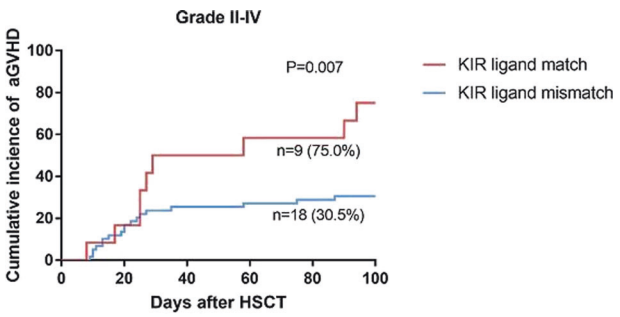
Background: Multiple factors have an impact on the success of hematopoietic stem cell transplantation (HSCT). Identifying the best donor for recipients has always been an essential role to improve patients´ outcomes. In recent years, huge amounts of studies have demonstrated that patients with myeloid malignancies could benefit from donor-derived NK cell alloreactivity. While, data about lymphoid diseases were limited, especially in the setting of T cell-replete haploidentical HSCT using Anti-thymocyte globulin (ATG) as conditioning regimen.

Methods: 71 patients (including 62 patients with acute lymphoblastic leukemia and 9 with lymphoma) who received haploidentical HSCT at our center between January 2015 to June 2017 were retrospectively analyzed. Patients were divided into two groups according to the killer cell immunoglobin-like receptor (KIR) ligand mismatch model.

Results: Among these patients, 12 patients (16.9%) presented all ligands, while the other 59 (83.1%) patients lacked at least 1 ligand for donor inhibitory KIRs. Patient characteristics such as patients age, disease types, disease risk index (DRI), condition regimen, ATG source, MNC cells and $CD34^+$ cells were comparable between the two groups. During the early stage after HSCT (within 100 days), we found that patients lacking ligands for donor inhibitory KIRs experienced a much higher EBV reactivation rate than patients presenting all ligands (47.5 vs 16.7%, P=0.049). It was also observed that patients using ATG-Genzyme pre-HSCT had an increased rate of EBV reactivation than ATG-Fresenius (72.7 vs 36.7%, P=0.044). In the multivariate logistic analysis, both of KIR ligands mismatch (P=0.033, HR=7.738) and ATG-Genzyme (P=0.019, HR=7.769) were identified as independent risk factors of EBV reactivation within 100 days post-transplantation. However, patients in the KIR ligand mismatch group presented a significantly lower cumulative incidence of grade II-IV acute graft versus host disease (aGVHD) (30.5 vs 75.0%, P=0.007). Sex mismatch had a tendency to a higher risk of developing grade II-IV aGVHD (28.2 vs 50.0%, P=0.072) than sex match group. Cox regression analysis showed that KIR ligand mismatch (P=0.010, HR=0.349) was the only protective factor of grade II-IV aGVHD. Besides, the cumulative incidence of moderate/severe chronic GVHD, relapse, overall survival (OS), transplant-related mortality (TRM) and disease-free survival (DFS) were comparable between the two groups.

Conclusions: In conclusion, our study found that KIR ligand mismatch in lymphoid disease significantly reduced the cumulative incidence of grade II-IV GVHD but increased the EBV reactivation rate in the early stage after HSCT, and it showed no impact on relapse and survival. And the finding still needs to be studied in larger cohorts.



[Cumulative incidence of grade II-IV aGVHD according to KIR ligand mismatch model]

Disclosure: Nothing to declare.

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Indications and Safety of Multiple Bone Marrow Harvests in Pediatric Donors for Matched Sibling Recipient Transplantation

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Background: Allogeneic Hematopoietic Cell Transplantation (HCT) is a curative treatment modality for many malignant and non-malignant disorders; in families with more than one affected individual, one healthy sibling might be the only suitable donor for them necessitating subsequent bone marrow (BM) harvest(s) from the same donor. The aim of this retrospective study is to review the indications and efficacy of multiple harvests from pediatric donors for pediatric recipients.

Methods: Data were retrieved from medical and electronic records for pediatric donors (age at harvest ≤ 14 years) who underwent more than one BM harvest for full matched sibling HCT at our institution from January 1993 to December 2017. A total of 1768 allogeneic HCT were performed from 1372 donors, 110 donors had multiple BM harvests for 233 (13%) transplants. Fifty out 110 multiple harvests (45%) were from pediatric donors and are the subject of this analysis of healthy pediatric donor; 56% (28) were female with a median age at BM harvest of 6.11 years (0.9 - 11.2 years.), 98% (49) were matched-sibling donors. Twenty-nine (58%) donors donated twice to same recipient following graft failure, and 21 (42%) donors donated to two different affected siblings (18: twice; 1: three times; 1: four-times). The median time between two harvest procedures was 15.44 months (1.15 - 50.72 months), median BM volume per donor's weight : 12.08 ml/ kg at first harvest with a median CD34+ cell count of 7.18 x 10^6/kg (2.46 x 10^6 /kg - 16.43 x 10^6/ kg) at first harvest and 11.48 ml/kg with a CD34+ cell count of 7.47 x 10^6 /kg (1.71 x 10^6/kg - 15.86 x 10^6) at second harvest with no significant difference in volume collection and cell yield (p-value > 0.05), donor cell priming with (G-CSF) was practiced in 20% (21) maximum with 3 doses prior to harvest procedure. Recipient diagnosis was leukemia's, 28% (14), immune deficiencies, 24% (12); hemoglobinopathies, 22% (11), bone marrow failures, 18% (9), Histiocytic disorders, 6% (3), metabolic diseases.

Results: All harvest procedures were performed under general anesthesia with a median duration of 50 minutes (20 - 90 min.), no donor required hospitalization or had significant complication apart from self-limiting pain managed conservatively. Mean donor hemoglobin level was 12.0 g/dl ; platelet count :323000 pre- harvest while Hgb level :11.0g/dl ; platelet count: 273000 post-harvest (p-value < 0.001) none required blood transfusion while iron replacement therapy administered, post-harvest with donor follow-up at 30 days, 6 months and 1 year with complete blood count recovery.

Conclusions: In our pediatric population, the main indication of multiple BM harvests is inherited genetic disorders and graft failure is main indication for the second HCT in the same patient, CD34+ yield of second harvest as optimal as first one, and GSCF administration may not be necessary. Our data suggest that Multiple BM harvests is a safe practice in pediatric donors however longer follow-up including psychological assessment is recommended.

Clinical Trial Registry: na

Disclosure: na

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Alternative Donor Hematopoietic Stem Cell Transplantation (HSCT) with Post-transplant Cyclophosphamide in Patients with Inherited Disorders

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Background: Allogeneic HSCT (allo-HSCT) is a curative for many inherited disorders, including hemoglobinopathies, bone marrow failure syndromes (BMFS), inborn errors of metabolism (IEM) and immunodeficiencies (PIDs). Allo-HSCT from HLA-matched related and unrelated donors is the standard of care, while use of alternative donors has been associated with increased graft failure, graft versus host disease (GVHD), and transplant-related mortality (TRM). Bone marrow (BM) is currently recommended as graft source in patients with non-malignant disorders. The risk of GVHD and mortality is higher in peripheral blood stem cells (PBSC) recipients. Post-transplantation cyclophosphamide (PTCy) is used for hematologic malignancies with engraftment rate, GVHD,

and TRM comparable to that seen with HLA-matched related donors. There are limited reports of allo-HSCT in non-malignant disorders using alternative donors and PTCy.

Methods: The study included 97 pts, predominantly pediatric (median age -3 y.o., range 7 month - 30 y.o.) with different types of inherited disorders (β-thalassemia - 9, BMFS - 28, IEM - 45, PIDs - 15). HLA-mismatched donors were used in 28 cases (MMUD - 18 pts., haplo - 10 pts.), HLA-matched donors - in 69 cases (MRD - 12 pts., MUD - 57 pts.). PBSC as graft source was used in 22 pts. BM - in 75 pts. Conditioning regimen was: MAC- 46 pts., RIC - 51 pts. PTCy 50 mg/kg days +3, +4 based GVHD prophylaxis was used in 36 pts.

Results: Five-year OS was 70%. OS was higher in HLA-matched donor group, but the difference wasn't statistically significant (79 vs 55%, p=ns). Engraftment was achieved in 62/69 cases from HLA-matched donors, in 23/28 cases allo-HSCT from HLA-mismatched donors (p=ns). Cumulative (CI) of aGVHD 2-4 grade was 41% in HLA-matched donor group vs 40% in alternative donors group (p=ns). The choice of graft source didn't significantly affect OS, 68% in recipients BM vs 58% in PBSC recipients, p=ns. Only 1 pt. (1/22) had rejection in PBSC group, 11 pts. (11/75) in BM group (p=0,003). Incidence of aGVHD 2-4 grade was higher in PBSC group, 55% vs 37%, p=0,045. PTCy didn't affect OS or engraftment rate, but significantly reduced acute GVHD rate in HLA-mismatched recipients group (18% vs 56%, p=0,048) and in PBSC recipients group (40% vs 62%, p=ns)

Conclusions: The use of alternative donors has made allo-HSCT available to patients with inherited disorders in the absence of HLA-matched donors, prior to detrimental outcomes. PTCy-based GVHD prophylaxis can be effective options for reduce risk of acute GVHD.

Disclosure: Nothing to declare.

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Young Male Donors may Result in Better Outcomes of Haploidentical Hematopoietic Cell Transplantation for Acute Leukemia with PT-Cy

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Background: Haploidentical transplantation with post-transplantation cyclophosphamide (PT-Cy) became a widely used, safe and efficacious platform in the treatment of hematologic malignancies. Each patient may have multiple readily available haplo donors. The criteria to select the best haplo donor are controversial

Methods: We studied the effect of haplo donor characteristics (age, sex, donor relationship, major ABO mismatch and graft source)

Donor	Age		Sex		Relationship		Major ABO Mismatch	BM Stem Cell Source
Characteristics	< 30	≥ 30	Female	Male	First degree relative (Sib, Kid)	Parent		
Number#	31	24	19	36	45	10	6	47
Percent%	56.4%	43.6%	34.5%	65.5%	82%	18%	11%	85.5%

[Table 1]

on the CD34 collection (more or less than 2.5×10^6) and the outcome of haplo transplantation including the neutrophil engraftment, the risk of aGVHD or cGVHD, and the overall survival (OS). A total of 55 patients with a diagnosis of ALL (23.6%), AML (67.4%) or MDS (9%) who received a haplo transplantation with PT-Cy were included in the study.

Results: Haplo donor age less than 30 and being a first degree relative (sibling or kid) rather than a parent were strongly correlated with a better CD34 dose (p-value= 0.04, and 0.05 respectively) and less risk of cGVHD (p-value= 0.05, and 0.009 respectively). In addition, male haplo donors were associated with a decreased risk of graft failure with significantly better neutrophil engraftment (p-value= 0.04). Major ABO mismatch resulted in a considerable decrease in the total nucleated stem cell collection due to in vitro RBC depletion. However, it didn't affect the risk of GVHD or the OS. In addition, graft source either BM or PB didn't affect the outcome of haplo as most of the graft were collected from the BM. The 5 years median OS was 27 months. Patients transplanted from female donors had a median OS of only 9 months. However, male haplo donors led to a superior OS (p-value= 0.01) (p-value= 0.01)

Conclusions: Haploidentical hematopoietic cell transplantation is a rising approach in treating acute leukemia worldwide. Donor selection algorithms were developed and incorporated many factors. Our study showed that young male donors probably a sibling or a kid were significantly associated with an improved haplo transplant outcome with a better CD34 stem cell collection, a lower risk of cGVHD and a superior OS.

Disclosure: Nothing to declare.

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Donors of Peripheral Hematopoietic Stem Cells, our Experience for Last 10 Years

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Background: Peripheral hematopoietic stem cells (PBPC) are obtained by apheresis from donors after mobilization by G-CSF. The aim of the apheresis is to collect the required transplant dose with respect to donor safety. There have been seen changes in the requirements for donors and their eligibility for collection with the introduction of haploidentical transplantations in our department since 2014. We were interested in the differences between individual donor groups. We follow up the health condition of the donors after mobilization and separation.

Methods: There were donors in period from 1/2010 to 9/2019. Groups of the donors were indicated as R (related) and UR (unrelated). Groups were categorized by age (≤40 yrs., >40 yrs.). Their eligibility for collection was assessed. Separation was started after the 4th dose of G-CSF. All separations were performed in Spectra Optia and Cobe Optia (Terumo BCT, USA). Only the first separations were evaluated. Donors who had CD34+ in peripheral blood less than 20 μl, were the poor mobilizers. The required transplant dose was 4-5 x10^6CD 34^+/ kg of the recipient. Donors were monitored after one week, 6 months and 12 months after the collection and once in a year. Statistical analyze was performed by using Mann-Whitney test. Values less than 0.05 are statistically significant.

Results: There were 294 donors in our study (R 234, UR 60), same number of male and female by age in R. There was 73% male donors under 40 yrs in UR. The highest representation of donors with a medical history was in R over 40 years (38%). This increasing trend has been shown since the introduction of haploidentical transplantation. The most frequent was arterial hypertension (41%), thyroid (17%) and psychiatric (14%) disease. 27% R needed a central venous catheter. Donors were mobilized by the same dose of filgrastim. The proportion of poor mobilizers was similar in both groups (R 7%, UR 6%). Higher number of complications was found in both groups of R (38%) but only 14% in UR. The median of apheresis dose CD 34^+ (10^6)/kg recipient was 5,7. Higher collection yields in UR. In R group over 40 years, there were needed most frequently two collections (39%). 89% of donors visited for medical examination after week, 74% after 6 months and 55% after 12 months. We did not find significant changes in health status of donors.

Conclusions: It has been proved that requirement for related donors and their eligibility for collection has been changing. The number of related donors with medical history increases with the introduction of haploidentical transplantations without impact of efficiency and safety collection. The experience of the Department of Apheresis with care of these donors is important. It's needed close cooperation between Apheresis and Clinical Department. Trends in unrelated donors are not changing.

Disclosure: Nothing to declare.

P654

Comparison of Transplant Outcomes and Economic Costs in Allogeneic Stem Cell Transplantation for AML and MDS Between The Different Type of Donors

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Background: The costs associated with the different types of donors, sibling (Sd), unrelated (Ud) or haploidentical (Hd) are not well described. In this retrospective single center cohort study of 75 adult AML or MDS patients with a fludarabine based conditioning regimen, we analyzed cost, healthcare utilization and patient outcomes for the first year post allogeneic stem cell transplantation (alloSCT).

Methods: From March 2012 to November 2018, 117 patients with AML or MDS received a 1st alloSCT in our center. Fourty-two patients were excluded because of myeloablative (BuCY or CY-TBI) or sequential conditioning regimen (17), clinical trial (18) or received a 2nd alloSCT within the first year due to graft failure or disease relapse (7). Source and travel costs were estimated from charges recorded in the Spanish Health Ministry Information and the Spanish Bone Marrow Donors Registry (REDMO). Inpatient costs (only human resources) were calculated according to our hospital´s system.

Results: Seventy-five patients (15 Sd, 35 Ud, 25 Hd) were included. Mean age at transplant was 55.1 years (Sd), 54.7 years (Ud) and 61.3 years (Hd), p= 0.103. The conditioning regimen and graft versus host disease (GVHD) prophylaxis was different in Hd, p< 0.001. Bone marrow was the main stem cell source in Sd (93%) and Hd (84%) but was used in only 51% of Ud, p < 0.001. HCTI, DRI score and CMV serological status was similar among the 3 groups (Table 1). Ud came mainly from Germany (n=21, 60%).

The incidence of CMV reactivation among the first year of transplant was 10% in Sd, 54% in Ud and 36% in Hd,

p=0.086. ≥2 CMV reactivation was only seen in Ud (19%) and Hd (14%), p=0.644. The overall incidence of grade III-IV acute GVHD in Sd, Ud and Hd was 0%, 21% and 0%, respectively, p= 0.263. With a median follow-up of 41.7 months in Sd, 39.8 months in Ud and 24.8 months in Hd, the incidence of extensive chronic GVHD in Sd, Ud and HD was 20%, 12% and 5%, p=0.283. Overall survival at 2 years in Sd, Ud and Hd was 60%±12.6, 71%±7.8 and 64%±9.6, respectively.

Based on the costs of stem cell source obtention and transportation, Ud was ≈ 9000 € more expensive than Rd or Hd, p< 0.001. However, the length of hospitalization in the first year post-alloSCT was slightly higher for Hd 38 days vs. 33 days and 32 days for Rd and Ud, respectively, p = 0.606. Taken all together, the costs between the 3 groups were not statistically different 21960 € (Sd) vs. 30368 € (Ud) vs. 25120€ (Hd), p=0.165.

Conclusions: Allo-SCT from an unrelated donor is associated with higher costs derived from the stem cell source obtention and its transport, but the prolonged hospitalization increases the costs, especially in allo-SCT from Haploidentical donor. The impact on the costs of several factors such as the donor and patient age, DRI and HCTI score, CMV reactivation and GVHD development, as well as the chemotherapy and GVHD prophylaxis given is being analyzed.

Disclosure: Nothing to declare.

P655

High Disease-free Survival of the Second Allogeneic Hematopoietic Stem Cell Transplantation with Donor Change and Mainly Reduced-intensity Conditioning in Relapsed Hematological Malignancies

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Background: The major obstacles of the second allogeneic hematopoietic stem cell transplantation (allo-HSCT) are high relapse rate and non-relapse mortality (NRM). In our previous study, we found some first related donors with a quite similar hematological and immunological hereditary predisposition gene variants to their recipients who relapsed after the first allo-HSCT. In present clinical study, the second allo-HSCT were performed with donor change and mainly reduced-intensity conditioning (RIC) regimens to improve the transplant outcomes.

Methods: Between April 2018 and December 2019, total 18 consecutive patients with hematological malignancies (AML 7, ALL 7, MDS 2, NHL 2) who underwent second allo-HSCT in our hospital were enrolled. They all relapsed in the other centers after the first transplantation (haploidentical 13, unrelated 2, autologous 3). The median age was 29.5 (5-55) years old. Before second allo-HSCT, eleven patients were in CR (MRD- in 8; MRD+ in 3) and 7 cases were with relapsed disease (ALL 3, MDS 2, AML 1, and NHL 1). The median interval between the first and second HSCT was 17 (5-47) months. Hematological and immunological hereditary predisposition genes of the patients, their parents and the first and potential related donors were detected before the second allo-HSCT with whole exon sequencing and validation by sanger sequencing. Different donors were used for the second transplant (haploidentical 13, unrelated 5) based on the HLA, hematological and immunological hereditary predisposition genes, and the functional tests of hematopoiesis and immunity. For the patients in CR, RIC regimens were used with TBI 4Gy for 2 days, cytarabine 1-2g/m^2 for 3 days, fludarabine 30mg/m^2 for 5 days, Me-CCNU 250mg/m^2 for 1 day, and ATG-F 4mg/kg for 4 days. Busulfan (0.8mg/kg for 3 days) was instead of TBI in 3 cases. For the patients with relapsed disease, individualized conditioning regimens were applied. Decitabine (20mg/m^2 for 3-5 days) or azacitidine (75mg/m^2 for 5 days) was added in AML or MDS, and etoposide (15mg/kg for 2 days) was administrated in ALL.

Results: The median time for neutrophil and platelet recovery was 14 (11-18) days and 15 (11-32) days. Seventeen patients became full donor chimerism, and one case who gave up early after second allo-HSCT due to financial issue could not be evaluated for chimerism and died from pneumonia one month after the transplant. NRM was only 5.6%. The incidences of grade II-IV aGVHD and cGVHD were 17.6%, 29.4%, respectively. The incidences of CMV and EBV reactivation were 23.5% and 17.6%. One ALL patient became MRD positive 4 months post-transplant and achieved MRD negative with BiTE. A refractory NHL patient was MRD positive 1 month after the second allo-HSCT and attained MRD negative with daratumumab and venetoclax. With a median follow-up of 8 (1-19) months, disease-free survival (DFS) and overall survival (OS) were all (17/18) 94.4%.

Conclusions: With the strategies of donor change and mainly RIC regimens, low incidences of relapse, aGVHD, cGVHD, CMV and EBV reactivation, and NRM were noted which has translated into very high DFS and OS. Long-term follow-up is warranted.

Disclosure: Nothing to declare.

P656

Epidemiological Study of Rare Antigens of the Main Histocompatibility Complex Among Hematopoietic Stem Cell Donors in Belarus

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Background: The National Bone Marrow Donor Program (NMDP) study (2014) demonstrated that 75% of Caucasian patients are likely to be identified as 8/8 HLA-matched unrelated donors, while this rate is much lower for ethnic minorities and mixed-race patients. This fact may be explained by the higher genetic diversity of HLA haplotypes in African and Asian populations compared to Caucasian and the lower representation and poorer availability of ethnic minority donors in the worldwide pool.

Methods: Epidemiological analysis of the anonymized HLA-typing results from the information database of (hematopoietic stem cell) HSC donors of the Central Registry of Belarus was performed. There were totally 105894 antigens of locus A, 105882 antigens of locus B and 55794 antigens of locus DRB1 analyzed.

Given the wide polymorphism of antigens of HLA system, we have assumed that cases with frequency of occurrence of the antigen of more than 5% of the antigens are common, while cases with prevalence less than 1% antigen are defined as rare.

The statistical processing of 27885 phenotypes (person) of potential HSC donors of the Central Registry of the Republic of Belarus, typified by loci A, B and DRB1, was carried out. We considered phenotype with one and more rare antigen as rare phenotype.

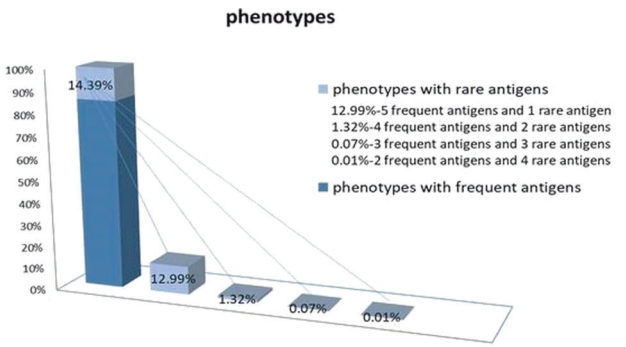
Results: The results of the study frequency of rare antigens of potential HSC donors of the Central Registry presented in Table 1.

The results of statistical processing of 27885 phenotypes of potential HSC donors of the Central Registry presented in Figure 1.

Conclusions: 1. The rare antigens identified (Table 1) in the studied phenotypes occur in 14.39% of cases and the distribution of these antigens within the phenotype structure is different.

2. The presence of even one rare antigen significantly complicates the selection of a donor-recipient pair.

3. By increasing the number of rare antigens in the phenotype structure the mobility of finding a compatible donors decreases from 12.99% (when 1 rare antigen) to 0.01% (when 4 rare antigen).



[Fig 1. The ratio of rare and frequent antigens in the phenotype]

Disclosure: Nothing to declare.

antigen	frequency(%)	antigen	frequency(%)	antigen	frequency(%)	antigen	frequency(%)
A*34	0.044	B*37	0.7905	B*55	0.9586	DRB1*9	0.7133
A*36	0.0094	B*42	0.0397	B*58	0.6507	DRB1*10	0.8370
A*43	0.0009	B*45	0.3882	B*67	0.0009	-	-
A*66	0.6289	B*46	0.1379	B*73	0.1058	-	-
A*68	0.522	B*47	0.2106	B*78	0.0019	-	-
A*69	0.0104	B*48	0.1587	-	-	-	-
A*74	0.0038	B*50	0.8878	-	-	-	-
A*80	0.0028	B*53	0.1407	-	-	-	-
-	-	B*54	0.0331	-	-	-	-

[Table 1. Rare antigens (<1%) and their frequency in the population of potential HSC donors of the Central Registry of the Republic of Belarus]

P657

Impact of Donor-recipient Sex Mismatch in Patients Receiving Partial T-cell Depleted Allogeneic Stem Cell Transplantation for Hematological Malignancy: A Retrospective Monocentric Study

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Background: The donor-recipient sex mismatch is a recognized risk factor for GVHD and increased non-relapse mortality. Conversely, partial T-depletion (pTCD) permits to lower risk of both these parameters without a negative impact on the overall outcome. The purpose of our study is to analyse whether the outcomes of pTCD were influenced by the donor-recipient sex mismatch.

Methods: A single-center retrospective analysis was conducted at our clinic in all adult patients (18 ≥years) that received their first partial T-cell depleted allogenic stem cell transplantation for a hematological malignancy from 2005 to 2018. pTCD was performed ex vivo using alemtuzumab, and it is offered to low-risk patients in CR, 1st, or beyond. Only matched donors were considered.

Results: Overall, 192 patients were identified. 111 had sex-matched and 81 had sex-mismatched donor. Median age for both groups was 51 years with a median follow up of 74 and 78 months, respectively. 68% of subjects in sex-matched and 67% mismatched cohort underwent myeloablative conditioning (MAC), and the most frequent indication for transplant was AML (51% and 40%, respectively). Globally, the groups were well balanced for the other characteristics, except for donor type which was an HLA-identical sibling in 36 and 65 % of cases in sex-matched and mismatched groups, respectively ($p< 0.01$), and in vivo T-cell depletion: ATG was used in 68 and 52% of patients, respectively ($p=0.04$). Peripheral blood was the primary source of stem cells in both groups. Median time to neutrophil engraftment did not differ between cohorts (16 and 17 days). No difference in 3-year probabilities was noted for overall survival (OS, 67.3% in sex-matched and 67.0% in sex-mismatched, $p=0.63$) and disease-free survival (DFS, 59.3%, and 52.7%, respectively). Cumulative incidence of non-relapse mortality (NRM) and relapse incidence (RI) at 3 years did not differ between sex-matched or mismatched donor (NRM: 12.7% vs. 11.6%, $p=0.89$; RI: 31.7% vs 37.6, $p=0.50$). Rates of grade II to IV acute GVHD were significantly lower in sex-matched cohort (11.3 vs. 20.0, $p=0.03$). No differences were noted for both all grade and extensive chronic GVHD 2-year rates (12.6 and 8.1% for matched patients; 11.1 and 7.4% for mismatched, $p=0.89$ and 0.73, respectively). Regarding the composite endpoint of GVHD-free/relapse-free survival (GRFS), the 1-year estimate GRFS was 59.4% in the sex-matched and 61.0% in the sex-mismatched group ($P=0.67$). In multivariable analysis for OS, having a matched unrelated donor (MUD) and a Karnofsky Performance Status (KPS) of 90 or less were associated with worse prognosis (HR= 2.0 for MUD, $p< 0.01$ and HR=2.46 for KPS, $p< 0.01$) while having a sex donor-recipient mismatch didn't retain significance.

Conclusions: In conclusion, ex-vivo pTCD offers similar overall results in the presence of sex-matched or mismatched donor, albeit a higher aGVHD rate was observed in the latter group without an impact on non-relapse mortality. Thus, in a context of partial T-depletion, the gender-mismatch seems not to impact the OS and NRM anymore which allow to have more choices in the presence of matched donors. A more large and homogeneous cohort should be exanimated to validate this approach.

Disclosure: Nothing to declare.

P658

Haploidentical Donor Selection and Its Implications in Transplantation Outcome. Our Experience at Hudgc Dr. Negrín

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Background: HSCT constitutes the only curative therapy for many hematological disorders. Frequently, numerous haploidentical donors are available for every patient. Thus, it is crucial to carefully select the patient´s most suitable donor in order to minimize the potential risks derived from such procedure.

Methods: We present a retrospective study of 53 patients who received haploidentical HSCT between January 2015 - September 2019. Detailed analysis between trasplantation outcomes and haploidentical donors´ features (including donor´s parameters during apheresis process, CMV reactivation, engraftment and acute GVHD development) were performed. The statistical program used was R Core Team 2019 (version 3.6.1).

Results: 53 Haploidentical HSCT were performed: 23 female, 30 male. Recipients´ average age: 44.9 years old (17-70). They suffered from: AML (30), B-ALL (6), Hodgkin´s lymphoma (5), MDS (3), Ph-ALL (2), aplastic anemia (1), bilineal leukemia (1), T-ALL (1), CLL-B (1), T-NHL (1), Multiple Myeloma (1), CMML (1). 66.7% entered transplantation in complete remission, whereas 33.3% presented refractory disease / MRD+.

Out of the donors´ sample: average age 35.4 years old (10-65). There were 19 female and 34 male. Donor/recipient relationship: siblings (43,4%), offspring (41,5%) and parents (15,1%). Stem cells´ source: 52/53 mobilized peripheral blood (86,5% peripheral venous access; 13,5% CVC) and bone marrow (1/53). All donors had been mobilized with Lenograstim (5mcg/Kg/12h), starting the cell collection on day 5 (Cobe Optia). Neither incidents nor immediate complications during mobilization or apheresis processes. In 52/53 cases, a CD34 dose > 4 x 10^6/Kg was obtained and in 17/53 patients, the achieved CD34 dose was > 6 x 10^6/Kg. 8/53 patients with 1º graft failure (7: sepsis, 1: SOS). There were no statistically significant correlation between CD34 dose and engraftment and CD34 dose and aGHVD (Fishers´ exact test). No statistically relevant differences noticed between CD34 dose and days of neutropenia (Mann-Whitney U test).

Donor´s blood tests were evaluated prior and post-apheresis process (hemoglobin, platelets, sodium, potasium and calcium). A significant decrease in both platelets and potasium were found (paired student T-test). Donors did not present any clinical implications, including 2 cases where post- platelet absolute count dropped down to 90 x 10^3/uL.

100% CMV reactivations occurred in R+ (D+/R+: 50% vs. D-/R+: 33.3%). No CMV reactivations noted in the rest of combinations.

Conclusions: We present our experience of haploidentical HSCT, concluding that recipient´s positive CMV serological status led to a poorer outcome due to CMV reactivation (100% CMV reactivation were R+). We found no statistically relevant correlation between infused CD34 dose and ability of engraftment or aGHVD development. It was observed a significant decrease in both platelets and potasium during the apheresis process ($p < 0.05$), which had no clinical implications to donors. Further analysis need to be performed so that to assay the implications of donor-recipient relationship in terms of overall survival as well as pre-transplantation disease status.

Disclosure: Nothing to declare.

P659

Outcome after Allogeneic Stem Cell Transplantation According to Donor Availability, Duration from Diagnosis to Transplant And donor-specific Parameters - A Single Center Analysis

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Background: Allogeneic blood stem cell transplantation (aBSCT) is the only curative treatment option for many hematologic malignancies taking patients´ disease status, comorbidities and age into consideration. Stem cell donors are essential for a successful transplantation and donor parameters such as HLA-match, CMV-status, age, gender and related or unrelated donors have an impact on patients´ outcome.

Methods: Donor searches (n=476) from August 2012 - August 2017 at our center were retrospectively analysed with regard to donor availability, donor-specific parameters, duration of defined milestones from donor search initiation until transplantation and patients´ outcome after transplantation.

Results: A search for an either related or unrelated donor was initiated for 476 patients (median age 54 years, range 18-74 years, 62% male), of whom 420 had an unrelated donor search with a median duration from first diagnosis to search initiation of 95 days. Diagnoses were: AML (43.5%), MDS (23.9%), ALL (6.9%), myelofibrosis (5%), CML (2.1%), NHL (7.2%), myeloma (4.7%) and others (6.7%). At the time of search initiation 93.3% of the patients were in good physical condition (Karnofsky index 90-100%: 93.3%), rates of comorbidities were low (HCT-CI 0: 63%, HCT-CI 1: 18.8%). Median donor search duration was 37 days. Threehundred and fifteen aBSCT were performed: 66 (21%) with a related donor and 249 (79%) with an unrelated donor. Concerning unrelated donors either a 10/10- or a 9/10-matching donor could be identified in 90.7%. In 3.3% haploidentical transplantations were performed. Finally 38.6% of patients could be transplanted with an "ideal" unrelated donor (10/10-match, male, ≤35 years, CMV-match). Unrelated donors were significantly younger than related donors (29 vs. 51 years, $p< 0.0005$), in most cases unrelated male donors were preferred (related 56.5% vs unrelated 73.5%, $p=0.009$). Conditioning intensity (MAC/RIC), remission status and disease risk index (DRI, Armand et al. Blood 2014) did not differ significantly between patients transplanted with a related or unrelated donor (p=n.s.). Outcome for CMV-negative patients with a CMV-negative donor was significantly better than compared to other CMV constellations ($p=0.044$). TRM was significantly higher in patients with a related donor in comparison to those with an "ideal" unrelated donor (12.6% vs. 25.8%, $p=0.035$). In 152 patients, aBSCT was declined due to the following reasons: death (16.5%), palliative procedures (3.9%), patients´ decision (7.2%), reevaluation

of feasibility for aBSCT (11.2%), comorbidities (16.5%), lack of donor availability (3.3%), unknown (41.4%).

Conclusions: Suitable donors can be identified for most patients within a short time period. However several procedural steps from diagnosis to transplantation have further room for improvement, especially earlier initiation of donor searches. Donor-specific parameters have a significant impact on patients´ outcome and should therefore be considered at the time of donor selection.

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P660

The Benefits of HLA-matched Related Donors for Patients Lacking HLA-identical Sibling in The Absence of Powerful Local Unrelated Registry in Countries with Prevalent Cousin Marriages

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Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative therapy for variety of malignant and nonmalignant disorders. As only 25% of patients have HLA-identical sibling, another choice is unrelated or haplo-identical donors. Iran is amongst the countries where there is a high prevalence of consanguineous marriage, so the HLA similarities are more likely among non-sibling family members. Therefore, a valuable available source of donor for HSCT is parents and other relatives.

Methods: A total of sixty-one patients (37 male and 21 female) underwent other relative HSCT between January 2018 and March 2019 in the Children´s Medical Center, Teharn, Iran. The median age of patients at the time at transplantation was 5.7 years (range, 0.16-). Underlying diseases for HSCT were primary immunodeficiency (n=20), inborn error of metabolism (n=12), acute leukemia (n=11), bone marrow failure (n=9), thalassemia major (n=8) and Glanzmann thrombasthenia (n=1). HLA-matched family donors who were found by family extended search, were parents (n=26), uncles and aunts (n=21), cousins (n=7), grandparents (n=5) and far related (n=2). Stem cell sources were consisted of peripheral blood in 58 and bone marrow in 3 transplants. Fludarabine based reduce intensity regimen was used in PID patients and Busulfan based myeloablative regimen in patients with other underlying diseases. All patients received Anti-thymocyte immunoglobulin (ATG) as a part of conditioning regimen.

Results: Primary engraftment reported in 57 patients. At the present time, 50 of them are full chimerism and 7 have stable mix chimerism. Primary graft failure occurred in 3 patients who received HSCT from mother, grandfather and cousin each in 1 and all of them received second transplantation. 1 patient died before checking chimerism on day 15. Acute GvHD grade I-II and III-IV were developed in 24% and 32.7 %, respectively. Chronic GvHD occurred in 7 patients (6 limited and 1 extensive). With the median follow-up of 19 months (range, 1-34), 43 (70.5%) patients are alive and 42 of them are disease free. The most common cause of death were relapse and infection.

Conclusions: The obtained data confirm that HSCT from HLA-matched family donors has the excellent outcome in pediatric setting. Using this family bank in Iran and where consanguineous marriage is not forbidden can be increase the chance of finding HLA matched donor for patients in need of HSCT.

Clinical Trial Registry: no

Disclosure: There is no conflict of interest.

P661

Donor Age Influences the Graft-versus-host-disease-free and Relapse-free Survival after Allogeneic Stem Cell Transplant in Elderly Patients in Latin America

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Background: Data about the outcome of allogeneic stem cell transplantation (Allo-SCT) in elderly patients is growing. In this population, survival free of the major complications of Allo-HCT becomes particularly important. We aimed to determine the graft-versus-host-disease (GVHD)-free and relapse-free survival (GRFS) in patients ≥ 65 years old that underwent Allo-HCT.

Methods: We analyzed retrospectively a cohort of ≥ 65 years patients from eleven centers in Argentina and one center in Brazil who underwent Allo-HCT between 2007 and 2019. GRFS was defined as the time from transplantation to the development of grade 3-4 acute GVHD (aGVHD), moderate or severe chronic GVHD (cGVHD) or relapse.

Results: 98 patients (median age 68 years, range 65-76; male 63; 36 ≥70 years), with the following diagnosis: acute myeloid leukemia (n=47), myelodysplastic syndrome (n=34), myelofibrosis (n=8), acute lymphoblastic leukemia (n=2), lymphoproliferative disease (n=5) and multiple myeloma (n=1). Median HCT-CI was 1 (range 0 - 6); being diabetes and a previous solid tumor the more frequent comorbidities. Donors were matched related (MRD) n=41, matched unrelated (MUD) n=31 and haploidentical (HID) n=26. The median age of donors was 66, 35 and 41 years old for MRD, MUD and HID respectively (p< 0.001). Conditioning regimen was myeloablative in 26 patients and in 72 patients was reduced-intensity: busulfan-based n=59 (13 PK-guided busulfan), melphalan-based n=25 and others n=14. At day 30, engraftment of neutrophils and platelets was 91% (95%CI 83-95) and 67% (95%CI 57-76), respectively, with a lower incidence in HID (88% and 61%; p=0.039 and p=0.020; respectively). In a median follow-up of 23 months, 42 patients developed aGVHD (grade 3-4 n=13), 19 patients cGVHD (moderate and severe n=10), 23 patients relapsed and 48 patients died. Death causes were: relapse n=19, infections n=11, GVHD n=5, cardiac toxicity n=4, graft failure n=2, and others n= 7. One-year and 2-year GRFS were 41% (95%CI 31-51) and 38% (95% CI 28-48) respectively, with a tendency to better GRFS in patients who underwent HID (p=0.120). Factors associated independently with a worse GRFS were donors ages ≥ 39 years (HR 2.08; 95%CI 1.09-4.01; p=0.027) and an HCT-CI ≥ 3 (HR 1.85; 95%CI 1.04-3.29; p=0.036). Patients with an HCT-CI < 3 who underwent transplant with a young donor had the best GRFS (1-year 63%; 95%CI 37-81; p=0.029). One-year non-relapse mortality (NRM) was 26% (95%CI 17-35) with a tendency to poor outcome in patients who underwent melphalan-based conditioning (44%; 95% CI 24-62) and to lower NRM in patients receiving pk-guided busulfan (8%; 95%CI 0.1-0.3); p= 0.096. One-year incidence of grade 2-4 aGVHD was 43% (95%CI 32-52) with a lower rate in tacrolimus-based vs. cyclosporine-based prophylaxis (p=0.022). Two-year overall survival was 52% (95%CI 41-62), without difference between donors (45%, 48% and 50% for MSD, MUD and HID, respectively; p=0.999); an HCT-CI < 3 was associated independently with better overall survival (p=0.011).

Conclusions: In our series of Latin American elderly patients that underwent Allo-SCT, donor age and comorbidities influenced the composite outcome GRFS. The role of the conditioning regimen in this population deserves further investigation.

Disclosure: Nothing to declare.

P662

Withdrawl of Volunteer Donors from the International Registries: A Single Centre Experience

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Background: The selection of the most suitable donor and stem cell source is a critical part of the transplantation procedure. The best donor for HSCT is an HLA-identical sibling, associated with the lowest risk of GvHD, graft rejection and transplantation-related-morbidity and mortality(TRM), but only 25% of patients have an HLA-matched sibling, so in the absence of a suitable related donor, Matched Unrelated Donor (MUD) from international registers is a good alternative source for HSCT in patients with haematological and non-haematological diseases. A well-matched donor is important to the success of transplantation: a close match between a patient´s and donor´s tissue type can improve the chances of a successful transplantation. The probability to find a 100% HLA compatibility among un-relative HLA-identical donor is

1/100000. So is important increase the number of volunteer donors in the registers.

Every year, 80000 patients worldwide need a MUD transplantations; in Italy the need is for more than 1600 patients.

Nowadays, thanks to the use of social media, the message is spreading more and more, with a good result in terms of raising awareness on the subject. Referring to the situation in Italy, in fact, over the last few years there has been a significant increase in the number of subscribers. Comparing data provided by Italian Bone Marrow Donor Registry(IBMDR) in 2017 and 2018, the number of new donors increased by more than 12000 subscribers(25010 in 2017 and 37835 in 2018).

The donation is always free and unpaid and the donor is free to withdraw in every moment as clearly stated in the section "Rights and protection of the donor" on the official website of the IBMDR. However the problem of the withdrawal of donors may adversely affect the patient outcomes.

Methods: We analyze 217 MUD transplantations performed from january1992 to december 2019 in our center to investigate this problem also comparing the Italian situation.

Results: In our experience, out of a total of 217 MUD transplantations performed,10.6 % of requests were cancelled after the verification typing stage(finally selected donors). In Italy IBMDR has registered similar percentage:10-15%, if considering withdrawal of donors after this stage, but is higher(25%) if we consider the withdrawal before the verification typing.

In our experience donor-related reasons were responsible for deferral in 21 cases:14 donor withdrawal for personal grounds(in this group 1 donor withdrew from donation permanently), 5 medical reasons, in 2 cases donors were unable to meet requested stem cell source. Other 2 requests were cancelled due to error(was requested a donor that should no longer have been on the register) and to unknown cause(a case occurred in 2008, of which IBMDR could not find the archived documents).

Conclusions: The problem of donor withdrawal is a clinical emergency, with strong negative impact on patient´s therapeutic process and psychological and social effects also on the patient's family.

The increase in volunteer donor enrollment in the register is an important advance for the success of MUD transplantation. However donor awareness should be increase to improve the availability and reliability of volunteer donors on the register.

Disclosure: Nothing to declare.

P663

Hepatitis E Virus (HEV) Contaminated Hematopoietic Stem Cell Graft in a Matched Unrelated Donor Transplantation

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Background: Transfer of HEV infection from a stem cell donor might cause severe infection in the recipient being highly vulnerable early after a HSCT since severe and fatal infections have been reported. This case describes to our knowledge the first case where stem cells from a HEV PCR positive unrelated donor were infused.

Methods: We here report on a female patient, who underwent her second HSCT after FLAMSA-RIC conditioning treatment due to AML relapse and received HEV PCR positive graft from unrelated donor.

During the screening process, the donor was asymptomatic, had normal lever values, and a negative HEV PCR. On the day of donation HEV PCR was found to be positive and we received this information one day after infusion of the peripheral blood stem cells (PBSC). Patient pretransplant samples were checked for HEV PCR and were negative. The donor center confirmed later that HEV RNA was positive but low (< 50 IU/mL). Patient received prophylactic treatment with ribavirin immediately 600 mg/daily and continued with it for 8 weeks.

Results: The patient developed multiple complications after HSCT including mucositis grade 3-4, hemorrhagic cystitis, neutropenic fever. Patient also had elevated transaminases due to drug toxicity (normal bilirubin and aspartate aminotransferase; alanine aminotransferase 2.92 mikrokat/L, γ-glutamyltransferase 3.5 mikrokat/L). HEV PCR screening was performed once a week during the first 8 weeks post-transplant, all samples were negative. Repeated standard screening for other hepatotropic viruses after HSCT was negative. Unfortunately, patient developed increasing MRD and recipient cells already 7 weeks after transplant, which did not respond to decreasing of immunosuppression. After stopping all immunosuppression at 11 weeks post-transplant, thepatient went in CR but developed acute gut GVHD. Follow-up is continuing.

Conclusions: The incidence and course of HEV-infection have been studied in patients having undergone allogeneic HSCT including at our center. This case report shows that HEV infection may develop in HSCT donors even in a low-endemic countries. In most donor centers, screening for HEV by PCR is not routine and therefore the consequences of HEV transfer from donors are unknown. More information is needed to understand the natural history and consequences of HEV transfer by donor grafts.

Disclosure: Nothing to declare.

Stem cell mobilization, collection and engineering

P664

A new BSA-based Threshold Predicts Optimal PBSC Collection in T-cell Depleted HLA-haploidentical Stem Cell Transplantation

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Background: In the last decade, T-cell depleted haploidentical HSCT has been increasingly used, particularly in the pediatric age. In order to overcome the limitation of the HLA-barrier in this setting, ensuring good engraftment rates, a mega-dose of hematopoietic stem cells (HSC) has been successfully used. However, it is not always easy to collect adequate numbers of CD34+ cells, because of poor mobilization and/or patient body weight. In our previously published cohort (Locatelli, Blood 2017), donors received standard G-CSF (Kroger, Br J Haematol 2000) to promote peripheral mobilization of CD34+ HSC. In order to predict a good collection of HSC we used the threshold of 40/mcL. Here we reviewed all mobilization procedures done at our Institution in order to find a more performing threshold to be used in clinical practice.

Methods: Donors were given G-CSF for 4 days at 10-12 μg/kg body weight in 2 divided doses; when on day 4 the CD34+ cell count was < 40/mcL and/or the predicted apheresis yields was ≤12x10^6 CD34+ HSC/kg recipient's body weight, Plerixafor was given at 0.24 mg/kg with the aim of boosting mobilization of hematopoietic stem/progenitor cell. Large-volume apheresis was performed on day 5 on the Spectra Optia Cell Separator using MNC program (Terumo BCT, Leuven, Belgium). We conducted a retrospective analysis collecting data about characteristics of the mobilization procedures.

Results: Between 05/2012 and 10/2019, at Bambino Gesù Children's Hospital a total of 473 haploidentical donors underwent apheretic collections followed by TCRαβ/CD19 depletion. Median donor age was 37.7 years (range 18.0-59.6). Ninety-three donors (19.8%) received Plerixafor, while 16 (3.3%) underwent a second apheresis on day 6. Moreover, in 123 cases (26%), the apheretic collection was manipulated with 2 different procedures (either 2 negative depletions or 1 negative depletion and 1 positive selection), because the total number of nucleated cells exceeded the maximum (60 billion of nucleated cells) allowed per manufacturer's standards. In no case, the collection was insufficient to perform the transplant. Median number of CD34+ count in PB on day 4 (t1CD34+) was 30.8/mcL (range 2.3-179.2) while on day 5 (t2CD34+) was 107.9/mcL (range 23.4-380.6). No correlation between donors age and t1CD34+ or t2CD34+ was found. Median number of HSC collected per kg of the recipient was 22.8x10^6 (range 5.6-82.2). As expected, t1CD34+ poorly correlated with the total number of CD34+ collected in the following day (Slope 0.01, p=0.4). By contrast, t1CD34+ normalized per recipient body surface area (BSA, sqm) had a strong predictive value (Slope 0.14, p< 0.0001). Counting as events the use of Plerixafor, a double collection or the use of 2 different procedures, the new proposed threshold of 40 CD34+/mcL/sqm in PB the day before the apheresis robustly predicted a successful collection (AUC 0.81, p< 0.0001; positive predictive value 56.3).

Conclusions: Based on a large cohort of mobilized donors, we propose a new threshold (i.e., 40 CD34+/mcL/sqm in PB the day before the apheresis) to predict optimal PBSC collection in T-cell depleted haploidentical stem cell transplantation.

Disclosure: Franco Locatelli: Miltenyi Honoraria

P665

Phase 1 Clinical Study of MGTA-145 in Combination with Plerixafor Shows Rapid Single-day Mobilization and Collection of CD34+ HSCS Without G-CSF

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Background: G-CSF mobilization of hematopoietic stem cells (HSCs) requires 4-7 days of injections that are associated with significant side effects and potential for severe complications in some patient populations (e.g. sickle cell disease, multiple sclerosis). MGTA-145 is a biologic

(GROβT) that activates CXCR2 on neutrophils, and with plerixafor rapidly mobilizes HSCs in mice and non-human primates. The combination promises to be a same-day, G-CSF-free mobilization regimen.

Methods: This healthy volunteer phase 1 study consisted of four parts- Part A: single-agent MGTA-145 or placebo; Part B: MGTA-145 or placebo given immediately or 2 hours after plerixafor; Part C: MGTA-145 or placebo given 2 hours after plerixafor on 2 consecutive days; Part D: MGTA-145 given 2 hours after plerixafor, just prior to apheresis cell collection.

Results: Monotherapy of MGTA-145 mobilized CD34+ cells within minutes and peaked within 1-hour post MGTA-145 (median 11 CD34+ cells/μL, 7-fold increase vs baseline). White blood cells and neutrophils followed a similar pattern. Importantly, markers of neutrophil activation were relatively unchanged (≤2-fold vs baseline).

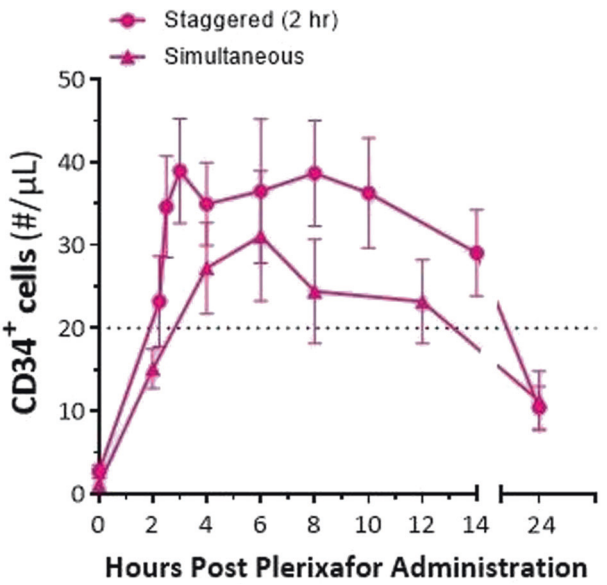
MGTA-145 combined with plerixafor increased CD34+ cell mobilization, whether given simultaneously or 2h after plerixafor (Figure 1). Mobilization was highly enriched for CD34+CD90+CD45RA- HSCs, which tracked closely with the total CD34 count. At the 0.03 mg/kg dose with 2h stagger, median peak CD34+ peripheral blood mobilization was ≥40 cells/μL in Part B. On a second consecutive day of dosing, MGTA-145 + plerixafor mobilizes HSCs to levels comparable to day 1. Initial data from the ongoing Part D show that sufficient numbers of cells (median 4.3 x 10^6 CD34+ cells/kg) for transplant were collected in one day with same day dosing and apheresis. Preliminary data from NSG mouse transplant studies show higher engraftment rates of MGTA-145 + plerixafor mobilized HSCs, compared to G-CSF-mobilized HSCs.

MGTA-145 monotherapy was well tolerated with no significant adverse events (AEs). Grade 1, transient lower back pain that dissipated within minutes was reported. The combination of MGTA-145 with plerixafor was well tolerated, with some subjects experiencing grade 1/2 gastrointestinal AEs commonly observed with plerixafor and one grade 2 back pain with MGTA-145 at 0.075 mg/kg that resolved within minutes.

Conclusions: MGTA-145 monotherapy is safe, well-tolerated, and induced rapid mobilization of significant numbers of HSCs. CD34+ cell mobilization with plerixafor + MGTA-145 was immediate and superior to plerixafor alone. These data suggest that the combination enables the collection of sufficient HSCs for transplant in one day. Further clinical development as a first line mobilization product is warranted in autoimmune diseases, gene therapy and hematologic malignancies.

Subject	Total CD34+ Yield (x106 cells)	CD34+/kg (x106 cells)	CD90 + (%)
801	319	4.1	39%
807	322	4.4	41%
817	500	5.3	26%
821 (*completed only 13L of planned 20L collection)	239	2.7	19%
Median	**321**	**4.3**	**33%**

[Table. Single-day Mobilization and Apheresis Cell Yields in Part D]



[Figure 1]

Clinical Trial Registry: NCT03932864

Disclosure: Haley Howell, Veit Schmelmer, Jason Neale, Anthony Boitano, Kevin Goncalves, Glen Raffel, Will Savage, Patrick Falahee, and John Davis are employees of Magenta therapeutics with equity ownership. Dwight Morrow, Jonathan Hoggatt, John Dipersio, and Michael Cooke have equity ownership in Magenta Therapeutics.

P666

Depletion of αβ T-cells and B-cells Before HLA-haploidentical HSCT in Children with Malignant and Non-malignant Hematological Disorders: A Report of 473 Procedures

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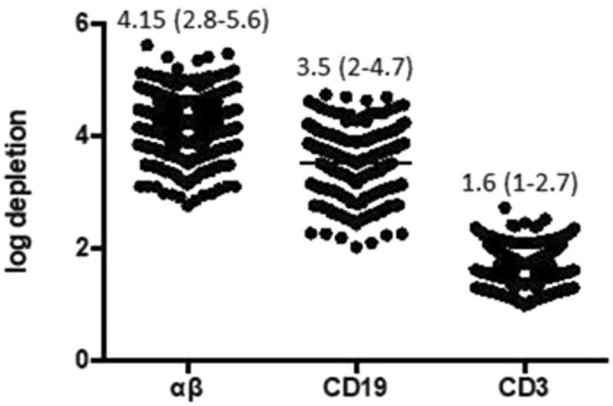
Background: HLA-haploidentical donors represent a valuable option for children in need of hematopoietic stem cell (HSC) transplantation to treat malignant and non-malignant hematological diseases. Depletion of αβ T-cells and B-cells has been introduced to remove alloreactive T-cells responsible for GvHD and B-cells responsible for PTLD, respectively. In addition to CD34 progenitors, this manipulation preserves NK cells, γδ T-cells and monocytes/dendritic cells, contributing to anti-leukemia activity and protection against infections. We already reported on 200 procedures performed between 2012 and 2016. Here we update our results on 473 manipulations.

Methods: 473 donors underwent HSC mobilization with G-CSF. In 93 cases (20%), poor-mobilizing donors received Plerixafor in addition to G-CSF. Large-volume leukapheresis was performed on day 5 with CD34 counts >20 cells/μl. Donors had a median age of 37.7 years (18-59.6). Apheresis bags containing up to 60x10*9 nucleated cells (NC) underwent TCRαβ/CD19-cell depletion using the CliniMacs device (Miltenyi Biotech, Germany).

Results: Plerixafor increased the CD34 counts of poor mobilizers to levels comparable to those of good mobilizers given G-CSF alone. Aphereses contained a median of 50x10*9 (12-65) NC, 13x10*9 (1.8-51) polymorphonuclear cells (PMNC) and 442x10*6 (96-1122) CD34 cells, 13x10*9 (2.3-25) αβ T-cells and 2.8x10*9 (0.3-12) CD19-cells. αβ T-cell depletion produced a median 4.15 log reduction (2.8-5.6) and B-cell depletion a median 3.55 log reduction (2-4.74) (Fig. 1). No significant differences in cell depletion were detected over time; 79% of depletions with ≤4 αβ logs had ≤15x10*9 PMNC in the starting apheresis suggesting that PMNC contamination has a negative effect on αβ T-cell depletion efficiency (moderate inverse correlation p= -0.51). Median recovery of CD34 cells, CD3 γδ T-cells and NK cells was 96.7% (53.3-100), 82.4% (25.7-100) and 84% (19-100) respectively. After depletion, the product bags contained a median of 19.9x10*6 (4-74) CD34 cells/kg, 11.5x10*6 (0.6-286) CD3 γδ T-cells/kg, 38.8x10*6 (1.6-250) NK cells, 0.034x10*6 (0.0012-0.29) αβ T-cells/kg and 0.026x10*6 (0.009-1.5) B-cells/kg. All patients received < 10*5 αβ T-cells/kg in the infused graft.

Conclusions: The addition of Plerixafor to G-CSF in healthy haploidentical donors who mobilize insufficient numbers of HSC allows collection of adequate numbers of CD34 cells. Depletion of αβ T-cells and B-cells was reproducible and robust. Good depletions (≥4 logs) were more frequent with ≤15x10*9 PMNC. CD34 cells, γδ T-cells and NK cells were recovered with high efficiency (>85%). Performance of this procedure was maintained overtime. A retrospective analysis of the procedures with inadequate depletion efficiencies that required a second processing round to reach pre-set depletion standards (15/473 procedures, 3%) is currently ongoing.



[Fig. 1 Depletion efficiency of αβ T cells, CD20 B cells and CD3 T cells]

Disclosure: Nothing to declare.

P667

Acoustophoresis Enables the Label-free Separation of Distinct Subsets from Cultured Bone Marrow Stromal Cells

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Background: Mesenchymal stromal cells (MSC) are promising candidates for clinical cell-based therapies within regenerative medicine and immune-modulation. MSCs are generated by in vitro expansion, which leads to functionally heterogeneous and poorly defined cell populations. We therefore aimed to establish acoustophoresis, a microfluidic ultrasound-based sorting technology, as a potential tool for the label-free enrichment of functionally better-defined MSC preparations.

Methods: Acoustophoresis uses local acoustic standing wave fields produced in a microchannel by piezoelectric transducers to differentially affect the movement of cells depending on their acoustophysical properties, such as size, density, and compressibility. Depending on these properties, cells are either collected in the center or side outlet of the microchip used in this study. Separation of cells is modified by adjusting the applied acoustic energy. MSCs were generated by adherent culture of human bone marrow mononuclear cells in xenofree medium. MSC preparations were sorted with acoustophoresis, and sorted cell fractions were analyzed for viability, cell diameter, phenotype (surface marker and gene expression), cell cycle phases, proliferation, clonogenic, and differentiation capacity, as well as immunomodulatory function.

Results: Acoustophoretic cell processing did not compromise cell phenotype or function, nor did it significantly affect cell viability (generally 87-98%). Acoustophoresis could be used to purify samples, e.g. by removing cell debris or larger cells, and to selectively enrich for cell subsets with certain size ranges. Up to 40% higher proliferation and 2.7-fold increased clonogenic potential (measured as colony-forming units, fibroblast, CFU-F) were observed in smaller MSCs collected in the side outlet. Furthermore, higher expression of genes related to proliferation and stem cell properties (i.e. Ki-67 (2.4-fold), Nanog1 (4.1-fold), Oct4 (2.1-fold), and CXCL12 (2.8-fold), n=3) were recorded in the sorted side fraction which was enriched for smaller cells (average diameter 14.5±0.4 μm) compared to the center outlet fraction (average diameter 17.1±0.6 μm). Fractions of MSCs in G_0/G_1 cell cycle phase were significantly enriched in the side fraction and an up to 2.8-fold increase of cells in $S/G_2/M$ were observed in center fractions. Acoustophoresis did not compromise the ability of sorted MSCs to differentiate into the adipocytic, osteoblastic or chondrocytic lineage, nor the ability to suppress T-cell proliferation. However, no significant difference in growth inhibition was observed between cells sorted into side versus center outlet.

Conclusions: These results demonstrate that label-free acoustic sorting can be used to enrich functionally different MSC populations to generate more defined stromal cell products from cultured MSCs. Hence, acoustophoresis is a potentially promising separation technology to provide improved cell products for research and possibly future clinical use.

Disclosure: TL and SS are cofounders and shareholders of Acousort AB, Lund, Sweden.

P668

Feasibility of Modified CD45RA Negative Donor Lymphocytes Infusion after Haploidentical Stem Cell Transplantation (HAPLO-SCT) with Post-transplantation Cyclophosphamide (PT-Cy) in Patients with Hematological Malignancies

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Background: Although haplo-SCT with PT-Cy is safe and efficacious, infections still remain a major cause of morbidity and mortality.

As CD45RA+ naïve T cells are mostly causing GvHD, we performed an interventional, non-randomized prospective study to evaluate if haplo-DLIs depleted of CD45RA+ cells, promoting the transfer of T cell memory can reduce viral infections while limiting GvHD.

Methods: CD45RA+ T cells were significantly depleted from the infusion product (mean CD45RA on CD4+ and CD8+, respectively: 38.2% and 69.9% before and 3.4% and 10.8% after), resulting with an increased CD4:CD8 T cell ratio (1.3 to 5.9). The vast majority of the infused T cells displayed a central memory or effector memory phenotype. B cells and NK cells, which are mostly CD45RA+, were virtually absent from the product (mean 1.6% and 0.9% of lymphocytes). We performed 3 DLIs on Day +50, +80 and +110 at the dose of 0.5, 1 and $5x10^6$ CD3+/kg, respectively.

Results: Of the 13 patients infused since September 2018, only one experienced grade I aGVHD of the skin, after the second infusion and regressed spontaneously, without discontinuation of the following scheduled infusions. Importantly, 4 patients received DLIs with ongoing grade I aGVHD of the skin, which did not evolve to a higher grade. Overall, 72% of patients experienced at least 1 CMV reactivation. Among the infused population, 4 out of 12 patients never reactivated CMV. Seven patients had already experienced at least 1 CMV reactivation before the first infusion. Six patients had multiple CMV reactivations despite the DLIs. Infection other than CMV reactivation after at least 1 infusion, occurred in 4 patients: 1 patient experienced Parvovirus B19 viremia, 1 patient had FUO, 1

patient had C.difficile-associated diarrhea and 1 patient developed pneumonia without microbiological findings. Of note, no fungal infection was observed during follow-up.

Conclusions: CD45RA-depleted DLIs after HSCT with PT-CY is safe and well tolerated. Immunological studies aimed at investigating T cell reconstitution and repertoire are ongoing.

Clinical Trial Registry: ONC-2016-002

Disclosure: Nothing to declare.

P669

Beyond Stem Cells- Does It Matter What´s in the Bag in Autologous Stem Cell Transplantation for Multiple Myeloma and Lymphoma?

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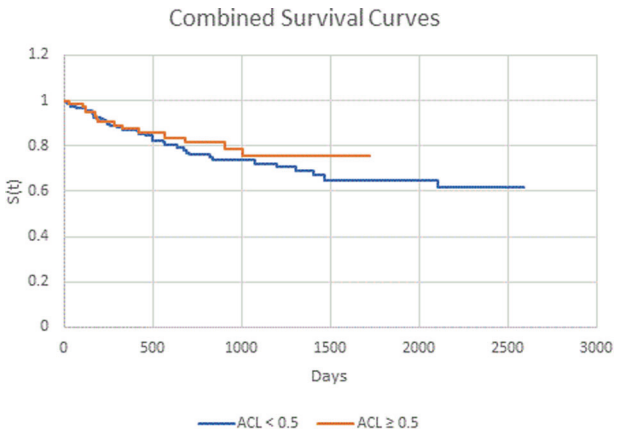
Background: Retrospective studies performed previously suggest that superior long-term disease control post Autologous Stem Cell Transplantation is associated with early immune recovery at Day +15 post transplantation, but the composition of immune cells in the stem cell product and the dynamics of early immune reconstitution have not been systematically and prospectively explored.

We compared the long-term outcomes of 223 patients transplanted in a single institution, according to achieving an early lymphocyte recovery of equal or higher than 0.5x10e9/l at Day +15 or not. Furthermore, in a pilot explorative study the immune cell composition of the stem cell product re-infused to 6 patients in 2017 was assayed from cryopreserved pilot vials and from the freshly harvested stem product of further 7 patients transplanted between May and August 2019. Prospective, serial flow-cytometric assays of early immune reconstitution were performed in the peripheral blood between Day+14 and Day+30 post transplantation from these patients and will be correlated prospectively to survival and disease control in this cohort.

Methods: Retrospectively, records of patients transplanted at St. George´s Hospital were accessed. Outcome data was gathered from Med-A reporting and Lymphocyte recovery at Day +15 data from electronic laboratory records.

Defrosted cryovials of previously transplanted stem cell products were flow-cytometrically assayed for immune cell content with monoclonal antibodies against CD4, CD8, CD19 and CD56 to establish the T,-B, and Natural Killer (NK)subsets. The Neutrophil content of the stem cell product was also established. Cell doses were related to the patient´s body weight.

The stem cell product characterisation and immune cell reconstitution of recently transplanted patients was performed with an identical panel of antibodies. Outcome data on the prospective cohort of patients will be collated from hospital records and Med-A reporting files.



[Fig. 1 Survival of patients according to Lymphocyte counts at Day +15 post Autologous Transplantation]

Results: Data on 315 patients were retrospectively studied (Myeloma178, Lymphoma 115, other diagnoses 23). 223 patients were included in the final analysis, excluding patients with missing D+15 lymphocyte counts and missing follow-up reporting. First analysis reveals differences in survival according to achieving early lymphocyte reconstitution or not, confirming results from previous retrospective studies (Fig.1). Further detailed uni-variate and multi-variate analysis will be undertaken.

6 patient´s (5 Myeloma, 1 Hodgkin´s Lymphoma) defrosted cryo-vials of stem cell products revealed considerable variability of immune-cell content. Particularly high number of NK cells were observed in two patients whose malignant disease remained in remission after transplantation (Hodgkin´s s disease and Myeloma), whereas patients with lower NK cell content in the stem cell product have relapsed early.

Recently transplanted patients, likewise, show a highly variable immune cell composition of stem cell product, likely reflecting immune status at time of harvest.

Conclusions: Natural Killer cells are a significant component of early immune reconstitution after autologous transplantation and may convey anti-tumour responses together with tumour- recognizing T-cells. Early B-cell recovery is weak in the majority of prospectively studied patients.

Further longitudinal studies over longer periods of time are required to determine the role of individual immune cell populations in maintaining control over malignant disease. This may inform stem cell mobilisation and harvesting strategies.

Disclosure: Nothing to declare.

P670

Lipegfilgrastim Combined with Chemotherapy was More cost-effective Than Pegfilgrastim In The Mobilization of CD34$^+$ Cells in NHL Patients

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Background: Autologous stem cell transplantation (auto-SCT) in a commonly utilized treatment procedure after the first-line therapy or relapse in NHL patients. Granulocyte-colony stimulating factors (G-CSFs) have a crucial role in the mobilization setting and filgrastim (FIL) with its biosimilars have been the only approved G-CSFs for mobilization purposes. Scarce data exist on the pegylated G-CSFs lipegfilgrastim (LIPEG) compared to pegfilgrastim (PEG) after chemotherapy regarding the mobilization of CD34$^+$ cells, post-transplant hematologic recovery and mobilization cost in NHL patients.

Methods: The population of this prospective non-interventional study encompassed 104 NHL patients who were mobilized with chemotherapy plus either PEG 6 mg (n = 59) or LIPEG 6 mg (n = 45) between May 2012 and December 2018 as a part of Graft and Outcome in Autologous stem cell transplantation (GOA) study. The efficacy to mobilize blood grafts and post-transplant hematological recovery and outcome were analysed according to the G-CSF used.

Results: Chemomobilization with LIPEG proved to be superior regarding blood (B-)CD34$^+$ cell count of the first apheresis session and the total collected graft (**Table 1**). In patients mobilized with high dose cytarabine (n = 45) LIPEG produced higher B-CD34$^+$ cell peak (60 vs. 29 x 10^6/L, p = 0.043) and total number of collected CD34$^+$ cells (4.6 vs. 3 x 10^6/kg, p = 0.015). The tempo of engraftment after high-dose therapy was roughly comparable between the two G-CSF groups and the choice of G-CSF had no impact on PFS or OS. The median mobilization costs were 43 % lower (4197€ vs. 7416€, p < 0.001) in the LIPEG group based on the fewer apheresis sessions and less hospitalization days needed to achieve the adequate grafts.

Conclusions: This prospective study suggests lipegfilgrastim to be more potent and cost-effective G-CSF compared with pegfilgrastim added to chemotherapy to mobilize B-CD34$^+$ cells. A prospective randomized study is warranted to confirm the superiority of lipegfilgrastim in the mobilization of CD34$^+$ cells including the economic aspects.

Variable	PEG group n = 59 (%)	LIPEG group n = 45 (%)	Significance, p
WBC count x 109/L at the time of the first apheresis, median (range)	7.8 (0.9-45.1)	11.2 (2.5-45.6)	0.104
B-CD34+ cell count x 106/L at the time of the first apheresis, median (range)	23 (5-159)	41 (1-314)	0.002
Peak B-CD34+ cell count x 106/L, median (range)	31 (5-163)	59 (8-314)	0.006
Peak B-CD34+ cell count < 20 x 106/L, n (%)	12 (21)	7 (16)	0.534
Peak B-CD34+ cell count > 100 x 106/L, n (%)	3 (5)	13 (29)	0.001
CD34+ cell yield x 106/kg of the first apheresis, median (range)	1.7 (0.4-10.2)	2.7 (0.2-16.5)	0.051
Total yield CD34+ cells x 106/kg harvested, median (range)	2.9 (0.8-10.2)	4.5 (0.6-16.5)	0.001
The number of apheresis, n (%) 1 2 3	27 (46) 24 (40) 8 (14)	27 (60) 13 (29) 4 (7)	0.126
PLER use, n (%)	20 (35)	12 (27)	0.395

[Table 1. The mobilization and collection of CD34+ cells in 104 non-Hodgkin lymphoma patients according to G-CSF used after mobilization chemotherapy]

Disclosure: Dr. Partanen reports honoraria from Behring and has participated Medical Advisory Board meetings organized by Abbvie. Dr. Valtola reports honoraria from Sanofi and Jansen-Cilag. Dr. Varmavuo reports consultancy fees from Abbvie, Amgen, Celgene, Roche, and Sanofi. Dr.

Jantunen reports honoraria from Amgen and Sanofi as well as Medical Advisory Board meetings organized by Amgen, Takeda and TEVA. The other authors declare. no conflicts of interest.

P671

Mobilization and Harvest of Peripheral Blood Stem Cells (PBSC) for Allogeneic Stem Cell Transplantation from 335 Pediatric Sibling Healthy Donors

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Background: The PBSC are the source of haematopoietic stem cells (HSC) currently most used in the allograft of malignant and non malignant haematological diseases in our practice. If the procedure of mobilization and collection is similar for adult and children, of many technical sides must be taken into account in the paediatric apheresis because of extracorporal volume related to the weak weight of the donors. We report our experiment of collection of PBSC in pediatric sibling donors (less than 18 years old) over one 14 years period for allogeneic stem cell transplantation.

Methods: From January 2005 to December 2018, 335 pediatric donors (< 18 years), including 172 of male sex, had a collection of PBSC by technic of apheresis after parental consent. Their median age was 11 years (3-17) of whom 103 (30;7%) have less than 10 years. Their median body weight was 42 kg (13-103) of whom 27 (8%) were lower than 20 kg. Stem cell mobilization was obtained by once-daily subcutaneous injections of G-CSF (10µg/kg/day) for five consecutive days. PBSC were collected using a continuous flow blood cell separator (Cobe spectra or Optia) at the 5th day and repeated, if necessary, at the 6th and 7th days. Two donors (0,5%) had red blood cells priming the extracorporeal line before blood processing.

Results: All of the donors tolerated the whole procedures. Insertion of a femoral catheter was avoided in 50 donors (15%). The maximum WBC level obtained after G-CSF is on average 51.10^9/l (21-109). Obtaining an adequate CD 34+ rate required one apheresis in 170 donors (51%), 2 apheresis in 151 (45%) donors and 3 apheresis in only 14 (4%) donors. The median duration of the complete procedure was 225 minutes (150-450) and the median volume of collection was 208 ml (89-422). The median rate of CD34+ obtained was $8,16.10^6$/kg (0,34-36,1) of whom 56 (16,7%) < 4.10^6/kg and 76 (22,6%) >10.10^6/kg. The median rate of MNC: $9,7.10^8$/kg (3,8-30,6). Symptoms of hypocalcaemia observed in 78 donors (23%). After apheresis, 37 donors (11%) had haemoglobin lower of 10 g/dl and only 07 (2%) had thrombopenia <70.10^9/l. Only 6 (1,6%) donors expressed a refusal to give again.

Conclusions: Our study shows that the PBSC obtained in the sibling donors, less than 18 years, is an effective procedure of collection on the condition of being realized minutely by a team specialized with a perfect control of apheresis technics.

Disclosure: Nothing to declare.

P672

Evaluation of Via Freeze™ Quad for Liquid Nitrogen-free CGMP-compatible Controlled-rate Freezing of Hematopoietic Progenitor Cell Grafts

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Background: Controlled-rate cryopreservation of hematopoietic progenitor cell (HPC) grafts has historically been performed using systems integrating liquid nitrogen (ex. DigitCool). Recently, a cGMP-compatible conduction-cooling alternative that eliminates the risks and infrastructure costs associated with liquid nitrogen has become available: VIA Freeze™ Quad (GE Healthcare).

Methods: Buffy coats (n=3) or excess cells of apheresis collections from rhG-CSF-mobilized donors or patients (n=5) were equally divided into two bags and cryopreserved in HES 6% + 10% DMSO using either VIA Freeze™ Quad or DigitCool. Upon thawing, a sample is collected and diluted at 1/10 with HES 6% without washing. Quality controls were then performed by single platform flow cytometry measuring: CD45+/CD34+ cell recovery/viability (buffy coats or HPC, respectively).

Results: CD34+ cell recovery was comparable per product between VIA Freeze™ Quad and DigitCool, with the former having slightly better recovery (mean ± SEM, 86.6 ± 6.5% versus 83 ± 9.5%, respectively). CD45+ cell viability was equally comparable with no differences among both methods (70 ± 4 versus 68.9 ± 6, respectively). As such, both methods resulted in products that passed our center's release criteria: CD34+ cell recovery (absolute viable CD34+ cell counts post thawing versus pre-cryopreservation) >70%; CD45+ cell viability >50%. Buffy

coats showed a comparable output in terms of CD45+ cell recovery (VIA Freeze™ Quad 89.7 ± 7% versus DigitCool 84.8 ± 5.8%) and viability (91.4 ± 0.6% versus 88.6 ± 4.6%, respectively). In compliance to cGMP standards for traceability, both instruments document similar controlled-rate freezing curves. In terms of capacity and time-consumption, VIA Freeze™ Quad can simultaneously cryopreserve, within the cleanroom, two 100 mL HPC units at a time, with a total processing time (from program selection to -100°C) of 90 minutes, allowing for consecutive cycles of cryopreservation throughout the day as apheresis products are collected. DigitCool, on the other hand, has a much larger capacity, providing the option of collecting apheresis products throughout the day and a single cryopreservation run in the afternoon in the cryopreservation facility, consuming 45 minutes from instrument preparation to -140°C. Therefore, the advantages that each of these instruments has over the other need to be viewed in relation to the level of activity in the facility and the distance between the cryopreservation area and the cleanrooms.

Conclusions: Our data describes the capacity of a liquid nitrogen-free cGMP compatible system, VIA Freeze™ Quad, to produce comparable outputs as the historically-used device, DigitCool. Although the latter has responded to our needs and activity for the past 20 years, the former provides a cleanroom-compatible option to consecutively cryopreserve HPC units in the lab, shortening the time between apheresis collection and cryopreservation: this is particularly important when substantial manipulations, such as immunomagnetic selection for example, are to be performed after thawing.

Disclosure: Nothing to declare.

P673

CD34 + Cell Subsets in Stem Cell Products and Their Relationship with Engraftment Kinetics

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Background: Hematological recovery after the stem cell transplantation depends on amount of CD34+ cells in the graft. The aim of this study is to evaluate the effect of three different mobilization regimes (G-CSF vs Chemotherapy + G-CSF vs Plerixafor) on CD34 subsets. In addition, we also evaluated the effect of CD34 subsets on engraftment kinetics as the mobilization regimens.

Methods: A total of 27 patients with multiple myeloma (MM) and Lymphoma who were planned to undergo autologous peripheral stem cell transplantation (auto-PSCT) were included in the study after written informed consents were obtained from each patient and the institutional review boards approved the protocol. Patients were divided into three groups as G-CSF (n=9), Chemotherapy plus G-CSF (n=9) and Plerixafor (n=9). After mobilization, 7-AAD, CD34 and its subgroups (CD45 / CD45RA / CD133 / CD10 / CD19 / CD38 / CD7 / CD33 / CD3) were analyzed by flow cytometry in blood product collected by apheresis method. The effect of three different mobilization regimens on CD34 subsets were evaluated. The engraftment kinetics for platelet and neutrophil were monitored in 22 patients who underwent auto-PSCT and the effect of CD34 subsets on engraftment kinetics was evaluated.

Results: Fourteen females (51.9%) and 13 males (48.1%) were included in the study. The median age was 53 years (range: 26 to 68 years) and the median body weight was 76 kg (range: 52 to 125 kg). While 8 patients (25.9%) were diagnosed as lymphoma, 19 patients (70.4%) were MM. The median number of apheresis cycles was 2 (range: 1-3). Prior to stem cell collection, median pCD34 count was higher in GCSF group (median: 88/uL) than Plerixafor group (median: 36/uL) ($p = 0.03$). While median collected MPP, LMPP and EMP were higher in G-CSF arm, median late GMP were higher in Plerixafor arm (Table 1). Median subsets of MLP and BLP were not seen or rare (median values: 0) in the whole groups. In our study cohort, 22 out of 27 patients (81.5%) underwent auto-PSCT. There were no significant differences between neutrophil and platelet engraftment days as three different mobilization regimens ($p>0.05$). There was no statistically significant relationship between neutrophil engraftment and given cell levels as MPP, LMPP, GMP and late GMP. No significant correlation was found between the given cell levels and platelet engraftment of MPP and EMP. The cost per patient to evaluate of CD34+ cell subsets by flow cytometry is around 250 US Dollars.

Conclusions: Although G-CSF alone mobilized more primitive progenitor cells, plerixafor shifted toward the more committed cells by mobilized late GMP in the patients with poor mobilizer. In accordance with the literature data, the three different mobilization regimens did not provide adequate MLP and BLP in the peripheral blood. Early engraftment kinetics were not affected by given CD34+ cell subsets. Therefore, the examination of CD34+ cell subsets does not cost-effective in daily practice. In conclusion, our results need to be supported by future prospective randomized studies with larger and homogeneous patient populations.

Disclosure:

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P674

Performance Qualification of Lovo™ Medical Device for Washing and Concentrating 3 and More Hematopoietic Progenitor Cell Cryopreserved Bags

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Background: Some patients mobilize poorly upon treatment with recombinant human granulocyte colony-stimulating factor (rhG-CSF) in preparation for an autologous hematopoietic progenitor cells (HPC) graft. Consequently, successive cell collections can result in the cryopreservation of more than two bags, representing a challenge to efficiently wash and concentrate several bags to a small volume.

Methods: Closed system volume-reduction can be performed manually by centrifugation or automatically by a pelletizing system (Sepax-2) or non-pelletizing spinning membrane filtration (Lovo™). We hereby report on the Performance Qualification (PQ) of the Lovo™ medical device for washing and concentrating more than 3 bags at the same time, according to a validation plan and acceptance criteria. Quality controls were performed on unwashed samples (diluted at 1/10 with HES 6%) by single platform flow cytometry. Measurable outputs were: viable CD34+ cell recovery/viability and CD45+ cell viability.

Results: We first performed a paired comparison using two bags from deceased patients, one washed by each device: Lovo™ or Sepax-2 (the device currently used in our facility). Median CD34+ cell recovery/viability and CD45 + cell viability were comparable between both instruments, passing the set acceptance criteria: CD34+ cell recovery (absolute viable CD34+ cell counts post-wash versus pre-cryopreservation) >70%; CD45+ cell viability >50%.

Due to the limited volume (250 mL) of the Sepax processing compartment, sequential processing of 3 bags lasts more than 90 min. Therefore we performed validation runs on the Lovo™, owing to its capacity to process up to 21L, to wash and concentrate 3 or 4 bags, sequentially or in replicates, respectively. Upon washing and concentrating HPC bags using Lovo™, outputs were compared to historical Sepax-2 data. All processes passed acceptance criteria, showing satisfactory viable CD34+ cell recovery (median, min-max: 104%, 90-109%), as well as CD34+ cell viability (97%, 95-98%) and CD45+ cell viability (73%, 60-90%). The time necessary for washing and concentrating processes was 60 min for the 4 units (replicate after replicate) and 75 min for 3 units (sequential), suggesting that the use of replicates is more advantageous. Historical data from Sepax-2 reports a washing/concentrating time of 75 min for 2 units.

Conclusions: Our data indicates that Lovo™ is a reliable device to wash and concentrate >3 HPC bags for its better output and its time-saving capacity, as compared to manual or currently available automated devices. It is important to stress that the cell concentration technology (spinning membrane filtration) characteristic of the Lovo™ might explain the better output as compared to traditional, centrifuge-based techniques.

Disclosure: Nothing to declare.

P675

From Work-up Request to Donation in Three Weeks: A Dedicated Registry Integrated Unrelated Donor Stem Cell Collection Center is Safe, Efficient and Convenient for Donors

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Background: Collection of G-CSF mobilized PBSC is a widely used procedure in the allogeneic stem cell transplantation setting. The efficacy and safety of this mobilization schedule in healthy donors has previously been documented. Ezer Mizion is the largest health support non for-profit organization in Israel. The Ezer Mizion Israeli National Bone Marrow Donor Registry (EMBMDR) was established in 1998 and as of October 2019 includes 1,000,805 donors, with a high percentage of young males. In order to improve availability and donor experience during the procedure, Ezer Mizion has recently established its own dedicated Stem Cell Collection Center which has been accredited by the Ministry of Health and is now operating for more than 1 year.

Methods: Donors received 10 μg/kg of recombinant G-CSF once a day subcutaneously for 4 days prior to collection and until apheresis was completed. Apheresis was performed using a continuous blood cell separator (Spectra

Optia version11, Terumo BCT) through bilateral peripheral blood venous access (253 donors), or a combination of an arterial line and venous access (20 donors). The total amount of blood to be processed was 2-4 times the donor´s total blood volume per day; each process was adapted depending on the mid-apheresis CD34+ cell count and the recipient weight. We have compared the results of the collection procedures performed in EMBMDR donors in the newly established collection center (273), to those performed in our registry affiliated collection centers in 4 large hospitals in Israel during the previous two years (632).

Results: Between October 2018 and September 2019 273 donors underwent PBSC collection in the newly established collection center. No severe adverse events have been observed. Major parameters of the two cohorts are presented in Table 1.

	No. of Collections	Two days Collections (%)	Mean procedure time (hours)	Requested CD34+ reached (%)	Reaching $4X10^6$/kg CD34+ in one day collection (%)	Reaching ≥2 the cell dose requested (%)
Ezer Mizion Collection Center	273	10(3.7)	04:21	251(91.9)	263(96.3)	144(54.8)
Hospital based collection centers	632	32(5.1)	04:25	571(90.3)	594(94)	262(41)

[Table 1]

As seen in Table 1 there were no differences between the results obtained in the newly established collection center as compared to those obtained in the hospitals. The donor's experience has dramatically improved as documented in feedback questionnaires.

Conclusions: The Ezer Mizion dedicated Stem Cell Collection Center proved to be a safe and efficient site for the procurement of stem cells from unrelated donors. The team consisting of technicians, nurses, physicians and administrator, is dedicated to providing a timely and optimal stem cell product for the patient, while supporting the donor throughout the donation process and thereafter. Delays in donor procurement have been shown to adversely affect patient outcome and might result in the cancellation of the transplant procedure due to deterioration of the patient's health during the prolonged wait. The combination of a large registry with its own dedicated collection center can shorten the whole process while creating a better environment for the volunteer donors.

Disclosure: Nothing to declare.

P676

Low-dose Cyclophosphamide + G-CSF is no More Effective than G-CSF Alone When Mobilizing and Collecting Stem Cells for Autologous Transplant in Multiple Myeloma Patients

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Background: High-dose chemotherapy with stem cell reconstitution plays an important role in the treatment of Multiple Myeloma (MM) patients even in the era of new therapies. Cyclophosphamide (CY) at different dose levels has been widely used with granulocyte colony-stimulating factor (G-CSF) to mobilize and collect stem cells for transplant. In our centre we use G-CSF +/- low-dose cyclophosphamide (1.5 gr/m^2) based on medical criteria but it remains unclear if CY at this dose level is more effective than G-CSF alone when mobilizing MM patients for transplant.

Methods: We retrospectively analysed clinical and transplant records of 51 MM patients (median age 58 years, range 35-69 years) mobilized with G-CSF or G-CSF+CY (1.5 gr/m^2) from 2013 to 2018. Study endpoints considered to evaluate the impact of low-dose cyclophosphamide in this setting were peripheral blood CD34 + cells counts pre-apheresis in every mobilization course previous to plerixafor administration (if it was used) and CD34+ cells/kg collected per apheresis. Additionally we evaluated the efficiency collection as it has been demonstrated that is negatively correlated with high peripheral leukocyte counts pre-apheresis, a common finding when G-CSF alone is employed. Analysis of group differences was performed using the Student t-test and the Mann-Whitney U-test depending upon the distribution of the continuous variables.

Results: Fifty-six mobilization courses were performed in 51 patients: 32 with G-CSF and 24 with G-CSF+low dose CY. Plerixafor was employed due to low CD34+ count pre-apheresis in 13 mobilization courses: 7/32 (21.5%) in the G-CSF group and 6/24 (24%) in the G-CSF +CY group (p=0.78). Five patients needed a second course of mobilization, 4 in the G-CSF group and 1 in the G-CSF +CY group (p=0.37). Finally, 70 apheresis sessions were carried out: 40/70 (57.1%) in the G-CSF group and 30/70 (42.8%) in the G-CSF+CY group. No cyclophosphamide related toxicities were reported. No patients with long-term exposure to lenalidomide were included. Previous to evaluate efficiency collections we demonstrated a significant higher peripheral leukocyte count pre-apheresis in the G-

CSF group. Data related to study endpoints are showed in the following table.

	Growth factor only (32 mobiliz. courses)	Growth factor + CY (24 mobiliz. courses)	
Blood CD34+cells/mcl pre-apheresis (median)	36,0	36,5	p=0.95
	Growth factor only (40 apheresis)	Growth factor + CY (30 apheresis)	
CD34+cells/Kg collected (median).	3,71x10e6	4,16 x10e6	p=0.61
Blood leukocytes count pre-apheresis (mean)	39.100/mcl	30.030/mcl	p=0.01
Efficiency collection (mean).	60,4%	62,1%	p=0.77

[Mobilization results.]

Conclusions: Mobilizing stem cells in MM patients with G-CSF+low-dose cyclophosphamide showed no advantages over mobilizing with G-CSF alone even though cyclophosphamide administration was safe. Different approaches to improve the efficacy of stem cell mobilization, including the use of alternative chemotherapies with G-CSF and plerixafor use optimization, should be explore in order to decrease the number of apheresis sessions needed to get enough CD34+ cells for transplant.

Disclosure: No conflict of interest.

P677

First Interim Results of NIS Optimob - Nationwide Trial of Mobilization and Collection of Hematopoietic Stem and Progenitor Cells in Multiple Myeloma and Lymphoma Patients

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Background: Autologous stem cell transplantation (ASCT) remains the standard of care for transplant-eligible multiple myeloma (MM) and lymphoma patients, despite the development of new targeted treatments. Consequently, mobilization prior to apheresis (aph) plays an important role within the treatment. In clinical routine estimated 15% of patients are classified as poor mobilizers (PM) requiring several aph sessions. Stem cells are mobilized with chemotherapy + G-CSF +/- plerixafor (PLX) or G-CSF +/- PLX. The OPTIMOB study is a large prospective observational trial evaluating stem cell mobilization in patients with MM and lymphoma.

Methods: Patients with MM, non-Hodgkin lymphoma (NHL) or Hodgkin lymphoma (HL) eligible for ASCT are included in the non-interventional study (NIS) OPTIMOB. Depending on the mobilization status (PM, good mobilizer (GM)) the mobilization and collection parameters are documented and analyzed in detail. PMs are defined as follows: never achieved ≥ 20 CD34+ cells / µL before 1st aph, receive PLX at any time point of mobilization, the initially planned stem cell yield had to be reduced or patients have not received apheresis due to low $CD34^+$ count in peripheral blood. Primary endpoint is the success rate of mobilization in PM measured by stem cell yield on day 1 of aph (>2.0 x 10^6 /kg $CD34^+$).

Results: First preliminary results of the OPTIMOB study are shown. Up to now (Dec. 2019) 274 patients from 22 centers are registered in this ongoing trial. About two thirds of documented patients have MM (60%) and one third have malignant lymphoma (40%). The median age is 61 years and fewer females (37,3%) are included in the study. For almost half of the patients the mobilization status is already identified with 53 PM and 70 GM. Most patients were mobilized with chemotherapy plus G-CSF (82%) and 19% of these patients received PLX. 11% were mobilized with G-CSF only whereas 6% were treated with G-CSF plus PLX. The number of CD34+ cells/µl was determined at the day before aph. as well as at the first day of aph. On average the number of CD34+ cells at the first day of apheresis doubled compared to the number of CD34+ cells at the day before aph. For 26 of 123 patients of the OPTIMOB study at least one adverse event (AE) has been reported. Most frequently, patients suffered from infections and infestations (10,6%) general disorders and administration site reactions (9.8%) as well as gastrointestinal disorders (GIT, 8.1%).

Conclusions: First preliminary results of the NIS OPTIMOB are shown. Results might change with further

patient enrollment. Results of the study will contribute to a better understanding of stem cell mobilization and collection for patients with MM or lymphoma prior to ASCT.

Clinical Trial Registry: This non-interventional trial is supported by Sanofi.

BfArM-study number: 7186

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AMGEN: Other

Pfizer: Other

JAZZ Pharmaceuticals: Other

Celgene: Research Funding, other

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Wilhelm Sander Foundation: Research Funding

P678

The Impact of Plerixafor "on Demand" on the Hematopoietic Stem Cell (HSC) Collection, Product's Quality and Engraftment

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Background: Autologous hematopoietic stem cell transplantation (ASCT) is a standard treatment for several hematological malignant diseases. However, 5% to 40% of patients fail to mobilize sufficient CD34+ cells and are not eligible for ASCT. Plerixafor, a CXCR4 inhibitor, is able to induce an effective mobilization of PBSC when used in combination with G-CSF, alone or with chemotherapy in poor mobilizer patients. Moreover, recent studies show that Plerixafor is also effective when given "on demand" as a preemptive strategy to avoid mobilization failure in poor mobilizers but the best timing for its use is still matter of debate. Further, it is well known that the quality of the PBSC collection impacts on the transplant outcome and the high PMN count negatively affects the platelet recovery but data about the effects of Plerixafor on the graft composition and engraftment lack. **AIM** of our study is to evaluate the impact of the Plerixafor use "on demand" on the quality of the PBSC collection and engraftment, related to the collection timing and WBC count.

Methods: We retrospectively examined 404 collection procedures from 264 hematological neoplastic adult patients, 31 of whom received Plerixafor 'on demand' at the recommended dose of 0.24 mg/kg/day, while 233 received standard mobilization regimen. Overall, 168 ASCT (17 Plerixafor vs 151 no Plerixafor) were performed and data outcome were analyzed. Moreover, 12/17 patients who achieved a collection ratio CD34+/WBC > 1 upon Plerixafor underwent ASCT and were considered as "early Plerixafor use group".

Results: Patients treated with Plerixafor "on demand" achieved a median value of pre collection CD34+ and WBC count, significantly higher (p= 0.0000000021) and lower (p= 0.012) than no Plerixafor group (CD34 27 vs 43 ml and WBC 43 vs 94 $x10^3/\mu l$), respectively. Collection efficiency was significantly higher (p= 0.04) in the Plerixafor group. Moreover, the collection yield of CD34+ x 10^6/Kg was significantly higher (p=0.0012) in the no Plerixafor group while the PMN count of the collected product was significantly higher (p=0.00000003) in the Plerixafor group. No differences between collection length (p=0.36), processed volume (p=0.4) and platelets count of collected product (p=0.12) were observed between the 2 groups. Concerning the transplant outcome, median time of PMN and PLTS engraftment (Plerixafor PMN/PLTS= 12/20 days vs no Plerixafor 11/13 days, p=0.72 and 0.51) was similar in the 2 groups. The same differences occurred in the "early Plerixafor use group", except for collected platelets, that resulted significantly lower (p=0.005) compared to no Plerixafor group.

Conclusions: Our data confirm that the products collected with Plerixafor "on demand" have significantly higher PMN count than those collected with standard mobilization whereas the products collected by the "early Plerixafor use group" have a significant lower content of PLTS. However, no clinical significant impact on PMN and PLTS engraftment was observed in the 2 subset. Further studies are needed in order to understand if CD34+/WBC ratio > 1, associated or regardless to the WBC count, may be identified as the best timing for Plerixafor introduction in the clinical practice.

Disclosure: Nothin to declare.

P679

Elevated Serum Lactate Dehydrogenase after Stem Cell Mobilisation Predicts Successful Stem Cell Collection in Children

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Background: The pre-apheresis absolute peripheral blood CD34+ cell count (PBCD34) has been used as the most important determinant of successful stem cell harvest. The number of stem cells collected is dependant on the cancer diagnosis, extent of treatment, mobilisation technique, type and dose of the growth factor used. However, obtaining PBCD34 is not always feasible for patients who live far from bone marrow transplant centres. Delayed in PBCD34 result may affect the quality of stem cell harvest. A readily available surrogate marker that can predict adequate stem cell harvest yield is needed when PBCD34 is not available to plan apheresis. Elevated serum lactate dehydrogenase (LDH) has been observed in patients who have leucocytosis following G-CSF priming. Therefore, we examined the utility of LDH as a predictor of successful stem cell collection.

Methods: Demographic and laboratory parameters from paediatric patients undergoing stem cell harvest for autologous stem cell transplantation were obtained over 18 months period. Adequate harvest yield was defined as $\geq 2\times10^6$ cells/kg. LDH rise was calculated as the change in LDH levels at baseline and post stem cell mobilisation. The association between the LDH rise and PBCD34 harvest yield was assessed using Spearman's correlation. The optimal level of LDH rise to predict successful harvest was determined by plotting the ROC curve.

Results: 24 paediatric patients with solid tumours (46 apheresis procedures) were included in the study. The median LDH rise was 287 units/L (IQR 110-574), median pre-apheresis PBCD34 was 19.11 $x10^6$ cells/L (IQR 6.30-39), and the median harvest PBCD34 yield was 1.75×10^6 cells/kg (IQR 0.94-3.49). As predicted, the correlation between pre-apheresis PBCD34 and actual harvest yield was high ($r = 0.927$, $p < 0.0005$). In comparison, there is also statistically significant correlations between the LDH rise and pre-apheresis PBCD34 ($r = 0.563$, $p < 0.0005$), and actual harvest yield ($r = 0.712$, $p < 0.0005$). The optimal LDH rise for successful harvest yield was determined at 400 units/L (AUC 0.717, $p = 0.012$), with a 75% sensitivity and a 65.4% specificity.

Conclusions: LDH, as a readily available measurement in most hospitals, is a good surrogate marker for pre-apheresis PBCD34. An LDH rise of 400 units/L is the optimal level to predict successful stem cell collection.

Disclosure: Nothing to declare.

P680

Influence of the DMSO Wash Strategy on Adverse Reactions during Infusion of Hematopoietic Progenitors

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Background: Infusion of cryopreserved peripheral blood hematopoietic progenitors (PBHP) is associated with a rate of adverse reactions (AR) up to 50%. In our centre, a historical study (n=29) reported an AR incidence of 41% in patients who were transplanted before January 2016 infusing PBHP without washing. To reduce this toxicity, we started to wash PBHP units to avoid DMSO and decrease AR rate. We study the efficacy of washing PBHP.

Methods: We perform a prospective single-centre study. CD34 infused was at least 2 x 10^6 CD34/Kg in autologous setting, $4x10^6$ CD34/Kg in allogeneic and $5x10^6$ CD34/Kg in haploidentical. Each unit of PBHP (≤150ml) to be frozen maintains a cell concentration of $< 2x10^5$ cells/μl and 10% DMSO. Patients with a predicted DMSO amount infused >15ml (more than 1 PBHP unit) received washed PBHP, so all patients received a maximum amount of 15ml DMSO. Washing procedure was performed with a solution (37.5 ml 20% albumin, 15ml ACD-A, 247.5ml saline serum) with a cellular processor (Cobe). Infusions were made through a central venous catheter by gravity. Patients that received unwashed product was treated with paracetamol and antihistaminic before infusion. Cellular viability was evaluated by blue-trypan method. Chi-square test was used to compare the qualitative variables and Mann-Whitney U for quantitative variables.

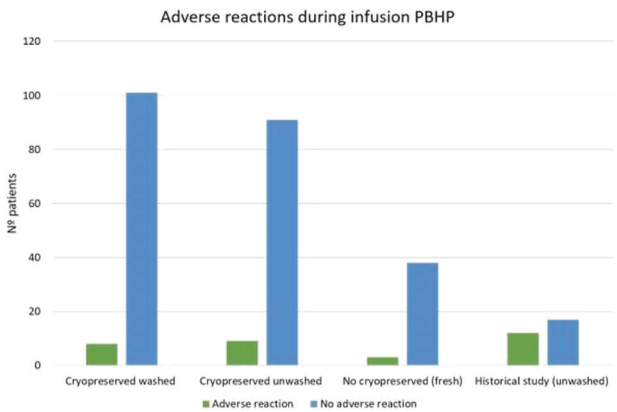
Results: Patients baseline characteristics are shown in Table 1. From January 2016 to March 2019, a total of 250 infusions of PBHP were registered, divided in: cryopreserved with washing ($n = 109$), cryopreserved without washing (DMSO ≤15ml) ($n = 100$) and fresh infused products ($n = 41$). AR incidence was similar between the three groups (Graph 1), supporting benefit of washing DMSO in patients who will receive more than 15 ml. Twenty patients

Products	AML/ MSD	Acute lymphoblastic leukemia	Lynphoma	Multiple myeloma	Others	Autologous transplant	Allogenic transplant	Age years (range)	Sex (male/ female)
Cryopreserved washed (n=109)	31	2	33	36	9	68	41	53 (18-54)	62/47
Cryopreserved unwashed (n=100)	19	2	20	44	11	24	76	52 (20-72)	59/41
No cryopreserved (fresh) (n=41)	28	1	6	1	7	1	40	47 (18-66)	26/15
Historical study (unwashed)(n=29)	6	0	10	5	8	29	0	26 (2-49)	22/7

[Patients characteristics: Underlying disease, transplant modality, age and sex distribution. AML: Acute Myeloid Leukemia. MSD: Myelodysplasic syndrome]

(8%) suffered AR, 4 moderate-severe degree (e.g. encephalopathy, unstable angina, hemodynamic instability and atrial fibrillation with high rate responsed) and 16 in mild degree (nausea, vomiting, hypotension or mild hypoxemia). The AR rate decreased significantly compared to our historical cohort (8% vs 41%; p< 0.0001) (Graphic 1), coinciding with the implementation of washing PBHP with DMSO >15ml. In comparison, those patients who presented AR received a significantly greater amount of non-viable nucleated total cells (0.89 x 10^{10} vs 0.69 x 10^{10}; p = 0.01). No differences were found in total nucleated cells, CD34/Kg, CD3/Kg, total leukocytes or total volume infused.

Conclusions: The washing strategy in products with DMSO> 15ml is a useful strategy to reduce the AR rate. A standardized protocol performed by highly qualified staff is required. Moreover, a greater amount of non-viable nucleated cells were associated with higher rate of RA and higher incidence of infusion related AR, suggesting the role of non-viable cells in AR.



[Graphic 1: Adverse reactions during infusion of PBHP]

Disclosure: Nothing to declare.

P681

Bone Marrow Donor Characteristics: Influence on Harvest Yield and Donor Recovery

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Background: Previous studies have found that optimal harvest yield (TNC ≥4 x 10^8/kg recipient weight) is associated with improved patient survival. Few studies to date have examined donor characteristics and variations in donation procedure as factors associated with achieving an optimal yield.

While bone marrow (BM) harvest donation is generally a safe procedure, a number of factors have been associated with delayed donor recovery, including older age and female gender. Nevertheless, data remains limited in this field.

This study contributes to addressing those research gaps and explores the impact of donor and procedure related factors on harvest yield and donor recovery.

Methods: 134 unrelated BM donations performed in four collection centres between April 2015 and September 2017 were analysed using donor medical records and donor self-reported recovery questionnaires completed at two days and one week post-donation.

The primary outcome was achievement of optimal harvest yield (TNC ≥4 x 10^8/kg recipient weight). The secondary outcomes were self-reported a) physical recovery, b) general symptoms (tiredness, insomnia, nausea, dizziness and temperature/chills), c) pain and d) emotional health issues - all coded as binary outcomes.

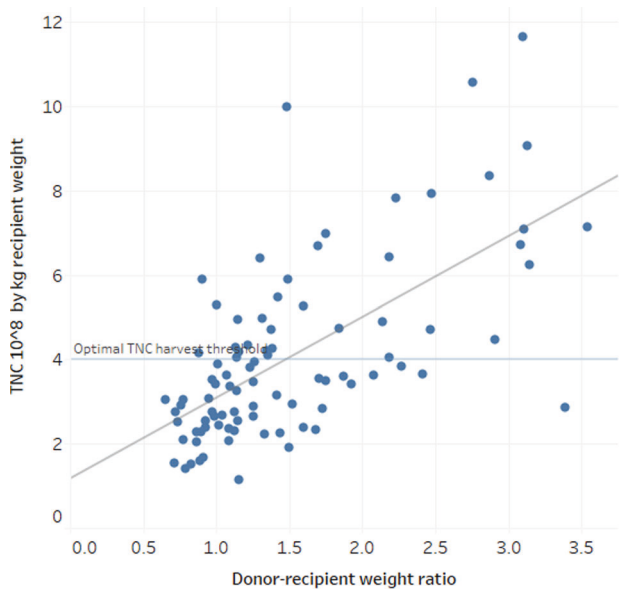
Univariate (Chi-squared, Wilcoxon rank sum, and Kruskal-Wallis tests) and binary logistic regression analyses were performed where appropriate.

Results: Donor-recipient weight ratio was significantly associated with achieving optimal yields ($p < 0.001$): less than 10% of donations where the donor was lighter than the recipient achieved an optimal yield (see figure). Higher-volume harvests (≥1351ml) were significantly less likely to achieve the optimal yield compared to lower-volume harvests (< 1050ml) (8% vs 68%, $p< 0.001$). The rate of the optimal harvest yield achieved varied significantly between the four collection centres (17%, 72%, 47% and 30%, $p = 0.01$).

Women were significantly more likely to report physical symptoms, pain, and general symptoms compared to men (see table). There is a trend of donors with lower Haemoglobin pre-donation level experiencing a delayed physical recovery ($p = 0.07$) and an association of donors having not recovered emotionally being significantly less likely to have recovered physically ($p = 0.04$) in the univariate analyses. However, in the multivariate analyses, gender emerged as the only significant factor impacting physical recovery: female donors were more likely to report any physical symptom ($p = 0.04$, OR 3.6), pain ($p = 0.04$, OR 3.7) and general symptoms ($p = 0.004$, OR 3.8).

Conclusions: Donor-recipient weight ratio is the most critical factor in achieving an optimal BM harvest and should be considered in unrelated donor selection. In addition, procedure-related factors, such as collection centre variation and extracted harvested volume, highlight the importance of ensuring the expertise of operators in achieving the required yield.

Since female gender is significantly associated with delayed physical recovery, donor registries should tailor information on BM harvest recovery to this group.



[Scatterplot TNC 10^8/kg recipient weight and donor-recipient weight ratio]

	Day 2 post-donation survey responses N = 118	Day 2: Experienced physical symptoms N = 93 (79%)	1 week post-donation survey responses N = 120	1 week: Experienced physical symptoms N = 46(38%)	1 week: Experienced pain symptoms N = 43 (36%)	1 week: Experienced general symptoms N = 46 (38%)
Gender		**p = 0.02**		**p < 0.001**	**p < 0.001**	**p < 0.001**
Female	34	32 (94%)	33	21 (64%)	20 (61%)	21 (64%)
Male	84	61 (73%)	87	25 (29%)	23 (26%)	25 (29%)

[Self-reported donor recoveryby gender at 2 days and one week post-donation]

Disclosure: Nothing to declare.

P682

Plerixafor Salvages Autologous Stem Cell Mobilisation Procedures in Myeloma Patients Previously Treated with Lenalidomide or Autologous HSCT: Cost-effectiveness of Upfront use should be Explored

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Background: Plerixafor is a high-cost drug and NHS use restricted to failing or failed mobilisation procedures (Use of Plerixafor for Stem Cell Mobilisation, NHS England 2015). In addition to patient impact, this results in unused apheresis sessions and unpredictable workloads for stem-cell laboratories. Our aim was to identify subsets of myeloma patients that may benefit from upfront plerixafor.

Methods:

Data were captured on consecutive autologous peripheral blood stem cell mobilisation procedures performed between January 2017 and August 2018. Mobilisation was with either GCSF or cyclophosphamide-GCSF. Target stem cell yield was 2.5 or 5x10^6 CD34+ cells/Kg for one or two planned autologous haematopoietic stem cell transplants (autoHSCT). In practice some harvests did not meet strict targets but at clinician discretion were considered sufficient. Up to 3 doses of Plerixafor at 240 mcg/kg were administered either pre-emptively for failing mobilisations, or as a subsequent rescue procedure following failed mobilisation.

All significant findings were concordant between sufficient and strict targets.

Results: 138 patients underwent first mobilisation during the study period with 17(12.3%) receiving GCSF and 121 (87.7%) cyclophosphamide-GCSF. 34(24.6%) failing mobilisations met criteria for administration of pre-emptive plerixafor. Nine plerixafor rescue mobilisations were performed during study period. The mean CD34+ cell yield for the 96(69.6%) of mobilisations considered sufficient was 6.23 (range 1.35-15.72)x10^6/Kg. Retrospectively, 88 (63.8%) mobilisations met strict criteria with a mean CD34 + cell yield of 6.82(range 2.83-15.72)x10^6/Kg. There was no difference in rates of sufficient harvest when comparing males with females (71.4% vs. 66.7%, p=0.57), age < 65 with >/=65 (70.7% vs. 67.9%, p=0.85), GCSF with cyclophosphamide-GCSF (58.9% vs. 71.1%, p=0.4) and patients who had and had not received DT-PACE (57.1% vs. 71.8%, p=0.2). In multivariable analysis, previous exposure to lenalidomide (OR 0.24, 95%CI 0.08-0.65, p=< 0.05) and previous autoHSCT (OR 0.19, 95%CI 0.06-0.61, p< 0.05) were independently associated with insufficient harvest. Pre-emptive and rescue plerixafor were similarly effective amongst patients who had and had not been treated with lenalidomide and/or autologous HSCT, with a cumulative rate of sufficient harvest of 70% and 87% respectively (table 1). For pre-emptive plerixafor mean sufficient CD34 + cell yield was 5.14(1.9-12.99)x10^6/KG and at rescue was 3.9(range 1.77-9.25)x10^6/Kg.

Conclusions:

In patients previously exposed to lenalidomide or autoHSCT, we identified a high rate of failing or failed mobilisation procedures of 64.7-80% with GCSF or cyclophosphamide-GCSF protocols. Pre-emptive plerixafor was successful in 84.6% of failing mobilisations indicating an upfront strategy may also be effective for patients and contribute to a more streamlined apheresis service; previously published data suggests this is the case (Ogunniyi et al. Leuk Lymphoma 2017). NHS review of cost-effectiveness for this select group of patients is warranted.

	Sufficient Pre-emptive harvest, n (%) (n=34)	P	Sufficient rescue harvest, n(%) (n=9)	P	Cumulative n (%)	P
Previous Lenalidomide and/or autoHSCT						
No (n=23)	18/21(85.7)		2/2 (100)		20 (87.0)	
Yes (n=20)	11/13 (84.6)	0.93	3/7 (42.9)	0.44	14 (70.0)	0.26

[Success of plerixafor in previously treated patients]

Disclosure: Nothing to declare.

P683

Effect of Shipping Time and Transport Conditions on the Viability of Cord Blood Leukocytes

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Background: The aim of this analysis was to assess the influence of the shipping time and thermal conditions during transport on the viability of cord blood (CB) leukocytes (CD45+).

Methods: The analysis included 1988 umbilical CB samples from clients who gave birth in Poland between 01.01.2018 and 24.10.2018. The approval of the National Centre for Tissue and Cell Banking in Warsaw, Poland was obtained before tissue collection, and the parents signed an agreement for commercial banking of biological material. In accordance with AABB criteria, donor eligibility was first assessed by means of a mother's questionnaire. Data regarding type, date and hour of delivery, minimal and maximal temperature during transport from hospital to laboratory, date and hour of the beginning of processing, maternal age, and amount of blood harvested were collected. Cell viability was assessed, and the blood samples were analyzed by flow cytometry and cultured. In order to evaluate their viability, the CB stem cells (CD 45+) were labeled with 7-aminoactinomycin D (7-AAD), and viability was assessed based on the proportion of cells not stained with 7-AAD. Spearman rank correlation was significant for viability and minimal temperature (-0.28), maximal temperature (-0.16), delta temperature (0.26), and time (-0.34), and a multifactor linear regression model was created.

Results: The best multifactor regression model included the time from delivery to the beginning of processing, the minimal temperature, and natural delivery at night (compared to C-section during the day). The R^2 for this model was 0.195. In comparison, the R^2 for the interaction between the blood volume, minimal temperature, and time was 0.079.

The risk of bacterial contamination was associated with the season. The percentage of positive cultures was 11% in winter, 9% in the interim season, and 13% in summer. The difference between summer and the winter and interim seasons taken together was significant (p=0.02). However, microbiological contamination did not influence viability. The difference in minimal values was 6.0 percentage points and was not significant.

CB volume was greater after C-section than after vaginal birth. The median viability and quartiles 1 and 3 were lower after natural birth, but the minimal value was lower in the C-section subgroup ($p< 0.000001$). However, due to the large sample size, several C-section samples did not receive this minimal value. We noticed a similar situation after grouping the delivery mode based on daytime (day and night). Although the median difference was significant for comparisons based on daytime, only natural birth at day guaranteed a viability suitable for transplantation. The lowest minimal value was recorded the subgroup that underwent C-sections during the day.

Conclusions: Over 80% variability in leukocyte viability was explained by factors other than the transport conditions. This observation requires a detailed analysis that will lead to an improvement in CB harvesting.

Disclosure: Izabela Zdolińska-Malinowska, Dariusz Boruczkowski, Maciej Rojek, and Michał Piątek are the employees of the Polski Bank Komórek Macierzystych S.A. (FamicordGroup), Warsaw, Poland

P684

Optimization of a Stem Cell Mobilization Strategy for Patients with Multiple Myeloma and Lymphoma

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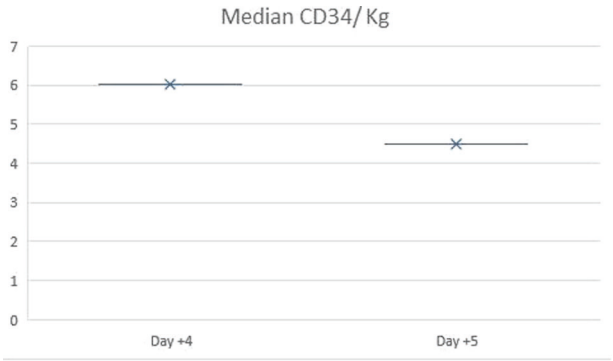
Background: Traditional mobilization strategies use growth factor (G-CSF) for 5 to 7 days because $CD34^+$ cell levels in the blood usually peak on the fifth day of G-CSF according to first published data. Our objective is to demonstrate that patients with myeloma (MM) or lymphoma candidates for autologous steam cell transplant (ASCT) could benefit from a hematopoietic progenitor (HP) mobilization strategy with G-CSF at a dose of 5μg/kg /12h after only 4 days.

Methods: We retrospectively reviewed G-CSF-mobilized MM and lymphoma patients in our transplant center between January 2015 and September 2019. The standard practice until June 2016 included G-CSF at a dose of 5μg/Kg/12h and CD34 assessment in peripheral blood (PB) on day+ 5 in patients without risk factors for poor mobilization (thrombocytopenia, alkylating agents, radiotherapy, >60 years old, lenalidomide, >3 chemotherapy lines, prior mobilization failure) and on day +4 for patients with risk factors who could benefit from early administration of plerixafor. Henceforth, the new mobilization strategy assessed PB CD34 on day +4 in all patients. Cases with chemomobilization were excluded. Data collected included demographic variables, diagnosis, risk factors for poor mobilization, day of mobilization, use of plerixafor, number of leukapheresis performed, PB and product CD34 yield. Target CD34 / kg were 2 million in lymphomas and 4 in most MM.



[Median CD34/ Kg].

Results: The mobilization strategy was G-CSF in 147 (86.98%) and G-CSF plus plerixafor in the remainder. The target dose was 2 million CD34/kg in 106 (62.72%) and 4 million in 63 (37.28%). 45.8% mobilized in day+ 4 and 35.1% in day+ 5. 13% mobilized in day+ 6 or later and 6.1% did not mobilize PB.

Overall, 135 (79.89%) patients attained target dose and 89.3% obtained 2 million CD34/kg. Among those who mobilized in day +4, 151 (89.35%) patients achieved 2 million CD34/Kg. Of the patients who sought to mobilize in day +4, there is no greater proportion of patients who require second leukapheresis than those in day+ 5.

There were no statistically significant differences in risk factors between patients with day +4 and +5 mobilization, nor were there any when these factors were analysed independently. The CD34 count in PB was higher in day+ 4 than in day+ 5.

Median age	58 years	Range 18-74
Sex	92 males	77 females
Median CD34+ cells collected	6 million (day +4)	4.5 million (day +5)
Factors of poor mobilization	No risk factors	45 (26.63%)
	1 risk factor	89 (58.66%)
	2 risk factors	28 (16.57%)
	3 risk factors	7 (4.14 %)

[Patient characteristics]

Conclusions: Mobilization with filgrastim 5μg/12h for 4 days proved to be an effective strategy in our experience obtaining the required cell dose for ASCT in most patients. The benefits of this strategy include limiting G-CSF exposure without requiring additional apheresis. We were not able to identify specific subgroups that would need one more day of mobilization/second apheresis as no differences in risk factors or demographic variables were found.

Disclosure: Nothing to declare.

P685

Autologous Lymphapheresis for the Production of CAR-T Cells

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Background: CAR-T cells are a promising new immunotherapy. The first step in manufacturing is to collect autologous CD3 lymphocytes by apheresis, through which blood mononuclear cells are collected and subsequently processed.

Once collected, the cells undergo a procedure to eliminate monocytes and to enrich the T cells and transduce them. Subsequently, are activated exvivo and transduced with a lentiviral vector containing the anti-CD19CAR transgene and finally the ex vivo Tcell expansion is performed to achieve the desired final dose.

The apheresis procedure is variable, because patients often have low white blood cell counts, have received multiple chemotherapy lines including bone marrow transplantation and/or radiotherapy.

We present our experience in the collection of autologous T lymphocytes for the manufacture of CAR-TCD19 cells in adult patients with refractory or recurrent diffuse large cell lymphoma and follicular lymphoma refractory or in relapse after one line treatment, whose indication was approved by the transplant committee and advanced therapies.

Methods: 18 lymphoapheresis procedures were performed on a Spectra Optia machine, using the CMMN cell program, with a collection target of 1 $x10^9$ CD3 and 2 $x10^9$ total nucleated cells.

The data of the determinations prior to the onset of apheresis were collected: the blood counts included in the blood count, biochemistry and CD3, the parameters of apheresis, the products and the adverse events that occurred before were also collected and after apheresis. Finally, the production data of the CAR-T lymphocytes were collected and correlated with the apheresis data. The dose of CAR-T lymphocytes is 0.6 - 6x108.

Results: 18 procedures with a mean age of 48 years. Patients underwent apheresis with variable counts of absolute lymphocytes, with an average of 5044 cells/ml.

No patient had a CD3 + < 350 / uL count, the average was 959/uL. The TNC target was obtained in 94.4%. One patient needed 2 apheresis to reach the goal of TNC and the production of CAR-T cells was possible in 72%. There were 2n 2 patients production failures and in 2 patients there was microbial contamination that forced the apheresis product to be disposed of. The collection efficiency was 52%. The correlation between the pre-aphaeresis CD3 and the CD3 collected at the end of the procedure was 0.479; It indicates that there is a positive correlation between both variables.

61% of lymphoapheresis was performed by peripheral venous access.

One patient (5%) presented a minor adverse event during the apheresis procedure, no serious adverse effects were recorded.

The mean of CAR-T received was 1.97 x 108 and the average of CNT was 0.97 x108, the quality controls were correct. The average viability was 98.57% and the average transduction was 22.39%. The correlation between the CD3 sent to the manufacturing center and the total number of TCAR obtained 0.26; which indicates a positive correlation between both variables.

Conclusions: Mononuclear cell apheresis for CART cell therapy is well tolerated and safe, and it is possible to obtain an adequate amount of CD3 for the manufacture of CART cells in very pretreated patients who have low lymphocyte counts.

Disclosure: No disclosure

P686

Red Blood Cell Depletion and/or Volume Reduction in Bone Marrow Processing: A Comparison of Two Methods

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Background: Red blood cell (RBC) depletion and volume reduction of Bone Marrow (BM) grafts is often required due to donor:recipient ABO incompatibility or due to high volume of harvested BM relative to recipient weight. We have compared two methods of BM RBC depletion and volume reduction: Density Gradient (DG) separation with hydroxyethyl starch polymer vs. the "BM processing" module of the Spectra Optia apheresis system.

Methods: BM from 10 allogenic donations was processed using the "BM processing" (BMP) module of the Spectra Optia apheresis system (Terumo, Lakewood CO, USA) and 10 allogenic BM donations were processed using DG with Hespan [BRAUN, Bethlehem, PA, USA]. 12 out of 20 procedures (7 BMP Optia separations and 5 DG separations) were performed to achieve near-complete (0.1 ml packed red blood cell mass per kg recipient weight) RBC depletion due to donor:recipient ABO incompatibility. The Optia procedure was performed according to the manufacturer´s instructions; DG separations were performed using our in-house standard operating procedure. Pre and post procedure samples were taken to analyze mononuclear cell (MNC) recovery, the extent of RBC volume depletion, and sterility. We recorded the duration of each procedure. All procedures were performed at Schneider Children´s Medical Center between 02/18-10/19.

Results: Mean MNC recovery was similar (81.4±10.4 % using the Optia BMP module and 82.4±8.9% with the DG method). RBC depletion in the 12 procedures where it was required was nearly complete using both methods (99.2±0.5 % reduction with the Optia BMP module and 99.6±0.4 % reduction with the DG method). By contrast, processing time was markedly shorter using the Optia BMP method (1.5 hours) vs the DG procedure (4.5 hours). Volume reduction using the automated Optia system was efficient (90.8±2.1%), final volume of DG preparations was driven by physician request. Sterility tests were negative for all 20 procedures.

Conclusions: The BM processing using the BMP Optia module is simple, reliable and safe. It is significantly less time consuming and less operator dependent as compared with DG separation. The reduced procedure time required for BM processing by BMP Optia module make it the preferred method for use for future procedures at our center.

Clinical Trial Registry: NA

Disclosure: NA

P687

Correlation of Intra-operative Total Nucleated Count and Donor Characteristics with Final Allogeneic Bone Marrow Graft Characteristics and Recipient Clinical Outcomes

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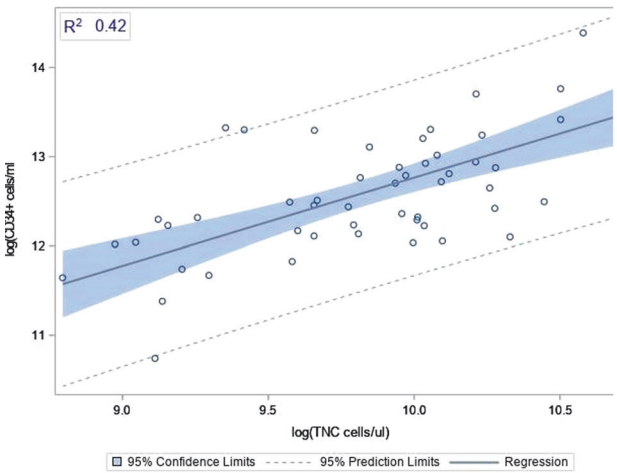
Background: Bone marrow graft cell content is known to impact engraftment potential and kinetics after allogeneic hematopoietic cell transplantation (alloHCT). However, use of intra-operative surrogates, such as total nucleated cell count (TNC), are of unclear utility in predicting final graft characteristics. In addition, demographic and clinical factors may influence graft cellular profile and recipient engraftment.

Methods: We retrospectively reviewed bone marrow harvests at our institution performed over an 11 year period (2009-2019), and limited the data analysis to donor-recipient pairs for whom intra-operative TNC (ioTNC) was available (autologous back-up grafts were excluded). During this time, standard of care was to perform ioTNC after 50% of the projected final graft volume was collected, to guide collection volume targets. Simple linear regression was used to assess unadjusted association between ioTNC (cells/μL) and final graft CD34+ cells/mL. LASSO regression with Schwarz Bayesian Information Criterion determined patient and donor characteristics associated with final graft CD34+ cells/mL.

Results: A total of 74 bone marrow harvests were performed, of which 14 were autologous and an additional 7 lacked ioTNC data, leaving 53 donor-recipient pairs for analysis. Patients were transplanted for hematologic malignancies (n=26, 49%) or nonmalignant conditions (n=27, 51%), using either myeloablative conditioning (n=33), reduced intensity conditioning (n=18), or without conditioning (n=2). Median (range) donor and recipient ages were 13 (0.7-28) years and 9 (0.2-21) years, respectively. The median ratio of donor/recipient weight was 1.225 (range 0.31-7.13); 11 donors weighed less than the recipient and only 3 donors were < 75% donor weight. Donors had a median pre-operative total leukocyte count of 7110/μL (range 3430-16600). Median total volume of harvested marrow was 15.3ml/kg (range 4.3-20.4ml/kg) of donor weight and 19.4ml/kg (range 4.7-87.4ml/kg) of recipient weight. Median ioTNC was 20930/μL (range 6600-44310/ μL) or $2.1x10^9$/mL, corresponding to median predicted final graft TNC of 3.59 $x10^8$/kg recipient weight (krw) (range 1.28-19.42$x10^8$/krw). Of six grafts with

projected TNC< $2x10^8$/krw, none resulted in a graft with < $2x10^6$ of CD34+ cells/krw. Four patients (7.6%) experienced graft failure; of engrafting patients, neutrophil and platelet engraftment occurred at a median of 18 (range 8-27) and 26 (12-160) days, respectively. Simple linear regression between ioTNC and CD34+ cells/mL resulted in an R^2 of 0.42 (Figure 1). LASSO regression identified ioTNC, donor age, donor weight as moderately predictive of final graft CD34+ cells/mL (adjusted R-squared=0.66). A 10% increase in ioTNC corresponded to approximately a 6% increase in final graft CD34+/mL, while age and weight were inversely associated with final CD34+ cells/mL. Donor complications were minimal; no healthy donors required blood product support, and 2 required additional care for anesthesia-related issues (nausea/vomiting/pain).

Conclusions: ioTNC correlates moderately with marrow product CD34+ cells/mL. However, even when ioTNC predicted suboptimal final graft cell characteristics, all grafts ultimately were adequate in terms of CD34+ cells/krw. Other donor characteristics (BSA, age) also were moderately predictive of marrow cell counts and should be incorporated into decisions regarding donor selection and marrow collection targets.



[Simple linear regression of intraoperative TNC and final CD34+ cells/mL]

Disclosure: Nothing to declare.

P688

Multicentre Evaluation of The HPC Modus (XN-20) for Timing the Harvest of Stem Cells from Peripheral Blood

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Background: Timing of apheresis is usually determined by CD34+ cell count in peripheral blood by flow cytometry. However, this method is very time consuming (+/- 1h30), costly and requires highly trained and experienced laboratory technicians and dedicated equipment. We evaluated the automated haematopoietic progenitor cell (HPC) modus on a XN-20 Sysmex analyser which can deliver HPC results in 4 min. This method uses differences in membrane lipid composition between HPC and more mature progenitor cells or other haematopoietic cells for quantification of HPC (% and cells/μL). The clinical advantages of the HPC modus is a significantly shorter turnaround time simplifying patient management.

Methods: Peripheral blood of healthy subjects (n=20, centre A) and non-stimulated patients (n=42, centre C) were analysed to assess HPC background (XN-20 analyser). HPC measurements (n=318) on XN-20 of peripheral blood of patients were compared to CD34+ cells measured with flow cytometry following ISHAGE single platform protocol in all centres. Patients had diverse hematologic malignancies (acute myeloid leukaemia, B-non Hodgkin lymphoma, multiple myeloma and others) and were stimulated with standard regimens for mobilisation. Related stem cell donors for allogeneic transplantation were also included. Five centres participated in our study. Statistical analysis was performed using MedCalc.

Results: Median HPC in healthy controls (centre A) and non-stimulated in-house patients (centre C) was 10 cells/μL (range 0 - 29 cells/μL) and 9 cells/μL (range 0 - 37 cells/μL) respectively. A moderate correlation (R>0,80) was found between HPC and CD34+ cells for non-myeloma patients (n=158). In general R was < 0,80 for myeloma patients (n=160) except for centre D (R=0,96). Mean bias was higher for myeloma compared to non-myeloma patients except for centre D. HPC cut-offs for starting apheresis (equivalent to 20 CD34+ cells/μL) were 29-30 cells/μL for the non-myeloma group (sensitivity 70,8 - 100%, specificity 88,2 - 100%) and 22-52 cells/μL for the myeloma group (sensitivity 81,8% - 100%, specificity 75,0 - 88,9%).

Conclusions: HPC showed substantial background (median of 10 cells/μL) in this study. Although correlation in our study was good for non-myeloma patients, a significant overestimation by HPC method was found in myeloma patients in some centres. Due to this variability

HPC cut-offs for starting apheresis were defined per centre. Overestimation of HPC method in multiple myeloma patients has been described in the literature[1]. The reasons for this variability have not yet been elucidated. However there are also publications describing equivalent HPC and CD34+ results[2]. The differences found in our study between the participating centres and in the literature require further investigation.

1. Dima F, Barison E, Midolo M, Benedetti F and Lippi G. Assessment of haematopoietic progenitor cell counting with the Sysmex XN-1000 to guide timing of apheresis of peripheral blood stem cells. 2019 Jul 25:1-9. https://doi.org/10.2450/2019.0086-19

2. Grommé M, Russcher H, Braakman E, Klinkspoor JH, Dobber JA, de Greef I et al. Multicentre study to evaluate a new enumeration method for hematopoietic stem cell collection management. Transfusion 2017;57;1949-1955.

Disclosure: Nothing to declare.

P689

Impact of Change of Mobilisation Method on Adequacy of Stem Cell Collection in Multiple Myeloma Patients - Single Centre Experience

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Background: Despite the emergence of many new treatments, high dose Melphalan and autologous stem cell transplantation (ASCT) remains the standard of care for younger patients with Multiple Myeloma (MM). Effective ASCT is dependent on an adequate collection of haematopoietic stem cells (HSC) from the patient, usually by peripheral stem cell harvest. Critical to this process is effective mobilisation of HSC from the bone marrow into peripheral blood. In our centre, a decision was made to move from a preference from mobilisation with cyclophosphamide and GCSF, to GCSF alone in most cases. This study evaluates the impact of this change on overall rates of stem cell collection adequacy.

Methods: In broad terms, the two main mobilisation strategies are the use growth factors alone (Granulocyte-colony stimulating factors, (G-CSF), or of growth factors in combination with chemotherapy (Chemo-mobilisation). In addition, chemokine receptor antagonists (Plerixafor) can be used to improve the efficacy of mobilisation by both methods. The methods are known to have differing advantages and disadvantages. Chemo-mobilisation may increase adequacy compared to GCSF alone, but is known to increase toxicity and delay mobilisation, increasing the numbers of days of harvest required. In these times of limited inpatient bed resources, in 2017, decision was made to increase the number of patients receiving chemo-free mobilisation in order to reduce the need for day unit spaces in our haematology department for chemo-administration and reduce chemotherapy induced toxicity in our patients. The impact of this policy change on adequacy of stem cell harvest was then evaluated.

An adequate collection is considered to be a harvest of a minimum of 2×10^6 CD34+ cells/kg for a single ASCT and a least 4 $\times10^6$ CD34+ cells/kg for two ASCTs. Mobilization failure is usually defined as the inability to procure 2×10^6 CD34+ cells/kg despite 3 apheresis sessions

Results:

During the 2017/18 period a total of 97 Myeloma patients underwent HSC collection (2017, n=48, 2018, n=49). The change in centre mobilisation policy led to marked differences in the rates of chemo-mobiliation vs chemo-free (2017= 10.4% vs 89.6%; 2018= 71.4% vs 28.6%). Rates of adequacy of collection were not significantly different when comparing the two mobilisation regimes, chemo-mobiliation vs chemo-free (2017-88% vs 100%, 2018- 92.8% vs 94.2%). There was however, an increase in the need for a second collection day chemo-mobiliation vs chemo-free (2017 -30% vs 60 %, 2018-29% vs 54%)

Conclusions: In conclusion, in our single centre experience, a switch to a preference for chemo-free mobilisation can be undertaken without impact on adequacy of stem cell collection. An increase in the requirement for collection days was observed. We need to further look at inpatient admissions with infection between mobilisation and autograft.

Clinical Trial Registry: nil

Disclosure: nothing to declare.

P690

Two Different Plerixafor Stem Cell Mobilization Strategies. A Multicenter Experience

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Background: A significant proportion of patients with non-Hodgkin's lymphoma (NHL), Hodgkin's disease (HD) or multiple myeloma (MM) are hard-to-mobilize with conventional mobilization regimens but depending on disease 5-25% of patients considered for high-dose therapy failed to mobilize or have a suboptimal mobilization. Plerixafor is used to improve mobilization of blood stem-cells. We present our experience in patients who failed a previous mobilization attempt and compare then with patients who plerixafor was added if poor first mobilization was demonstrated.

Methods: We retrospectively collected data from 5 spanish centres on 125 patients affected by NHL, HD, MM while receiving plerixafor in mobilization. From January 2008 to December 2017 30 patients received plerixafor associated G-CSF in a second attempt at mobilization when they have already failed a first mobilization, and 95 patients pre-emptively received plerixafor who seem mobilize poorly: (1) blood CD34+ cells/μL < 10 on the day before or the programmed day to initiate aphaeresis after G-CSF or (2) < 1 x 10e6/kg after the first aphaeresis process.

Results: Second mobilizations: 30 patients received plerixafor in this setting. The median age was 61y (25-70). 15 had NHL, 13 MM and 2 HD. 29 received standard plerixafor dosage, 1 patient received adjusted dosage by renal insufficiency, and all of patients received G-CSF with a median dose of 10 μg/kg/d (10-20). Median number of plerixafor injections was 2 (1-4) and median CD34+ cells count after the first plerixafor injection was 14/μL (7-113). 25 (84%) of them initiated aphaeresis. A median of 2.23 x 10e6/kg (0-10.71) CD34+ cells were collected with a median of 1 (1-4) aphaeresis. >2 x 10e6/kg CD34+ cells were achieved in 19 (63%) patients (61.53% in NHL, 66.6% in HD and 84.61% in MM).

Pre-emptive use: plerixafor was administered to 95 patients (47 MM, 43 NHL and 5 HD) with a median age of 58y (23-75). The reason to use plerixafor pre-emptively where low blood CD34+ counts in 63 patients an poor yield collection in 32. All received standard plerixafor dosage before 4-day G-CSF therapy with a median dose of 10 μg/kg/d (10-20). Median number of plerixafor injections was 1 (1-4). Median CD34+ cells after the first plerixafor administration was 7.8/μL (0.84-11.39). The day the patient should start apheresis, the peripheral CD34+ count has increased to a median of 35,12/μL (1.33-118). All patients with a CD34>5/μL cell count started apheresis and only 5 patients did not mobilize. A median of 3.275 x 10e6/kg (1.52-15.97) CD34+ cells were collected with a median of 1 (1-4) aphaeresis. >2 x 10e6/kg CD34+ cells were achieved in 79 (87%) patients.

Conclusions: Results from this study showed that plerixafor is a safe and active mobilising agent in the two strategy arms with 63% efficacy using it in remobilization and 87% as pre-emptive strategy. Although pre-emptive use may not be able to completely eliminate the need for a second attempt to mobilize, this strategy seems more efficient and should be considered in patients judged as poor mobilizers using it to optimize patient outcome and reduce of other hospital resources.

Disclosure: SANOFI INVESTIGATION FOUNS

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Autologous Peripheral Blood Stem Cells (PBSCS) Mobilization and Collection-princess Noorah Oncology Center Experience, Kamc - Jeddah - Saudi Arabia

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Background: The use of high dose chemotherapy with autologous peripheral blood stem cell rescue for treatment of high risk haematological malignancies is contingent upon collection of a minimum CD34+cell dose of $\geq 2\times10^6$/kg.

Although PBSC mobilization and collection are highly effective in the majority of patients, poor mobilization (PM) has been reported in approximately 15% of patients.

Regimens for mobilization of PBSCs for ASCT differ according to the disease entity. The following two basic principles are common practice: chemotherapy followed by growth factor (G-CSF) or use of G-CSF alone. The CXCR4 inhibitor plerixafor can be administered to increase CD34+cell yields in both approaches. Due to its high cost, in a resources-limited economics, plerixafor is generally restricted to patients failing to reach sufficient peripheral blood (PB) CD34+level (pre-emptive use).

Methods: We retrospectively analyzed all patients undergoing PBSC mobilization and collection at our institution between February/2014 and September/2019 (n=174).

Plerixafor was administered pre-emptively in case of PM, for chemo-mobilization a plateau of < 10 CD34+/μl PB under continued G-CSF stimulation (i.e. leukocytes $>1\times10^9$/L and no increase of CD34+level) and after G-CSF mobilization a CD34+count of < 8/μl in PB at day 4 triggered pre-emptive application of plerixafor. Between CD34

+levels of 10-15/μl PB (at maximum stimulation), plerixafor will be used at the discretion of the treating physician.

Stem cells were collected using Spectra Optia® machine and Mononuclear Cell collection.

Results: The minimum number of 2×10^6 CD34+cells/kg, representing one transplant, was achieved in 172(99%) patients.

We reported PM (peak PB CD34+levels < 10/μl) in 17 (10%) patients and borderline PM (peak CD34+levels between 11-19/μL at maximum stimulation) in 11(6%) patients. 84% of the patients had a CD34+levels ≥20/μl at the peak of stimulation.

Pre-emptive plerixafor was administered to 20(11%) of the patients, among them three patients had CD34+levels between 10-15/μL. Five of 20 patients (25%) failed first pre-emptive dosing of plerixafor and thus had inadequate mobilization and collection of CD34+cells. Of the 5 patients who failed to respond to pre-emptive dosing of plerixafor, 3 underwent successful PBSC harvest after additional plerixafor.

In total, 2(1%) of the patients had inadequate of CD34 +cells mobilization (< 10 $CD34^+$cells/μL in PB before apheresis). Graph1

Conclusions: With the use of pre-emptive plerixafor, (15/20,75%) patients achieved the primary endpoint, preventing the need for a second mobilization session. The collection failure rate (20/174,11%) was reduced to (5/174,3%) in the present data, rendering the collection of at least a single transplant with a single mobilization attempt a realistic goal in all patients undergoing PBSC mobilization.

The pre-emptive plerixafor administration after chemotherapy or G-CSF mobilization demonstrated a reduced rate of PM (never reaching threshold of PB CD34+≥10/μl) from 10% to 1%. On autologous PBSC mobilization suggests plerixafor not necessary if peripheral CD34+count >15/μl on predicted day of apheresis & recommends Pre-emptive plerixafor if peripheral CD34+count is < 10/μl at maximum stimulation. Between 10-15/μl, suggests "dynamic-approach" with case-by-case decision-making. Pre-emptive plerixafor (during initial mobilization episode) is almost certainly better for the patient than re-mobilization with G-CSF+plerixafor, since it avoids delay to transplant and anxieties about possible failure at second attempt.

Disclosure:

Nothing to declare.

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Review of Plerixafor use in a Tertiary Paediatric Oncology Centre

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Background: Plerixafor is indicated in combination with G-CSF to enhance mobilisation of haematopoietic stem cells in children with lymphoma or solid malignant tumours who have had harvest failure with G-CSF alone[1]. In our centre, it is used third line when G-CSF alone or in combination with chemotherapy mobilisation has failed to mobilise sufficient stem cells. While mobilisation harvest failure rates with G-CSF plus plerixafor have been quoted in the adult literature as high as 40%[2, 3], failure rates in paediatrics have not been published. Poor mobilisers are those patients whose peripheral blood $CD34^+$ count fails to rise above 10 x 10^6/L.[2]

In March 2019, the EMA published details of a paediatric study as part of its consideration for a paediatric license[4]. This included new information that a trigger CD34+ level of 7 x 10^6/L was used in order to initiate Plerixafor and a minimum threshold of $CD34^+ \geq 20 \times 10^6$/L to perform subsequent apheresis. A retrospective review of all patients who received Plerixafor was then conducted to evaluate its use and efficacy in our centre.

Methods: Medical records, Pharmacy dispensing software (Cliniscript®) and apheresis records were used to collate the data

Results: Nine patients received Plerixafor during the review period. The mean age was 6yrs (range 1-14yrs) and mean body weight was 26kg (range 13-62kg). Five patients had primary metastatic neuroblastoma while four had relapsed neuroblastoma.

All patients received steady state G-CSF 10microgram/kg/day. Six patients then had G-CSF plus chemotherapy mobilisation. Patients received between 1 and 3 doses of Plerixafor (mean 1.8 doses). Doses of Plerixafor were correct and time between Plerixafor administration and apheresis was 11 hours for the initial 6 patients treated but was then reduced to 4hours for the subsequent 3 patients.

If we had applied a $CD34^+$ count criterion of >7 x 10^6/L to initiate Plerixafor, only one patient would have met that criterion. The mean $CD34^+$ count in response to Plerixafor was 8.2x 10^6/L (range 0.52 - 27 x 10^6/L), measured pre-apheresis. Four of 9 patients failed to reach a $CD34^+$count of >10 x 10^6/L and could be labelled as poor responders. Only one patient met the retrospective criterion of ≥20 x 10^6/L to start apheresis.

None of the patients reached their target yield following Plerixafor; the average response was 43% of target yield. Mean yield in the primary metastatic neuroblastoma patients was 1.9 x 10^6 $CD34^+$ cells/L (target yield 6 x 10^9/L) while in the relapsed group it was only 1 x 10^9 $CD34^+$/L (target 3 x 10^9/L). Collection efficiency reached the target efficiency (≥40%) in all cases.

All patients had been heavily pretreated with myelosuppressive chemotherapy prior to harvesting.

Conclusions: The patients who received Plerixafor all had either neuroblastoma or relapsed neuroblastoma. The response to steady-state G-CSF plus Plerixafor was poor, with no patient reaching their target apheresis yield. Response to Plerixafor was worse in patients with relapsed neuroblastoma. However, had the criteria to initiate Plerixafor been known at the time, only one patient would have received it and proceeded to apheresis.

Disclosure: nothing to declare.

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Leukocytapheresis - One Technique, Diverse Opportunities in the Therapy of Patients

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Background: Leukocytapheresis (LA) is a specific apheresis technique with predominant collection of leukocytes. It is routinely utilized for the reduction of the extent of leukocytes in patients with hyperleukocytosis as well as in hematopoietic stem cell collections (PBPC) in mobilized donors and patients. Recently, LA plays an important role in non-mobilized mononuclear cells (MNC) collections. MNC have been increasingly used in more specific antitumor therapy (vaccines based on dendritic cells function, CAR-T cells, γδ lymphocytes etc).

The aim of the study was to evaluate and compare the results of LA in the MNC, and PBPC collections in different groups of patients and donors.

Methods: MNC and PBPC collections were performed in groups of:

1. Non-mobilized patients and donors.

a) In patients: with acute and chronic GVHD (a/c GVHD, 119 procedures, 8 patients), with prostate cancer (CaP, 20 procedures, 20 patients), and with ALL/DLBCL (5 procedures, 5 patients). MNC were collected for extracorporeal photochemotherapy (ECP), for vaccines based on dendritic cells function, and for CAR-T cells.

b) In healthy donors: who were collected for DLI (7 procedures, 7 donors).

2. Mobilized PBPC donors: for allogeneic HSCT transplantation (70 procedures, 47 donors, Zarzio).

Collections were performed using Spectra Optia, v. 11, Terumo, CMNC, MNC (2016-2019). The precollection numbers of leukocytes in blood, as well as the numbers of leukocytes, percentage (%) of MNC, CD 3+ cells, and CD 34+ cells in products were evaluated. The results are expressed as medians and their ranges.

Results: Total blood volumes processed (×TBV) were in patients and donors: GVHD 1.4 (1-1.7), CaP 1.5 (1-1.8), ALL/DLBCL 2.6 (2.2 - 2.7), DLI 1.4 (0.8-1.6), PBPC 3 (1.6-4.5).

We found in the MNC products:

- numbers of leukocytes: GVHD 7 (4-12), CaP 13 (6-32), ALL/DLBCL 17 (11-28), DLI 7 (4-12), PBPC 62 (24-112) $\times 10^9$;
- percentage of MNC: GVHD 86 (45-97), CaP 86 (52-94), ALL/DLBCL 87 (70-99), DLI 86 (54-98), PBPC 72 (42-99) %;
- percentage of CD 3+ cells: GVHD 52 (19-92), CaP 75 (53-88), ALL/DLBCL 89 (86-99), DLI 42 (14-50), PBPC 24 (9 -78) %;
- the median yield of CD 34+ cells from one collection in PBPC donors: 3.6 (0.6-17)Í10^6/kg b.w. of patient.

Conclusions: Spectra Optia was proved to be an efficient system in the process of MNC and PBPC collections. We obtained the sufficient numbers of MNC, CD 3+ and CD 34+ cells for therapy of the patients. Percentage of MNC in the products was in non-mobilized patients and donors higher than in mobilized PBPC donors. Percentage of CD 3+ cells in non-mobilized patients was higher than in donors of DLI and PBPC (non-mobilized and mobilized). The cause of such differences is not clear yet, and will be studied in near future. There may also be an opportunity for optimizing the collection regimen. No serious adverse reactions in the course of collections have been observed.

Disclosure: Nothing to declare.

Stem cell source

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Impact of HLA-mismatch on Outcomes after Unrelated Bone Marrow Transplantation in Pediatric Patients: A Retrospective Analysis by The JSHCT HLA Working Group

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Background: A previous Japanese study revealed that a human leukocyte antigen (HLA) mismatch was associated with higher overall mortality after unrelated bone marrow transplantation (UBMT) and the effects of single HLA-C and -DRB1 allele mismatches significantly differed over the time periods in adult patients (Br J Haematol. 2013, 161:566). As different effects of HLA disparity on transplant outcomes after single-unit cord blood transplantation between pediatric and adult patients with leukemia was reported (Haematologica. 2013, 98:814), we investigated the impact of HLA-mismatch on outcomes after UBMT in pediatric patients using Japanese registry data.

Methods: We analyzed patients with leukemia (ALL, AML, and CML) or myelodysplastic syndrome who underwent the first UBMT (n =1,334) aged 15 years or under between 1993 and 2017 in Japan. The effect of HLA-mismatch on overall survival (OS), relapse, and non-relapse mortality (NRM) was analyzed after adjusting for other significant variables.

Results: The HLA-mismatch was significantly associated with a low relapse rate (1 allele mismatch; hazard ratio (HR) 0.75, $p = 0.033$, 2 allele mismatch; HR 0.67, $p = 0.023$), especially in the standard-risk groups (1 allele mismatch; HR 0.54, $p = 0.001$, 2 allele mismatch; HR 0.54, $p = 0.012$) as compared with HLA-match. However, the NRM was higher in HLA-mismatch group (1 allele mismatch; HR 1.76, $p < 0.001$, 2 allele mismatch; HR 2.13, $p < 0.001$). These resulted in the significant association between HLA-mismatch and low OS in one allele mismatch (HR 1.34, $p = 0.006$) and two allele mismatches (HR 1.41, $p = 0.008$). In the locus mismatch analysis, 2 allele mismatch and C locus mismatch were significantly associated with a low relapse rate (2 allele mismatch; HR 0.67, $p = 0.023$, C locus mismatch; HR 0.62, $p = 0.022$). However, the significant higher NRM in 2 allele and C locus mismatch (2 allele mismatch ; HR 2.17, $p < 0.001$, C locus mismatch ; HR 2.17, $p < 0.001$) resulted in significantly low OS in 2 allele mismatch and C locus mismatch (2 allele mismatch HR 1.41, $p = 0.007$; C locus mismatch HR 1.47, $p = 0.006$). There is no significant difference of OS in DRB1 allele mismatch (HR 1.11, $p = 0.468$), unlike in adult patients. In the time period analysis (1993-2009 and 2010-2017), the differences of OS in 2 allele mismatches persisted, however, the hazard risk in C locus mismatch seemed to be lowered in the recent period. (1993-2009: 2 allele mismatch HR 2.15, $p < 0.001$; C locus mismatch HR 2.25, $p < 0.001$, DRB1 locus mismatch HR 1.54, $p = 0.079$; 2010-2017: 2 allele mismatch HR 2.33, $p = 0.032$; C locus mismatch HR 2.06, $p = 0.070$, DRB1 locus mismatch HR 1.08, $p = 0.180$).

Conclusions: Similar to adult patient, we could confirm that HLA-matched donor should be the first candidate in pediatric patients because of its association with high overall survival rates. On the other hand, the effects of HLA disparity differed between children and adults, also in UBMT outcome.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare.

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Title: Clinical Impact of Donor Epitope-specific HLA Antibodies and Third-party HLA Antibodies in Haploidentical Hematopoietic Cell Transplantation

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Background: Haploidentical hematopoietic cell transplantation (HaploHCT) made access to HCT possible for patients who have no matched donor available, however the risk of graft failure remains high in this population. Donor specific antibodies (DSA) against mismatched HLA have been reported to have a negative impact on engraftment and outcome of HaploHCT. However, little is known about the clinical impact of donor epitope-specific HLA antibodies (EPSA) and third-party HLA antibodies (TPA) frequently seen in the sera of allosensitized patients receiving HCT from a haploidentical donor.

Methods: We retrospectively analyzed 208 consecutive patients receiving HaploHCT at City of Hope from 04/2014 to 12/2018. Pre-HaploHCT serum samples were tested for HLA antibody using LABScreen Single Antigen (One Lambda) and flow cytometric lymphocyte crossmatch. EPSA analysis was performed using Matchmaker Fusion 4.3. TPA is defined as the antibody with the highest mean fluorescence intensity (MFI) excluding EPSA and DSA. TPA was categorized into 3 risk groups: low (1-5 K), moderate (5-10 K), and high (>10 K). The EPSA is defined as the cumulative MFI for mismatched epitope(s) excluding patients with clinically significant DSA. The EPSA was

categorized into 2 risk groups based on the highest total MFI level: low (1-10 K) and high (>10 K). Calculated Panel Reactive Antibody (cPRA) was obtained for all detectable HLA antibodies in each sample. Univariate and multivariable analyses were performed to examine the associations between HLA antibodies and outcomes. All tests were 2-sided at the significance level of 0.05.

Results: Median age of receipts and donors was 45 years (range: 2-73) and 31 (range 10-68), with 61% of patients being male. Diseases included: acute leukemia (61%), MDS/MPN (17%), and lymphoma (11%). Disease risk index was intermediate in 36% and high/very high in 36% of patients. HCT- comorbidity index was more than 2 in 39% of patients. While graft-versus-host (GvHD) prophylaxis was PTCy combined with tacrolimus and mycophenolate mofetil in all patients, graft source was peripheral blood stem cells in 81% and ablative conditioning regimen was used in 41% of patients in this cohort.

DSA, EPSA and TPA were detectable in 12% (n=24), 9% (n=18) and 45% (n=93) of the patients, respectively. While, 75% of DSA was EPSA + with accumulative MFI increase (72% of EPSA with a total MFI level >10K), none of them were crossmatch positive. The majority of TPA (71%; n=66) were of weak risk, and the rest were of moderate (9%; n= 8) and high (20%; n=19). cPRA was >75% in 22 (24%) of patients and 72% had class I antibodies compared to 66% with class II among patients with TPA. In multivariable analysis, there was no statistically significant difference in neutrophils or platelet engraftment, NRM or OS in the presence or absence of TPA or EPSA irrespective of total MFI level measured, HLA class (I or II) and cPRA.

Conclusions: Unlike DSA effect previously reported, levels of pre-transplant EPSA, TPA and cPRA have not shown any deleterious impact on patients undergoing haploHCT and may not be critical in the donor selection process.

Disclosure: nothing to disclose

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The Use of Post-transplant Cyclophosphamide (PT-Cy) in Unrelated Umbilical Cord Blood Transplantation

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Background: There has been a decrease in the use of unrelated cord blood transplants (UCBT) in the past years: this is probably due to slow hematologic and immune recovery, resulting in a relatively high non relapse mortality (NRM). The addition of anti-thymocyte globulin (ATG) in the conditioning prevents graft versus host disease (GvHD) but makes immune recovery very slow. In addition there is a growing competition of unmanipulated haploidentical transplants.

We have opened a pilot study to test whether high dose post-transplant cyclophosphamide (PT-CY) would prevent GvHD but still allow for robust immune and hematologic recovery. ClinicalTrials.gov Identifier: NCT03802773

Methods:

Patients

The median patients' age was 58 (43-66), and the median weight was 75 kg (54-85) the diagnosis was AML in 8 patients, Ph'+ALL in one and RAEB in one patient; 6 patients were in remission and 4 had active disease.

CB units

The HLA matching of the CB unit was 5/8 antigens/alleles (A, B, C, DRB1) in six patients, 4/8 in two and 2/8 in one. The median nucleated cell dose was 3.1x10^7/kg (range 1.8- 4.5). The ABO was mismatched in all 10 patients.

Conditioning regimen and GvHD prophylaxis

The conditioning regimen was thiotepa (10 mg/kg), busulfan 9.6 mg/kg and fludarabine 150 mg/m^2 (TBF). GvHD prophylaxis was cyclosporin (CSA) starting day 0 (3 mg/kg/day(i.v.), mycophenolate (MMF) 30 mg/kg starting day +1 (p.o), and PT-CY 30 mg/kg days +3 and +5.

Results: Hematologic recovery

Median time to neutrophils 0.5x10^9/l was day 23 days (range 17-27) and the median time to a platelet count of 20x10^9/L was 38 days (range 34-40). The median counts on day +50 were as follows : Hb 9,1 gr/dL (range 8.7-11.1), Neutrophils 2,3 x10e9/L (range 1-5), PLTs 56 x10e9/L (10-90). Two patients failed to engraft and received a second transplant:one from an unrelated donor, which was successful, and one from a haplo mismatched family member which was unsuccessfull. No patient developed pure red cell aplasia despite 9/10 being ABO major mismatched.

CD4 recovery

The median CD4 count on day +50 was 74 /cmm (range 67-116) and on day +100 it was 111/cmm(range 100-136). CMV requiring treatment occurred in 3/6 evaluable patients

Outcome

Two patients with advanced disease, died early of infections, within day +20. GvHD was seen in 1 patient as a transient rash. No patient was treated for GvHD. No patient developed chronic GvHD. No patient relapsed. Seven patients survive in remission, with a median follow

up of 231 days, and a projected one year actuarial survival of 70%. Readmissions were extremely rare.

Conclusions: These first 10 patients suggest that UCBT followed by PT-CY, CSA, MMF, as GvHD prophylaxis is feasible and leads to encouraging hematologic and immunologic recovery. We were particularly impressed with the lack of GvHD, the absence of relapses and the good quality of life.

Disclosure: Nothing to disclose

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Comparative Study of Haploidentical Transplant Followed by Post-transplant Cyclophosphamide and Selective Ex Vivo T-cell Depletion vs Unrelated Cord Blood Transplant for Adults with Haematological Malignancies

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Background: Outcomes after haploidentical (Haplo) haematopoietic cell transplantation (HCT) and after unrelated cord blood transplantation (UCBT) are encouraging and have become alternative options to treat patients with high-risk haematological malignancies without human leukocyte antigen (HLA) matched related or unrelated donor. There is paucity of data comparing the outcome of UCBT and haplo HCT. We retrospectively analyse and compare the outcome of adult patients with haematological malignancies receiving UCBT and haplo HCT using two different platform for graft-versus-host disease (GVHD) prophylaxis: selective ex-vivo T cell (TCRαβ and CD45RA+) depleted haplo HCT (Koh LP et al. Blood 2018; 132: 2093a) vs unmanipulated T cell replete haplo HCT with high dose post-transplant cyclophosphamide (PTCy).

Methods: We studied 169 adults patients receiving allogeneic HCT using 4-6/6 HLA matched UCB (n=100) graft or Haplo (n=69) for various haematologic malignancies between Aug 2006 and July 2019, following myeloablative (MAC, n=76) or reduced intensity conditioning (RIC, N=93) regimen. 37 Haplo patients received unmanipulated non ex-vivo, T cell depleted graft followed by PT Cy for graft-versus-host disease (GVHD) prophylaxis (Haplo PTCy), whereas 32 patients received haplo-HCT with selective ex vivo T cell (TCRαβ and CD45RA+) depleted grafts for GVHD prophylaxis (Haplo-TCD).

Results: Two year overall survival (OS) for patients undergoing UCB, Haplo PTCy and Haplo-TCD transplant were 46%, 54% and 55% (p=0.379), and event free survival (EFS) were 41%, 50% and 45% (p=0.573), respectively; these were not significantly different among the 3 groups. Two year cumulative incidence (C.I.) of non-relapse mortality (UCB 32% vs Haplo PT Cy 20% vs 31%; p=0.514), relapse-related mortality (RRM) (UCB 24% vs Haplo PT Cy 21% vs 16%; p=0.596) and grades 3 - 4 acute GVHD at 6 months (UCB 9% vs Haplo PT Cy 6% vs 10%; p=0.758) were not significantly different among the 3 groups. However, C.I. of chronic GVHD at 2 years was higher in PTCy as compared with others (Haplo PT Cy 28% vs UCB 4% and Haplo TCD 5%, respectively, P< 0.001). Multivariable analysis showed a significant association with OS and EFS for disease risk index (DRI) (p< 0.001) and HCT comorbidity index (p< 0.001), with no statistically significant impact from the type of stem cell graft used. In patients with low/intermediate risk DRI, the 2 year OS for TCD, PTCy and UCB were 71%, 55% and 56%, respectively (p=0.729), and the corresponding 2 year LFS were 59%, 54% and 48%, respectively (p=0.994). In patients with high/very high risk DRI, the 2 year OS for TCD, PTCy and UCB were 19 %, 51% and 18%, respectively (p=0.177), and the corresponding 2 year LFS were 0 %, 18% and 18%, respectively (p=0.774).

Conclusions: Haploidentical HCT using either unmanipulated graft and PTCy or selective Ex Vivo TCRαβ and CD45RA+ depleted graft results in equivalent outcome to those HCT performed using UCB. It provides additional alternative for patients lacking HLA matched donors.

Clinical Trial Registry: NA

Disclosure: No disclosure

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Use of G-CSF Mobilized Bone Marrow Grafts in HLA-haploidentical Bone Marrow Transplantation (BMT) with Post-transplantation Cyclophosphamide (PT-Cy) Decreases Risk of Severe Acute GVHD

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Background: Use of G-CSF-primed bone marrow (GBM) graft increases harvest yield and results in faster engraftment,

which is particularly appealing in haploidentical transplantation. However a growing body of evidence suggests there is more to GBM than mere count improvement and neutrophil recovery. It appears that it has an immunomodulatory effect on donor APCs and T cell function, and that by inducing tolerance GBM can further reduce GVHD incidence. Here we analyzed outcomes of 45 consecutive patients receiving GBM grafts from HLA-haploidentical donors.

Methods: In the time period between 5/2012 and 6/2019 45 patients received HLA-haploidentical BMT using PT-CY platform. Donors received G-CSF (10 mcg/kg BW sc) on days -2, -1 and 0 before BM harvest. Forty patients (89%) received non-myeloablative FluCyTBI conditioning, while 5 patients (11%) received myeloablative conditioning (BuCy or TEC RIC). Along with PT-CY on day +3 and +4, all patients received tacrolimus and MMF form day +5.

Results: Median age was 44 years (19-63), 19 were female and 26 male patients. Sixteen patients had HL, 15 AML, 6 ALL, 4 NHL and 1 CML. Thirty nine patients (87%) were in remission, while 3 HL and 1 NHL patients were in PR, and 2 AML patients had minimal residual disease. Median number of infused TNC was $5.04x10^8$/kg BW (1.76-8.21); CD34+ cells 1,81 $x10^6$/kg BW (0.71-4.47) and CD3+ cells 2.46 $x10^7$/kg BW (0.37-6.2).

Median follow up was 636 days (range 189-1598). Engraftment was achieved in 39 (87%) patients, 2 patients (4%) later had secondary rejection, 2 patients (4%) had primary rejection and 3 patients (6%) died in aplasia. Median days to neutrophil recovery (ANC>500) was 24 (12-38), median days to platelet recovery (PLT>$20x10^9$/L) was 36 (15-81). In all patients MMF was discontinued at D +35. Cumulative incidence of grade II-IV aGVHD in this cohort was 20% (95% CI 9-32). Of note is that there was just one case of grade III aGVHD, developing after DLI for failing chimerism, while all other cases of aGVHD were grade II, with satisfactory response to steroid therapy. Cumulative incidence of chronic GVHD was 3% (95% CI 0-10). Cumulative incidence of relapse was 32% (95% CI 18-46). Overall survival was 62% (95% CI 49-79), with significantly shorter survival in patients not in remission at time of transplant (p=0.04).

Conclusions: Even though the number of transplants showed here using with GBM graft in the HLA-haploidentical setting with PT-CY is relatively small, it shows that, as expected, G-CSF priming is beneficial in terms of TNC yield. However, GBM graft seems to contribute to GVHD control as the incidence of both aGVHD and cGVHD is lower than expected. Furthermore, we have not seen severe grade III-IV aGVHD apart from one patient developing GVHD after DLI. While further studies in larger number of patients are warranted, this data provides additional evidence to the concept of immunomodulatory effect of G-CSF on BM graft.

Disclosure: Nothing to declare.

P699

CMV-specific Functional Immune Reconstitution is Slower after Umbilical Cord Blood Compared with Matched Sibling Donor Hematopoietic Cell Transplantation

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Background: We previously reported more rapid quantitative recovery of NK-cells but slower recovery of T-cell (CD3+, CD8+ and CD4+) subsets along with higher frequency of viral infections after umbilical cord blood (UCB) compared with peripheral blood (PB) matched sibling donor (MSD) hematopoietic cell transplantation (HCT). However, it remains unclear whether increased propensity for viral infections in UCB recipients is only explained by slower quantitative or also by slower functional recovery of virus-specific PB mononuclear cells (PBMC).

Methods: We here examined the differences in functional recovery of virus-specific PBMC after UCB (N=17) vs. PB MSD (N=9) using previously collected PB patient samples at various time points (days +60, +100, +180 and +365) after HCT. Interferon gamma (INF-g) ELISpot assay was used to quantify the frequencies of T- and NK-cells, measured by mean spot-forming cell (SFC) count per 100,000 PBMC, that secrete INF-gin response to 10 antigens specific to 5 viruses: IE1 and PP65 for CMV; U90 for HHV6; LMP2, EBNA1 and BZLF1 for EBV; VP1 and large T (LTA) for BK virus; and hexon proteins for adenovirus. All study patients received the same RIC regimen (Flu/Cy/TBI 200cGy), non-ATG containing GVHD prophylaxis (CSA/MMF) and had no relapse, acute/chronic GVHD or systemic steroids after HCT.

Results: Comparing UCB vs. MSD, we observed lower median absolute count/mL of PB CD3+ (208.8 vs. 408.3, p=0.03), CD8+ (39.1 vs. 112.1, p=0.02) and CD4+ (136.1 vs. 264.1; p=0.11) T-cells at day +60 after HCT. In contrast, the recovery of NK-cells after UCB was more rapid and particularly pronounced at day +100 (306.0 vs. 114.9; p< 0.01) and thereafter. There were 4 (28.6%, all UCB) cases of CMV reactivation out of total 14 (10 UCB and 4 MSD) CMV seropositive patients. The frequencies of CMV-reactive PBMC were higher in CMV seropositive vs. seronegative patients. However, their frequency in CMV seropositive patients, particularly in those with CMV

reactivation, was lower after UCB compared with MSD throughout one year of HCT. Other viral events included 6 HHV6 (all UCB), 1 EBV (MSD) and 1 adenovirus (UCB). We observed no differences in virus-specific PBMC responses towards HHV6, EBV, BK and adenovirus antigens between UCB vs. MSD.

Conclusions: Our data suggest that CMV-specific functional immune reconstitution is slower within first year of HCT in CMV seropositive patients receiving UCB vs. PB MSD. Our findings support implementing strategies to suppress CMV reactivation such as letermovir and to accelerate immune reconstitution such as CMV-vaccines or CMV-specific T-cell adoptive transfer in CMV seropositive patients receiving UCB HCT.

Disclosure: Nothing to declare.

P700

Reduced Intensity (RIC) vs Myeloablative Conditioning (MAC) in Cord Blood Transplantation for AML (40-60 Years) Across Mismatched HLA Barriers - Analysis by Ctiwp/eurocord of EBMT

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Background: Allogeneic stem-cell transplantation (HSCT) is the most effective way to control and treat intermediate and high risk acute myeloid leukaemia (AML). On the basis of prospective studies, myeloablative (MAC- including reduced toxicity) regimen is generally preferred over reduced intensity conditioning (RIC) for younger and fit individuals, and when using peripheral stem cell grafts (PBSC-related and unrelated). Also, large registry data showed no advantage of using RIC over MAC (reduced transplant related mortality - TRM counterbalanced by increased incidence of relapses) when using alternative donor (cord blood) source, despite higher graft vs leukaemia (GVL) effects. However, similar to PBSC, myeloablation in cord transplant (UCBT) was still associated with high TRM in patients (>40 years), especially having higher HLA disparity, thus limiting wider applications. We hypothesized that the TRM advantage of RIC and higher GVL associated with greater HLA disparity would make RIC a more favourable option for this particular subgroup of patients and we took advantage of the Eurocord registry data to compare RIC and MAC regimen.

Methods: Inclusion criteria: age 40 to 60 years, de novo AML in CR1 or CR2/advanced disease, transplantation between 2005 and 2018, receiving standard RIC or MAC regimen, UCBT (from at least 2 HLA mismatches- A, B at antigen level and DR at high resolution).

Results: A total of 288 patients were included, of which 122 and 166 patients were conditioned with MAC and RIC regimen, respectively. Median follow-up was 33 and 47 months for the MAC and RIC groups. Fludarabine/thiotepa/busulfan (70%) and fludarabine/cyclophosphamide/TBI (70%) was most frequently used for MAC and RIC, respectively. As compared to RIC, the MAC group included relatively younger patients (median age 47 years vs 53 years), having had received more single UCBT (73.8% vs 28.9%, p=< 0.001), with lower total nucleated cell count (3.9 vs 4.7, p=< 0.001), and more in vivo t cell depletion using antithymocyte globulin (ATG) (86.6% vs 27.6, p=< 0.001). Median time to neutrophil engraftment (RIC-21 vs MAC-22 days), infections (bacterial, viral and fungal), as well as grade II-IV acute and chronic graft vs host disease-GVHD (37% vs 30%, p=0.221, and 27% vs 31%, p=0.28, for RIC vs MAC respectively) were similar in both groups. There was no difference in overall survival (OS) at 3 years (RIC 41% vs MAC 31% p=0.073); however, RIC regimen was associated with significant reduction in TRM (25% vs 43%, p=0.001) and increased 3-year relapses (41% vs 27%, p=0.019, at a median interval of 5.5 and 4.8 months- RIC and MAC, respectively). Use of double UCBT, and avoiding ATG were associated with better OS and TRM. In the multivariate analysis OS (HR-0.98, p=0.9), TRM (HR-0.68, p=0.2) and relapse (HR-0.75, p=0.3) was not different. Disease status (active disease) was associated with worse survival.

Conclusions: RIC and MAC have similar outcomes for patients (40-60 years) receiving highly mismatched cord blood transplants for AML. Based on the recommendation, use of UCB-unit with 2 or more HLA mismatches is not common. Using double cord and avoiding use of ATG would be advisable.

Clinical Trial Registry: Not applicable

Disclosure: No conflicts of interest to declare.

P701

Cost of Hematopoietic Stem Cell Transplantation in the Real World: An Analysis using The Japanese National Database

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Background: In Japan, medical costs are mostly covered by the universal health insurance system. This system, along with innovative transplant strategies, has increased the number of hematopoietic stem cell transplantation (HSCT), particularly in high-risk populations with various comorbidities and/or high risk of relapse. New agents such as antiviral drugs or immunosuppressants have been increasingly used. Accordingly, medical costs for HSCT are supposed to increase, which could put a financial squeeze on our national healthcare system. However, limited analysis of the cost of HSCT using the national data has been performed. Here, we analyzed the post-HSCT medical cost using the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), which covers more than 95% of insurance claims data.

Methods: All medical prescription data of patients who received HSCT were extracted from the NDB. A total of 12,343 patients who received HSCT from 2012 to 2015 were eligible for the analysis (autologous graft, n=5,803; allogeneic BMT, n=3,244; allogeneic PBSCT, n=1,147; CBT, n=2,149). The conversion ratio was 119.5 yen per euro (11/14/2019).

Results: Approximately 85% of all patients who received autologous or allogenic HSCT were included in this study. The average 1-year costs for autologous and allogeneic HSCT were €37,837 and €153,371, respectively (P< 0.001). For allogeneic HSCT, the medical costs in the elderly groups (age: 60-69, €158,491; >70 years, €155,972) were comparable to those in the other adult age groups (age 20-39, €151,747; age 40-59, €157,774) all of which were higher than the medical cost in the young age group (age 0-19, €136,699). The cost for CBT was higher (€192,398) than that for PBSCT (€139,350) and for BMT (€132,475, P< 0.001). The total cost for allogenic HSCT showed a gradual increase from €114,110 (2012) to €171,309 (2015). This increase in the annual cost was less remarkable for autologous HSCT (€34,809 in 2012 and €35,633 in 2015). The cost for transfusion (BMT, €79,026; PBSCT, €86,835; CBT, €130,287) and antimicrobial agents (BMT, €39,577; PBSCT, €39.805; CBT, €46,475) accounted for the majority of the total cost of allogeneic HSCT.

Conclusions: The costs associated with allogeneic HSCT in Japan were high, and they were comparable to those reported in Western countries. Although this cost is increasing annually, it is still less than that for chimeric antigen receptor T cell (CAR-T cell) therapy (>€280,000 for a single injection) in Japan. The cost for CBT was the highest, possibly due to the high expenses incurred because of administration of transfusions and antimicrobial agents administered for a more prolonged period in CBT than in BMT and PBSCT. With the aim of making HSCT a sustainable medical treatment option, efforts to reduce the transplantation costs should be made. Furthermore, studies comparing different HSCT strategies, such as conventional regimens and post-transplant cyclophosphamide administration, and those contrasting HSCT with other alternative strategies such as CAR-T cell therapy are warranted.

Disclosure: Nothing to declare.

P702

Association Between the Dose of CD3+ and CD34+ Cells in the Graft and Post-transplant Outcomes

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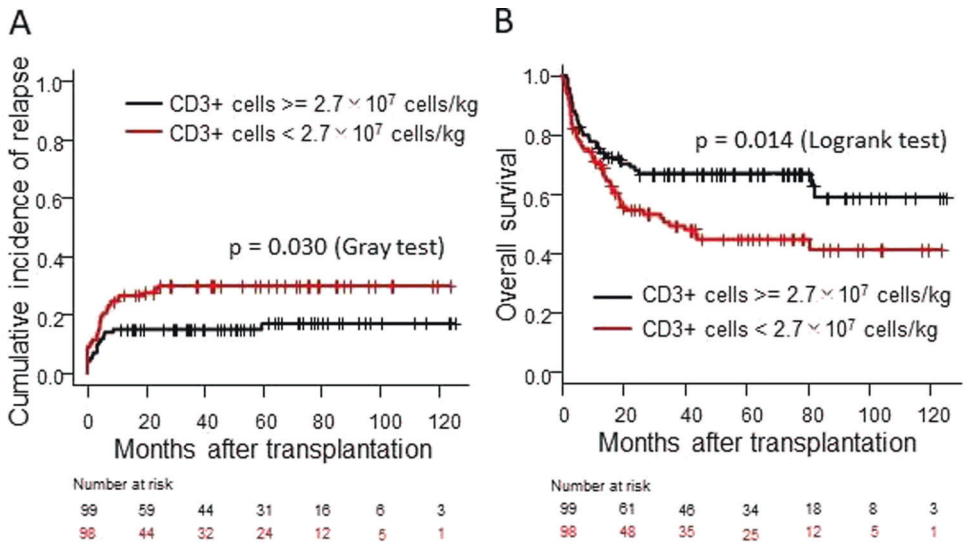
Background: Higher CD34+ cell doses in the graft is thought to be correlated with better outcomes after allogenic hematopoietic stem cell transplantation (allo-HSCT), whereas there are limited data about CD3+ cells. We performed this study to assess the association between CD3+ and CD34+ cell doses and post-transplant outcomes by graft source.

Methods: A total of 350 patients who underwent first allo-HSCT for hematological malignancies from 2009 to 2018 in Japanese Red Cross Nagoya First Hospital were retrospectively analyzed.

Results: The median age was 45 years (range, 16-68 years). Diagnosis included acute myeloid leukemia (n = 158), acute lymphoblastic leukemia/lymphoma (n = 80), myelodysplastic syndromes (n = 65), and others (n = 47). Donors were related (n = 86) and unrelated (n = 264). Graft sources were bone marrow (BM) (n = 197), peripheral blood stem sell (PBSC) (n = 83) and cord blood (CB) (n = 70). Most patients received myeloablative conditioning regimen (75%) and tacrolilmus-based graft-versus-host disease (GVHD) prophylaxis (84%). Median follow-up



[Fig. 1 Cumulative incidence of relapse (A) and probabilities of OS (B) in BMT patients.]

period for survivors was 4.4 years (range, 0.3-10.4 years). Median graft CD3+ and CD34+ cell doses (cells/kg) were 2.7×10^7 and 1.9×10^6 in BM, 2.2×10^8 and 3.4×10^6 in PBSC and 3.5×10^6 and 1.3×10^6 in CB, respectively. CD3+ and CD34+ cell doses were correlated moderately in BM ($\rho = 0.59$, $p < 0.001$) and weakly in CB ($\rho = 0.14$, $p = 0.25$), however, not in PBSC ($\rho = -0.059$, $p = 0.60$). In multivariate analysis in BM transplantation, lower CD3+ cell doses significantly associated with higher relapse (hazard ratio [HR], 2.45; 95% confidence interval [CI], 1.3-4.6; $p = 0.005$) and lower overall survival (OS) (HR, 1.75; 95% CI, 1.1-2.8; $p = 0.018$), and lower CD34+ cell doses significantly associated with slower neutrophil (HR, 0.54; 95% CI, 0.40-0.73; $p < 0.001$) and platelet (HR, 0.67; 95% CI, 0.47-0.96; $p = 0.028$) recovery and had marginally significant impact on transplantation related mortality (TRM) (HR, 1.72; 95% CI, 0.9-3.1; $p = 0.078$). On the other hand, CD3+ and CD34+ cell doses had no impact on the incidence of acute and chronic GVHD. In CB transplantation, only higher CD34+ cell doses had a tendency to associate with higher TRM (HR, 4.46; 95% CI,0.89-22.3; $p = 0.068$) and lower OS (HR, 2.37; 95% CI, 0.99-5.70; $p = 0.053$) accompanied by the increase of post-transplant events related to immune reaction. There was no significant association between CD3+ and CD34+ cell doses and outcomes in PBSC transplantation.

Conclusions: This study suggests that higher CD3+ cell doses in BM graft could reduce relapse without increase of GVHD and could improve survival after transplantation. On the other hand, CD3+ cell doses might no influence on post-transplant outcome in usual clinical setting for CB and PBSC transplant patients.

Disclosure: Nothing to declare.

P703

Hematopoietic Stem Cell Transplantation from a Related Donor with HLA-1 Antigen Mismatch in the Graft-versus-Host Direction using Low-dose Anti-thymocyte Globulin: Multicenter Phase II Trial

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Background: Hematopoietic stem cell transplantation (HSCT) from a related donor with HLA-1 antigen mismatch without in vivo T cell depletion is associated with a high risk of severe acute and chronic graft-versus-host (GVH) disease (GVHD) and poor survival. To improve the outcomes, we conducted a multicenter phase II trial of HSCT from a related donor with HLA-1 antigen mismatch using low-dose anti-thymocyte globulin (ATG, thymoglobulin 2.5 mg/kg) with tacrolimus and methotrexate.

Methods: We recruited patients aged 16-65 years with leukemia, myelodysplastic syndrome, or lymphoma who planned to receive HSCT from a related donor with HLA-1

antigen mismatch in the GVH direction at the HLA-A, -B, and -DR loci. Pretransplantation ATG (thymoglobulin, 1.25 mg/kg/day, day-4 and day-3) was administered with standard GVHD prophylaxis of tacrolimus and methotrexate (days 1, 3, and 6 ±11). The primary endpoint was 1-year survival without relapse/grade III-IV acute GVHD/severe chronic GVHD (GVHD-free relapse-free survival, GRFS).

Results: Thirty-nine patients were registered, and 38 patients were eligible for the analysis. One-fourth of the patients had high/very high refined disease risk indices (rDRIs). One-third of the patients had 2 allele mismatches in the GVH direction at the HLA-A, -B, and -DRB1 loci, and nearly half of the patients had 2 or 3 allele mismatches at the HLA-A, -B, -C, and -DRB1 loci. Most patients (87%) received peripheral blood stem cells. The median follow-up period of the survivors was 2.8 years.

The 1-year GRFS was 47% (90% CI, 33-62%); the lower limit of the 90% CI exceeded the predefined threshold of 20%. The 3-year overall survival (OS) was 57% (95% CI, 39-71%). Age less than 50 years was associated with better OS (80% vs. 38%, P=0.004). OS in patients with high/very high rDRIs was comparable to that in those with low/intermediate rDRIs (70% vs. 53%, P=0.318). The 3-year cumulative incidences of relapse and non-relapse mortality (NRM) were 28% and 24%, respectively. The 100-day cumulative incidences of grade II-IV and III-IV acute GVHD were 45% and 18%, respectively. HSCT from a related donor with two allele mismatches at the HLA-A, -B, and -DRB1 loci showed higher incidences of grade II-IV and III-IV acute GVHD (grade II-IV: 62% vs. 36%, P=0.093; grade III-IV: 23% vs. 16%, P=0.583), and patients with pre-ATG administration lymphocyte counts above the median (>310/μL) showed higher incidences of grade III-IV acute GVHD (26% vs. 11%, P=0.227), although these were not statistically significant. Three-year cumulative incidences of moderate to severe or severe chronic GVHD were 13% and 3%, respectively.

Conclusions: HSCT from a related donor with one locus mismatch at the antigen level using low-dose ATG showed lower incidences of acute and chronic GVHD compared with those using previous strategies without in vivo T cell depletion. These led to acceptable GRFS, OS, relapse, and NRM. However, higher incidences of grade II-IV acute GVHD were observed with two allele mismatches. A higher ATG dose may be required for HSCT from a related donor with 2 or more allele mismatches.

Clinical Trial Registry: UMIN000011192
https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000012652&type=summary&language=J

Disclosure: Conflict of interest: Nothing to declare.

P704

Intra-bone Cord-blood Transplant of Unwashed Units with ATG-free and Sirolimus-based GVHD Prophylaxis: Fast Immune-reconstitution and Long-term Disease Control in 22 Patients with High-risk Diseases

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Background: Potential advantages of cord-blood transplantation (CBT) are less stringent HLA-matching, no risk for donors and rapid availability. However, CBT use is limited in adults for delayed engraftment, graft failure risk and slow immune-reconstitution. Double CB, intra-bone (IB) infusion, CB expansion are studied to overcome these issues. We report our experience with IB unwashed CBT to reduce cell loss and cell-washing associated risks, with an ATG-free GvHD prophylaxis to boost immune recovery.

Methods: From 2010 to 2019, 22 patients with hematological malignancies received CBT; median age 45y [range (r) 22-69]. Disease Risk Index (DRI) was intermediate in 13 patients and high/very high in 9 pts. Median HCT-CI was 3 [r 0-7]; 10 pts had prior allo-HSCT. All pts received Treosulfan and Fludarabin-based conditioning, intensified with Melphalan in 17 and TBI 4Gy in 3 pts. HLA matching was 3/6, 4/6, 5/6, 6/6 in 1, 12, 6, 3 cases, respectively. GvHD prophylaxis was Sirolimus and MMF.

After thawing, CB units were diluted with albumin-dextran solution and immediately infused bedside under local anesthesia, with procedural sedation. Median time from thawing to infusion was 10 minutes. All patients were treated according to Institutional guidelines.

Results: The median cryopreserved number of CD34+ and CD45+ were 0.12 $x10^{6/}$kg [r 0.06-0.32] and 2.9 $x10^{7/}$kg [r 2.04-5.68]; after thawing, the median infused CD34+ and CD45+ were 0.08 $x10^{6/}$kg [r 0.01-0.23] and 1,4 $x10^{7/}$kg [r 0.69-3.21]. Median volume infused was 95ml [r 62-215]; starting from a 10% DMSO concentration, the median DMSO infused was 3.16% [r 2.16-5.36]; no infusion reactions, DMSO or procedure-related toxicities were observed.

Four patients died of infections (IFD=2, bacterial=1, viral=1) before day +30 and weren't evaluable for engraftment. One patient rejected the transplant and neutrophils engraftment was achieved by 17 out of 18 evaluable patients (94%), platelets engraftment by 15/18 (83%); median time was 25 [r 16-59] and 53 [r 25-166] days, respectively. Profiles of immune-reconstitution at day 30-90-180-365 showed a fast $CD4^+$ recovery at any time-point. At day +90 median number of $CD3^+$ was 270/mL [r 18-2131] and $CD4^+$ was 240/mL [r 13-898], with a normal $CD4^+/CD8^+$ ratio.

TRM at day 100 was 27%. Relapse rate was 32% (7 pts), median time 180 days [r 89-650]. Four patients received a subsequent SCT, one is still alive in remission. Relapse rate in CR1 pts was 11% (1 pt).

Median time to Sirolimus withdrawal was 154 days [r 20-412]. Three patients had grade III-IV acute GvHD, median time 42 days [r 17-59]. Two pts developed severe chronic GvHD and one is still on immunosuppressants. No pts died of GvHD.

Overall, after a median follow-up of 721 days [r 427-2855], 9 patients are alive and well.

Conclusions: Intra-bone infusion of diluted unwashed cord-blood units reduces cell loss and is safe and easy to perform. Our data confirm that calcineurin-free, ATG-free GvHD prophylaxis is associated with full hematopoietic engraftment, good profiles of immune-reconstitution and low rates of GvHD; considering the very high-risk population, our data suggest interesting long-term disease control, deserving further investigation in early phase disease.

Disclosure: Nothing to declare.

P705

Mesenchymal Stem/stromal Cell Production Compliant with Good Manufacturing Practice: Comparison Between Bone Marrow and Wharton's Jelly

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Background: Many clinical trials report mesenchymal stem/stromal cells (MSCs) efficacy in various indications. Therefore, standardization of MSC production becomes necessary. MSC properties are impacted by tissue origin especially if they are from fetal tissue or adult sources. Indeed, in a previous work we compared the in vivo properties of MSCs according to their tissue source (Bone Marrow (BM) versus Wharton's Jelly (WJ)) in a murine caecal ligation and puncture (CLP) model of sepsis that mimics a human peritonitis. We observed that both types of MSCs regulated leukocyte trafficking and reduced organ dysfunction, while only WJ-MSCs were able to improve bacterial clearance and survival (Laroye et al, 2019). In a second time, to mimic a clinical approach in humans, we investigated the effect of a randomized controlled double-blind administration of WJ-MSCs, produced in clinical grade, in a relevant pig model of septic shock. In this study, hemodynamic parameters were continuously recorded and hypotension, hyperlactatemia, and organ failure were significantly decreased by WJ-MSC infusion (Laroye et al, 2018). For this reason, we evaluated the impact of MSC tissue origin on production and compared WJ-MSCs to the gold standard in clinic : BM-MSCs.

Methods: Three productions of MSCs from Wharton's Jelly or from bone marrow were performed according to good manufacturing practice. Identity (phenotype, differentiation and clonogenic capacities), safety (karyotype, telomerase activity, sterility and donor qualification) and functionality (viability, mixed lymphocyte reaction) of each cell batch were analyzed.

Results: Some slight differences between MSC sources were observed on phenotype. Moreover, a significant higher clonogenic potential was observed with WJ-MSCs compared to BM-MSCs highlighting the more primitive behavior of WJ-MSCs. This was emphasized by a low telomerase activity (hTERT level) in one WJ-MSC batch while it was never detected in BM-MSC batches. Given the tumorigenic risk associated with a high level of hTERT, regulatory agencies may require an absence of hTERT on the MSC productions for clinical use. We recommend studying hTERT activity at an early passage of culture (P0) in order to stop culture and avoid high costs of production.

Conclusions: Both sources have made it possible to obtain clinical grade MSCs quickly and easily. However, as availability of the source seems to be essential, WJ appears more advantageous than BM. All the pre-clinical work previously carried out on WJ-MSCs led us to initiate a clinical trial with WJ-MSCs in septic shock, which recently benefited from an authorization from the French regulatory agency and will begin in 2020.

Disclosure: Nothing to declare.

P706

Efficient DMSO Removal and High Cell Recovery with Lovo Cell Processing System in HPC-a Concentrates: A Single Centre Experience

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Background: Dimethylsulfoxide (DMSO) infusion may be responsible for several side effects in patients undergoing hematopoietic stem cell transplantations. Automated washing systems are useful for removing cryoprotectant solutions from hematopoietic progenitor cell (HPC) concentrates but cell recovery must be carefully monitored to avoid cell loss.

Methods: Between June and December 2019, 10 thawing and washing tests were performed on cryopreserved HPC-A concentrates. All units underwent thawing (water bath at 37°C) and washing for DMSO removal with Fresenius Kabi LOVO Cell Processing System (Fresenius Kabi, Germany). Complete blood count on post-thawing, post-washing and waste samples was performed to evaluate cell concentration and yields. Post-thaw and post-wash samples were tested for TNC (Total Nucleated Cell) and CD34 viability with flow cytometric method (staining with CD45, CD34, 7-AAD).

Results: All washing procedures were successfully concluded within 40 minutes including the set up of the device and the installation of the disposable kits. Data are shown in Table 1 (data are expressed as median ±IQR). We had a high TNC recovery (91.6%, 87.6-100) in all HPC-A concentrates. Platelet count was greatly reduced in the HPC-A concentrates: 72.9% (63.3-104.1) of the initial platelet contamination was in the waste bag. Percentage of TNC and CD34 viability tends to increase after washing with a mean increase of 10.1% and 9.9%, respectively. These data might be due to the preferential removal of dead cells.

Conclusions: Fresenius Kabi LOVO Cell Processing System seems to be a excellent and fast device for washing HPC concentrates. Removing cell debris as well as platelets may also have a positive effect on viability testing.

	After thawing	After washing	Waste bag
Volume (mL)	90 (77.5-106)	101 (88.2-110.3)	386.5 (339-422)
TNC (10e9)	18.4 (15.2-24.3)	16.9 (14.7-22.7)	0.40 (0.05-0.7)
PLT (10e11)	0.41 (0.33-1.41)	0.18 (0.13-0.31)	0.57 (0.45-1.66)
TNC viability (%)	71.6 (42.3-81.3)	76.5 (63-85.8)	Not done
CD34 viability (%)	89.3 (79.2-95.9)	97.3 (92.5-99)	Not done

[Characteristics of the HPC-A concentrates after thawing, after washing and in the waste bag.]

Disclosure: none