EBMT

ABSTRACTS COLLECTION

The 48th Annual Meeting of the European Society for Blood and Marrow Transplantation: Physicians – Poster Session (P001 – P578)

Bone Marrow Transplantation (2022) 57:100–416; https://doi.org/10.1038/s41409-022-01798-0

19 – 23 March, 2022 ● Virtual Meeting

Sponsorship Statement: Publication of this supplement is sponsored by the European Society for Blood and Marrow Transplantation. All content was reviewed and approved by the EBMT Committee, which held full responsibility for the abstract selections.

ACUTE LEUKAEMIA

P001

Post-transplant cyclophosphamide based anti-GVHD prophylaxis in patients with all treated in cr with ALLO-HCT from haploidentical vs HLA-mismatched unrelated donors: An ALWP EBMT analysis

A. Nagler[1], M. Labopin[2], M. Arat[3], P. Reményi[4], Y. Koc[5], D. Blaise[6], E. Angelucci[7], J. Vydra[8], A. Kulagin[9], G. Socié[10], M. Rovira[11], S. Sica[12], M. Aljurf[13], Z. Gülbas[14], N. Kröger[15], E. Brissot[16], Z. Peric[17], S. Giebel[18], M. Mohty[16]

[1]Chaim Sheba Medical Center, Ramat Gan, Israel, [2]Saint-Antoine Hospital, AP-HP, Paris, France, [3]Demiroglu Bilim University, Istanbul, Turkey, [4]Dél-pesti Centrumkórház – Országos Hematológiai és Infektológiai Intézet, Budapest, Hungary, [5]Medicana International Hospital Istanbul, Istanbul, Turkey, [6]Institut Paoli-Calmettes, Marseille, France, [7]Ospedale San Martino, Genova, Italy, [8]Institute of Hematology and Blood Transfusion, Prague, Czech Republic, [9]Raisa Gorbacheva Memorial Research Institute for Paediatric Oncology, St Petersburg, Russian Federation, [10]AP-HP Hospital Saint Louis, Paris, France, [11]Institute of Hematology & Oncology, Barcelona, Spain, [12]Universita Cattolica S. Cuore, Istituto di Ematologia, Rome, Italy, [13]King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, [14]Anadolu Medical Center Hospital, Kocaeli, Turkey, [15]University Hospital Eppendorf, Hamburg, Germany, [16]Hôpital Saint-Antoine, AP-HP, Paris, France, [17]University Hospital Center Zagreb, Zagreb, Croatia, [18]Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice, Poland

Background: Post-transplant cyclophosphamide (PTCy)-based anti-GVHD prophylaxis pioneered in haploidentical (Haplo) transplantation is being increasingly used in other transplantation settings. Both Haplo and mismatched unrelated donor (MMUD) transplantation are valid options in patients with ALL in the absence of a MRD.

Methods: The study aim was to compare the outcomes of adult patients with ALL in CR who underwent Haplo versus 9/10 MMUD transplantation with PTCy in 2010-2020. Multivariate analysis adjusting for potential confounding factors was performed using a Cox's proportional-hazards regression model for main outcomes.

Results: This study included 781 pts: Haplo-678, MMUD-103. Median follow-up was 24 (range, 11.3-45.6) and 19 (5.3-39.0) months, respectively ($p = 0.61$). Median age was 38 (18-75) and 40 (19-73) years ($p = 0.51$) and 65% and 66% were male, respectively ($p = 0.76$). Year of transplant was 2018 vs 2017 ($p = 0.68$). 39% and 43% were Ph-, 35% and 38% were Ph +, and 26% and 19% had T ALL, respectively ($p = 0.3$). Disease status at transplant was CR1 in 67% and 64%, and CR2 in 33% and 36% of the patients, respectively ($p = 0.54$). Conditioning was myeloablative in 70% and 69%, ($p = 0.19$) in Haplo and MMUD, respectively. Fewer Haplo than MMUD patients received TBI (48% vs 59%, respectively, $p = 0.038$) while more Haplo compared with MMUD were performed with a BM graft (37% vs 16%, $p < 0.0001$), respectively. The most frequent immunosuppression agents added to PTCy were MMF/cyclosporine A, and MMF/tacrolimus. ATG was administered in 8% and 21% of the transplants, respectively ($p < 0.0001$). Engraftment (day 60) was 96.5% vs 97.1% ($p = 0.77$) in Haplo vs MMUD, respectively. Incidence of day 180 aGVHD grade II-IV and III-IV was 31.6% vs 21.4% ($p = 0.034$), and 11.1% vs 8.2% ($p = 0.34$), respectively. 2-y cGVHD and extensive cGVHD were 33% vs 36% ($p = 0.69$), and 12% vs 10% ($p = 0.55$) in Haplo vs MMUD, respectively. Main causes of death were leukemia (42% vs 57%), infection (30% vs 13%), and GVHD (14% vs 7.7%). 2y relapse incidence (RI), NRM, LFS, OS and GRFS were 26% vs 31% ($p = 0.18$), 22% vs 13% ($p = 0.1$), 52% vs 55% ($p = 0.45$), 61% vs 70% ($p = 0.45$), and 42% vs 45% ($p = 0.60$), for Haplo and MMUD, respectively. On multivariate analysis, NRM and RI were similar between Haplo and MMUD, HR = 1.45 (95% CI 0.8-2.6, $p = 0.21$) and HR = 0.8 (95% CI 0.5-1.3, $p = 0.38$), respectively. LFS, OS and GRFS were comparable, HR = 1.0 (95% CI 0.7-1.5, $p = 0.8$), HR = 1.2 (95% CI 0.8-1.8, $p = 0.46$) and HR = 1.0 (95% CI 0.8-1.5, $p = 0.7$), respectively. aGVHD was significantly higher with Haplo, HR = 1.7 (95% CI 1-2.8, $p = 0.023$), while aGVHD grade III-IV and cGVHD did

not differ significantly between the 2 transplant groups. Additional prognostic factors for HSCT outcomes were disease status for all parameters excluding GVHD; age for NRM, LFS and OS. Ph^+ was a favorable predictive factor for RI and OS. RI was higher with reduced intensity conditioning while OS was lower with PB grafts. A female to male donor/recipient combination was associated with a higher incidence of cGVHD.

Conclusions: Outcomes of Haplo and MMUD transplants for pts with ALL in CR are similar, apart from a higher incidence of aGVHD with Haplo transplants.

Disclosure: Nothing to declare

P004

Sequential conditioning with high dose melphalan followed by busulfan and fludarabine in eldery patients with relapsed or refractory (r/r) acute myeloid leukemia (AML)

M.-A. Urbahn[1], C. Reicherts[1], A. Pohlmann[1], S. Call[1], E. Eßeling[1], M. Floeth[1], J. Marx[1], J. Albring[1], J.-H. Mikesch[1], C. Schliemann[1], G. Lenz[1], M. Stelljes[1]

[1]University Hospital Münster, Münster, Germany

Background: During the last decades, outcomes of patients with AML, receiving an alloSCT in complete remission (CR) have improved significantly, whereas the prognosis of patients transplanted with r/r AML remained dismal. Sequential conditioning regimens (e.g. FLAMSA-based or high-dose melphalan based) might improve outcomes of patients with r/r AML, particular in younger patients. A recent retrospective analysis showed promising survival data in younger patients conditioned with high dose melphalan, followed by 8 Gy TBI and fludarabine, while for elderly patients this intense therapy was associated with significant toxicities.

Methods: In our retrospective study 99 patients, aged > 55 years, with r/r AML transplanted at the BMT-center of University Hospital of Muenster between 2014 and 2021, were included. Median age was 67 years (range 55-76), the median HCT-CI-score was 2 (range 0-10). Thirteen patients were initially diagnosed with favorable risk, 37 patients with intermediate risk, and 49 patients with adverse risk AML (ELN 2017). At transplant, 65 patients had primary refractory AML, 15 patients had AML refractory to salvage treatment and 19 patients had untreated relapsed AML. Median bone marrow (BM) blast count prior to start of conditioning was 30% (range 5-90%). 75 patients received melphalan on day -11 at a dose of 100 mg/m^2 and 24 patients at a dose of 140 mg/m^2 followed by fludarabine (4 x 30 mg/m^2) and busulfan (cumulative dose on 2 days of 6,4 mg/kg body weight) on days -5 to -1 prior to transplant. One patient received a BM graft, all other patients received peripheral stem cell grafts from matched-related donors (MRD, 16 patients), from matched-unrelated donors (MUD, 10/10 HLA-matched, 62 patients) or from mismatched-unrelated donors (MMUD, 9/10 matched, 21 patients). Median follow-up of surviving patients was 749 days after transplant.

Results: Overall survival (OS) rates at 1 and 2 years were 51% (95% CI, 41-61%) and 42% (95% CI, 32-53%), respectively. Cumulative incidences (C.I.) of relapse and non-relapse mortality (NRM) at 1 and 2 years were 14% (95% CI, 8-23%), 19% (95% CI, 12-30%) and 35% (95% CI, 26-46%), and 37% (95% CI, 29-49%), respectively. The 2-year-OS of patients with primary refractory AML, secondary refractory AML or untreated relapse showed no significant difference, with 46% (95% CI, 33-59%), 37% (95% CI, 9-65%) and 28% (95% CI, 7-50%), respectively. Patients with low disease burden (<20% BM blasts prior start of conditioning) had a C.I. of relapse of 6% (95% CI, 2-23%), compared to 28% (95% CI, 16-50%) and 32% (95% CI, 17-59%) for patients with 20-50% or >50% BM blasts (p .04). Furthermore, patients transplanted from a MMUD donor had a significantly higher risk of NRM of 70% (95% CI, 53-95%), as compared to patients transplanted from a MUD (30%, 95% CI, 21-45%) or MRD (24%, 95% CI, 9-63%) (p .001).

Conclusions: Our data suggest that high dose melphalan-based sequential conditioning combined with busulfan and fludarabine followed by alloSCT is a feasible treatment option in elderly patients with r/r AML, which allows long term survival of >40% in this high-risk patient group.

Disclosure: Nothing to declare.

P005

HLA-haploidentical transplantation with PTCY in AML patients with active disease at transplantation: Better survival with bm than with PBSC in patients >55 years

F. Baron[1], M. Labopin[2,3,4], J. Tischer[5], F. Ciceri[6], A.M. Raiola[7], D. Blaise[8], S. Sica[9], J. Vydra[10], R. Fanin[11], F. Stölzel[12], A. Busca[13], J.L. Diez-Martin[14], Y. Koc[15], A. Nagler[16], M. Mohty[2,4,3]

[1]Laboratory of Hematology, GIGA-I3, University of Liege and CHU of Liege, Liege, Belgium, [2]EBMT Paris Study Office/CERTEST-TC, Paris, France, [3]Saint Antoine Hospital, Paris, France, [4]INSERM UMR 938, Paris, France, [5]Klinikum Grosshadern, Med. Klinik III, Munich, Germany, [6]Ospedale San Raffaele s.r.l., Haematology and BMT, Milano, Italy, [7]IRCCS Ospedale Policlinico San Martino, Genova, Italy, [8]Programme de Transplantation & Therapie Cellulaire, Centre de Recherche en Cancérologie de Marseille, Institut Paoli Calmettes, Marseille, France, [9]Fondazione Policlinico Universitario A. Gemelli IRCCS, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Roma, Italy, [10]Institute of Hematology and Blood Transfusion, Prague, Czech Republic, [11]Azienda Ospedaliero Universitaria di Udine, Division of Hematology, Udine, Italy, [12]University Hospital Dresden, Medical Clinic I, TU Dresden, Dresden, Germany, [13]S.S.C.V.D Trapianto di Cellule Staminali, A.O.U Citta della Salute e della Scienza di Torino, Torino, Italy, [14]Hospital Gregorio Marañón, Sección de Trasplante de Medula Osea, Madrid, Spain, [15]Medicana International Hospital, Bone Marrow Transplant Unit, Istanbul, Turkey, [16]Division of Hematology and Bone Marrow Transplantation, The Chaim Sheba Medical Center Tel Hashomer, Ramat Gan, Israel

Background: The best stem cell source for T-cell replete HLA-haploidentical transplantation with post-transplant cyclophosphamide (PTCy) remains to be determined. In patients with active acute myeloid leukemia (AML) at transplantation, one could speculate that the use of peripheral blood stem cells (PBSC) versus bone marrow (BM) could be associated with higher graft-versus-leukemia effects. These considerations prompted us to perform a retrospective study within the EBMT registry to assess this question.

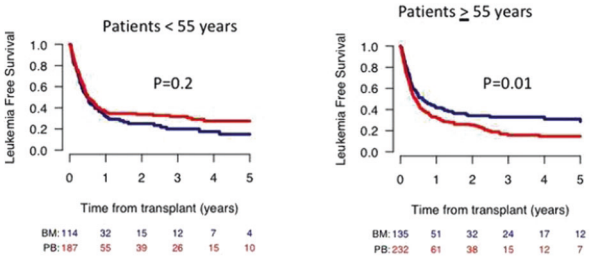
Methods: Inclusion criteria included adult AML patients with primary refractory or relapsed AML, first allogeneic transplantation with an HLA-haploidentical donor with PTCy as graft-versus-host disease (GVHD) prophylaxis, transplantation between 2010 and 2020, and no in vivo T-cell depleted grafts. Primary endpoint was leukemia-free survival (LFS).

Results: A total of 668 patients (249 BM and 419 PBSC recipients) met the inclusion criteria. This include 380 patients with primary refractory AML, 229 in first relapse and 59 in second relapse at transplantation. Median follow-up was 36 months. Median age was 57 years (IQR, 45-64 years). There was a statistical interaction between patient age and stem cell source on LFS ($P < 0.01$ for age $<$ or $\geq$ 55 years). The analyses were thus performed separately for patients $<$ or $\geq$ 55 years of age. In multivariate Cox models, among patients $<$ 55 years

(n = 301, 114 BM and 187 PBSC), the use of PBSC versus BM resulted in comparable relapse incidence (HR = 0.85, P = 0.34), nonrelapse mortality (HR = 0.91, P = 0.8), LFS (HR = 0.82, P = 0.2; Figure 1) and overall survival (OS; HR = 0.81, P = 0.2) in multivariate Cox models.

The use of PBSC was associated with higher incidence of grade II-IV acute GVHD (HR = 2.02, P = 0.01) and no significant difference in incidence of chronic GVHD (HR = 1.42, P = 0.3). In contrast, in patients ≥ 55 years of age (n = 367, 135 BM and 232 PBSC), the use of PBSC versus BM was associated with higher nonrelapse mortality (HR = 1.64, P = 0.015), comparable relapse incidence (HR = 1.17, P = 0.43), lower LFS (HR = 1.39, P = 0.02, Figure 1) and lower OS (HR = 1.35, P = 0.03). Incidences of grade II-IV acute (HR = 1.55, P = 0.13) and chronic (HR = 1.2, P = 0.55) GVHD were comparable in the 2 groups of patients.

Figure 1: LFS according to age



Conclusions: Our data suggest that in patients > 55 years of age with active AML at HLA-haploidentical transplantation, the use of BM instead of PBSC as stem cell source results in lower nonrelapse mortality and better LFS and OS. In contrast among younger patients, the use of PBSC results in at least comparable LFS and OS.

Disclosure: The authors have no COI to disclose

P006

Molecular genetic changes and mrd after first induction chemotherapy were related with prognosis in acute lymphoblastic lkukemia

X. Sun[1], X. Liu[2], Y. Li[3], Y. Jiang[1,3], X. Sui[1,3], X. Wang[1,3,4,5], X. Fang[1,3]

[1]Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China, [2]The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, China, [3]Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China, [4]School of Medicine, Shandong University, Jinan, China, [5]Shandong Provincial Engineering Research Center of Lymphoma, Jinan, China

Background: The changes of genetic information play an important role in the pathogenesis and recurrence of acute lymphoblastic leukemia (ALL), but there is no consistent conclusion about the impact of molecular genetic changes on the diagnosis and prognosis of the disease. The purpose of our study was to investigate the frequency spectrum of gene mutation and its prognostic significance in combination with minimal residual disease (MRD) and hematopoietic stem cell transplantation (HSCT) in adolescents and adults ALL patients aged ≥15 years old.

Methods: The basic characteristics, cytogenetics, molecular genetics, MRD, treatment regimen and survival outcome of ALL patients who were first diagnosed in Shandong Provincial Hospital and Yantai Yuhuangding Hospital from January 1, 2014 to May 1, 2021 were collected. Correlation analysis and survival analysis were performed by R and SPSS25 software, respectively.

Results: A total of 353 patients were included in this study, of which 90.6% of the 128 patients with next-generation sequencing (NGS) results had at least one mutation, and 66.41% of the patients had polygenic (≥ 2) mutations. NOTCH1, PHF6, RUNX1, JAK3 and PTEN were the most common mutations in T-ALL, while FAT1, TET2, NARS, KMT2D, FLT3 and RELN were the most common in B-ALL. The incidence of NOTCH1, JAK3, PTEN, PHF6 and JAK1 in T-ALL is higher than that in B-ALL. Correlation analysis revealed common mutation patterns, which were significantly different between T-ALL and B-ALL. Then the prognostic factors of 92 patients with B-ALL were analyzed, including sex, age, white blood cell count, Ph chromosome status, HSCT, hepatitis B virus infection status, MRD level and bone marrow remission status after induction chemotherapy, and genes with mutation frequency ≥ 6. Univariate analysis showed that FLT3 mutation (P = 0.048), TP53 mutation (P = 0.088) and RELN mutation (P = 0.037) were adverse factors affecting the overall survival (OS) of B-ALL patients. Patients with negative MRD after induction therapy (P = 0.007) and receive HSCT (P = 0.003) had better OS. Multivariate analysis revealed that MRD ≥ 1% after induction chemotherapy (P = 0.007), RELN mutation (P = 0.022) and TP53 mutation (P = 0.012) were independent risk factors for OS. Patients who undergo HSCT tended to have better OS, but there was no statistical significance in multivariate analysis (P = 0.079). NOTCH1 mutation (P = 0.018) and recurrence (P = 0.000) were independent adverse prognostic factors of event-free survival. In addition, our study also found that among the 52 patients who achieved negative MRD (MRD < 0.01%) after the first induction chemotherapy, there was no significant difference in OS between the transplantation group (n = 26) and the non-transplantation group (n = 26), and the average age of the non-transplantation group was significantly higher than that of the transplantation group (41.16 vs 32.58 years old, P = 0.049).

Conclusions: The distribution of gene mutations and the co-occurrence and repulsion of mutant genes in patients with ALL are closely related to the immunophenotype of patients. RELN and TP53 mutations are significantly associated with poor prognosis in patients with ALL. Patients with high sensitivity to chemotherapy do not seem to benefit from HSCT, which may be associated with high transplant-related complications and mortality and need to be confirmed in large prospective studies.

Disclosure: The authors declare that they have no competing interests.

Funding: This study was funded by the National Natural Science Foundation (grant nos. 82070203, 81770210, 81473486 and 81270598), the Key Research and Development Program of Shandong Province (grant no. 2018CXGC1213), the Technology Development Projects of Shandong Province (grant no. 2017GSF18189), the Translational Research Grant of NCRCH (grant nos. 2021WWB02 and 2020ZKMB01), the Technology Projects of Jinan (grant nos. 201704092 and 202019044), the Taishan Scholars Program of Shandong Province, Shandong Provincial Engineering Research Center of Lymphoma, and Academic Promotion Programme of Shandong First Medical University (grant no. 2019QL018).

P007

Autologous versus haploidentical stem cell transplantation in adult patients with acute myelogenous leukemia in first complete remission with undetectable minimal residual disease: Chinese data

J. Chen[1,2,3], Y. Ding[1,2,3], X. Zhang[4], E. Jiang[5], L. Liu[6], H. Huang[7], J. Hu[8], J. Wang[9], Y. Zhang[10], M. Labopin[11], I. Khevelidze[11], E. Polge[11], A. Nagler[11,12], M. Mohty[11], D. Wu[1,2,3], N.-C. Gorin[11]

[1]National Clinical Research Center for Hematologic Diseases, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University, Suzhou City, Jiangsu Province, China, [2]Institute of Blood and Marrow Transplantation, Collaborative Innovation Center of Hematology, Soochow University, Suzhou City, Jiangsu Province, China, [3]Key Laboratory of Stem Cells and Biomedical Materials of Jiangsu Province and Chinese Ministry of Science and Technology, Suzhou City, Jiangsu Province, China, [4]Medical Center of Hematology, Xinqiao Hospital, Chongqing, China, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China, [6]The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [7]The First Affiliated Hospital of Zhejiang University, Hangzhou, China, [8]Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [9]The Affiliated Hospital of Guizhou Medical University, Guiyang, China, [10]The Second People's Hospital of Huai'an, Huaian, China, [11]EBMT Global Committee and Acute Leukemia Working Party, Hopital Saint-Antoine APHP and Sorbonne University, Paris, France, [12]Division of Hematology and Bone Marrow Transplantation, The Chaim Sheba Medical Center, Tel-HashomerIsr, Israel

Background: Stem cell transplantation (SCT) is a potentially curative post-remission therapy for intermediate-risk acute myeloid leukemia (AML) patients. For patients in first remission (CR1) with negative measurable residual disease (MRD) and without a HLA-matched donor, both autologous SCT (ASCT) and haploidentical donor SCT (haplo-SCT) were acceptable options, but it is controversial that which one is preferred.

Methods: A retrospective study was conducted in 8 Chinese centers. The inclusion criteria were: 1) adult patients >18 years old; 2) diagnosis as AML with intermediate-risk according to ELN 2017; 3) ASCT or haplo-SCT underwent between 2010-2019; 4) in CR1 and MRD negative before transplant. The Primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS), cumulative incidence of relapse (CIR), treatment-related mortality (TRM), and graft-versus-host disease-free and relapse-free survival (GRFS).

Results:

Totally 299 patients were enrolled in this study, including 97 recepients after ASCT and 202 recipients after haplo-SCT (Table 1). The median follow-up was 28 months in ASCT group versus 35 months in haplo-SCT group. Compared to haplo-SCT, patients after ASCT had increased 3-year CIR (27.0% ± 0.2% versus 13.5% ± 0.1%, p = 0.004) but reduced 3-year TRM (3.5% ± 0.0% versus 12.0% ± 0.0%, p = 0.013), which led to similar 3-year OS (80.8% ± 4.3% versus 79.2% ± 3.1%, p = 0.796) and PFS (69.5% ± 5.0% versus 73.7% ± 3.3%, p = 0.504). Moreover, the 3-year GRFS was remarkable better in ASCT group (69.5% ± 5.0% versus 55.9% ± 3.6%, p = 0.009) (Figure 1), which implied a survival with superior quality of life (QoL). In multivariate analysis, haplo-SCT independently related to an improved CIR, while increased TRM and reduced GRFS. Additionally, age more than 50 was associated with the worse OS, CIR and GRFS.

Table 1 Characteristics of patients.

		Auto (n = 97)	Haplo (n = 202)
Age (median, range)		36 (18-64)	36 (18-62)
Sex (cases)	Male/ Female	57/40	121/81
Karyotype abnormalities at diagnosis (cases)		21	70
Molecular Abnormalities at diagnosis (cases)	FLT3-ITD	3	21
	NPM1	8	17
	WT1	22	27
Median interval from diagnosis to transplant (Months)		6	5
Single courses of induction before transplant (cases)		59	141
Courses of Consolidation before transplant ≤2 (cases)		33	151

Conclusions: We concluded that both ASCT and haplo-SCT were applicable for patients with intermediate-risk AML in MRD-negative CR1, but the absence of GVHD might potentially favor the QoL for patients receiving ASCT. Randomized trials are needed to confirm our conclusion.

Disclosure: Nothing to disclose

P008

Impact of donor and patient *TGFB1* − 1347C > T variant in acute myeloid leukemia after hematopoietic stem cell transplantation

I. Martin[1], A. Perez[1], M. Tormo[1], E. Villamon[1], J.C. Hernandez-Boluda[1], J.L. Piñana[1], C. Solano[1]

[1]Hospital Clínico Universitario de Valencia. INCLIVA Research Institute. University of Valencia., Valencia, Spain

Background: Transforming growth factor β1 (TGFβ1) is a pleiotropic regulatory cytokine secreted after hematopoietic stem cell transplantation (HSCT) by both donor T-cells and platelets and by recipient endothelial, connective and epithelial cells. *TGFB1* − 1347C > T variant affects *TGFB1* transcription and plasma levels and has been associated after HSCT with worse overall survival (OS) or graft versus host disease (GvHD).[1,2]

References:

1.-Arrieta-Bolaños E, et al. Polymorphism in TGFB1 is associated with worse non-relapse mortality and overall survival after stem cell transplantation with unrelated donors. Haematologica. 2016;101:382-90.

2.- Kövy P, et al. Investigation of TGFB1 -1347C > T variant as a biomarker after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2020;55:215-223.

Methods: The study included 65 patients who underwent HSCT for acute myeloid leukemia (AML) disease. HSCT were performed between April 2013 and January 2021 at our single centre. OS was calculated from the day of HSCT until death for any cause or last follow up. Genomic DNA from donor and patient pairs was extracted from pre-transplant peripheral blood. *TGFB1* − 1347C > T variant was determined by high resolution melting analysis on a LightCycler® 480 instrument (Roche Diagnostics) using an original primer design (Forward: 5′-CATGGGAGGTGCTCAGTAAA-3′; Reverse: 5′-AGGCTGGGAAACAAGGTAGG-3′). The effect of *TGFB1* − 1347C > T variant was assessed in all three models: genotypic (CC *vs*. CT *vs*. TT), recessive (CC&CT *vs*. TT) and dominant (CC *vs*. CT&TT). The association of the clinical characteristics with the genetic findings was analyzed with the SPSS statistical program (v.20.0) and *P* values <0.05 were considered as statistically significant.

Results: The median OS for patients after HSCT was 13 months (range, 0 – 78 months). Patient −1347C > T frequencies were CC: 24 (39%), CT: 27 (43%), TT: 11 (18%) [patient DNA was not

available in 3 cases] and donor −1347C > T frequencies were CC: 31 (49%), CT: 25 (40%), TT: 7 (11%) [donor DNA was not available in 2 cases]. In the overall series, patients with TT donor showed compared to CT&CC genotypes a trend towards a higher incidence of acute GvHD grade III-IV (29% *vs*. 4%, $P = 0.084$). In addition, patients with TT genotype and TT donor had a significantly higher frequency of acute GvHD grade III-IV than the remaining patients (40% *vs*. 4%, $P = 0.013$). Interestingly, in the non-myeloablative subgroup (n = 47), patients with TT genotype had a lower OS compared to CC and CT genotypes (median, 20 *vs*. 30 *vs*. 55 months, $P = 0.026$; Fig. 1). On the other hand, in myeloablative subgroup (n = 18), patients with CC donor had a lower relapse-free survival compared to CT&TT genotypes (median, 25 *vs*. 50 months, $P = 0.046$).

Conclusions: In our series of AML with HSCT analyzed, *TGFB1* − 1347C > T variant was screened using a rapid and novel procedure and was associated with patients' clinical outcome, especially in non-myeloablative conditioning. If these results were confirmed in a larger series, the analysis of that polymorphism could be useful in HSCT.

Disclosure: Nothing to declare

P009

Post-transplant cyclophosphamide separates graft-versus host disease (GVHD) and graft versus leukemia (gvl) effects after HLA- matched stem-cell transplantation (sct) for AML

A. Shimoni[1], C. Peczynski[2], M. Labopin[2], A. Kulagin[3], E. Meijer[4], J. Cornelissen[5], F. Ciceri[6], G. Choi[7], J. Sanz[8], M. Rovira[9], G. Van Gorkom[10], N. Kröger[11], Y. Koc[12], J. Vydra[13], J. Diez-Martin[14], C. Solano[15], P. Chiusolo[16], A. Nagler[1], M. Mohty[17]

[1]Chaim Sheba Medical Center, Tel-Hashomer, Israel, [2]ALWP EBMT, Paris, France, [3]First State Pavlov Medical University, St Petersburg, Russian Federation, [4]VU University Medical Center, Amsterdam, Netherlands, [5]Erasmus MC Cancer Institute, Rotterdam, Netherlands, [6]Ospedale San Raffaele, Milano, Italy, [7]University Medical Center Groningen, Groningen, Netherlands, [8]University Hospital La Fe, Valencia, Spain, [9]Hospital Clinic Barcelona, Barcelona, Spain, [10]University Hospital Maastricht, Maastricht, Netherlands, [11]University Hospital Eppendorf, Hamburg, Germany, [12]Medicana International Hospital, Istanbul, Turkey, [13]Institute of Hematology and Blood Transfusion, Prague, Czech Republic, [14]Hospital Gregorio Marañón, Madrid, Spain, [15]Hospital Clínico de Valencia, Valencia, Spain, [16]Universita Cattolica S. Cuore, Rome, Italy, [17]Saint-Antoine Hospital, Paris, France

Background: The association of GVHD and GvL after allogeneic SCT is well-established but has not been confirmed in recent years with the introduction of new transplantation techniques. Post-transplant cyclophosphamide (PTCy) has been used for GVHD prevention in haplo-identical transplantation and more recently also in HLA- matched SCT. We have shown that there was no association between GVHD and GVL in the haplo-identical setting with PTCy but it was not determined if this is related to the PTCy effect or to the haplo-identical setting itself.

Methods: We assessed the impact of acute and chronic GVHD on SCT outcomes in patients with AML following SCT with conventional GVHD prophylaxis or PTCy by using Cox proportional-hazard analysis with acute and chronic GVHD as time- dependent variables.

Results: 12,653 patients received a first allogeneic SCT between the years 2010-2019, from HLA- matched siblings (n = 6726, 53%) or 10/10 matched- unrelated donors (n = 5927, 47%), using standard GVHD prevention regimens. The median age was 52 years (range, 18-80). Status at SCT was CR1 (n = 10478, 83%) or CR2 (n = 2175, 17%). The conditioning regimen was RIC (n = 5711, 45%) or MAC (n = 6942, 55%). The incidence of acute GVHD grade II-IV and III-IV at 180 days was 23.8% and 7.5%, respectively. The incidence of chronic GVHD and extensive chronic GVHD at 2 years was 37% and 16.3%, respectively. Acute GVHD grade II was associated with lower relapse risk (HR 0.85, P = 0.002), higher risk of non-relapse mortality (NRM) (HR 1.5, P < 0.0001) and lower overall-survival (OS) (HR 1.49, P < 0.0001) in comparison with no or grade I GVHD. Similarly, acute GVHD grade III-IV was associated with lower relapse (HR 0.76, P = 0.003), higher NRM (HR 6.21, P < 0.0001) and lower OS (HR 6.1, P < 0.0001). Extensive chronic GVHD was associated with lower relapse (HR 0.69, P < 0.0001), higher NRM (HR 2.83, p < 0.0001) and lower OS (HR 2.74, P < 0.0001). Limited chronic GVHD was not associated with any of these outcomes.PTCy was given to 508 patients after SCT from HLA- matched siblings (n = 234, 46%) or 10/10 matched-unrelated donors (n = 274, 54%). The median age was 48.5 years (range, 18-72). Status at SCT was CR1 (n = 437, 86%) or CR2 (n = 71, 14%). The conditioning regimen was RIC (n = 215, 42%) or MAC (n = 293, 58%). The incidence of acute GVHD grade II-IV and III-IV at 180 days was 22.8% and 6.2%, respectively. The incidences of chronic GVHD and extensive chronic GVHD at 2 years was 35.5% and 17.7%, respectively.Acute GVHD II-IV was associated with a non-statistically different risk of relapse (HR 1.37, P = 0.15), higher risk of NRM (HR 3.34, P = 0.0005) and lower OS (HR 1.92, P = 0.001). Chronic GVHD was not associated with risks of relapse (HR 0.99, P = 0.98), NRM (HR 1.11, P = 0.83) or OS (HR 0.73, P = 0.19). The relatively low number of GVHD events in the PTCy setting did not allow differentiation between acute and chronic GVHD grading.

Conclusions: GVHD and GVL are strongly associated in contemporary allogeneic SCT. However, in the PTCy setting these two effects can be separated and GVHD is not associated with reduced risk of post-transplant relapse.

Disclosure: Nothing to declare

P010

Comparison of haploidentical and matched unrelated donor HSCT with uniform posttransplantation cyclophosphamide GVHD prophylaxis in de novo AML

D. Zhogolev[1], N. Volkov[1], A. Beynarovich[1], A. Smirnova[1], Y. Vlasova[1], E. Babenko[1], T. Gindina[1], I. Barkhatov[1], A. Alyanskiy[1], E. Morozova[1], I. Moiseev[1], S. Bondarenko[1], A. Kulagin[1]

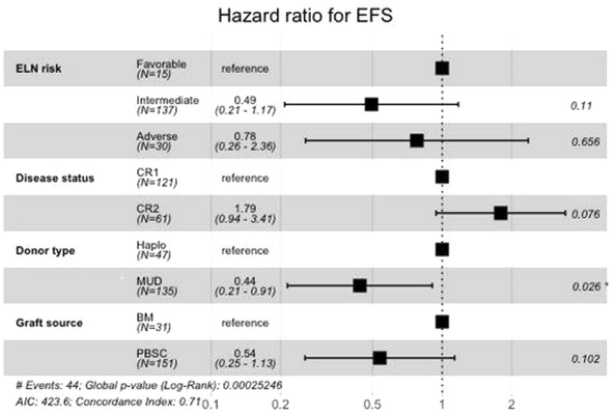
[1]RM Gorbacheva Research Institute, Pavlov University, St. Petersburg, Russian Federation

Background: Allogeneic hematopoietic stem cell transplantation (alloHSCT) from a haploidentical related donor (haploHSCT) is an important alternative for patients with acute myeloid leukemia (AML) in the absence of an HLA-matched donor. A substantial number of studies were published comparing matched unrelated donor (MUD) HSCT with conventional GVHD prophylaxis to haploHSCT with posttransplantation cyclophosphamide (PTCY). Several recent studies comparing both haplo and MUD HSCT with PTCY identified better outcomes after MUD HSCT. Our study aimed to compare the results of MUD and haploidentical alloHSCT both performed with PTCY prophylaxis.

Methods: A total of 182 adult patients with de novo AML in CR1/CR2, who underwent alloHSCT at RM Gorbacheva Research Institute (CIC 725) between 2013-2021, were included. HaploHSCT was performed in 47 patients (haplo group), MUD alloHSCT was performed in 135 patients (MUD group). Median age was

31 (range 18-68) and 33 (range 18-59) years, 22 (46%) and 60 (44.4%) patients were male respectively. Most patients in both groups had intermediate ELN risk: 36 (76.6%) and 101 (74.8%) respectively. The ratio of patients in CR1 and CR2 prior to HSCT was comparable: 27 (57.4%) and 20 (42.6%) in haplo group, 94 (69,6%) and 41 (30.4%) in MUD group. Most patients received conditioning regimens with reduced intensity: 41 (87.2%) and 112 (83%) respectively. All patients received PTCY-based GVHD prophylaxis. Groups were statistically different only by graft source due to much more frequent use of bone marrow in haplo group: 23 (48.9%) vs 8 (5.93%) in MUD group ($p < 0.001$).

Results: Median follow-up after alloHSCT in survivors was 26.6 months. Engraftment was achieved by 74,5% of patients in haplo group and 97% in MUD group ($p < 0.001$). Two-year OS was 55% and 82% ($p < 0.001$), EFS was 54% and 80% ($p < 0.0001$), GRFS was 38% and 53% ($p = 0.021$) in haplo and MUD groups respectively. The cumulative incidence of NRM at 2 years was 37% and 14% ($p = 0.0014$), RI was 19% and 7% ($p = 0.014$). Day-100 cumulative incidence of grade II-IV aGVHD was 27.7% and 11.1% ($p = 0.013$), with no significant difference for grade III-IV aGVHD ($p = 0.427$). In a more detailed study of the haplo group, it was found that the use of bone marrow as a graft source reduced EFS by 22% ($p = 0.036$) and increased RI by 27% ($p = 0.049$). In the multivariate analysis haploidentical donors had significantly reduced EFS ($p = 0.026$), status of CR2 significantly reduced GRFS ($p = 0.029$), bone marrow as a graft source did not significantly impact OS, EFS, GRFS.



Conclusions: In this study we demonstrated the significant superiority of MUD HSCT over haploHSCT for de novo AML in adult patients when both are performed with PTCY prophylaxis. At the same time, haploHSCT remains an important and often the only option for patients without an available HLA-matched donor. Due to the revealed possible difference in EFS and RI between graft sources in the haplo group, further research is needed to identify the best graft source for replete haploHSCT. A significant advantage in GRFS has been demonstrated in patients in CR1, which allows for early consideration of the HSCT in patients with primary AML.

Disclosure: Nothing to declare.

P011

Allogeneic transplantation for adults with acute megakaryoblastic leukemia, a study from acute leukemia working party of the european society for blood and marrow transplantation (ebmt)

E. Maffini[1], M. Labopin[2], A. Huynh[3], G. Choi[4], I.W. Blau[5], P. Lewalle[6], W. Bethge[7], M. Schaap[8], P. Chevallier[9], T. Schroeder[10], U. Platzbecker[11], E. Verburgh[12], G. Bug[13], J. Esteve[14], A. Bazarbachi[15], F. Lanza[1], A. Nagler[16], M. Mohty[17]

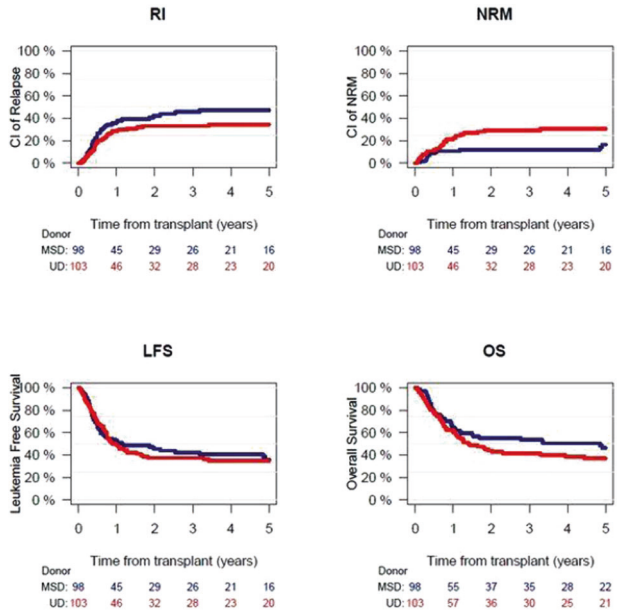
[1]Hematology and Stem Cell Transplant Unit, Ravenna Public Hospital and Romagna Transplant Network, Ravenna, Italy, [2]EBMT ALWP Office, Paris, France, [3]CHU - Institut Universitaire du Cancer Toulouse, Oncopole, I.U.C.T-O, Toulouse, France, [4]University Medical Centre Groningen, University of Groningen, Groningen, Netherlands, [5]Medizinische Klinik m. S. Hämatologie, Onkologie und Tumorimmunologie, Charité Universitätsmedizin, Berlin, Germany, [6]Jules Bordet Institute, Université Libre de Bruxelles, Bruxelles, Belgium, [7]University of Tuebingen, Medizinische Klinik, Tuebingen, Germany, [8]University Medical Center, Nijmegen, Netherlands, [9]CHU Nantes, Dept. d'Hematologie, Nantes, France, [10]University Hospital Dept. of Bone Marrow Transplantation, Essen, Germany, [11]Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, University Hospital Leipzig, Leipzig, Germany, [12]University of Cape Town, Clinical Haematology, Cape Town, Cape Town, South Africa, [13]Medizinische Klinik II, Hamatologie/onkologie, Universitätsklinikum Frankfurt Main, Frankfurt am Main, Germany, [14]Hospital Clínic of Barcelona, IDIBAPS, University of Barcelona, Barcelona, Spain, [15]American University of Beirut Medical Center, Beirut, Lebanon, [16]Sheba Medical Center, Tel-Hashomer, Tel-Aviv university, Tel Aviv, Israel, [17]Saint Antoine Hospital, Paris, France

Background: Acute megakaryoblastic leukemia (AMKL) is a rare subtype of acute myeloid leukemia, arising from megakaryocytes. As survival rates are extremely poor due to higher rates of disease relapse (RI), consolidation treatment with an allogeneic hematopoietic cell transplantation (HCT) might offer the best chance of cure for patients in remission.

Methods: We report on a retrospective analysis on adults affected by AMKL in first complete remission (CR1) that received a first allogeneic HCT, both from unrelated donors (UD) or HLA-matched sibling donors (MSD). Graft source was mainly peripheral blood (87%), or bone marrow (13%). All patients underwent transplantation between January 2000 and December 2020 and their data were reported to the ALWP of the EBMT.

Results: A total of 201 patients (median age 48 years, 117 male and 84 female) were included in the analysis. Median follow-up for the entire population was 5.2 years. Donors were HLA-matched siblings ($n = 98$), 10/10 UD ($n = 48$), 9/10 UD ($n = 17$) and 38 were missing data on UD HLA-compatibility. Patients transplanted from UD were older ($p < 0.01$), more often presented the combination female donor to male recipient ($p < 0.01$) and more frequently received a reduced-intensity-conditioning ($p < 0.01$). Cytogenetic risk was intermediate in 54 patients, poor in 54 and not available in 93. Ninety-eight % of patients engrafted. The estimated 5-year rates of overall survival (OS) were 41.4% (95% CI 33.6 - 48.9), leukemia-free survival (LFS) 35.6% (95% CI 28.3-43), RI 40.5% (95% CI 33.2-47.7) and non-relapse mortality (NRM) 23.9% (95% CI 17.7-30.6) (Fig.1). Five-year GVHD-free, relapse-free survival (GRFS) was 26.8% (95% CI 20.3 - 33.7) overall. Global incidence of grade III-IV acute graft-versus host-disease (GVHD) at day-180 was 8.8% (95% CI 5.3-13.3), while 2-year extensive chronic GVHD incidence was 17.5% (95% CI 12.1-23.7). In multivariate model, patients transplanted from UD tended to have a trend towards higher rates of NRM (hazard ratio [HR] 1.90, 95% CI 0.99-3.63, $p = .0053$). Patient age (as incremental value, per 10 years), was associated with higher rates of NRM (HR 1.30, 95% CI 1.03-1.66, $p = .03$) and worse OS (HR 1.21, 95% CI 1.05-1.40, $p = .01$), as well as adverse cytogenetics with RI (HR 2.17, 95% CI 1.30-3.61, $p = .003$) and LFS (HR 1.58, 95% CI 1.04-2.40, $p = .03$), in multivariate analysis.

Figure 1. Relapse incidence (RI), non-relapse mortality (NRM), leukemia-free survival (LFS) and overall survival (OS) for patients transplanted from HLA-matched siblings (blue line) and from UD (red line).



Conclusions: Allogeneic HCT could be curative in a proportion of adult AMKL patients in CR after induction treatment. Patients transplanted from UD had increased rates of NRM.

Disclosure: Nothing to declare

P012

Autologous versus haploidentical stem cell transplantation in adult patients with acute myelogenous leukemia in first remission with undetectable minimal residual disease: A European preliminary analysis

N.C. Gorin[1], J. Chen[2], M. Labopin[3], E. Nur[4], E. Borlenghi[5], J. Cornelissen[6], F. Ciceri[7], T. Zuckerman[8], G. Van Gorkom[9], D. Caballero[10], S. Sica[11], I. Khevelidze[3], E. Polge[3], A. Nagler[12], D. Wu[2], M. Mohty[1]

[1]Paris Sorbonne University, Paris, France, [2]National Clinical Research Center for Hematologic Diseases, Jiangsu Institute of Hematology, Suzhou, China, [3]Hopital Saint-Antoine APHP, EBMT Paris Office, Paris, France, [4]Amsterdam University Medical Centers, Amsterdam, Netherlands, [5]Spedali Civili, Hematology Division, Brescia, Italy, [6]Erasmus MC Cancer Institute, Rotterdam, Netherlands, [7]Ospedale San Raffaele s.r.l., Milano, Italy, [8]Rambam Medical Center, Haifa, Israel, [9]University Hospital, Maastricht, Netherlands, [10]Hospital Clínico, Salamanca, Spain, [11]Universita Cattolica S. Cuore, Roma, Italy, [12]The Chaim Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel

Background: For adult patients with acute myelogenous leukemia (AML), numerous patient and disease prognostic factors have been shown to impact the outcome following stem cell transplantation.

In the past decade, several studies have shown the importance of the evaluation of minimal residual disease (MRD); undetectable MRD (uMRD) in particular at transplant, has been recognized as the most important predictor of favorable outcome, possibly erasing previously recognized poor prognostic factors.

At the present time, there is no consensus on the consolidation therapy to offer to intermediate-risk patients in CR. The recent GIMEMA AML 1310 trial of risk adapted MRD directed therapy has shown equivalent outcome for AML patients autografted (ASCT) in uMRD-CR1 or allografted in the case of persisting MRD positivity.

Methods: Using the EBMT registry, we collected data from 344 autografted patients and 200 patients who received a T-cell replete haploidentical (Haplo) transplant from January 2010 to December 2019.

Results: The distribution of molecular markers was not even: for autografted patients, a NPM1 mutation was present in 63% and FLT3-ITD in 24% while it was 46% and 50% for Haplo ($p < 0.0002$ for each). The stem cell source was peripheral blood in 97% for ASCT and 64% for Haplo ($p < 0.0001$). In the autografted population the myeloablative conditioning (MAC) consisted essentially (69%) of the combination of busulfan + cyclophosphamide or busulfan + high-dose melphalan. For Haplo the conditioning regimen was MAC in 48% and reduced intensity in 52%. All Haplo recipients received posttransplant cyclophosphamide (PTCY) for GVHD prophylaxis.

The outcome at 3 years posttransplant is indicated below (univariate p):

Relapse NRM LFS OS

Auto 50.5%[44.6-56.1] 7.1%[4.5-10.4] 50.3%[44.6-55.7] 67%[61.4-71.9]

Haplo 14.5%[9.3-20.7] 23.6%[17.5-30.2] 65.2%[57.6-71.8] 72.6%[65.3-78.6]

P value 0.001 0.001 0.005 0.5

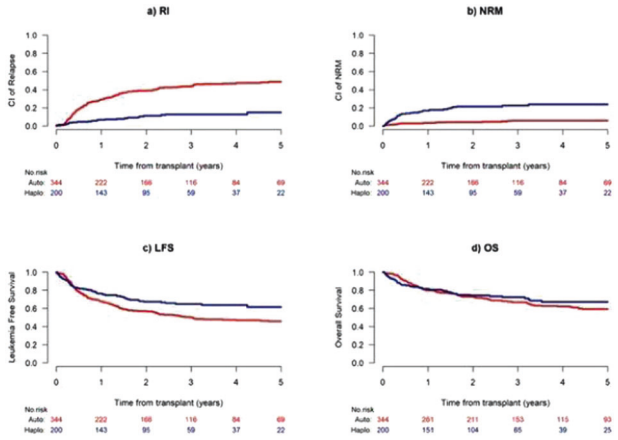
Post Haplo, the rates of acute GVHD grades III-IV, chronic GVHD, and severe chronic GVHD at 3 years were 7%, 42%, and 17% respectively. The GVHD/relapse-free survival (GRFS) was 54%.

31% of autografted patients and 6% of Haplo received a second transplant.

On multivariate analysis, Haplo was significantly associated with a higher NRM, a lower RI, and a higher LFS. Overall survival was not significantly different from ASCT. Other prognostic factors

	RELAPSE		NRM		LFS		OS	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Haplo vs Auto	0.18 (0.1-0.32)	<0.0001	4.59 (2.02-10.41)	0,0003	0.49 (0.32-0.75)	0.001	0.73 (0.43-1.23)	0.23
Age (per 10 years)	1.07 (0.95-1.21)	0.25	1.76 (1.33-2.34)	< 0.0001	1.18 (1.05-1.32)	0.006	1.35 (1.16-1.57)	<0.0001
Year of HSCT	0.99 (0.93-1.06)	0.82	0.87 (0.77-0.98)	0.022	0.98 (0.93-1.04)	0.47	0.95 (0.89-1.02)	0.15
Female vs Male R	0.93 (0.68-1.27)	0.63	1.2 (0.69-2.1)	0.52	1.01 (0.76-1.34)	0.94	1.27 (0.9-1.79)	0.18
Time diagnosis to HSCT (mo)	1.02 (0.95-1.1)	0.57	1 (0.91-1.11)	0.94	1.02 (0.96-1.08)	0.5	1.03 (0.96-1.11)	0.36
FLT3 ITD vs FLT3-wt	1.89 (1.3-2.75)	0.0009	1.94 (1.01-3.72)	0.047	1.91 (1.37-2.65)	0.0001	2.32 (1.57-3.41)	<0.0001
NPM1 vs no	0.43 (0.31-0.59)	<0.0001	0.62 (0.33-1.17)	0.14	0.47 (0.34-0.63)	<0.0001	0.42 (0.29-0.61)	<0.0001
PBSC vs BM	0.83 (0.45-1.52)	0.54	0.85 (0.41-1.77)	0.66	0.78 (0.48-1.26)	0.31	0.78 (0.44-1.37)	0.38

were patient age, and the presence of NPM1 and FLT3ITD mutations. No center effect was observed.



Conclusions: For adult patients with AML with uMRD-CR1, Haplo with PTCY resulted in a superior LFS of 65% versus 50% at 3 years and a GRFS of 54%. By intention to treat there was no difference for OS.

Disclosure: No conflict of interest

P013

Influence of the expression of genes characteristic of leukemic stem cells on the results of allogeneic HSCT in children with acute myeloid leukemia

Z. Rakhmanova[1], O. Paina[1], I. Barkhatov[1], I. Kazantsev[1], A. Sadykov[1], P. Kozhokar[1], A. Frolova[1], L. Tsvetkova[1], E. Babenko[1], T. Gindina[1], A. Alyanskiy[1], A. Kulagin[1], I. Moiseev[1], E. Semenova[1], L. Zubarovskaya[1]

[1]RM Gorbacheva Research Institute, Pavlov University, Saint Petersburg, Russian Federation

Background: Leukemic stem cells (LSCs), which play a crucial role in pediatric AML, are distinguished by a specific mRNA-expression signature. Recently, a six-gene leukemic stem cell score (pLCS6) value have been shown to be an effective prognostic marker independent of minimal residual disease (MRD) (Abdelrahman H. Elsayed et al., 2020). However, although initial high-pLCS6 status is associated with worse prognosis even in subsequent alloHSCT recipients, there is yet no data on pre-transplant pLCS6 measurement prognostic value.

Methods: Gene expression profiling by RT-PCR was performed in 50 AML patients receiving alloHSCT in different disease status. Complete remission 1 (CR1) or CR2 was documented in 74% (n = 37) of children, 26% (n = 13) of patients had active disease before alloHSCT. The retrospective study cohort included 37 children with AML at CR1 or CR2 receiving alloHSCT from matched related (n = 3, 8%), matched unrelated (n = 15, 41%) or haploidentical donor (n = 19, 51%) in RM Gorbacheva Research Institute during 2014-2021 period. The median age was 6(1-18) years. In 28 (76%) cases myeloablative and in 9 (24%) non-myeloablative conditioning regimen was used. In 78% (n = 29) of cases the GVHD prophylaxis regimen included post-transplant cyclophosphamide. The gene expression profiling was performed via RT-PCR for DNMT3B, GPR56, CD34, SOCS2, SPINK2, IL2RA, FAM30A and ABL genes with subsequent pediatric six-gene leukemic stem cell score (pLSC6) calculation by previously described equation: (DNMT3b x 0.189) + (GPR56 x 0.054) + (CD34 x 0.0171) + (SOCS2 x 0.141) + (SPINK2 x 0.109) + (FAM30A x 0.0516).1 If an appropriate sample was available, the post-transplant pLSC6 value was also evaluated. After the median pLSC6 was determined all patients were divided into low-pLSC6 and high-pLSC6 groups.

Results: A total of 18/37 (49%) patients had high-pLSC6 pre-transplant score value. Only 6/18 of high-pLSC6 patients with CR1-2 were MRD-positive. The post-transplant pLSC6 value was measured in 14 patients, in 85% cases the pre-transplant high-pLSC6 values converted to low-pLSC6. The linear regression analysis including patients with pre-transplant response as well as patients with active disease showed no association between blast count/MRD and pLSC6 values (OR 1.002; 95% CI: 0.979, 1.025). The 1-year RFS in CR patients was not significantly different between low-pLSC6 (78.9%) and high-pLSC6 (66.7%) patients (p = 0.62). However, while none of the clinical factors were significant in the multifactor analysis, the early relapse rate in CR patients was significantly higher in high-pLSC6 subgroup compared to low-pLSC6 (22% and 0%, accordingly; p = 0.03).

Conclusions: Although current results do not support pLSC6 assay value as an indication for alloHSCT, there is still a tendency to worse prognosis in children with pre-transplant high-pLSC6 score in spite of the evidence of graft-versus-leukemia effect on LSCs. The pre-transplant high-pLSC6 status may, therefore, be a factor for pre-emptive post-transplant intervention in the future independent of blast count and MRD. As the effectiveness of this study is limited by its retrospective design, it warrants further research in a larger prospective cohort.

Disclosure: The study was supported by Fund for promoting innovation «Fund-M», grant № 0059546.

P014

The clinical characteristics and prognosis of aya and older adult early t-cell precursor leukemia/lymphoma: A real-world multicenter study in China

J. Xiao[1], Z. Cai[2], H. Wang[3], X. Li[1], B. Zhou[1], Y. Liu[1], Y. Wang[1], P. Xu[4], L. Wang[5], D. Wu[1], L. Dou[3], H. Zhou[2], Y. Xu[1]

[1]The First Affiliated Hospital of Soochow University, Suzhou, China, [2]Nanfang Hospital, Southern Medical University, Guangzhou, China, [3]Chinese PLA General Hospital, Beijing, China, [4]Nanjing Drum Tower Hospital, Nanjing, China, [5]Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Early T-cell precursor lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) is a hematological malignancy originating from immature T lymphoblastic cells with high rate of treatment resistance and poor long outcome. Hitherto, studies of survival outcomes in ETP-ALL/LBL were still controversial. Data of large cohort in ETP-ALL/LBL are still lacking.

Methods: In this retrospective analysis, we performed a real-world multicenter study to explore the clinical characteristics and prognosis of adolescent and young adults (AYA) and older adult ETP leukemia/lymphoma. A total of 103 patients with ETP-ALL/LBL in five centers in China between January 2016 and February 2021 were included in this study. Outcomes were assessed in terms of overall survival (OS) and relapse-free survival (RFS).

Results: The median age was 29 years (range, 15–70 years). Next-generation sequencing was performed in 94 patients and revealed that NOTCH1 (35.1%, 33 cases) was the most frequently mutated gene, followed by JAK3 (16.0%, 15 cases), PHF6 (13.80%, 13 cases) and EZH2 (11.70%, 11 cases). Complete remission (CR) was obtained in 74.2% (72/97) of patients, and 6 relapsed/refractory patients received a decitabine combined with AAG priming regimen as reinduction therapy with a CR rate of 50%. With a median follow-up of 18 months (0.5–60 months), the 2-year overall survival (OS) and relapse-free survival (RFS) rates for the

entire cohort were 54% and 57.7%, respectively. Allogeneic stem cell transplantation (allo-SCT) was performed in 59.8% (58/97) of patients. Patients who experienced transplantation in CR had better OS than transplantation in NR (P = 0.029, HR: 0.3625, 95%CI 0.1005 to 1.308), while the RFS was no statistical significance. (P = 0.078, HR:0.4431, 95% CI 0.1340 to 1.465). Patients who were MRD negative at transplantation had better OS and RFS than those who were MRD positive (OS: P = 0.032, HR: 0.3306, 95%CI 0.09829 to 1.112; RFS: P = 0.0035, HR: 0.2492, 95%CI 0.07993 to 0.7770). Additionally, there was no statistical significance in the OS and RFS of HLA-matched and HLA-mismatched patients (OS: P = 0.63, HR: 0.7996, 95% CI 0.3144 to 2.034, RFS: P = 0.97, HR: 0.9844, 95% CI 0.3982 to 2.433). The 2-year OS of patients was 68% in the allo-SCT group and 26% in the chemotherapy group (p < 0.001, HR: 0,2567, 95% CI 0.1336 to 0.4932). A multivariate analysis suggested that allo-SCT and CR after the first course induction were independent prognostic factors for OS.

Conclusions: Collectively, we reported the largest cohort study with AYA and older adult ETP-ALL/LBL, and we found that ETP-ALL/LBL was highly invasive and had a poor long-term prognosis. Allo-SCT could significantly improve ETP-ALL/LBL patient survival.

Disclosure: Nothing to declare.

P015

Outcome prediction by the knowledge bank approach in AML patients undergoing allogeneic stem cell transplantation

L. Herrmann[1], L. Bischof[1], D. Backhaus[1], D. Brauer[1], G.-N. Franke[1], V. Vucinic[1], U. Platzbecker[1], M. Jentzsch[1], S. Schwind[1]

[1]University of Leipzig Medical Center, Leipzig, Germany

Background: In acute myeloid leukemia (AML) current risk stratification (e.g. by the European LeukemiaNet (ELN) 2017) relies on diagnostic genetic aberrations and help to inform treatment decisions, including those for an allogeneic stem cell transplantation (HSCT) in first remission. Recently Gerstung et al. (Nature Genetics, 2017) developed a knowledge bank (KB)-based algorithm based on demographic, clinical, and genetic data to predict individual outcomes. Two studies validated the feasibility of KB prediction in AML patients consolidated with chemotherapy. However, a validation in a HSCT-treated cohort, crucial with respect to informed decisions towards HSCT, is missing.

Methods: We analyzed 545 AML patients (median age at diagnosis 62, range 21-77 years) receiving a non-myeloablative (77%) or reduced-intensity (23%) HSCT (60% were in first remission). Clinical variables included in the KB were available for our cohort, while our gene mutation panel did not include 17/58 of genes included in the KB. KB predictions 3 years after diagnosis were calculated by using the adapted transplant strategy and compared to the observed outcomes using receiver operating characteristics (ROC) curves. In addition, the measurable residual disease (MRD) status at HSCT was evaluated in patients with material available and based on NPM1 mutation and BAALC, MN1, and WT1expression.

Results: The KB approach had an area under the curve (AUC) to predict 3-year OS of 0.69 (95% CI 0.62-0.72) which was not significantly different compared to the AUC of the ELN2017 risk stratification (0.66 [95% CI 0.57-0.71], $P = 0.23$), and worse compared to the published results in patients receiving chemotherapy ($AUC_{KB} = 0.80$, Bill *et al*. 2021). However, in a multivariate analysis the KB prediction for 3-year OS significantly impacted OS (OR 6.25, CI 2.9-13.2) after adjustment for the MRD-corrected remission status at HSCT and Aikaike Information criterion (AIC) comparison with a model including the ELN2017 classification demonstrated the model containing the KB prediction as preferable. When introducing arbitrary cut-offs according to the KB prediction for OS at 3 years, we observed a clear separation of OS curves according to a KB value of <20, 20-39, and ≥ 40 (with higher values indicating a higher likelihood for OS, $P < 0.001$). Regarding other endpoints for which the KB algorithm provides outcome prediction, we observed the highest probability to correctly predict non-remission death ($AUC_{KB} = 0.75$), restricted prediction for death in first remission ($AUC_{KB} = 0.61$) or after relapse ($AUC_{KB} = 0.63$), but good outcome prediction for being alive after relapse ($AUC_{KB} = 0.77$) or being alive in first remission ($AUC_{KB} = 0.69$).

Conclusions: For HSCT treated AML patients the KB-based outcome prediction for HSCT treated patients was inferior compared to previous studies of patients receiving chemotherapy. The likely reason for the inferiority is the introduction of confounders (*e.g*. donor selection, graft-versus-host-disease), especially for treatment-related mortality, not integrated in and not predictable by the current KB algorithm. Inclusion of these additional factors might allow for a more precise outcome prediction for AML patients receiving HSCT.

Disclosure: Nothing to disclose

P016

Midostaurin maintenance vs ALLO SCT vs W&W in flt3 mutated AML. A "real life" multicenter study

A. de la Fuente[1], M. Diaz Beya[2], P. Beneit[3], A. Fernandez[4], M. Arnan[5], A. Garrido[6], S. Vives-Polo[7], M. Garcia Fortes[8], A. Sampol[9], J. Labrador[10], A. Garcia Guinon[11], C. Gil[12], J. Bergua Burgues[13], M.t. Olave Rubio[14], M.L. Amigo[15], X. Ortin[16], M. Cervera[17], M. Estevez[1], A. Diaz Lopez[18], J. Serrano[19], M. Tormo[20]

[1]MD Anderson CC Madrid, Madrid, Spain, [2]H. U. Clinic IDIBAPS, Barcelona, Spain, [3]H. U. San Juan de Alicante, Alicante, Spain, [4]H. Central de Asturias, Oviedo, Spain, [5]ICO Hospitalet L'Hospitalet de LLobregat, Barcelona, Spain, [6]H. de la Santa Creu i Sant Pau, Barcelona, Spain, [7]ICO H. Germans Trias i Pujol, Barcelona, Spain, [8]H. Virgen de la Victoria, Malaga, Spain, [9]H. U. Son Espases, Palma de Mallorca, Spain, [10]H. U. de Burgos, Burgos, Spain, [11]H. U. Arnau de Vilanova, Lleida, Spain, [12]H. U. General de Alicante, Alicante, Spain, [13]H. U. San Pedro de Alcantara, Caceres, Spain, [14]H. U. Lozano Blesa, Zaragoza, Spain, [15]H. U. Morales Meseguer, Murcia, Spain, [16]H. U. Verge de la Cinta Instituto Perz Virgili, Tortosa, Spain, [17]ICO H. U. Joan XXIII, Tarragona, Spain, [18]Fundacion MD Anderson, Madrid, Spain, [19]H. U. Reina Sofia, Cordoba, Spain, [20]Clinico Universitario Instituto de Investigación Sanitaria INCLIVA, Valencia, Spain

Background: Introduction: FLT3-ITD mutation is associated with adverse prognosis (ELN2017, Dohner et al, Blood 2017) and SCT has been the standard of treatment for FLT3 mutated AML for decades. Midostaurin (Midos) has been approved in combination with intensive chemotherapy (IC) for FLT3-mutated AML, midostaurin maintenance was part of the treatment schedule in the RATIFY trial but not randomly explored (Stone et al, N Engl J Med 2017).

Methods: Aims: The aims of this study are to analyze safety and effectiveness of midostaurin maintenance in FLT3 AML in a "real-world" setting and to evaluate maintenance versus alloSC versus W&W and the impact of risk factors.

Methods: We carried out a retrospective multicenter study (MDA-AML-2018-06) in 27 Spanish centers. Inclusion criteria: age >18 years, FLT3-mutated AML diagnosis according to WHO criteria and start of treatment with midostaurin in combination with IC between June 2016 and December 2020. We evaluated the response according to 2017 ELN criteria, toxicity according to

CTCAE v4.0 and overall survival (OS) by Kaplan-Meier. Statistical analysis was performed using SPSS program version 20.0.

Results: Results: A total of 175 (93 female) patients were included, median age 53 (18-76) median OS for the whole population not reached, 24months OS 68%. Of those who achieved CR after Induction1or2 144 (81.4%) patients, 24p received maintenance, 76p were consolidated with alloSCT and 41p proceed to W&W (table 1).

Safety: AE during maintenance were one case of QT prolongation which required Midos discontinuation. No cases of febrile neutropenia and no cases of deaths related to Midos.

Regarding OS the ELN2017 classification resulted in a trend of differences in all groups maintenance, alloSCT and W&W. We observed significant differences for maintenance versus W&W (p0.001) in low and intermediate risk patients. Comparing maintenance vs alloSCT we observe no differences in the Int ELN2017 group.

Table 1

Patients who achieved CR after Induction1 and/or Induction2 Total n 144			
	Maintenance	**alloSCT**	**W&W**
Total	24	76	41
Madian Age	61 (31-73)	51 (18-69)	56 (23-76)
ELN2017 Low	16	11	21
ELN2017 Int	7	45	16
ELN2017 High	0	16	3
Lost	1	4	1

Conclusions: Conclusions: Our experience confirms safety of maintenance therapy in AML FLT3 patients after intensive chemotherapy. We also observed a benefit for maintenance versus W&W in low and intermediate risk population.

Clinical Trial Registry: Not registered at Clinical Trials
Approved by National Ethics Comitie

Disclosure: Study founded by Novartis

P017

The ebmt disease risk stratification system (drss) allows prediction of relapse after allogeneic hematopoietic cell transplantation for acute myeloid leukemia

Y. Kadri[1], M. Phan[1], J. Bergeron[1], N. Bambace[1], L. Bernard[1], S. Cohen[1], J.-S. Delisle[1], T. Kiss[1], S. Lachance[1], D.-C. Roy[1], J. Roy[1], G. Sauvageau[1], O. Veilleux[1], I. Ahmad[1]

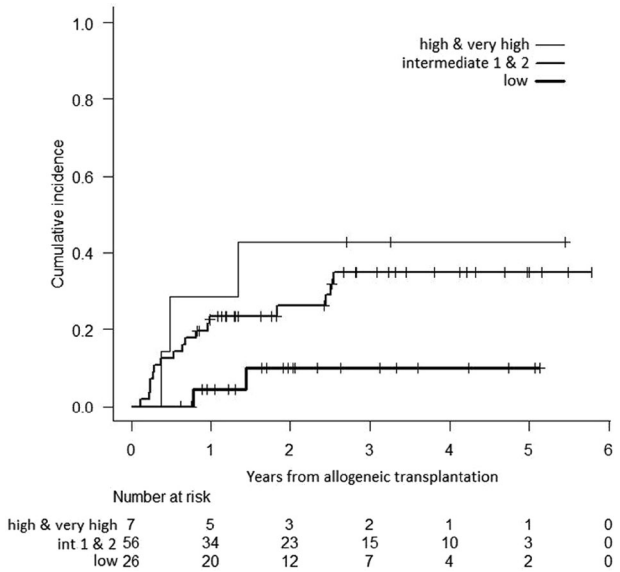
[1]Institut universitaire d'Hémato-Oncologie et de Thérapie cellulaire - Hôpital Maisonneuve-Rosemont - Université de Montréal, Montreal, Canada

Background: Using EBMT registry data, the DRSS has been proposed to predict relapse risk after allogeneic hematopoietic cell transplantation (HCT) across disease subtypes and remission states ordered in 55 categories and 5 risk levels (Shouval R et al. *Lancet Haematol*. 2021). For acute myeloid leukemia (AML) the DRSS combines ELN risk group, remission rank, and de novo vs. secondary AML in 19 categories. We sought to determine its reproducibility in a cohort of subjects transplanted for AML.

Methods: Data from a single-centre cohort of adult AML patients transplanted between 01/07/2015 and 30/06/2020 was analysed retrospectively. Baseline characteristics and outcomes were extracted, and Fine-Gray regression was used to determine the association between cumulative incidence of relapse (CIR) and patient, disease, and transplant characteristics, as well as the influence of graft-versus-host disease (GVHD) as a time-dependent covariate. Model selection techniques were used to select the least number of significant predictors of CIR.

Results: In this cohort of 89 patients, median follow-up was 2.7 years (interquartile range: 0.9-3.2) and CIR was 29% at 5 years (95% confidence interval: 19-40). The study of the association between CIR and patient age >60 years, donor type (related matched, haploidentical, matched unrelated, cord blood), DRSS category, chronic (c) GVHD yielded a model using two covariates: DRSS and cGVHD, to predict CIR (hazard ratio (HR) 0.38, $p = 0.03$ and HR 0.43, $p = 0.12$, respectively). Univariate graphic representation of CIR according to DRSS is shown in Figure 1.

Figure 1 – CIR according to DRSS score



Conclusions: In adults with AML, cumulative incidence of relapse after allogeneic HCT can be predicted by DRSS across all donor types and age groups.

Disclosure: Nothing to declare.

P018

Structural analysis of leukemia-associated protein tyrosine phosphatase ptpn21 and protein interaction network analysis of its wild type and mutants

Z. Qian[1,2], L. Chen[2], J. Zhang[3], Y. Zheng[2], C. Zhou(corresponding auther)[3,2], H. Xiao(corresponding auther)[1,2]

[1]Sir Run Run Shaw Hospital, Hang Zhou, China, [2]Zhejiang University School of Medicine, Hang Zhou, China, [3]Sir Run Run Shaw Hospital, Hang Zhou, China

Background: Protein tyrosine phosphatase non-receptor type 21 (PTPN21) gene mutations and its elevated expression level have been reported in different type of tumors. We have also found that PTPN21 gene mutations are associated with disease relapse in B-cell acute lymphoblastic leukemia (B-ALL) patients. However, the

structure and molecular mechanism of PTPN21 wild type and mutations remain to be determined.

Methods: We use protein crystallization and X-ray diffraction to determine the structure of protein PTPN21. We further used miniTurbo-mass spectrometry analysis to study the difference of protein interaction networks between PTPN21 wild-type protein and PTPN21 mutant proteins in living cells.

Results: We have determined the structure of FERM domain and PTP domain of PTPN21. We also found that compared with PTPN21 wild-type protein, three PTPN21 mutant proteins, which were involved in the pathogenetic process of relapse of B–ALL, significantly reduce the binding affinity to 202 proteins and increase the interaction with 119 proteins in cells. The KEGG pathway analysis showed involvement in the vesicle docking, extra-cellular matrix(ECM) receptor interaction, MAPK pathway and so on. Notably, the most remarkably decreased interacting proteins of all three PTPN21 mutations are centrosome associated protein HP5, the Hippo pathway component WWC2, the trafficking protein TMED10, actin binding protein FSCN1 and a newly emerged cell fate regulators as well as the Hippo pathway kinase LATS1.

Conclusions: ALL-associated PTPN21 mutant proteins may promote cell-matrix interaction, MAPK signaling, the Hippo pathway and the expansion of centrosomal amplification to assist B-ALL cells to survive chemotherapy and disease relapse.

Disclosure: Nothing to declare

P019

Thiotepa, busulfan and fludarabine: A conditioning-regimen for adult patients with acute lymphoblastic leukemia

A. Banet[1,2], A. Bazarbachi[3], M. Labopin[1,2], R. Duléry[1,2], F. Malard[1,2], Z. Van de Wyngaert[1,2], A. Bonnin[1], V. Radici[1], R. Belhocine[1], S. Sestili[1], J. El-Cheikh[3], M. Mohty[1,2], E. Brissot[1,2]

[1]APHP, Hôpital Saint-Antoine, Service d'Hématologie Clinique et de Thérapie Cellulaire, Paris, France, [2]Sorbonne Université, INSERM UMR 938, Centre de Recherche Saint-Antoine (CRSA), Paris, France, [3]Bone Marrow Transplantation Program, American University of Beirut Medical Center, Beirut, Lebanon

Background: For acute lymphoblastic leukemia (ALL) patients, total body irradiation (TBI) based conditioning regimens are often the first choice, considering their positive impact on relapse incidence. However, TBI is associated with toxicity and long-term morbidity, and its accessibility can be a major issue for many hematological centers. Several studies have shown an equivalence in clinical outcomes with chemotherapy-based conditioning, notably with the use of thiotepa. We performed a retrospective bicenter study to evaluate the outcome of adult ALL patients who had received, before allogeneic hematopoietic stem cell transplantation (allo-HCT), a thiotepa-busulfan-fludarabine (TBF) myeloablative conditioning regimen with reduced toxicity.

Methods: Fifty-five patients (not eligible to high dose TBI) from Saint-Antoine Hospital (Paris, France) or the American University of Beirut Medical center (Beirut, Lebanon), received a TBF regimen consisting of 1-2 days of thiotepa (5mg/kg/day), 2-3 days of busulfan (130 mg/m2), and 5 days of fludarabine (30 mg/m2). The repartition of conditioning-regimen was 34.5% of T2B3F, 32.7% of T1B3F, 30.9% of T1B2F, and 1.8% of T2B2F. The median age of the patients was 51 years (range 17 to 72.4). Twenty-eight (50.9%) were male. Most patients had a diagnosis of B-ALL (93%) and 7% of T-ALL. Forty-two (76.4%) patients had a high-risk cytogenetic ALL. At the time of transplant 52 (94.5%) patients were in complete remission, 2 patients had a positive minimal residual disease (MRD) and 1 patient was refractory. For assessment of minimal residual disease (MRD): 27 (50%) patients had a Philadelphia chromosome, 8 (14.8%) had an immunoglobulin (Ig) and/or T-cell receptor (TCR) rearrangement, and 4 (7.4%) had an MLL rearrangement. The remaining MRD assessments were carried out using multiparameter flow cytometry. Peripheral blood stem cells were the main stem cell source (90.9%). Twenty-seven (49.1%) patients were transplanted from a matched sibling donor, 12 (21.8%) from a matched unrelated donor, and 16 (29.1%) from a haploidentical donor. The graft-versus-host disease (GVHD) prophylaxis was cyclosporine A (CsA) alone (32.7%), or CsA with mycophenolate mofetil. In addition, antithymocyte globulin (ATG) was used for a median of 2 days, and patients with a haploidentical donor received low-dose ATG and post-transplant cyclophosphamide (PT-Cy). All patients engrafted at a median time of 15 days (range, 5-27).

Results: With a median follow-up of 43 months, 2- and 5-year overall survival (OS) was 73.2 % (95% CI: 58.9 - 83.2) and 64% (95% CI: 48.8 - 75.7), respectively. At 2 years, leukemia-free survival (LFS) and GVHD-free, relapse-free survival (GRFS) were 59.5% and 57.6%, and at 5 years, 53.4% and 51.8%, respectively. The 5-year non-relapse mortality (NRM) was 15%. The day 180 cumulative incidence (CI) of grade II-IV acute GVHD and grade III-IV acute GVHD were 44.7% and 6.4%, respectively. At 2 years, the CI of chronic GVHD and extensive chronic GVHD was 16.9% and only 1.9%, respectively.

Conclusions: Our retrospective study does suggest that using TBF as the conditioning regimen in adult ALL patients is a promising option with acceptable toxicity.

Disclosure: Nothing to declare

P020

Patterns of relapse and outcomes in patients with acute leukemia post allogenic transplantation

M. Saroha[1], N. Jindal[1], D.S. Philip[2], A. Chichra[1], S.P. Mirgh[1], A. Gokarn[1], S. Punatar[1], L. Nayak[1], A. Bonda[1], L.J Mathew[1], S. Kannan[1], N. Khattry[1]

[1]Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Centre, Mumbai, India, [2]Regional Cancer Centre, Trivandrum, India

Background: With improvement in transplant related mortality (TRM), relapse is the major factor affecting survival post HSCT. Prognosis of patients with acute leukemia (AL) relapsing after HSCT is dismal. We analysed incidence and patterns of relapse, factors predicting relapse and determinants of post relapse OS (PROS).

Methods: This is a single centre retrospective analysis of AL patients who underwent 10/10 or 9/10 matched related or unrelated ASCT from January 2008 to December 2019. AL included lymphoid (ALL), myeloid (AML) and mixed phenotypic (MPAL) leukemias. Nineteen patients with AML had active disease; rest were in complete remission at ASCT. Conditioning included either full intensity regimens [TBI-cyclophosphamide (Cy), busulfan (Bu) - Cy or Fludarabine (Flu) – Bu] or reduced intensity regimens (Flu based). GVHD prophylaxis consisted of calcineurin inhibitor (CNI) with either methotrexate or MMF or PTCY with CNI and MMF. Factors studied as predictors of relapse were DRI, EBMT risk score, HCT-CI, transplant conditioning intensity (TCI), mixed chimerism (MC) at day 30, 90, 180 and 360, grade II-IV aGVHD and cGVHD. Treatment after diagnosis of relapse was at the discretion of treating physician. Ongoing immunosuppresion (if any) was stopped. In general, patients received 1 or more DLI and/or immunomodulatory or targeted agents (lenalidomide, dasatinib or imatinib, nivolumab, palbociclib, etc). Patients with morphological

relapse were treated with chemotherapy with or without DLI. Some patients with extramedullary relapse (EMR) received radiotherapy. Factors analysed for effect on PROS were time to relapse (TTR), TCI, DRI and prior aGVHD or cGVHD. Cumulative incidence of relapse (CIR) was calculated using competing risk regression with TRM being the competing event.

Results: Total of 162 AL patients underwent HSCT. Sixty four (39%) relapsed. Of these, 52 (81%) had medullary relapse (MR), 8 had EMR and 4 had combined relapse. Among isolated MR, 41 (78.8%) were morphological, 3 were cytogenetic, 3 were flowcytometric, and 5 were molecular relapse. CIR at 1 yr and 2 yr was 24% (95%CI; 18%-31%) and 33% respectively (95% CI; 26%-40%).Significant factors associated with relapse were MC at day 90 ($p = 0.004$) and day 180 ($p = 0.001$) and absence of aGVHD ($p = 0.01$) and cGVHD ($p = 0.00$). However, cGVHD was present in 5/8 with EMR as compared to 12/56 with MR or combined relapse ($p = 0.026$). Similarly, more patients with MR and combined relapse had MC at relapse (28/51, 54.9%) compared to none with EMR ($p = 0.005$). Median PROS was 4.2 months while 1 yr PROS was 31.1%. Factors associated with better PROS included low - intermediate DRI (5.3 vs 1.1 months with high DRI, $p = 0.004$) and receipt of targeted therapy (median PROS 16.5 vs 6.4 months with conventional chemotherapy alone, $p = 0.016$).

Conclusions: About 40% of AL patients experienced relapse post ASCT. Patients with MC (at any time through day +180) and those without acute or chronic GVHD were more likely to have MR or combined relapse. Presence of aGVHD or cGVHD and full donor chimerism did not protect against EMR. Survival after relapse was poor, however those with low and intermediate DRI, and those who received targeted therapies post relapse fared better.

Disclosure: Nothing to declare

P022

Similar OS and DFS after atg or post-transplant cyclophosphamide (PT-CY) as GVHD prophylaxis in patients with all in cr 1 after allogeneic stem cell transplantation

C. Niederwieser[1], R. Massoud[1], C. Langebrake[1], R. Adjalle[1], D. Janson[1], F. Ayuk[1], W. Christine[1], N.-M. Kröger[1]

[1]UKE Hamburg Eppendorf, Hamburg, Germany

Background: Anti-thymocyte globulin(ATG) is widely used to prevent graft-versus-host disease(GVHD) after allogeneic peripheral blood stem cell transplantation(HSCT). High dose cyclophosphamide post-transplant is used as a potent agent for GVHD prophylaxis in matched related(MRD), matched unrelated (MUD), mismatched unrelated(MMUD) and haploidentical HSCT. In this retrospective analysis, we compared the use of ATG to post-transplant cyclophosphamide(PT-CY) on leucocyte engraftment, acute and chronic GVHD, overall survival(OS), disease free survival(DFS), non-relapse mortality(NRM) relapse incidence(RI).

Methods: A total of 57 patients with ALL in CR1 were treated with a preparative regimen of TBI 12Gy in combination with cyclophosphamide or fludarabine between 2002 and 2021. Of the 57, 38.6% patients received ATG and 61.4% PT-CY with calcineurin inhibitors±mycophenolate mofetil. Median age was 37(11-56) years and the majority were male(52.6%). ALL patients(35.1% *bcr/abl*$^+$) were treated according to GMALL protocols including prophylactic cerebral irradiation in 49.1%. MRD positivity was observed in 45.6% and negative in 43.9% of patients. Patients were positive for CMV in 57.9%. Karnofsky score was median 80(60-100)%. Donors were median 32(5-57) years old. More male(66.7%) than female donors and more unrelated(71.9%) than related(28.1%) were used. Included in this analyses were, for the PT-CY group MRD($n = 9$), MUD($n = 17$), MMUD($n = 4$) and haploidentical($n = 5$) and for the ATG group MRD($n = 2$), MUD($n = 14$), MMUD($n = 5$). Most of the donors were CMV positive(59.6%) and more PBSC 89.5% than bone marrow were given. Of the six patients receiving bone marrow four received PT-CY and two received ATG, two were related and four were unrelated.

Results: Patients characteristics were equally distributed in both treatment groups regarding patient age, gender and bcr/abl$^+$(Table 1), but statistically significant differences were noted in pre-transplant radiation therapy($p = 0.02$) and related/unrelated donors ($p = 0.01$). MRD status was not different between the groups. Engraftment was observed in all patients except two in the ATG group. Recovery of WBC was faster in PT-CY as in ATG group. No difference in acute and chronic GVHD was observed between the two groups. After a median follow-up of 2.77 (range 0.05-13.14) years, OS of all patients was 76.7% at 3 years, 72.0 ± 9% in the PT-CY group and 81.8%±8 in the ATG group. DFS of all patients resulted in 72.8% at 3 years, 66.7 ± 8.7% in PT-CY and 81.0 ± 8.6% in ATG treated patients. Only bone marrow source ($p = 0.03$) remained an independent factor for OS after accounting for type of SCT, ATG and prophylactic cerebral irradiation. For DFS type of SCT remained as a trend ($p = 0.07$). RI for PT-CY was 9.1 ± 5.1% and for ATG 4.5 ± 4.6%, while NRM was 21.2 ± 7.3 und für 13.6 ± 7.5% for PT-CY and ATG treated patients, respectively. When analysing only patients receiving peripheral blood, there only was a difference between the related and unrelated($p = 0.03$) and no difference in outcome and GVHD.

Conclusions: The use of PT-CY for GVHD-prophylaxis resulted in faster leucocyte engraftment, but similar acute and chronic GVHD incidence, OS and DFS. Bone marrow source was the only independent risk factor for OS. This finding needs to be confirmed in a larger more homogenous cohort.

Disclosure: Nothing to disclose

P023

Integrated genomic and single-cell molecular analyses of donor cell leukemia after haploidentical allogeneic hematopoietic stem cell transplantation

H. Chen[1], W. Pan[1], X. Zhao[1], H. Xiao (Corresponding auther)[1]

[1]Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains an efficient therapy for hematologic malignancies. Relapse of acute leukemia following allo-HSCT usually represents return of an original disease clone. The development of de novo hematological malignancies in cells of donor origin is a rare but severe complication, known as donor cell leukemia (DCL). To date, the reported patients with DCL are mainly following HLA-matched sibling or unrelated donor HSCT. We present here a rare case of late-onset DCL that developed in HSCT recipient and not in his HLA haploidentical father donor. To reveal the precise etiologic mechanisms of such DCL, we integrated genomic and single-cell molecular analyses.

Methods: We performed short tandem repeat (STR) analysis on bone marrow (BM) samples obtained from patient pre-HSCT and relapse post-HSCT, and donor PBSC sample. Genomic DNA was isolated and subjected to whole-exome sequencing (WES) from specimens of BM sample at relapse post-HSCT, and buccal mucosal specimen from the patient, as well as BM cells and the buccal mucosal specimen from the donor. 10x Genomics single-cell RNA sequencing was performed on patient's BM sample at relapse post-HSCT and donor's BM sample.

Results: STR analysis confirmed that leukemia cells originated from the donor. We compared data sets from donor and DCL samples in order to detect variants that expandedå 3-fold or de novo in DCL with WES. The mutation affected *C17orf97* (chr17: p.Asp220_Pro229-del) has been present in donor BM cells, while at a 7-fold higher frequency in the DCL sample, with variant allele frequency (VAF) from 3.85% to 30%. The evolution of DCL was further associated with the acquisition of mutations in *IDH1* (chr2: p.Arg119Trp; VAF = 6.98%) and *NSD1* (chr5: p.His2205Asp; VAF = 10%). In addition, we also found *ATF7IP* (chr12: p.Gly1122AspfsTer53) mutation with VAF = 5.41% and *ZNF33A* (chr10: p.Cys607Tyr) mutation with 9.64%, which have not been reported in leukemia.

To better reveal the hematopoietic hierarchy and leukemic transformation involved in DCL progression, 10X Genomics single-cell RNA sequencing was performed. We deciphered an atlas covering 22399 cells and 12 major cell types (20 clusters) according to the established markers of hematopoietic populations. We observed an increase in the fraction of granulocyte-monocyte progenitors, while decreased proportions of mature monocytes and neutrophils within DCL cells. We next performed differential gene expression analyses between healthy donor and DCL hematopoietic stem and progenitor cells ($CD34^{+}ckit^{+}$ cells), 245 differentially expressed genes ($p < 0.05$, $log2FC > 2$) was found. KEGG analysis revealed the top2 enrichment of pathways related to metabolic pathways and pathways in cancer. To understand the specific HSPC subpopulations involved in DCL, 4 transcriptionally distinct clusters were identified. HSPCs from donor and DCL harbour distinct transcriptional programs, and GO analysis in cluster2 (from DCL) showed enrichment of the pathway related to myeloid cell differentiation. *CRIP1* and *LGALS1*, recently reported associated with AML, are the top2 significantly differentially expressed genes in cluster2.

Conclusions: Our study distinguishes HSPCs from healthy haploidentical donor and DCL at a single-cell resolution. With the help of integrated genomic and single-cell molecular analyses, we provide more comprehensive mechanisms of DCL after allo-HSCT.

Disclosure: Nothing to declare

P024

Can allogeneic stem cell hematopoietic transplant with any type of donor be the standard post-remission treatment in intermediate-risk acute myeloid leukemia in first complete remission?

J.M. Cerezo Martín[1], A. Bermúdez-Rodriguez[1], M.d.l.M. Colorado[1], P. Munoz[2], S. Fernandez-Luis[1], L. Yañez[1], G. Martin[1], N. Fernandez[1], J.A. Calvo[1], A. Insunza Gaminde[1], C. Montes[1], S. González[1], A. Batlle[1], M. Briz[1], I. Romon[1], M. Sanchez-Escamilla[1], J.L. Arroyo[3], E. Ocio[1]

[1]Hospital Universitario Marqués de Valdecilla, Santander, Spain, [2]Instituto de investigación sanitaria Valdecilla (IDIVAL), Santander, Spain, [3]Banco de Sangre y Tejidos de Cantabria (BSTC), Santader, Spain

Background: Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) as post-remission treatment in cytogenetically defined intermediate-risk Acute Myeloid Leukemia (AML) in first complete remision (CR1) is effective, but has been associated with high transplant-related mortality (TRM). The aim of this study is to analyze the outcome of this procedure using HLA-identical sibling, unrelated or alternative donors.

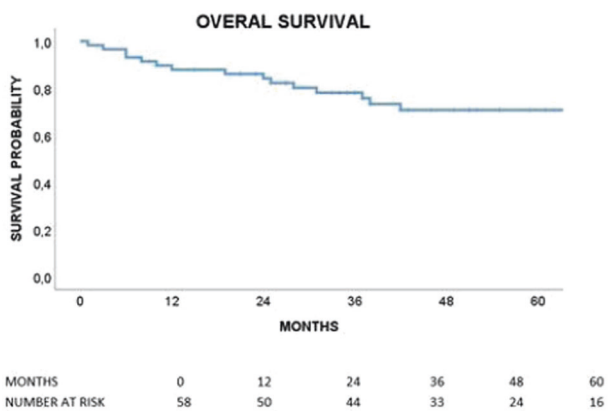
Methods: We conducted an observational retrospective study in all patients with intermediate-risk cytogenetically defined (Upon The European LeukemiaNet 2017 criteria) AML in CR1 who underwent an allo-HSCT in our center between 2010 and 2020. The primary endpoint was OS, secondary outcomes were relapse-free survival (RFS), cumulative incidence of relapse and TRM. Minimal residual disease (MRD) was measured by flow cytometry (using a cut off of 0,01%) and/or RT-PCR (NPM1). A multivariate Cox regression model was performed.

Results: We analyzed 58 patients with a median age of 58 (R 19-82) years. Ten (17,2%) patients had negative MRD and 29 (50%) had an unrelated donor (5 had a 9/10 HLA allelic match) at the moment of transplant. Forthy three (74,1%) patients received myeloablative conditioning regimens (Table 1). The median time from diagnosis to transplant was 5 (IR 4-7) months.

With a median follow up of 40 months, the OS at 1, 2 and 3 years was 88% (95% CI 77-98%), 84% (95% CI 72-96%) and 78% (95% CI 64-92%) respectively (Figure 1). The RFS at 1 and 3 years was 88% (95% CI 77-99%) and 73% (95% CI 58-88%), the cumulative incidence of relapse at 1 and 3 years was 7% (95% CI 2-15%) and 14% (95% CI 7-25%) and the TRM at 1, 2 and 3 years was 7% (95% CI 2-15%), 11% (95% CI 4-20%) and 15% (95% CI 7-26%) respectively.

Among all the clinical features which could be related to OS: group of age, gender, conditioning, MRD and type of donor were included in the multivariate analysis. A non-myeloablative conditioning (HR 15 $p = 0,01$) an haplo-identical donor (HR 6 $p = 0,03$) and an unknown/undefine MRD (HR 13 $p = 0,03$) were associated with a significant higher risk of death. Age and gender showed no differences.

Group of age		**Type of Donor**	
<50	20 (34,5%)	HLA-identical sibling	15 (25,9%)
50-65	23 (39,7%)	Unreleated	29 (50%)
>65	15 (25,9%)	Haplo-identical	14 (24,1%)
Gender		**Minimal residual disease**	
Men	32 (55%)	Negative	10 (17,2%)
Conditioning		Positive	31 (53,4%)
Myeloablative	43 (74,1%)	Undefined/Unknown	17 (29,3%)
Non myeloabaltive	15 (25,8%)		



Conclusions: Allo-HSCT in patients with an intermediate-risk LMA in CR1 is the standard consolidation therapy at our institution mainly when a HLA identical sibling or unrelated donor is available, and especially when using a myeloablative conditioning, as it is associated with low TRM and a high RFS.

Disclosure: Nothing to declare

P025

Risk factors for central nervous system relapse after allogeneic H-SCT in flt3-mutated AML

K. Kouidri[1], R. Toenges[1], S. Pfaff[1], S. Lindner[2,1], J. Riemann[1], F. Lang[1], H. Serve[1], A. Cremer[1], G. Bug[1]

[1]Goethe University Hospital Frankfurt am Main, Frankfurt, Germany, [2]Memorial Sloan Kettering Institute, New York, United States

Background: Nearly 30% of AML patients harbour a *FMS*-like tyrosin-kinase 3-gene alteration (FLT3) driver mutation. The increased relapse risk associated with internal tandem duplications (ITD) may be counteracted by allogeneic hematopoietic stem cell transplantation (allogeneic HSCT) followed by FLT3 inhibitor (FLT3i) maintenance.

We here describe risk factors for post-HSCT central nervous system (CNS) relapse, an uncommon but prognostically extremely unfavourable event in adult FLT3-mutated AML.

Methods: We retrospectively analysed data of 39 patients with FLT3-ITD (n = 34) and/or TKD-mutated AML (n = 5) who were transplanted 2017-2020 at our institution. Minimal residual disease (MRD) was determined prior to and 60-100 days after allogeneic HSCT by qRT-PCR (NPM1mut, n = 26; KMT2A-PTD, n = 2; JAK2mut, RUNX1/RUNX1T1, NUP98-NSD1, n = 1 each) or multicolour flow cytometry, (n = 8). Cumulative incidence of relapse (CIR) was calculated with non-relapse mortality as competing risk and survival probabilities were compared by log-rank test.

Results: At the time of allogeneic HSCT, 6 patients (15%) were in MRD-negative CR (molCR), 24(61%) in MRD-positive CR and 9(23%) had active disease. All patients achieved CR with 30(77%) molCR and FLT3i was started prophylactically (n = 11) or pre-emptively (n = 11) at a median of 54(range, 41-713) days post-HSCT for a median of 12.6 months. Reasons for no FLT3i were allogeneic HSCT before 2019 (n = 12), renal insufficiency (n = 1), FLT3-TKD only (n = 3) and early relapse (n = 1).

With a median follow-up of 27 months in surviving patients, probability of OS was 67.9% at 3 years. Ten patients relapsed at a median of 9.3(range, 3.3-33.6) months post-HSCT, the CIR was 32%. Survival was significantly longer in patients with molCR vs no molCR post-HSCT (OS: not reached vs. 30.4 months, p = 0.004; relapse-free survival: not reached vs. 9.1 months, p < 0.001), while other factors, such as cytogenetic risk, total body irradiation-based conditioning, RIC vs MAC, use of FLT3i pre-HSCT or post-HSCT had no significant impact on survival.

Meningeal leukemia (n = 5) or CNS chloroma (n = 1) were observed as late events at a median of 16.3 months post-HSCT and occurred on Sorafenib (n = 2), Gilteritinib (n = 1) or decitabine-based salvage therapy after failure of FLT3i (n = 3). All patients with CNS relapse had active disease at allogeneic HSCT (median: 14% bone marrow blasts) and no molCR post-HSCT. CNS relapse was preceded by hematologic relapse in 5/6 patients by a median of 2.7 months.

Conclusions: Patients with FLT3-mutated AML and active disease at the time of allogeneic HSCT, combined with failure to achieve MRD-negativity after allogeneic HSCT have a high risk of CNS-relapse and leukemic death. This was not abrogated by pre-emptive or salvage-therapy with FLT3i or HMA and prophylactic intrathecal therapy may be considered to avoid CNS relapse.

Disclosure: Gesine Bug, Honoraria: Jazz, Celgene, Gilead, Novartis, Hexal, Pfizer, Eurocept

P026

Allogeneic hematopoietic stem cell transplantation for adult acute lymphoblastic leukemia: A multicenter retrospective study

D. Alzetta[1], C. Borghero[2], I.M. Cavattoni[3], F. Benedetti[4], M. Krampera[4], A. Billio[3], M. Ruggeri[2], C. Tecchio[4]

[1]IRCSS Centro di Riferimento Oncologico (CRO) di Aviano, Aviano, Italy, [2]Ospedale San Bortolo di Vicenza, Vicenza, Italy, [3]Ospedale centrale di Bolzano, Bolzano, Italy, [4]Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy

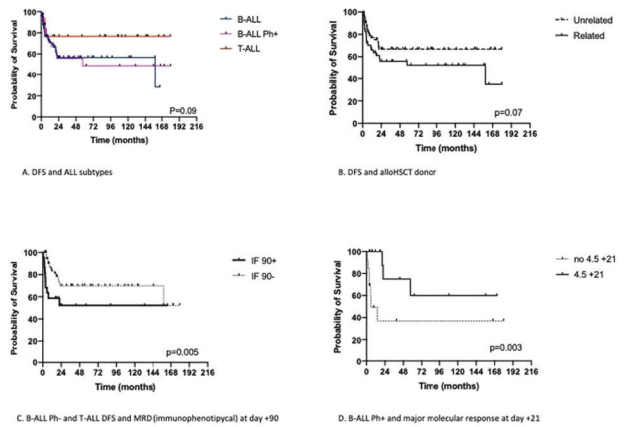
Background: Despite progress in therapies, allogeneic hematopoietic stem cell transplantation (alloHCT) still plays a pivotal role in the treatment of adult Acute Lymphoblastic Leukemia (ALL). Nevertheless, relapse and non-relapse mortality remain a significant concern. The aim of this retrospective real-life study was to evaluate overall survival (OS), disease-free survival (DFS) and non-relapse mortality in a multicenter series of adult ALL patients undergoing alloHSCT.

Methods: The study included adult patients, affected by either B-ALL (Ph negative or positive) or T-ALL, who underwent alloHSCT in three Italian Bone Marrow Transplant Centers between July 2003 and July 2020. Patient outcomes were evaluated by univariate analysis based on variables defined as pre-alloHSCT [i.e., ALL phenotype, white blood cell count (WBC) at diagnosis, number of complete remissions (CR)], alloHSCT-related [i.e., EBMT risk score, donor type], and post-alloHSCT [Graft versus Host Disease (GvHD) and minimal residual disease (MRD)]. The observation period ended on October 2020.

	Patient Characteristics (*N* = 39, median age=53)			***N* (%)**		
Sex	**male**		**female**	**22 (56)**		**17 (44)**
Mutations	FLT3-ITD/NPM1	FLT3-ITD	FLT3-TKD	22 (56)	12 (30)	5 (12)
Genetic Risk Group (ELN 2007)	favourable	intermediate	adverse	7 (18)	23 (59)	9 (23)
Donor Type	matched related		haploidentical	10 (26)		5 (13)
	matched unrelated		mismatched unrelated	18 (46)		6 (15)
Conditioning Regimen	myeloablative		reduced intensity	29 (74)		10 (26)
Remission Status pre-HSCT	CR1 or CR2		refractory disease	30 (77)		9 (23)

Results: 133 subjects with a median age of 40 (range: 18-70) years were enrolled. Patients were affected by Ph- (66) or Ph + (33) B-ALL (33), and T-ALL (34). With a median follow-up of 18.5 (range: 0.9-187.5) months, OS was 47.4% (median survival: 37.4 (range: 0.9-187.5) months) and DFS 67.7% (median survival not reached). Relapse mortality accounted for 24% and non- relapse mortality for 28.6% of deaths.

According to univariate analysis, DFS had a better trend in patients with T as compared to B phenotype ($p = 0.09$) (A) and in those with negative MRD (immunophenotypic detection) before alloHSCT ($p = 0.08$). The number of pre-alloHSCT complete remissions (CR1 vs CR > 1) did not affect DFS ($p = 0.08$). Patients with matched unrelated donors had a better DFS as compared to those with matched related ($p = 0.07$) (B). DFS was significantly higher in patients with GVHD ($p = 0.002$). Among B-ALL patients, a WBC count at diagnosis > 30.000/mmc had a negative impact ($p = 0.09$). Ph- B-ALL and T-ALL patients with a negative immunophenotypic MRD at day +90 after alloHSCT showed a better DFS ($p = 0.005$) (C), Ph+ B-ALL patients with a major molecoular response at day +21 had better DFS ($p = 0.003$) (D). OS and non-relapse mortality were lower in patients with EBMT score ≥ 4 ($p = 0.01$)



Conclusions: This real-life study confirms that in adult ALL patients alloHSCT is effective, though associated to a significant transplant-related mortality that can be predicted by the EBMT score. A negative post-alloHSCT immunophenotypic MRD (day + 90) and a major molecular response (day + 21) are predictive for a favorable outcome in Ph- B- and T-ALL, and Ph+ B-ALL, respectively.

Disclosure: Nothing to declare

P027

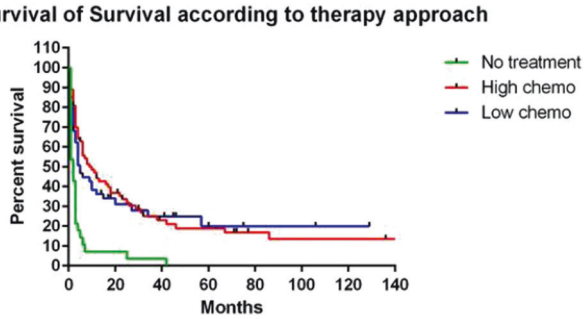
The outcome of AML and mds patients relapsed after allogeneic transplantation, single centre experience

M. Šťastná Marková[1], A. Vítek[1], V. Válková[1], M. Kouba[1], L. Nováková[1], P. Cetkovský[1], J. Vydra[1]

[1]Institute of Haematology and Blood Transfusion, Praha 2, Czech Republic

Background: Although allogeneic transplantation in high risk myeloid malignancies is the best way of consolidation, relapse of the original disease remains the major cause of transplant failure, the treatment is difficult and until now there is no definite way how to deal with it.

Methods: We retrospectively evaluated 186 AML and 51 MDS patients transplanted between years 2001 and 2021 who relapsed after transplantation. The therapeutic approach was individual considering the status of the patient, risk of the disease assessment and the patient's will. For the evaluation the patients were divided into three groups. 1) no chemotherapy approach (including immunosuppression tapering and DLI only), 2) low dose chemotherapy considering of either low dose ARA-C or 5-azacytidine or both, including five patients treated with addition of gilteritinib, 3) high dose chemotherapy considering of antracyclin and ARA-C base regimens, or/and second transplant. The majority of the patients were in parallel additionally treated with DLI.



Results: In AML: the survival in 1, 2 and 5 years was 7%, 3% and 0% in no chemotherapy gr., 38%, 31% and 19% in low dose gr.,and 42%, 32%, and 20% in high dose gr. In MDS 7% in no chemotherapy gr., 15%, 13% and 12% in low dose gr., 51% 36% and 32% in high dose group. No statistical difference in OS was found between treated groups. Time of relapse from transplant significantly influenced the overall survival in all tested time points (3, 6 and 12 months) OS in 2 years 25%, 22% and 32%. Not surprisingly the patients who achieved remission with any type of chemotherapy had OS better in 2 years comparing to those, who did not (60% vs 5%). Anyway 43% of patients suffered from subsequent relapse. 21% of patients who achieved remission died from treatment related complications (toxicity or GVHD). There was no substantial difference in the outcome between AML and MDS patients.

Conclusions: Although the outcome of the AML/MDS patients relapsed after transplantation is very poor, many of them can profit from additional treatment and some of them achieve further remission. Immunomodulation with DLI is considered to play substantial role and its prophylactic and preemptive use is promising. New drugs such as venetoclax or gilteritinib need to be introduced and evaluated.

Disclosure: I have no conflict of interest.

P028

Control leukemia by inducing anti-cancer immune reactivity in vivo? potential of a dc-triggered mechanism

H. Schmetzer[1], D. Amberger[1], L. Klauer[1], E. Rackl[1], M. Atzler[1], S. Ugur[1], A. Rank[2], M. Inngjerdingen[3], T. Baudrexler[1], B. Eiz-Vesper[4], C. Schmid[2]

[1]University Hospital Großhadern, Ludwig-Maximilians-University Munich, Munich, Germany, [2]University Hospital Augsburg, Ludwig-Maximilians-University, Augsburg, Germany, [3]Oslo University Rikshospitalet, Oslo, Norway, [4]Institute for Transfusion Medicine, Hannover Medical School, Hannover, Germany

Background: There are virtually no treatment options for therapy-refractory or relapsed AML/MDS and high rates of relapse in successfully treated patients.

Methods: The combination of the (clinically approved) immune-modulatory compounds GM-CSF + Prostaglandine 1 (PGE1; the combination referred to as *KIT M*) converts myeloid blasts into dendritic cells of leukemic origin (DC_{leu}). After stimulation with DC_{leu},

antileukemic (T) cells are activated. Kit M treatment may be an attractive tool for immunotherapy in myeloid leukemia.

Results: 1. ex vivo: Treatment of 65 leukemic WB samples with *KIT M* does not induce blast proliferation, but triggers generation of mature DC/DC_{leu} and reduces tolerogenic DC. Kit treated WB *activates* the adaptive and innate immune system after MLC (T cell proliferation, antitumor-supportive T cells (TCRgd,Tb7), memory cells (Tcm,Tb7cm) and *downregulates* immune suppressive T cells (Treg4 and 8). Moreover *leukemia specific* (interferon g ($_g$) and/or degranulating ($_{deg}$)) adaptive ($_{g\text{-}deg}$T4,T8,TCRgd,Tb7,Tcm) and innate cells ($_{g\text{-}deg}$NK,NKb7,CIKb7) are *increased* and regulatory cells ($_{g\text{-}deg}$Treg4) *downregulated*. In addition, blast lysis is increased vs control. Ex vivo achieved blast lysis correlates *positively* with frequences of mature DC/DC_{leu}, leukemia specific T3,T4,T8,TCRgd,Tb7 and NK cells and *negatively* with Treg4 and 8. Blast lysis does not correlate with age, sex, ELN risktype, blast counts, or response to chemotherapy.

2. In vivo **- rats:** *Kit M* treatment of 3 leukemically diseased (vs 3 control) rats (followed by sacrification after treatment) leads to reduced blasts and Tregs in blood and spleen and increased DC_{leu} and memory-like T cells.

3. In vivo **- human:** *Kit M* therapy was offered to a 72 year old pancytopenic male as an individual salvage attempt (applied as continuous infusion), after discussion with the ethical commitee, the patient's information about the experimental nature of the treatment and his written consent. The treatment was well tolerated and the patient improved clinically. Neutrophils in WBC increased from 10% to 50%, thrombocytes reached 100 G/l after 24 days. Immune monitoring showed a continuous increase of proliferating and non-naïve Tcells, NK, CIK- and NKT-, TH17 cells, B_{mem}-cells and DC in PB. The production of IFNg producing T-, CIK and NKT-cells was demonstrated, suggesting an in vivo production/activation of (potentially leukemia-specific) cells. Immune stimulatory effects decreased after discontinuation of therapy. After 4 weeks of treatment, the patient was discharged in good clinical condition. Unfortunately, at two weeks from discharge, AML progressed and the patient died few days later.

Conclusions: Treatment of WB ex vivo with Kit M leads to activation of adaptive and innate (leukemia specific) immune reactive cells (and downregulated suppressive mechanisms) via a DC/DC_{leu} triggered mechanism – resulting in significantly improved blast lysis compared to controls (independent of patients' risk classification, MHC, age or sex). In vivo treatment of leukemically diseased rats or humans was well tolerated, led to an increase of platelets and granulocytes and stable (low) blast counts in PB – probably mediated by a (leukemia specifically) DC/DC_{leu} activated immune system. A dose defining clinical trial in carefully selected patients to confirm clinical safety and underscore clinical efficacy is being prepared.

Disclosure: Helga Schmetzer is associated with Modiblast Pharma GmbH

P029

Second allogeneic hematopoietic cell transplantation in relapsed acute myeloid leukemia – retrospective analysis of the outcome

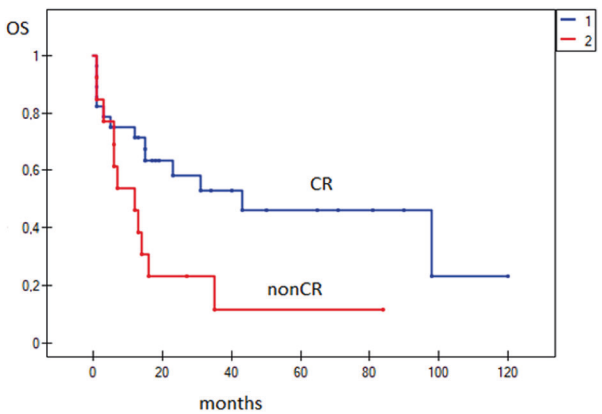
A. Lojko-Dankowska[1], M. Matuszak[1], E. Bembnista[1], D. Dytfeld[1], A. Nowicki[1], A. Wache[1], L. Gil[1]

[1]Poznan University of Medical Sciences, Poznań, Poland

Background: The second allogeneic hematopoietic stem cell transplantation (alloHSCT) is the most effective treatment option for patients (pts) with acute myeloid leukemia (AML) who relapsed after the first alloHSCT. The strategy of this procedure, especially optimal reinduction, choice of donor and type of conditioning remain unknown.

Methods: We retrospectively analyzed the outcome of the second alloHSCT in 40 pts (21 women, 19 men) with AML, transplanted in one center between 2005 and 2020. At the first alloHSCT most pts (36) were transplanted in complete remission (CR) – 26 pts in CR1, 8 pts in >CR1, 4 pts were transplanted with active disease (nonCR). Most pts (32) received myeloablative first conditioning. Donor at first alloHSCT was sibling (16), unrelated (23) or haploidentical (1). The median time between first alloHSCT and relapse of disease was 10 (3-120) months; 13 pts relapsed within 6 months, 6 pts later than 2 years, one after 10 years. Only seven pts presented graft versus host disease (GvHD) symptoms after first alloHSCT. At the time of the second transplant median age was 41 (20-69) years. All but two pts received reinduction chemotherapy (based on Flag or Clag – 28 pts, HDAraC- 9 pts) before the second alloHSCT. At the time of the second transplant 28 pts were in CR, 12 were transplanted in nonCR. Before the second alloHSCT pts received myeloablative (n = 14) or reduced-intensity (n = 26) conditioning regimen and peripheral blood stem cells (PBSC) (n = 39) or bone marrow cells (n = 1) from matched sibling donors (n = 11), matched/mismatch unrelated donors (n = 13) or haploidentical donors (n = 16). 22 pts received second alloHSCT from the same donor as for the first transplant, 18 from different ones.

Results: Neutrophil engraftment was achieved in 35 patient, with median time 22 days, range 10-47. Eight pts (20%) died up to 100 days due to transplant related reason (infection, MOF). GVHD was seen in 7 pts only – acute in 5 pts, chronic in 3. Relapse occurred in 17 (42%) pts and was the cause of death in 15 of them. The median time between the second alloHSCT and relapse was 7 (2-30) months. After the median follow-up of 40 months, 15 (37%) pts remained alive with 14 in remission of disease. Median overall survival (OS) was 16 months. The one-year and five-year OS was 63% and 35%, respectively. In Cox-model-based tests only disease status at time of second alloHSCT (CR vs nonCR) significantly improve OS – one-year and five-year OS was 76% and 48% vs 49% and 15% respectively (HR 95% CI 0.39 (0.17-0.89); p = 0,02), with no influence of time to relapse, conditioning, donor type and GvHD status. Of the patients who have been transplanted in CR 14 (50%) remain alive, while of those who were not in CR only one is alive.



Ryc.1 Overall survival – disease status at second alloHSCT

Conclusions: The second alloHSCT remains a curative option for patients with AML relapsing after first alloHSCT, however achievement of complete remission before transplantation is required for successful treatment. The rate of transplant related mortality is high. Most patients died due to relapse of disease.

Disclosure: Nothing to declare

P030

Pre-conditioning endothelial activation and stress index (easix) predicts allogeneic hematopoietic stem cell transplantation outcomes

K.Y. Kim[1,2], D. Kwag[1,2], J.Y. Lee[1,2], J.H. Lee[1,2], T.Y. Kim[1,2], G.-J. Min[1,2], S.-S. Park[1,2], S. Park[1,2], J.-H. Yoon[1,2], S.-E. Lee[1,2], K.-S. Eom[1,2], Y.-J. Kim[1,2], S. Lee[1,2], C.-K. Min[1,2], S.-G. Cho[1], J.W. Lee[1], B.-S. Cho[1,2], H.J. Kim[1,2]

[1]*Catholic Hematology Hospital, Seoul St. Mary's Hospital, Seoul, Korea, Republic of,* [2]*Leukemia Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea, Republic of*

Background: Endothelial Activation and Stress Index (EASIX)—lactate dehydrogenase (U/L)×creatinine (mg/dL)/thrombocytes (10^9/L)—was reported to be useful in predicting outcomes after allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, due to controversies regarding the validity and usefulness of this simple predictive marker, EASIX needs to be verified in various cohorts. Thus, we investigated whether the EASIX measured before allo-HSCT conditioning (EASIX-pre) correlates with transplant-related outcomes in acute myeloid leukemia (AML) patients who underwent allo-HSCT at a single center in Korea, and compared its predictive ability with the established prognostic indices.

Methods: We conducted a pilot study with AML patients who received allo-HSCT in 2017 among a prospective observation cohort for acute leukemia, in the Catholic Hematology Hospital, Korea (CRIS# KCT0002261). Each patient's EASIX-pre was calculated one day before allo-HSCT conditioning. We evaluated the association between EASIX-pre and overall survival (OS) or failure (relapse or non-relapse mortality)-free survival (FFS) after allo-HSCT using the Kaplan-Meier estimates and the Cox model. We inspected whether EASIX-pre correlates to cumulative incidences of non-relapse mortality (NRM), relapse, acute graft versus host disease (aGVHD), transplant-associated thrombotic microangiopathy (TA-TMA) and sinusoidal obstruction syndrome (SOS), using cumulative incidence estimates and the Fine-Gray model. The usefulness of EASIX-pre in predicting death in 2 years after allo-HSCT was compared with other known predictive indices—The European Group for Blood and Marrow Transplantation (EBMT) risk score, Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI), Pretransplant Assessment of Mortality Score (PAM score)—using receiver operating characteristic (ROC) curves and their area under curve (AUC).

Results: A total of 117 patients were included in this study. In our analyses, EASIX-pre showed strong association with OS and FFS. The hazard ratios for OS and FFS per 1 increment in EASIX (log 2 scale) were 1.37 (95% confidence interval (CI): 1.20–1.55, $p < 0.001$) and 1.36 (95% CI: 1.19–1.54, $p < 0.001$), respectively. EASIX-pre correlated with OS and FFS in each subgroup stratified according to their pre-HSCT disease status, cytogenetic risk, HSCT donor, and conditioning intensity. Also, EASIX-pre showed significant relationship with the cumulative incidence of NRM (coefficient of Fine-Gray subdistribution hazard model: 1.38, 95% CI: 1.14–1.66, $p < 0.001$), rather than those of relapse (coefficient: 1.17, 95% CI: 0.97–1.37, $p = 0.055$). There were no significant associations of EASIX-pre with the cumulative incidence of aGVHD ($p = 0.756$), TA-TMA ($p = 0.893$), and SOS ($p = 0.923$) after allo-HSCT. In predicting death in 2 years after allo-HSCT, EASIX-pre showed high predictability, of which AUC of ROC curve was 0.7534, which was comparable to other established prognostic indices (Figure 1). EASIX-pre cut-off of highest accuracy was 2.1 (log 2 scale).

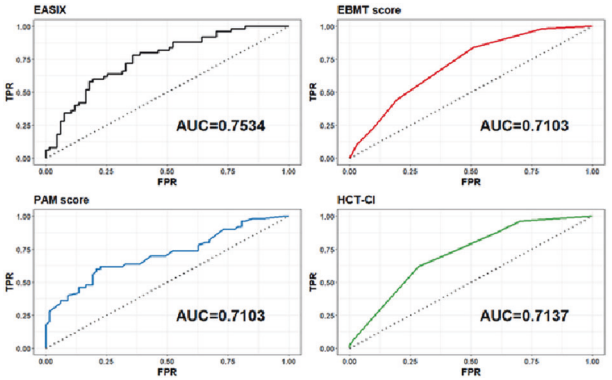


Figure 1. Receiver operating characteristic (ROC) curves of prognostic markers. EASIX-pre, endothelial activation and stress index-pre-conditioning; EBMT, European Group for Blood and Marrow Transplantation; PAM, pretransplant assessment of mortality score; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; TPR, true positive rate; FPR, false positive rate; AUC, area under the receiver operating characteristic curve

Conclusions: This study is the first to show the validity of EASIX-pre as a prognostic index in a cohort of Asian patients with AML. EASIX-pre significantly associated with the patient's OS, FFS, and NRM. EASIX-pre had comparable predictive capacity with established prognostic scores. Although EASIX is known to be a marker that reflects endothelial stress, we did not find a significant association with vascular stress-related complications, such as GVHD, TA-TMA, and SOS. This pilot analysis warrants further validation with larger prospective cohorts.

Clinical Trial Registry: CRIS# KCT0002261 https://cris.nih.go.kr/cris/search/detailSearch.do?seq=8588&search_page=L&search_lang=E&lang=E

Disclosure: Nothing to declare

P031

Allogenic stem cell transplantation and peri transplant strategies in patients with relapsed/refractory or intermediate/high risk npm1 mutated acute myeloid leukemia – a single center experience

P. Jäger[1], C. Rautenberg[2], J. Kaivers[1], S. Geyh[1], U. Germing[1], K. Nachtkamp[1], T. Schroeder[2], G. Kobbe[1]

[1]*University Hospital Düsseldorf, Düsseldorf, Germany,* [2]*Hospital Essen, Essen, Germany, Essen, Germany*

Background: The prognosis of patients with nucleophosmin 1 gene mutated ($NPM1^{mut}$) acute myeloid leukemia (AML) depends on the presence of concomitant chromosomal aberrations and mutations. Although, patients with isolated NPM1 mutation are considered to convey a favorable prognosis, relapse still remains the most common cause of treatment failure and allogeneic hematopoietic blood stem cell transplantation (alloHSCT) as second line therapy is required to achieve durable molecular remissions. Patients who relapse molecularly or morphologically after or during conservative chemotherapy require immediate therapy to achieve a molecular or at least hematological remission again prior transplant. Patients with ratio > 0.5 of FMS-like tyrosine kinase 3 internal tandem duplication ($FLT3\text{-}ITD^{high}$) or adverse chromosomal aberrations have a poorer outcome and are therefore considered as candidates for first line alloHSCT in first remission.

Methods: Here we demonstrate our single center experience concerning alloHSCT and peri-transplant strategies in 73 patients with relapsed/refractory good or intermediate/high risk $NPM1^{mut}$ AML out of whom 55 patients received an alloHSCT at our center since 2008.

Results: After a median follow-up of 2.7 years from alloHSCT,

patients with hematologic complete remission (CR) compared to patients with morphological active disease (HR +) had an estimated 2-y-OS of 73% vs. 62% (ns) and an estimated 2-y-RFS of 63% vs. 20% (P = 0.0070). Focusing on patients with CR before alloSCT, those with no detection of minimal residual disease (MRD-) showed a trend towards higher RFS compared to MRD + patients with a 2-y-RFS of 79% versus 47% (ns). This was not reflected in a different 2-y-OS (78% vs 75%, ns). Patients with FLT3-ITD^{high} and MRD + CR before alloHSCT showed a trend towards a lower 2-y-RFS compared to patients without FLT3-ITD^{high} (29% vs 62%, ns). Focusing on patients with second line indication for alloHSCT because of inadequate response or relapse post or during therapy we analyzed status of high dose cytarabine based salvage chemotherapy (S-CT). Thirteen patients got s-CT with 8 patients achieving CR (MRD- n = 6, MRD + n = 2). Sequential conditioning with FLAMSA without previously performed S-CT showed similarly good OS but a high risk of relapse. Patients with HR + showed a 2-y-OS of 52% and a 2-y-RFS of 24%, whereas patients with MRD + CR and MRD- CR showed quite similar 2-y-OS of 80% and 83% but a different 2-y-RFS of 62% and 83%, suggesting effective relapse strategies like hypomethylating agents (HMA) and donor lymphocyte infusion (DLI), especially in case of late and molecular relapse, detected by intensive MRD monitoring.

Conclusions: Patients with second line indication for alloHSCT have an excellent chance of long-term remission if they are MRD- before alloHSCT. Patients with MRD + CR also have a good chance of long-term remission if no FLT3-ITD^{high} mutation is present. To achieve a second remission S-CT is effective. Only the group of patients with HR + during therapy present a clinical challenge. For all groups, sufficient relapse strategies after alloHSCT such as HMA and DLI exist, especially if the relapse occurs late and was diagnosed early by intensive MRD monitoring.

Disclosure:
Thomas Schroeder
JAZZ, Pfizer, BMS advisory boards, lecture fees
JAZZ, BMS research funding

P032

Viale-t: A randomized, open-label, phase 3 study of venetoclax in combination with azacitidine after allogeneic stem cell transplantation in patients with acute myeloid leukemia

C. Craddock[1], U. Platzbecker[2], M. Heuser[3], V. Pullarkat[4], S. Chaudhury[5], D. Wu[6], S. Addo[7], B. Chyla[7], Q. Jiang[7], P. Lee[7], J.E. Wolff[7]

[1]University of Birmingham, Birmingham, United Kingdom, [2]University Hospital in Leipzig, Leipzig, Germany, [3]Hannover Medical School, Hannover, Germany, [4]City of Hope, Duarte, United States, [5]Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern Feinberg School of Medicine, Chicago, United States, [6]The First Affiliated Hospital of Soochow University, Soochow, China, [7]AbbVie Inc, North Chicago, United States

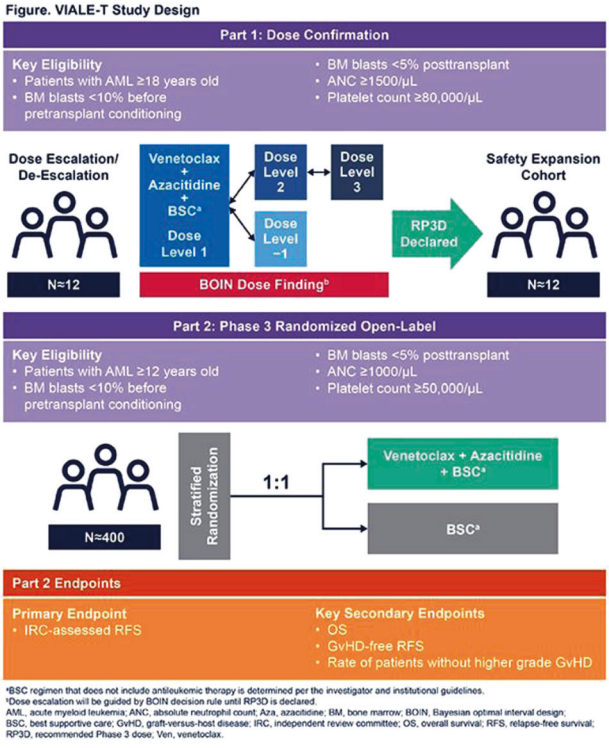
Background: Acute myeloid leukemia (AML) is an aggressive malignancy and is the most common and second most common form of acute leukemia in adults and children, respectively. The combination of the highly selective BCL-2 inhibitor venetoclax and the hypomethylating agent azacitidine was shown to be safe and effective in clinical trials (DiNardo et al. *Blood*. 2019;133:7-17; DiNardo et al. *N Engl J Med*. 2020;383:617-629) and is approved by the United States Food and Drug Administration and European Medicines Agency for the treatment of patients with AML who are not eligible to receive intensive chemotherapy. Following allogeneic stem cell transplantation (alloSCT), most patients do not receive antileukemic therapy; however, an unmet need remains as disease relapse and graft-versus-host disease (GvHD) commonly occur posttransplant. In addition to the antileukemic effect of venetoclax shown in clinical studies, preclinical studies suggest venetoclax may mitigate the risk of GvHD. VIALE-T is a Phase 3, randomized, open-label trial in progress (NCT04161885) evaluating the safety and efficacy of venetoclax in combination with azacitidine versus best supportive care (BSC) as maintenance therapy following alloSCT in patients with AML.

Methods: This Phase 3 study consists of 2 parts (Figure). Key inclusion criteria include diagnosis of AML; plans to receive alloSCT or have received alloSCT within the past 30 days; bone marrow blasts <10% before pretransplant conditioning and <5% posttransplant; have received myeloablative, or reduced intensity, or nonmyeloablative pretransplant conditioning protocols. Grafts are allowed from various sources (bone marrow, peripheral blood stem cells, cord blood cells). Patients must be ≥18 years old for Part 1 and ≥12 years old for Part 2. Additionally, patients must meet key laboratory values for absolute neutrophil count (Part 1, ≥1500/μL; Part 2, ≥1000/μL), platelet count (Part 1, ≥80,000/μL; Part 2, ≥50,000/μL), bilirubin ≤3 times the upper limit of normal, and creatinine clearance >30 mL/min. Patients who have received venetoclax and had no history of disease progression while receiving venetoclax are eligible.

Part 1 evaluates dose levels of venetoclax combined with azacitidine to determine the recommended Phase 3 dose (RP3D), which will be confirmed in approximately 12 additional patients enrolled in the Safety Expansion Cohort. Part 2 will be a randomized, open-label evaluation of the RP3D of venetoclax combined with azacitidine and BSC versus BSC only in adults and children aged 12 years or older. All venetoclax-treated patients will receive antibiotic prophylaxis during Cycle 1.

The primary endpoint for Part 1 is the frequency of dose-limiting toxicities. The primary endpoint for Part 2 is relapse-free survival as assessed by an independent review committee. Key secondary endpoints for Part 2 include overall survival, GvHD-free relapse-free survival, and the rate of patients without higher grade GvHD at 90 days after randomization. Enrollment into the Safety Expansion Cohort will be completed in 2021. Part 2 will enroll approximately 400 patients across approximately 175 participating study sites in 17 countries, with recruitment beginning in 2022.

Figure. VIALE-T Study Design



[a]BSC regimen that does not include antileukemic therapy is determined per the investigator and institutional guidelines.
[b]Dose escalation will be guided by BOIN decision rule until RP3D is declared.
AML, acute myeloid leukemia; ANC, absolute neutrophil count; Aza, azacitidine; BM, bone marrow; BOIN, Bayesian optimal interval design; BSC, best supportive care; GvHD, graft-versus-host disease; IRC, independent review committee; OS, overall survival; RFS, relapse-free survival; RP3D, recommended Phase 3 dose; Ven, venetoclax.

Results: N/A

Conclusions: N/A

Clinical Trial Registry: NCT04161885 https://clinicaltrials.gov/

Disclosure: CC has served as a consultant for AbbVie and Bristol Myers Squibb; has participated in speakers' bureaus for AbbVie and Bristol Myers Squibb; and has received research support from Bristol Myers Squibb. **UP** has received honoraria from AbbVie and Bristol Myers Squibb. **MH** has served as a consultant for AbbVie, Agios, Bristol Myers Squibb, Daiichi Sankyo, Jazz Pharmaceuticals, Kura Oncology, Novartis, Pfizer, PinotBio, Roche, and TOLREMO; has received honoraria from AbbVie, Eurocept Pharmaceuticals, Jazz Pharmaceuticals, Janssen, Novartis, and Takeda; and has received research support from Astellas, Bayer AG, BerGenBio, Daiichi Sankyo, Jazz Pharmaceuticals, Karyopharm, Novartis, Pfizer, and Roche. **VP** has served as a consultant and an advisory board member for AbbVie, has participated in speakers' bureaus for AbbVie, and has received honoraria from AbbVie. **SC** has participated in advisory boards for bluebird bio, Viacord, and AbbVie; and has received research support from Bristol Myers Squibb and Karius. **DW** reports no conflict of interest. **SA, BC, QJ, PL, and JW** are employees of AbbVie and may hold stock or stock options in AbbVie.

Venetoclax is being developed in collaboration between AbbVie and Genentech. AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Medical writing support was provided by Laura Ruhge, PhD of Bio Connections, LLC, funded by AbbVie.

P033

Optimization of fludarabine-pharmacokincetics to reduce the ri in AML patients after allogeneic stem cell transplantation

T. Thavayogarajah[1], D. Müller[2], G. Nair[1], S. Balabanov[1], M.G. Manz[1], U. Schanz[1]

[1]University Hospital Zurich, Zürich, Switzerland, [2]University Hospital Zürich, Institute of Clinical Chemistry, Zürich, Switzerland

Background: Acute myeloid leukemia (AML) is a hematological, clonal malignancy of the myeloid stem cell precursors, which is proliferative and is characterized by clonal evolution and genetic heterogeneity. For adverse risk acute myeloid leukemias, allogeneic stem cell transplantation (allo HCT) is one of the most potent curative options. Unfortunately, disease relapse is still around 40% in the first year after HSCT.

In allo HCT, fludarabine is a frequently used agent, mainly in reduced intensity conditioning regimes. It is often combined with busulfan for which dose individualization based on pharmacokinetics with area under the curve (AUC) determination is used successfully for many years.

It was already shown that fludarabine exposure might be predictive for the survival in allo HCT and it is suggested that individualized dosing can improve the survival after transplantation within the first year. Actually for the fludarabine dose calculation in adults, only the body surface area is used, which might either result in too high exposition causing increased toxicity or with too low exposure and increased relapse incidence (RI).

With the aim to reduce RI we established pharmacokinetic measurements for fludarabine in addition to the established ones for busulfan.

Methods: Fludarabine was measured with a validated LC-MS/MS method. The exposure as AUC was calculated for each patient using a three-compartmental model (adapted from *Langenhorst* et al.) in n = 13 consecutive patients receiving a conditioning regime with fludarabine being diagnosed with the acute myeloid leukemia.

Fludarabine was given on days -7 to -2 with a dose calculation based on 30mg/m^2 with an infusion rate of 30 minutes. The time points of analysis were 30 minutes, 4h, 6h, and 7h after the end of infusion. In addition patients received peroral busulfan 4mg/kg bw on days -3 and -2 and ATG 10mg/kg bw (Grafalon®) on days -4 to -1.

Results: So far, there is no dose individualization based on pharmacokinetic parameters for fludarabine specifically suggested in AML patients. The general study published by *Langenhorst et al*. that mixed up benign and malignant hematological malignancies, suggests lower fludarabine AUC than we observed in our patients.

We have seen that the fludarabine AUC were higher within our patients. In the analysis of *Langenhorst et al*. the optimal AUC was postulated to be 20 mg*h/l. In our (n = 19) AML patients the median of the AUC was 42.97 (+/− 11.5) mg*h/l, twice as high than the suggested level for an optimal toxicity profile. However, none of our patients experienced any acute toxicity (within 30 days after transplant).

Moreover, there was also no major toxicity seen at day 100. So far, we did not see a reduced RI, despite the AUC was much higher than the suggested optimal levels.

Conclusions: In a regimen with more (6 vs 4), but lower single fludarabine dosage (30mg/m2 vs 40mg/m2) and a shorter infusion duration (30min vs 60min) resulting in higher AUC (40mg*h/l vs 20 mg*h/l) than previously published, we did not observe an increase in transplant-related toxicity or a lower RI in AML patients.

Disclosure: Tharshika Thavayogarajah - Research grant from the Kurt-and Senta Herrmann Foundation

Nothing further to declare.

P034

Relevance of vitamin d in patients undergoing HLA matched allogenic stem cell transplant for acute leukaemia

N. Jindal[1], M. Saroha[1], S.P. Mirgh[1], A. Chichra[1], A. Gokarn[1], S. Punatar[1], P. Chavan[1], L. Nayak[1], A. Bonda[1], L.J Mathew[1], S. Kannan[1], N. Khattry[1]

[1]Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Centre, Navi Mumbai, India

Background: In HSCT, vitamin D deficiency has been associated with increased complications, primarily chronic GvHD, with a potential impact on survival. Results from various studies however, have not been consistent. At our center, vitamin D levels are done in all patients as part of pre-transplant assessment. This analysis was conducted to study the incidence of vitamin D deficiency, its correctability following oral replacement and the impact of vitamin D levels on transplant outcomes.

Methods: This was a single center retrospective study. Patients of Acute leukaemia (AL) who underwent fully matched or 9/10 transplants (related/unrelated) between 2008 and 2019 were included. In all patients, vitamin D levels were measured at the time of referral to the transplant unit for HSCT counselling (baseline vitamin D). Vitamin D deficiency was defined as 25-hydroxy vitamin D3 level less than 20 ng/mL. Prior to January 2012, patients with vitamin D deficiency did not receive correction. From January 2012 onwards, those with deficiency received replacement with oral vitamin D (60,000 IU weekly for 8 weeks followed by maintenance with 800 IU/day). For patients who received correction, vitamin D level was repeated after 4 months. Based on vitamin D level within 120 days of transplant (peri transplant vitamin D), patients were categorised as either

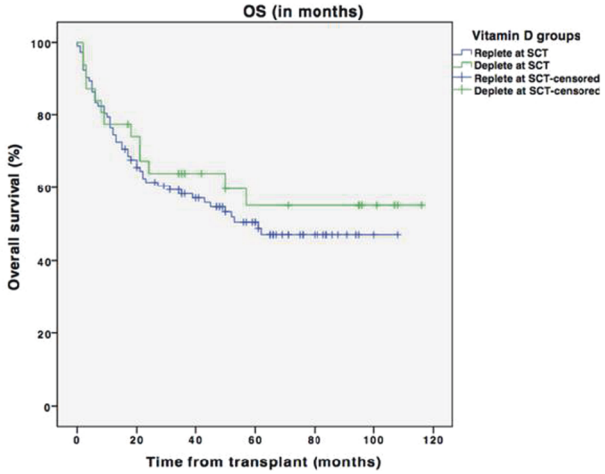
vitamin D replete (>20 ng/ml) or deplete (≤20 ng/ml). Transplant outcomes were compared between these two groups.

Results: One hundred and sixty two patients of AL underwent HLA matched transplants during the study period. Baseline vitamin D levels were available for 145 patients. Of these, 126 (86.9%) were deficient at baseline. One hundred and six out of these 126 patients with vitamin D deficiency (84.1%) received correction. Eighty three patients (78.3%) achieved levels above 20 ng/ml and 11 remained deplete. For 12 patients, repeat levels were not available and these were excluded from subsequent analysis. In all, 31 patients were deplete and 102 were replete in the peri-transplant period.

The median peri-transplant serum vitamin D level was 34 ng/ml (range 20.4-102.4 ng/ml) in the replete group and 15.0 ng/ml (7.7-19.8 ng/ml) in the deplete group. Both groups were matched for age, diagnosis, EBMT score and disease risk index (DRI). Between the deplete and replete groups, there were no significant differences in time to neutrophil or platelet engraftment, CMV reactivation, day 100 absolute lymphocyte count, aGVHD, cGVHD and TRM. PFS and OS (figure 1) were also comparable between the two groups.

Figure 1: Overall survival in vitamin D replete and deplete groups

Figure 1: Overall survival in vitamin D replete and deplete groups



Conclusions: The incidence of vitamin D deficiency was high in our patients. In a majority of patients, the levels normalized following adequate oral supplementation. Patients who were vitamin D deficient in the peri-transplant period did not have inferior outcomes, suggesting a limited role of vitamin D in influencing transplant outcomes in our patient cohort.

Clinical Trial Registry: Not applicable.

Disclosure: Nothing to declare.

P035

Evaluation of different maintenance treatment strategies after allogeneic hematopoietic stem cell transplantation in flt3 positive AML patients

E. Stauffer[1], A. Fraccaroli[1], H. Drolle[1], M. von Bergwelt[1], J. Tischer[1]

[1]University Hospital Munich, Munich, Germany

Background: Relapse remains the most frequent type of treatment failure after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Particularly patients with FLT3 mutations have an increased risk of relapse and thus a lower chance of cure. Hence, there is further medical need to evaluate different maintenance therapies strategies after allo-HSCT regarding their impact on outcome including the classic one with application of prophylactic donor lymphocyte infusion (pDLI) only.

Methods: We performed a retrospective study of 132 FLT3-positive patients who underwent allo-HSCT at our center from 2005-2021. Patients in complete remission (CR) were put under maintenance therapy if lacking any signs of higher grade GvHD, severe infection or organ toxicity. Since 2005 pDLIs were used applied in up to three escalating doses with respect to the donor type. Sorafenib was regularly administered from 2018 onwards, starting with 200mg up to 800mg daily for an expected duration of 24 months. Overall survival (OS), progression-free survival (PFS), non-relapse mortality (NRM) as well as adverse events (AEs) were evaluated, retrospectively.

Results: We identified 19 patients (15%) from our underlying cohort who were considered for maintenance therapy and of whom eleven were treated with Sorafenib and eight underwent pDLI only. Of the entire cohort, 21 died from early death, 35 suffered from GvHD requiring steroid treatment and 14 were lost to follow up while the rest of the patients was not eligible for other reasons including corresponding comorbidities.

Independent of the chosen post transplantation treatment strategy the estimated one- and two-year OS for the entire cohort was 78/70% with a median follow up of 2.1 years (range 7 months-6.3 years). One- and two-year PFS was 72/64%, respectively. Our preliminary analysis points towards an increased therapy efficacy in the Sorafenib group compared to the DLI group. 2 out of 8 patients in the DLI group died, one due to relapse. Up to now, no relapse or death was recorded in the sorafenib group. Further, we did not observe major differences in both groups when regarding AEs leading to similarly therapy interruption in both groups (Sorafenib $n = 3$, DLI $n = 3$).

Conclusions: Maintenance therapy after allo-HSCT has gained increasing importance in recent years. Our data indicate that Sorafenib and pDLI only are both well tolerated after transplantation. However, patients treated with Sorafenib might have a more prominent survival benefit. In our cohort only a minority of patients was eligible for a maintenance therapy while median follow up differed significantly among the groups. Further studies might elucidate whether more patients are applicable when inclusion criteria were extended.

Disclosure: Nothing to declare

P036

Outcome of acute leukemia in infants: A report from a single third level center in madrid, spain

B. Ochoa Fernández[1], V. Galán-Gómez[1], P. Guerra-García[1], S. Sanromán[1], I. Martínez Romera[1], I. Losantos Garcia[1], B. González[1], A. Pérez-Martínez[1]

[1]La Paz University Hospital, Madrid, Spain

Background: Leukemia in infants is rare, and one of the most challenging diseases in pediatric hematology/oncology. Survival rates are poor compared with leukemia in older children despite the use of maximally intensified standard therapies, and the indication for hematopoietic stem cell transplantation (HSCT) is restricted to specific subgroups with poor-risk factors.

Methods: We reported a retrospective analysis of a cohort of 39 patients diagnosed with infant leukemia during the period 1990-2020 who received treatment at the Pediatric Hemato-Oncology Service of a tertiary hospital in Madrid, Spain.

Results: Within our study period, we diagnosed 39 cases with infant leukemia out of 588 cases of childhood leukemia (incidence of 6.6%). 61.5% were females and 38.5% were males. The median age at diagnosis was 5.8 months (IQR 5.4) and 20 (51.2%) patients were under 6 months of age. A total of 27 (69%) patients were affected by acute lymphoblastic leukemia (ALL), 11 (28%) patients by acute myeloblastic leukemia (AML), and 1 (3%) patient by mixed phenotype acute leukemia. At diagnosis, 12 (30.8%) had leukocytosis >300.000/mm3, 22 (59.5%) presented MLL gene rearrangements and 2 (5.1%) suffered from CNS involvement. Induction failure and relapse occur in 8 (20.5%) and 14 patients (35.9%) respectively. The median duration of first remission before relapse was 4 months (IQR: 6.7). A total of 26 patients (66.6%) received HSCT, 24 (92.3%) in first complete remission. With a median follow-up period of 15 months, the 5-year event-free survival and 5-year overall survival at 5 years was 56.7% (SD 4.6) and 44.9% (SD 4.2) respectively. In a multivariate analysis, younger age at diagnosis was associated with poor outcome ($p = 0.027$). HSCT reduced the risk of mortality by 81.8% ($p = 0.001$), with transplant patients in first complete remission having a longer survival compared to the rest ($p = 0.002$). Transplanted related mortality was 31.6% and relapse after HSCT occurs in 7 patients (17.9%).

Conclusions: Most of the infant leukemias diagnosed in our center were ALL. The main risk factors (hyperleukocytosis, MLL) and relapse were found more frequently in the group of patients with ALL, although this difference was not statistically significant. Most of the patients received HSCT, with a favorable impact on overall survival, especially when it was performed in first complete remission. Our results suggest that HSCT seems to be a good and efficient choice of treatment for selected patients. However, there is still a big issue to decide which patient should undergo transplantation and more studies are needed to reevaluate the eligibility criteria for HSCT in this group of patients.

Disclosure: nothing to declare

P037

Post-transplant treatment in high-risk acute myeloid leukaemia: A single center real-life experience

G. Cavallaro[1], A. Grassi[1], C. Pavoni[1], M.C. Micò[1], A. Algarotti[1], D. Taurino[1], G. Rizzuto[1], F. Lussana[1], A. Rambaldi[1]

[1]ASST Papa Giovanni XXIII, Bergamo, Italy

Background: Disease relapse is still the major cause of transplant failure and it is associated with a dismal outcome. In the last years, a better characterization of genomic profile of acute myeloid leukemia made post-transplant target therapies available in cases deemed at high risk of relapse, or frankly relapsed. We report our experience in the use of innovative target therapies (FLT3 inhibitors, venetoclax with or without hypomethylating agents or low dose cytarabine) as pre-emptive therapy in high-risk disease or in cases of molecular or hematological relapse.

Methods: We analyzed 24 patients transplanted in our Centre from 2015 to 2021, with a median follow-up of 10 months (range 2.5-70.5). Our study population comprises acute myeloid leukemia cases, the majority of which (18/24) is considered at high risk, either according to ELN 2017 classification (6/24) or due to high-risk clinical features (12/24, hyperleukocytosis, s-AML, advanced disease). Donor was matched unrelated in 79% of patients and peripheral blood stem cells was the graft source in 91.7% of cases. Conditioning regimen was myeloablative in 54.2% of cases. Only 12.5% of patients achieved a complete remission disease status at transplant; the rest of the study group had pre-transplant active disease (41.7%) or minimal residual disease (MRD) positivity (45.8%).

Results: Our study population started a post-transplant therapy either for hematological (12/24) or molecular relapse/persistent disease (12/24) and median time to treatment start was 2.4 months. 54.2% of patients was started on FLT3-inhibitors (gilteritinib 3/24, sorafenib 10/24) and 45.8% was started on venetoclax with or without a second drug (venetoclax and hypomethylating agents in 5/24, venetoclax and cytarabine in 3/24, venetoclax single agent in 3/24). We performed a univariate analysis on overall survival (OS) and leukemia free survival (LFS). OS for our study population was 39%, as shown in Figure 1. We observed no significant difference regarding the type of conditioning regimen, the donor type and the graft source. Similarly no differences were seen if, at conditioning before transplant, patients had an active hematological disease or an MRD positivity. On the contrary, a timely beginning of the post-transplant therapy to treat minimal residual disease rather than an overt hematological relapse was significantly associated to a better LFS (P 0.0274). Finally, patients with FLT3 mutated patients are those benefit the most of post-transplant treatment.

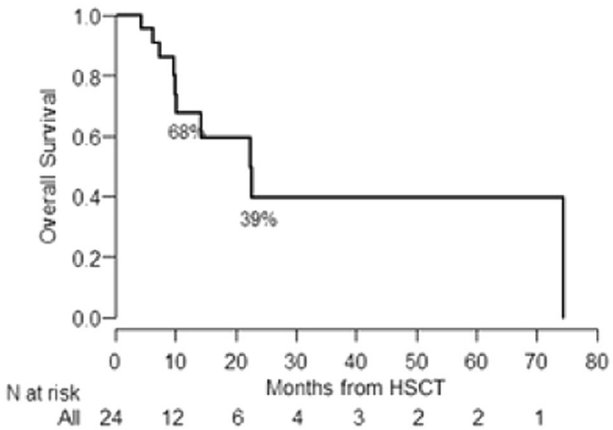


Figure 1

Conclusions: Post-transplant therapy is feasible and induces a significant improvement in LFS in a very high-risk AML patient population. The clinical benefit seems more pronounced for patients treated with FLT3 inhibitors, especially when therapy is promptly started before an overt relapse.

Disclosure: Nothing to declare

P038

Off-label venetoclax in combination with hympomethylating agents for post-allogeneic HSCT AML relapse

F. Serpenti[1], S. Mariarita[1], G. Galassi[1], G. Saporiti[1], F. Grifoni[1], N. Rampi[1], F. Cavallaro[1], K. Barbullushi[1], E. Tagliaferri[1], M. Goldaniga[1], L. Baldini[1], N.S. Fracchiolla[1], F. Onida[1]

[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Background: Recently, Venetoclax-hypomethylating agents (HMA) combination improved outcomes of untreated and relapsed/refractory acute myeloid leukemia (AML). We hereby report our experience of venetoclax + HMA +/− DLI for post-transplant AML at our center.

Methods: We conducted an observational retrospective study to report response rate and safety of venetoclax + HMA in a cohort of AML patients relapsed after HSCT. Venetoclax was administered off-label in association with or added to ongoing HMA therapy. Venetoclax was given after a short ramp-up continuously until response and then in 21 out of 28 days cycles. Dosage was reduced in case of concomitant CYP3A4 inhibitors. Venetoclax was temporarily discontinued in case of grade 4 cytopenia or infection. In case of

multiple neutropenic febrile episodes, grade >3 infection or worsening of ECOG > 2, venetoclax was permanently discontinued.

Results: From September 2016 to March 2021, 11 patients were treated with venetoclax + HMA for post HSCT AML relapse. Their characteristic are summarized in Table 1. One patient was treated for molecular relapse, all others for hematological relapse. Venetoclax was added to HMA after a median of 2 cycles of HMA (0-10); three patients started directly with the combination therapy; all had active disease at start of venetoclax. Five (45%) patients received DLI, with one infusion per cycle at incremental doses. Reasons for not giving DLI were active GvHD, no availability and previous use.

Nine (82%) patients experienced grade ≥3 toxicity (8 hematological, 3 infectious, 1 gastroenteric). Five (45%) patients had to stop venetoclax prematurely after a median time of 35 days (25-46); two of them still proved to have benefited from therapy (1 CRi and 1 MRD negativity after molecular relapse). Both had received DLI, with a median response duration of 1,5 month.

Six patients did not permanently discontinue venetoclax, but at least one temporary suspension was required in four of them. Median duration of therapy was 90 days (37-341). Among these six patients, four had NR (3 DLI), one had PR and one achieved CR with MRD negativity, lasting 12 months.

Median OS was 122 days from venetoclax start.

		Range
Median age	65 y	31-72
ELN risk: favorable (3), intermediate (5), adverse (3)		
Disease status at transplant: CR1 (4), CR2 (4), PR2 (1), active (2)		
Median time from transplant to relapse	196 d	27-1443
Median number of previous lines	3	1-4
DLI: yes (5), no (6)		
HMA: Azacitidine (10), Decitabine (1)		
Venetoclax dose (mg): 400 (no interaction, 4), 200 (concomitant isavuconazole, 2), 50 (concomitant posaconazole, 5)		

Conclusions: Venetoclax-HMA combination induced CR in 27% of these heavily pre-treated patients. The major challange lies in optimizing venetoclax therapy due to higher toxicity rates compared to historical pre-transplant cohorts. At end of study, all patients eventually relapsed, suggesting long-term control is difficult without a second HSCT. Further studies focusing on appropriate patient selection and treatment schedule are warranted in this setting.

Disclosure: No disclosure

P039

Allogeneic bone marrow transplant in infant with acute leukemia

M. Ben Khaled[1], A. Nasri[2], S. Rekaya[3], I. Ben Fraj[4], M. Fathi[5], O. Monia[5]

[1]immune hematology pediatrix departement, Tunis, Tunisia, [2]immune-hematology pediatric departement, Tunis, Tunisia, [3]immune hematology pediatric departement, Tunis, Tunisia, [4]immune hematology pediatric deparetment, Tunis, Tunisia, [5]immune hematology departement, Tunis, Tunisia

Background: Despite significant therapeutic progress in recent years, acute leukemia that appears early in the first two years of life still have a poor prognosis with high mortality rate as well as a considerable risk of relapse. The bone marrow transplant improved the prognosis especially by integrating Haplo-identical hematopoietic stem cell transplantation (haplo-HSCT). This study, aimed to describe the outcome of a single center experience with HSCT in early childhood acute leukemia in Tunisia.

Methods: This was a retrospective study carried out in immune-hematology pediatric department of Tunisia between 2010 and 2020 and including children aged under 2 years old who underwent HSCT for acute leukemia.

Results: Among 21 patients included, 11 had acute myeloid leukemia, 9 had acute lymphoid leukemia and one patient had an ambiguous Lineage leukemia. Most patients (n = 20) were in their first complete remission (CR1), only one was in his second remission (n = 1) (CR2). Ten patients (48%) underwent geno-identical HSCT, and 11 (52%) underwent an haplo- HSCT. The median age of the patients was 14 months old with a sex ratio= 0.3. Ten of these patients had a positive MRD before HSCT. Most patients had Thiotepa-busulfan-fludarabine as a conditioning regimen. The graft-versus-host disease prophylaxis was based ciclosporin (n = 10) and post transplant cyclophosphamide + MMF + ciclosporin (n = 11). Four patients presented CMV reactivation. Three patients had a grade III/IV acute graft-versus-host disease (GVHD). Four patients died after relapse following HSCT. One patient died of transplant-related causes. The 2-years overall survival and disease-free survival (DFS) are 79% and 73%, respectively. The haplo-HSCT and geno-identical HSCT offered similar outcome.

Conclusions: These results support the fact that HSCT is a great option in the treatment of the early childhood acute leukemias, especially when used in CR1. Further studies should be performed to determine the long-term effects of the HSCT.

Disclosure: we confirm that there are no competing interests to declare and no relevant financial or non financial interests to report.

P040

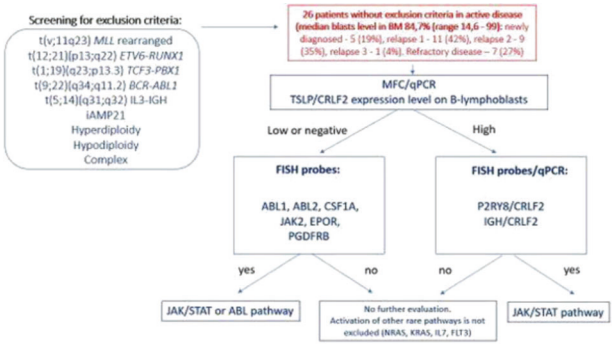
Philadelphia chromosome-like acute lymphoblastic leukemia: First experience of diagnostics and description of clinical cases

K. Afanaseva[1], O. Pirogova[1], A. Evdokimov[1], A. Smirnova[1], I. Barkhatov[1], E. Babenko[1], T. Gindina[1], I. Moiseev[1], S. Bondarenko[1], A. Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, St. Petersburg, Russian Federation

Background: Ph-like ALL is a subtype of ALL with poor prognosis and undefined prevalence in Russian population of adult patients mainly due to diagnostic challenges. Simultaneously, there is no standard approach to the diagnosis and most of the methods used are not financially and technically available in clinical laboratories. Here we present the screening diagnostic algorithm and description of several clinical cases.

Methods: The study included 26 patients with B-ALL, median age 31 (19-78) years, who were diagnostically screened for Ph-like ALL from 2020 to 2021. It is cost and time consuming to screen for Ph-like ALL by searching directly for specific translocations with the particular gene-partners and mutations. Due to this reason the screening algorithm used in our laboratory is based on the determination of the signaling pathways involved in a particular case in order to choose targeted therapy (TKI/JAK-inhibitor). Algorithm is based on measurement of B-lymphoblasts' cell-surface TSLP levels with further screening for rearrangements in genes by DNA-specific FISH probes (ABL1, ABL2, CSF1R, PDGFRB, JAK2, CRLF2) or qPCR (CRLF2) (Figure 1).



Results: According to the diagnostic algorithm the Ph-like incidence was 8 of 26 cases (30,7%). The most frequent finding was CRLF2 gene rearrangement (n = 4, 15,4%) (Table 1). Two patients were diagnosed with Ph-like during primary diagnosis of ALL, while others in 1st or subsequent relapses. Five patients proceed to alloHSCT, 4 of them are still in CR at the moment of last follow-up. Two patients received dasatinib after alloHSCT: patient #1 with the prophylactic aim, patient #2 in combination with chemotherapy in 3rd relapse. Despite early dasatinib administration, patient #2 demonstrated r/r course of the disease after alloHSCT. Patient #3 with both EPOR and CRLF2 rearrangements died in the progression without response to the combination therapy with Inotuzamab ozogamicin and ruxolitinib. At the same time, patients #5 and #8 with CRLF2 rearrangement and extramedullary disease did not receive JAK2-inhibitors and still in CR after alloHSCT for 12 and 45 months, respectively.

Conclusions: Diagnosis of Ph-like ALL may not rely on the definite gene expression phenotype, but rather on the identification of a genetic aberration in the signaling related genes. A panel of FISH probes covering the most common translocations can be employed as a screening tool. Our limited clinical experience demonstrated potential resistance even to combination therapies with TKI and JAK inhibitors. Apparently, these patients are likely to benefit from alloHSCT as soon as possible in CR, but optimal strategies are yet to be determined.

Disclosure: Nothing to declare

P041

Real-life validation of prognostic risk stratification according to eln 2017 in patients with AML and allogeneic hematopoietic stem cell transplantation

C. Aparicio Pérez[1], F. Salas Hernández[1], A.C. González Teomiro[1], E. Paumard Rodríguez[1], E. García Torres[1], R. Rojas Contreras[1], J. Sánchez García[1,2], J. Serrano López[1,2], C. Martín Calvo[1]

[1]Reina Sofia University Hospital, Cordoba, Spain, [2]IMIBIC, Cordoba, Spain

Background: The impact of genetic risk profiles on the outcomes of patients with acute myeloid leukemia (AML) following allogeneic hematopoietic stem cell transplantation (HCT) has not yet been fully established. The objective of this work is to study whether the application of European LeukemiaNet (ELN) 2017 scale improves prognostic risk stratification with respect to ELN2010 and Medical Research Council (MRC).

Methods: We included 37 adult AML patients treated with PETHEMA AML chemotherapy protocols and who underwent allogeneic HCT at our institution between June 2017 and November 2021 and were studied at diagnostic using the Spanish PLATAFOLMA PETHEMA. NPM1 and FLT3-ITD were determined by melting curve analysis and standard PCR-EC technique according to Thiede et al (Blood 2002) in ABI 3130 Analyzer (Thermofisher). For NGS, the commercial panel Myeloid SolutionTM (Sophia Genetics) KAPA Kit amplification libraries and sequencing on ILUMINA Myseq platform were used. Variant analysis was performed using DDM software (Sophia Genetics).

Baseline demographic, disease characteristics, transplant procedures and mutations by functional groupsare summarized in

Table 1. Ph-like ALL patients' characteristics

Nº. Age	ALL status at the time of Ph-like	Rearrangement	Method of diagnostics	Karyotype/ molecular findings	Targeted therapy before alloHSCT	Allo HSCT	Targeted therapy after alloHSCT	Follow-up time since Ph-like was diagnosed (mo.)	ALL status at the time of FU
1.20	Relapse 2	ABL1	FISH	46, XX	Dasatinib	Haplo	Dasatinib	19	CR3
2.39	Relapse 2, neuroleukemia	ABL2	FISH	46, XX IKAROS deletion	No	Haplo	Dasatinib + DLI + intrathecal chemo	16	Relapse 3
3.28	Relapse 1	CRLF2/ P2RY8, EPOR	qPCR, FISH	46, XX, t(1;2)(p34;p23)[4]/ 46,XX[11] WT1 overexpression	Ruxolitinib	No	-	2	Death in relapse 1
4.36	Relapse 1	JAK2/ PAX5	Both FISH and fragment analysis	46, XY BAALC	No	MMUD	1 mo after alloHSCT	4	CR2
5.22	Relapse 2, extramedullary disease	CRLF2/P2RY8	qPCR	46, XX WT1 overexpression BAALC	No	MMUD	No	12	CR3
6.55	Newly diagnosed	EPOR	FISH	46, XY	No	-	-	4	CR1
7.63	Newly diagnosed	CRLF2/P2RY8	FISH	46, XY	No	-	-	1	Active disease (primary refractory)
8.25	Relapse 1, extramedullary disease	CRLF2	FISH	46 XY IKAROS deletion	No	MUD	No	45	CR2

Table 1. The prognostic risk was established according to MRC, ELN2010 and ELN2017 classification.

Variable	Total cohort ($n = 37$)
Age (years)	
• Median (range)	56 (30-59)
Sex (%)	
• Female	14 (40.5)
• Male	22 (59.5)
Diagnostic (%)	
• De novo	31 (83.8)
• s-AML	6 (16.2)
MRC cytogenetic (%)	
• Favorable	2 (5.4)
• Intermediate	25 (67.6)
• Unfavorable	10 (27)
ELN 2010 (%)	
• Favorable	2(5.4)
• Intermediate	24 (64.9)
• Unfavorable	11(29.7)
ELN 2017 (%)	
• Favorable	4 (10.8)
• Intermediate	16 (43.2)
• Unfavorable	17 (46)
Status preHCT (%)	
• CR1	25 (67.6)
• CR2 or more	4 (10.8)
• Refractory	10 (21.3)
Donor type (%)	
• Related matched	10 (27)
• Unrelated matched	4 (18.8)
• Haploidentical related	21 (56.8)
Functional mutations group (%)	
• Signaling pathways/kinases	19 (51.4)
• Epigenetic modification	20 (54.1)
0. DNA methylation	4 (10.8)
1. Chromatin Modifiers	7 (18.9)
• Nucleophosmin	2 (5.4)
• Tumor suppressors	8 (21.6)
• Transcription factors	5 (13.5)
• Spliceosome complex	2(5.4)
• Fusion transcription factors	

Results: The majority of the patients (91.6%) had at least one mutation at diagnosis. The median number of mutations was 3 (0-6). Grouped by functional groups, the most frequent were those related to DNA methylation (54.1%) and signaling/kinase pathways (51.4%). The most prevalent were FLT3 (45.9%), IDH1/IDH2 (24.3%), TET2 and NPM1 (18.9%) followed by N-RAS and DMT3A (16.2%).

The overall survival (OS) analysis according to ELN17, although not showing statistically significant differences between the 3 groups (LongRank $p = 0.219$) with a 2-year OS estimate of 100%, 65.8% and 50.2% in the favorable, intermediate and unfavorable group; respectively, establishes greater differences between intermediate and unfavorable group than the risk stratification according to ELN 2010 and MRC ($p = 0.702$ and $p = 0.614$, respectively).

Progression-free survival (PFS) according to ELN2017 did not reach statistical significance, possibly due to the small number of patients included ($p = 0.465$) with an estimated 2-year PFS of 50%, 30.8% and 45.8% in the favorable, intermediate and unfavorable group, respectively.

Our data show a higher OS in patients with mutations in genes involved in signaling pathways (including FLT3) compared to non-mutated patients with a 2-year OS estimate 71.8 % vs 47.8 %; reaching statistical significance ($p = 0.037$). In addition, FLT3 mutated patients showed a lower risk of relapse compared to non-mutated patients with a cumulative incidence of relapseat two years of 32.6% vs. 65.1% ($p = 0.034$). No other individual mutations showed differences in survival or cumulative incidence of relapse.

Conclusions: In our series, ELN 2017 shows better prognostic stratification between intermediate and unfavorable groups, although without statistically significant differences with respect to ELN 2010 and MRC. FLT3 mutated patients showed a strikingly lowrisk of relapse, related in part to treatment with FLT3 inhibitors prior and/or after transplant. New studies including a larger number of patients are needed to corroborate our results.

Disclosure: Nothing to declare

P042

Treatment of children with acute lymphoblastic leukemia and history of high-risk relapse with bone marrow transplantation at the national institute of pediatrics, Mexico

A. Olaya-Vargas[1], C. Galvan-Diaz[1], H.d.P. Salazar-Rosales[1], G. Lopez- Hernandez[1], A. Del Campo-Martinez[1], N. Ramirez-Uribe[1], Y. Melchor-Vidal[2], R. Rivera-Luna[2], A. Olaya-Nieto[3]

[1]Instituto Nacional de Pediatria, Mexico City, Mexico, [2]Centro Medico ABC, Mexico City, Mexico, [3]Saint Luke Escuela de Medicina, Mexico City, Mexico

Background: Acute lymphoblastic leukemia (ALL) is a malignant disease that arises from several cooperative genetic mutations in a single B or T lymphoid progenitor. The collaborative work of the last 60 years has led ALL to be a fatal disease in all of the cases, to a curable disease in more than 90% of cases in developed countries, however in Mexico a high percentage of children with ALL have high-risk relapses and the prognosis is less than 16% with conventional treatments only with chemotherapy, the objective of the present study was to determine the survival of patients treated with bone marrow transplant patients with high-risk relapsed ALL

Methods: An observational, analytical and retrospective study was carried out INP patients of either sex from 0 to 18 years old who had received hematopoietic progenitor cell transplantation with a diagnosis of "ALL" and high-risk relapse were included. The patients received an allogeneic transplant with conditioning based on TBI/CFM/VP16: With the statistical program SPSS version 25, descriptive statistics were obtained according to the type of variable. A Kolmogórov-Smirnov test will be performed to fit a normal distribution. Of the qualitative variables, absolute frequencies and percentages were obtained. Survival curves for global and disease-free survival were performed using the Kaplan Meier method and the influence of risk factors will be evaluated using the log-Rank method.

Results: A total of 47 patients undergoing stem cell transplantation with a diagnosis of high-risk relapsed ALL were included, with a predominance of males with a male: female ratio of 3: 1, the minimum age of the patients was 3 years and a maximum of 19 years, in 47% of the cases the transplant was performed after the first

relapse, in 89% of the cases the leukemias were precursors B. The overall survival was 79 and the event-free survival was 71 with a 5-year follow-up, among the variables that were analyzed as: Initial risk assigned (0.112),Hypodiploidy (0.133), Development of ElCHa (0.242), ALL Ph + (0.312), Year in which the TCPH was carried out (0.348), source cell (0.570), Remission number (0.598), CNS + (0.694), 100% compatibility (0.738), Immunophenotype of ALL at Dx (0.825), Relapse rate (0.911). No statistical significance was found.

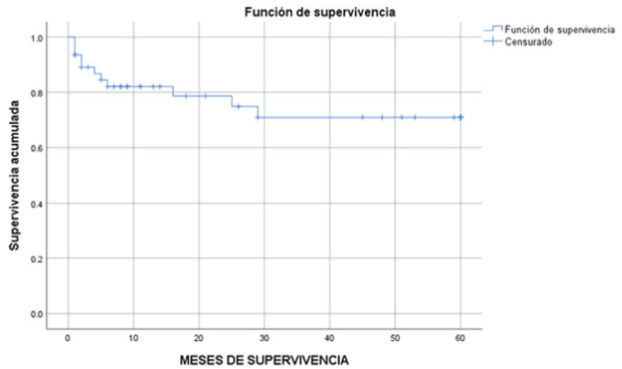


Figure 1. Among the 47 patients, a follow-up of between 1 and 114 months was achieved. For the purposes of the survival study, the Kaplan-Meier method established a maximum limit to the follow-up time of 60 months (5 years), obtaining a probability of that patients survive 5 years after HSCT of 0.71.

Conclusions: The survival of children with high-risk relapse ALL in the study was 71% at 5 years compared with the survival of less than 16% of children who received 2nd-line chemotherapy treatment reported by other groups in Mexico.

Disclosure: All authors declare that they have no conflict of interest with the publication of this study.

Cesar Galván-Diaz, Haydee Salazar-Rosales Gerardo Lopez-Hernandez, Nideshda Ramírez-Uribe, Ángeles Del Campo-Martínez, Yadira Melchor-Vidal, Roberto Rivera-Luna, Alberto Olaya-Nieto, Alberto Olaya-Vargas.

P043

Feasibility of myeloablative ALLO-SCT from haploidentical donor in AML patients older than 70 years: A single-centre experience

K. Barbullushi[1], F. Cavallaro[1], F. Serpenti[1], A. Bosi[1], C. De Magistris[1], N.S. Fracchiolla[1], G. Galassi[1], F. Grifoni[1], M.C. Goldaniga[1], M.C. Mocellin[1], G.N. Saporiti[1], M. Sciumè[1], N. Rampi[1], L. Baldini[1], F. Onida[1]

[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

Background: Median age of acute myeloid leukemia (AML) onset is around 68 years old. Allogeneic hematopoietic stem cell transplantation (allo-SCT), the curative landmark for high-risk AML, is generally not recommended to patients older than 70 years due to higher transplant-related morbidity and mortality. However, with recent improvements in transplant procedures, allo-SCT could be offered to thoroughly selected older patients. Here we report favorable outcome in a series of patients aged ≥70 transplanted from HLA-haploidentical donors following treosulfan-based myeloablative conditioning (MAC).

Methods: We retrospectively collected data of 4 patients older than 70 consecutively transplanted from 11/2019 to 10/2021 at our Centre. The conditioning regimen (TTF) included treosulfan 10 or 12 g/mq from day -6 to day -4, fludarabine 30 mg/mq from day -6 to day -2 and a single dose of thiotepa 5 mg/kg on day -3. Patients underwent allo-SCT from haploidentical donor with peripheral blood as a stem cell source; graft versus host disease (GvHD) prophylaxis included ATG 1.25 mg/kg on days -3 and -2, post-transplant cyclophosphamide (PTCy) 50 mg/mq on days +3 and +4, mycophenolate mofetil (MMF) and cyclosporine (CsA) from day +5. CMV-positive patients underwent prophylaxis with letermovir until day +100.

Results: Patient and transplant characteristics are shown in Table 1. Median time from diagnosis to allo-SCT was 219 days (175-640). Treosulfan dose was 10 g/mq in the 3 patients aged 74-yo and 12 g/mq in the patient aged 71-yo. Median number of days to neutrophil and platelet engraftment was 18.5 (16-22) and 13 (11-23), respectively. Early complications included neutropenic fever (highest grade III), atrial fibrillation (highest grade III) and mucositis (grade II). Two patients developed grade I acute GvHD involving only the skin, fully recovered with low-dose prednisone. One patient developed mild chronic cutaneous GvHD with no indication to treatment. Worsening of cardiac ejection fraction from 52% at baseline to 45% was documented in one patient 400 days post allo-SCT. After a median follow-up of 361 days (51-539), all patients were alive in complete remission, with full donor chimerism.

Conclusions: Positive outcome of this case series confirms the feasibility of haploidentical myeloablative allo-SCT for AML patients older than 70 years, with no major complications. The TTF conditioning regimen with single administration of thiotepa

Table 1 Patients characteristics at transplant

	Patient 1	Patient 2	Patient 3	Patient 4
Age, Sex	71y, M	74y, M	74y, M	74y, M
Indication	High-risk AML	Secondary AML	Therapy-related AML	Secondary AML
Number of previous therapy lines (type)	2 (intensive chemotherapy, azacitidine +venetoclax)	1 (azacitidine + venetoclax)	1 (azacitidine + venetoclax)	3 (decitabine, intensive chemotherapy, azacitidine +venetoclax)
Disease status	CR2	CR1	CR1	CR2
HCT-CI	4	0	7	0
DRI	Very high	Intermediate	Intermediate	Intermediate
EBMT-score	5	4	3	5
Donor/recipient				
CMV	Pos/pos	Neg/neg	Neg/neg	Pos/pos
Sex	F(daughter)/M	M(son)/M	M(son)/M	M(son)/M
ABO	A pos/AB neg	A pos/B pos	A pos/A pos	0 pos/A neg

was very well tolerated. Low dose ATG associated to the classic PTCy/CsA/MMF platform seems to be very effective in preventing both acute and chronic GvHD. Altogether, our experience support the inclusion of fit patients older than 70 years in MAC allo-SCT programs.

Disclosure: Nothing to declare

P044

Allogeneic hematopoietic stem cell transplantation in elderly patients with acute myeloid leukemia: A single center experience

O. Ilhan[1], G. Yavuz[1], G. Cengiz Seval[1], S. Civriz Bozdag[1], M. Kurt Yuksel[1,1], P. Topcuoglu[1], O. Arslan[1], M. Ozcan[1], T. Demirer[1], G. Gurman[1], M. Beksac[1]

[1]Ankara University, Ankara, Turkey

Background: The incidence of most hematologic malignancies increases with age. Aging is related with a greater prevalence of impaired functional status and comorbidities. Although cure of malignant and non-malignant hematological diseases is potentially possible with alloHSCT, it could lead to significant transplant-related mortality. Decision making about referral to allo-HSCT in older adults is a challenging task. In this study we aim to present our geriatric allo-HSCTs.

Methods: From 2004 to 2021, 31 patients (age ≥ 60) underwent allo-HSCT in our center included to this retrospective study. Pre-transplant status as well as posttransplant toxicities, complications and outcomes were determined.

Results: Patient characteristics and transplant results are summarized in Table-1. Twenty-three patients were between the ages of 60-65, and 8 patients were over 65 years of age. Neutrophil engraftment (>0.5x109 /L) occurred in a median of 19 days (range: 11-38) and platelet engraftment (20x109 /L) in 24 days (range: 15-36). Post-transplant complications are detailed in the table. Acute graft versus host disease (aGvHd) was occured in 9 patients (29%) and chronic graft versus host disease (cGvHD) seven patients (22%) were diagnosed with a relapse and 1 year relapse-free survival was 45%. The 1-year and 2-year OS were detected as 45% and 19%. At the end of the long-term follow-up of the patients, 20 patients died, the most common cause ofdeath was relapse of the primary disease.

Table 1: Patient characteristics and transplant complications

Characteristics	Frequency (n,%)	PosttransplantComplications	Frequency (n,%)
Diagnosis AML Secondary AML	26 (%83)5 (%17)	Acute GVHD Grade 2 Gastrointestinal Grade 3 Gastrointestinal Grade 4 Gastrointestinal + hepatic Grade 1 skinGrade 2 skin	2 (%7)1(%4)2(%7)3(%10)1(%4)
Stem Cell Source Peripheral Blood Bone Marrow	29(%93)2 (%7)	Kronik GVHD GastrointestinalSkinEye	7 (%22)3(%10)2(%7)
Donor Type Full Match Relative Donor Full Match Unrelative Donor 1 Mismatch Unrelative Donor Haploidentical	9(%29)10(%32) 9(%29)3(%10)	Viral InfectionsSitomegalovirüs (CMV)	10 (%32)
PretransplantDisease Status Active Disease Remission	9(%29)15(%48)		
Conditioning Regimen Reduced Intensity Myeloablative	23(%74)8(%26)		
Graft vs Host Disease Prophylaxis CSA+MTXCSA+MMFTakrolimus+MMFTakrolimus+MTX	17(%55)10(%32)2 (%7)1(%4)		

Conclusions: Since increasing number of older patients being diagnosed with hematologic malignancies, this trend of increasing number of allo-HSCT will continue. Tolerability and effectiveness are lesser, toxicity is higher in older adults. Although study population is relatively small, reduced-intensity conditioning and pre-transplant remission status may be related to beter survival. Comprehensive geriatric assessment may be considered prior to alloHSCT for global evaluation.

Disclosure: Nothing to declare.

P045

Long term follow-up after allogeneic stem cell transplantation in pediatric acute myeloid leukemia patients

H. Bouarab[1], M. Benakli[1], F. Mehdid[1], N. Rahmoune[1], M. Baazizi[1], D. Ait Ouali[1], S. Zerkout[1], F. Louar[1], F. Harieche[1], R.-M. Hamladji[1], R. Ahmed Nacer[1]

[1]Pierre and Marie Curie Center, Algiers, Algeria

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) in pediatric acute myeloid leukemia (AML) patients (pts) is widely recommended with an HLA identical donor. This retrospective study describes the long-term results of this procedure in a single-center series, among pts whose age is less than 18 years.

Methods: Between September 1998 and December 2020, 161 pts younger than 18 years with AML underwent allo-HSCT. Median age was 11 years (4-17) and sex-ratio (M/F):1. The average time from diagnosis to transplant was 9 months (3-73). At the time of the transplant, 132 pts were in first complete remission (CR1), 21 pts in second CR and 8 pts in active disease. Myeloablative conditioning regimens based on Busulfan were used in 155 pts with Cyclosporine-Methotrexate as prophylaxis of GVHD. Six pts were transplanted from a haploidentical donor with addition of mycophelonate as prophylaxis of GVHD. The grafts used are peripheral blood stem cells in 147 pts with an average rate of CD34 cells:8,07.10^7/kg (1,5-23,9), bone marrow in 13 pts with an average rate of nucleated cells: 3,33.10^8/kg, and cord blood in 2 pts with a rate of NC: 4,4.10^8/kg. At September 2021, the minimal follow-up (FU) was 11 months and maximal FU was 276 months.

Results: Aplasia was observed in all pts with median day of neutrophils engraftment was 15 days (13-29). Eighty thirteen pts (60%) required RBC transfusions (1,4 unit/pt) and 150 pts (97%) needed platelet transfusions (1,7 units/pt). Three pts presented a moderate veino-occlusive disease. Acute GVHD occurred in 44 pts (28%) including 34 (22%) grade II-IV. Chronic GVHD was seen in 53 pts (38%) with extensive form in 39 pts. Twenty-one pts (13%) showed CMV reactivation on average at day 72 (19-237). Forty pts (26%) relapsed (26 pts in CR1, 8 pts in CR2 and 6 pts with blast crisis at the time of the transplant). Disease status before transplant (CR1 vs CR2) affect the incidence of relapse (p:0,05). After follow-up of 103 months (11-276), 91 pts (56,5%) are alive in CR and 70 pts (43,5%) died within 30 pts (18,6%) from TRM (acute GVHD:16, severe infection:9, early rejection :2, capillary leak syndrome:1, kidney failure:2) and 40 from relapse (24,8%). The overall survival (OS) and disease free survival (DFS) are 54% and 53% respectively. CR1 is associated with better EFS in univariate analysis (60% vs 29%, p:0,05).

Conclusions: In our practice, on the absence of cytogenetics and molecular genotyping analysis, allo-HSCT from an HLA matched family donor became the standard of care for treatment of childhood AML. This retrospective study with long-term follow-up shows interesting results; however, monitoring for long-term complications after HSCT needs special consideration.

Disclosure: Nothing to declare

APLASTIC ANAEMIA

P046

Correlation of donor chimerism and outcomes in children with severe aplastic anemia after hematopoietic stem cell transplantation

126

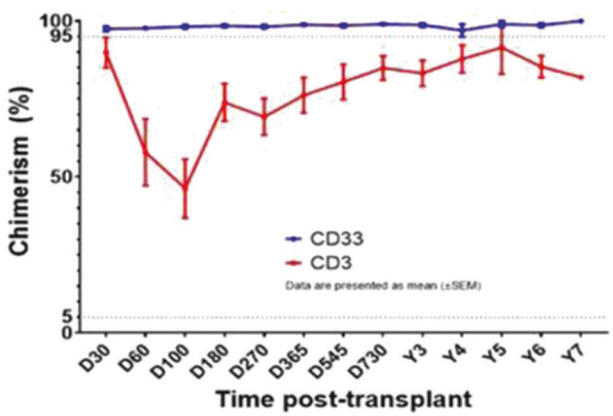
S. Crowell[1], R. Abu-Arja[1], H. Rangarajan[1], V. Pai[1], J. Stanek[1], R. Bajwa[1]

[1]Nationwide Childrens Hospital, Columbus, United States

Background: Routine blood counts and donor chimerism studies are monitored regularly after engraftment in patients with severe aplastic anemia (SAA) following HSCT. Mixed chimerism (MC) may be associated with cytopenia, graft rejection/failure or poor graft function

Methods: This is a retrospective chart review of patients with SAA who underwent allogeneic HSCT at Nationwide Children's hospital between 2007-2021. Whole blood and sorted chimerism (CD3 and CD33) were performed using PCR-based testing. Mixed chimerism was defined as donor chimerism of 5-95%. Data on patient demographics, transplant details and outcomes were collected in a secure database and results were analyzed using descriptive statistics.

Results: Eighteen patients (10 males) with SAA underwent HSCT, with 14 patients having sufficient chimerism and outcome data to be included in this study. Median age at HSCT was 9 years (range: 4-17); 7 received HSCT from MSD, 5 from MUD and 2 from haploidentical donors. Cyclophosphamide with or without fludarabine, and alemtuzumab or rabbit ATG (n = 10) were the common conditioning regimens with low dose TBI used in 4 patients. At day +30, mean whole blood (WB), CD3 and CD33 donor chimerism were 97%, 90%, and 98%, respectively. While the mean CD33 donor chimerism, stayed >95% at all time points studied, the mean CD3 donor rapidly fell and reached a nadir of 46% (range:11-99%) by day +100 (Fig 1). With continued immunosuppression, the CD3 chimerism gradually increased to 74% (range:48-100%) by day +180 and then stabilized around a mean of 85% (range:62-100%) on follow-up. A similar pattern was observed for patients given either Alemtuzumab or rATG. Overall, mixed chimerism were seen in 7/14 patients (50%) in whole blood, 11/14 (79%) in the CD3 fraction and 2/14 (14%) in CD33 fraction on at least one timepoint post-HSCT. One patient with Down syndrome, died from pneumococcal septicemia but had WB, CD3, and CD33 chimerism of 98, 98 and 99% respectively at 4 years after HSCT. Two patients developed recurrence of SAA at 45 and 21 months after MSD HSCT, had donor chimerism of 79 and 91%, 74 and 90%, and 89% and 100% in WB, CD3 and CD33 fractions respectively at the time of recurrence of SAA. One underwent a successful second HSCT while the other is in planning stages for a second HSCT. Cytopenia was noted in 3/14 (21.4%) patients (excluding the 2 with recurrence of SAA) at a mean of 107 days (range 89-130) after HSCT but fully recovered subsequently. Thirteen patients are alive at the time of this report with a mean follow up of 4 years (range 0.5 to 10).



Conclusions: After HSCT, patients with SAA showed sustained and stable mean CD33 donor chimerism of ≥95% at all time points while the CD3 chimerism reached a nadir of 46% around day +100, before slowly recovering in all patients. More importantly, there was no correlation between CD3 chimerism at any time point after HSCT with conditioning regimen, serotherapy, development of cytopenia, overall survival, graft failure or recurrence of SAA.

Disclosure: All authors have nothing to declare

P049

Long-term outcome in fanconi anemia patients from the italian national database

E. Ricci[1], F. Bagnasco[1], M. Faraci[1], G. Dell'Orso[1], A. Risitano[2], P. Farruggia[3], A. Zatterale[4], E. Cappelli[1], A. Todiere[5], C. Dufour[1], F. Pierri[1]

[1]Istituto G. Gaslini, Genova, Italy, [2]AORN San Giuseppe Moscati Avellino, Avellino, Italy, [3]A.R.N.A.S. Ospedali Civico, Di Cristina e Benfratelli, Palermo, Italy, [4]Formerly ASL Napoli 1, Napoli, Italy, [5]IRCCS Ospedale San Martino, Genova, Italy

Background: Bone marrow failure (BMF) is the main cause of morbidity and mortality in Fanconi Anemia (FA) patients. Hematopoietic Stem Cell Transplantation (HSCT) is the only therapeutic option capable to durably correct hematopoiesis. However, HSCT also negatively affect development of post-transplant solid tumors namely especially head and neck or lower gynecological squamous-cell carcinoma (SCC). A previous analysis of 97 FA patients from the Italian national database (Svahn J et al Am J Hematol 2016), demonstrated that the majority of patients developed cytopenia during the follow-up but 32 subjects maintained a mild/moderate cytopenia without need for HSCT. Overall survival (OS) of the whole original cohort was 74.2%.

Methods: This is an extension study in which we evaluate, over a longer follow-up (ended on 31/05/2021), the cohort of 32 FA patients who had a marginally compromised hematopoiesis in the original study. Demographic data, presence, grade and trend of cytopenia, defined according to international guidelines, HSCT characteristics and the development of secondary cancer were recorded.

Results: Of the 32 patients evaluated cytopenia was present in 90.6% at diagnosis. At the time of the first pathological blood count, 53.1% had mild cytopenia, 40.6% moderate and 6.3% severe; at the end of the follow up of the original study 9.4% had no cytopenia, 43.8% mild, 31.2% moderate and 15.6% severe. Among 32 patients only 26 were evaluable with a median follow-up of 9.5 years (IQR 6.25-12.75, range 0-27.0). 38.5% (10/26) maintained stable cytopenia (1 have no cytopenia, 6 mild, 2 moderate, 1 severe), in 11.5% (3/26) cytopenia worsened, while 50% (13/26) underwent HSCT.

Indications for HSCT were: progression of BMF (10/26, 76.9%) clonal evolution (2/26), unknown (1/26). Donor type was: matched-sibling (MSD) (46.2%), alternative (AD) (23.1%) or haplo (15.4%). The source of cells was bone marrow (38.5%), peripheral blood (30.8%) and bone marrow + cord blood from the same donor (15.4%).

One patient developed a uterine cervix SCC and two women a precancerous lesion (in both cases HPV-related low-grade squamous intraepithelial lesions of uterine cervix**)**. They were all FANCA mutated and none underwent HSCT. The 5.8 years OS of this cohort was 92.3% (2/26 died for transplant-related mortality).

Conclusions: This extension study confirms that in FA cytopenia tends to progress overtime but that a proportion of

patients maintain a stable level of hematopoiesis. These data outline the need for a close and prolonged follow-up to identify the more suitable moment to transplant FA patients, considering the different variables, like the available donor, the HLA matching and the patient's comorbidities.

Disclosure: Nothing to declare

P050

Haploidentical stem cell transplantation with post-transplant cyclophosphamide in patients with aplastic anemia: A gatmo-tc experience

A.L. Basquiera[1], P.G. Longo[2], G.A. Ferini[3], A. Cia[4], S. Cruset[5], M.L. Rizzi[6], M.V. Suen[1], P. Duarte[7], M. Cattaneo[8], G. Kusminsky[2], J. Bordone[5], G. Jaimovich[4]

[1]Hospital Privado Universitario de Córdoba, Córdoba, Argentina, [2]Hospital Universitario Austral, Pilar, Argentina, [3]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [4]Fundación Favaloro, Buenos Aires, Argentina, [5]Hospital de Alta Complejidad El Cruce, Florencio Varela, Argentina, [6]Sanatorio Allende, Córdoba, Argentina, [7]CEMIC, Buenos Aires, Argentina, [8]CETRAMOR, Rosario, Argentina

Background: Aplastic Anemia is a benign disease associated with significant morbidity and mortality in severe forms. For those patients without an HLA-identical donor or not responding to immunosuppression treatment, a related HLA-haploidentical donor is an immediately available donor source.

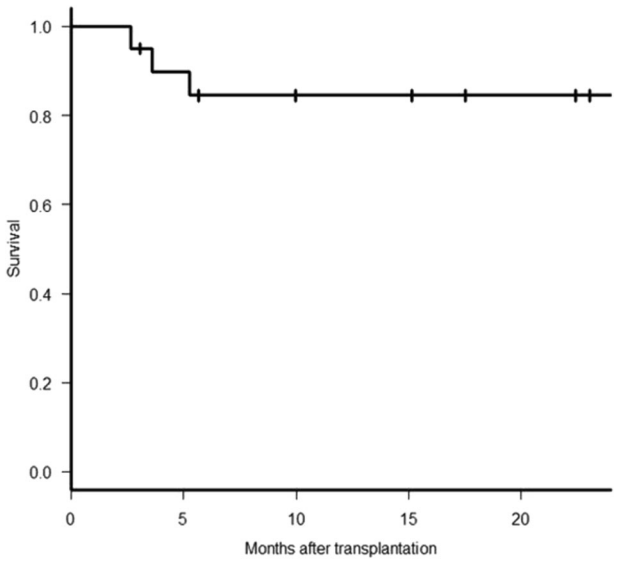
Methods: Retrospective study of patients with a diagnosis of severe or very severe aplastic anemia who underwent haploidentical stem cell transplantation (Haplo-SCT) using post-transplant cyclophosphamide (PT-Cy) between 2016 and 2021 from Argentine centers affiliated to GATMO-TC. We analyzed overall survival, the cumulative incidence of acute and chronic graft versus host disease (aGVHD and cGVHD), and graft failure.

Results: A total of 20 patients were reported (median age 19; IQR 12-27; 65% below 21 years), without response to immunosuppression treatment (n = 18).

The median interval from diagnosis to transplant was 9.72 months (IQR 5.5 – 14.9) and the median pre-transplant serum ferritin level was 2956 ng/ml (IQR 1532 - 3355).

Donors (median age 32.8 years) were: parents (n = 12; 60%), siblings (n = 7; 35%) and children (n = 1; 5%). Stem cell source was peripheral blood (n = 11; 55%) and bone marrow (n = 9; 45%). The conditioning regimen was predominantly a combination of fludarabine, Cy, and low dose total body irradiation (TBI) (n = 15; 75%). All patients received PT-Cy, antithymocyte globulin was used in 11 patients (55%), and all patients received either tacrolimus (n = 12; 60%) or cyclosporine (n = 8; 40%).

The cumulative incidence at day 28 of neutrophil recovery was 95% (median 16 days), and day-28 platelet recovery of more than 20,000/microliters and 50,000/microliters was 80% (median 18.5 days) and 65% (median 24.5 days), respectively. Two patients developed primary graft failure and secondary graft failure, respectively; both received bone marrow as a stem cell source. The cumulative incidence of aGVHD at day 100 was 42.3% (Grade I: 12.5%; Grade II: 75%; y Grade III: 12.5%); with a trend to a higher rate with peripheral blood (54.5% vs 27.5%; p = 0.074). One-year cumulative incidence of cGVHD was 26.1% (Mild: 57.6%; Moderate: 11.1%; and Severe: 33.3%). Two-year overall survival was 84.4% (CI95% 59-95). Variables associated with better survival were: age below 21 years (100% vs 57%; p = 0.020), tacrolimus-based prophylaxis (100% vs 62%; p = 0.041) and conditioning regimen Baltimore-type vs others (93% vs 60%; p = 0.079). Death causes were: refractory GVHD (n = 1), primary graft failure and sepsis (n = 1).



Conclusions: Haplo-SCT with PT-Cy is an option for patients without response to immunosuppression treatment and without an HLA-identical donor. Advantages such as the widespread availability and a lower cost of graft acquisition compared with other alternatives sources make Haplo-SCT the best choice. Some key factors such as conditioning regimen and GVHD prophylaxis might have an impact on the results of the procedure.

Disclosure: Nothing to declare.

P051

Hematopoietic stem cell transplantation (HSCT) to treat pure red cell aplasia (PRCA)

S. Zhou[1], M. Xiong[2], J. Zhu[2], W. Ling[2], H. Wang[2], G. Wang[2]

[1]Bone Marrow Transplantation Beijing Ludaopei Hospital, Beijing, China, [2]Bone Marrow Transplantation, Hebei Yanda Ludaopei Hospital, Langfang, China

Background: Pure red cell aplastic anemia (PRCA) is a heterogeneous syndrome characterized by a simple erythroid hematopoietic disorder. The main clinical symptom is anemia. Most patients become transfusion dependent, and are at considerable risk for infection and of the syndrome to evolve into leukemia. At present, about 50% of patients can achieve remission,mainly through immunosuppressive therapy. Hematopoietic stem cell transplantation (HSCT) has also been used in patients who are unresponsive to glucocorticoids, but data on outcomes on these patients are scarce in China.

Methods: We retrospectively analyzed the clinical characteristics of 6 patients with PRCA who underwent HSCT in our hospital from May 2019 to November 2021. Two patients had a congenital form of PRCA and 4 patients had acquired PRCA. All patients were unresponsive to glucocorticoids prior to HSCT. The male to female ratio was 2:4. The median age was 30.5 months (range: 17-42 months). The median disease course from diagnosis to transplant was 29 months (range: 13-42). Four patients received umbilical cord blood-HSCT. The conditioning regimen was fludarabine (40mg/m^2/d×5days IV) + Ara-C (2g/m^2/d×5days IV) + Bu(0.8mg-1.2mg/Kg Q6h×4days) + cyclophosphamide (1.8g/m^2/d×2days) +ATG (thymoglobuline, Sanofi, 1.25mg/Kg/d×2days). One patientunderwent a matched unrelated donor (MUD) HSCT. Another patientunderwent a haplo-HSCT with the following conditioning regimen: fludarabine

(40mg/m^2/d×3days IV) + Ara-C (2g/m^2/d × 3days IV) + Bu(0.8mg-1.2mg/Kg Q6h×4days) + cyclophosphamide (1.5g/m^2/d×2days) +ATG (thymoglobuline, Sanofi, 1.25mg/Kg/d ×4days). For GVHD prophylaxis, we used CsA/tacrolimus plus sMTX for all of the patient.

Results: All 6 patients tolerated the pre-treatment well. The total implantation rate was 100%. The median time of neutrophil engraftment was 12.5 days (range: 11-21 days). The median time to platelet engraftment was 18.5 days (range: 11-75 days). During the median follow-up period of 25.5months (range: 6-30 months), all patients had complete donor chimerism and became transfusion-independent by subsequent normalization of hemoglobin levels. The incidence of CMV was 50% (3 of 6 patients). Following transplantation, EBV DNA load was undetectable among all of patients who were infected with EBV. Grade II aGVHD occurred in 1 patients (16.7% incidence) . One patients had cGVHD. All patients survived, with an overall survival rate of 100%.

Conclusions: In our small cohort of 6 PRCA patients, we demonstrate that HSCT has a high implantation rate and overall survival rate, and may become a viable therapeutic option for these patients. Nevertheless, because of the risk of transplant-related death, careful selection of HSCT candidates and the optimal timing of HSCT is necessary. Future studies need to examine the PRCA patient characteristics that are likely to result in a successful HSCT as well as the optimal time for a patient to undergo transplantation.

Disclosure: Nothing to declare

AUTOIMMUNE DISEASES

P052

NT-proBNP measurements during cyclophosphamide conditioning in patients undergoing autologous haemopoietic stem cell transplantation for systemic sclerosis suggest increased cardiac strain

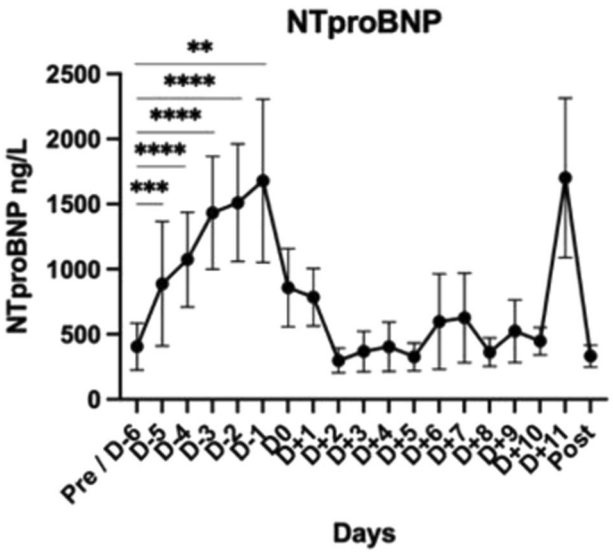
R. Penglase[1], E. Brenu[2], H. Englert[1], S. Milliken[1], B. Withers[1], N. Karki[1], J. Perram[1], H. Tao[1], L. Girgis[1], A. Jabbour[1], E. Kotlyar[1], D. Ma[1], J. Moore[1]

[1]St Vincent's Hospital, Sydney, Australia, [2]University of Notre Dame, Sydney, Australia

Background: Autologous haematopoietic stem cell transplantation (AHSCT) is a well-established therapeutic option for severe systemic sclerosis (SSc), however application is limited by treatment-induced cardiotoxicity apparent during conditioning, particularly in the setting of established cardiac disease. In this study we examined the impact of cyclophosphamide conditioning therapy on cardiac enzymes over the transplantation period.

Methods: The records of all patients from 2017 who underwent AHSCT for SSc at our hospital were retrospectively reviewed to identify those with cardiac enzyme measurement pre- and during conditioning therapy. All patients who received treatment were enrolled in AHSCT clinic trials approved by the St Vincent's Hospital ethics committee. Statistical analysis was performed by one way analysis of variance (ANOVA) or Mann-Whitney U test.

Results: Chart review identified 22 patients with measurement of proBNP and/or troponin I during conditioning. Four patients underwent a repeat AHSCT procedure, giving a total of 26 conditioning episodes. All patients received cyclophosphamide (Cy) conditioning at doses between 50-200mg/kg divided over 4 days (D-5 to D-2); patients who received <200mg/kg had either pre-existing cardiac disease or other significant risk factors. Patients who received lower doses of Cy conditioning had significantly higher NTproBNP at baseline compared to the standard dose group (265 vs 67.5 ng/L, $p < 0.01$). In all patients, NTproBNP was significantly increased from D-5 to D-1 compared to baseline ($p < 0.01$) with a peak at D-1. Peak NTproBNP was higher in the lower dose group compared to the standard dose group, however this was not statistically significant. The relative increase of NTproBNP was higher in the standard dose group (1329% vs 271%), however this did not reach statistical significance ($p = 0.09$). Following transplantation, the median NTproBNP returned to baseline. There was no significant changes in troponin I during Cy conditioning.



Conclusions: In summary, these data suggests that Cy conditioning induces markers of cardiac stress in an already high-risk population. Further data are needed to explore the relationship between relative NTproBNP increase during conditioning and Cy dose. Measures to reduce cardiovascular risk during the conditioning period are warranted.

Clinical Trial Registry: ACTRN12617000216314 https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=371990.

Disclosure: Nothing to declare

P053

Residual recipient t-cells are responsible for severe lupus nephritis in rals-associated lupus nephritis persistence after allogeneic, matched sibling donor transplant

S. Senthil[1], R. Hanasoge-nataraj[1], D. Bonney[1], H. Campbell[1], P. Riley[1], M. Shenoy[1], S. Hughes[1], R. Wynn[1]

[1]Royal Manchester Children's Hospital, Manchester, United Kingdom

Background: RAS-associated lymphoproliferative syndrome (RALS) is a relatively new entity causing defects in intrinsic pathways of apoptosis. Although management has been mainly with immunosuppression, we report haematopoietic stem cell transplant for refractory autoimmunity and for lupus-associated nephritis. We report persistent lupus nephritis despite achievement of fully donor myeloid and B-lymphoid engraftment and speculate that residual recipient T-cells are responsible for persistent disease manifestations.

Methods: Retrospective review of the patient's case records and laboratory investigations was undertaken.

Results: An 18 months old boy presented with autoimmune haemolytic anaemia and immune thrombocytopenia with leucocytosis and monocytosis. He had a gross splenomegaly, a leucoerythroblastic blood picture and raised fetal haemoglobin

raising concerns of underlying Juvenile myelomonocytic leukemia (JMML). Further investigations revealed a high titre of anti-double stranded DNA antibodies and antinuclear antibodies. Investigations for Autoimmune lymphoproliferative syndrome (ALPS) were negative. Bone marrow assessment revealed hypercellular marrow with no increase in blast population with normal cytogenetic studies. Next generation sequencing from peripheral blood revealed a somatic gain of function mutation of NRAS leading to a diagnosis of RALS. The immune cytopenias were refractory to treatment with steroids and multiple immunosuppressants. In view of refractory autoimmunity, he was treated with a matched sibling donor(MSD) bone marrow transplant with Fludarabine, treosulfan and thiotepa conditioning at 30 months of age. He engrafted at 22 days after transplant with a donor chimerism of 90%. However, there was a rapid loss of donor chimerism with concurrent autologous haematopoietic reconstitution. Consequently, he had recurrence of primary disease manifesting as monocytosis with splenomegaly alongside lupus nephritis.On account of refractory and severe, biopsy-proven lupus nephritis induced by the underlying RALD, he had a second MSD bone marrow transplant from a different sibling at 38 months of age with Fludarabine, busulfan and alemtuzumab conditioning. He remains engrafted with 100% donor myeloid and B-lymphoid chimerism, but with persistent rising mixed T cell chimerism. He has relapsed, persistent lupus nephritis and a recurrently raised titre of anti-DS-DNA antibodies, despite treatment with steroids, immunosuppresants, Rituximab, Bortezomib. After a diligent multidisciplinary input, it is decided to use Daratumomab, a CD38 directed monoclonal antibody in an attempt to eradicate the recipient T cells, which is inferred to be the principal cause of the underlying lupus nephritis.

Conclusions: HCT for treatment of autoimmunity in RALS has not been documented in literature to the best of our knowledge. Further data is needed to ascertain the unique complications associated with HSCT in RALS.While mixed T cell chimerism does not affect outcome in non malignant transplants in general, it is proposed that residual inflammatory activated autologous cells here drive persistent disease manifestations, and that full donor T cell chimersim is required to fully control disease.

Disclosure: Nothing to declare.

P054

Encephalitis and thrombotic microangiopathy after mrna sars-cov2 vaccine in a patient with chronic GVHD: A case report

C. Mayor Bastida[1], A. Puchol Crespo[1], S. Diaz Lopez[1], A. Figuera Alvarez[1], A. Alegre Amor[1], B. Aguado Bueno[1]

[1]Hospital La Princesa, Madrid, Spain

Background: Hematopoietic stem cell transplantation (HCT) recipients have a high risk of mortality with COVID-19 because of severe immune dysregulation[1]. Several vaccines have been developed whose safety has been proven, however, infrequent complications include neurological complications[2] or autoimmune phenomena[3]. Moreover, there are still scarce data on its safety and tolerability in recipients of allogenic hematopoietic stem cell transplant[4].

Methods: We report a case of acute encephalopathy and subsequent thrombotic microangiopathy within two weeks of receiving the first dose of mRNa SARS-COV2 vaccine (Moderna).

Results: 68-year-old male recipient of allogenic matched unrelated donor transplantation in 2009 because of AML. Since then in complete remission.

As postransplant complications he presented extensive severe chronic sclerotic cutaneous, ocular and pulmonary chronic graft-versus-host disease (cGVHD) that required immunosuppressive treatment with systemic steroids and photopheresis for several years. In addition to chronic kidney disease and adrenal insufficiency for which he was under treatment with steroids until now.

He presented to the emergency department with motor aphasia, generalized tremor and fever. The patient had received the first dose of mRNa SARS-COV2 vaccine (Moderna) 20 days earlier. In laboratory tests, hemoglobin 15 g/dL, platelets 212,000/mm^3 and leukocytosis of 19,920/mm^3 with neutrophilia and lymphocytosis. CT brain scan and lumbar puncture were performed whitout significant alterations. We started antibiotic therapy with Ceftazdime, Ampicillin, Vancomycin and Acyclovir. The study was extended with brain MRI and electroencephalogram, which ruled out ischemic phenomena. Negative onconeurolane and PF4–heparin antibodies. Everything suggested that the most likely cause was acute post-vaccinal encephalitis. We started treatment with high dose steroids and plasma replacements with symptom improvement 48 hours later. All microbiological cultures were negative.

One week after admission, anemia and thrombopenia were observed, reaching a platelets 40,000/mm^3 with worsening renal function, increase LDH up to 415U/L, uncontrolled hypertension, 4% of schistocytes in blood smears and ADAMTS13 within normal range. Bone marrow study was performed and was in complete remission. Steroids 1 mg/kg/12h and immunoglobulins were administrated with initial response the first week with subsequent worsening after 10 days. Plasma exchange was restarted with clinical and analytical response after two weeks: recovery of thrombopenia, optimal blood presure control and disappearance of schistocytes.

All this established a possible diagnosis of thrombotic microangiopathy secondary to post-vaccinal autoimmune phenomena.

Conclusions: Hematopoietic transplant recipients who developed COVID-19 have worse prognosis. Vaccination of these patients is one of the best preventive strategies. However, the efficacy and safety of these vaccines in transplant recipients is currently lacking[4,5] The most frequently hematological adverse effects are cytopenias and worsening or establishment of GVHD[6].

This is a patient with severe cGVHD who, after first dose of vaccine, presented with encephalopathy without infectious or ischemic cause, with favourable outcome after immunosuppressive treatment and plasma exchanges. One week later, he presented thrombopenia, anemia, impaired renal function and schistocytosis; test to rule out vaccine induced immune thrombotic thrombocytopenia (VITT) was negative.

So we conclude that it was an autoimmune thrombotic microangiopathy, reflecting a complex inumnologic process in patient with cGVHD with the vaccine as the only identified trigger factor.

Disclosure: Nothing to declare

CAR-BASED CELLULAR THERAPY – CLINICAL

P055

3rd-generation CD19-directed chimeric antigen receptor t-cells (carts) for relapsed/refractory chronic lymphocytic leukemia (cll) – results from an academic phase 1/2 trial (hd-car-1)

P. Derigs[1], A. Kunz[1], P. Dreger[1], A. Schmitt[1], M.-L. Schubert[1], M. Brüggemann[2], H. Bernhard[3], G. Kobbe[4], A. Lindemann[5], M. Rummel[6], L. Wang[1], B. Michels[1], P. Waldhoff[1], F. Korell[1], P. Pavel[7], A.D Ho[1], C. Müller-Tidow[1], M. Schmitt[1]

[1]University Hospital Heidelberg, Heidelberg, Germany, [2]University Hospital Kiel, Kiel, Germany, [3]Klinikum Darmstadt, Darmstadt, Germany, [4]University Hospital Düsseldorf, Düsseldorf, Germany,

[5]Onkologie in Ettlingen, Ettlingen, Germany, [6]University Hospital Giessen, Giessen, Germany, [7]Institute for Clinical Transfusion Medicine and Cell Therapy (IKTZ), Heidelberg, Germany

Background: CD19-directed CART therapy has become a standard of care in various B-cell malignancies. However, application of CD19 CARTs in CLL has been hampered by the disease-inherent T-cell dysfunction. Here, we show preliminary results obtained with HD-CAR-1, a 3rd generation CD19-directed CART, in patients with high-risk r/r CLL.

Methods: HD-CAR-1 is an investigator-initiated trial evaluating efficacy and safety of escalating doses of CD19-directed CARTs comprising CD28 and 4-1BB as costimulatory molecules in patients with advanced B-cell malignancies after fludarabine/cyclophosphamide lymphodepletion. Leukapheresis, manufacturing, administration, patient monitoring and follow-up were all conducted in-house at the Heidelberg University Hospital. Patients with CLL were eligible if they had failed chemoimmunotherapy and at least one pathway inhibitor and/or alloHCT.

Results: Between Oct 2018 and Nov 2021, 32 patients were enrolled of whom seven had CLL. Patients with CLL had a median age of 62 years and had received two to ten prior treatment lines. All patients were r/r to therapy with at least one pathway inhibitor, and three patients were in addition r/r to alloHCT. TP53 abnormalities were present in six of seven patients. Disease status at lymphodepletion was CR in three patients, PR in two patients, SD in one patient and PD in one patient. Despite heavy pretreatment, leukapheresis yielded sufficient T-cell numbers for production in all instances. CART manufacturing was successful for all seven patients. Dose levels administered were I ($=0.1x10^7$ CARTs/m^2) in one patient, II ($=0.5x10^7$ CARTs/m^2) in one patient, and V ($=10x10^7$ CARTs/m^2) in five patients. Rapid CART expansion was observed in four of five patients evaluable so far. Peak levels ranged between 37,792 and 369,756 copy numbers/µg PBMC DNA and correlated with administered CART dose level. Toxicity was moderate with a single case of CRS > G2 and no severe neurotoxicity. However, prolonged G4 neutropenia occurred in one of five patients with ANC recovery on day +32. Responses were observed in all five patients evaluable for response with CRs in three patients treated at dose level V.

Conclusions: Homebrewed 3rd generation HD-CAR-1 CART could be successfully generated for heavily pretreated patients with high-risk CLL and exerted a promising safety and efficacy profile.

Clinical Trial Registry: ClinicalTrials.gov Identifier: NCT03676504

Disclosure: P.De.: received an honorarium for a scientific presentation by MSD. M.S.: funding for collaborative research from Apogenix, Hexal and Novartis, travel grants from Hexal and Kite, financial support for educational activities and conferences from bluebird bio, Kite and Novartis, board member for MSD and (co-)PI of clinical trials of MSD, GSK, Kite and BMS, as well as co-Founder and shareholder of TolerogenixX Ltd. P.Dr.: consultancy for AbbVie, AstraZeneca, Gilead, Janssen, Novartis, Riemser, Roche; speakers bureau for AbbVie, Gilead, Novartis, Riemser, Roche; research support from Neovii and Riemser. C.M.-T.: consultancy Advisory Board for Pfizer and Janssen, and has received grants and research support from Pfizer, Daiichi Sankyo, BiolineRx and Bayer AG. A.S.: travel grants from Hexal and Jazz Pharmaceuticals, research grant from Therakos/Mallinckrodt and co-founder of TolerogenixX LtD. M.-L.S.: consultancy for Gilead. All other authors report no potential conflicts of interest.

P056

Cost-effectiveness of axicabtagene ciloleucel as second-line therapy for patients large b-cell lymphoma (lbcl) in the united states

M.-A. Perales[1], J. Kuruvilla[2], J. Thornton Snider[3], S. Vadgama[3], R. Blissett[4], F. El-Moustaid[4], N. Smith[4], A. Patel[3], P. Johnston[5]

[1]Memorial Sloan Kettering Cancer Center, New York, United States, [2]University of Toronto, Toronto, Canada, [3]Kite Pharmaceuticals, Santa Monica, United States, [4]Maple Health Group, LLC, New York, United States, [5]Mayo Clinic, Rochester, United States

Background: ZUMA-7 (NCT03391466) is a global, randomized, Phase 3 trial of axicabtagene ciloleucel (axi-cel), an autologous anti-CD19 chimeric antigen receptor T-cell (CAR T) therapy, vs. standard of care (SoC: salvage chemoimmunotherapy followed by high-dose therapy with autologous stem cell rescue [auto-SCT] for responders) in second-line large B-cell lymphoma (2L LBCL). Axi-cel demonstrated a statistically significant and clinically meaningful improvement in event-free survival, and despite 56% of the SoC arm receiving third-line (3L) CAR T therapy, a trend toward improved OS was observed. This study estimated the cost-effectiveness of axi-cel versus SoC from a third-party US payer perspective in the 2L setting.

Methods: We developed a three-state partitioned-survival model to estimate lifetime cost and benefits. Health care resource use, adverse event (AE) rates, and survival data were taken from the ZUMA-7 trial where possible, costs (including acquisition, administration, monitoring, auto-SCT, 3L treatment [including 3L CAR T after SoC treatment], and AEs) from published sources (in 2021 USD), and utilities from the literature. Long-term EFS and OS were estimated using mixture cure modelling methods. A 3% discount rate was applied to costs and health effects. The model estimated expected life years (LYs), quality-adjusted life years (QALYs), total costs, and the incremental cost-effectiveness ratio (ICER). Additional model outputs included health state occupancy, spending on 2L/3L treatments and granular costs. One-way and probabilistic sensitivity analyses were performed to test model robustness.

Results: The model projected median OS was 59 months for the axi-cel arm and 25 months for the SoC arm (Figure 1). Incremental LY and QALY gains for axi-cel versus SoC were 1.34 and 1.37, respectively. The discounted incremental cost for axi-cel versus SoC was $119,055. Despite the higher upfront treatment costs with axi-cel, the high cost of 3L treatment in the SoC arm due to CAR T use was one key cost category that reduced the difference in cost between the two arms (axi-cel: $144,281; SoC: $373,162; difference: -$228,341). Incremental costs and QALY differences resulted in an ICER of $87,026/QALY versus SoC. At a willingness-to-pay threshold of $150,000/QALY, probabilistic sensitivity analysis demonstrated that axi-cel has a 72% probability of being cost-effective versus SoC.

Figure 1. Projected 5-Year Survival Outcomes for Axi-Cel and SoC

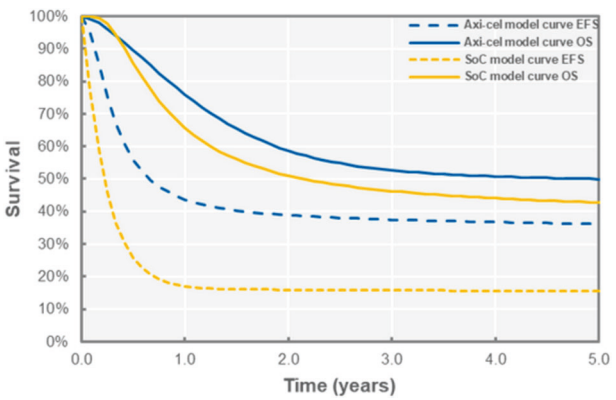


Table 1. Discounted Cost-Effectiveness Results

	LYs	Costs	QALYs
Axi-cel	9.14	$683,698	7.08
SoC	7.80	$564,642	5.71
Incremental	1.34	$119,055	1.37
Incremental cost effectiveness ratio, axi-cel vs. SoC			**$87,026**

Abbreviations: Axi-cel: axicabtagene ciloleucel; SoC, standard of care; LYs, life-years; QALYs, quality-adjusted life-years

Conclusions: Findings from this study suggest a sizable improvement in quality and length of life after axi-cel compared to SoC. While incremental costs are higher with 2L CAR T use, the offsets in 3L CAR T use lead to a limited incremental cost difference resulting in a highly cost-effective ICER by US standards. In addition to meaningfully improving key clinical endpoints, axi-cel is a cost-effective treatment option that can address an important unmet need.

Clinical Trial Registry: Not applicable

Disclosure: JTS, SV, and AP are employees and shareholders of Kite Pharmaceuticals.

FE, RB, and NS received consulting fees from Kite Pharmaceuticals.

MP: employment with Memorial Sloan Kettering Cancer Center; honoraria from AbbVie, Astellas, Bellicum, Celgene, Bristol Myers Squibb, Incyte, Karyopharm, Kite, a Gilead Company, Miltenyi Biotech, MorphoSys, Nektar Therapeutics, Novartis, Takeda, VectivBio AG and Vor Biopharma; consultancy or advisory role for Merck, Omeros, OrcaBio; research funding from Incyte, Kite, a Gilead Company, and Miltenyi; and other relationships with DSMB, Cidara Therapeutics, Medigene, Sellas Life Sciences and Servier.

JK: honoraria from Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, Gilead, Janssen, Karyopharm, Merck, Novartis, Roche, and Seattle Genetics; consultancy or advisory role for AbbVie, Bristol Myers Squibb, Gilead, Karyopharm, Merck, Roche, and Seattle Genetics; and research funding from Roche and Janssen.

PJ: nothing to disclose.

P057

Predicting grade 2-4 crs with the modified easix (measix) score in patients with nhl treated with anti cd19 car-t cells

E. Galli[1,2], A. Di Rocco[3], F. Sorà[1,2], F. Autore[1], M.A. Limongiello[1], I. Innocenti[1], S. Giammarco[1], E. Metafuni[1], U. La Rocca[3], W. Barberi[3], S. Pepe[3], M. Ansuinelli[3], L. Laurenti[1,2], A. Bacigalupo[1,2], P. Chiusolo[1,2], A.P. Iori[3], M. Martelli[3], S. Hohaus[1,2], S. Sica[1,2]

[1]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy, [2]Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Rome, Italy, [3]Dipartimento di Medicina Traslazionale e di Precisione, Università di Roma Sapienza, Rome, Italy

Background: Prediction and management of CAR-T cells specific toxicities, mainly cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS), represent a challenge for physicians. An emerging role is being assigned to the interaction between inflammation and endothelium. In the setting of allogeneic stem cells transplantation, Endothelial Activation and Stress Index (EASIX) can predict endothelial impairment and patients outcomes. We aimed to assess the predictive value of a modified EASIX (mEASIX) towards occurrence of CRS.

Methods: m-EASIX was calculated as described by Pennisi et al (BloodAdv 2021) as [CRP (mg/dL) x LDH (mg/dL)/ platelets count (109 cells/L)]; we applied log transformation using base 2 (log2) in order to reduce skewness. We retrospectively analyzed 33 patients with DLBCL/PMBL treated in the two adults CAR-T centers in Rome from 2019 to 2021 both with tisa-cel and axi-cel. mEASIX was assessed at baseline, and 2 and 4 days after CAR-T cells infusion. We then explored the role of procalcitonin and the ability of mEASIX to predict outcomes.

Results: Seven patients had no CRS, seven had a grade 1 CRS, while 19/33 (56%) patients had grade 2-3 CRS. Patients with grade 2-4 CRS had higher mEASIX at baseline (median -0.9 vs 4.5, $p > 0.001$) and at day 0, 2 and 4. In order to assess if mEASIX calculated on day 2 or 4 after CAR-T cells infusion could predict the development of a grade 2-4 CRS on the same day, we performed a ROC analysis and identified that mEASIX of 6.4 had 100% sensitivity and 71% specificity in predicting grade 2-4 CRS. An mEASIX of 6.4 or more at day 2 or 4 had associated with grade 2-4 CRS in 27% of cases during the same day (vs 2% among patients with mEASIX lower than 6.4, $p = 0.002$). Moreover, higher mEASIX during day 2 and 4 also predicted CRS 2-4 anytime during hospitalization. Procalcitonin (PCT) was not different in patients with CRS graded 0-1 vs 2-4 (0.16 vs 0.21 ng/ml, $p = 0.11$). However, patients with PCT > 0.5 ng/ml had higher mEASIX (median, 4,6 vs 7,8, $p = 0,001$).Patients with higher mEASIX (>6.4) were more likely to develop grade 3-4 cytopenia between day 30 and 90. Progression free survival was similar both for patients who experienced grade 0-1 vs 2-4 CRS ($p = 0.58$) and for patients with mEASIX higher or lower than 6.4 at any timepoint.

Conclusions: In this analysis, anyway, we confirmed that baseline mEASIX correlated with higher risk for developing grade 2-4 CRS. Nevertheless, patients with higher mEASIX had also higher procalcitonin, thus infectious etiology of hyperpyrexia still needs to be carefully investigated when CRS is suspected. With the limitations of our study, we were not able to confirm the correlation between mEASIX and ICANS and PFS as reported elsewhere. We identified a daily cut-off of mEASIX as able in forecasting the development of a CRS of grade 2-4; this information could alarm the physician and lead to intensified patients monitoring before severe CRS occurrence, possibly facilitating an immediate intervention.

Disclosure: Nothing to declare.

P058

Long-term (5 year) overall survival in zuma-1, the pivotal study of axicabtagene ciloleucel (axi-cel) in patients with refractory large b-cell lymphoma (LBCL)

C.A. Jacobson[1], F.L. Locke[2], A. Ghobadi[3], D.B. Miklos[4], L.J. Lekakis[5], O.O. Oluwole[6], Y. Lin[7], B.T. Hill[8], J.M. Timmerman[9], A. Deol[10], P.M. Reagan[11], P. Stiff[12], I.W. Flinn[13], U. Farooq[14], A.H. Goy[15], J. Muñoz[16], T. Siddiqi[17], R.R. Shen[18], A.A. Bot[18], J. Dong[18], K. Singh[18], C. Spooner[18], R. Karalliyadda[18], J.J. Kim[18], Y. Zheng[18], S.S. Neelapu[19]

[1]Dana-Farber Cancer Institute, Boston, United States, [2]Moffitt Cancer Center, Tampa, United States, [3]Washington University School of Medicine, St. Louis, United States, [4]Stanford University School of Medicine, Stanford, United States, [5]Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, United States, [6]Vanderbilt-Ingram Cancer Center, Nashville, United States, [7]Mayo Clinic, Rochester, United States, [8]Cleveland Clinic Foundation, Cleveland, United States, [9]UCLA David Geffen School of Medicine, Los Angeles, United States, [10]Karmanos Cancer Center, Wayne State

University, Detroit, United States, [11]University of Rochester School of Medicine, Rochester, United States, [12]Loyola University Chicago Stritch School of Medicine, Maywood, United States, [13]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, United States, [14]University of Iowa, Iowa City, United States, [15]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, United States, [16]Banner MD Anderson Cancer Center, Gilbert, United States, [17]City of Hope National Medical Center, Duarte, United States, [18]Kite, a Gilead Company, Santa Monica, United States, [19]The University of Texas MD Anderson Cancer Center, Houston, United States

Background: Axi-Axi-cel, an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, is approved for treatment of patients with relapsed/refractory LBCL with ≥2 prior therapies. In the 2-year analysis of ZUMA-1 (NCT02348216), the objective response rate (ORR) was 83%, with a 58% complete response (CR) rate (Locke et al. Lancet Oncol. 2019). After ≥4 years of follow-up, median OS was 25.8 months with a 4-year OS rate of 44% (Jacobson C, et al. ASH 2020. #1187). Event-free survival (EFS) has emerged as a robust surrogate of OS in hematologic cancers. Here we report updated survival results from phase 2 of ZUMA-1 after ≥5 years of follow-up, including an exploratory evaluation of the association of 5-year OS and EFS at 12 and 24 months.cel, an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, is approved for treatment of patients with relapsed/refractory LBCL with ≥2 prior therapies. In the 2-year analysis of ZUMA-1 (NCT02348216), the objective response rate (ORR) was 83%, with a 58% complete response (CR) rate (Locke et al. Lancet Oncol. 2019). After ≥4 years of follow-up, median OS was 25.8 months with a 4-year OS rate of 44% (Jacobson C, et al. ASH 2020. #1187). Event-free survival (EFS) has emerged as a robust surrogate of OS in hematologic cancers. Here we report updated survival results from phase 2 of ZUMA-1 after ≥5 years of follow-up, including an exploratory evaluation of the association of 5-year OS and EFS at 12 and 24 months.

Methods: After leukapheresis, eligible patients received conditioning chemotherapy followed by a target dose of 2×106 anti-CD19 CAR T cells/kg. The primary endpoint was ORR. Comparisons of OS by EFS, defined as the time from axi-cel infusion until progressive disease (PD), initiation of new lymphoma therapy (excluding stem cell transplant [SCT]), or death by any cause, were analyzed via Kaplan-Meier estimates.

Results: As of August 11, 2021, 101 patients received axi-cel with a median follow-up of 63.1 months. With ≥5 years of follow-up, median OS was 25.8 months with a 5-year OS rate of 42.6% (95% CI, 32.8-51.9). The median OS among complete responders was not reached (5-year OS rate, 64.4% [95% CI, 50.8-75.1]). Since the 4-year analysis, 1 death and 1 PD were observed. Median EFS was 5.7 months, with a 12-mo EFS rate of 42.8% (95% CI, 33.0-52.3) and a 24-mo EFS rate of 37.7% (95% CI, 28.3-47.2), respectively. In patients with an EFS event by Month 12 (EFS12; n = 57) versus without EFS12 (n = 44), 5-year OS rates were 5.3% (95% CI, 1.4-13.2) versus 90.9% (95% CI, 77.6-96.5), respectively. In patients with an EFS event by Month 24 (EFS24; n = 62) versus without EFS24 (n = 39), 5-year OS rates were 11.3% (95% CI, 5.0-20.5) versus 92.3% (95% CI, 78.0-97.5), respectively.

Since the 4-year analysis, there have been no new safety signals. Overall, 34 patients (34%) were still alive and received no subsequent therapy (excluding SCT) or axi-cel retreatment; median time to next therapy was 8.7 months, as previously reported. Of treated patients, 59 (58%) have died, primarily due to PD (45%; n = 45), followed by other reasons (9%; n = 9), adverse events (4%; n = 4), and secondary malignancy unrelated to axi-cel (1%; n = 1).

Median peak CAR T-cell levels were numerically higher in patients with ongoing response at Month 60 and were considerably lower in patients who relapsed and nonresponders. A similar trend was observed with CAR T-cell expansion by area under the curve from Day 0 to 28.

Conclusions: In this long-term survival analysis of ZUMA-1 with ≥5 years of follow-up, axi-cel induced long-term OS with no new safety signals. Axi-cel demonstrated longer OS in patients without EFS12 and EFS24 versus patients with events at these timepoints. These data potentially support EFS as a surrogate endpoint for long-term OS in refractory LBCL.

Clinical Trial Registry: Clinical Trial Registry: NCT02348216 https://clinicaltrials.gov/ct2/show/NCT02348216

Disclosure: Caron A. Jacobson: honoraria from Kite, a Gilead Company, Celgene, Novartis, Bluebird bio, Epizyme, Humanigen, Pfizer, Precision BioSciences, Nkarta, Lonza, and AbbVie; consultancy or advisory role for Kite, a Gilead Company, Celgene, Novartis, Pfizer, Humanigen, Precision BioSciences, Nkarta, Bluebird bio, Lonza, Pfizer, Ispen and AbbVie; speakers' bureau participation for Axis and Clinical Care Options; research funding from Pfizer; and travel support from Kite, a Gilead Company, Celgene, Novartis, Precision Biosciences, Lonza, Pfizer, and Humanigen.

P059

Outcome after relapse post cd19 car t-cells in children and young adults with relapsed/refractory b-cell precursor acute lymphoblastic leukemia (R/R B-ALL)

A. Alonso-Saladrigues[1], A. Faura Morros[1], A. Català Temprano[1,2,3], S. Pont Martí[1,4,3], E. García Rey[1], M. Camós Guijosa[1,2,3], J.L. Dapena Diaz[1], N. Conde Cuevas[1], I.M. Isola[1], N. Vega-García[3,4], E. Esperanza-Cebollada[4,3], I. Jordan García[1], S. Bobillo Perez[1], L. Alsina-Manrique[1], A. Deyá[1], C. Rivera-Pérez[1], J. Marsal[1], J. Vinent-Genestar[1], C. Llanos Principe[5], G. Pedrals Portabella[1], G. Morón-Cazalilla[1], M. Juan[6,7], M. Torrebadell[4,3,2], S. Rives[1,3,2]

[1]Hospital Sant Joan de Déu, Esplugues de Llobregat, Spain, [2]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER). Instituto de Salud Carlos III, Madrid, Spain, [3]Leukemia and other Pediatric Hemopathies, Developmental Tumors Biology Group. Institut de Recerca Hospital Sant Joan de Déu, Esplugues de Llobregat, Spain, [4]Hematology Laboratory. Hospital Sant Joan de Déu, Esplugues de Llobregat, Spain, [5]Fundació Sant Joan de Déu, Esplugues de Llobregat, Spain, [6]Hospital Clínic, Barcelona, Spain, [7]Plataforma Inmunoteràpia SJD-Clínic, Esplugues de Llobregat, Spain

Background: CAR-T therapy has improved the outcome of pediatric patients with R/R B-ALL. However, about half of them (41-51%) relapse. There is scarce information about treatment and prognosis in patients relapsing after CAR-T.

The aim of the study is to describe the type of relapse, management and outcome in pediatric and young adults patients with R/R B-ALL relapsing CD19 CAR T-cells.

Methods: We analyzed a cohort of consecutive patients under 25 years relapsing after CAR19 T-cells in a single center from Jan-2016 to Nov-2021.

Results: Fifty-six patients were infused (Tisagenlecleucel: n = 39, ARI_0001-cells: n = 17) and 51 (91%) achieved complete remission (CR) with negative measurable residual disease. Twenty-one (42%) relapsed at a median of 8.9mo (range:2.2-28.4), 5 beyond 1 year. Thirteen patients (62%) had CD19- relapses, all in bone marrow (BM); median 4.9mo (range:2.2-18.6). Eight patients had CD19 + relapses, median 15.1mo (range:3.0-28.4); 3/8 in BM, 2 combined (BM and CNS) and 3 isolated extramedullary disease (EMD) (testes, breast, subcutaneous). All patients with CD19- relapses had persistent B-cell aplasia (BCA) whereas among

CD19 + relapses all except two with isolated EMD had lost BCA before relapse. With a median follow-up of 28.6mo, the cumulative incidence of relapse at 24mo was 30.7%(19.5-46.4)

Regarding treatment and outcome of patients relapsing after CAR T-cells (Table1), 3 patients relapsing <1mo from data cut-off were excluded. Among 18 relapsed patients, 8 died from progressive disease (PD). Ten patients achieved a subsequent CR (5 with inotuzumab, 3 with chemotherapy and 2 with blinatumomab). Two died from PD; 7/10 were bridged to HSCT. Three died from transplant-related mortality (TRM). Only 5 patients remained in CR at the data cut-off, 4/5 bridged to transplant. Of these, 2 are in remission >1 year after HSCT and 2 patients are <3 months since HSCT.

Reinfusion with CAR19 T-cells was performed in 3 patients (CD19 + relapses) and was unsuccessful. Two achieved CR with blinatumomab after reinfusion failure.

Five patients are alive with disease: 2 patients with CD19- relapse with a follow-up since relapse <1 month and 3 CD19 + with 1, 2, and 11mo of follow-up, respectively.

Relapsed patients ($n = 21$)	**CD19- relapse ($n = 13$)**	**CD19 + relapse ($n = 8$)**
Female	7	2
Age at infusion (years)	7 (1-24)	9 (5-18)
Prior EMD	5	5
Prior HSCT/Inotuzumab/ Blinatumomab	8/1/1	6/0/0
TREATMENT AND OUTCOME AFTER RELAPSE		
Inotuzumab/Blinatumomab/ Reinfusion	6[a]/0/0	0/2[b]/3[c]
Chemotherapy/Palliative	3[d]/1	2[e]/1
HSCT after CR	4 (3 alive in CR)	3 (alive in CR)

[a]1 patient discontinued inotuzumab and died from PD, 5 achieved CR, 4 were bridged to HSCT, one died from TRM and 3 are alive in CR (28, 3 and 0.5 months after HSCT). [b]Both achieved CR, one was bridged to 2nd HSCT and died from TRM, in the other a 2nd HSCT is planned. [c]Reinfusion was unsuccessful in the 3 patients.[d]One achieved CR and was bridged to HSCT (<1 mo after SCT at data cut-off). [e]Both achieved CR, 1 died from TRM, 1 is alive in CR 27months after HSCT.

Conclusions: The outcome of patients who relapse after CART19 therapy is very poor and therapeutic options are scarce. Although CR can be achieved in some patients with inotuzumab or blinatumomab (CD22 + and CD19 + disease, respectively) consolidation with HSCT treatment is needed and long-term remission is very rare.

Clinical Trial Registry: CTL019: EudraCT 2013-003205-25/ EudraCT 2016-001991-31 and approved tisagenlecleucel; ARI-0001 cells EudraCT 2016-002972-29

Disclosure: A.A.S: consultant or advisory role (Novartis), travel grants (Novartis),

S.R.: consultant or advisory role (Novartis, Jazz-Pharma, Shire/ Servier, Amgen, Cellectis, Celgene/Bristol Myers Squibb), travel grants (Novartis, Jazz-Pharma, Shire/Servier, Amgen, Celge), honoraria (Novartis, Jazz-Pharma, Celgene, Shire/Servier, Amgen),

A.C.: consultant or advisory role (Novartis, Celgene), travel grants (Novartis, Celgene), honoraria (Novartis,Celgene).

M-T: consultant or advisory role (Novartis), travel grants (Novartis), honoraria (Shire/Servier),

M.J.: Consultant role at Grifols in 2018.

P060

A glimpse of clinical & laboratory features of carhlh syndrome in patients receiving bcma car-t cells

C. Zu[1], K. Wang[1], Q. Zhang[1], F. Ni[1], L. Zhou[1], M. Zhang[1], A.H. Chang[2], Y. Zhang[2], J. Cui[1], Y. Hu[1], H. Huang[1]

[1]the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China, [2]Shanghai Yake Biotechnology, Ltd., Shanghai, China

Background: CAR-T cell therapy has been one of the most arresting immunotherapies in the treatment of cancers. With its widening application, a number of characteristic toxicities have also been identified, and amongst them is an increasingly recognized severe toxicity resembling hemophagocytic lymphohistiocytosis (carHLH).

Methods: We retrospectively identified and profiled patients who developed carHLH following BCMA CAR-T therapy in our center. For this work, the diagnostic criteria of carHLH proposed by Neelapu et al were adopted. Patients received CAR-T therapy were then divided into 3 groups: patients developed CRS and carHLH (carHLH group), patients developed grade ≥ 3 CRS alone (severe CRS group), and patients developed grade ≤ 2 CRS or no CRS (mild/no CRS group). And factors associated with or predictive of carHLH were explored.

Results: Amongst 99 patients treated with BCMA CAR-T cells, a considerable portion (20.2%) have developed carHLH. In the context of CRS (96 patients), we report a carHLH rate of 20.8% (21 patients). Preliminary cytokine profiling revealed a cytokine storm partially resembles that of severe CRS (e.g., elevated levels of IL-4 and IL-6), but significant elevation in the peak levels of IFN-γ and IL-10 were found in carHLH group in comparison to severe CRS group, indicating a different cytokine network lying under the development of carHLH. Thus, further investigation using a broadened panel is being conducted, and the results are still incomplete. Coagulopathy has been proposed to be one of the manifestations of carHLH, but our analysis of related biomarkers showed only a decrease in fibrinogen with a potential risk to bleed, which might alternatively relate to liver injury.Regarding baseline characteristics, disease burden is a prominent factor associated with the development of carHLH (median: 11.04% in carHLH group vs. 1.495% in severe CRS and mild/no CRS groups together). In addition, we found that baseline T:NK ratio in peripheral blood was negatively related to the development of carHLH, the patients who experienced carHLH had a lower T:NK ratio at the baseline (median: 2.8422 in carHLH group vs. 5.894 in severe CRS and mild/no CRS groups together), which is the opposite of one of the previous carHLH study in the context of anti-CD22 CAR-T. Whether this was a coincidence or this represented different features of carHLH following CAR-T therapies of different targets need more investigations to elucidate.

Conclusions: Although for now, we generally believe that carHLH develops on the basis of CRS, but additional pathophysiological mechanisms, apart from the shared ones, definitely play a role in the evolution between these inflammatory syndromes. And in view of the life-threatening complications which CarHLH can be associated with, it's imperative to establish precise recognition and proper management of carHLH. Both require more detailed description of carHLH in different contexts.

Clinical Trial Registry: NCT03716856

Disclosure: The research was funded by the National Natural Science Foundation of China (grant No. 81730008, 81770201, He Huang), Key Project of Science and Technology Department of Zhejiang Province (grant No. 2019C03016, 2018C03016-2, He Huang), and Key R&D Project of Zhejiang Science and Technology Department (grant No. 2020C03G201358, He Huang). The authors declare no other potential conflict of interest.

P061

Cytokine scoring system can effectively evaluate the severity of crs after cart

H. Wang[1], D. Wang[1], M. Chen[1], L. Qiu[1], X. Li[1], S. Fu[1]

[1]Hebei Yanda Lu Daopei Hospital, Langfang, China

Background: Cytokine detection is an important basis for evaluating Cytokine Release Syndrome (CRS). To study the role of cytokines in CRS evaluation and to make a rapid and simple quantitative scoring system, we conducted this study.

Methods: From March 2020 to February 2021, 111 patients with refractory relapsed B-ALL were treated with CD19-CAR T at Hebei Yanda Lu Daopei Hospital. Blood samples were collected after CART treatment D0, D4, D7, D14, D21 and D28.the concentrations of 24 serum cytokines were detected by flow cytometry: IFNγ, IL-1β, IL-2, IL-6, IL-10, IL-12p70, TNFα, TNFβ, IL-4, IL-5, IL-8, IL-17A, IL-17F, IL-22, IL-2RA, MCP-1, MIP-1α, GM-CSF, IL-15, GranzymeB, REG3a, ST-2, TNFRI, and Elafin. The integral formula was made according to the test values of 34 cases, and the test values of the other 77 cases were calculated by the formula.

Results: The changes of IL-1β, IL-2, IL-6, IL-10, IL-17F, GM-CSF, ST-2, TNFRI, REG3a and IFN-γ were statistically different at different time points (all $P < 0.05$). D7-d10 was the peak, and D28 basically returned to normal, which was consistent with the clinical manifestations of the patients, the proportion and cell number of CAR T cells, CD3 + T cells and CD8 + T cells in peripheral blood. It can also distinguish different levels of CRS. The scoring formula $= \sum \beta i * Si$, where βi refers to the weight of the ith cytokine; Si refers to the score of the ith cytokine. The score of the ith cytokine is determined according to whether the peak level of the ith cytokine exceeds 3 times of the base value. The 34 patients with different CRS grades were randomly selected, and the weight of each cytokine was found to be: IFN-γ, IL-2, IL-6, IL-10, ST-2, IL-8, and GM-CSF was 2 points. The weight of IL-2RA, IL-17F, REG3a, IL-1β, McP-1 and TNFRI was 1 point. The weight of IL-4, IL-5, IL-22, IL-15 and IL-12P70 was 0.5 points; The weight of Elafin, TNFα and Granzyme B was -1 point. If the score is ≤8, belongs to CRS 0-1; if > 8, < 18, CRS 2; if ≥18, CRS 3-4. Tested in the other 77 patients, the sensitivity was 89.61%, the specificity was 96%, the positive predictive value was 95.83%, and the negative predictive value was 90%. In particular, the sensitivity was 91.55%, the specificity was 99%, the positive predictive value was 98.48%, and the negative predictive value was 92% in the identification of patients with grade 0-1.

Conclusions: The evaluation method of immune status after treatment of CART obtained in this study provides an effective tool for simple, scientific and rapid evaluation of high information data, especially for objective judgment and early detection of CRS.

Disclosure: Nothing to declare

P062

Cytomegalovirus impact in b-cell lymphoma patients treated with chimeric antigen receptor t-cell therapy

E. Marquez-Algaba[1], B. Pernas[2], J. Esperalba[1], I. Los-Arcos[1], C. Carpio[1], G. Iacoboni[1], P. Barba[1], I. Ruiz-Camps[1]

[1]Vall d'Hebron University Hospital, Barcelona, Spain, [2]University Hospital of A Coruña, A Coruña, Spain

Background: CD19-directed chimeric antigen receptor (CAR) T-cell has revolutionized the treatment paradigm of relapsed/refractory B-cell Non-Hokdgkin's lymphoma (B-NHL). Bacterial and fungal infections have been well described, but many questions remain unanswered regarding the role of cytomegalovirus (CMV) in this setting. We studied the incidence and risk factors associated to CMV reactivation and CMV disease.

Methods: We retrospectively reviewed the consecutive CMV viral load determinations of B-NHL treated with CAR T-cells from July 2018 to September 2021. CMV-seronegative patients, and previous allogeneic stem cell transplant recipients were excluded. Significant CMV viral load was defined as higher than 1000 IU/mL.

Results: Overall, 98 patients met the inclusion criteria. Median age was 61 years (IQR 53-68), and 63 were men (64.3%). Median number of previous therapeutic lines was 2 (IQR 2-3). All patients had a clinical follow-up of 2 months, and 83 patients had at least 3 CMV viral load determinations during the first 2 months after CAR-T treatment.

Among patients who fulfilled the inclusion criteria, 44 (44.9%) had at least one positive CMV determination in peripheral blood. Of them, 24 patients (24.5%) had a significant CMV viral load (CMV > 1000), and in 7 patients it was greater than 10000 UI/mL (Log > 4). Six patients were excluded from the analysis for presenting CMV reactivation before receiving CAR-T therapy. Median time from treatment to reactivation was 18 days (IQR 7-15.5), and the median duration of viremia was 8 days (IQR 5-24).

Baseline variables as age, median number of previous lines, median number of CD3 cell count, ferritin levels, or D-dimer levels before lymphodepleting chemotherapy were not related with CMV > 1000.

The only independent risk factor associated with a higher risk of CMV > 1000 was having received dexamethasone and/or tocilizumab within the first month (72.2% vs. 27.8%; adjusted OR 3.07 [IC 95% (1.2-8.0) $p = 0.021$]. No relationship was observed with hypogammaglobulinemia, or the product administered. The median lymphocyte count in the moment of reactivation was 0.5 x 10^9/L (IQR 0.2-0.6 x 10^9/L).

No patient had evidence of CMV disease, and only the patients with viral load superior to 10000 UI/mL received treatment with ganciclovir or valganciclovir. Of these, one presented valganciclovir-induced neutropenia.

Conclusions: CMV monitoring can be useful during the first 2 months after CAR T-cell therapy, especially in those receiving dexamethasone and/or tocilizumab. CMV replication has doubtful clinical significance in this setting, so treatment should be carefully individualized assessing risk-benefit in terms of toxicity.

Disclosure: We declare no conflict of interest. This study was not funded.

P063

Autologous stem cell transplantation induces an higher percentage of exhausted t-cells in dlbcl patients before leukapheresis for car-t cells. Do we need timely leukapheresis strategies?

M. Farina[1], M. Chiarini[2], A. Beghin[3], A. Leoni[1], E. Accorsi Buttini[1], K. Bosio[1,4], F. Colnaghi[1], I. Volonghi[5], L. Poli[5], C. Almici[6], E. Ferrari[6], M.L. Sala[6], A. Bianchetti[6], D. Moratto[2], S. Bernardi[1,4], N. Polverelli[1], A. Turra[1], E. Morello[1], D. Brugnoni[2], F. Porta[7], A. Lanfranchi[3], A. Re[8], M. Malagola[1], D. Russo[1]

[1]Unit of Blood Diseases and Bone Marrow Transplantation, Cell Therapies and Hematology Research Program, University of Brescia,

ASST Spedali Civili di Brescia, Brescia, Italy, [2]Flow Cytometry Unit, Section of Hematology and Blood Coagulation, Clinical Chemistry Laboratory, ASST Spedali Civili di Brescia, Brescia, Italy, [3]Stem Cell Laboratory, Section of Hematology and Blood Coagulation, Clinical Chemistry Laboratory, ASST Spedali Civili di Brescia, Brescia, Italy, [4]Research Center Ail (CREA) - ASST Spedali Civili di Brescia, Brescia, Italy, [5]U.O.C. Neurology, Center for Neuromuscular Diseases, University of Brescia, ASST Spedali Civili di Brescia, Brescia, Italy, [6]Laboratory for Stem Cells Manipulation and Cryopreservation, ASST Spedali Civili di Brescia, Brescia, Italy, [7]UO Pediatric OncoHematology, ASST Spedali Civili di Brescia, Brescia, Italy, [8]UOC Hematology, ASST Spedali Civili di Brescia, Brescia, Italy

Background: CAR-T cells therapy is an highly effective third line salvage treatment in relapsed/refractory diffuse large B-cell lymphomas (DLBCL), primary mediastinal B-cell lymphomas (PMBCL) and Acute Lymphoblastic Leukemia (ALL), but up to 60% of patients still relapse. CAR-T cells generated from "exhausted" T-lymphocyte (Ly) have been correlate with a worse response. In this prospective study, we assessed the fitness of pre-apheresis Ly for evaluating the impact of previous treatments on the T-cells repertoire.

Methods: From January 2021, Ly-subsets were evaluated at the time of leukapheresis in 13 patients: 11 DLBCL, 1 PMBCL and 1 ALL. Since cryopreservation of the apheresed Ly is allowed for Kymriah, 8 DLBCL patients were enrolled in a "pre-emptive" Ly-apheresis program, scheduling leukapheresis as soon as possible in patients selected for the following poor prognostic risk factors: refractory to first line of treatment; PET positivity before ASCT; first complete response less than 12 months.

Combinations of monoclonal antibodies directed against CD45RA, CCR7, CD3, CD4, and CD8 were used by Flow Cytometry to evaluate the following CD4 + /CD8 + T-ly subsets: T-naïve (CD45RA + CCR7 +); T-central memory (CD45RA-CCR7 +); T-effector memory (CD45RA-CCR7-); T-terminally differentiated (CD45RA + CCR7-). All stained samples were acquired on a Canto II (BD Bioscience) flow cytometer and analyzed using DIVA software version 8.0.2. Continuous variables were compared using Mann-Whitney test.

Results: Table1 shows the main patients' clinical characteristics. Mainly, 8/11 High-Risk DLCBL patients received one line treatment (R-DAEPOCH or R-CHOP), including ASCT according to the Centre policy. Only ASCT had a significative impact on Ly-subsets distribution. In particular, in patients who had not previously received ASCT, CD4/CD8 ratio, percentage of CD4-naïve and CD8-naïve were significantly higher ($p = 0,04$; $p = 0.006$ and $p = 0.012$, respectively). The effects of ASCT on Ly-subsets distribution were detected even after one year from ASCT. No other significant differences were found between patients who received previously ASCT or not, except for age (66 [57-70] vs. 49 [29-59], $p = 0.01$). Patients with ALL or PMBCL had few circulating naïve T-cells, similarly to the patients who underwent ASCT before leukapheresis.

Table1

	Results (range)
Patients	13
Median age (ys)	61 (29-70)
Male/Female	3/8
Disease	
• *DLBCL*	*11*
• *PMBCL*	*1*
• *ALL*	*1*
High/Inter-High IPI score DLBCL	6
Status disease at leukapheresis:	
• *Refractory/relapse*	7
• *Complete/partial response*	6
ASCT before leukapheresis	7
CAR-T cells infused	7

Conclusions: Previous ASCT in DLBCL patients can result in a significant more percentage of "exhausted" T-Ly at the time of leukapheresis. This may lead to an higher percentage of "exhausted" CAR-T cells and, potentially, to their reduced efficacy. In patients at higher risk of relapse after ASCT a "pre-emptive" leukapheresis should be considered a timely clinical option to cryopreserve more "fit" T-Ly to be sent for manufacturing in case of relapse.

Disclosure: Nothing to declare

P064

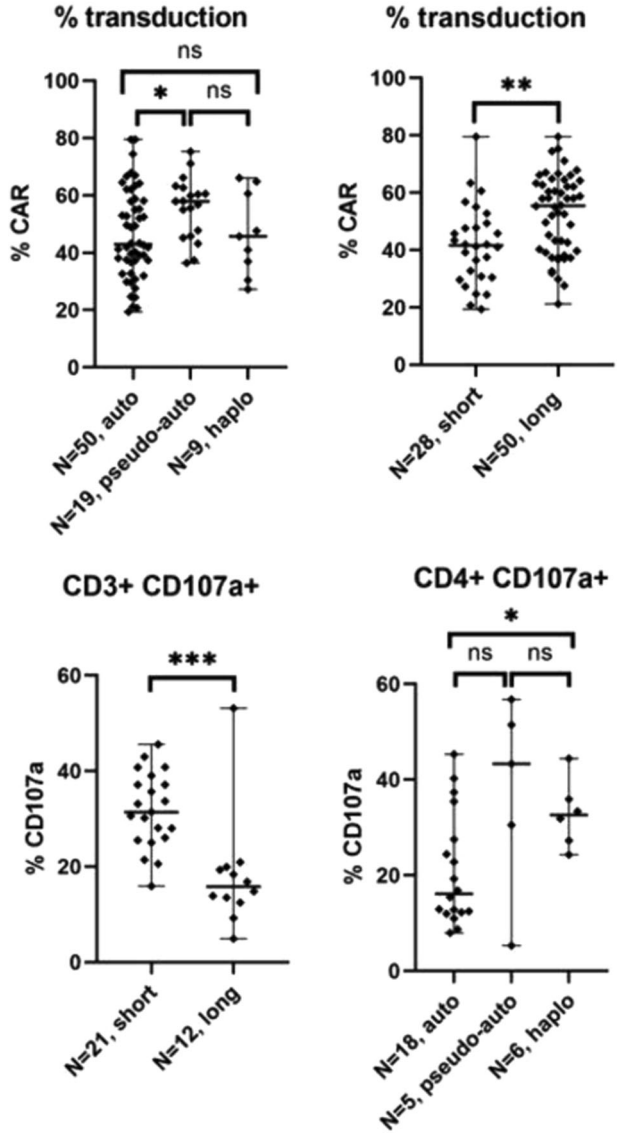
Characterization of cd19car-t cells produced with the clinimacs prodigy® platform: Effects of production cycle length and clinical history of the donor with regard to HSCT

E. Malakhova[1], D. Pershin[1], E. Kulakovskaya[1], V. Vedmedskaya[1], M. Fadeeva[1], T. Sozonova[1], S. Glushkova[1], A. Kazachenok[1], Y. Muzalevskii[1], G. Novichkova[1], M. Maschan[1]

[1]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation

Background: Chimeric antigen receptor (CAR) T cells targeting CD19 antigen provide a highly effective immunotherapy for B cell malignancies. The anti-tumor effect depends on high proliferative and cytotoxic activity of CAR T cells, hence the importance of proper in vitro assessment of the CAR T cell functionalities. This study compares functional properties of CD19 CAR T cells obtained from patients without a history of HSCT vs. HSCT recipients vs. healthy donors, and CAR-T manufactured with either a short (7 day) or long (11 day) protocol.

Methods: The study enrolled patients with relapsed/refractory B cell acute lymphoblastic leukemia who met inclusion criteria for the clinical protocol at the Dmitry Rogachev National Medical Research Center of pediatric hematology, oncology and immunology. A total of 78 cell products were derived from patients who never received HSCT ('auto', $n = 50$), patients who received HSCT within 4 to 24 months before ('pseudo-auto', $n = 19$), or haploidentical healthy donors ('haplo', $n = 9$). The production was performed based on the automated CliniMACS Prodigy® system with the full cycle lasting 11 days ($n = 50$) or 7 days ($n = 28$). The lentiviral vector transduction efficiency was determined for all CAR T cell products by direct staining. Functional testing of the final CAR T cell products included degranulation assay (measuring CD107a externalization by CD4 + and CD8 + lymphocytes, $n = 33$) and TNFα and IFNγ secretion assay upon incubation with the target cell line JeKo-1 ($n = 41$). The flow cytometry measurements were based on the customary surface and intracellular staining protocols with commercially available antibodies. Cytotoxicity of CAR T cells towards the target cell line JeKo-1 was assessed using the Incucyte® Live-Cell Analysis system.



Results: T lymphocytes from pseudo-autologous donors were transduced with lentiviral vectors more efficiently than the cells from autologous donors. Besides, the longer 11-day manufacturing afforded significantly higher transduction efficiency than the shorter 7-day cycles. On the other hand, CAR T cells manufactured over 7-day process showed higher rates of degranulation than the 11-day cycle products. CD 4+ CAR T cells from haploidentical donors showed a higher level of degranulation compared to autologous donors. The rates of cytokine production and cytotoxic activity of CAR T cells were similar in all groups ($p > 0.05$).

Conclusions: The established protocol affords a stable cell product with high anti-tumor activity and functional properties largely independent of clinical history of the donor. Moreover, CAR T cells produced in an expedite time-frame of 7 days exhibit the same (and in certain aspects even higher) anti-tumor activity as the cells obtained in 11-day production cycles. For patients with rapid progression, reduction of the waiting time between apheresis and CAR T cell infusion to 7 days may be vital.

Disclosure: Nothing to declare

P065

Dynamics of car-t cells therapy associated cytopenias: A single-center experience

R.M. Martin-Rojas[1], R. Bailén[1,2], G. Oarbeascoa[1,2], M. Bastos-Oreiro[1,2], I. Gómez-Centurión[1,2], P. Fernández-Caldas[1,2], D. Conde-Royo[1,2], C. Muñoz[1,2], S. Sabell[1,2], J. Anguita[1,2,3], J.L. Díez-Martín[1,2,3], M. Kwon[1,2]

[1]*Hospital General Universitario Gregorio Marañon, Madrid, Spain,* [2]*Gregorio Marañon Health Research Institute, Madrid, Spain,* [3]*Universidad Complutense de Madrid, Madrid, Spain*

Background: CAR-T cell therapy is approved for adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) or primary mediastinal lymphoma (PML) after two or more lines of therapy. Prolonged cytopenias have been reported in 30-60% of patients undergoing CAR-T cell therapy, but information about its dynamics and etiology is scarce.

Methods: We conducted a retrospective study of consecutive patients with a DLBCL or PML undergoing commercial CAR-T cell therapy in our center between June 2019 and September 2021. We analyzed blood cell counts pre-lymphodepletion and during hospitalization. This information was correlated with clinical and analytical parameters.

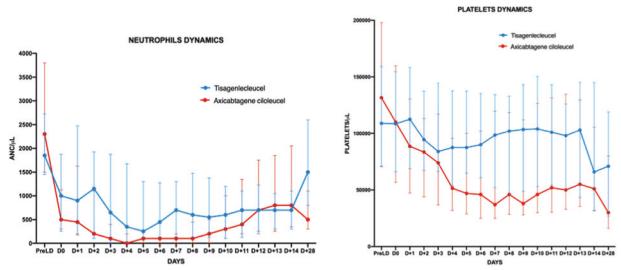
Results: 54 patients were included. Median age was 58 years (range 22-79). 34 patients (63%) were treated with Axicabtagene ciloleucel (Axi-cel).Patients had received a median of 2 prior lines of therapy (range 2-6) and 35.2% had undergone a previous HSCT. 47 patients (87%) received bridging therapy **(Table 1)**.

TABLE 1. PATIENTS GENERAL CHARACTERISTICS

	Axi-cel (n = 34)	Tisa-cel (n = 20)	p
Age, median (range)	57.5 (22-79)	62.5 (35-75)	0.154
Sex, female (%)	19 (55.8%)	7 (35%)	0.138
DLBCL, n (%)	27 (79.41%)	16 (80%)	0.505
Bone marrow infiltration at diagnosis, n (%)	5 (14.7%)	3 (15%)	0.977
Previous transplantation, n (%)	10 (29.4%)	9 (45%)	0.247
Prior lines, median (range)	2 (2-5)	2 (2-6)	0.692
Bridging Therapy, n (%)	31 (91.2%)	16 (80%)	0.238
CRS, n (%)	31 (91.2%)	16 (80%)	0.238
ICANS, n (%)	15 (44.1%)	3 (15%)	0.055

Median hospitalization was 23 days (range 11-87) and 47 patients (87%) showed profound neutropenia (ANC ≤ 500/μL), lasting >7 days in 42 patients (77.8%). 28 patients (51.9%) showed profound thrombocytopenia (≤50000/ μL) and 31 (57.4%) anemia (≤8g/dL). Cytopenias during hospitalization were more frequent with Axi-cel, with higher rates of neutropenia (97% vs 70%; $p = 0.004$), thrombocytopenia (61.7% vs 35%; $p = 0.05$) and prolonged cytopenias (90.9% vs 60%; $p = 0.007$, **Figure 1)**.

FIGURE 1. CYTOPENIAS DURING HOSPITALIZATION



On day +28 post CAR-T, 28 patients (56%) showed persistent cytopenias: 3 (6%) neutropenia, 9 (18%) thrombocytopenia and 16 (32%) both, with higher rates of cytopenias at day +28 with Axi-cel (36.8% vs 67.7%; $p = 0.03$).

Cytopenias during hospitalization were related to treatment with Axi-cel ($p = 0.004$) and bridging therapy ($p < 0.001$), while its prolonged duration was associated with Axi-cel ($p = 0.007$), bridging therapy ($p = 0.011$) and progressive disease ($p = 0.05$). Cytopenias on day +28 were related to Axi-cel ($p = 0.03$), bridging therapy ($p = 0.03$), higher ferritin levels ($p = 0.01$), CRS ($p = 0.003$) and ICANS ($p = 0.05$).

A multivariate analysis using logistic regression showed that bridging therapy (OR 25.4; 95% CI 2.2-29.1; $p = 0.009$) and treatment with Axi-cel (OR 17.9; 95% CI 1.3-24.7; $p = 0.03$) were independent predictors for profound cytopenias during hospitalization, while no independent predictor was found for its duration nor for day +28 cytopenias.

Conclusions: Profound cytopenias were frequent in our cohort, with up to 87% of cases during hospitalization and 56% on day +28, being bridging therapy and use of Axi-cel independent predictors for its development. Improving the knowledge on these cytopenias can contribute to a better outpatient management.

Disclosure: Nothing to declare

P066

CD19-specific car-t cells for the treatment of cns chloromas in children with relapsed/refractory b-cell acute lymphoblastic leukemia

S. Shahid[1], M. Cancio[1], S.S. Haque[1], Y. Khakoo[1], E. McWilliams[1], B.D. Santomasso[1], A. Scaradavou[1], B. Spitzer[1], S.L. Wolden[1], J.J. Boelens[1], K.J. Curran[1]

[1]Memorial Sloan Kettering Cancer Center, New York, United States

Background: Chimeric antigen receptor (CAR)-T cell therapy has revolutionized the treatment paradigm for children with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL). Effective treatment of extramedullary central nervous system (CNS) B-ALL with CAR-T cells has been reported, however little is known about the effectiveness of CAR-T cells for bulky CNS disease. While CNS chloromas are an extremely rare presentation of R/R B-ALL, they have been reported, are difficult to treat in heavily pre-treated patients, and are associated with poor outcomes. Herein, we report the effectiveness and safety of CD19-directed CAR-T cell consolidation with tisagenlecleucel in two pediatric patients with B-ALL CNS chloromas.

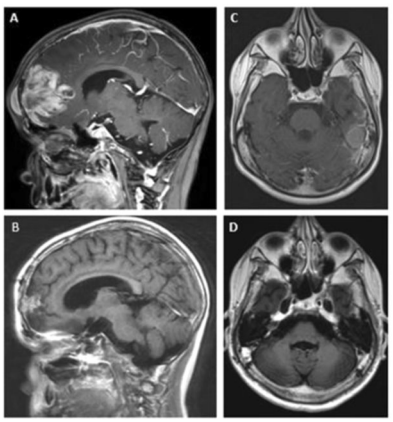
Methods: Medical records of 2 pediatric patients with R/R pre-B-ALL treated with tisagenlecleucel for CNS chloromas at MSKCC were reviewed. Clinical course, treatment, and outcomes are discussed here. Additionally, all pediatric patients who received tisagenlecleucel from 2018-2021 at MSKCC were evaluated based on CNS disease (spinal fluid flow cytometry/cytology and/or presence of chloroma) at time of treatment to evaluate toxicities and clinical outcomes.

Results: Patient 1 was diagnosed with standard-risk pre-B-ALL (CNS1) at age 5. She had 2 isolated CNS relapses followed by a concurrent medullary and CNS relapse, which was treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT) and post-transplant intrathecal chemotherapy for CNS prophylaxis. Sixteen months after allo-HSCT, she was found to have a CNS chloroma with a concurrent medullary relapse. She underwent subtotal surgical resection of the chloroma, focal proton radiation (2400cGy), and bridging chemotherapy (vincristine/mercaptopurine) followed by tisagenlecleucel. She experienced minimal toxicities: grade I cytokine release syndrome (CRS) and grade II immune effector cell-associated neurotoxicity syndrome (ICANS) requiring 2 doses of dexamethasone. She achieved a complete response (CR) at 1-month after tisagenlecleucel with a negative brain MRI, and she maintained disease control for 6 months. She developed an isolated CNS2 relapse 6 months post-treatment, responded to a second infusion of tisagenlecleucel with no toxicities, and is now undergoing a second allo-HSCT.

Patient 2 was diagnosed with standard-risk pre-B-ALL (CNS1) at age 3. Fourteen years after initial diagnosis, he had a late isolated CNS relapse. He subsequently had a second isolated CNS relapse 3.5 years later followed 2 years later by a third isolated CNS relapse. Fourteen months after his third relapse, brain MRI revealed a CNS chloroma, which was treated with surgical resection, focal proton radiation (2400cGy), and then tisagenlecleucel. He experienced minimal toxicities: grade I CRS and no ICANS. He achieved a CR at 1-month after CAR-T cell treatment. Thirteen months later, he has maintained no evidence of disease.

Upon further review of all pediatric patients treated with tisagenlecleucel at MSKCC ($n = 20$), 30% ($n = 6$) had CNS disease at time of tisagenlecleucel treatment, of which 33% ($n = 2$) developed ICANS (both grade II), 33% ($n = 2$) relapsed after treatment, and 83% ($n = 5$) remain alive to date.

Figure 1: Representative brain MRI images from patient 1 at CNS chloroma diagnosis (Panel A) and 1 month after CAR-T cell infusion (Panel B) and patient 2 at CNS chloroma diagnosis (Panel C) and 1 month after CAR-T cell infusion (Panel D).



Conclusions: Two pediatric patients with R/R B-ALL with CNS chloromas were successfully treated with tisagenlecleucel, both achieving a CR at 1-month post-treatment. Both patients had minimal treatment-associated CNS toxicities. Our experience highlights consideration of CD19-directed CAR-T cell therapy in pediatric patients with CNS chloromas.

Disclosure:

Boelens, Jaap J. discloses consulting or advisory roles (Avrobio; Advanced Clinical; Bluerock; Omeros; Race Oncology; Sanofi; Equillium; Medexus; Sobi). Curran, Kevin J. discloses consulting or advisory role (Novartis; Mesoblast) and research funding (Juno Therapeutics; Novartis; Celegene; Cellectis). The remaining authors have no conflicts of interest to declare relevant to this abstract.

P067

Early lymphocyte collection for cart production in patients with relapsed/refractory diffuse large b cell lymphoma improves t cell parameters

S. Grisariu[1,2], T. Sharon[1], B. Avni[1,2], M. Assayag[1], A. Bitansky Kremer[1], N. Goldschmidt[1,2], N. Asherie[1], S. Kfir-Erenfeld[1], M. E.Gatt[1,2], P. Stepensky[1,2]

[1]Hadassah University Hospital, Jerusalem, Israel, [2]The Hebrew University of Jerusalem, Jerusalem, Israel

Background: The majority of patients with diffuse large B cell lymphoma (DLBCL) undergoing adoptive transfer of CD19-directed CAR T cells have been exposed to multiple rounds of cytotoxic therapies. It has been noted that the quality of the collected T cells is a significant factor determining their toxicity and efficacy. In order to explore the influence of early T cell collection, we have conducted a study comparing T cells parameters of patients who underwent lymphocyte collection after failure of first line therapy for DLBCL (early apheresis) with patients who underwent lymphocyte collection after second line therapy or later (late apheresis).

Methods: Patients were assigned to groups according to referral time: early versus late. Blood samples were collected at the day of apheresis, representing the starting material for manufacturing. Immune phenotyping (FACS) was performed for T cell subpopulations, differentiation and exhaustion markers (CD3, CD4, CD8, CD45RA, CCR7, CD27, CD28, TIM-3, LAG-3). T cell activation and proliferation were analyzed using PBMCs labelled with carboxyfluorescein succinimidyl ester (CFSE) and anti-CD3/CD28 or (phytohemagglutinin) PHA.

Results: Thirty-six patients were enrolled: 15 to the early group and 21 to the late group. The mean percentage of circulating CD3 + lymphocytes was 48.9 ± 3.5 and 58.5 ± 1 in the late and early group, respectively ($p < 0.05$) (Fig.). The early group had a significantly higher proportion of CD8 + lymphocytes ($p < 0.05$) and a lower proportion of CD4 + lymphocytes ($p < 0.01$) compared to the late group (Fig.). Among CD4 + and CD8 + T cells, the early samples showed increase of both naïve ($p = 0.07$, $p < 0.005$) and central memory T cells (T_{CM}) ($p < 0.0005$, $p < 0.05$), and a reduction of effector memory (T_{EM}) ($p < 0.05$, $p < 0.005$) and effector T cells (T_{EF}) ($p < 0.05$, ns), respectively. (Fig.) Both CD4 + and CD8 + T lymphocytes showed higher expression of the exhaustion markers, TIM-3 and LAG-3 in the late apheresis group ($p < 0.0001$). CD8 + cells analysis revealed a significant increase of senescent $CD27^-/CD28^-$ T-cells, in the late group compared to the early group ($p < 0.05$). In the early samples there was a significant increase in T-cell proliferation, in response to either stimulus: anti CD3/CD28 or PHA in both CD4 ($p < 0.001$) and CD8 ($p < 0.05$) subsets.

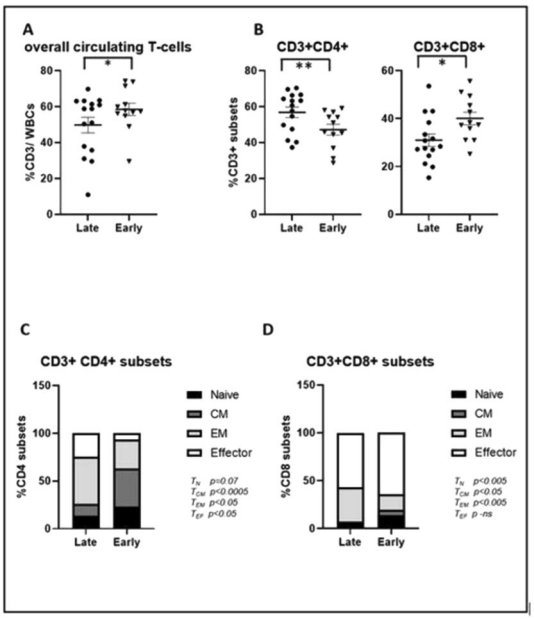


Figure 1. Comparison of T cells parameters between early and late samples

A. Percentage of overall CD3+ T cells **B**. Percentage of CD4 T cells and CD8 T cells **C**. Percentage of T cells subtypes among CD4 cells **D**. *Percentage* of T cells subtypes among CD8 cells
T_N – Naïve, T_{CM} - Central Memory(CM,) T_{EM} - Effector memory(EM), T_{EF} – Effector, * p<0.05 ** p<0.001

Conclusions: Early apheresis, after first line of chemotherapy, shows abundance of T lymphocytes, mainly CD8 + cells, with an improved quality of the starting material, represented by a higher percentage of naïve, less exhausted and senescent cells. Furthermore, early apheresis shows a higher T cell proliferation potential. These improved parameters in the initial collected product may have an influence on the manufacturing process and eventually on the efficacy of the infused CAR T cells.

Disclosure: "Nothing to declare"

P068

Chimeric antigen receptor t-cell therapy in the czech republic

F. Folber[1], R. Pytlík[2], K. Polgárová[3], L. Sramkova[4], J. Šrámek[5]

[1]Masaryk University Hospital Brno, Brno, Czech Republic, [2]Institute of Haematology and Blood Transfusion, Praha, Czech Republic, [3]General University Hospital, Praha, Czech Republic, [4]Charles University and University Hospital Motol, Praha, Czech Republic, [5]University Hospital Pilsen, Plzeň, Czech Republic

Background: The program of cellular therapy with chimeric antigen receptor T-cells (CAR-T) has been established in the Czech Republic in 2019. Since then, five centers have been certified for tisagenlecleucel (tisa-cel), axicabtagene ciloleucel (axi-cel), or both. This report summarizes all the treatment that has been administered so far.

Methods: All patients treated with commercial tisa-cel or axi-cel in the Czech Republic until August 2021 were included into this retrospective analysis. The data were analysed for overall response rate (ORR) and complete remission (CR) rate, incidence and severity of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), and

progression-free (PFS) and overall survival (OS). CRS and ICANS were graded according to ASTCT consensus criteria.

Results: A total number of 66 patients were included into this analysis, 51 treated with tisa-cel and 15 with axi-cel.

Tisa-cel was infused in 43 patients with B-cell non-Hodgkin lymphomas (B-NHL). ORR was observed in 47% patients, while CR was reached in 35%. CRS occurred in 74% of cases (grade 3 or higher in 16%), and ICANS in 23% (grade 3 or higher in 2%). Six-month PFS and OS estimates were 37% and 52%, respectively. Better PFS was observed in patients with pre-treatment CRP below median ($p = 0.02$), and in patients who developed CRS ($p = 0.03$).

Tisa-cel was infused in 8 patients with B-cell precursor acute lymphoblastic leukemia (B-ALL), of whom 5 were children and young adults under the age of 18. All patients but one (88%) achieved a CR. CRS occurred in 63% of cases (none grade 3 or higher), and ICANS in 25% (one grade 4). Six-month EFS and OS estimates were 50% and 88%, respectively.

Axi-cel was infused in 15 B-NHL patients (including primary mediastinal B-cell lymphoma, PMBCL). ORR was observed in 69% of cases, CR in 46%. CRS occurred in 80% of cases (none of them grade 3 or higher), and ICANS in 33% (grade 3 or higher in 3 patients). Six-month PFS and OS estimates were 69% and 74%, respectively. Better survival was observed in patients with PMBCL but the difference was not statistically significant.

Conclusions: Cellular therapy with commercial CAR-T products is a well-established treatment modality for patients with relapsed/refractory B-NHL and B-ALL. Real world data observed in our nation-wide cohort are comparable to already published results of larger patient populations.

Disclosure: Nothing to declare

P069

CD34 selected stem cell boost can safely improve cytopaenias following car-t therapy

K. Mullanfiroze[1], A. Lazareva[1], J. Chu[1], L. Williams[1], S. Burridge[1], J. Silva[1], R. Chiesa[1], K. Rao[1], G. Lucchini[1], S. Ghorashian[1], R. Hough[2], C. Roddie[2], P. Amrolia[1]

[1]Great Ormond Street Hospital, London, United Kingdom, [2]University College London Hospitals, London, United Kingdom

Background: Prolonged cytopaenias are an under-recognised toxicity of Chimeric Antigen Receptor-T cell(CART) therapy for B-cell malignancies(53% of B-ALL patients in the ELIANA study had grade 3-4 neutropenia persisting beyond day 28). Persistent cytopaenias post-CART have been associated with baseline cytopaenias and pro-inflammatory milieu(Rejeski *et al*, Blood, 2021). Cytopaenias generally resolve spontaneously over 2-3 months post-CART therapy but some patients develop prolonged cytopaenias associated with susceptibility to infection(s) and/or transfusion dependence and a hypoplastic bone marrow(BM). Cytopaenias can be treated with an unconditioned CD34 stem-cell boost in those who have undergone prior stem cell transplant(SCT).

We reviewed our institutional data on outcomes with this approach.

Methods: Data was retrospectively analysed from paediatric and young adults with relapsed/refractory(r/r) B-ALL treated with CART therapy and who received CD34 stem-cell boost from their SCT donor between May 2016 and December 2021 at 2 centres in the UK. Demographic details, disease status and cytopaenias pre-CD34 stem-cell boost, toxicity and outcomes were collated.

Results: Over 5 years, 103 patients received CART therapy for r/r B-ALL. Seven (6.7%) of these patients received an unconditioned CD34 stem-cell boost from their SCT donor due to severe grade 3-4 cytopaenia (pancytopenia in 6/7, bicytopenia in 1/7) beyond 1 month after CART. CD34 stem-cell boost was infused at median of 2.6 months (range 2-16.5m) after CART therapy. All 7 demonstrated BM hypoplasia for age without a clear drug or viral etiology and were MRD negative. Three(43%) had ongoing invasive fungal infections at CD34 stem-cell infusion. Median age at CD34 stem-cell boost was 16 years(range 11-27y). All patients were heavily pre-treated and had undergone previous SCT and 6/7 received CART in $\geq$ 2 relapse. Four(3 CD19, 1 CD19/CD22 directed) received CAR as per CARPALL study(*NCT02443831)*, 1 received CD19/CD22 directed CAR as per AMELIA study(*NCT03289455*), 1 received licensed product Tisagenlecleucel and 1 received allogenic CD19 directed CAR as per CARD study(*NCT02893189)*. Median CD34 and CD3 doses in the infused product were 6.75 $x10^6$/kg(range 2.5-11.2$x10^6$/kg) and 0.19$x10^4$/kg(range 0.07-1.22$x10^4$/kg) respectively. CD34 boost was well tolerated:1 patient developed grade 2 cytokine release syndrome(CRS) at day 10 but no acute or chronic GVHD was observed. Two patients were not evaluable for response to CD34 stem-cell boost:1 died due to gastro-intestinal haemorrhage caused by disseminated Mucormycosis on day 24 and 1 relapsed at day 38. Of the 5 evaluable patients one had transient recovery of the bicytopenia followed by ongoing cytopenias until demise while 4 patients recovered neutrophils >1$x10^9$/L without GCSF, were blood and platelet transfusion independent by a median of day 42 (range 11-192 days), day 33 (range 4-106 days) and day 33 (range 7-73 days) respectively. At a median follow-up of 9 months(range 24 days-2.5 years) from CD34 stem-cell boost, 5 died (2:relapse, 2:infections, 1: further therapy related complications) and 2 were alive, in CR with normal blood counts at last follow up.

Conclusions: Unconditioned CD34 stem-cell boost is well tolerated and can ameliorate prolonged cytopaenias post-CART therapy. However, CRS is a potential complication after the infusion due to the presence of $CD19^+$ progenitors within the CD34 selected product.

Disclosure: None

P070

Bridging chemotherapy strategies in children undergoing cart-cells for all

M. Oporto Espuelas[1], S. Burridge[1], K. Watt[2], D. Bonney[2], A. Vora[1], V. Pavasovic[1], S. Samarasinghe[1], J. Bartram[1], A. Rao[1], P. Ancliff[1], S. Farish[1], R. Chiesa[1], K. Rao[1], G. Lucchini[1], J. Montibeller Furtado-Silva[1], A. Lazareva[1], K. Mullanfiroze[1], M. Ballasch[1], P. Amrolia[1], S. Ghorashian[1]

[1]Great Ormond Street Hospital, London, United Kingdom, [2]Royal Manchester Childrens Hospital, Manchester, United Kingdom

Background: Low tumour burden prior to CART-cell infusion for B-ALL is associated with less CRS toxicity and improved survival[1,2]. The choice of bridging chemotherapy (BCT) is crucial to achieve adequate disease control and avoid toxicity-related infusion delays; however, there is no consensus as to which is the optimal strategy.

We have analysed the use of BCT in two of the UK's largest CART-cell centres in terms of both feasibility to deliver CART-infusion on time and efficacy in reducing large/bulky tumour burden.

Methods: We performed a descriptive analysis on restrospectively collected data. BCT was defined as systemic anti-leukaemic treatment given between leukapheresis and lymphodepletion. A BCT course was defined as a particular chemotherapy schedule given with the intent to control disease. Disease burden was

measured by flow cytometry or molecular MRD for patients with <5% disease and confirmed by a local consultant in each case.

Results: Data was collected from 49 paediatric patients who underwent 70 BCT courses (median number of courses per patient was 1, range 0-3). Patient characteristics are shown in Table 1. Thirty-two patients (65.3%) received their CART-cell infusion on the expected date, whereas 15 patients (30.6%) suffered a delay, 1 patient (2%) died prior to infusion. A total of 20 patients (40.6%) experienced some kind of toxicity, leading to an infusion delay in 15 (75%) of them. The majority (n = 11) of these suffered from an infection or likely infection. Other non-infectious reasons for delay included leukoencephalopathy, small bowel obstruction and difficulties in disease control (n = 3, 20%). BCT regimens were heterogeneous; we have grouped them in 5 categories in decreasing order of popularity: Capizzi-like (n = 28; MTX + VCR as per UKALL-2011 - up to 9 variations were recorded in this cohort), Maintenance (n = 12; oral 6MP + MTX), Inotuzumab (n = 11; single 0.5-0.8 mg/m2 doses to avoid toxicity), HiDAC (n = 7; AraC in doses 9-12 g/m2), and Other (n = 12; including exclusive intrathecal therapy, TKI and other miscellaneous schedules). Maintenance was usually given to hold/maintain low-level disease. Inotuzumab was not given as upfront BCT. Both Inotuzumab and Capizzi regimens seemed effective in debulking disease.

Table 1. Patient characteristics.

Median age	7.9 y (0.9-15.7)
Female/male	22 (44.9%)/27 (55.1%)
CART (Tisagenlecleucel/CARPALL)	48 (98%)/1 (2%)
Infant/Ph+ ALL	11 (22.4%)/3 (6.1%)
Prior SCT	24 (49%)
Isolated CNS disease	7 (14.3%)
BM + Extramedullary disease - CNS/Other	12 (24.5%) - 5/7
Refractory	29 (59.2%)
Median number of relapses	1 (0-4)
Previous CART-cell therapy	2 (4.1%)

Conclusions: The ideal BCT schedule should achieve adequate disease control with minimal toxicity facilitating timely CART-cell infusion. Capizzi-like and Inotuzumab regimens may be suitable agents to debulk disease. Infection is the most common reason for delays in infusion.

Disclosure: No conflict of interest of any of the authors.

P071

Humoral and t cell immune responses to anti-sars-cov-2 vaccines in pediatric & patients with anti-cd19 car-t-induced b-cell aplasia

A. Jarisch[1], E. Wiercinska[2], S. Huenecke[2], M. Bremm[1], C. Cappel[1], J. Hauler[1], E. Rettinger[1], J. Soerensen[1], H. Hellstern[2], H. Boenig[2], P. Bader[1]

[1]Division of Pediatric Stem Cell Transplantation and Immunology, University Hospital Frankfurt, Frankfurt, Germany, [2]German Red Cross Blood Service BaWüHe, Institute Frankfurt, Frankfurt, Germany

Background: COVID-19 disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); its course can be severe, the overall mortality approaching 1.5%. Patients with malignant diseases and an impaired immune system, especially patients after hematopoietic stem cell transplantation (HSCT) and immune cell therapy, have an increased risk of an aggravated course of the disease or death and despite the expectation of less than optimal vaccine responsiveness were granted prioritized access. Inherently, patients with anti-CD19 CAR-T-mediated B-cell aplasia would be incapable of generating humoral responses, so that assessment of the vaccine-induced cellular immunity was all the more important to gauge whether the vaccine can induce meaningful protection.

Methods: The prospective study included 8 patients aged >12 years (and hence, eligible for SARS-CoV-2 vaccination) diagnosed with multiply relapsed B-cell precursor acute lymphoblastic leukaemia (ALL) and treated with anti-CD19 chimeric antigen receptor T-cell (CAR-T19) therapy between 2016 and 2021.

The primary endpoint was the detection of humoral and cell-mediated response to vaccine. Secondary endpoints included the incidence of grade 3 or 4 adverse events and GVHD exacerbation and the influence of the vaccine to CAR T cells and lymphocyte subset.

Results: Even though half the patients exhibited sub-normal lymphocyte counts and marginal CD4/CD8 ratios, after two vaccinations all showed brisk T-cell responsiveness to spike protein, predominantly in the CD4 compartment which was qualitatively well within the range of healthy controls.

In none of the patients severe vaccine-associated (grade 3 or 4) adverse events were observed. None of the eight patients developed a cytopenia post vaccination.

When looking at the differentiation of the CD4 + and CD8 + T cells into naïve, central-, effector memory and EMRA T cells, also no significant changes in composition could be observed. The slight changes which could be seen in an increase of the naïve T4 and T8 cell subpopulation is probably related to the restoration of the naïve T-cell pool in the course of immune regeneration after stem cell transplantation. The effectory compartment (TEM and TEMRA) showed no significant changes with respect to expansion of these cells.

Conclusions: We posit that SARS-CoV-2 mRNA vaccines induce meaningful cellular immunity in patients with isolated B-cell deficiency due to anti-CD19 CAR-T therapy.

Clinical Trial Registry: The study was approved by Goethe University Medical Center's ethics committee (case number 2021-180).

Disclosure: "Nothing to declare"

P072

Validation of collection and cryopreservation of autologous mononuclear cells intended for car-t cells production

I. Bojanic[1], S. Mazić[1], V. Rimac[1], I.L. Burnać[1], K. Gojčeta[1], B. Golubić Ćepulić[1], I. Aurer[1]

[1]University Hospital Centre Zagreb, Zagreb, Croatia

Background: Apheresis and cell processing facilities, although experienced in HPC collection, could face challenges when introducing the collection and storage of cells intended for manufacturing of cellular therapy products, because the validation of collection and cryopreservation of other cell types is needed. The aim is to present results of validation of collection and cryopreservation of autologous mononuclear cells (MNC) and lymphocytes subpopulation intended for CAR-T cells production.

Methods: Collection and cryopreservation of lymphocytes for production of autologous T cell immunotherapy tisagenlekleucel (Kymriah, Novartis) in University Hospital Centre Zagreb started at

the end of 2019. Leukapheresis were performed on Spectra Optia system (Terumo BCT) using CMNC procedure and acid citrate dextrose A (ACD-A) anticoagulant. All patients received prophylactic continuous intravenous calcium gluconate. Leukapheresis product was considered eligible for CAR-T product manufacturing if specification requirements were met: total nucleated cells (TNC) ≥ $2x10^9$, CD3 + lymphocytes ≥$1x10^9$, and ≥3% CD3 + lymphocytes. Collection efficiency (CE1) for MNC and CD3 + cells was calculated based on pre- and postapheresis MNC and CD3 + cells peripheral blood counts. Cells were cryopreserved with DMSO cryoprotectant and controlled-rate freezing. The effect of cryopreservation on the recovery of lymphocyte subpopulations was evaluated in cryovials representative of cryopreserved products using flow cytometer BD FACSCanto II.

Results: From December 2019 to November 2021, two children and two young adult patients with ALL, and 23 adults with DLBCL underwent leukapheresis. The median age was 57 years (range 5-71), and median body weight was 75 kg (range 21-109). 15 patients required central venous catheter, while in 12 patients peripheral veins were used. In all patients, except in one child, the target number of cells was obtained with one leukapheresis. The median of total blood volume (TBV) processed was 2,1 (range 1,4-2,8) during 240 min (range 160-300). In two procedures heparin was added to resolve clotting. In only one patient mild symptoms of hypocalcaemia were observed. Median of collected TNC was 8,9x10E9 (range 0,7-27,7), and CD3 + cells 4,1x10E9 (range 0,7-11,1). Median of CE1 for MNC was 24% (range 2,4-32), and for CD3 + cells 43,4% (range 18,9-56,8). The number of CD3 + cells in peripheral blood significantly correlated with CD3 + cell yields (correlation coefficient $r = 0.680$, $p < 0,0001$). All leukapheresis products were cryopreserved on the day of apheresis. The median recovery of CD3 + cells after cryopreservation was 79% (range 34,8-106,4), CD4 + cells 83,5% (range 15,1-136,9), CD8 + cells 84,8% (range 34,1-145,7), CD19 + cells 96,3% (range 41,8-107,7) and CD56 + cells 74,7% (range 8,3-121,1).

Conclusions: Leukapheresis is an efficient and safe procedure for the collection of cells for cellular therapy production. CE1 calculated for CD3 + lymphocytes exhibited a relatively wide range, therefore further evaluation of factors affecting apheresis performance is necessary. Results of CE1 validation for CD3 + cells allow calculation of required TBV processing based on patient's pre CD3 + count and optimization of the apheresis procedure. The recovery of different lymphocyte populations after thawing was lower compared to the results of our previous validation of CD34 + cell recovery, and further clarification of the different tolerance to cryopreservation of cell subpopulations in apheresis products is needed.

Disclosure: Nothing to declare.

P073

Study of specific lineage chimerism as an early biomarker of risk of relapse after anti-cd19 cart therapy in patients previously treated with an allogeneic HSCT

I. Martínez-Romera[1], V. Galán Gómez[1], B. González Martínez[1], P. Guerra García[1], S. San Román Pacheco[1], D. Corral Sánchez[1], Y. Mozo del Castillo[1], D. Bueno Sánchez[1], L. Sisinni[1], A. González Guerrero[1], S. Castellano Dámaso[1], A. Balas Pérez[2], A. Pérez-Martínez[1]

[1]University Hospital La Paz, Madrid, Spain, [2]Centro de Transfusión, Madrid, Spain

Background: Treatment based on target CD19 protein by a chimeric antigenic receptor expressed on T lymphocytes (antiCD19 CAR-T) is a novel immunotherapy that has led to a revolution in the management and treatment of relapse and refractory (r/r) B cell acute lymphoblastic leukemia (B-ALL) even after an allogenic hematopoietic stem cell transplant (HSCT) relapse. After antiCD19 CART therapy, the successful functionally effective of the CAR-T is monitored by bone marrow negative minimal residual disease but also by the absence of peripheral $CD19^+$ B lymphocytes (B cell aplasia). In addition, continuous chimerism monitoring after HSCT is a routinely well-established method which is critical for early therapeutic interventions. So, in patients who have received an allogenic-HSCT prior to treatment with antiCD19 CAR-T, monitoring of chimerism and lineage-specific chimerism on $CD19^+$ and $CD3^+$ cells could be a helpful complementary tool to early evaluate the risk of relapse and it could also help to propose early treatment.

Methods: We describe four B-ALL pediatric patients who received anti-CD19 CART therapy in the setting of a relapse after an allogeneic HSCT. They all received fludarabine and cyclophosphamide (FluCy) lymphodepleting regimen. Lineage chimerism in peripheral blood (PB) and bone marrow (BM) was done in all of them periodically after the CART infusion.

Results: In patient 1, mixed chimerism was observed specifically in the $CD3^+$ lineage, and it reverted with the administration of serial donor lymphocyte infusion (DLI). In the case of patients 2 and 4, a loss of chimerism was observed in the $CD19^+$ lymphocytes subset without being accompanied by a loss of B cell aplasia. In these patients, treatment with DLI, although it could turn back to complete chimerism in patient 2, did not prevent the later progression to relapse in both. In patient 3, mixed chimerism in $CD19^+$ subset was associated with very early loss of B cell aplasia. Given that after these findings an allogenic HSCT was indicated, he did not receive DLI.

Conclusions: The $CD19^+$ lineage mixed chimerism but not $CD3^+$ lineage mixed chimerism monitored by single tandem repeat (STR) techniques could anticipate earlier than B cell aplasia determined by flow cytometry, the antiCD19 CAR-T lack of persisting functionally effective and leukemia relapse. Treatment with DLI would not avoid relapse but could recover $CD3^+$ full donor chimerism. We suggest that continuous lineage chimerism analysis should be a routinely tool for monitoring in patients who received anti-CD19 CART after an allogeneic HSCT and achieved complete remission, because it could help to propose early treatment. However, the role of DLI in this setting looks useless, although prospective studies should be proposed.

Disclosure: Nothing to declare.

P074

Autologous stem cell boost for prolonged severe cytopenia after treatment with cd19-car-t-cells for refractory diffuse large b-cell lymphoma –two case reports

L. Gaksch[1], B. Huber-Krassnitzer[1], B. Uhl[1], A. Bainschab[1], I.A. Sifferlinger[1], H. Sill[1], P. Schlenke[2], K. Rosskopf[2], C. Beham-Schmid[3], P. Neumeister[1], H.T. Greinix[1]

[1]Division of Hematology, Medical University of Graz, Graz, Austria, [2]Medical University of Graz, Graz, Austria, [3]Diagnostic and Research Institute of Pathology, Medical University of Graz, Graz, Austria

Background: CD19-targeted chimeric antigen receptor modified T-cell (CAR-T) infusion is an established treatment in relapsed or refractory diffuse large B-cell lymphomas (DLBCL). While early adverse events like cytokine release syndrome (CRS) and neurotoxicity are well investigated, in late occurring complications like prolonged cytopenias the underlying mechanisms are still unclear. Grade 3-4 neutropenia, anemia and thrombocytopenia at

day 30 have been reported in 48% of patients given axicabtagene-ciloleucel (axi-cel) infusion in the ZUMA-1 and ZUMA-9 trials. We present two patients who received an autologous peripheral blood stem cell (PBSC) boost for prolonged severe cytopenias.

Methods: Patient A, a 65 year old man, received an autologous PBSC transplantation for DLBCL in partial remission, but relapsed 106 days later. Patient B, a 69 year old woman had an early relapse of a DLBCL and was not eligible for autologous PBSC transplantation due to progression under salvage treatment. Both patients fulfilled the criteria of the Austrian CAR-T-cell platform and thus, were eligible for anti-CD19 CAR-T-cell infusion with axi-cel (Yescarta ®) after lympho-depleting chemotherapy with 3 doses of cyclophosphamide 500mg/m^2 and fludarabine 30mg/m^2 body surface area. While patient A did not reveal any acute adverse events after CAR-T-cell infusion, patient B developed CRS grade I and obtained consecutively tocilizumab on days +9 and +10. Both individuals suffered from prolonged WHO grade 4 neutropenia, anemia and thrombocytopenia beyond day 30 including G-CSF refractory neutropenia. Therefore, bone marrow examination was performed at days 40 and 33 after CAR-T-cell infusion revealing no signs of DLBCL or myelodysplastic syndrome (MDS) but severely hypoplastic marrow involving all three cell lines. Therefore, we administered stored autologous PBSCs of 2.99 and 2.86 x10^6 CD34$^+$/kg body weight 48 and 33 days after CAR-T-cell infusion.

Results: Leukocyte engraftment (ANC > 500/µL) supported by G-CSF stimulation occurred 3 and 11 days after autologous PBSC boost. Platelet engraftment with platelets over 20.000/µL was observed in patient A 40 days after autologous PBSC boost. In patient B no platelet engraftment could be achieved within an observation period of 52 days after autologous PBSC boost. No signs of clinical infection or bleeding were observed both patients showed persistent complete metabolic remission of their malignancies at days +158 and +63 after CAR-T-cell infusion.

Conclusions: Autologous PBSC boost seems to be a rescue therapy for prolonged severe cytopenia after CAR-T-cell therapy. Reducing the duration of late cytopenia could lower risk of infectious complications and improve outcome of patients given CAR-T-cell therapy.

Disclosure: Nothing to declare

P075

CD72 is a promising substitute for cd19 as a malignant b cell target in immunotherapy and a rough b gating marker for flow cytometry detection

H. Wang[1], A. Wang[1], M. Gong[1], M. Chen[1], X. Wu[1], J. Zhen[1]

[1]*Hebei Yanda Lu Daopei Hospital, Langfang, China*

Background: CD19-Chimeric Antigen Receptors T cell(CAR-T) has made a very big progress in treatment of B acute lymphoblastic leukemia(B-ALL) and lymphoma. CD19 is a very good target for CAR-T treatment and pan- B marker for Flow Cytometry(FCM) detection for it's high coverage on B malignancies. However, 13%-60% cases were CD19 dim or negative when relapsed after CD19-CAR-T, so it's urgent to find a substitute for CD19 not only as a new target of CAR-T but pan-B marker for FCM detection.

Methods: From October 2020 to August 2021, 315 newly diagnosed patients with hematological tumor in Hebei Yanda Lu Daopei Hospital were investigated for immunophenotyping. 350 bone marrow minimal residual diseases(MRD) tests were performed in 200 B-ALL patients. 3 Laser 10-color FACS Canto Plus was used for FCM detection, and Diva and kaluza softwares were used to analyze data. Combining rough B gates were set as CD24 or CD19 positive and CD72, cCD79a or CD19 positive, and MRD were detected by multi dimensional radar photos for quick and intuitive observation.

Results: 1. In 315 patients with hematological tumors, the positive rate of CD72 was 97.73%(129/132) in ALL-B, and 100%(32/32) in lymphoma, which includes 3 Burkitt lymphoma, 5 chronic lymphocytic leukemia (CLL), 8 diffuse large B-cell lymphoma (DLBCL), 2 follicular lymphoma (FL), 1 hair cell leukemia (HCL), 1 lymphoplasmacytic lymphoma (LPL), 4 mantle cell lymphoma (MCL), 7 marginal zone lymphoma (MZL), and 1 small cell lymphoma (SLL). CD72 positive rate was 10.27%(17/151) in non-B-cell tumors, including 10.85%(14/129) in AML, 40%(2/5) in mixed phenotype acute leukemia(MPAL), 14.29%(1/7) in T-ALL/LBL, and 0%(0/10) in multiple myeloma(MM). These results suggest that CD72 is a marker comparable to CD19 for its coverage, specificity and expression intensity are comparable to that of CD19, it can be used as a rough B gating marker for FCM MRD of post-targeted therapy and a highly effective target for further CAR-T therapy of CD19-negative relapsed cases. 2. In MRD detection, CD72 combined with CD19 and cCD79a can cover all B cells, with sensitivity and specificity as high as 100%. 3. different from old analysis methods in which many gate strategies and dot plots were used to analyze data, a multi-parameter and multi-dimention radar photo could offer a quick and high efficient method.

Conclusions: CD72 is highly expressed in B-cell tumors and may be an effective B cell marker after CD19. It can be used not only as a gating marker of B-ALL MRD, but also as a highly promising biomarker for further targeted therapy of CD19 negative relapsed cases.

Disclosure: Nothing to declare

P076

Developing a dietetic service for patients undergoing car-based cellular therapy; evaluated with patient reported experience and outcome measures

J. Morgan[1], H. Long[1]

[1]*Cardiff & Vale UHB, Cardiff, United Kingdom*

Background: There is limited evidence regarding the role of nutrition during a CAR-based cellular therapy transplant. However, patients experience similar nutritional challenges to a HSCT. Patients will have increased nutritional requirements and experience side effects of their underlying condition including side effects of the transplant, which affects nutritional intake. Malnourished patients have poorer outcomes than well-nourished patients with 10% weight loss being regarded as a clinical prognostic factor. Nutrition & Dietetics at the University Hospital Wales has set up a service for CAR-T patients.

Methods: The dietitian benchmarked the service, developed the Dietetic nutrition pathway, worked as part of the CART MDT, developed patient nutritional resources and developed nutritional guidelines. Patients had a consultation with the dietitian during or just after apheresis for nutritional assessment and information sharing. The patients were supported with nutritional prehabilitation until admission, for those who required it. Nutrition support and advice was provided by the dietitian during their inpatient stay for their CART cell therapy which continued until 30 days post- CART. Following this, patients who had ongoing nutritional challenges continued to have dietetic support regularly. All patients continued to have nutritional assessment, advice and support at 3 month and 6 month clinic appointments. Data collected for outcome measures included weight and patients reported experience measures (PREMs) using a questionnaire.

Results: 14 patients received their CART and experienced the dietetic service. All patient's received nutritional support dietary advice in the pre-hab phase. 21% (n = 14) of patients required more aggressive nutritional pre-hab including nutritional supplementation. 100% (n = 14) of patients received nutrition support dietary advice and nutritional supplements during their inpatient stay with 14.3% (n = 14) of patients requiring nasogastric feeding during their CART. Mean weight loss in the pre-hab phase was 3.4% (range 0-12.5% median 2.3%) and mean weight loss from pre-hab to discharge at 30 days post-transplant was 6.6%.(range 0-23.2%, median 6.78%). Regarding PREMs, 100% (=14) of patients reported they strongly agreed that the dietetic input was clear, concise, easy to understand and empowered them to make dietary changes. 100% (n = 14) also reported they strongly agreed that they benefited from the dietetic service and patient information.

Conclusions: 21% (n = 14) of patients experienced weight loss above the 10% clinical prognostic factor. Patients experience of the dietetics service was very positive. The dietetic service to the CART patients will continue. Future development of this service will also include outcomes including bioelectrical impedance analysis (BIA) and hand grip strength.

Disclosure: Nothing to declare

P077

CAR-T as a bridge therapy in a case of all late resistant relapse

M. Comini[1], A. Beghin[1], V.M. Folsi[2], M. Chiarini[3], E. Soncini[2], F. Bolda[1], D. Russo[4], A. Lanfranchi[1], F. Porta[2]

[1]Stem Cell Laboratory, Section of Hematology and Blood Coagulation, Clinical Chemistry Laboratory, ASST Spedali Civili, Brescia, Italy, [2]Pediatric Onco-Hematology and BMT Unit, Children's Hospital, ASST Spedali Civili, Brescia, Italy, [3]Flow Cytometry Unit, Section of Hematology and Blood Coagulation, Clinical Chemistry Laboratory, ASST Spedali Civili, Brescia, Italy, [4]Dipartimento di Scienze Cliniche e Sperimentali, University of Brescia, Brescia, Italy

Background: CAR-T is an innovative anti-cancer therapy, treating B-cell ALL in children and young adults up to age 25. Despite a significantly increased survival in patients with ALL in the last decades, 2-3% of patients show a disease refractory to chemotherapy treatments and about 10-15% eventually relapse.

Methods: The first pediatric patient candidate to CAR-T therapy at the Children's Hospital of Brescia was a 12-years-old girl diagnosed in 2015 with Non-Hodgkin B Lymphoma, stage III involving bone, CNS with BOM negative. She underwent therapy according to the LNH-97 protocol and achieved stop therapy in July 2017.

In January 2021, relapse occurred with a common B-ALL phenotype, CNS negative, AIEOP LLA REC 2003 protocol was started. Over the end of the therapy, persistence of blasts was present with strongly positive MRD. Therefore InterALL-HR-2010 R3 + Bortezomib protocol was given with, nevertheless, persistence of disease at the end of the treatment, with a marrow infiltrate of 12%.

In March 2021, she was enrolled in CAR-T program and autologous T lymphocytes were collected.

Results: In May 2021, after lymphodepleting therapy, 1.6 x 10^8 CD3 + CAR-T cells were infused (Kymriah).

On post infusion day+4, patient presented fever, hypotension, hypoxemia attributable to CRS grade II associated with an increase of IL-6 (peak at day+7, 266 ng/L, range<7 ng/L). She was treated with a single dose of Tocilizumab with benefit and resolution of symptoms.

On day+17,+ 30,+ 60 MRD was negative.

At days+1,+3,+7,+10,+14,+16,+30,+86,+115,+120,+146 the presence of CAR-T was analyzed by flow cytometry and by a highly sensitive technique: digital droplet PCR(ddPCR), CAR-T were detected already on day+1 in ddPCR with a peak at day+10.

Five months after CAR-T infusion, patient lost B cell aplasia and MRD resulted positive with a rapid loss of CAR T cells.

Soon after she received HSCT from MUD after conditioning therapy with total body irradiation, Fludarabine and Thymoglobulin. HSCT was performed with a positive selection of CD34 + (10x10^6 CD34 + /Kg infused) cells and T controlled addback (30x10^6 CD3 + /Kg infused) from PBSC.

After HSCT, patient was monitored and MRD became negative in presence of cutaneous GvHD stage II. Donor chimerism performed on CD34 + cells from BM was 97.3%. Analysis of BM, moreover, showed persistence of CAR-T cells. The surprisingly persistence of CAR-T after HSCT can be explained by the results of the study of donor chimerism performed with ddPCR, that show 12% of autologous cells.

Conclusions: Monitoring of CAR-T cells with a very highly sensitive techniques, such as ddPCR, is of critical importance because it has been demonstrated that even low concentrations of CAR-T could have a therapeutic function.

However, in this case, the sudden decrease of CAR-T circulating cells and the appearance even of a very low number of B cells, suggested to immediately proceed to HSCT. In fact, MRD short after became slightly positive. CAR-T is an innovative therapy, several studies nevertheless, are ongoing to understand if it is a definitive therapy or a bridge to transplant. In our case it was the latter. It's no clear if persistence of CAR-T after allogeneic HSCT could have a role of relapse prevention.

Disclosure: Nothing to declare

P078

Feasibility of autologous stem cell transplantation as bridging therapy prior to cd19 car-t in r/r large b cell lymphoma

E. Galli[1,2], F. Sorà[1,2], S. Hohaus[1,2], S. Bellesi[1], F. Autore[1], M.A. Limongiello[1], I. Innocenti[1], E. Metafuni[1], S. Giammarco[1], L. Laurenti[1,2], P. Chiusolo[1,2], A. Bacigalupo[1,2], S. Sica[1,2]

[1]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy, [2]Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Rome, Italy

Background: Peripheral blood autologous stem cells transplantation (PBSCT) has played pivotal role as consolidation for relapsed or high risk lymphomas, while its role is discussed in CAR-T cells era. Lower disease burden has been associated with better outcome after treatment with CAR-T cells; the intensity and role of bridging therapy has not been clearly stated. In this study, we aimed to assess the feasibility of PBSCT as bridging therapy before treatment with CAR-T cells in the setting of relapsed/ refractory B cell lymphomas.

Methods: We retrospectively analyzed six patients who had received FEAM-conditioned PBSCT as a bridging to CAR-T: we focused on cytopenias, specific CAR-T toxicities and outcomes.

Results: At the time of eligibility for CAR-T, all patients had ECOG 0-1, three had elevated LDH and five out of six had an IPI score of 3 or more. All patients had either refractory or early relapsed NHL. After lymphocyte collection was completed, patients were hospitalized for receiving PBSCT. Median time from lymphocyte collection to the beginning of bridging with PBSCT therapy was 6 days (range 1-44 days). Main toxicities related to PBSCT were grade 3 infections and grade 4 cytopenias. No

unexpected toxicities were observed. Patients were discharged at a median of 12 days (range 11-15) after PBSCT. CAR-T manufacturing process took a median of 31 days. At the time of arrival of the product in our center, five of the six patients had been already discharged from the hospital after PBSCT. Prior to CAR-T cell conditioning, disease response to bridging with PBSCT was evaluated using PET-CT. Three patients obtained complete (CR) or partial (PR) response, two were in stable disease (SD) and one in progressive disease (PD) (Figure 1A).

Before the start of lymphodepletion, complete blood counts (CBC) had recovered from PBSCT with no grade 4 cytopenia. Median time from arrival of frozen CAR-T cells at our center and start of lymphodepletion was 22 days (12-46). Median time from PBSCT to CAR-T cells infusion was 50 days (48-74).

All patients experienced CRS, with only one grade 3 CRS, and no ICANS was documented. In terms of anti-lymphoma efficacy of PBSCT bridging, overall response at one month from CAR-T cell infusion was obtained in five out of six patients (83%), with three (50%) CR and two PR; responses were stable with those five patients still being alive without disease progression at median follow-up of 6 months after CAR-T.

Conclusions: We conclude that PBSCT is a feasible option as bridging therapy prior to CAR-T, with reasonable toxicities and efficient action on disease bulk. We than provide a review of literature on this topic.

Disclosure: Nothing to declare.

P079

Commercial manufacturing experience of tisagenlecleucel in europe: >3 years journey

M. Rodrigues[1], D. Kuzan[2], A. Yallouridis[3], J.-M. Saffar[2], B. Eschgfaeller[1]

[1]Novartis Pharma AG, Basel, Switzerland, [2]Novartis Pharmaceutical Corporation, East Hanover, United States, [3]Novartis (Hellas) S.A.C.I, Athens, Greece

Background: Tisagenlecleucel (Kymriah), an autologous CD19-directed CAR-T-cell therapy, has been approved by the European Medicines Agency in Aug 2018 for the treatment of children and young adults (aged up to and including 25 years) with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia and adults with r/r diffuse large B-cell lymphoma. Here, we discuss >3-year commercial tisagenlecleucel manufacturing experience across the four manufacturing sites in Europe and US (Les Ulis, France; Stein, Switzerland; Fraunhofer, Germany; and Morris Plains, US), for patients in Europe.

Methods: Tisagenlecleucel manufacturing process involves leukapheresis to collect patients' peripheral blood mononuclear cells, which are cryopreserved and shipped to the manufacturing site. This is followed by enrichment and activation of T cells, transduction of the lentiviral vector containing the anti-CD19 CAR transgene, activation with anti-CD3/CD28 antibody-coated beads, expansion in cell culture, washing, and formulation of the viable cells into a cryopreservation medium, and shipping back for infusion (Tyagarajan, 2020).

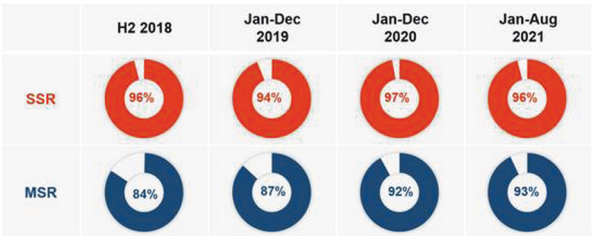
Manufacturing success rate (MSR) was defined as the proportion of patients for whom the manufactured product met the commercial release criteria of the total number of patients leukapheresed. Shipment success rate (SSR) was defined as the proportion of patients for whom the manufactured product was shipped for infusion.

Results: Novartis has a significant global commercial manufacturing footprint with six sites located across the globe (US, France, Switzerland, Germany, Japan, and Australia) and a treatment network of >340 certified centers worldwide, including 164 centers in Europe. This allows for immediate manufacturing availability, thereby meeting the needs of patients. As of Aug-2021, tisagenlecleucel has been manufactured for more than 5300 patients worldwide.

For patients in Europe, the SSR was consistently high at 96%, and the MSR increased progressively from 84% in 2018 to 93% in 2021 **(Figure)**. The corresponding out-of-specification (OOS) rates decreased considerably between 2018 and 2021 from 13% to 5%, with the viability OOS rates decreasing from 9% to 0%. The median turnaround time (apheresis pickup to delivery back to center) has improved from 33 days at launch in 2018 to 26 days currently.

Since the approval of tisagenlecleucel in 2018, a key goal has been to upscale and continuously improve manufacturing success, decrease OOS rate, and minimize the turnaround time in the commercial settings to meet the needs of a global patient population. In July 2021, two key process and analytical improvements have been introduced. Firstly, an alternate serum source (5% plasma-derived human AB serum) which further improves process robustness with a trend towards improved growth and higher peak cell counts. Secondly, a simplified sample preparation procedure for final product cell count and viability measurement, which is more reflective of final product at infusion.

Figure. Shipping success rate (SSR)[a] and manufacturing success rate (MSR)[b]



[a]SSR: proportion of patients for whom the manufactured product (meeting commercial release criteria + out-of-specification [OOS] released based on positive benefit:risk profile) was shipped to centers for infusion; [b]MSR: proportion of patients for whom the manufactured product met the commercial release criteria out of the total number of patients leukapheresed.

Conclusions: Tisagenlecleucel's current global commercial manufacturing footprint and treatment network are well-positioned to meet the anticipated increase in demand for CAR-T therapies. Over the last 3 years, SSR remained high at 96% and MSR improved to 93%. Continuous investment in process improvements has helped improve manufacturing capacity, robustness of manufacturing and testing processes, as well as speed and reliability to deliver tisagenlecleucel to patients in need of treatment.

Disclosure: All authors are employees of Novartis.

P080

Universal anti-cd123 car-γδt cells combined with donor lymphocytes infusion for relapsed acute myeloid leukemia after allogeneic hematopoietic stem cell transplantation

R. Zhang[1], R. Jiang[1], X. Chen[1], J. Yao[1], Q. Liu[1], Y. Shi[1], Y. Cao[1], M. Gong[1]

[1]Chinese Academy of Medical Sciences & Peking Union Medical College,Institute of Hematology & Blood Diseases Hospital, Tianjin, China

Background: Patients with acute myeloid leukemia (AML) relapsed after allogenic hematopoietic stem cell transplantation (allo-HSCT) have poor prognosis although some therapeutic options including hypomethylating agents, chemotherapy, donor lymphocyte infusion (DLI), or a second allo-SCT could be adopted. The anti-CD123 chimeric antigen receptor-γδT (CAR-γδT), which is a promising therapeutic target for AML, might be a new way for relapsed AML after allo-HSCT.

Methods: A 43-year-old male patient with AML transformed from myelodysplastic syndrome underwent haploidentical-SCT in June 2019. Before transplantation, the percentage of primordial monocytes in bone marrow was 22%. Flow cytometry showed: primordial monocytes expressed CD34, CD123, HLA-DR. He received a myeloablative conditioning regimen and a successful hematopoietic reconstitution. Bone marrow examination showed complete remission with minimal residual disease (MRD) negative. Segment tandem repeat (STR) showed complete donor chimerism. To prevent relapse, the patient received 6 cycles of Azacytidine (50mg/m^2/d*5d, once a month) since 4 months after haplo-SCT.

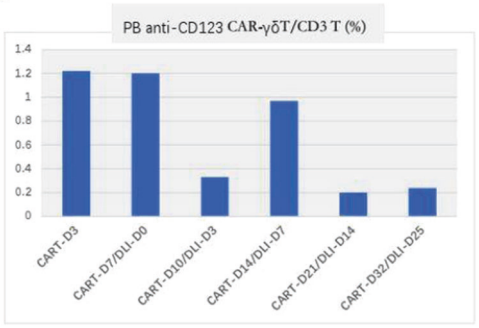
He suffered MRD positive (1.47%) relapse in July 2020. One cycle of Azacytidine combined with low-dose Cytarabine (20mg/m^2/d*7) and 2 courses of Venetoclax (400mg/d*28) were administered successively. After above treatment, he experienced extensive chronic graft versus host disease (cGVHD) involving skin, eyes and mouth. Unfortunately, in December 2020, 1.5 years after haplo-SCT, he suffered hematological relapse. The percentage of primordial monocytes was 9.5% and STR dropped to 78.83%.

Universal anti-CD123 CAR-γδT cells were prepared from a third party umbilical cord blood. In brief, the γδT cells were selected using TCRg/d + T Cell Isolation Kit (Miltenyi) and stimulated with an anti-gd TCR antibody. Activated gd T cells were transduced with an anti-CD123 CAR-carrying lentivirus. Cell product were manufactured by Senlangbio company.

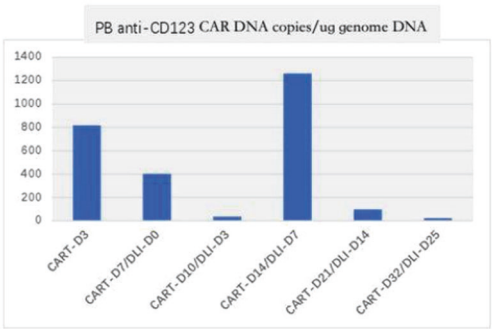
Pre-treatment was Fludarabine 50mg/d*5 and Melphalan 50mg/d *2. The patient received universal anti-CD123 CAR-γδT (2.5×10^6/kg) and 7-days later, G-CSF mobilized and cryopreserved donor mononuclear cells (1.98×10^8/kg) were infused including 0.693×10^8/kg CD34 + stem cell and 1.67×10^7/kg CD3 + T cell. Sirolimus(0.5mg/d) was started after donor cells infusion for GVHD-prophylaxis.

Results: After pre-treatment, MRD was 3.69% and STR was dropped to 61.12%. The universal anti-CD123 CAR-γδT proliferated rapidly from day+3 to day+7 and then decreased. The patient experienced grade 1 cytokines release syndrome including fatigure, nausia, headache and without neurotoxic syndrome. Seven days after CAR-γδT infusion, the bone marrow test showed: AML-MRD was negative and STR was increased to 90.24% and then donor mononuclear cells were infused. On day17 after CAR-γδT infusion, he was in agranulocytosis stage and suffered bacteremia and received antibiotic treatment. The patient achieved MRD negative remission and complete donor chimerism 21-days after CAR-γδT infusion. He did not develop acute GVHD or new onset cGVHD and sirolimus was stopped 1 month after donor lymphocyte infusion. There was an interesting finding that the number of universal anti-CD123 CAR-γδT increased again after donor cells infusion which might be due to the CD123 antigen expressed on donor cells (Figure-A,B). Six months later, the patient suffered hematological relapse again and received supportive treatment.

Figure



A: Percentage of anti- CD123 CAR-γδT in $CD3^+$ T lymphocyte of the patient's peripheral b



Conclusions: Universal anti-CD123 CAR-γδT combined with donor lymphocytes infusion seems to be an effective and safe treatment for AML relapsed after allo-HSCT.

Disclosure: no conflict of interest statement

P081

Successfull management of post- car-t cell cold aglutinin mediated refractory autoimmune hemolytic anemia with daratumumab

E. Erdoğan[1], M. Uluköylü Mengüç[1], K. Yalçın[2], C. Hemşinlioğlu[3], E. Ovali[3], S. Ratip[1]

[1]Acıbadem Altunizade Hospital, Istanbul, Turkey, [2]Medical Park Hospital, Istanbul, Turkey, [3]Acıbadem Labcell Cellular Therapy Center, Istanbul, Turkey

Background: CAR-T cell is an effective treatment in B cell malignancies. Cytokine Release Syndrome and CNS toxicity are the most frequent adverse reactions following CAR-T cell infusion. Although hemolytic anemia has been reported following hematopoietic stem cell translantation, cold aglutinin mediated hemolytic anemia after CAR-T cell infusion has not been reported. Anti CD20 therapies are the preferred first line therapy in cold agglutinin-mediated hemolytic anemia but response is usually not sustainable. Daratumumab, a novel anti CD38 monoconal antibody which has been approved for treatment of plasma cell dyscrasias is a logical option in refractory immune hemolytic anemia when conventional therapies fail as it targets autoantibody-producing plasma cells.

Methods: A 22 years old male patient received anti CD-19 directed academic CAR-T cell (ISIKOK-19) infusion due to relapsed acute lymphoblastic leukemia following haploidentical stem cell transplantation from his mother. He presented with post CAR-T

cell refractory autoimmune hemolytic anemia. The case report presents treatment approach with Daratumumab for this patient.

Results: Patient with relapsed acute lymphoblastic leukemia following haploidentical stem cell transplantation was discharged on day +43 of CAR-T cell infusion but had to be re-admitted with acute Coombs positive hemolytic anemia on day +87. Bone marrow analysis was consistent with morphological and flow cytometric remission with full donor chimerism. Peripheral blood CAR-T cell level was adequate. Initial work-up excluded infectious and post-transplant lymphoproliferative etiologies. Low dose methylprednisolone of 20mg was chosen as first line treatment in order to avoid CAR-T cell apoptosis by steroid treatment. When there was no response IVIG was administered. Again no response was obtained. Autoantibodies were determined to be cold agglutinin in nature and weekly rituximab was commenced on day +92 . Anemia requiring massive transfusion persisted with severe hyperbilirubinemia reaching 30 mg/dL. Patient was administered a total of 97 units of RBC transfusion from beginning of hemolytic anemia and considering patient's severe condition and lack of rituximab response, Daratumumab 16 mg/kg per week was commenced on day + 137. Following the first dose patient's hemoglobin level continued to fall and blood transfusion and pulse steroid treatment at 250mg of prednisolone for 3 days had to be performed. Second, third and fourth doses of Daratumumab were administered weekly as scheduled. Transfusion requirement decreased from the second dose of Daratumumab, but patient received a total of 18 units of RBC transfusion whilst on 2 weeks of Daratumumab therapy. Steroid treatment was weaned down and stopped while consecutive weekly doses of Daratumumab continued. Patient reached a stable hemoglobin level following the third dose of daratumumab and remains steroid and transfusion free following the 4th and final dose of Daratumumab.

Conclusions: Cold agglutinin mediated hemolytic anemia post CAR-T cell treatment is a complex entity with lack of evidence based treatment . Anti CD38 monoclonal antibody daratumumab induces rapidly depletion of antibody producing plasma cells and can be an option in steroid, IVIG and Rituximab refractory cold agglutinin mediated autoimmune hemolytic anemia in CAR-T cell patients.

Disclosure: No conflict of interest

CAR-BASED CELLULAR THERAPY – PRECLINICAL

P082

Enhancement of long-term functionality of cd19 car-t cells by overexpression of tcf-1

H. Yao[1], L. Wang[1], T. Sauer[1], S. Wang[2], M. Lin[1], Q. Chen[1], H. Han[1], Y. Ding[1], G. Jiang[1], B. Neuber[1], M.-L. Schubert[1], C. Kleist[1], V. Eckstein[1], C. Müller-Tidow[1], A. Schmitt[1], M. Schmitt[1]

[1]Heidelberg University, Heidelberg, Germany, [2]Jiangsu Province People's Hospital, Nanjing, China

Background: Chimeric antigen receptor T (CAR-T) cells mediate impressive anti-tumor effects in B cell malignancies, but fewer than 50% of patients experienced long-term disease control due to T cell exhaustion, which is a state of antigen-specific T cell dysfunction and subsequent physical deletion. During exhaustion, T cells can upregulate various inhibitory receptors, including PD-1, Lag-3, Tim-3, and progressively loss their effector function and proliferative capacity. The transcription factor T cell factor 1 (TCF-1) plays an important role in T cell development and maturation. T cells expressing a high level of TCF-1 exhibit a stem-cell-like phenotype and maintain a better proliferative capacity. To investigate the role of TCF-1 in CD19 CAR-T cells, we performed this study.

Methods: CD19 CAR-T cells were manufactured using the third-generation retroviral CAR vector (SFG.CD19.CD28/4-1BB/ζ). Double transduced T (DT-T) cells were generated using the same CD19 CAR vector with an extra TCF-1 vector (SFG.CD70_1F6.CH3-IgG4h-CH2-IgG4h.Tcf7.NGFR). The expansion of CAR-T cells during the manufacturing was determined by cell counting. The apoptotic state of CAR-T cells at the end of generation was evaluated by western blot using anti-PARP, anti-caspase-3, and anti-cleaved caspase-3 antibodies. The cytokine release capacity of CAR-T cells was analyzed by an intracellular cytokine staining. Moreover, a co-culture system was applied to determine the long-term function of CAR-T cells, where effector cells and target cells were plated at a 1:1 or 1:2 ratio, followed by a repetitive tumor challenge. The proliferative capacity of CAR-T cells, the number of challenging procedures, the number of residual tumor cells, and the exhaustion status of CAR-T cells were investigated in a co-culture assay using flow cytometry.

Results: Both CD19 CAR-T cells and DT-T cells were successfully generated with a stable transduction efficiency (CD19 CAR-T cells: 80.2%±5.21, DT-T cells: 55.1% ± 5.91) as well as a potent and specific killing capacity. Of note, DT-T cells at the end of generation showed downregulated expression of PARP and cleaved caspase 3, suggesting a lower tendency to apoptosis than CD19 CAR-T cells. The array resulted in a greater cell number of DT-T cells than CD19 CAR-T cells. Although DT-T cells showed a lower killing efficiency in a 4-hour killing assay due to the reduction of cytokines (CD19 CART group: TNF-α 67.68% ± 4.57, IFN-γ 42.6% ± 10.1, CD107a 82.4% ± 4.2, DT group: TNF-α 52.3 ± 3.9, IFN-γ 29.6%±8.1, CD107a 61.8%±8.1), they exhibited a superior functionality than CD19 CAR-T cells in the long-term killing assay. An improved proliferative capability was observed in DT-T cells throughout the co-culture, showing a great expansion(-Day11, NT 41.97E7 ± 15.37E6, CD19 CART 28.53E6 ± 9.6E6, DT46.61E6 ± 10.69E6). The inhibitory receptors (PD-1, Tim-3, and Lag3) were reduced on DT-T cells when compared with CD19 CAR-T cells. The long-term killing ability of DT-T cells was dramatically improved, which was evidenced by an increased number of challenging procedures and a powerful reduction of residual tumor cell number.

Conclusions: Overexpression of TCF-1 might constitute a novel way to improve the functionality of CAR-T cells through the reduction of apoptosis, the improvement of proliferation, and the enhancement of the resistance to exhaustion.

Disclosure: Nothing to declare

P083

Disruption of cin85 enhances proliferation and cytotoxicity of cd19-specific car-t cells

M. Lin[1], Q. Chen[1], L. Wang[1], D. Sedloev[1], B. He[1,2], X. Yu[1], H. Han[1], G. Jiang[1], H. Yao[1], A. Schmitt[1], M. Schmitt[1], C. Müller-Tidow[1], T. Sauer[1]

[1]University Clinic Heidelberg, Heidelberg, Germany, [2]Nanfang Hospital, Guangzhou, China

Background: CD19-specific chimeric antigen receptor (CAR) T-cells (CD19CARTs) have significantly improved the outcome of patients with relapsed B-cell malignancies such as acute lymphoblastic leukemia (ALL) and certain type of non-Hodgkin's lymphoma (NHL). However, despite treatment with CD19CARTs, a significant proportion of patients eventually relapse, highlighting the need to further improve the functionality of CD19-CAR T-cell products. CIN85 protein, also known as SH3 domain-containing kinase-binding protein1 (SH3KBP1), has been shown to inhibit T-cell activation through its interaction with phosphatase

suppressor of TCR signaling-2 (Sts-2) within the T-cell receptor (TCR) complex. As the CAR-mediated activation of T-cells depends on pivotal components of the TCR, we hypothesized that the disruption of CIN85 may lead to the enhancement of CAR-mediated T cell activation, hereby improving the proliferation and anti-tumor efficacy of CD19 CAR T-cells.

Methods: Two days after activation using CD3 and CD28-specific antibodies, T-cells from healthy donors were retrovirally transduced with a third generation CD19 CAR construct containing the CD28 and 4-1BB co-stimulatory domain followed by a CRISPR/Cas9-mediated disruption of the CIN85 gene using ribonucleoprotein (RNP) complexes on day 6 (CIN85KO-CD19CARTs). Successful CAR transduction and CIN85 gene disruption were confirmed by flow cytometry (FACS) and western blot (WB) respectively. Subsequently, we performed in vitro studies to evaluate proliferation capacity, viability/apoptosis, and potential changes in the T-cell phenotype of CIN85KO-CD19CARTs. In addition, cytokine production upon antigen stimulation was determined by intracellular cytokine staining (ICS) and cytotoxicity was tested using a standard chromium (Cr51) release assay.

Results: During ex-vivo expansion, CIN85KO promoted enhanced proliferation of CD19CARTs compared to non-modified CD19CARTs leading to a higher expression of the proliferation marker Ki67 as detected by flow cytometry. In addition, we noticed a higher percentage of CAR expressing T cells in the CIN85-KO-CD19CART product compared to the control CAR T-cells. CIN85KO-CD19CARTs showed a higher surface expression of markers associated with T-cell activation such as CD69, CD25, HLA-DR, Tim-3, PD-1 and LAG-3 than CD19CARTs whereas CIN85 disruption did not affect the CD4/CD8 composition of the CAR T-cell product. Importantly, higher activation status did not lead to a higher rate of apoptosis and cell death on CIN85KO CD19 CAR T-cells. In both, the CD4 positive and CD8 positive subpopulations, a higher percentage of CIN85-CD19CARTs expressed surface markers associated with a central memory and effector memory phenotype whereas a lower percentage of CIN85-CD19CARTs exhibited a terminally differentiated T cell phenotype compared to non-modified CD19-CARTs. Functionally, CIN85-CD19CARTs secreted a significantly higher amount of activating cytokines such as IFN-γ, TNF-α and IL-2 and exhibited a stronger cytotoxic activity in the 51Cr release assay upon stimulation with CD19-positive tumor cells than CD19CARTs.

Conclusions: Disruption of CIN85 enhances proliferation, activation, and cytotoxic activity of CD19CARTs, while at the same time skewing the cells to a more favorable T-cell phenotype. Our results warrant further in-vitro and in-vivo studies to determine the potential of this approach to improve the functionality of CAR T-cells products .

Disclosure: Nothing to declare

P084

Impact of serum-free media on the expansion and functionality of cd19.car t cells

F. Eberhardt[1], A. Keib[1], A. Hückelhoven-Krauss[1], G. Jiang[1], A. Reichman[1], A. Schmitt[1], C. Müller-Tidow[1], M. Schmitt[1]

[1]University Hospital Heidelberg, Heidelberg, Germany

Background: Fetal bovine serum (FBS) or human serum (HS) is widely used in the production of chimeric antigen receptor T cells (CARTs). To overcome a lot-to-lot inconsistency and a risk of contamination the use of chemically-defined, animal-component free medium would be desirable. In this study, we compared three serum-free media to CART medium containing FBS.

Methods: After 12 days of CD19.CART culture, we assessed expansion, viability, transduction efficiency and phenotype by flow cytometry. Functionality of CARTs was tested by intracellular staining, chromium release assay and long-term co-culture assay: CARTs co-cultured with tumor cells for the period of 30 day were subjected to multiparametric flow cytometry.

Results: CARTs were cultured in different media such as Fujifilm™ Prime-XV™ T Cell CDM (FF), Takara Bio™ LymphoONE™ T-Cell Expansion Xeno-Free Medium (TB) or CellGenix™ TCM GMP-Prototype (CG). These CART cultures did not vary in terms of expansion and viability when compared to FBS-containing medium. Transduction efficiency and CD4 + /CD8 + ratio of CARTs were significantly lower for CARTs cultured in TB (64.5% vs. 86.5%, $P = 0.0167$; 1.4 vs. 2.8, $P = 0.0319$) and CG (65.8% vs. 86.5%, $P = 0.0358$; 1.5 vs. 2.8, $P = 0.0232$) compared to CARTs of serum-containing medium. The functionality of CARTs was tested by intracellular staining and chromium release assay. CARTs of CG had the highest frequency of IFNγ + and IFNγ + TNF-α + CARTs compared to CARTs cultured with serum (22.5% vs. 7.6%, $P = 0.0194$; 15.3% vs. 6.2%, $P = 0.0399$). IFNγ-expression of CARTs cultured in TB was also significantly higher (16.9% vs. 7.6%, $P = 0.0336$). These findings corresponded to the results of chromium release assay. On average of four effector-to-target cell ratios CARTs of CG showed the highest cytotoxicity ($P = 0.0182$), CARTs of FF showed a similar high effectiveness ($P = 0.0482$) and CARTs of TB had also a higher rate of killed tumor cells ($P = 0.0428$) than CARTs cultured with FBS. Phenotyping on day 12 of CART production did not show a significant difference in expression of exhaustion markers PD-1, LAG-3 and TIM-3. CARTs cultured in FF had a higher percentage of central memory CARTs (40.0% vs. 14.3%, $P = 0.0470$) than CARTs cultured with FBS, whereas CARTs of CG (9.8% vs. 14.3%, $P = 0.0092$) and TB (6.1% vs. 14.3%, $P = 0.0210$) had a significantly lower frequency. In contrast, CARTs of FF (6.2% vs. 24.2%, $P = 0.0029$) and CG (11.0% vs. 24.2%, $P = 0.0468$) had a lower frequency of naïve CARTs. Long-term cytotoxicity was tested by co-culture assay. Cells cultured with FBS showed the highest CART expansion and lowest expansion of target cells indicating the best long-term cytotoxicity of CARTs. On day 30 of co-culture CARTs cultured in FF, TB and CG had a higher expression of LAG-3 (non-significant; 91.7% vs. 41.1%, $P = 0.0306$; 86.8% vs. 41.1%, $P = 0.0205$) and TIM-3 (77.3% vs. 32.5%, $P = 0.0159$; 90.8% vs. 32.5%, $P = 0.0034$; 68.1% vs. 32.5%, $P = 0.0294$) compared to CARTs cultured with FBS.

Conclusions: We could demonstrate that functionality and expansion of CARTs are maintained in serum-free media. Given the advantages of freedom from bovine material and consistent quality, serum-free media keep promise for the future development of the field of GMP manufacturing of CARTs.

Disclosure: A.S.: Hexal and Jazz Pharmaceuticals (travel grants), Therakos/Mallinckrodt (research grant), TolerogenixX Ltd. (co-founder and part-time employee). C.M.-T.: Bayer AG (research support), Pfizer and Janssen-Cilag GmbH (advisory board member), Pfizer, Daiichi Sankyo, BiolineRx (grants and/or provision of investigational medical products), Pfizer (clinical trial financial support). M.S.: Apogenix, Hexal and Novartis (research support), Hexal and Kite (travel grants), bluebird bio, Kite and Novartis (financial support for educational activities and conferences), MSD (advisory board member), MSD, GSK, Kite and BMS ((co-)PI of clinical trials), TolerogenixX Ltd. (co-founder and shareholder). The other authors have no COI.

P085

Thomsen-friedenreich antigen cd176 as a new target of car-t cells to control multiple carcinomas

L.M. Beermann[1], M. Umland[1], A. Bonifacius[1], A.C. Dragon[1], L. Ruhl[1], P. Kehler[2], J. Gellert[2], T. Lischke[2], K. Zimmermann[1], S. Riese[1], F. Thol[1], B. Maecker-Kolhoff[1], A. Schambach[1], R. Blasczyk[1], M. Hudecek[3], B. Eiz-Vesper[1]

[1]Hannover Medical School, Hannover, Germany, [2]Glycotope, Berlin, Germany, [3]University Hospital Würzburg, Würzburg, Germany

Background: The generation and administration of Chimeric Antigen Receptor (CAR)-T cells represents a therapeutic approach that is approved for the treatment of distinct hematological malignancies and evaluated intensively for the extension to other tumor entities including solid tumors. CAR-T cell therapy relies on autologous lymphocytes, which are transduced to express a tumor antigen-specific CAR and transferred back into the patient, where they exhibit potent anti-tumor activity. However, CAR-T cells also cause adverse side effects such as the potentially life-threatening cytokine release syndrome. Moreover, CD19 CAR-T cell therapy does not distinguish between healthy and malignant B cells, indicating the necessity to develop CAR-T cells against more suitable target molecules. Nearly 80% of carcinomas and leukemia are positive for glycan structures from the Thomsen-Friedenreich (TF) antigen family, one of whose members is CD176 (Galβ1-3Gal*N*Acα1-R). Due to different modifications (e.g. sialylation or fucosylation), CD176 is not accessible for ligand binding on healthy cells, but exposed on several carcinomas including hepatocellular, breast, colorectal and lung carcinomas as well as various leukemic cells. Thus, CD176 is a potential target for immunotherapy of multiple carcinomas.

Methods: We designed a 2nd generation CAR to direct T cells against the carbohydrate epitope CD176. The ability of this CD176 CAR to initiate T cell signaling upon distinct target recognition of different carcinomas was tested in a reporter assay using a variety of tumor cell lines with different levels of CD176 expression as target cells. These included healthy CD176-negative cells, CD176-positive lung, breast and pancreatic cancer, as well as acute myeloid leukemia cell lines. Furthermore, primary CD176 CAR-T cells were generated and their functionality assessed in co-cultures with the same target cells evaluating the potential treatment of different tumor entities.

Results: A reporter assay revealed that T cell activation initiated by the CD176 CAR constructs upon recognition of cell lines derived from different carcinomas was specific to the presence of CD176. Upon co-cultivation of primary CD176 CAR-T cells with the same CD176-positive cells, the expression of activation markers (e.g. CD69) and the release of pro-inflammatory cytokines (e.g. IFN-γ, TNF-α) was equally upregulated in a target-specific manner. Moreover, the engineered T cells released cytotoxic mediators (e.g. granzyme B, granulysin) and exhibited cytotoxicity towards different cancer cell lines determined by 7-AAD staining in flow cytometry and confirmed by real-time impedance measurements (xCELLigence). Taken together, CD176-specific CAR-T cells were generated and showed a CD176-specific cytotoxicity towards a variety of different cancer cell lines.

Conclusions: Due to its differential modification – being accessible for ligand or antibody binding on malignant cells, but not accessible on healthy tissue – the carbohydrate antigen CD176 is a promising target for cancer immunotherapy. Our results demonstrate that CD176-specific CAR-T cells specifically recognize and react towards target cells from different tumor entities. Generating CAR-T cells targeting a structure present on a variety of tumor entities might allow for the simultaneous targeting of multiple carcinomas in the future.

Disclosure: Nothing to declare.

P086

Cell therapy based on nkg2d-car transduced cytotoxic cells against acute myeloid leukemia

L. Córdoba[1,2], E. Castellano[1,2], A. Valeri[1,2], P. Rio[3], A. García-Ortiz[1,2], J. Encinas[1], E. Maroto[1,2], D. Lee[4], D.J Powell Jr[5], J. Martínez López[1,2], A. Leivas[1,2]

[1]Hospital Universitario 12 de Octubre, Madrid, Spain, [2]Centro Nacional de Investigaciones Oncológicas, Madrid, Spain, [3]Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas, Madrid, Spain, [4]The Research Institute at Nationwide Children's Hospital, Ohio, United States, [5]University of Pennsylvania, Philadelphia, United States

Background: Acute Myeloid Leukemia (AML) is a hematological malignancy still incurable for almost all patients. Chimeric Antigen Receptor (CAR) therapy is showing astonishing results in other hematological disorders but remains challenging in AML since no specific antigens have been described yet. Using NKG2D as a CAR, a natural NK receptor with 8 ligands (NKG2DLs) overexpressed in several tumors, could surmount AML targeting limitations. T cells are considered the gold standard immune effector cells for CAR therapy, but they show some toxicities that could be overcome using other cells such as activated and expanded natural killer cells (NKAE), that can be used in an allogeneic context with no GvHD, have natural anti-tumor properties and have demonstrated to be clinically safe. In this project we analyze the anti-leukemia activity and safety of peripheral blood NKAE cells lentivirally transduced with an NKG2D-41BB-CD3z CAR.

Methods: Peripheral blood mononuclear cells (PBMCs) from healthy donors (HD) and/or AML patients were cocultured during 7 days with the irradiated cell line k562-mb21-41BBL, when NKAEs were isolated by magnetic immunodepletion and lentivirally transduced with an NKG2D-41BB-CD3z CAR. CAR expression was measured up to 13 days post-transduction by flow cytometry. Cytotoxic activity against AML cell lines was performed by Propidium Iodide and Annexin V staining. Toxicity was evaluated by Europium-TDA assays. Effector cells were characterized by flow cytometry and Cytometric Bead Arrays were done to study cytokine release profile.

Results: AML can be targeted with an NKG2D CAR since all patients studied express at least one NKG2DL. Primary NK cells can be lentivirally transduced with an NKG2D CAR, showing a modest but stable CAR expression up to 13 days after transduction (23% ±4,7% NKG2D +, 33,35% ±4,25% GFP +). CAR-NKAE cells perform robust cytotoxicity towards MOLM-13 AML cell line after 24h of coculture at an effector:target ratio of 1:1, exerting a quasi-total lysis of AML cells. This represents a significant increase in anti-leukemia effect compared to untransduced NKAE (92,6% ±0,3% vs 72,2% ±10%, $p = 0{,}0138$). Surface expression of relevant molecules for NK activity showed that NKp30, NKp44 (natural cytotoxicity receptors), CD69 (early activation marker), CD25 (IL2R alpha chain), FasL (mediates FasL-mediated cytotoxicity), NKp80 (C-type lectin-like surface-activating receptor) and TRAIL (TNF-Related Apoptosis Inducing Ligand) were more expressed by transduced NKAE. Cytokine release profile revealed a higher production of IL-6, IL-17A, sFasL and IFNg by CAR-NKAE. These results suggest that the studied mechanisms could be underlying the increased anti-tumor activity shown by CAR-NKAE. We did not observe relevant toxic effect of none of the cells against PBMCs from HD. Low toxicity was found against NL-20 lung cell line, but there were no differences between NKAE and CAR-NKAE.

Conclusions: Our preliminary results show that primary NK cells from HD and/or AML patients can be lentivirally transduced with a second generation NKG2D CAR, exerting a robust anti-leukemia activity towards AML cell lines and a safe profile over healthy tissues. Therefore, NKG2D CAR NKAE could be considered a promising approach to treat AML.

Disclosure: DJPJ holds patents in CAR-T-cell therapy field. DAL declares an equity interest, advisory role, and intellectual property

licensing to CytoSen Therapeutics and Kiadis Pharma, and advisory role with Caribou BioSciences and Courier Biosciences. PR has licensed medicinal products and receives research funding and equity from Rocket Pharmaceuticals, Inc., Patents & Royalties, Research Funding. The remaining authors declare no competing interests.

P087

Comparison of second and third generation car33-t cells in terms of proliferation and cytotoxicity in acute myeloid leukemia

A. Lauk[1], Y. Liu[1,2,3], H. Yao[1], M.-L. Schubert[1], S. Wang[1,4,5], M.F. Blank[1], C. Cui[1,6], M. Janssen[1], C. Schmidt[1], S. Göllner[1], C. Kleist[1], F. Zhou[1], J.-U. Rahfeld[7], T. Sauer[1], M. Schmitt[1], C. Müller-Tidow[1,2,3]

[1]University hospital Heidelberg, Heidelberg, Germany, [2]Molecular Medicine Partnership Unit (MMPU), Heidelberg, Germany, [3]European Molecular Biology Laboratory (EMBL), Heidelberg, Germany, [4]First Affiliated Hospital of Nanjing Medical University, Nanjing, China, [5]Collaborative Innovation Center for Cancer Personalized Medicine, Nanjing, China, [6]Shanghai University of Medicine and Health Sciences, Shanghai, China, [7]Fraunhofer Institute for Cell Therapy and Immunology IZI, Halle (Saale), Germany

Background: Since CD33 is expressed on over 90% of acute myeloid leukemia (AML) blasts and leukemic stem cells and is indispensable for cell survival, it is a promising target for immunotherapy in AML, such as CAR-T cells or antibody drug conjugates.

Methods: To compare the functionalities of second generation CARs and third generation CARs we generated two second generation anti-CD33 CAR (CAR33) with either 4-1BB or CD28 as costimulatory domains and a third generation CAR33. We evaluated the proliferation and cell viability of second and third generation CAR33-T cells. The cytolytic capacity of the CAR33-T cells against AML cell lines, primary AML blasts and human stem and progenitor cells (HSPCs), was determined by Chromium51 release assay and the antigen-specific response by cytokine secretion assay. The long-term killing capacity was assessed by coculturing CAR-T cells with target cells for 10 days with rechallenging of the CAR-T cells on every second day. To prove the antigen specificity of CAR33-T cells, functional assays were performed against CD33 positive and negative target cells.

Results: First, the cytotoxicities of CAR33-T cells are antigen-specific and antigen-dependent. Only CD33-positive, but not CD33-negative cells were killed by CAR33-T cells and could stimulate CAR33-T cells to secrete cytokines. Second, we found that the second generation CAR33-T cells with CD28 as costimulatory domain (2G.CD28.CAR33-T) had comparable viability but reduced proliferation capacity compared to the third generation CAR33-T cells (3G.CAR33-T), whereas the second generation CAR33-T cells with costimulatory domain 4-1BB (2G.4-1BB.CAR33-T) expanded less with lower viability. In terms of short- and long-term killing capacity and levels of cytokine release 2G.CD28.CAR33-T cells and 3G.CAR33-T cells showed similar abilities, while 2G.4-1BB.CAR33-T cells exhibited the lowest potential.

Conclusions: In summary, third generation CAR33-T cells exhibited improved properties in terms of viability and proliferation as well as short- and long-term anti-tumor activity when compared to second generation CAR33-T cells.

Disclosure: Maximilian Felix, Blank: Molecular Health GmbH (consultant)

Maria-Luisa, Schubert: Kite/Gilead, Takeda (consultant).

Michael, Schmitt: Apogenix, Hexal and Novartis (research support). Hexal, Kite/Gilead (travel grants). Bluebird bio, Kite, Novartis (financial support for educational activities and conferences). MSD (advisory board member). MSD, GSK, Kite, BMS ((co-) PI of clinical trials). TolerogenixX Ltd. (co-founder and shareholder).

Carsten, Müller-Tidow: Bayer AG (research support). Pfizer, Janssen-Cilag GmbH (advisory board member). Pfizer, Daiichi Sankyo, BiolineRx (grants and/or provision of investigational medicinal products).

Christian, Kleist: TolerogenixX Ltd. (co-founder and shareholder).

Tim, Sauer: Pfizer, Gilead, Amgen, Takeda, Astellas, BMS (advisory board member), AbbVie, Pfizer (financial support for educational activities and conferences), Matterhorn Biosciences, Ridgelien Discovery (consultant).

P089

Cd19-car-inkt cell activity is enhanced by pd-1 checkpoint inhibition while preventing alloreactivity

E. Moraes Ribeiro[1], A.-M. Nitulesco[1], R. Schairer[1], H. Keppeler[1], F. Korkmaz[1], B. Neuber[2], C. Schneidawind[1], M. Schmitt[2], D. Schneidawind[1]

[1]University Hospital Tuebingen, Tuebingen, Germany, [2]University Hospital Heidelberg, Heidelberg, Germany

Background: Relapse and graft-versus-host disease (GvHD) are the main causes of morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT). We recently showed that human iNKT cells inhibit alloreactive donor T cells and promote graft-versus-leukemia (GvL) effects. Now, we aim to further enhance the antileukemic potential of iNKT cells by introducing a chimeric antigen receptor (CAR) while maintaining their tolerogenic properties making them an ideal cytotherapeutic candidate to treat relapse after allogeneic HCT.

Methods: CD19-CAR-iNKT cells were co-cultured with acute lymphoblastic leukemia (ALL) and Burkitt lymphoma (BL) cells. Cytotoxicity was analyzed by subsequent multiparametric flow cytometry and multiplex analysis. To assess the immunomodulatory properties of CD19-CAR-iNKT cells, T-cell activation (flow cytometry) and proliferation (CFSE dilution) of conventional T cells were analyzed after co-culture with allogeneic mo-DCs in presence or absence of CD19-CAR-iNKT cells.

Results: CD19-CAR-iNKT cells showed robust cytotoxic activity against ALL and BL cell lines and primary patient cells. Multiplex analysis revealed the release of inflammatory cytokines such as IFN-γ and TNF as well as cytotoxic effector molecules like granzyme A, granzyme B and perforin. Interestingly, PD-1 expression was increased on CD19-CAR-iNKT cells after being challenged with lymphoma cells. Consequently, adding the checkpoint inhibitor nivolumab further increased the activity of CD19-CAR-iNKT cells. Regarding their tolerogenic properties, CD19-CAR-iNKT cells retained their ability to induce apoptosis of mo-DCs through CD1d signaling independent of the CAR resulting in reduced activation and proliferation of alloreactive T cells.

Conclusions: We demonstrate that CD19-CAR-iNKT cells efficiently lyse CD19 + leukemia and lymphoma cells through their CAR while preventing alloreactive T cell responses interacting with dendritic cells. Checkpoint inhibition may further increase their cytotoxic activity without exacerbating the risk of GVHD after allogeneic HCT making them an ideal cytotherapeutic to treat relapse in this challenging clinical setting.

Disclosure: Nothing to declare

P090

Functionality and endurance of gmp-standard bcma-car-t cells at different timepoints

G. Jiang[1], A. Keib[1], U. Höpken[2], B. Neuber[1], J. Joedicke[2], D. Sedloev[1], L. Wang[1], A. Reichman[1], A. Hückelhoven-Krauss[1], B. He[1], F. Eberhardt[1], C. Müller-Tidow[1], M. Wermke[3], A. Rehm[2], A. Schmitt[1], M. Schmitt[1]

[1]University Clinic Heidelberg, Heidelberg, Germany, [2]Max-Delbrück Center for Molecular Medicine (MDC), Berlin, Germany, [3]University Hospital Carl Gustav Carus Dresden, Dresden, Germany

Background: Multiple myeloma is a hematological disease characterized by an uncontrolled proliferation of plasma cells. New therapeutical agents developed survival rates but the outcome of the disease remains to be improved. The search for target antigens for CAR-T cell therapy against multiple myeloma yielded with the B-cell maturation antigen (BCMA) a possible candidate. Several studies of BCMA-directed CAR-T-cell therapy showed promising results.

Methods: Second generation BCMA-CAR-T cells were manufactured at GMP standard by using the CliniMACS Prodigy® device. Cytokine-release in BCMA-CAR-T cells after stimulation with BCMA positive versus negative myeloma cell lines, U266/HL60, was determined by intracellular staining and flow cytometry. The short-term cytotoxic potency of CAR-T cells was evaluated by chromium-51 release, while the long-term potency used co-culture (3 days/round) at the effector:target cell ratio of 1:1 and 1:4. To evaluate the activation and exhaustion of CAR-T cells, exhaustion markers were assessed by flow cytometry. Stability was tested by comparison of these evaluation on different timepoints: d0 as well as d + 14 and d + 90 of cryopreservation.

Results: BCMA-CAR-T cells can release much more cytokines upon stimulation with U266 cells in all donors (20.29 ± 4.868 and 1.193 ± 0.560, $P = 0.0199$; 20.16 ± 5.122 and 0.764 ± 0.597, $P = 0.0194$; 62.21 ± 2.029 and 1.348 ± 0.134, $P = 0.0004$) but not HL60 cells (1.820 ± 0.866 and $1{,}193 \pm 0.560$, $P = 0.3102$; 1.533 ± 0.627 and 0.764 ± 0.597, $P = 0.0921$; 2.922 ± 0.667 and 1.348 ± 0.134, $P = 0.0602$). Interestingly TNFa release was higher than IFNg on every timepoint (58.80 ± 8.890 and 18.92 ± 4.604, $P = 0.0188$; 59.35 ± 4.000 and 20.68 ± 5.198, $P = 0.0179$; 72.19 ± 2.379 and 63.32 ± 0.723, $P = 0.0266$). For CD8 + BCMA-CAR-T cells, TNFa and IFNg had the same level of cytokine-release (47.61 ± 10.07 and 30.00 ± 1.143, $P = 0.076$; 40.99 ± 10.42 and 33.88 ± 8.733, $P = 0.1922$; 72.85 ± 4.142 and 68.48 ± 4.195, $P = 0.4590$). However, CD4 + BCMA-CAR-T cells had lower level of IFNg than TNFa (10.40 ± 3.332 and 61.86 ± 10.57, $P = 0.0065$; 63.99 ± 6.929 and 13.50 ± 5.956, $P = 0.0134$; 49.82 ± 4.682 and 76.72 ± 4.737, $P = 0.0345$). There was no significant difference in cytokine-release after cryopreservation: neither double positive CAR-T cells ($P = 0.9350$) nor single positive (TNFa/IFNg) CAR-T Cells ($P = 0.2786$, $P = 0.2489$). Killing efficiency of U266 cells correlated with the dose of CAR-T cells in a classical 4-hour chromium-release assay. There was no significant difference after cryopreservation on timepoints d + 14 or d + 90 ($P = 0.1300$, $P = 0.9602$). As for long-term potency, after 3-rounds co-culture, BCMA-CAR-T cells reached to dominant position while U266 cells nearly disappeared at both ratios. As for endurance of BCMA CAR-T cells function, BCMA CAR-T cells kept their ability to kill all U266 cells over six rounds. Exhaustion markers were detected to evaluate CAR-T cells: LAG3 declined when CAR-T cells were activated and proliferated but decreased when they failed to kill; PD1 showed a similar trend as LAG3 but TIM3 had a curve trend.

Conclusions: BCMA-CAR-T cells manufatured under GMP conditions possessed the ability for robust and specific killing of target tumor cells with a higher release of cytokines. Even after 14 or 90 days of cryopreservation, their cytotoxic functions were maintained at the same level. This give clinicians enough time to schedule the timepoint of BCMA CAR-T cell application to the patient.

Disclosure: Nothing to declare

CELLULAR THERAPIES OTHER THAN CARS

P091

Unmanipulated donor lymphocyte infusion (dli) after ab-t and b-cell depleted haploidentical stem cell transplantation

C. Rosignoli[1], F. Galaverna[1], D. Pagliara[1], M. Algeri[1], R. Carta[1], M. Becilli[1], E. Girolami[1], S. Biagini[1], G. Li Pira[1], G. Leone[1], A. Meschini[1], S. Lazzaro[1], G. Del Principe[1], E. Boccieri[1], F. Quagliarella[1], M.L. Catanoso[1], C. Canino[1], F. Del Bufalo[1], P. Merli[1], F. Locatelli[1,2]

[1]Istituto di Ricovero e Cura a Carattere Scientifico Ospedale Pediatrico Bambino Gesù, Rome, Italy, [2]Sapienza University, Rome, Italy

Background: Allogeneic hematopoietic stem cell transplant (allo-HSCT) represents an effective curative option for several malignant diseases; relapse remains the main cause of treatment failure. ab-T and B-cell depleted haploidentical HSCT offers a unique platform to evaluate the effect of post-HSCT Donor Lymphocyte Infusion (Haplo-DLI) in high-risk patients.

Methods: Between August 2016 and July 2021, 32 high-risk patients received unmanipulated haplo-DLI after an ab-T and B-cell depleted haploidentical-HSCT (tab.1). Haplo-DLI were prophylactic in 19 cases due to high-risk disease [very high risk at diagnosis, previous allo-HSCT and positive minimal residual disease (MRD) at HSCT] and pre-emptive in 13 cases due to early post-transplant positive MRD.

Results: Haplo-DLI were infused at median time of 4,2 months after transplant (range 1-43). Median CD3 +, CD4 + and CD8 + infused cells were 0,473x10^6/kg (range 0,059-3,044), 0,289x10^6/kg (range 0,022-2,140) and 0,160x10^6/kg (range 0,012-0,069), respectively. Fifteen patients received more than one infusion (table 1). Six patients developed grade III-IV acute GvHD at a median of 43 days after Haplo-DLI (range 34-76), the cumulative incidence of this complication being 19% (95% CI 9-38%). Seven out of 13 patients (54%) who received pre-emptive Haplo-DLI remained disease-free over time, while response rate for prophylactic haplo-DLI was 74% (14/19). With a median follow-up of 24 months, global progression free survival (PFS) and overall survival (OS) were 64% (95% CI 45-78%) and 71% (95% CI 50-84%), respectively; non relapse mortality (NRM) was 13% (95% CI 5-13%).

Table 1. Patients characteristics.

Median age at transplant, ys (range)	7 (0-24)
Sex, M/F	16/16
Disease, n (%)	
ALL	21 (66)
AML	7 (22)
MDS	2 (6)
CML	1 (3)
HL	1 (3)

Disease status at HSCT, n (%)	
MRD-	13 (41)
MRD +	14 (44)
active disease	5 (16)
Previous allo-HSCT, n (%)	7 (22%)
Conditioning, n (%)	
MAC	28 (87)
RIC	4 (12)
DLI indication, n (%)	
prophylaxis	19 (57)
pre-emptive	13 (43)
Time interval between HSCT- 1^ DLI	
median days (range)	120 (24-1238)
Number of DLI, n (%)	
2	17 (53)
3	8 (25)
4	7 (22)
CD3x10^6/kg (median) (range)	0,473[MP1] (0,059-3,044)
CD4 × 10^6/kg (median) (range)	0,289 [MP2] (0,022-2,140)
CD8 × 10^6/kg (median) (range)	0,130[MP3] (0,012-0,069)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; DLI, donor lymphocyte infusion; GvHD, graft versus hosti disease; HL, Hodgkin lymphoma, HSCT, hematopoietic stem cell transplant; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MRD, minimal residual disease; RIC, reduced intensity conditioning.

Conclusions: Unmanipulated haplo-DLI after ab-T and B-cell depleted haploidentical-HSCT were feasible and safe, with encouraging result in terms of PFS and clearance of MRD.

Disclosure: Nothing to declare

P092

Use of mesenchymal stromal cells under special situations for complications of allogeneic HSCT. A single center experience

R. Alonso Trillo[1], M. Vicente[2], M.E. Martínez-Muñoz[3], C. Fernández-Maqueda[3], C. De Miguel[3], G. Bautista[3], R. Sánchez[1], T. Martín[1], R. Zafra[1], N. Panadero[3], I. Salcedo[3,2], F.R. Duarte[1,3,2]

[1]Fundación para la Investigación Biomédica Hospital Universitario Puerta de Hierro, Majadahonda, Spain, [2]Universidad Autónoma de Madrid, Madrid, Spain, [3]Hospital Puerta de Hierro, Majadahonda, Spain

Background: Mesenchymal Stromal Cells (MSC) are multipotent non-hematopoietic cells with immunomodulatory and regenerative properties that are being used as a treatment for allogeneic HSCT complications. Access to advanced-therapy medicinal products on a named-patient compassionate-use basis is available in special situations and requires pharmacovigilance and subsequent audit and investigation of their safety and efficacy.

Methods: Retrospective analysis of the use of MSC in our center in a compassionate-use basis for complications of allogeneic HSCT (2006 to 2021). Use of MSC in clinical trials are excluded. We use an AEMPS approved investigational MSC product derived from bone marrow of healthy donors and expanded under GMP conditions (PEI 10-146).

Results: Sixty-two allogeneic HSCT recipients (37 male, 60%; median age 48 years, range 17-73; 29 AML/MDS, 10 ALL, 8 NHL/CLL, 4 MM, 4 SAA, 7 other indications; 27 matched related, 15 matched unrelated, 14 cords and 6 haploidentical donors) received a total of 248 infusions (median 4, range 1-16) of approximately $1x10^6$ MSC cells/kg for the following transplant complications: 50 GVHD (81%), 8 hemorrhagic cystitis (HC; 13%), 3 cytopenia (5%) and 1 transplant-associated thrombotic microangiopathy (2%). GVHD target organ involvement included 39 gastrointestinal (78%), 34 cutaneous (68%) and 18 hepatic (36%), with severity score 2, 3 and 4 in 20 (40%), 17 (34%) and 13 (26%), respectively. One GVHD case with concomitant CMV infection received MSC as first-line to spare further immunosuppression with corticosteroids, but all others had MSC as second-line after failure of corticosteroids, alone in 14 cases (29%) and in association with other drugs (etanercept, ruxolitinib, alemtuzumab, basiliximab and vedolizumab) in the rest. Thirty-seven patients (74%) achieved an overall response at day +28 from MSC treatment, including 17 (34%) with complete response and 20 with partial response (40%). All-cause mortality was 26% (13/50) at 90 days from treatment. Clinical response to MSC was associated with survival at day 90 ($p = 0.003$). Eight cases with grade 3 (3, 37%) or 4 (5, 63%) HC refractory to first-line therapy (most commonly continuous saline irrigation and hyaluronic acid) received MSC as a named-patient compassionate-use basis, achieving 3 complete responses, 2 partial responses and 3 refractory cases by day +28 from treatment. By day +90, four patients died and the other four were in complete response from their HC. Overall, in our named-patient compassionate-use series in the various indications, overall response rate at day +28 was 69%, complete response rate 32%, and 44 patients (71%) were alive 90 days after the first MSC infusion.

Conclusions: In the absence of formal regulatory approval, access to MSC in special situations including named-patient compassionate-use is available for life-threatening transplant complications which cannot be treated satisfactorily with authorized alternatives. This study audits our practice with MSC in transplant complications and suggests that their use is safe and effective in this setting.

Disclosure: Nothing to declare

P094

The role of donor gamma delta t cells in acute myeloid leukemia control after allogeneic hematopoietic cell transplantation

N. Bejanyan[1], M. Davila[1], C. Cubitt[1], X. Yu[1], J. Kim[1], J. Kroeger[1], B. Bhatnagar[2], J. Conejo-Garcia[1], C. Anasetti[1]

[1]Moffitt Cancer Center, Tampa, United States, [2]Wheeling Hospital, Wheeling, United States

Background: Relapse after allogeneic hematopoietic cell transplantation (HCT) is the leading cause of mortality in patients with acute myeloid leukemia (AML). Increased recovery of γδ T lymphocytes after HCT is associated with better disease-free survival. The γδ T cells have MHC-independent, potent cytotoxic activity against AML and other neoplastic cells. Thus, donor γδ T cells can play an important role in regulating AML relapse after

HCT. We assessed if γδ T cell clonality, distinct clones or specific receptor expression can predict AML relapse prevention after HCT.

Methods: We used previously frozen banked bone marrow biopsy samples containing viable mononuclear cells, obtained at AML diagnosis, at 3 months and at relapse after HCT. We performed flow cytometry sorting of γδ T cells, extraction of genomic DNA and γδ T cell clonality assessment by T cell receptor γ locus (TRG) sequencing (ImmunoSEQ platform). Multiparametric flow cytometry was used to assess the expression of γδ T cell receptors and AML blast ligands.

Results: We identified 24 adult (18 years and older) patients with available bone marrow samples who received their first HCT for AML in complete remission: 12 patients did not relapse, and 12 patients relapsed after HCT. Non-relapsed patients had higher TRG clonotype diversity at 3 months post-HCT as compared to the relapsed patients. Non-relapsed vs. relapsed patients had higher expression of TIGIT (46.5% vs. 34.2%, $p = 0.03$) and CTLA4 (72.8% vs. 34.6%, $p = 0.05$) receptors on γδ T cells (CD3 + /γδ TCR +) but similar expression of NKG2D/CD314 (60.2% vs. 79.2%, $p = 0.15$). The expression of corresponding ligands on AML blasts at diagnosis for CD155 (TIGIT ligand) was 11.4% vs. 17.9% ($p = 0.85$), for CD86 (CTLA-4 ligand) was 69.3% vs. 64.7% ($p = 0.88$) and for MICA/B (NKG2D ligand) was 3.2% vs. 0.26% ($p = 0.1$) in non-relapsed vs. relapsed patients, respectively.

Comparing 3-month and relapsed samples in patients relapsing after HCT, there was decreased TRGV9-1, TRGV7-1 and TRGJP-1 repertoires from 3 months to relapse. Conversely, the usage of TRGV5-1 gene was increased at the time of relapse.

Conclusions: We found that higher diversity of donor TRG clonotypes are associated with AML relapse prevention after HCT. In addition, decreased usage of TRGV9-1 and TRGV7-1 genes influences higher relapse risk after HCT. This study findings can help to implement γδ T cell immunotherapy strategies against AML.

Disclosure: Funding Source: ORIEN NOVA Award M2Gen

COI: Nelli Bejanyan serves on advisory board for Medexus pharma, Magenta therapeutics and CTI Biopharma.

Marco Davila has equity in Adaptive Biotechnologies and Precision Biosciences, and has received licensing fees and research support from Atara Biotherapeutics and CRISPR.

P095

Sequential conditioning with flamsa-fludarabine-busulfan does not improve outcomes after allogeneic-stem cell transplantation when compared with treosulfan-fludarabine conditioning in higher risk mds patients

R. Massoud[1], E. Klyuchnikov[1], H. Naim[1], N. Gagelmann[1], A. Kunte[1], C. Langebrake[1], R. Adjalle[1], D. Janson[1], F. Ayuk[1], C. Wolschke[1], N. Kröger[1]

[1]University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Sequential therapy as conditioning in allogeneic stem cell transplantation (SCT) is frequently used in higher risk MDS, but comparisons with another regimen are rare.

Methods: In this retrospective study conducted at the University Medical Center Hamburg/Germany we compared the impact of FLAMSA-Busulfan-Fludarabine ($n = 81$) with Treosulfan-Fludarabine ($n = 95$) conditioning on post-transplant outcomes in MDS. FLAMSA-FB regimen consists of fludarabine (30 mg/m^2; total dose 120 mg/m^2), amsacrine (100 mg/m^2; total dose 400 mg/m^2), and cytarabine (1 g/m^2; total dose 4 g/m^2) therapy from days -11 to -8, followed by a three-day interval without therapy and busulfan from day -4 to -3 with a total dose of 6.4mg/Kg and fludarabine on day -4 and -3 (30 mg/m^2, total dose 60mg/m^2). Treo-Flu regimen consisted of Treosulfan (12 g/m^2, total dose 36 mg/m^2) on days -6 to -4 and fludarabine (30 mg/m^2; total dose 150 mg/m^2) on days -6 to -2.

Results: In the FLAMSA-FB group 11 patients (13%) had related donor (MRD 11% MMRD 2%) and 70 patients (86%) had unrelated donors (MUD 54% MMUD 32%), compared to 17 patients from MRD (18%) and 78 patients from unrelated donor (MUD 61% MMUD 21%) in the Treo-Flu group ($p = 0.1$). ATG was the major GvHD prophylaxis in both arms. Second allograft was seen only in the Treo-Flu group ($n = 9$) and the median number of blasts in bone marrow at transplantation were higher in the FLAMSA-FB than in the Treo-Flu group (9vs 2%, $p < 0001$) IPSS- low, intermediate 1 and 2 and high risk was 3%,15%,57% and 26% in the FLAMSA-FB arm and 13%, 53%, 25% and 9% in the Treo-Flu arm, respectively.

Median platelet and neutrophil engraftment were significantly delayed in the Treo-Flu group when compared to the FLAMSA-FB group: 15 vs 12 days($p = 0.02$) and 13 vs 12 days ($p = 0.009$).

The cumulative incidences of aGVHD grade II-IV, III-IV and cGvHD were similar between the two groups: 37%, 9% and 49% in the FLAMSA-FB group and 37%, 16% and 47% in the Treo-Flu group ($p = 0.2$; $p = 0.7$ and $p = 0.9$, respectively).

The cumulative incidence of non-relapse mortality at 5 years and relapse was 23% and 35% in the FLAMSA-FB and 14% and 23% in the Treo-Flu group ($p = 0.07$ and $p = 0.06$, respectively). After a median follow-up of 30 months (range, 1-218), the 3-year overall Survival (OS) and progression free survival (PFS) were in a univariate analysis higher in the Treo-Flu group: 72 vs 51% ($p = 0.001$) and 58 vs 45% ($p = 0.04$), respectively.

In a multivariable analysis for OS only low IPSS (low-intermediate I vs Intermediate II-high risk) (HR = 0.2, 95%CI 0.2-0.95, $p = 0.037$) was associated with improved OS. Conditioning regimen, patient age (≤61 vs >61) donor age ((≤34 vs >34), type of Donor (MRD vs MUD vs MMRD vs MMUD), status at transplant (progressive/refractory disease vs others) and blasts in bone marrow (≤3.5 vs >3.5) had no significant impact on OS.

Conclusions: Acknowledging the retrospective nature of our study, our results suggest that sequential conditioning with FLAMSA-FB does not improve survival in MDS-patients undergoing allo-SCT.

Disclosure: nothing to decalre

P096

Gene editing of the immune checkpoint nkg2a enhances allogenic nk cell mediated cytotoxicity against patient-derived primary multiple myeloma cells

T. Bexte[1,2,3], J. Alzubi[4,5], L.M. Reindl[1,2], P. Wendel[1,2,3], R. Schubert[6], E. Salzmann-Manrique[7], I. von Metzler[8], T. Cathomen[4,5], E. Ullrich[1,2,3]

[1]Experimental Immunology, Hospital of the Goethe University Frankfurt, Frankfurt, Germany, [2]Frankfurt Cancer Institute, Goethe-University, Frankfurt am Main, Germany, [3]German Cancer Consortium (DKTK) partner site Frankfurt/Mainz, Frankfurt am Main, Germany, [4]Institute for Transfusion Medicine and Gene Therapy, Medical Center – University of Freiburg, Freiburg, Germany, [5]Center for Chronic Immunodeficiency, University of Freiburg, Freiburg, Germany, [6]Hospital of the Goethe University Frankfurt, Frankfurt, Germany, [7]Hospital of the Goethe University Frankfurt, Frankfurt am Main, Germany, [8]Hospital of the Goethe University Frankfurt, Frankfurt am Main, Germany

Background: Natural Killer (NK) cells are known for their high intrinsic cytotoxic capacity and the possibility to be applied as

'off-the-shelf' third party donor cell therapy. In cancer patients suffering from multiple myeloma (MM), an elevated number of NK cells has been correlated with a higher overall-survival rate. However, NK cell function can be impaired by upregulation of inhibitory receptors, such as immune checkpoint NKG2A (natural killer group 2A).

With the aim to overcome suppression of anti-tumor NK cell function, we used the CRISPR-Cas9 nuclease to knockout (KO) the *killer cell lectin like receptor C1* (KLRC1) locus encoding NKG2A in primary NK cells, which led to significant increase in NK-cell mediated cytotoxicity against both MM cell lines and patient-derived MM cells.

Methods: Primary NK cells were isolated from PBMCs from healthy donors. Upon transfer of *KLRC1*-targeting CRISPR-Cas9 nuclease, *KLRC1* KO-NK cells were expanded using IL-15 cytokine under feeder-cell free conditions. *KLRC1* KO was analyzed using Tracking of Indels by Decomposition (TIDE), T7 endonuclease I (T7E1) assay and next-generation sequen cing (NGS). NKG2A expression of KO-NK cells was compared to non-edited NK cells (NT-NK cells) by flow cytometry. Cytotoxicity of NK cells was analyzed against MM-tumor cell lines and allogenic MM patient-derived tumor cells.

Results: The chosen CRISPR-Cas9 nuclease disrupted 70-86% of *KLRC1* alleles, as evaluated by T7E1 (70%), TIDE (75%), or NGS (86%). *KLRC1* KO significantly reduced NKG2A expression on gene-edited NK cells analyzed after three weeks of cultivation compared to NT-NK cell population (KO-NK cells 43.5% vs NT-NK cells 90%; $n = 10$, $p < 0.05$).

Inhibition of NKG2A-expressing NK cells is mainly related to HLA-E ligand expression, which is often over expressed in anti-tumor response and can be particularly upregulated by IFN-γ. After 24h co-culture of IFN-γ pre-stimulated U266 tumor cells, they showed increased lyses induced by NKG2A KO-NK cells compared to NT-NK cells at different effector:target (E:T) ratio (E:T 2.5:1, 40% vs 15.5%, 1:1, 42.2% vs 13.4%, 0.5:1, 12.3% vs 5.6%; $n = 4$, $p < 0.05$). Additionally, after co-culture of NK cells with non-stimulated MM1.S, significantly higher lyses for NKG2A KO-NK cells compared to NT-NK killing capacity could be shown (E:T 2.5:1, 82% vs 70%; 1:1, 82.2% vs 61%; 0.5:1, 72.3% vs 38.9%; $n = 5$, $p < 0.5$).

To address the increased killing capacity in a preclinical setting, we isolated primary tumor cells from bone marrow aspirates of differently treated MM patients. Allogenic NKG2A KO-NK cells showed significantly higher primary MM tumor cells lyses as compared to allogenic NT-NK cells (E:T 2.5:1, 40.7% vs 35.5%, 1:1, 36.7% vs 30.8%, 0.5:1, 29.7% vs 25.6%; $n = 10$ $p < 0.05$).

Conclusions: Taken together, the deletion of inhibitory *KLRC1*-NK cell receptor resulted in a significantly increased NK cell-mediated cytotoxicity against allogenic patient-derived MM cells.

Our protocol for gene editing of NK cells provides a robust platform to perform variety of further modulations to design NK cell-based therapeutic approaches to overcome immune check-point inhibition against different tumor entities.

Disclosure: E.U. has a sponsored research project with Gilead and BMS. T.C. has a sponsored research collaboration with Cellectis and is a scientific advisor to Excision BioTherapeutics. The other authors declare no competing financial interest.

P098

Cerebrospinal fluid parameters in patients with progressive multifocal leukoencephalopathy receiving allogeneic t cell therapy

N. Möhn[1], L. Grote-Levi[1], S. Nay[1], P. Schwenkenbecher[1], F. Hopfner[1], K.-W. Sühs[1], A. Bonifacius[1], S. Tischer-Zimmermann[1], B. Maecker-Kolhoff[1], B. Eiz-Vesper[1], G. Höglinger[1], T. Skripuletz[1]

[1]Hannover Medical School, Hannover, Germany

Background: Progressive multifocal leukoencephalopathy (PML) is a serious opportunistic viral disease of the brain caused by the human polyomavirus 2 (HPyV-2) (previously known as: JC polyomavirus). It usually affects patients with significantly impaired cellular immune defenses. The majority of patients suffer from an underlying malignant hematological disease. The natural course of PML is usually fatal, especially in this group of patients; about 90% die within a few months. To date, there is no approved therapy for PML and all antiviral strategies have failed in trials. Since 2018 several case reports and case series reporting successful treatment with allogeneic virus-specific T cells have been published.

Methods: Sixteen PML patients have received at least one infusion of virus-specific T cells at the Department of Neurology at Hannover Medical School on a compassionate use basis. T cells were manufactured from HLA-partially matched healthy donors using cytokine capture system and immunomagnetic selection. According to current publications, this is the largest cohort worldwide as far as we know. Enriched human polyomavirus 1 (HPyV-1) specific T cells, a close relative of HPyV-2, were used in all of the cases. All patients were closely monitored by clinical examination, MRI imaging and laboratory analysis. CSF analysis included cell count, albumin quotient, detection of oligoclonal bands, determination of HPyV-2 viral load, analysis of HPyV-2 antibody specificity index, and measurement of neurofilaments (phosphorylated heavy chain, pNfH).

Results: Therapy has been completed in 16 patients, who received between one and five T-cell infusions with an interval of usually two or four weeks between doses. As underlying diseases they suffered from lymphoproliferative disorders ($n = 9$), auto-immune diseases ($n = 3$), lymphopenia ($n = 2$), acquired immune deficiency syndrome ($n = 1$), and breast cancer ($n = 1$). Median observation time between first T-cell administration and last follow-up was 3 months (1-12 months). Improvement in neurological symptoms occurred in 10 cases (62.5%), and symptoms remained stable in two cases (12.5%). A total of four patients (25%) experienced worsening of symptoms during therapy, of which three patients (19%) died of PML. The median cell count at baseline lumbar puncture prior to the first infusion was 1/µl (1-16/µl), the median albumin quotient was 7.4 (3.3-11.6), and the proportion of patients with positive oligoclonal bands as evidence of intrathecal immunoglobulin G synthesis was 71% at the first CSF analysis and as high as 80% at the second. Comparison of first and last CSF analysis showed a decrease in CSF pNfH in patients with improvement or stabilization of symptoms, while the values increased in patients with poor outcome ($p = 0.0040$). Furthermore, a decrease in HPyV-2 viral load between first and last CSF analysis correlated with a positive outcome ($p = 0.0013$).

Conclusions: Therapy with allogeneic virus-specific T cells leads to an improvement or stabilization of neurological symptoms in the majority of patients. Close monitoring of patients is crucial, and a reduction in viral load as well as a decrease in pNfH in the CSF indicate to be positive prognostic markers. However, controlled clinical trials are needed to better assess the efficacy of the therapy and to identify further prognostic factors.

Disclosure: Nothing to declare.

P099

Patient-tailored adoptive immunotherapy with ebv-specific t cells from related and unrelated donors

A. Bonifacius[1], S. Tischer-Zimmermann[1], B. Lamottke[1], R. Schultze-Florey[1], L. Goudeva[1], H.-G. Heuft[1], L. Arseniev[1],

R. Beier[1], G. Beutel[1], G. Cario[2], B. Fröhlich[3], J. Greil[4], L. Hansmann[5], J. Hasenkamp[6], M. Höfs[7], P. Hundsdörfer[5], E. Jost[8], K. Kafa[9], N. Kröger[10], S. Mathas[5,11], R. Meisel[12], M. Nathrath[13], M. Putkonen[14], S. Ravens[1], E. Sala[15], M. Sauer[1], R. Schroers[16], N.-K. Steckel[7], R.U. Trappe[17], M. Verbeek[18], E.-M. Wagner-Drouet[19], D. Wolff[20], R. Blasczyk[1], B. Eiz-Vesper[1], B. Maecker-Kolhoff[1]

[1]Hannover Medical School, Hannover, Germany, [2]University Hospital Schleswig-Holstein, Kiel, Germany, [3]University Children's Hospital Muenster, Muenster, Germany, [4]University Children's Hospital Heidelberg, Heidelberg, Germany, [5]Charité - Universitätsmedizin Berlin, Berlin, Germany, [6]University Medicine Göttingen, Göttingen, Germany, [7]University Hospital of Essen, Essen, Germany, [8]Rheinisch-Westfälische Technische Hochschule Aachen University, Aachen, Germany, [9]Martin Luther University Halle-Wittenberg, Halle, Germany, [10]University Hospital Eppendorf, Hamburg, Germany, [11]Max-Delbrück-Center (MDC) for Molecular Medicine, Berlin, Germany, [12]Heinrich Heine University Düsseldorf, Düsseldorf, Germany, [13]Klinikum Kassel, Kassel, Germany, [14]Turku University Hospital, Turku, Finland, [15]University Hospital of Ulm, Ulm, Germany, [16]Knappschaftskrankenhaus University Hospital, Bochum, Germany, [17]Ev. Diakonie-Krankenhaus, Bremen, Germany, [18]Technical University of Munich, Munich, Germany, [19]Johannes Gutenberg-University Medical Centre, Mainz, Germany, [20]University of Regensburg, Regensburg, Germany

Background: Epstein-Barr virus (EBV) causes significant morbidity and mortality in immunocompromised patients. Functional EBV-specific cellular immunity can be restored by adoptive T-cell transfer in patients with EBV-associated complications following transplantation or immunosuppression. The current study explores results of a personalized T-cell manufacturing program evaluating donor, patient, T-cell product and outcome data.

Methods: Patient-tailored clinical-grade EBV-specific T cells from stem cell, haplo-identical family or third-party donors were manufactured by stimulation and immunomagnetic selection using the CliniMACS Plus or Prodigy device and PepTivator EBV EBNA-1 and Select. T-cell donors were selected by best HLA-matching (minimum 3/6 matches in HLA-A, -B, -DR) and EBV-specific T-cell precursor frequency in peripheral blood. Consecutive manufacturing processes were evaluated and patient outcome and side effects were retrieved by retrospective chart analysis. In a subset of 18 patients, EBV-specific T cell frequencies were monitored in peripheral blood by interferon-γ ELISpot assay following stimulation with peptide pools.

Results: Forty clinical-grade EBV-specific T-cell products from stem cell (n = 13), family (n = 9) or unrelated third-party donors (n = 18) were generated between 2015 and 2019 for n = 37 patients with hematopoietic stem cell (HSCT, n = 27), solid organ (SOT, n = 5) or no (n = 5) transplantation history. Median time from initiation of third party donor search to CTL manufacturing start was 10.1 days. There was no significant difference in terms of cell yield and purity in the final T-cell products from stem cell, family or third party registry donors. Three products have not been infused due to prior death or cure. Thirty-four patients received 1-12 (median 2.0) EBV-CTL products (fresh and cryopreserved); the median number of transferred cells for the first transfer was $2.7x10^4$ $CD3^+$ cells/kg body weight (bw) in stem cell donor products and $1.4x10^4$ $CD3^+$ cells/kg bw when derived from third party donors. EBV-CTL led to complete clinical response in 19 of 31 patients, who survived at least three weeks after transfer. Complete viral clearance was documented in 13 of 20 HSCT patients, for whom data were available. Responses did not correlate with transferred CTL numbers. While no infusion-related toxicities were reported, two HSCT patients developed de novo GvHD (skin °I, n = 1; liver °IV, n = 1) after T-cell transfer, both had received EBV-CTL from the stem cell donor. These two patients had received CTL numbers above median ($3.04x10^4$ and $5.0x10^4$ $CD3^+$ cells/kg bw, respectively). EBV-specific T cells could be detected in 15 of 18 monitored patients (83.3 %) after transfer and detection of antiviral T-cell responses correlated with a favorable clinical response in these patients.

Conclusions: Personalized clinical-grade manufacturing of EBV-CTL from stem cell, family or third-party donors is fast and feasible. Adoptive transfer of manufactured EBV-CTL is effective and safe regardless of EBV-CTL donor origin. Timely production of EBV-CTL from pre-characterized registry donors is a valuable alternative to cryopreserved CTL lines for patients lacking an EBV-positive stem cell donor. Transfer of EBV-CTL to patients being immunocompromised for other reasons than in a transplantation context provides an attractive new option, which should be further explored in clinical trials.

Disclosure: Nothing to declare.

P100

Spectral flow cytometry of t-cell subsets in donor lymphocyte infusions reveals phenotypical differences associated with therapeutic outcome in patients with myeloid malignancies

R. Sikora[1], I. Odak[1], L.M. Bayir[1], M. Beck[2,1], M. Drenker[2], Y. Xiao[1], J. Schneider[2,1], E. Dammann[2], M. Stadler[2], M. Eder[2], A. Ganser[2], R. Förster[1], C. Könecke[2,1], C.R. Schultze-Florey[2,1]

[1]Institute of Immunology, Hannover Medical School, Hannover, Germany, [2]Hannover Medical School, Hannover, Germany

Background: Donor lymphocyte infusions (DLI) hold the potential to re-induce remission in patients suffering from relapsed myeloid malignancies after allogeneic hematopoietic stem cell transplantation (HSCT). Analysis of the cell product with regard to prediction of response to DLI is largely missing. Here, we perform in-depth investigation of surface molecules present on donor T-cells in respect of clinical outcome.

Methods: In this prospective clinical study, we enrolled 14 patients with relapsed myeloid malignancies (Table1) after HSCT, who were treated with unmodified DLI. The median follow-up was 22 months post first DLI. An aliquot of the infused DLI product was collected and 30 color-spectral flow cytometry for extensive immunophenotyping of T-cells was performed. Functional markers, such as 4-1BB, LAG3, NRP1, PD1, TIGIT, TIM3, VISTA were included in the staining panel. Results were evaluated both, via conventional 2D-gating and complementary unsupervised cluster analysis by Uniform Manifold Approximation and Projection (UMAP). Statistical analyses were performed with unpaired t-test or Mann-Whitney-Wilcoxon test.

	No relapse after DLI (n = 5)	Relapse after DLI (n = 9)
Age at DLI, median (range)	67 (22-75)	51 (24-61)
Disease		
AML	4	7
sAML	1	1
MDS	-	1
No. of DLI, median (range)	2 (2)	2 (1-3)
Time point 1st DLI, mo post-HSCT, median (range)	24 (6-28)	11 (2-47)
Dose 1st DLI, median $CD3^+$/kg BW, median (range)	0.7×10^7 ($0.5\text{-}1.1 \times 10^7$)	1×10^7 ($0.5\text{-}1.8 \times 10^7$)
GvHD post DLI, median	4	6
Patients alive at 24 months post DLI, n (%)	3 (60)	2 (22)

Results: After DLI treatment, 5 patients had a durable remission, whereas 9 patients developed a subsequent relapse (Table1).

Patients without relapse after DLI had received significantly lower numbers of $CD4^+$conventional (Tconv) effector-memory ($CD45RA^-CCR7^{+/-}$, EM) cells compared to relapsing patients (1.4×10^6/kg BW (range 4.6×10^5-1.4×10^6) vs. 3.6×10^6/kg BW (1.4-6.3×10^6), P = .03). Also, the absolute numbers of EM-like regulatory T-cells was lower in patients without relapse (0.6×10^5/kg BW (4.5-8.9×10^4) vs. 1.6×10^5/kg BW (3.7×10^4-2.3×10^6), P = .02). Additionally, frequencies of $CD4^+$ naïve ($CD45RA^+CCR7^+$) Tconv were higher in patients without relapse (53.75% (31.34-84.77%) vs. 32.65% (14.96-53.59%), P = .01).

UMAP analysis of DLI cell products revealed a subpopulation of $CD4^+$EM-like cells, which had lower frequencies in patients without relapse. Moreover, lower frequencies of $CD8^+$EM-like cells were seen in this group. Of note, $CCR5^+$ expression within this $CD8^+$EM-like population was significantly lower in patients without relapse (1.34% (0.23-2.98%) vs. 5.04% (1.74-13.33%), P = .002).

Next, functional markers were analysed based on their mean fluorescence intensity (MFI). Patients without relapse showed lower MFI values of VISTA on $CD4^+$naïve and EM-like cells. Along the same lines, we observed lower PD1 expression on $CD8^+$naïve-like and $CD4^+$EM-like cells in the same group .

With regard to GVHD post DLI, UMAP analysis of functional markers revealed lower PD1 expression on $CD8^+$effector-like cells in patients developing GVHD when compared to patients without GVHD.

Conclusions: In conclusion, we identified phenotypical differences of T-cells within the DLI cell product comparing patients with and without relapse after DLI. Therefore, deep phenotyping of the DLI product might be useful for prediction of response to therapy, including GVHD. However, this dataset is limited by the small cohort size. Further validation in a larger cohort is underway.

Disclosure: Nothing to declare.

P102

Relapse prophylaxis post-haploidentical bone marrow transplantation and cyclophosphamide (haplo/cy) by infusion of donor-derived expanded/activated γδ t cells: A phase i trial

L. Lamb[1], S. Abhyankar[2], R. Soder[2], M. ter Haak[1], T. Bruns[2], S. Youngblood[1], J. McGuirk[2]

[1]IN8Bio, Inc., Birmingham, United States, [2]The University of Kansas Cancer Center, Westwood, United States

Background: Effector γδ T cells immediately recognize and kill malignant cells in a broad-based non-MHC restricted manner. Increases in circulating donor-derived γδ T cells during post-bone marrow transplant (BMT) recovery have been significantly associated with improved disease-free survival (DFS). Relapse post-Haplo/Cy BMT occurs in approximately 45% of patients. We sought to mitigate relapse in this context by expanding, activating, and infusing donor-derived haploidentical γδ T cells. We now report preliminary clinical and biologic correlative findings from the first cohort of patients who have been treated with ex vivo expanded and activated donor γδ T cells (EAGD). This single-center Phase I clinical trial represents the first systemic infusion of allogeneic EAGD cells in the post-BMT setting

Methods: Standard of care reduced-intensity flu/cy/TBI conditioning was followed by an unmanipulated bone marrow graft and 50mg/m^2 Cy on days +3 and +4 post-transplant. EAGD were manufactured using the Miltenyi Prodigy® bioreactor and cryopreserved. The product was infused intravenously within 5 days of neutrophil engraftment (ANC > 500/μL X 3d). Peripheral blood was collected at EAGD infusion and monthly thereafter through day +90, with additional collections every 6 months through 1 year. Biologic parameters included multiparameter flow cytometric immunophenotyping and single cell cytokine analysis of the EAGD graft. Peripheral blood analysis includes leukocyte count and differential, immunophenotyping, and serum Th1/Th2/Th17 cytokine analysis. Primary endpoints include dose-limiting toxicities (DLT) and grade 3-4 adverse events while secondary endpoints include incidence of acute and chronic GvHD, relapse, and overall survival.

Results: Three patients have received the first dose level of 1 x 10^6 EAGD/kg. All three patients remain in morphologic complete remission at 20.1, 17.8, and 6.1 months post-BMT. One patient is receiving ongoing hypomethylating therapy for the occurrence of recipient chimerism. Grade 1-2 toxicities include constipation, CMV reactivation, emesis, fatigue, and hypomagnesaemia. Steroid-responsive cutaneous acute Grade I-II GVHD has been observed in all patients with one patient experiencing Grade II intestinal GvHD. No chronic GVHD, DLTs, treatment-related ≥ grade 3 adverse events, or cytokine release syndrome has occurred. EAGD grafts contained 88.7%-99.2% Vγ9Vδ2 + γδ T cells with small populations of NK cells and <1.0 x 10^5 αβ T cells/kg. EAGD principally expressed Granzyme B, MIP1α, MIP1β, and IL-2. Significant peripheral lymphodepletion persisted through the first 100 days post-BMT followed by slow recovery of CD4 +, CD8 +, γδ T and B cells. NK cells remained within the low normal range throughout. T cells transitioned from a CD45 + CD27- effector phenotype to $CD45RA^-CD27^{+/-}$ central to effector memory phenotype as recovery progressed. $CD3^+CD4^+CD25^{hi}FoxP3^+$ Treg cells remained <3% of circulating T cells. Preliminary serum cytokine analysis revealed an initial inflammatory environment with predominant expression of IFNγ, and TNFα and T cell expression of Granzyme B, MIP1α, IFNα, and TNFα that gradually decreased as recovery progressed.

Conclusions: Early indications suggest that EAGD transfusion with the initial dose level of 1 x 10^6 EAGD/kg has manageable toxicity and an appropriate immune recovery profile with 3 of 3 patients alive and progression-free.

Clinical Trial Registry: https://clinicaltrials.gov/ct2/show/NCT03533816

Disclosure: The clinical trial is conducted as an Investigator-Initiated Trial with the Kansas University Cancer Center as the sponsor and Dr. Joseph P. McGuirk as the Principal Investigator. The trial is funded by IN8Bio, a US public biopharmaceutical company. Dr. McGuirk also received funding through the Kansas University Cancer Center from Kite, Novartis, Bristol Myers Squibb, and Allovir as a site investigator for ongoing clinical trials. Dr. Lawrence Lamb, Mariska ter Haak, and Samantha Youngblood are employees of IN8Bio.

P103

Influence of t-memory cell doses on post-transplant infections and GVHD rates

P.L. Tan[1,2,3,4], C. Vyas[5], F. Yeap[1,2,3,4], L.P. Koh[1,2,3,4]

[1]National University Hospital, Singapore, Singapore, [2]National University Cancer Institute, Singapore, Singapore, [3]National University Health System, Singapore, Singapore, [4]National University of Singapore, Singapore, Singapore, [5]Jaslok Hospital and Research Centre, Mumbai, India

Background: Allogeneic T-memory cells (Tm) co-infused with T-cell depleted (TCD) peripheral blood stem cells (PBSC) is known to protect against post-transplant infections. However, the effective Tm dose for infections protection relative to engraftment/ cytokine release syndrome (ES/ CRS) and graft-versus-host disease (GVHD) risks is unknown. Many programs, including ours,

Table 1: Tm Dose Strata and Transplant Outcomes

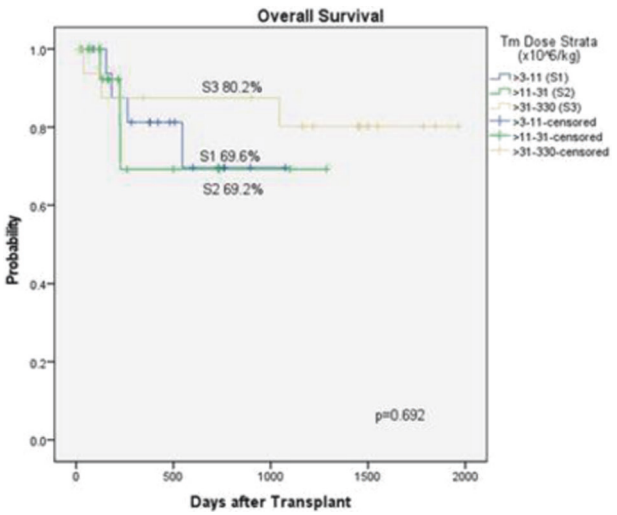
Strata (Tm Doses, 106/kg)	N	CMV Infections	ADV Infections	BKV Infections	Fungal Infections	GF	ES/ CRS	Acute GVHD	Chronic GVHD
S1 (>3 to 11)	17	52.9%	5.9%	17.6%	5.9%	17.6%	35.3%	58.8%	23.5%
S2 (>11 to 31)	20	35.0%	10.0%	5.0%	20.0%	25.0%	50.0%	25.0%	10.0%
S3 (>31 to 330)	17	35.3%	17.6%	5.9%	23.5%	23.5%	5.9%	64.7%	41.2%
p value		*0.465*	*0.540*	*0.352*	*0.340*	*0.856*	*0.015*	*0.02*	*0.123*

set Tm doses arbitrarily because data guiding Tm dosing is lacking. Between 2014 and 2019, we systematically reduced Tm doses in 54 paediatric patients transplanted consecutively using published experiences and our patients' outcomes as guidance.

Methods: We retrospectively reviewed transplant outcomes, including infections, graft failure (GF), ES/ CRS and GVHD rates in patients given Tm (denoted by CD45RO +) doses categorised in 3 strata (S): S1: > 3 to 11 x 10^6/kg (N = 17); S2: > 11 to 31 x 10^6/kg (N = 20), and S3: > 31 to 330 x 10^6/kg (N = 17). Transplant indications included cancers (N = 42) and non-cancers (N = 12) diseases. PBSC were T-cell depleted as the main form of GVHD prophylaxis with: CD34 + selection (N = 4), CD3 + depletion (N = 48) or alpha-beta T-cells depletion (N = 2). The majority of patients (N = 34) received non-radiation based preparative regimens. Anti-microbial prophylaxis included echinocandins and ganciclovir. ES/CRS and GVHD were pre-emptively treated.

Results: The median age of patients in the 3 strata were: 94 (range, 9 to 231); 84 (range, 10 to 192); 48 (range, 6 to 183) months; and their donors: 38 (range, 14 to 56); 37 (range, 21 to 52); 38 (range, 31 to 52) years, respectively. The CD34 + cell doses co-infused with Tm in the 3 strata were: 18 (range, 14 to 32); 18 (range, 7 to 45); and 20 (range, 13 to 57) x 10^6/kg, respectively. The CD3 + cell doses in the stem cell products averaged 1.72 (range, 0.0 to 4.97) x 10^4/kg. Transplant outcomes including cytomegalovirus (CMV), adenovirus (ADV), BK virus (BKV), and fungal infections, GF, ES/ CRS, acute and chronic GVHD rates in the 3 strata are summarised in Table 1. Infections, GF and chronic GVHD rates were not statistically different among patients in the 3 strata. However, ES/CRS and acute GVHD rates were statistically different in patients receiving different Tm doses. At a median follow-up of 452.5 (range, 18 – 1965) days, the 3-year overall survival was not statistically different among patients in the 3 strata (Figure 1): (S1) 69.6% vs. (S2) 69.2% vs. (S3) 80.2% (p = 0.692).

Figure 1: Overall Survival of 54 patients Given Different Tm Doses



Conclusions: There appears to be no infection protective advantage with higher Tm doses. However, ES/CRS and acute GVHD rates were significantly different with different Tm doses. This preliminary data supported the Tm dosing strategy used in our program.

Disclosure: Nothing to declare.

P104

Processing of one total blood volume is sufficient to perform extracorporeal photopheresis with spectra optia cmnc protocol. A study with focus on a patient safety

R. Małachowski[1], A. Borowik[1], M. Mordak[1], I. Dereń-Wagemann[1], J. Lange[1], K. Suchnicki[1], M. Sędzimirska[1], D. Sosnowska[1], J. Dybko[1]

[1]The Lower Silesian Oncology Center in Wrocław, Wrocław, Poland

Background: The total blood volume (TBV) to process during extracorporeal photopheresis (ECP) and sufficient number of collected mononuclear cells (MNCs) is not clearly defined. Cell yields vary between apheresis devices. The duration of ECP may affect the clinical benefit but also pose a threat to a patient's safety. In this study we have made an attempt to determine if the blood volume processed can be minimized to increase the patient's safety, concurrently preserving the ECP therapeutic effect.

Methods: 23 patients (F/M – 12/11, median age 52 (17-66)) who have underwent allogeneic hematopoietic cells transplantation complicated by steroid resistant chronic graft-versus-host disease were enrolled in the study. A median number of 10 (3-30) procedures was performed between January 2019 and October 2021 with 1 or 2 TBV being processed.

ECP was achieved in an offline manner. MNCs were collected with the Spectra Optia device (Terumo BCT) continuous mononuclear cell collection (cMNC) protocol. The final product was irradiated with UVA-PIT (PIT Medical Systems GmbH).

Results: 100 ECP procedures with 1TBV processed and 79ECP procedures with 2TVB processed procedures were performed. No statistical difference in patient age, body weight and TBV was observed between the compared sets of data. The procedures where 1TBV was processed resulted in shorter duration than 2TVB procedure: 114 min (88-189) vs 224 min (158-253), p < 0,001; lower product volume 104 mL (65-200) vs 210 mL (139-237), p < 0,001, lower MNC content $4{,}42 \times 10^{12}$ (0,08-20,84) vs 11,3 (2,4-30,1), p < 0,001 and lower MNC content per kg body weight 159,8 $\times 10^6$/kg body weight (24,4-373,1) vs 75,7 (2,1-235,4), p < 0,001. The MNC CE1 collection efficiency was 37,3% (4,1-99,9) for 1TBV and 44,9% (14,3-81,6) for 2TBV, p = 0,004. Parameters characterizing the patient safety i. e. platelet drop and ACD(A) infused per patient were lower for the procedures with 1TBV processed: 18,1% (-71,2-63,4) vs 34,2% (-15,0-48,1), p < 0,001 and 449 mL (161-694) vs 752 mL (439-1101), p = 0,004 respectively.

Pt ID	time after HSCT, months	treatment specificity	ELISpot positivity for IFNγ, days	resolution of viremia, days	increase in CD3 + CD45RA- CD197- effector memory cell counts	condition before the treatment	clinical response
Pt 1	19	CMV	14 (CMV)	28	-	CMV viremia, active CMV retinitis	alleviation of CMV viremia and CMV retinitis
Pt 2	3	CMV, ADV, SARS-CoV-2, BKV (LT, Vp1)	28 (CMV, ADV, BKV)	60	+	CMV viremia, BK viremia	alleviation of CMV and BKV viremia
Pt 3	9	CMV, ADV, SARS-CoV-2, BKV (LT, Vp1)	-	-	+	persistent BKV viruria, BKV viremia	no improvement
Pt 4	1	CMV, ADV, SARS-CoV-2	28 (SARS-CoV-2)	28	+	COVID-19 pneumonia	SARS-CoV-2 clearance
Pt 5	5	CMV, ADV, SARS-CoV-2, BKV (LT, Vp1)	28 (CMV, ADV, SARS-CoV-2, BKV)	-	+	severe hypofunction of the graft, pancytopenia; viral damage to hematopoiesis, BKV-associated	alleviation of symptoms, viral clearance

The clinical response rate was 77,3% for the skin (n = 22), 100,0% for the liver (n = 5), 0,0% for the gastrointestinal (GI) tract (n = 5), 42,9% for ocular GVHD (n = 7), 55,6 for oral GVHD (n = 9), 50,0% for the musculoskeletal system (n = 2), and 100,0% for bronchiolitis obliterans (n = 2).

Conclusions: Although there is no consensus on the MNC cell dose to be irradiated in ECP, Worel et al. has indicated a cut-off MNC level $13{,}9\times10^6$ /kg body weight which predicts 75% overall response. Except for one patient who was leukopenic, all of our patients have reached (and often significantly exceeded) the cut-off MNC /kg body weight level. The MNC count collected during 1TVB cycle was comparable or higher to those reported by other authors who have also concluded an efficacious ECP therapeutic effect. This preliminary analysis shows that it is possible to collect sufficient number of MNC through processing of one total blood volume. Moreover, this approach increases patient's safety by lowering the ACD(A) volume infused, lowering platelet loss and improving patient comfort by lowering the time of the procedure. The presented data and response ratio support processing 1TBV with Spectra Optia cMNC protocol for UV irradiation.

Disclosure: Nothing to declare.

P105

Clinical experience of using multivirus-specific t cells produced by ifnγ-directed immunomagnetic separation in patients with post-HSCT severe viral infections

V. Vedmedskia[1], D. Pershin[1], M. Fadeeva[1], A. Kazachenok[1], R. Nikolaev[1], E. Malakhova[1], E. Kulakovskaya[1], S. Glushkova[1], T. Sozonova[1], E. Osipova[1], L. Shelikhova[1], M. Maschan[1], G. Novichkova[1]

[1]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation

Background: Viral infections is a major cause of post-HSCT complications and transplant-related mortality. Delayed post-HSCT immune reconstitution fails to support the resistance to common infections with CMV, AdV, EBV and other opportunistic agents. In the context of other post-HSCT complications such as graft-vs-host disease and graft hypofunction, this failure may lead to longer-term immune deficiency with severe consequences. The CliniMACS Prodigy® platform (Miltenyi Biotec) allows obtaining IFNγ-secreting virus-specific lymphocyte-enriched cell products by immunomagnetic separation (IMS). Here we present clinical experience of using such products in patients with post-HSCT viral infections.

Methods: The study enrolled 5 patients with post-HSCT viral complications, receiving infusions of virus-specific cell products. Magnetic separation of IFNγ + lymphocytes obtained from a haploidentical donor by leukapheresis was performed using the CliniMACS Prodigy platform in accordance with the recommended protocol. In vitro stimulation was performed with PepTivator® peptide pools (Miltenyi Biotec) in combinations corresponding to the current condition of the patient and possibly preventing related complications (see the Table). Subpopulation composition of cell product was assessed by flow cytometry using routine surface staining for CD3, CD4, CD8 and IFNγ. The median content of viable T lymphocytes in the cell product was 35%. The median content of virus-specific interferon-expressing T cells in the graft was 90%.

The median infusion dose was $39.27 \cdot 10^3$ of viable CD3 + cells per kg weight (min $11 \cdot 10^3$/kg, max $432 \cdot 10^3$/kg). The median time after HSCT at the moment of infusion was 125 days (min 30 days, max 1.5 years). Viremia was monitored by PCR. Detection and monitoring of virus-specific donor T cells was performed by IFNγ ELISpot assay.

Results: Robust response to the treatment correlating with the ELISpot data was observed in 4 of 5 patients. Clinical and laboratory indicators for the patients are given in the Table:

Conclusions: Infusions of multivirus-specific lymphocytes obtained by IFNγ-directed IMS provide effective treatment of viral complications that arise during post-HSCT immune reconstitution. Polyspecific antigenic stimulation performed in advance may facilitate prevention of viral complications during post-HSCT immune reconstitution.

Disclosure: Nothing to declare

P106

Stem cell therapy in children with neurological disease: Association between adverse effects and total nucleated cells parameters

H. Ramírez Durán[1], J.C. López Quezada[1], S.A. Sánchez García[1], C.A. de la Cruz de la Cruz[1], I.Y. Velasco Ruiz[1], O. González Llano[1], C. Mancías Guerra[1]

[1]*Hospital Universitario "Dr. José Eleuterio González", Monterrey, Mexico*

Background: Subarachnoid placement of bone marrow (BM)-derived total nucleated cells (TNCs) has been reported to be safe and relatively easy to perform in children with cerebral palsy (CP) and autism spectrum disorder (ASD).

Methods: This was a retrospective, open-label trial to assess the side effects, safety, and tolerability of a single subarachnoid BM-derived TNC injection in patients with CP and ASD. Patients aged between 1 and 18 years were included in this study. The outpatient-based autologous BM stimulation consisted of 10 mg/kg/day G-CSF subcutaneously for 3 days. The procedure was performed under sedation and local anesthesia. We harvested 8 mL/kg of body weight of BM, filtered on a laminar flow cabiet, centrifuged, and enumerated using CD34 + and CD45 + flow cytometry.

Caretakers were instructed to contact the research team if they developed symptoms.

Results: Between May 2009 and December 2021, 640 patients were treated with BM-derived TNCs, 303 patients with ASD (47.3%) and 337 patients with CP (52.7%). The median age was 6 years (range,1 month to 18 years). Males comprised 71.6% of the study population, and 28.4% were women. Almost half of the patients (n = 309,48.3%) presented with any symptoms after the procedure. The characteristics of the study population are summarized in Table 1.

Among the patients with ASD, the most common symptom was vomit/nausea in 63 patients (20.5%). Headache/irritability affected children over 60 months of age ($p = 0.038$). There was an association in patients reporting vomiting and nausea with a larger TNC volume infused (median 6.2 ml) ($p = 0.003$) and with fewer absolute neutrophil count (ANC) infused ($p = 0.026$).

In children diagnosed with CP, symptoms were present in 160 patients (51.8%). We found an association between age >60 months and headache/irritability ($p = 0.004$).

Conclusions: There was no association between symptomatic patients and leukocyte count or CD34 + x106/kg infused. The study reported an incidence of up to 309 (48.3%) symptoms after subarachnoid TNC administration. These secondary effects were not related to the laboratory parameters of the cells (leukocyte count or CD34 + x106/kg infused), but only the volume infused was associated with nausea and vomiting in children with autism older than five years of age. In most cases, these symptoms can be satisfactorily controlled without hospital admission, so we can consider it a safe procedure and possibly improve the quality of life of patients.

Disclosure: Nothing to declare

P107

Adoptive transfer of allogenic hpyv-1-virus specific t cells improves clinical outcome of patients suffering from progressive multifocal leukoencephalopathy

L. Grote-Levi[1], N. Möhn[1], S. Nay[1], P. Schwenkenbecher[1], F. Hopfner[1], W. Sühs[1], A. Bonifacius[1], S. Tischer-Zimmermann[1], B. Maecker-Kolhoff[1], B. Eiz-Vesper[1], G. Höglinger[1], T. Skripuletz[1]

[1]*Hannover Medical School, Hannover, Germany*

Background: Progressive multifocal leukoencephalopathy represents an opportunistic viral infection of the brain with potential fatal outcome. Triggered by an immunosuppressive constitution, e.g. oncological diseases, chronic viral infections or immunosuppressive therapy in autoimmune disease/transplantation, affected individuals suffer reactivation of latently existing infection by human polyomavirus 2 (HPyV-2, former: JCV), which leads to lytic destruction of the brain parenchyma. The diagnosis is based on a triade of suitable clinical symptoms, typical MR-imaging findings and detection of HPyV-2 in cerebrospinal fluid (CSF)/brain biopsy. No approved effective therapy exists to date, but adoptive transfer of allogenic human polyomavirus 1 (HPyV-1) specific T cell proves to be a promising approach - basing on induction of immune reaction by cross-reaction due to partial equal epitopes of HPyV-1 and HPyV-2.

Methods: Since March 2020, patients referred to our clinic suffering from defined, progressive PML were analyzed regarding endogenous amount of HPyV-1/ HPyV-2-virus specific T cells. If examination presented insufficient amount, adoptive HPyV-1-specific T cell transfer, extracted from partially human leukocyte antigen compatible donors, was initiated. Dosage varied between 2.0 × 10e4 and 1.0 × 10e4 CD3 + T cells per kg body weight. Targeted therapy regime included at least two doses of allogenic T cells. Follow up investigations included routine neurological examination which partially included examination of 55 m walking distance and Montreal cognitive assessment scale, CSF analysis to investigate HPyV-2 level, virus specific T cells within blood and magnetic resonance imaging.

Results: Sixteen PML-patients received at least one dose of allogenic T cells and were followed up > six weeks after therapy initiation, fifteen patients completed aimed application of two doses. Follow up examination time varied between 42 and 379 days. The majority, eleven patients, suffered from oncological disease, two patients had a history of immunosuppressive disease, two patients suffered from idiopathic lymphopenia and one patient had acquired immune deficiency syndrome but developed PML despite sufficient antiretroviral therapy. In total, ten of sixteen patients showed improvement of symptoms, two patients presented with clinical stabilization and four patients suffered from progression of disease. Of ten patients course-controlled by walking distance/Montreal cognitive assessment scale, two patients showed objective improvement within walking distance and cognition with one further patient exhibiting improvement within cognition alone. Other investigated patients suffered from severe paresis or aphasia, so that examination tools did not fit to exhibit improvement demonstrated by elsewhere diagnostic.

Conclusions: Allogenic HPyV-1-virus specific T cell therapy shows promising therapeutic approach in patients suffering from PML leading to an improvement or stabilization within the majority of treated patients, but examination of walking distance and cognition by Montreal cognitive assessment scale alone appears to be inadequate to show full therapy response. Despite the need of large controlled clinical trials to better assess the efficacy of therapy, further investigations regarding specific clinical scores are needed.

Disclosure: Nothing to declare.

P109

Invariant natural killer t cells protect from cytomegalovirus reactivation after allogeneic hematopoietic cell transplantation

D. Schneidawind[1], S. Duerr-Stoerzer[1], H. Keppeler[1], R. Beck[2], K. Hamprecht[2], L. Kanz[1], C. Schneidawind[1]

[1]University Hospital Tuebingen, Tuebingen, Germany, [2]Institute of Medical Virology and Epidemiology of Viral Diseases, Tuebingen, Germany

Background: Cytomegalovirus (CMV) reactivation is common after allogeneic hematopoietic cell transplantation (HCT) and may result in fatal CMV disease. Invariant natural killer T (iNKT) cells are potent modulators of the immune system preventing graft-versus-host disease (GVHD) while promoting graft-versus-leukemia (GVL) effects. It is thought that iNKT cells selectively influence mediators of both innate and adaptive immunity. Here, we investigated the impact of iNKT cells on virus control after allogeneic HCT.

Methods: We report a single-center prospective observational study designed to investigate the impact of graft iNKT cells on early CMV reactivation in peripheral blood measured by weekly PCR from patient plasma. The primary endpoint was defined as detection of CMV DNA within 100 days following allogeneic HCT. Secondary endpoints were incidence of GVHD, non-relapse mortality (NRM), event-free survival (EFS) and overall survival (OS). The graft composition was studied by flow cytometry.

Results: Median age of patients (n = 50) was 57 years (range 25-76). Two thirds of patients were CMV IgG seropositive and about half of donors were latently infected with CMV. Reactivation of CMV was noted in 23 (46%) patients after a median of 39 days (range 11-59). iNKT-cell numbers were significantly decreased (0.1% vs. 0.3%, $p = 0.0001$) in patients with early cytomegaloviremia. We also found a significantly reduced cumulative incidence of CMV reactivation after 100 days in patients with higher numbers of iNKT cells in their allograft (24% vs. 68%; $p = 0.002$). Acute GVHD °II-IV was observed in 5 (10%) patients. Also, extensive chronic GVHD occurred in 5 (10%) patients. Cumulative incidence of relapse or progression and NRM as competing risks at 2 years were 26% and 28%, respectively. 38% of all patients died during a median follow-up of 27 months resulting in a 2-year EFS of 47% and a 2-year OS of 61%.

Conclusions: This study provides evidence that graft iNKT cells improve post-transplant immunity towards reactivation of latent virus infections. Therefore, iNKT-cell enriched grafts or adoptive transfer of iNKT cells are compelling cytotherapeutic strategies to improve outcomes after allogeneic HCT.

Disclosure: Nothing to declare.

P110

Allogeneic stem cell transplantation with 3-days busulfan plus fludarabine as conditioning regimen for patients with relapsed or refractory t- and nk/t-cell lymphomas

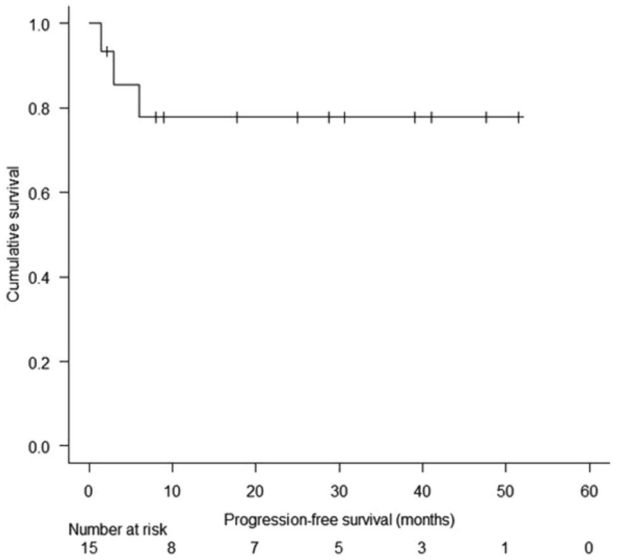
J.H. Lee[1], D.-H. Yang[2], J.-C. Jo[3], Y.J. Lee[3], W.-S. Lee[4], Y.S. Choi[5], J.H. Moon[6], Y.R. Do[7]

[1]Dong-A University College of Medicine, Seogu, Korea, Republic of, [2]Chonnam National University Hwasun Hospital, Hwasun, Korea, Republic of, [3]Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea, Republic of, [4]Busan Paik Hospital, Inje University College of Medicine, Busan, Korea, Republic of, [5]Ajou University School of Medicine, Suwon, Korea, Republic of, [6]Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Korea, Republic of, [7]Keimyung University School of Medicine, Dongsan Medical Center, Daegu, Korea, Republic of

Background: Peripheral T-cell lymphomas (PTCL) and NK/T-cell lymphoma (NKTCL) share common characteristics of high chemotherapy resistance with frequent relapses and rapid disease progression. Efforts to improve outcome have incorporated autologous (auto-SCT) and allogeneic stem-cell transplantation (Allo-SCT). Allo-SCT has been to show a plateau of survival in responding patients, and even complete responses in patients who relapsed after various chemotherapy regimens. Although attempts to apply Allo-SCT in adult PTCL and NKTCL are steadily increasing, cases are still scarce so that there are very few prospective trials. Even though Allo-SCT could improve survival in relapsed and refractory patients who would otherwise have grave prognosis, there are several unsolved problems: suitable patient populations, HSCT timing (first relapse versus beyond first-relapse) and proper conditioning intensity and regimens (myeloablative conditioning vs. reduced-intensity conditioning).

Methods: Peripheral T-cell lymphomas (PTCL) and NK/T-cell lymphoma (NKTCL) share common characteristics of high chemotherapy resistance with frequent relapses and rapid disease progression. Efforts to improve outcome have incorporated autologous (auto-SCT) and allogeneic stem-cell transplantation (Allo-SCT). Allo-SCT has been to show a plateau of survival in responding patients, and even complete responses in patients who relapsed after various chemotherapy regimens. Although attempts to apply Allo-SCT in adult PTCL and NKTCL are steadily increasing, cases are still scarce so that there are very few prospective trials. Even though Allo-SCT could improve survival in relapsed and refractory patients who would otherwise have grave prognosis, there are several unsolved problems: suitable patient populations, HSCT timing (first relapse versus beyond first-relapse) and proper conditioning intensity and regimens (myeloablative conditioning vs. reduced-intensity conditioning).

Results: Fifteen patients received Allo-SCT with Bu3Flu6 conditioning regimen for relapsed and refractory T- and NK/T-cell lymphomas. Median age was 54 years (range, 33-65 years) and median previous lines of therapies was 2 (range, 1-3). 53.3% of the patients had received auto-SCT. Stem cell source were PB and CB in 14 patients and 1 patient, respectively; stem cell donor type were full-matched sibling and unrelated donor in 46.7% and 40% of the patients, respectively. After a median 3 cycles of salvage chemotherapies, 66.7 % and 33.3% of the patients were in CR and PR, respectively, before enrollment to the study, and for 5 patients who were in PR before Allo-SCT, 3 patients further achieved CR after Allo-SCT with Bu3Flu6. After a median follow-up duration of 17.7 months (range, 2.13-51.47 months), 2-year PFS and OS were 77.8% (95% CI, 45.5-92.3%), and 68.4% (95% CI, 35.9-86.8%), respectively. All patients engrafted neutrophils and platelets rapidly with a median of 12 and 12 days, respectively. There were no unexpected regimen-related toxicities including sinusoidal obstruction syndrome, hemorrhagic cystitis, and sepsis. Grade 3-4 acute graft-versus-host disease (GVHD) and moderate-to-severe chronic GVHD occurred in 40% and 60% patients, of which chronic GVHD combined with infection lead to death in 2 patients.



Conclusions: 3-days Bu and 6-days Flu combination as a conditioning regimen is effective with tolerable safety profile for relapsed or refractory T- and NK/T-cell lymphoma patients who are undergoing Allo-SCT.

Clinical Trial Registry: NCT02859402

Disclosure: This work was supported by Korea Otsuka Pharmaceutical Co., LTd. This study would not have been possible without the cooperation of the Korean lymphoma transplantation group (KLTG) and the Consortium for Improving Survival of Lymphoma (CISL). The authors have no conflicts of interest to declare.

P111

Fibroblast-like cells present in an apheresis collected haematopoietic progenitor cell fraction

R. Cockeran[1], T.N. Glatt[1]

[1]South African National Blood Service, Johannesburg, South Africa

Background: The collection of haematopoietic progenitor stem cells (HPSC) using an apheresis method for the treatment of various haematological malignancies is a standard procedure performed by the South African National Blood Service. Mesenchymal stromal cells (MSC) are CD45 negative fibroblast-like cells that have the potential to regulate immune and inflammatory responses, including possibly preventing and treating engraftment failure and graft-versus-host disease. This study investigated the possibility of the presence of MSCs in the HPSCs collection fraction. This would allow for using the same collection to obtain both HPSC and MSCs, thereby not only treating the malignancy, but also the potential side effects of the treatment.

Methods: The HPSC collections were performed in mobilized donors as per standard apheresis protocols. Signed consent was obtained to use excess HPSC that were not required for the patients for research purposes. The HPSC collections were de-identified prior to being sent to the research laboratory. The mononuclear cells were isolated using a density gradient, followed by a CD45 bead isolation. The CD45 negative mononuclear cells were incubated in Dulbecco's Modified Eagle Medium (DMEM) in the presence of 10% foetal bovine serum (FBS), or 5% human platelet lysate (HPL - produced by SANBS) and 2% penicillin-streptomycin, in a humidified 37°C CO_2 incubator. Cell culture media was changed every 2-3 days, with trypsonising and splitting of cell numbers when 80% confluence was reached. The presence of fibroblast-like cells was visually evaluated using a phase-contrast microscope.

Results: A total of three donations were obtained and the cells processed. The cells for each donation were grown in both FBS and HPL. The presence of fibroblast-like cells was seen in both culture conditions; Figure 1 shows the unstained fibroblast-like cells grown in the presence of HPL.

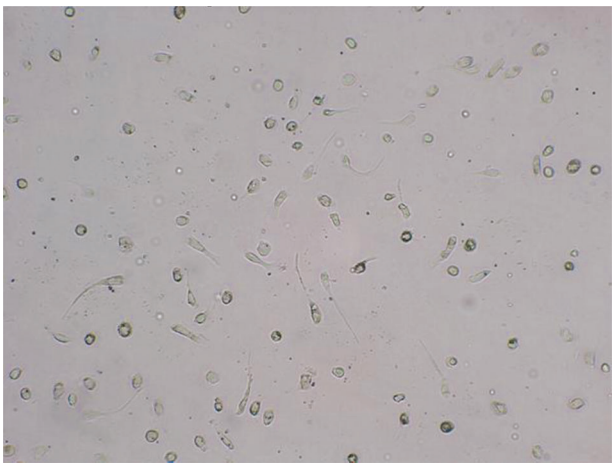


Figure 1: Fibroblast-like cells grown in HPL (unstained) from HPSC apheresis collection

Conclusions: The presence of fibroblast-like cells in three HPSC apheresis donations shows promise for the use of this fraction as a potential source of MSCs that can regulate immune and inflammatory responses. Future research will include the culturing of the fibroblast-like cells to larger numbers to facilitate the identification of these cells and confirm if they are indeed MSCs.

Clinical Trial Registry: N/A

Disclosure: Nothing to declare

P112

Granulocyte transfusion in patients with mucositis after allogeneic hematopoietic stem cell transplantation

E. Yildizhan[1], F. Varol[2], S. Ciftci[2], E. Tubay[2], A. Unal[2]

[1]Kayseri City Hospital, Kayseri, Turkey, [2]Erciyes University, Kayseri, Turkey

Background: Allogeneic hematopoietic stem cell transplantation (HSCT), provides curative treatment chance for many patients with hematologic malignancy. But the complications such as infections, mucositis, and graft versus host disease are the main obstacles to be overcome in the post-transplantation period. Moreover, each of

these complications can provoke the others. Granulocyte transfusion can be a reasonable option to support this critical neutropenic period, however, there are not enough randomized controlled trials, and the utility of this approach is controversial. This study aimed to evaluate the efficacy of granulocyte transfusion in allogeneic HSC recipients.

Methods: We retrospectively examined the data of patients who underwent allogeneic HSCT because of acute leukemia, in Erciyes University Hospital, Bone Marrow Transplantation Center, between 2019 and2020. Thirty-one patients who have severe neutropenia lasting more than 15 days (absolute neutrophil count ≤0.5x 10^9/L) or severe infection or mucositis (grade 2-4) were considered eligible for granulocyte transfusion. Eleven patients who have an appropriate donor received granulocyte transfusion. The remaining 20 patients were considered as a control group and received conventional treatment for mucositis and infection. The clinical course was considered as 'favorable' if neutrophile recovery was achieved or the clinical symptoms and signs improved proceeding one week of treatment.

Granulocyte concentrates were collected using apheresis from donors stimulated with corticosteroid and GCSF.

Results: The number of patients suffering from mucositis was 6 (54.5%) in the granulocyte receiving group and only two of them responded to granulocyte transfusion favorably. Fourteen (70.0%) patients had mucositis in the control group and 5 of them were responsive to conventional treatment. Engraftment failure was seen in 3 patients in the granulocyte receiving group and there was no engraftment failure in the control group. Engraftment times for neutrophil and platelet were not significantly different between the two groups. The duration of hospitalization after transplantation was significantly longer in the granulocyte receiving group ($p < 0.05$). There was no adverse event related to granulocyte transfusion.

Conclusions: In the present study, granulocyte transfusion did not provide any clinical benefit in the treatment of mucositis and in neutrophile recovery. Given the small size of the population, more comprehensive studies are needed.

Disclosure: Nothing to declare

CHRONIC LEUKAEMIA AND OTHER MYELOPROLIFERATIVE DISORDERS

P113

The outcome of allogeneic hematopoietic stem cell transplantation for patients with primary myelofibrosis

K. Sun[1], X.C.-H. Tsai[1], J.-H. Liu[2], S.-C. Hsu[1], W.-C. Chou[1], X.-W. Liao[2], H.-A. Hou[1], B.-S. Ko[2], H.-F. Tien[1], J.-L. Tang[2], M. Yao[1]

[1]National Taiwan University Hospital, Taipei, Taiwan, Province of China, [2]National Taiwan University Cancer Center, Taipei, Taiwan, Province of China

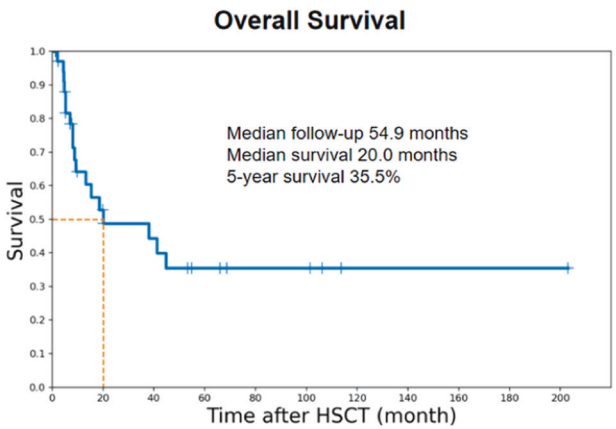
Background: Primary myelofibrosis (PMF) is a clonal myeloproliferative neoplasm and is associated with marrow fibrosis, extramedullary hematopoiesis, and the propensity of leukemia transformation. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative option, but the reports regarding outcomes of patients with PMF receiving allo-HSCT the literature were heterogeneous. In this study, we aimed to evaluate the efficacy and safety of allo-HSCT in patients with PMF.

Methods: From 1996 to 2020, we consecutively enrolled 35 PMF patients who received allo-HSCT at our institute. Next-generation sequencing focusing on 54 myeloid disease-related gene mutations was performed in 29 patients who had enough specimens. The survival was calculated from the date of allo-HSCT.

Results:

The median age at allo-HSCT was 57.6 years. According to the Dynamic International Prognostic Scoring System plus (DIPSS-plus) risk stratification right before the HSCTs, 8.6% of patients were categorized in the intermediate-1; 40%, intermediate-2; and 51.4%, high-risk group. Nineteen (54.3%) patients had *JAK2* V617F mutation, 2 (5.7%) *MPL* mutation, 5 (14.3%) *CALR* mutation, 1 triple-negative, and 6 (17%) unknown because there was no specimen for retrospective analysis (mostly diagnosed before 2006). Eleven (31%) patients had high molecular risk mutations (HMR), defined as *ASXL1*, *EZH2*, *SRSF2*, and *IDH1/2* mutations. Twenty-five (71.4%) patients received reduced-intensity conditioning, which is associated with better NRM compared to myeloablative conditioning (MAC) (not reached vs. 7.9 months, $P = 0.05$), and earlier leukocyte engraftment (12 days vs. 15 days, $P = 0.02$).

The median duration from diagnosis to allo-HSCT was 13.5 months (range 1.2-279.9 months). Eighteen (51.4%) patients received spleen management before allo-HSCT, including 5 with splenectomy and 13 with splenic irradiation. With the median follow-up of 54.9 months, the median overall survival (OS) was 20.0 months and the 5-year survival rate was 35.5% (Figure 1). The 1-year cumulative incidence of relapse (CIR) was 26.6% and 1-year non-relapse mortality (NRM) was 25.2%. Of the 18 mortality cases, 9 patients died of infection (including 1 graft failure), 4 died of the disease, and 4 died of graft-versus-host disease (GvHD). The 100-day cumulative incidence of grade 2-4 acute GvHD was 47%. Intriguingly, age or donor source has no prognostic impact on OS, NRM, or CIR. Similarly, there was no difference in terms of CIR, NRM, and OS among patients with various DIPSS-plus risks. Intriguingly, patients with spleen management had a trend of lower NRM but similar CIR and OS compared with those without. Furthermore, the patients with HMR share similar outcomes with those without HMRs, suggesting that HSCT may alleviate the negative prognostic impact of HMR mutations.



Conclusions: Allo-HSCT has the potential to cure some PMF patients. However, it remains to be a challenging task. Finding strategies to reduce CIR and NRM and improve the outcome is warranted. The role of spleen management before allo-HSCT needs to be further clarified in larger cohorts.

Disclosure: Nothing to declare

P114

Results of therapy for patients with advanced phases of chronic myeloid leukemia

E. Morozova[1], M. Barabanshchikova[1], Y. Vlasova[1], K. Yurovskaya[1], T. Gindina[1], I. Barkhatov[1], I. Moiseev[1], A. Kulagin[1]

162

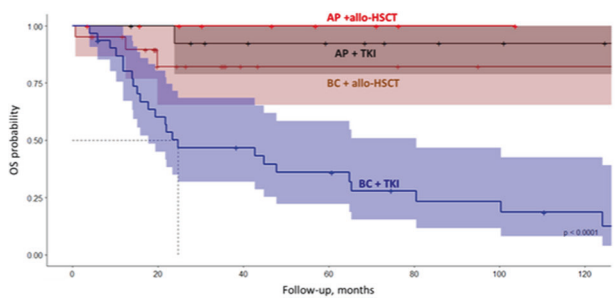
[1]RM Gorbacheva Research Institute, Pavlov University, St. Petersburg, Russian Federation

Background: Despite the widespread use of 2nd and 3rd generation tyrosine kinase inhibitors (TKIs), patients with advanced phase CML, blast crisis (BC) or accelerated phase (AP), still have poor prognosis. This study compares the results of conservative therapy and allo-HSCT in patients with advanced CML

Methods: This retrospective study includes 162 patients with CML BC/AP. All patients received TKIs, in some cases (n = 62/20) followed by allo-HSCT. All patients received allo-HSCT with a reduced dose intensity conditioning regimen (fludarabine 180 mg/m2, busulfan 8-14 mg/kg or melphalan 140 mg/m2). In post-transplant period TKIs, mostly dasatinib (n = 36), were reinitiated in 42 cases. Non-transplant group consisted of patients with disease progression, late transplant center referral, or patients refusing the procedure. In these cases TKIs (2nd or 3rd generation in most cases) were continued as monotherapy (n = 60) or in combination with chemotherapy (n = 20). Allo-HSCT and TKI groups did not differ in age, sex, comorbidity, disease phase or presence of additional chromosomal aberrations (ACAs) (Tab.1). OS and EFS were defined as the time from treatment initiation (allo-HSCT/TKI) to death and/or loss of response/post-transplant relapse. The response was assessed in accordance with the recommendations of the European Leukemia Net.

Results: A total of 71 (86%) patients engrafted. Gr2-4 aGVHD developed in 21(29%), Gr3-4 aGVHD in 14(20%), and cGVHD in 18(27%) of cases (severe cGVHD in 4 cases). Within 100 days past allo-HSCT the cumulative risk of relapse and NRM were 10% and 18%, accordingly. With a median follow-up of 44(1–344) months the cumulative relapse rate was 39% with 26 patients receiving subsequent DLIs and TKIs achieving complete molecular response (CMR) in 9, and progressing in 19 cases, accordingly. In TKIs group 71 patients were available for follow-up with 36(59%) progressing on therapy, and 25 achieving complete hematologic (CHR, n = 22), cytogenetic (CHR, n = 1) or molecular (CMR, n = 2) response, accordingly. Among 10 patients without history of BC one did not respond to therapy, while 9 achieved CHR (τ=5), CCR (n = 2) or CMR (n = 2). Sixty-nine patients died due to disease progression.

The allo-HSCT effect on OS of patients with AP or BC was also assessed by landmark analysis for 2 and 3 years with maximal phase onset chosen as a starting point. In 2 years the allo-HSCT significantly improved OS in patients with history of BC (71%) compared to TKI recipients (28%; p < 0.0001). In Cox's regression model allo-HSCT was also associated with higher OS compared to TKIs (HR 0.37; 95%CI 0.15-0.89; p = 0.026). Three-year landmark analysis have also demonstrated allo-HSCT advantage with 82% OS compared with 32% in TKIs recipients (p < 0.0001; Fig 1) with this advantage retained in Cox regression model with allo-HSCT being a positive (RR 0.22; 95% CI 0.07-0.74; p = 0.014) and history of BC a negative (RR 20.5; 95% CI 2.77-151.45; p = 0.003) influence on 5-year OS.



Conclusions: Despite of TKIs being the mainstay of therapy in CP CML, allo-HSCT still remains the only curative option for poor-prognosis patients. A timely referral to transplant center may salvage a patient in AP or BC.

Disclosure: Nothing to declare

P115

What can we do to improve the management of HSCT eligible patients with cmml in latin america?

F. Duarte[1], F. Onida[2], T.E.J.S. Sousa[3], V. Funke[4], V.A. Colturato[5], N. Hamerschlak[6], N. Vilela[7], M.C. Macedo[8], A. Vigorito[9], R.D.A. Soares[10], A. Paz[11], M. Stevenazzi[12], A.E. Hallack Neto[13], G. Bettarello[14], B. Gusmão[15], M.A. Salvino[16], R.F. Calixto[17], M.C.R. Moreira[18], G.M. Teixeira[19], C.C. Silva[6], R.P.G. Lemes[3], Y.O. Garcia[3], E.J.d.A. Paton[20], V. Rocha[21], A. Enrico[22], C. Bonfim[23], R. Chiattone[24], A.J. Simioni[5], C. Arrais[25], É.O.M. Coelho[26], L. Diaz[12]

[1]University Hospital Walter Cantídio, Hematology, Fortaleza, Brazil, [2]Universidade de Milão, Milão, Italy, [3]Hematology Research Laboratory - Federal Universityof Ceara, Fortaleza, Brazil, [4]Federal University of Paraná, Bone Marrow Transplantation, Curitiba, Brazil, [5]Hospital do Câncer Amaral Carvalho - Fundação Amaral Carvalho, Bone Marrow Transplant, Jaú, Brazil, [6]Hospital Israelita Albert Einstein, Bone Marrow Transplant, São Paulo, Brazil, [7]Hospital de Câncer Infantojuvenil de Barretos, Bone Marrow Transplant, Barretos, Brazil, [8]Instituto Brasileiro de Controle do Cancer, Bone Marrow Transplant, São Paulo, Brazil, [9]Universidade Estadual de Campinas - UNICAMP/ Hemocentro, Bone Marrow Transplant, Campinas, Brazil, [10]Natal Hospital Center, Bone Marrow Transplant, Natal, Brazil, [11]Hospital das clínicas de Porto Alegre, Bone Marrow Transplant, Porto Alegre, Brazil, [12]Centro TPH-SMI Serviço Médico Integral, Bone Marrow Transplant, Montevideo, Uruguay, [13]Hospital Universitário Universidade Federal de Juiz de Fora, Bone Marrow Transplantation, Juiz de Fora, Brazil, [14]Unidade de Transplante de Medula Óssea Pietro Albuquerque - ICDF, Bone Marrow Transplantation, Brasilia, Brazil, [15]Hospital São José, Bone Marrow Transplantation, São Paulo, Brazil, [16]Hospital Universitário Prof. Edgard Santos, Bone Marrow Transplantation, Salvador, Brazil, [17]Real Hospital Português de Beneficência em Pernambuco, Bone Marrow Transplantation, Recife, Brazil, [18]CEMO-INCA, Bone Marrow Transplantation, Rio de Janeiro, Brazil, [19]Hospital das Clínicas -Universidade Federal de Minas Gerais-Transplante de Medula Óssea, Belo Horizonte, Brazil, [20]ONCOBIO Serviço de Saúde S.A., Bone Marrow Transplantation, Nova Lima, Brazil, [21]Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Bone Marrow Transplantation, São Paulo, Brazil, [22]Hospital Italiano La Plata, Bone Marrow Transplantation, La Plata, Argentina, [23]Hospital Pequeno Principe, Bone Marrow Transplantation, Curitiba, Brazil, [24]Hospital Samaritano de São Paulo, Bone Marrow Transplantation, São Paulo, Brazil, [25]Hospital Sírio Libanês, Bone Marrow Transplantation, São Paulo, Brazil, [26]Hospital Santa Joana, Bone Marrow Transplantation, Recife, Brazil

Background: Hematopoietic Stem Cell Transplantation (HSCT) in Chronic Myelomonocytic Leukemia (CMML) has a very important role, for being the only curative procedure in high-risk patients. Despite this statement, there is a small number of transplants in this pathology in Latin America. OBJECTIVE to evaluate the HSCT scenario in Latin America.

Methods: Data from 29 patients with LMMC from 32 centers of the Latin American Registry of Transplantation in MDS, from April/ 1988 to December/2020, were analyzed. Statistical analysis was performed using the R program. Survival was analyzed using the Kaplan Meier curve and the prognostic factors, by Cox proportional risk.

Results: The mean age was 56, 52 years, with a predominance of males (79,31%, n = 23) and Caucasian (89,66%, n = 26). According to R-IPSS stratification patients were Very Low risk (3,45%,n = 1), Low risk (10,34%, n = 3), Intermediate (17,24%, n-5), High Risk/ Very High Risk (13,80%, n = 4). About 55,17% had not stratification. A total of 24,14% of patients received more than 20 unities of red blood cells and 27,59% received more than 15 unities of platelets. A total of 23 (79,31%) of patients underwent treatment before BMT, in which 47,82% took Hypomethylating. The Myeloablative regimen was the most frequent (62,07%, n = 18), followed by the Reduced Intensity (20,69%, n = 6) and Non-myeloablative (17,24%, n = 5). In 72,41% of cases, the donors were related, and of these, 10.34% were haploidentical; 17.24% not related. The main sources of cells used were peripheral blood (62,07%, n = 18) and bone marrow (37,93%, n = 11). Post-transplant complications were observed in 72.41% (n = 21. The most frequent was infection (57.14%), mainly by CMV (45.45%); acute GVHD (42.86%), chronic GVHD (33.33%) and veno-occlusive disease (9.52%). Recurrence occurred in 30% of cases. The frequency of deaths was 37.93% (n = 11). The survival probability of transplanted patients was 47.40% in 5 years. In the Cox regression model, the risk of death was 6.72 times greater in ≥ 65 years patients (p = 0.015) (CI95%: 1,44 - 31,40). Cox's model was evaluated using the proportional hazards hypothesis. The Global and individual Schoenfeld test was performed and the adequacy of the model was demonstrated. Patients were also stratified according to Bournemouth scores: 55,1% (n = 16) were high risk and 44,9%, (n = 13)were low risk. For MDAPS score patients were classified as: Low (13,7%, n = 4); Intermediate 1 (3,44%, n = 1), Intermediate 2 (20,6%, n = 6) and high (58,6%, n = 18). Regarding Mayo score, patients were stratified as: low (17,24%, n = 5); intermediate (17,24%, n = 5); high (65,51, n = 19%).

Conclusions: This is the first study of HSCT in CMML performed in Latin American. It presents the difficulties of correct diagnosis and possibilities of HSCT and reflects the efforts of different centers for conducting patients to the correct diagnosis therapeutic strategies, including the management of pre and post HSCT. Age at HSCT was the only factor that influenced in OS. The advances in technology around molecular features of this disease are gradually being incorporated into clinical protocols and has been show a powerful tool for better predicting outcomes. However, in some centers the molecular approach is still a challenge.

Disclosure: Nothing to declare

CONDITIONING REGIMENS

P118

Thiotepa-based reduced-intensity conditioning are a valid alternative to total-body irradiation-based regimens in patients with acute lymphoblastic leukemia: A study of the alwp of the ebmt

G. Battipaglia[1], M. Labopin[2], S. Mielke[3], A. Ruggeri[4], Z. Nur Ozkurt[5], J.H. Bourhis[6], W. Rabitsch[7], I. Yakoub-Agha[8], G. Grillo[9], J. Sanz[10], W. Arcese[11], Y. Novis[12], N. Fegueux[13], S. Giebel[14], A. Nagler[15], M. Mohty[16]

[1]Federico II University of Naples, Naples, Italy, [2]EBMT Statistical Unit, Paris, France, [3]Karolinska University Hospital, Dept. of Hematology, Stockholm, Sweden, [4]Ospedale San Raffaele s.r.l., Haematology and BMT, Milano, Italy, [5]Gazi University Faculty of Medicine, Hematology, Besevler, Ankara, Turkey, [6]Gustave Roussy Cancer Campus, BMT Service, Villejuif, France, [7]Internal Medicine I, BMT-Unit, Vienna General Hospital-Medical University of Vienna, Vienna, Austria, [8]CHU de Lille LIRIC, INSERM U995, Université de Lille, Lille, France, [9]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy, [10]Hematology University Hospital La Fe, Valencia, Spain, [11]Tor Vergata¨ University of Rome, Stem Cell Transplant Unit, Policlinico Universitario Tor Vergata, Rome, Italy, [12]Hospital Sirio-Libanes, Hematology Bone Marrow Transplant Unit, Sao Paulo, Brazil, [13]CHU Lapeyronie, Département d`Hématologie Clinique, Montpellier, France, [14]Maria Sklodowska-Curie Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland, [15]Chaim Sheba Medical Center, Tel-Hashomer, Israel, [16]Sorbonne Universités, UPMC Univ Paris 06, INSERM, Centre de Recherche Saint-Antoine (CRSA), Paris, France

Background: Total body irradiation (TBI) at myeloablative doses is superior to chemotherapy-based regimens in young patients with acute lymphoblastic leukemia (ALL) undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, in elderly and unfit patients, where reduced-intensity conditioning (RIC) regimens are preferred, whether a TBI- or chemotherapy-based approach is better is an unexplored issue. Thiotepa is an alkylating agent with radiomimetic activity and capability to cross the blood-brain barrier, that is used as part of ALL conditioning regimens. The aim of the current study is to compare transplant outcomes after RIC with TBI- or thiotepa-based regimens in ALL.

Methods: Included were patients aged ≥40 years undergoing allo-HSCT for ALL in first complete remission between 2000-2020, receiving a RIC regimen containing either TBI- (4-6 Grays, Gy) or thiotepa-based regimen.

Results: We identified a total of 265 patients, including 117 receiving TBI- (4 Gy, n = 65; 6 Gy, n = 52) and 148 receiving a thiotepa-based RIC regimen. Median age was 56 (range 40-72) versus 59 (range 40-75) years for TBI and thiotepa, respectively (p = 0.32). Thiotepa was more frequently associated to busulfan and fludarabine (n = 88) while TBI was more frequently associated to cyclophosphamide and fludarabine (n = 52), fludarabine alone (n = 27) or cyclophosphamide alone (n = 17). Most patients were diagnosed with Philadelphia positive ALL in both groups (59% for TBI and 55.4% for thiotepa, p = 0.14); T-ALL was diagnosed in 26 and 24 patients receiving TBI or thiotepa, respectively. HLA-identical and mismatched sibling donors were more frequent with thiotepa (35% versus 31% for matched and 21% versus 11% for mismatched siblings) while unrelated donors were more frequent in the TBI group (58% versus 44%) (p = 0.03). A longer interval from diagnosis to transplant was observed with thiotepa (6.7 versus 5.5 months, p < 0.01). Stem cell source was predominantly peripheral blood (94% for TBI and 81% for thiotepa, p < 0.01). The mainly used graft-versus-host disease (GVHD) prophylaxis was cyclosporine with either methotrexate or mycophenolate mofetil in both groups. In vivo T-cell depletion was more frequently used in the TBI group (54% versus 40%, p = 0.02). No imbalances for Karnofsky score (<90 in in 22% and 23% for TBI and thiotepa, p = 0.81) were observed. A Sorror score of 1-2 or ≥3 was observed in 19% and 20% of patients receiving TBI and 26% and 27% of those receiving thiotepa, respectively (p = 0.19). In univariate analysis, no differences were observed in transplant outcomes (for TBI vs thiotepa: relapse 23% versus 28%, p = 0.24; non-relapse mortality, 20% versus 26%, p = 0.61; leukemia-free survival, 57% versus 46%, p = 0.12; overall survival, 67% versus 56%, p = 0.18; GVHD/relapse-free survival, 45% versus 38%, p = 0.21; grade II-IV acute GVHD, 30% in both groups, p = 0.84; grade III-IV acute GVHD, 9% versus 10%, p = 0.89) except for chronic GVHD that was higher for TBI-based regimens (43% versus 29%, p = 0.03). However, in multivariate analysis we observed no differences in transplant outcomes according to the conditioning regimen used.

Conclusions: In patients aged more than 40 years receiving a RIC regimen, use of thiotepa-based regimen may represent a valid alternative to TBI-based regimens due to no differences in the main transplant outcomes.

Clinical Trial Registry: In patients aged more than 40 years receiving a RIC regimen, use of thiotepa-based regimen may represent a valid alternative to TBI-based regimens due to no differences in the main transplant outcomes.

Disclosure: No COI to disclose

P119

Excellent outcome with fb4 regimen in patients with myeloid malignancies older than 55 and with hct-ci score

D. Avenoso[1], M. de Farias[1], H. Alshehri[1], P. Krishnamurthy[1], V. Mehra[1], A. Kulasekararaj[1], S. Gandhi[1], A. Pagliuca[1], F. Dazzi[1], H. Wood[1], M. Kenyon[1], Y.T. Leung[1], A. Eaton[1], M. Cuadrado[1], P. Hardefeldt[1], V. Potter[1]

[1]*King's College Hospital NHS Foundation Trust, London, United Kingdom*

Background: Allogeneic haematopoietic stem cell transplant (HSCT) is considered a curative strategy for acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) with excess of blasts or complex/adverse cytogenetic.

The evaluation of comorbidities with HCT-CI score and the upper limit of 55 years for administering myeloablative conditioning (MAC) are common strategies to minimise HSCT non-relapse mortality (NRM). Despite multiple studies performed previously, this remains an area of uncertainty and precise data guiding MAC selection are still needed.

Herein we report the outcome of patients affected with AML and MDS conditioned with MAC.

Methods: HSCT was performed with GCSF mobilised peripheral blood stem cells. Conditioning protocol was with fludarabine 30 mg/m^2 days -7, -6, -5, -4, -3 busulfan 3.2 mg/Kg days -6, -5, -4, -3 (FB4); graft versus host disease (GVHD) prophylaxis consisted of thymoglobulin (ATG 5 mg/Kg) or Campath 60 mg (27 and 94 patients, respectively) and single-agent ciclosporin 3 mg/Kg (therapeutic level of 150-200) until d + 56 and then tapered in absence of GVHD.

Results: Between January 2016 and November 2020, 121 patients (77 AML, 44 MDS) with a median age of 56 (19-73) had FB4 conditioning. A median of 5.5x10^6 CD34 + /Kg was infused (3.1 – 8). Donors were: 21 full matched siblings, 76 full matched unrelated donors, 24 mismatched unrelated donors.

Patients aged > 55 were 64 (53%). HCT-CI score <2 and ≥2 was present in 48 and 73 patients, respectively.

Two years overall survival (OS) was 55% with a median OS of 42 months. No septic death before engraftment or primary graft failure were noted. Median time to neutrophils ≥1000/mL was 12 days (10-18), and 10 days (8-48) to platelets ≥ 20.000/mL. Median CD3 and CD15 chimerism at day 365 were 98% and 100%. Incidence of acute GVHD was 60% (grade III-IV 9%); overall chronic GVHD rate was 33% (moderate 14%, severe 7%). Incidence of venous occlusive disease (VOD) was 7%, no VOD-deaths were recorded. Cumulative incidence of relapse was 19%. Flow cytometry minimal residual disease (MRD) was positive in 28 patients at the time of HSCT and didn't affect the OS. There was no significant difference in OS when patients were stratified according to age even if there is a non-significant trend for patients younger than 55.

Age at HSCT did not influence NRM but was higher in patients with higher HCT-CI: 10% versus 43% if HCT-CI was <2 and ≥2, respectively (P 0.04). Two years OS for patients aged ≥ 55 and with HCTI-CI < 2 and for those with HCTI-CI ≥ 2 were 63% (median OS not reached in this group) and 45%, respectively. Three years OS was 57% and 42%, respectively.

Conclusions: This analysis supports the feasibility of FB4 conditioning in patients affected with AML and MDS regardless of age. The decision for myeloablation should rely on comorbidities and disease characteristics rather than chronological age, especially for those with positive MRD at the time of HSCT.

Disclosure: Nothing to declare

P121

Comparison of fludarabine/melphalan(flumel) with fludarabine/melphalan/bcnu or thiotepa(fbm/ftm) in patients with AML undergoing allogeneic hematopoietic cell transplantation – a registry study on behalf of the ebmt alwp

J. Duque-Afonso[1], J. Finke[1], M. Ngoya[2], M. Labopin[2], E. Nicholson[3], P. Kottaridis[4], C. Craddock[5], E. Tholouli[6], R. Protheroe[7], E.M. Wagner-Drouet[8], A. Bloor[9], T. Valerius[10], K.M.O. Wilson[11], B.N. Savani[12], A. Spyridonidis[13], A. Nagler[14], M. Mohty[15]

[1]*University of Freiburg/Klinik für Innere Medizin I, Freiburg, Germany,* [2]*EBMT Paris Study Office/Hopital Saint Antoine, Paris, France,* [3]*Royal Marsden Hospital, London, United Kingdom,* [4]*University College London Hospital, London, United Kingdom,* [5]*Birmingham Centre for Cellular Therapy and Transplantation/Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom,* [6]*Manchester Royal Infirmary, Manchester, United Kingdom,* [7]*University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, United Kingdom,* [8]*University Medical Center Mainz, Oncology and Pneumology, Mainz, Germany,* [9]*The Christie NHS Foundation Trust, Stem Cell Transplantation Unit/Manchester University, Manchester, United Kingdom,* [10]*University Medical Center Schleswig-Holstein, Kiel, Germany,* [11]*University Hospital of Wales, Cardiff, United Kingdom,* [12]*Division of Hematology and Oncology, Vanderbilt University Medical Center, Nashville, TN, United States,* [13]*University Hospital of Patras, Patras, Greece,* [14]*Hematology Division, Chaim Sheba Medical Center, Tel Hashomer, Israel,* [15]*Sorbonne Université/Hopital Saint-Antoine, Paris, France*

Background: Conditioning protocols for patients undergoing allogeneic hematopoietic cell transplantation (allo-HCT) are developing continuously to improve their anti-leukemic efficacy and to reduce their toxicity. A recent developed score (transplantation conditioning intensity or TCI) considers the intensity of conditioning as a continuum and not as "classical" defined myeloablative or reduced intensity conditioning. In previous studies, we compared two of the most used conditioning protocols from the intermediate TCI score based on one alkylating agent as fludarabine/melphalan (FluMel) vs. fludarabine/treosulfan (FluTreo) using the EBMT ALWP registry, which serve as basis for the comparison of the present study.

Methods: In the present study, we compared the conditioning protocol FluMel with conditioning protocols based on FluMel (fludarabine 150 mg/m2, melphalan 140mg/m2) or with the addition of a second alkylating agent as FBM (fludarabine, mean 150mg/m2, carmustine 300-400mg/m2 and melphalan, mean 110 mg/m2) or FTM (fludarabine, mean 150mg/m2, thiotepa 5-10mg/kg and melphalan, mean 110 mg/m2). FBM and FTM have been shown to be equivalent at the dosages used in this study. We used following inclusion criteria: first allo-HCT from a matched sibling donor (MSD) or unrelated donor (UD) for patients with AML in complete remission (CR), (3) transplantation date between January 1st, 2009 and December 31st, 2020, (4) with an unmanipulated peripheral blood graft.

Results: We included 3417 adult patients with acute myeloid leukemia (AML) in complete remission (CR) from the registry of the

EBMT Acute Leukemia Working Party, 2567 patients were conditioned with FluMel and 850 patients in FBM/FTM. The median follow-up was 4.0 years in FluMel and 3.0 years in FBM/FTM cohorts.

Patients in the FBM/FTM group were older (59.9 years vs. 59.0 years, $p < 0.001$) and had a worse Karnofsky performance score (KPS < 90, 27.1% vs. 20.1%, $p < 0.001$). Additional transplant characteristics as female donor (FBM/FTM: 28.2% vs. 32.4%, $p = 0.02$), CR1 status at allo-HCT (FBM/FTM: 82% vs 78.1%, $p = 0.02$), matched sibling donor (FBM/FTM: 21.1 vs. 31.7%, $p < 0.0001$) and in vivo T-cell depletion (anti-thymocyte-globuline in 75.8% of FBM/FTM patients, alemtuzumab more used in 66% of FluMel patients) were different among cohorts.

In univariate analysis, patients in FBM/FTM group showed a better overall survival at 2 years (65.9% vs. 58.7%, $p = 0.03$) but a higher incidence of aGvHD II-IV at day 100 (25.8% vs. 16.8%, $p < 0.0001$) compared to patients treated with FluMel. In multivariate analysis, patients treated with FBM/FTM showed a trend for improved overall survival (FluMel with HR 1.17, 95%CI 1-1.38, $p = 0.057$) and leukemia-free survival (HR 1.14, 95%CI 1-1.3, $p = 0.059$) compared to FluMel treated patients. No significant differences were observed in relapse incidence (HR 1.12, 95%CI 0.94-1.33, p-value 0.21) and non-relapse mortality (HR 1.14, 95% CI 0.88-1.49, p-value 0.32).

Conclusions: In conclusion, the addition of a second alkylating agent (BCNU/carmustine or thiotepa) to FluMel as FBM/FTM conditioning seems to improve overall survival while maintaining similar toxicity in AML patients in CR undergoing allo-HCT. Due to several limitations of the study including the retrospective nature of the study and unbalanced patient characteristics, these data should be interpreted with caution.

Disclosure: Nothing to declare

P122

Fludarabine and melphalan conditioning with thiotepa versus total body irradiation for haploidentical hematopoietic stem cell transplantation (haplo-sct)

S. Saengboon[1], U.R. Popat[1], K. Alzahrani[1], R. Mehta[1], A. Olson[1], J. Chen[1], P. Kebriaei[1], E. Shpall[1], R.E. Champlin[1], S.A. Srour[1]

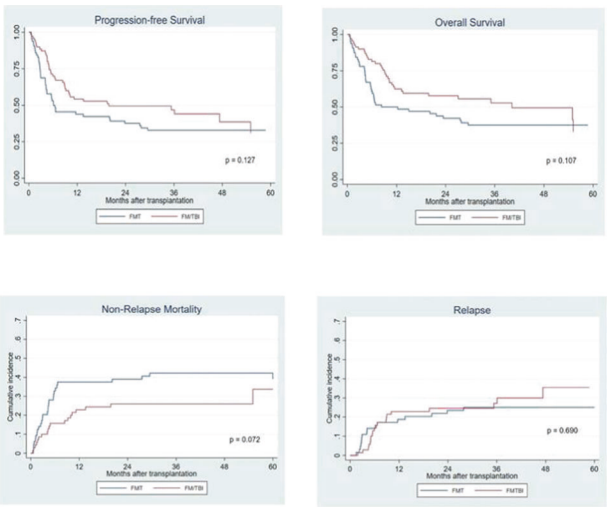
[1]The University of Texas MD Anderson Cancer Center, Texas, United States

Background: Remarkable improvements in haplo-SCT outcomes are made since the introduction of posttransplant cyclophosphamide (PTCy)-based GVHD prophylaxis. There remains, however, no consensus regarding best conditioning platform; choice of regimen is mostly dependent on center experience. Fludarabine (total 160 mg/m^2)/Melphalan (100-140 mg/m^2) combined with thiotepa (5 mg/kg) (FMT) vs 2 Gy total body irradiation (TBI) are two reduced-intensity regimens commonly used at our center. We present here the largest single center study to compare the transplant outcomes in patients with acute leukemia and MDS who underwent haplo-SCT using FMT vs FM/TBI.

Methods: We included all consecutive AML/MDS and ALL patients who underwent haplo-SCT between 01/2012 and 12/2019 and received FMT or FM/TBI with PTCy/Tacrolimus/MMF GVHD prophylaxis. Primary objectives were to compare PFS and OS by conditioning regimen. Secondary objectives included cumulative incidence (CI) of NRM, CIR, and GVHD.

Results: 134 patients with a median age of 52 (IQR 35-60) years were identified, 64 (48%) received FMT and 70 (52%) received FM/TBI. Table 1 summarizes baseline characteristics. At a median follow up of 3 years, the 3-year PFS/OS rates were 33%/47% and 37%/53% in the FMT and FM/TBI, respectively ($p = 0.127$ for PFS; $p = 0.107$ for OS). One-year NRM rates for FMT and FM/TBI were 37% and 23% (HR 0.585, 95% 0.325-1.050; $p = 0.072$). The CIR at 1/3 years were 19%/ 25% for FMT and 23%/27% for FM/TBI ($p = 0.690$). In UVA, age ≥ 55, high/very-high DRI, HCT-CI > 3, and reduced-dose melphalan 100 mg/m^2 were significantly associated with inferior PFS and OS. In MVA, high/very high DRI (HR 1.950, 95%CI 1.248-3.046; $p = 0.003$) and HCT-CI > 3 (HR 1.586, 95%CI 1.009-2.493; $p = 0.046$) were associated with worse PFS. In MVA for OS, age≥ 55 (HR 1.997, 95%CI 1.093-3.650; $p = 0.024$), high/very-high DRI (HR 2.020, 95%CI 1.263-3.231; $p = 0.003$) and HCT-CI > 3 (HR 1.747, 95%CI 1.090-2.798; $p = 0.020$) were associated with inferior survival. In MVA for NRM, age≥ 55 (HR 2.646, 95%CI 1.453-4.816; $p = 0.001$) was associated increased NRM, with a trend for lower NRM with FM/TBI (HR 0.617, 95%CI 0.341-1.115; $p = 0.110$). Grades 3-4 acute GvHD at day 100 were 5% and 6% for FMT and FM/TBI, respectively ($p = 0.8$). The CI rates of chronic GvHD at 3 years for FMT and FM/TBI were 19% and 12%, respectively ($p = 0.2$)

Variable	All Patients (N = 134)	Flu/Mel/Thio (N = 64)	Flu/Mel/TBI (N = 70)	P-Value
Age at transplant				
<55 years	71 (52.99%)	33 (51.56%)	38 (54.29%)	0.863
≥55 years	63 (47.01%)	31 (48.44%)	32 (45.71%)	
Gender				
Male	82 (61.19%)	40 (62.50%)	42 (60.00%)	0.86
Female	52 (38.81%)	24 (37.50%)	28 (40.00%)	
Disease Subtype				
AML/MDS	103 (76.87%)	48 (75.00%)	55 (78.57%)	0.684
ALL	31 (23.13%)	16 (25.00%)	15 (21.43%)	
KPS at transplant				
KPS 90 - 100	65 (57.52%)	38 (71.70%)	27 (45.00%)	0.005
KPS < 90	48 (42.48%)	15 (28.30%)	33 (55.00%)	
DRI				
Low/ Intermediate DRI	76 (57.14%)	32 (50.00%)	44 (63.77%)	0.118
High/Very High DRI	57 (42.86%)	32 (50.00%)	25 (36.23%)	
HCT-CI				
HCT-CI ≤ 3	83 (61.94%)	39 (60.94%)	44 (62.86%)	0.86
HCT-CI > 3	51 (38.06%)	25 (39.06%)	26 (37.14%)	
Melphalan dose				
100 mg/m^2	68 (50.75%)	25 (39.06%)	43 (61.43%)	0.015
140 mg/m^2	66 (49.25%)	39 (60.94%)	27 (38.57%)	
Patient CMV status				
Seropositive	122 (91.04%)	59 (92.19%)	63 (90.00%)	0.767
Seronegative	12 (8.96%)	5 (7.81%)	7 (10.00)	
Stem cell source				
Bone marrow	117 (87.31%)	60 (93.75%)	57 (81.43%)	0.039
Peripheral blood	17 (12.69%)	4 (6.25%)	13 (18.57%)	



Conclusions: FMT and FM/TBI conditioning with PTCy/Tacrolimus/MMF GVHD prophylaxis showed comparable survival outcomes in haplo-SCT. There was a trend for better outcomes with FM/TBI related to decreased NRM. Prospective controlled studies to optimize conditioning regimen for haplo-SCT are needed.

Disclosure: Nothing to declare

P123

Efficacy of treosulfan in combination with fludarabine as conditioning regimen in allogeneic transplantation as compared with a myeloablative conditioning using busulfan and fludarabine

J.Á. Calvo Sánchez[1], S. Fernández García[1], L. Aranguren del Castillo[2], S. Fernández-Luis[1], L. Yáñez San Segundo[1], A. Insunza Gaminde[1], N. Fernández Escalada[1], G. Martín Sánchez[1], M.M. Colorado Araújo[1], M. López Duarte[1], M. Sánchez Escamilla[1], C. Montes Gaisán[1], J.I. Romon Alonso[1], J.L. Arroyo Rodríguez[1], E.M. Ocio San Miguel[1], M.A. Bermúdez Rodríguez[1]

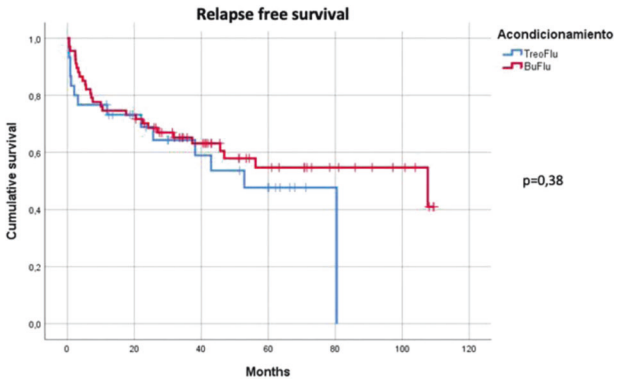
[1]Marqués de Valdecilla University Hospital, Santander, Spain, [2]Cruces University Hospital, Barakaldo, Spain

Background: Myeloablative conditioning schemes are the gold standard conditioning therapy in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) that underwent allogeneic haemopoietic stem cell transplantation.

Reduced toxicity conditioning regimens, such as treosulfan-fludarabine (Treo-flu), have been increasingly used for treating comorbid and elderly patients, and they could be as effective as standard myeloablative, with fewer toxicity and mortality rates in relation with the procedure.

Our primary objective was to compare overall survival (OS) and relapse free survival (RFS) in patients as contrast with standard myeloablative regimens. Our secondary objectives were evaluating toxicity and GVHD incidence.

Methods: We retrospectively studied 97 patients, diagnosed with AML (n = 71) and MDS (n = 26), that underwent allogeneic stem cell transplantation at our institution between the years 2012-2020. Control myeloablative conditioning regimen was Bu-Flu (n = 67)[Busulfan total dose: 9,6-12,8mgr/Kg, fludarabine 160mg/m2]. Treo-Flu was used in 30 patients [Treosulfan total dose: 30-42 g/m2 (in 5 and 25 patients), fludarabine 150mg/m2]. Busulfan levels were not extracted as a rule.



Results: Patient's characteristics of both conditioning regimens were similar, excluding age (62 vs 54 p = 0,003) and HCT-CI score >3 (66,7% vs 44,8% p = 0,037) that were higher in Treo-Flu patients, as shown in table 1. Treosulfan group had more patients with uncontrolled disease (33% vs 16% p = 0,057).

With a median follow up of 50,5 months (11,7-109,4 months), there weren't significant differences between treosulfan and busulfan in 3-year overall survival (64% vs 73% p = 0,101), relapse free survival (64% vs 65% p = 0,385) and relapse-free mortality (21% vs 14%; p = 0,164) .

The presence of grade >2 toxicity with treosulfan (40%) was lower than with busulfan (59,7%; p = 0,057). These results rely mostly on the presence of mucositis, which was significantly lower in treosulfan group (13,3% vs 49,3%; p = 0,001). There weren't significant differences on GI, hepatic, pulmonary, renal or cardiac toxicity between both groups. There were no differences between CMV or fungal infections.

There weren't significant differences between both conditioning regimens neither in 100-days cumulative incidence of severe aGVHD (7% vs 9%; p = 0,766) nor 3-year cumulative incidence of moderate-severe cGVHD (32% vs 34%; p = 0,591).

	All patients	**BuFlu**	**TreoFlu**	***p* value**
	***n* = 97**	***n* = 67**	***n* = 30**	
Age, median (min-max)	57 (19-73)	54 (19-70)	62 (26-73)	**0,003**
Sex, n (%)				0,107
Male	54 (55,7)	34 (50,7)	20 (66,7)	
Female	43 (44,3)	33 (49,3)	10 (33,3)	
Diagnoses, n (%)				0,595
AML	71 (73,2)	49 (73,1)	22 (73,3)	
MDS	26 (26,8)	18 (26,9)	8 (26,7)	
Disease status, n (%)				0,260
Complete remission	76 (78,4)	56 (83,6)	20 (66,7)	
Partial remission	5 (5,2)	3 (4,5)	2 (6,7)	
Progression/ refractory	11 (11,3)	5 (7,5)	6 (20)	
Never treated	5 (5,2)	3 (4,5)	2 (6,7)	
Prior treatment lines, median (min-max)	1 (0-4)	1 (0-4)	1 (0-3)	0,102

	All patients	BuFlu	TreoFlu	p value
	n = 97	n = 67	n = 30	
HCT-CI score, n (%)				0,037
<3	47 (48,5)	37 (55,2)	10 (33,3)	
≥3	50 (51,5)	30 (44,8)	20 (66,7)	
Donor, n (%)				0,566
HLA-matched sibling	29 (29,9)	22 (32,8)	7 (23,3)	
HLA-haploidentical sibling	19 (19,6)	11 (16,4)	8 (26,7)	
HLA-matched unrelated	44 (45,4)	30 (44,8)	14 (46,7)	
HLA-mismatched unrelated	5 (5,2)	4 (6)	1 (3,3)	
Stem cell source, n (%)				0,064
Bone marrow	64 (66)	48 (71,6)	16 (53,3)	
Peripheral blood	33 (34)	19 (28,4)	14 (46,7)	
GvHD prophilaxis, n (%)				0,243
Calcineurin inhibitor + MMF/ MTX	67 (69,1)	46 (68,7)	21 (70)	
Cy post + FK + MMF	20 (20,6)	12 (17,9)	8 (26,7)	
Cy post	10 (10,3)	9 (13,4)	1 (3,3)	
ATG	28 (28,9)	18 (26,9)	10 (33,3)	0,338

Conclusions: Considering patient selection and retrospective study limitations, in our experience treosulfan-fludarabine as allogeneic transplant conditioning regimen, regarding OS and RFS, offers similar results as myeloablative busulfan-based, despite patients were older with more comorbidity and poor disease status at transplantation.

Disclosure: Nothing to declare

P124

High dose intravenous busulfan increases risk for hemorrhagic cystitis in allogenic hematopoietic stem cell transplant patients

A. Santos Carreira[1], M.Q. Salas[2], M. Remberger[3], A. Datt Law[4], W. Lam[4], I. Pasic[4], D.(.H. Kim[4], F.V. Michelis[4], A. Viswabandya[4], A. Gerbitz[4], J.H. Lipton[4], R. Kumar[4], C. Cserti[5], T. Mazzulli[6], M. Hassan[7], J. Mattsson[1]

[1]University of Toronto/ Princess Margaret Cancer Centre, Toronto, Canada, [2]Hospital Clinic de Barcelona, Barcelona, Spain, [3]Uppsala University Hospital, Uppsala, Sweden, [4]University of Toronto/Princess Margaret Cancer Centre, Toronto, Canada, [5]University of Toronto/ University Health Network, Toronto, Canada, [6]University of Toronto/ Mount Sinai Hospital, Toronto, Canada, [7]Karolinska Institutet/ Karolinska University Hospital, Stockholm, Sweden

Background: This study investigates the incidence and risk factors for hemorrhagic cystitis (HC) in a large cohort of adults undergoing allogeneic hematopoietic stem cell transplantation (alloHSCT) from a single Institution.

Methods: Between January 2015 and June 2021, 960 adults underwent first alloHSCT at our Institution and included in the study. Data was collected retrospectively and updated in October 2021.

Results: Overall, the median age was 58 years, 45.7% of patients underwent MUD alloHSCT, and 252 received MAC regimens. Of the 252 patients transplanted using MAC regimens, 81.4% received high doses of intravenous busulfan (HD BU). PTCY was given to 72.4% patients, and among them, 91.4% received dual T-cell depletion with ATG.

Overall, the cumulative incidences of grade 2-4 and grade 3-4 HC at day +180 were 13.2% and 5.8%, respectively, and the median of days to grade 2-4 and 3-4 HC were 39 and 44 days. BK virus was analyzed on 95% of cases and only 60% with HC grade 2-4 were positive. Additionally, the level of BK did not correlate with severity. Those patients receiving HD BU (Day + 180 23.1% vs 10.5%) had higher incidences of grade 2-4 HC than those that did not. Patients receiving PTCY (the majority of them in combination with ATG-CsA) had comparable incidences of grade 2-4 HC (Day + 180 14.6% vs 10.5%, $P = 0.12$). Additionally, patients with blood group O had higher incidence of grade 3-4 HC than patients with other blood groups (7.7% vs 3.9%, $P = 0.002$).

A multivariate analysis exploring risk factors for grade 2-4 and 3-4 HC was calculated including conditioning regimen, HCT-CI, donor type, blood group, and GVHD prophylaxis. The administration of HD BU (HR 3.06, $P < 0.001$) and the use of PTCY (HR 1.69, $P < 0.001$) were found to be risk factors for being diagnosed with grade 2-4 HC.

Secondary to the results obtained in the cumulative incidence and MVA analyses, the effect of HD BU and PTCY was explored in detail. The 545 patients receiving HD BU without PTCY were 1.9 times more likely to have grade 2-4 HC compared with patients that did not received any of these drugs ($P = 0.038$). The 90 patients that received HD BU with PTCY-based GVHD prophylaxis were 4.6 times more likely to present grade 2-4 HC compared with patients that did not received any of these drugs ($P < 0.001$). The use of PTCY, without HD BU did not increase the probability of grade 2-4 HC in our analysis (HR 1.4, $P = 0.20$).

Conclusions: The incidence of grade 2-4 HC at our Institution was 13.2%. HD intravenous BU was found to be an independent predictor for grade 2-4 HC; and when combined with PTCY the risk increased x2.38 times. PTCY-based GVHD prophylaxis, alone, did not increase the probability of HC in our study.

Patients receiving MAC alloHSCT with HD intravenous BU combined with PTCY-based GVHD prophylaxis may need change in supportive care with forced diuresis and increased dose of MESNA.

Disclosure: Nothing to declare

P125

AUC targeted busulfan administration can overcome the negative impact of pre-transplant mrd positivity in intermediate risk AML patients

E. Klyuchnikov[1], A. Badbaran[1], C. Langebrake[1], R. Massoud[1], P. Freiberger[1], F. Ayuk[1], C. Wolschke[1], U. Bacher[2], N. Kröger[1]

[1]University Cancer Center Hamburg-Eppendorf, Hamburg, Germany, [2]University of Bern, Bern, Switzerland

Background: The pre-transplant minimal residual disease (MRD) has a negative impact on post-transplant survival in AML patients due to increased relapse risk. An increased busulfan dosage may lead to lower relapses, however it may be also associated with

increased NRM. Due to its narrow therapeutic index, the therapeutic drug monitoring approach based on the calculation of area under the curve (AUC) was developed to optimize the busulfan exposition. In this study, we compared post-transplant outcomes after the administration of personalized or fixed busulfan dosage in patients with intermediate risk AML focusing on pre-transplant MRD status.

Methods: 86 patients (male = 48; median age 56 years, 21-73) with intermediate risk AML and available pre-transplant MRD data (multicolored flow cytometry, "different from normal" approach, according to ELN guidelines), who received allografts (matched, n = 61; mismatched, n = 25) during 2015-2020 years at the University Cancer Centre Hamburg-Eppendorf were included. 33 patients received personalized busulfan dosage (AUC) after model-based AUC-calculation and 53 fixed busulfan dosage (12.8 mg/kg bw iv, n = 30; 9.6 mg/kg bw iv, n = 15, 6.4 mg/kg bw iv, n = 8). There were more females in the AUC group (67% vs 30%, p = 0.01). The myeloablative busulfan/fludarabine regimen was the most used in the both groups (82% and 58%, respectively). Patients from non-AUC group received more post-transplant cyclophosphamide than ATG as GvHD prophylaxis (25% vs 6%, p = 0.022).

Results: The median follow up was 27 months (1-61). The relapses were lower in pre-transplant MRD^{neg} patients (11%, 5-25% vs 35%, 22-51%, p = 0.008) and in those who received MAC (19%, 11-31%) vs RIC (65%, 20-93%, p = 0.04). The non-AUC led to higher relapses at 3 years (35%, 23-49% vs 6%, 2-19%, p = 0.02) resulting in lower 3-year LFS (55%, 40-70% vs 78%, 54-91%, p = 0.009) and OS (69%, 54-81% vs 82%, 60-93%, p = 0.05) comparing to AUC. The NRM at 3 years was not different (AUC: 7%, 2-19% vs non-AUC: 10%, 5-21%, p = 0.48). The aGvHD at 1 year (AUC: 21%, 11-37% vs non-AUC: 14%, 7-27%, p = 0.41) and cGvHD at 3 years (AUC: 57%, 40-73% vs non-AUC: 45%, 31-60%, p = 0.30) were not significantly different.

Of the pre-transplant MRD^{pos} patients, those from AUC group (n = 13) showed lower relapses at 3 years (8%, 1-36% vs 49%, 31-67%, p = 0.07) resulting in higher 3-year LFS (92%, 69-98% vs 41% 24-61%, p = 0.023) and OS (100% vs 58%, 39-75%, p = 0.032) compared with non-AUC group (n = 31). The NRM at 3 years was not significantly different (AUC: 0%, non-AUC: 10%, 3-28%, p = 0.24).

Of the pre-transplant MRD^{neg} patients, there were no significant differences concerning relapses at 3 years (5%, 1-24% vs 17%, 6-40%, p = 0.32), NRM at 3 years (6%, 1-28% vs 9%, 3-27%, p = 0.56), 3-year LFS (84%, 61-95% vs 74%, 52-88%, p = 0.43) and OS (84%, 61-95% vs 84%, 61-95%, p = 0.92) between AUC (n = 19) and non-AUC (n = 23) groups, respectively.

Conclusions: The personalized, AUC-based, busulfan administration as part of conditioning seems to overcome the negative impact of pre-transplant MRD positivity with acceptable NRM in patients with intermediate risk AML undergoing allo-HSCT.

Disclosure: Nothing to declare

P126

Optimising in vivo alemtuzumab levels in matched unrelated haematopoietic stem cell transplantation

M. Madkhali[1,2], C. Wright[1,3], K. Pearce[1], S. Pagan[1], P. Singh[1], L. Duncan[3], J. Lam[1], G. Erskine[1], J. Macdonald[1], A. Resteu[1], P. Milne[1], A. Publicover[1,3], E. Hurst[3], V. Bigley[1,3], G. Hale[4], M. Collin[1,3]

[1]Newcastle University/Translational and Clinical Research Institute, Newcastle, United Kingdom, [2]Ministry of Health/Jazan Health/ Samtah General Hospital, Samtah, Saudi Arabia, [3]Northern Centre for Bone Marrow Transplantation, Newcastle, United Kingdom, [4]Geoff Hale Developments, Oxford, United Kingdom

Background: Alemtuzumab is a humanised monoclonal antibody specific for CD52 that depletes T cells in vivo and reduces acute and chronic graft versus host disease (GVHD). Alemtuzumab is highly efficient at preventing acute and chronic GVHD in Fludarabine and Melphalan (FM) conditioning but at the cost of prolonged immunosuppression, increased infections, and relapse. The optimal dose and scheduling of Alemtuzumab is not defined, particularly in the matched unrelated donor (MUD) setting where empiric flat-dosing, unsupported by pharmacokinetics, is the rule.

Methods: In this retrospective single centre study we compared two empiric dose reductions from the original 100mg dose regimen (Kottaridis et al., 2000). These were introduced as policy changes in an attempt to minimise excessive T cell depletion. From 2015-2018, 48 patients received 60mg (30mg on days -4 and -2) (FMA60) and from 2019-2021,40 patients received 30mg delivered on day -1 (FMA30). Transplant serum samples were available from 21 FMA60 and 16 from FMA30 at days 0, +7 and +14. Alemtuzumab levels were measured by ELISA assay. All Patients were transplanted with fludarabine 150mg/m2 and melphalan 140mg/m2 conditioning chemotherapy at the Northern Centre for Bone Marrow Transplantation (Newcastle upon Tyne Hospitals UK). We compared the overall incidence and severity of acute GVHD in the two cohorts. Overall survival (OS) and relapse free survival (RFS) were analysed by Kaplan Meier compared with log-rank tests.

Results: On all days, the mean (SD) of Alemtuzumab concentration were significantly different between FMA60 and FMA30 cohorts. Respectively, Alemtuzumab on day 0 was 6.22 (2.09) ug/ml and 3.33 (0.97) ug/ml (p < 0.0002); on day+7: 2.385 (1.456) ug/ml and 0.8423 (0.4431) ug/ml (p = 0.0003), on day +14: 1.124 (0.8435) ug/ml and 0.4768 (0.4907) ug/ml (p = 0.0410). No differences were observed in the incidence and severity of acute GVHD between the two cohorts (Chi-square test p = 0.6801). In FMA60, GVHD was 43.75%, 8.33% and 2.08% compared with 50%, 2.5% and 2.5% in FMA30 for grades I, II and III, respectively. Comparable OS and RFS were observed; OS (log-rank test p = 0.742), the OS at 2 years were 66% and 68% in the FMA 60 and FMA 30, respectively. The hazard ratio for death in FMA 60 versus FMA 30 was 1.121 (95% CI 0.518-2.426) p = 0.772. RFS (log-rank test p = 0.698), the hazard ratio for death in FMA 60 against FMA 30 was 1.208 (95% CI 0.465-3.140) p = 0.698.

Conclusions: This retrospective analysis reports the in vivo level of Alemtuzumab on day 0, +7 and +14 in recipients of 60mg (delivered on days -4 and -2) and 30mg (day -1) in MUD transplant. The results confirm that 30mg of Alemtuzumab on day -1 is effective in preventing GVHD in MUD transplant.

Disclosure: No conflicts of interest to declare.

P127

Total body irradiation-based conditioning versus chemotherapy before allogeneic stem cell transplantation for adults with acute lymphoblastic leukemia

N. Ben Abdeljelil[1], R. Ouerghi[1], S. Ladeb[1], D. Belloumi[1], L. Torjemane[1], S. Mekni[1], T. Ben othman[1]

[1]Centre National de Greffe de Moelle Osseuse, Tunis, Tunisia

Background: Total body irradiation (TBI) is a part of the standard myeloablative conditioning regimen before allogeneic stem cell transplantation (allo-HSCT) for patients with acute lymphoblastic leukemia (ALL) but not available in all center. This study aimed to compare TBI-based conditioning to chemotherapy in term of graft-versus host disease (GVHD), overall survival (OS), event-free

survival (EFS), non-relapse mortality (NRM) and cumulative incidence (CI) of relapse.

Methods: Retrospective study was conducted in adult patients who underwent allo-HSCT from HLA-identical sibling donors between January 2012 and July 2021. Conditioning regimen consisted TBI plus etoposide or cyclophosphamide (Cy). Non TBI-regimen consisted of busulfan (iv) plus Cy (Bu-Cy) or fludarabine plus busulfan plus Cy (FBC) or thiotepa plus busulfan plus fludarabine (TBF). GVHD prophylaxis consisted of cyclosporine and short course of methotrexate +/− antithymocyte globulin (ATG).

Results: Sixty patients were included. Patient characteristics were similar between the two groups (table1). Patients conditioned with TBI were more likely to have delayed platelet engraftment and mucositis grade II-IV ($p = 0.03$, $p < 10^{-3}$, respectively). Cumulative incidences of acute GVHD grade II-IV and chronic GVHD were not significantly different between TBI and non-TBI groups (53.6% vs 34.4 %, $p = 0.11$ and 49.7% vs 33.1%, $p = 0.42$, respectively). CMV infection(s) were not significantly different between TBI and non-TBI groups (35.7% vs 31.3 %, respectively, $p = 0.11$). The median follow-up was 36 months (range, 2 - 116 months).There were no statistically significant differences between groups in terms of OS and EFS (65.7% for TBI group vs 50.6% for non-TBI group, $p = 0.22$ and 58.2% vs 49%, $p = 0.27$, respectively). Patients from both groups had a comparable CI of NRM (25.5% vs 19.1%, $p = 0.73$, respectively). TBI group had lower CI of relapse compared to non-TBI group with no significant difference (13.3% vs 29.3%, $p = 0.79$, respectively).

Table1. Patient characteristics.

Patient characteristics	TBI-based regimen ($n = 28$)	Non-TBI based regimen $n = 32$	*p*
Median age (range), years	28 (17-49)	32 (17-48)	0.31
Sex-ratio	1.33	3.6	0.08
Diagnosis			0.4
B-ALL, n (%)	14 (50%)	20 (62.5%)	
T-ALL, n (%)	12 (43%)	10 (31.3%)	
Mixed lineage leukemia, n (%)	2 (7%)	2 (6.2%)	
Median time diagnosis-allo-HSCT (range), months	6 (2-137)	7 (3-41)	0.05
Disease status before transplant, n (%)			0.55
CR1	21 (75%)	26 (81%)	
>CR1	7 (25%)	6 (19%)	
HCT-CI score ≥ 2, n (%)	8 (28.6%)	3 (9.4%)	0.05
ABO mismatch, n (%)			0.55
Matched	18 (64.3%)	17 (53.2%)	
Major or bidirectional or minor	10 (35.7%)	15 (46.8%)	
Stem cell source, n (%)			0.35
Bone marrow	12(43%)	10(31%)	
Peripheral blood stem cell	26(57%)	22(69%)	
GVHD prophylaxis			0.92
Cyclosporine and methotrexate +/−ATG	27(96.4%)	31(96.9%)	
Cyclosporine	1 (3.6%)	1 (3.1%)	

Conclusions: Chemotherapy-based conditioning seems to be an alternative to TBI-based conditioning. Prospective studies in adults ALL comparing TBI-based regimen to homogeneous group of chemotherapy-based regimen are warranted to validate this finding.

Disclosure: Nothing to declare

P129

Low dose anti t-lymphocyte globulin in high t-cell content PBSC graft: Improving transplant outcomes in post-transplant cyclophosphamide platform

E. Xue[1], F. Lorentino[1], M.T. Lupo Stanghellini[1], F. Giglio[1], S. Piemontese[1], D.T. Clerici[1], F. Farina[1], S. Mastaglio[1], A. Bruno[2], E. Campodonico[3], R. Nitti[3], M. Marcatti[1], A.A. Assanelli[1], C. Corti[1], F. Ciceri[1,3], J. Peccatori[1], R. Greco[1]

[1]IRCCS San Raffaele Scientific Institute, Milan, Italy, [2]Vita-Salute San Raffaele, Milan, Italy, [3]VIta-Salute San Raffaele, Milan, Italy

Background: For decades, anti-T lymphocyte globulin (ATLG) has been adopted as part of conditioning before hematopoietic stem cell transplants (HSCT). In recent years, the use of post-transplant cyclophosphamide (PT-Cy), initially introduced for haploidentical HSCT, has spread consistently throughout several HSCT settings, showing comparable results. We recently reported increased risk of both acute and chronic graft versus host disease (GvHD) in patients receiving a high $CD3^+$ cell counts within the graft. In this setting, we aimed to investigate the potential benefit of the co-administration with PT-Cy and a low, post-transplant ATLG dose.

Methods: Starting from 2019, 21 patients were transplanted using peripheral blood grafts containing more than $300*10^6$/kg and were administered PT-Cy 50 mg/kg on day+3 and day+4 with the addition of ATLG 5 mg/kg on day+5 (Grafalon, Neovii) (study group). Using a 1:2 matched-pair analysis, we compared the outcomes with 42 patients transplanted prior to 2019 with a PBSC graft containing a $CD3^+$ counts above $300*10^6$/kg, who received PT-Cy without additional ATLG (control group). In both groups, GvHD prophylaxis included sirolimus (with mycophenolic acid in HLA-mismatched and unrelated transplants).

Results: Patient and transplant characteristics are shown in **Table 1**. Median follow up was 538 days in the study group and 1450 days in the control group. 30-day cumulative incidence of platelet engraftment was lower in the study group (29% versus 45%, $p = 0.03$). There was a non-significant trend of higher rate of poor graft function in the study group (29% versus 19%, $p = 0.52$). In terms of immune-reconstitution, the long-term negative impact of ATLG was evident on the $CD4^+$ subsets. However, we documented no differences in term of CMV, HHV6, EBV, adenovirus and BK virus reactivation incidence, and there was a non-significantly higher incidence of invasive fungal infection (7/21 cases versus 9/42 cases $p = 0.36$). We observed a non-significant trend toward a lower day-100 CI of grade 3-4 aGvHD in the study group 10% versus 19% ($p = 0.48$), whereas 1-year CI of

cGvHD was significantly lower (15% versus 41%, p = 0.04). Survival outcomes were comparable between the groups: 1-year TRM 19% versus 19% (p = 0.9); 1-year relapse rate 25% versus 24% (p = 0.9); 1-year PFS 56% versus 57% (p = 0.9), 1-year OS was 75% versus 69% (p = 0.49).

Table 1 - Patient and transplant characteristics.

	Study Group PT-Cy + ATLG	Control Group PT-Cy	P value
	N = 21	N = 42	
Median patient age at HSCT (range)	60 (24-71)	56 (22-77)	0.691
Median donor age at HSCT (range)	41 (18-68)	34 (18-70)	0.41
Gender			
Female	N = 9	N = 16	0.71
Male	N = 12	N = 26	
Disease type			
ALL	N = 2	N = 6	0.974
AML	N = 13	N = 23	
MPN/MDS	N = 4	N = 8	
MM/Lymphoma	N = 2	N = 5	
Disease status			
CR1	N = 7	N = 13	1
CR > 1	N = 7	N = 13	
Not in CR	N = 7	N = 16	
Type of HSCT			
MRD	N = 4	N = 7	0.881
MUD	N = 4	N = 12	
MMUD	N = 4	N = 7	
MMRD	N = 9	N = 16	
Conditioning regimen[$]			
MAC	N = 13	N = 30	0.567
RTC	N = 8	N = 12	
Median $CD3^+$ infused (10^6/kg)	464 (409-496)	399 (347-511)	0.197

[$] Myeloablative regimen include: Treosulfan-Fludarabine +/−Melphalan/Thiotepa/Total body Irradiation, Reduced toxicity regimen include Treosulfan-Fludarabine

Conclusions: Combining PT-Cy with low ATLG dose in high T-cell content PBSC graft translated into a low rate of chronic GvHD incidence, without impacting relapse incidence and survival outcomes.

Disclosure: The authors declare no conflict of inter

P130

Full donor chimerism in patients undergoing HSCT with a reduced conditioning regimen after one or two alkylating agents: A single center experience

C. Arevalo[1], A. Paviglianiti[1,2], A. Mussetti[1,2], M. Peña[1,2], L. Hurtado[1], S. Gonzalez[1], K. Meriem[1], R. Parody[3], A. Sureda[1,2,4]

[1]Institut Catala d'Oncologia-Hospitalet, Barcelona, Spain, [2]Institut d'Investigacio Biomèdica de Bellvitge, Barcelona, Spain, [3]University Hospital of Virgen del Rocio, Sevilla, Spain, [4]University of Barcelona, Barcelona, Spain

Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for several hematological disorders, therefore improving conditioning regimens can have an important impact on outcomes. Hereby, we report a single center experience of HSCT with one or two alkylating agents as conditioning regimen with special focus on chimerism

Methods: We collected data from 2010 to 2020, identifying 75 adult patients, diagnosed with either lymphoid or myeloid disease undergoing HSCT from HLA identical siblings or matched unrelated donor (MUD), with reduced-intensity thiotepa-busulfan-fludarabine (TBF) in a dose of 10mg/kg (two days), 3.2mg/kg (two days) and 30mg/kg (3 days) respectively or busulfan-fludarabine (BF) (same doses, but busulfan for 3 days) as conditioning regimen and with available chimerism data. Full donor chimerism was defined as having >95% donor alleles. Graft source was peripheral blood stem cell in all patients. The study aimed to assess the rate of full donor (FD) chimerism at day 30 and 100, in patients receiving TBF or BF as conditioning regimen.

Results: Baseline characteristics of the population are described in figure 1. Summarizing, the median age was 58 years, 64% had an intermediate disease risk index and 88% of were in complete remission. Donor type was HLA identical sibling in 65%. Conditioning regimen was BF in 67% patients (n = 50). The median time of neutrophil and platelet engraftment were 16 (range 10–28) and 13 (range 5–45) days, respectively. Thirty-three patients experienced acute GvHD, 12 of them grade 4. The cumulative incidence (CI) of chronic GvHD was 16% (95% CI 9-28) at 1 year, there were no significant differences between BF and TBF conditioning (18% vs 11%, p = 0.90). The CI of non-relapse mortality (NRM) at 100 day and 1 year was 8% (95% CI 4-17) and 21% (95% CI 13-33), respectively. NRM was not significantly different between patients receiving BF vs TBF at 100 day (4% vs 16%) and at 1 year (20% vs 21%) (p = 0.17). The CI of relapse at 100 days and 1 year was 18% (95%CI 11-29) and 35% (95%CI 25-48), respectively. Relapse was not statistically different between the two groups (p = 0.45) at 100 day nor at 1 year. Overall survival and disease free survival were 57% (95% CI 39-72%) and 44% (95% CI 33-56%) at 1 year, respectively. Overall survival was not statistically different for patients receiving BF vs TBF (56% vs 58%; p = 0,61) nor was disease free survival (BF 40% vs TBF 56%; p = 0,51). A FD chimerism at 30 day was achieved for 62% (n = 21) of the patients receiving TBF while 96% of the patients in the BF group had less than FD chimerism (p < 0.001). At 100 days, almost all patients (95%) in the TBF group achieved a FD chimera comparing to BF group (42%) (p < 0.001). Nine patients received donor lymphocyte infusion, 8 of them in the BF group (6 = disease relapse; 1= mixed chimerism; 1= graft failure).

Figure 1. Baseline characteristics of allotransplant recipient patients.

Age at HSCT, years, median (range)	58 (27 - 69)
Sex male/female, n (%)	40 (53.3) / 35(46.7)
Diagnosis, n (%)	
ALL	2 (2.7)
NHL	4 (5.3)
AML	48 (64)
CML	3 (4)
MDS	14 (18.7)
MPN (not including CML)	2 (2.7)
Other	2 (2.7)
HCT-CI, n (%)	
0	35 (46.7)
1	8 (10.7)
2	15 (20)
>= 3	16 (21.3)
Disease risk index, n (%)	
Low	5 (6.7)
Intermediate	48 (64)
High	20 (26.7)
CR at transplantation, n (%)	
Yes	9 (12)
No	66 (88)
Donor Type, n (%)	
HLAid	49 (65.3)
MUD	26 (34.7)
Gender mismatch, n (%)	
No	63 (84)
Yes	12 (16)
Conditioning regimen, n (%)	
BF	50 (66.7)
TBF	25 (33.3)
ATG post transplantation, n (%)	
No	59 (78.7)
Yes	16 (21.3)
GVHD Prophylaxis, n (%)	
Sirolimus + Tacro	10 (13.3)
CsA + MMF	1 (1.3)
CsA + MTX	55 (73.3)
Tacro + MTX	4 (5.3)
PTCY + Tacro + MMF	3 (4.0)
PYTC + Tacro	1 (1.3)
CsA	1 (1.3)

ALL: *acute lymphoblastic leukemia;* NHL: non Hodgkin lymphoma; AML: Acute myeloid leukemia; CML: chronic myeloid leukemia; MDS: myelodysplastic syndrome; MPN: chronic myeloproliferative neoplasms; HCT-CI: ematopoietic cell transplant comorbidity index; CR: Cocmplete remission; ATG: antithymocyte globulin; GVHD: graft versus host disease; CsA: cyclosporine A; MMF: mycophenolate; mofeti MTX: Mmethotrexate ; Tacro: tacrolimus; PT-Cy: Post-transplant cyclophsphamide.

Conclusions: The combination of two alkylating agents is associated with a higher chance of achieving a FD chimerism at 30 days and 100 days without significant survival advantages.

Disclosure: No discloures

P131

Overall survival in advanced stage mantle cell lymphoma after early autologous stem cell transplantation with cisplatin, etoposide, cytarabine and melphalan (peam) as a conditioning regimen

D. Franco-Saenz[1], B.L. Acosta-Maldonado[1], J.F. Téllez-Manríquez[1], L.M. Valero-Saldaña[1], B. Gutiérrez-Gutiérrez[1]

[1]Instituto Nacional de Cancerologia, Ciudad de Mexico, Mexico

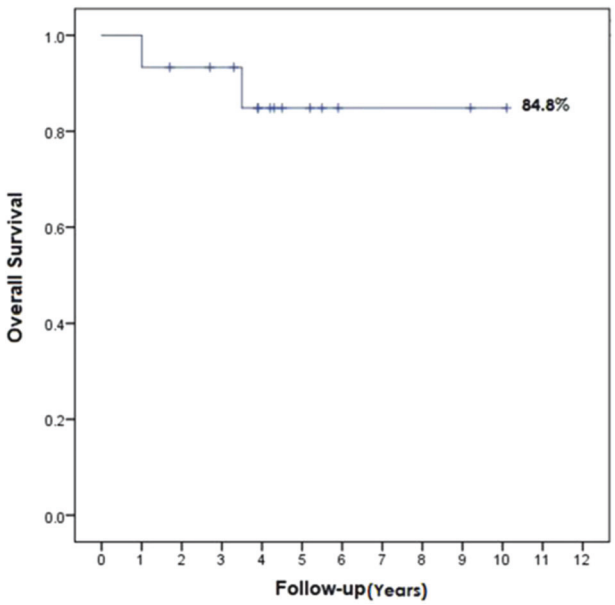
Background: Chemoimmunotherapy in advance stage mantle cell lymphoma is not curative. Autologous hematopoietic stem cell transplantation (ASCT) currently is the standard of treatment for patients in first remission diagnosed with Mantle cell Lymphoma (MCL) OS has been improved by using induction chemoimmunotherapy conventional and higher intensity, and maintenance therapy as by GELA study reports 75%. LyMa Trial has proven improvement in the global survival and progression-free survival. In this study we aimed to describe overall survival (OS) diagnosed Mantle cell lymphoma (MCL) with PEAM as a conditioning regimen.

Methods: A retrospective study was conducted on patients diagnosed with MCL and ASCT as consolidation therapy at the Instituto Nacional de Cancerología in Mexico City between 2011 and 2020. PEAM condition regimen: Cisplatin 100mg/m^2 (-4), etoposide 750 mg/m^2 (-4,-3), cytarabine 800mg/m^2 (-4,-3,-2) and melphalan 140mg/m^2 (-4). OS results were obtained using the Kaplan-Meier method.

Results: We analyzed 15 patients with MCL after ASCT as consolidation therapy, a median follow-up of 4.58 years, the median age at transplantation was 54-years (range 39-68y), with male predominance (86.7%). Nine patients with at least one comorbidity, the most predominant being diabetes mellitus type II (66.6%). All patients with clinical stage III-IV, 20% of them with bone marrow infiltration.

All patients received one line of chemoimmunotherapy, most were treated with R-CHOP plus /or R-DHAP(86%). Eleven patients (73.3%) with complete response, three (20%) with partial response before ASCT. Fourteen patients (93.3%) received PEAM plus rituximab as myeloablative conditioning regimen. Neutrophil recovery median was 10 days, nine patients (66.6%) developed febrile neutropenia. Twelve patients (80%) received maintenance with rituximab. Eleven (73.3%) had complete response at last follow up after ASCT, three (20%) with relapsed disease, one stable disease. Three patients relapsed, two (66.6%) died. The OS at 5-years was 84.8%.

Graph 1. Overall Survival



Conclusions: Conventional chemoimmunotherapy is effective followed by ASCT as consolidation therapy in mantle cell lymphoma with advanced stage disease. We describe higher OS 5-years (84.8%) as compared with other series (57% and 75%) with similar chemoimmunotherapy and conventional conditioning regimen.

Disclosure: Nothing to declare

P132

High-intensity treosulfan-etoposide-fludarabine conditioning can be safely used in combination with major GVHD prevention platforms in children with leukemia

E. Zhuravel[1], M. Perminova[2], G. Seregin[1], M. Ilushina[2], M. Zhuravel[1], R. Khismatullina[2], B. Kurmanov[1], M. Klimentova[2], E. Burtsev[1], L.S. Shelikhova[2], G. Bronin[1], M.M. Maschan[2]

[1]Morozov Children's Hospital, Moscow, Russian Federation, [2]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation

Background: Treosulfan-based conditioning regimens are widely used among children with leukemia. Treosulfan is usually combined with fludarabine and either melphalan or thiotepa. Due to frequent interruptions of market availability of melphalan and thiotepa, there is an unmet need for alternative safe and effective combinations. There are reports of the use of treosulfan/fludarabine/etoposide regimens among adult patients, but this approach is not well-studied in pediatric HSCT. We performed a retrospective analysis of the clinical use of treosulfan/fludarabine/etoposide regimen in a cohort of children with leukemia, treated at two sites in Moscow: Dmitriy Rogachev National Medical Researh Center of Pediatric Hematology, Oncology and Immunology and Morozov Children's Hospital, Moscow.

Methods: Sixty-five pediatric patients (41-male, 24-female) received conditioning with treosulfan (42g/m^2), fludarabine (150 mg/m^2) and etoposide (60mg/kg) before allogeneic HSCT between 2018 to 2021. HSCT indications included acute lymphoblastic leukemia (ALL), n = 43 (66%) (B-ALL n-31, T-ALL n-12), acute myeloid leukemia, n = 18 (27.7%), bi-lineage leukemia, n = 3 (4.6%) and JMML n = 1 (1.5%). In 8 patients, it was the 2nd HSCT. The source of HSC was PBSC in 60 cases (92%), and BM in 5 cases (8%). Haploidentical family donors were used in 52 cases (80%), matched related and unrelated donors in 10 and 3 cases, respectively. Three GVHD prevention approaches were used: 35 patients received posttransplant cyclophosphamide (PtCy) on days+3, +4 at 50 mg/m^2/day, tacrolimus and MMF with unmanipulated HSCs. In 26 cases ex-vivo αβ T cell depletion combined with abatacept and bortezomib was used. In 4 patients with a matched BM transplant calcineurin inhibitor-based regimen was used. Median follow-up was 12.5 months.

Results: Neutrophil and platelet engraftment was recorded in 61 of 65 cases. All cases of primary graft failure were seen among ex-vivo depletion cohort, of them 3 were successfully re-transplanted. The median time to neutrophil engraftment was 16 days (8-47), 12 days in ex-vivo depletion and 18 days in PtCy cohorts, respectively. The median time to platelet engraftment was 16 days (11 - 55), 13 in ex-vivo depletion and 25 in PtCy cohorts, respectively. Most common toxicities affected skin, liver and GI. Cutaneous toxicity grade I-IV was seen in 32 patients (49%), of them 5 cases with grade III-IV (15.6%). Hepatic toxicity grade I-II was observed in 19 patients (29.2%), no cases of grade III-IV liver toxicity were recorded. The most frequent type of toxicity was gastrointestinal toxicity, seen in 58 cases (89.2%). GI toxicity was graded as grade I-II in 46 patients (80%), grade III-IV in 12 patients (20%). Renal toxicity grade I-II was observed in 4 cases (6.5%). Acute GVHD II-IV was observed in 30 patients (36.1%), severe forms of acute GVHD, grade III-IV, were recorded in 10 patients (15.4%). Early (day + 100) non-relapse mortality was not recorded.

Conclusions: The conditioning regimen based on Treo42/Flu150/VP60 was safe, ensuring engraftment and tolerable short-term toxicity among children with acute leukemia. This regimen can be combined with two key GVHD prevention platforms, ex-vivo αβT cell depletion and PtCy, with minimal non-relapse mortality. Long-term outcomes should be evaluated prospectively.

Disclosure: Nothing to declare

P133

Chemokine receptor 4 directed endoradiotherapy with [^{177}lu]-pentixather in addition to total body irradiation as conditioning regimen for relapsed/refractory acute myeloid leukemia - a retrospective analysis

K. Braitsch[1], M. Hefter[1], K. Koch[1], K. Nickel[1], K.S Goetze[1], W. Weber[1], F. Bassermann[1], M. Eiber[1], M. Verbeek[1], P. Herhaus[1]

[1]Technical University of Munich, Munich, Germany

Background: Patients with relapsed or refractory (r/r) acute myeloid leukemia (AML) have poor prognosis but cure is possible with allogeneic hematopoietic stem cell transplantation (allo-HSCT). Myeloablative total body irradiation (TBI) based conditioning is often used in AML patients refractory to standard chemotherapy. Feasibility of chemokine receptor 4 (CXCR4) directed endoradiotherapy (ERT) has previously been shown in patients with CXCR4 expression on leukemic blasts. Here, we retrospectively report on six chemo-refractory, relapsed AML patients that received ERT with CXCR4-targeting [^{177}Lu]-Pentixather combined with TBI and chemotherapy prior to allo-HSCT.

Methods: In this retrospective, single center analysis data from six consecutive patients with r/r AML treated between February 2019 and September 2021 were included. All patients had active AML and were either refractory to induction and salvage chemotherapy or had refractory relapse. In-vivo CXCR4 expression on leukemic blasts was confirmed in all patients by [^{68}Ga]-Pentixafor PET-imaging. Conditioning consisted of [^{177}Lu]-Pentixather ERT as compassionate use on day (d) -15, TBI (8-10 Gy) on d-9 to d-7 and chemotherapy, based on donor type. Chemotherapy regimens were fludarabine 30mg/m^2 d-5 to d-2 or 60mg/m^{2}cyclophosphamide on d-5 and d-4 for matched donors and fludarabine 30mg/m^2 d-6 to d-2 plus cyclophosphamide 14,5mg/m^2 d-6 to d-5 for haploidentical or mismatch donors. Immunosuppression for matched donors consisted of antithymocyte globulin (5-10mg/kg d-3 to d-1), mycophenolatmotefil and a calcineurin inhibitor. For haploidentical donors post-transplant cyclophosphamide was used according to standard of care. In this retrospective analysis, we assessed response, toxicity, overall survival, engraftment rates and adverse events.

Results: Median patient age was 47 (42-57). 5 patients had de novo AML and one secondary (s)AML. In median, patients had previously received 4 (3-7) lines of intensive therapy, including allo-HSCT in n = 3 patients. Median injected activity of [^{177}Lu]-Pentixather was 12.6 GBq (11.5-16.1). All patients received a peripheral blood stem cell graft with a median of 5.9 (4.9-10.3) x 10^6 CD34 + cells/kg. During hospital stay, n = 4 patients required intensive care treatment and n = 2 mechanical ventilation. Response evaluation by bone marrow biopsy was available for n = 5 patients, n = 4 achieved complete remission with incomplete count recovery (CRi) and n = 1 morphologic leukemia-free state (MLFS). One patient was refractory and regenerated with 11% blasts in the peripheral blood at day 11. Time to leukocyte recovery in the n = 4 responding patients was 25 (16-28) days, one patient had received a stem cell boost after initial graft failure. Two patients are still alive at month 21 and 20 after allo-HSCT, n = 3 died during hospital stay and n = 1 after a relapse. Causes of death were respiratory failure (n = 1), sepsis (n = 1), refractory disease (n = 1) and relapse (n = 1). In the two surviving patients, kidney function remained normal with creatinine levels of 0.8 and 0.9 mg/dl, respectively.

Conclusions: Conditioning with CXCR4-directed ERT plus TBI is feasible and response rates in this heavily pre-treated patient cohort were promising. No acute kidney toxicity related to radiation dosage was observed and engraftment was not impaired in this small cohort. The results warrant prospective studies.

Disclosure: Nothing to declare

P134

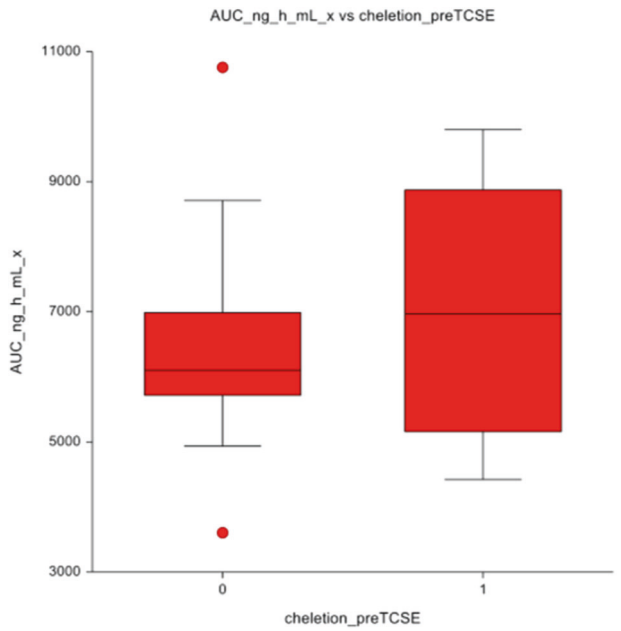
Potential pharmacokinetics interactions between busulfan and iron chelation in children given HSCT for non-malignant diseases

F. Compagno[1], A. Bartoli[2], S. De Gregori[2], S.I. Tripodi[1], A. Agostini[1], A. Panigari[1], S. Boghen[1], M. Siciliano[3], M. De Cicco[3], P. Comoli[3], G. Giorgiani[1], R. Albertini[4], M. Zecca[1]

[1]Pediatric Hematology/Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [2]Clinical Biochemistry - Clinical and Experimental Pharmacokinetics Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [3]Cell Factory, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [4]Clinical Biochemistry, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Background: Busulfan (BU) therapeutic drug monitoring (TDM) is performed in order to avoid over exposure and toxicity and/or under exposure and reduce efficacy. In our Center, BU TDM is performed for every patient receiving BU, and the dose is adjusted in order to achieve a target area under the curve (AUC) within the range 3696-5538 ng x h/m. We observed an unexpected increase in BU AUC in children who were treated before HSCT with deferasirox or deferoxamine for iron overload. BU undergoes glutathione conjugation and subsequent oxidative metabolism. Deferasirox inhibits multiple oxidative enzymes of the cytochrome P450 family, and this could explain the decreased clearance of BU.

Methods: We retrospectively analyzed 28 pediatric patients (age range, 1-16 years; median 6.7 years) affected by a non-malignant disease (10 thalassemia major, 17 sickle cell disease, 1 thalasso-drepanocitosis), who underwent allogeneic HSCT between 2018 and 2020. They received a Bu-based conditioning regimen (initial BU dose 1 mg/kg every 6 hours), in association with Thiotepa and Fludarabine. 25% of the patients had received pre-transplant iron chelation to treat/prevent iron overload, with deferasirox or deferoxamine, until the beginning of the conditioning regimen. Blood samples were collected at fixed time points after the first dose of BU, in order to calculate the median concentration at steady state (Css) and derivate the value of AUC.



Results: In all tested patients, BU exposure after the first dose, based on body weight, had a median level of 6422 ng x h/mL (range, 3604-10758). In the patient who received iron chelation, BU exposure was higher than expected (median 8459; range, 6872-10758), as compared to that of children who did not receive iron chelation (median 6017; range, 3604 - 8250) (Fig.1). A total of 8 patients required a Bu adjustment, 5 of them (62.5%) had received iron chelation before HSCT, whereas the other 3 (37.5%) had not, with a statistically significant difference (Chi-square $P = 0.009$). After BU dose reduction, AUC was measured again after the fifth/ninth dose and it decreased to 4484-7789 ng x h/mL. Unfortunately, for 2 patients the dose reduction was not sufficient to ensure an adequate BU exposure: in one of the patient BU dose was reduced by 18%, whereas in the other, even with a 40% dose reduction, an adequate plasma level could not be achieved. In the four patients with adequate exposure after dose reduction, Bu dose was reduced by 21% to 50%.

Conclusions: Pharmacokinetic studies dealing with drug-drug interactions between BU and iron chelation therapy are extremely limited. The administration of iron chelation immediately before the conditioning regimen may result in a systemic BU over-exposure. An earlier discontinuation of iron chelation treatment may be necessary in these patients, and TDM remains mandatory in order to optimize the dose for each patient.

Disclosure: Nothing to declare

P135

GVHD prophylaxis with post transplant cyclophosphamide after allo-HSCT with mismatched unrelated and haploidentical donors: Risk of CMV reactivation at letermovir discontinuation

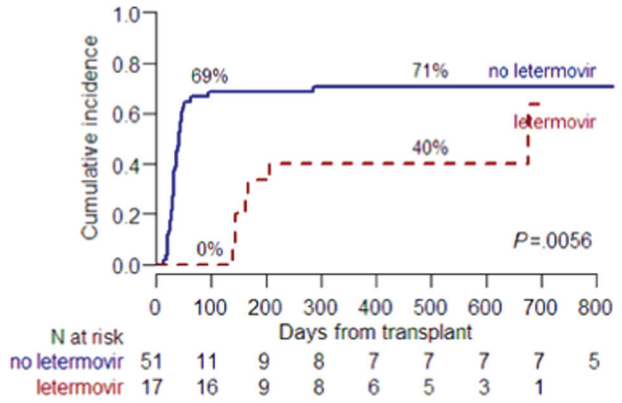
M.C. Mico'[1], A. Algarotti[1], C. Pavoni[1], D. Taurino[1], G. Borleri[1], G. Cavallaro[1], A. Grassi[1], A. Rambaldi[1,2]

[1]Division of Hematology, ASST Papa Giovanni XXIII, Bergamo, Italy, [2]University of Milan, Milan, Italy

Background: The use of post-transplant cyclophosphamide (PTCy) has significantly changed the approach to the graft versus host disease (GvHD) prophylaxis in patients undergoing allogenic stem cell transplantation (allo-HSCT). However, PTCy can increase the rate of infections, in particular of cytomegalovirus (CMV).

Methods: We retrospectively analyzed the clinical outcomes of 68 adult patients (AML = 38, MDS = 7, ALL = 9, NHL/CLL = 8, CML = 3, MF = 2, HD = 1) who underwent allo-HSCT (between December 2011 and September 2021) from mismatch unrelated (MMUD, 9/10) (n = 21), and haploidentical (Haplo) (n = 47) donors. All patients received PTCy as GvHD prophylaxis. Seventeen patients with a positive CMV serology, had a CMV prophylaxis with letermovir.

Results: With a median follow-up of 1.9 (range. 0.05-9.7) years, the Overall Survival (OS) of MMUD and Haplo was 73% vs 71% . The non-relapse mortality (NRM) was 16% vs. 11% for MMUD and Haplo, respectively. The incidence of relapse was 34% for Haplo and 17% for MMUD. The intensity of the conditioning regimen, reduced (n = 24) or myeloablative (n = 44) had no effect on these outcomes.By uni and multivariate analysis, more aGvHD (grade II-IV) was associated to MMUD than haplo donors (HR 4.77, CI 1.62-14. in univariate analysis; HR 5 .12, CI 1.57-16.7 in multivariate) with no difference in term of cGvHD. The use of PBSC was significantly associated to a better overall survival, better neutrophil engraftment and reduced risk of poor marrow function/ rejection with no impact on GvHD. None of the patients treated with letermovir had CMV reactivation during CMV prophylaxis (Fig. 1). However, those who had less than 50 CD4 + cells at discontinuation (day 100) invariably showed CMV reactivation, subsequently. By multivariate analysis, CMV reactivation was associated with a better DFS (HR 0.34, CI 0.14-0.83) and OS (HR 0.3; CI 0.12-0.96).



Conclusions: The main outcomes of allo-HSCT after MMUD and Haplo transplant with PTCy as GvHD prophylaxis, were similarly favorable although transplants with MMUD showed an increased risk of aGvHD. When letermovir was discontinued, patients with less than 50 CD4 + T cells in the peripheral blood were at high risk of CMV reactivation.

Disclosure: Nothing to declare

P136

Decreased glomerular filtration rate is related to increased mucositis in autologous stem cell transplantation conditioned with high dose melphalan

A. Lobo-Olmedo[1], J. Arzuaga-Méndez[1,2], A. Balerdi[1,2], E. Amutio[1,2], J.C. García-Ruiz[1,2]

[1]Cruces University Hospital, Barakaldo, Spain, [2]Biocruces Bizkaia Health Research Institute, Barakaldo, Spain

Background: Melphalan toxicity, in particular oral and intestinal mucositis, is increased in patients with low glomerular filtration rate (GFR). Thus, melphalan dose in autologous stem cell transplantation (ASCT) is adjusted from 200 mg/m^2 to 140 mg/m^2 in patients with adjusted GFR < 30 mL/min/1.73m^2. Our aim is to study the incidence of grade 4 mucositis in patients with mild reduction in GFR (GFR < 90 and >30 ml/min/1.73m^2) that underwent ASCT conditioned with melphalan 200 mg/m^2.

Methods: We retrospectively analysed the incidence of oral or intestinal mucositis that required parenteral nutrition (oral mucositis WHO grade 4 or intestinal mucositis CTCAE grade >3) in consecutive patients that underwent ASCT between January 2016 and June 2020, according to the patient GFR on the day of melphalan administration. Secondary variables were time from infusion to discharge, need of intensive care and transplant-related mortality on day +100 (TRM D100).

Results: Of the 129 patients included, 90 had a GFR ≥ 90 and 39 had a GFR between 30 and 90 ml/min/1.73m^2. 24 (26%) patients with GFR ≥ 90 and 22 (56%) with GFR < 90 presented mucositis that required parenteral nutrition (relative risk 2.11, p = 0.0011). Time from infusion to discharge was also higher in patients with GFR < 90 (median of 21 vs. 18 days, p = 0.035). There was no significant difference in the need of intensive care and there was no TRM D100 in any of the groups.

Conclusions: Patients undergoing ASCT conditioned with high dose melphalan are at increased risk of needing parenteral nutrition due to oral or intestinal mucositis if they have reduced GFR (90 to 30 ml/min/1.73m^2). This fact, however, does not translate into increased risk of intensive care need or transplant related mortality.

Disclosure: Nothing to declare

P137

Autologous stem cell transplantation using cyclophosphamide and total body irradiation for t- cell lymphomas

U. Şahin[1], A. Gokmen[1], S.M. Urlu[1], E. Soydan[1], M. Kurdal Okcu[1], Ö. Arslan[2], M. Özcan[2]

[1]Medicana International Ankara Hospital, Hematology and Bone Marrow Transplantation Unit, Ankara, Turkey, [2]Ankara University Faculty of Medicine, Ankara, Turkey

Background: T-cell lymphomas (PTCLs) constitute a rare and clinically aggressive group of lymphomas, which has more than 20 histologic subtypes according to WHO 2008 classification. PTCL not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma (AITL) and anaplastic large cell lymphoma (ALCL) are called nodal PTCL and account for approximately 60% of cases. The reported median survival ranges from 22 to 49 months and 5-year survival is less than 30%. High-dose chemotherapy followed by autologous stem cell transplantation (ASCT), has been proven to be beneficial both as a consolidation and in the relapse setting. However, the optimal conditioning regimen for ASCT in patients with T-cell lymphoma is not specified.

Methods: All adult T-cell lymphoma patients who underwent consolidative or salvage ASCT in our center between 2012 and 2021 have been identified and medical records were retrospectively reviewed. Standard CY (cyclophosphamide) - TBI (total body irradiation) regimen, which consisted of CY 120 mg/kg total dose and 12 Gy TBI in fractionated doses, was utilized for conditioning.

Results: A total of 36 patients, of whom 22 were male (61.1%), was identified. The median age at diagnosis was 51 (23-67). The histologic subtypes included: ALCL, ALK(-), n = 9 (25.0%); ALCL, ALK(+), n = 3 (8.3%); AITCL, n = 9 (25.0%), PTCL, NOS, n = 10 (27.8%), hepatosplenic T-cell lymphoma, n = 2 (5.5%); NK/T cell lymphoma, n = 2 (5.5%), enteropathy-associated T-cell lymphoma, n = 1 (2.8%). All patients with ALCL, ALK(+) were transplanted at either CR2 or for salvage of refractory disease. Most of the patients had advanced and high risk disease at diagnosis [Ann/Arbor stage 3-4 disease was present in 85.7% and international prognostic index (IPI) was intermediate or high in 80.0%]. Most of the patients underwent consolidative ASCT in CR1 (n = 4, 66.7%). The median follow-up was 10 months (0-106). The median time from diagnosis to ASCT was 7 months (4-45)Overall survival (OS) and progression-free survival (PFS) at 12 months after ASCT were 86.0% [95% confidence interval (CI): 74.2-97.8] and 45.0% (95% CI: 27.4-62.6), respectively. Non-relapse mortality (NRM) at 3, 6, 9 and 12 months after ASCT were 6.0% (95% CI: 0-13.8), 10.0% (95% CI: 0-39.4), 14.0% (95% CI: 2.2-15.8) and 14.0% (95% CI: 2.2-15.8), respectively. OS was better among patients transplanted at CR1, when compared to CR2 and primary refractory patients (p < 0.05). Four patients with aggressive and high risk disease could proceed to allogeneic transplantation, three of whom are still alive with a median follow-up of 14.5 months (7-77). Grade 3-4 adverse events were rare and neutrophil engraftment was achieved in all patients, except one with refractory disease after ASCT.

Kaplan-Meier plot comparing the OS for patients at CR1 versus CR2 and refractory disease (p < 0.05, log-rank test).

Conclusions: This study cohort included mainly nodal PTCLS (86%) with high risk and advanced disease profile. ASCT utilizing CY-TBI may provide an important benefit when used in consolidation and as a salvage without increasing toxicity and NRM. It may serve as a bridge for allogeneic transplantation in **patients with aggressive and high risk disease. Consolidation at CR1 may provide a greater benefit**.

Clinical Trial Registry: N/A

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

P138

Comparison of git toxicity of the beam vs team conditioning before autologous transplantation in patients with lymphomas

B. Břízová[1], A. Jungová[1], D. Lysák[1], Š. Jiří[1], V. Bergerová[1], P. Jindra[1]

[1]Faculty hospital Pilsen, Pilsen, Czech Republic

Background: High-dose chemotherapy followed by autologous transplantation (ASCT) is currently the standard of treatment for relapsed or refractory non-Hodgkin's lymphomas (NHL) and Hodgkin's lymphoma (HL). Despite the absence of direct data from prospective studies, BEAM, consist of carmustine (BCNU) in combination with etoposide, cytarabine and melphalan, is considered the common conditioning. The recent lack of BCNU has led to the search for alternative regimens. One of the most promising seems to be TEAM, in which BCNU is replaced by thiotepa. Thiotepa penetrates the CNS better, but there are concerns about increased, especially gastrointestinal, toxicity. At the same time, there is a lack of strong data demonstrating the comparable effectiveness of the two conditionings. Therefore, we decided to retrospectively compare the GIT toxicity of the TEAM regimen, which we started using in July 2018, with the previously used BEAM regimen.

Methods: Retrospective analysis of 142 consecutive patients with lymphomas autologous transplanted after the administration of the BEAM (2014-2018) or TEAM (2018-2021) conditioning at the Department of Hematology and Oncology.

Results: In the group of 142 patients with the age median of 58 years (21-74) there were 85 men (60 %). The BEAM regimen was administered to 82 patients (58 %) with the age median of 59 years (22-74), and TEAM to 60 patients (42 %) with the age median of 58 years (21-73) ($p = 0.83$). Of the diagnoses, the most common was DLBCL - 12 vs 27, HL - 21 vs 8, MCL - 16 vs 4, T-NHL - 12 vs 8, other lymphomas were represented sporadically, in total 16 vs 13 patients. There was no significant difference between the representation of diagnosis. In the first remission of the disease, we transplanted 43 vs 22 patients ($p = 0.29$), in the second and next remission 26 vs 22 patients ($p = 0.74$). 13 vs 16 patients ($p = 0.22$) were transplanted in the primary induction failure, it means progressive and chemorefractory disease. None or only very mild GIT toxicity (grade 0-I) was present in 53 resp. 28 patients ($p = 0.32$). Grade II GIT toxicity occurred in 11 resp. 12 patients ($p = 0.49$), grade III in 12 resp. 16 patients ($p = 0.21$) and finally the most severe grade IV with the need to move to the ICU in 1 resp. 3 patients ($p = 0.32$). In 5 resp. 1 patient it was not possible to determine GIT toxicity. Parenteral nutrition was used in 13 (16%) resp. 22 patients (37%) ($p = 0.04$). TRM during hospitalization was 0%, in 3 months 2% for both conditionings ($p = 1.0$).

Conclusions: Our data demonstrate that despite comparable objective GIT toxicity, the TEAM regimen has a significantly higher need for total parenteral nutrition. However, the overall TRM is comparatively low for both regimens.

Disclosure: Nothing to declare

P139

Clinical outcomes of reduced intensity tbf conditioning regimen in adult patients undergoing allogeneic stem cell transplantation for lymphoid malignancies

M. Peña Domingo[1,2], A. Paviglianiti[1,2], L. Hurtado Ortega[1], S. Gonzalez Rodriguez[1], M. Kara[2], E. Domingo-Domenech[1,2], E. Gonzalez-Barca[1,2,3], A. Mussetti[1,2], A. Sureda Balari[1,2,3]

[1]Institut Català d'Oncologia-Hospitalet, Barcelona, Spain, [2]Institut d'Investigacio Biomèdica de Bellvitge (IDIBELL), Barcelona, Spain, [3]Bellvitge Health Sciences Campus, University of Barcelona, Barcelona, Spain

Background: Reduced intensity conditioning (RIC) is associated with lower non-relapse mortality (NRM) and significant disease control in alloHCT recipients. The optimal conditioning regimen in alloHCT for lymphoid malignancies remains unclear. To date, no data are available regarding the use of thiotepa, busulfan and fludarabine (TBF) in adult patients allografted for lymphoma.

Methods: Between February 2019 and August 2021, 30 patients diagnosed with lymphoid malignancies received a first alloHCT conditioned with a TBF-based RIC regimen at our institution. All consecutive patients were included in the study and data were collected retrospectively. Low-dose TBF RIC was defined as the use of 5 mg/kg of thiotepa (2.5 mg/Kg/day from days -6 and -5) while a high-dose TBF-RIC was considered as the administration of 10 mg/Kg of thiotepa (5 mg/Kg/day from days -6 and -5). Low-dose thiotepa was generally administered to patients with an HCT-specific Comorbidity Index ≥ 3 or considered frail. Two doses of 3.2 mg/Kg/day of busulfan and 150 mg/m^2 (50 mg/m^2 from days -4 to-2) of fludarabine were administered in all patients. Post-transplant cyclophosphamide-based graft-versus-host disease (GVHD) prophylaxis was used for both haploidentical and matched unrelated donors (>9/10 HLA compatibility).

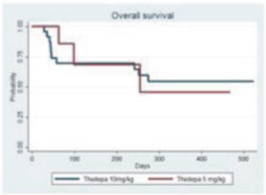
Main outcome variables were overall survival (OS), progression-free survival (PFS), NRM, relapse incidence/progression of disease (RI/POD), cumulative incidence of acute (aGVHD) and chronic GVHD (cGVHD), and hematological recovery. Probabilities of OS and PFS were calculated using the Kaplan-Meier estimator method, and NRM, RI/POD, GVHD and hematological recovery as cumulative incidences.

Results: Baseline characteristics are summarized in Figure 1. Overall, the median age was 55 (range 33-70) years, and 15 patients (50%) received haploidentical donor grafts. Nineteen (63.3%) patients were in complete remission prior to alloHCT. Median follow-up among survivors was 517 (range 96-993) days. At 18-months, OS, PFS, NRM and RI/POD were 53% (95% confidence interval [CI], 33-70%), 40% (95% CI, 21-58%), 38% (95% CI, 19-57%) and 22% (95% CI, 4-40%), respectively. Of the 13 patients who died during follow up, causes of death were: 2 relapses and 11 transplant toxicities (9 = infections, 1=aGVHD, 1= endothelial complications). Eighty-two % of toxicity-related deaths were observed during the first 3 months from transplant. The cumulative incidence of neutrophil engraftment at day +30 was 87% (95% CI, 75-99%). The cumulative incidence of grade II-IV and grade III-IV aGVHD at day +100 was 20% (95% IC, 6-34%) and 7% (95% CI, 0-16%), respectively. The cumulative incidence of all grade cGVHD at +18 months was 16% (95% CI, 1-31%), with only 3 patients presenting with moderate-severe cGVHD. On univariate

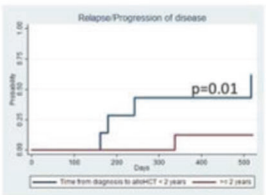
analysis, no prognostic factors were observed in terms of OS, PFS and NRM. However, having an interval between diagnosis and alloHCT ≥2 years was associated to decreased relapse risk (18 months NRM: 7% vs 52%, p = 0.01). Thiotepa dose was not significantly associated to clinical outcomes.

Baseline characteristics of alloHCT recipients	
Recipient age, years, median (range)	55 (33, 70)
Sex male/female, n (%)	18 (60) /12 (40)
Diagnosis, n (%)	
DLBCL	5 (16.7)
MCL	7 (23.3)
FL	9 (30)
HL	3 (10)
WM	2 (6.7)
Others	4 (13.3)
Disease status at transplantation, n (%)	
CR	19 (63.3)
PR	10 (33.4)
Active/progressive disease	1 (3.3)
Previous lines of therapy, n (%)	
1-2	4 (13.3)
3	18 (60)
≥4	8 (26.7)
Previous autologous HSCT, n (%)	18 (60)
Time from diagnosis to alloHCT, n (%)	
<2 years	9 (30)
≥2 years	21 (70)
DRI*	
Low	13 (43.3)
Intermediate	15 (50)
High	1 (3.4)
HCT-CI	
0	14 (46.7)
1-2	13 (43.3)
≥3	3 (10)
Donor selection	
MRD	6 (20)
MUD	8 (26.7)
Haploidentical	15 (50)
Identical twin	1 (3.3)
Donor age, years, median (range)	34 (18, 60)
Stem cell source, n (%)	
PBSC	30 (100)
Conditioning regimen, n (%)	
Low dose thiotepa (5 mg/kg)	7 (23.3)
High dose thiotepa (10 mg/kg)	23 (76.7)
GVHD prophylaxis, n (%)	
CsA/Tacro + MTX	5 (16.7)
CsA/Tacro + MMF + PT-Cy	24 (80)
CsA	1 (3.3)

Impact of the thiotepa dose on overall survival:



Impact of the interval of years between diagnosis and alloHCT on relapse/progression of disease:



Conclusions: In our series, RIC TBF allows efficient disease control at the expense of increased incidence of severe early toxicities. Despite a higher NRM, OS was similar to other RIC regimens used for lymphoid malignancies. This regimen could be considered for fit patients with high-risk lymphoid diseases.

Disclosure: The authors declare no conflicts of interest

P140

Update on a pilot study: Flumeltbi peripheral blood HLA-haploidentical stem cell transplantation with post-transplant cyclophosphamide and bortezomib (Cy2Bor3)

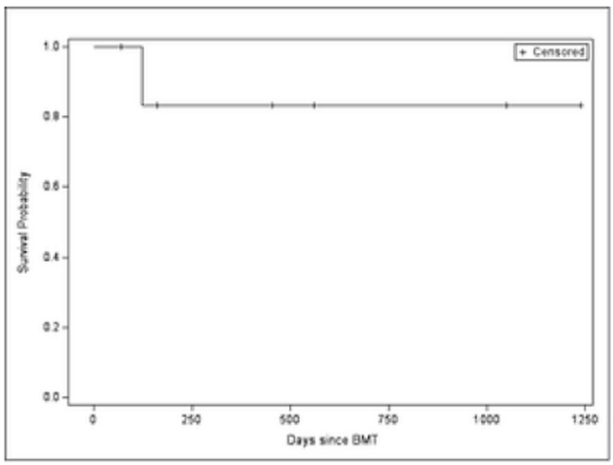
S. Vuyyala[1], E. Peres[1], K. Neme[1], N. Mikulandric[1], S. Wautelet[1], D. Pelland[1], N. Zagar[1], M.A. Trapp[1], S. Rohrer[1], E. Henne[1], S. Szymanski[1], J. Emole[1], M.H Abidi[1], S. Farhan[1]

[1]Henry Ford Health System, Detroit, United States

Background: Bortezomib (Bor) can inhibit the proliferation of dendritic cells (DCs) and block the expression of co-receptors CD80, CD86 and secretion of cytokines IL-12 and TNF-α and hence the ability of DCs to activate T cells. We started a pilot study incorporating the addition of bortezomib to post-transplant cyclophosphamide (PTCY) in the setting of peripheral blood (PB) HLA-haploidentical stem cell transplantation (Haplo-SCT).

Methods: This is a single center open label pilot study. Eligible patients received Fludarabine Melphalan TBI 200 cGy as conditioning followed by haplo-SCT and PTCY. Bor was administered at 1.3mg/m2 on day+1, 4 and 7. Tacrolimus and MMF were started at day+5

Results: Seven patients were enrolled so far, five males and 2 females. Median age was 58 years (26-60). Donors were 3 brothers, 3 sons and 1 mother. Disease risk index was high in 3, intermediate in 3 and low in 1. Three patients had AML, two had ALL and MM, one had ALL and one had CML. CMV recipient status was negative in one and positive in 6. Median HCT-CI was 3(1-4). Median CD34 and CD3 infused were 4.13 x10^6 and 1.7x10^8/ kg recipient respectively, all were cryopreserved except 2. Four patients had CRS before Cy infusion with ASTCT grade of 1. Six patients had grade 3 hypokalemia around day+ 4-5. Five patients had grade 3 mucositis and 2 had grade 1. Four patients had neutropenic fever and one patient had engraftment fever. Median neutrophils and platelets engraftment were 16 and 26 days respectively. Chimerism post SCT was > =99% donor at day 30 for all patients. Six patients are off tacrolimus with median time to be off it was 187.5 days. Five pts had aGVHD with maximum grade of I in 3 patients, II in one patient and III in one patient at a median 50days post SCT. None developed early hematuria, four had late hematuria with highest grade of 4. Two patients were positive for BK virus. One patient had reactivation of CMV, 2 had EBV and one had adenovirus, all resolved. Three pts had HHV6 that resolved. Of the 5 patients who were evaluable, one developed moderate chronic GVHD. So far the median time to follow up is 455 days (70-1239) with relapse and subsequently death in one patient who had high risk AML with 3 different inductions prior to SCT. . At 1 year for 4 evaluable patients IgG were >400 mg/dl and CD4 > 350 cells/ul.



Survival Probability

Conclusions: Cy2Bor3 post PB Haplo-SCT was well tolerated. Although small number of patients and limited but encouraging results so far. The trial is ongoing.

Clinical Trial Registry: ClinicalTrials.gov ID: NCT03850366.

Disclosure: Nothing to declare

P141

Allogeneic hematopoietic cell transplantation for hodgkin lymphoma post anti-pd1 inhibitors: Incorporation of post-transplant cyclophosphamide in the conditioning regimen

E. Gavriilaki[1], Z. Bousiou[1], P. Dolgyras[1], I. Batsis[1], D. Mallouri[1], M. Iskas[1], C. Damplia[1], S. Papaemmanouil[1], A. Syrigou[1], T. Asteri[1], T. Geroukis[1], G. Arsos[2], N. Stavroyianni[1], A. Anagnostopoulos[1], I. Sakellari[1]

[1]G Papanicolaou Hospital, Thessaloniki, Greece, [2]Aristotle University of Thessaloniki, Thessaloniki, Greece

Background: Although allogeneic hematopoietic cell transplantation (alloHCT) remains the only curative option for Hodgkin lymphoma (HL), efficacy and safety of anti-PD1 (Programmed cell death protein 1) inhibitors have revolutionized HL treatment. Importantly, complications of alloHCT post anti-PD1 inhibitors have raised questions regarding its feasibility. Therefore, we investigated efficacy and safety of alloHCT post anti-PD1 inhibitors compared to a historical group of alloHCT before the introduction of anti-PD1.

Methods: We retrospectively studied patients that underwent alloHCT for HL at our JACIE-accredited center over the last decade (2010-2020). We divided them into two groups according to the treatment period: anti-PD1 and historical control group. We analyzed pre-transplant (age, disease status, previous lines), transplant (donor, graft, conditioning), and post-transplant (graft-versus-host-disease/GVHD, treatment-related mortality/TRM, relapse, and overall survival/OS) characteristics.

Results: In total, 21 patients received alloHCT for HL. Among them, 3 patients from the historical control group received anti-PD1 due to relapse post alloHCT and were excluded from further analysis. We studied 18 patients (7 in the anti-PD1 period and 11 controls), with median age 32.5 years, suffering from classical HL (12:nodular sclerosis, 3:mixed cellularity, 1:lymphopenic). All patients had undergone autologous HCT at a median of 4 years earlier, 14 with primary refractory chemo-sensitive disease and 4 with chemo-resistant disease. Among them, 8 presented with a positive PET/CT scan after autologous and 10 with relapse at a median of 13.4 (range 8-19) months.

Brentuximab vedotin (BV) had been administered post autologous HCT only in patients of the anti-PD1 group; with 2 achieving partial remission, 1 complete metabolic remission (CMR) and 1 progressive disease. Upon progression, patients of the anti-PD1 group received nivolumab for 18 (5-32) cycles. The patient that had achieved CMR with BV, received a combination of nivolumab-BV. Historical controls proceeded to alloHCT following chemotherapy upon progression.

Both groups received alloHCT at a similar disease, 11 patients had active disease at alloHCT, while 7 CR ($p = 0.205$). Donors were mainly unrelated (12/18, $p = 0.421$). Reduced toxicity conditioning regimen was administered in both groups (Thiotepa-Fludarabine-Cyclophosphamide with Antithymocyte Globulin 5mg/kg in unrelated donors). Post-transplant cyclophosphamide (Baltimore's protocol) was also given in the 4 more recent patients ($p = 0.011$). All grafts were PBSC with a median of $5.45x10^6$ cells/kg ($p = 0.263$).

With a median follow-up of 16.3 (1.1-94.7) months, cumulative incidence (CI) of acute and chronic GVHD were similar between groups. Furthermore, 2-year TRM CI did not differ (28.6% in anti-PD1 versus 27.3% in historical controls, $p = 0.951$). Interestingly, the 4 patients that received post-transplant cyclophosphamide presented no TRM. Only one patient relapsed post alloHCT in the historical control group, while no patient from the anti-PD1. Therefore, 2-year OS was similar between groups (66.7% in the anti-PD1 versus 60.0% in controls, $p = 0.982$). OS was associated only with type of donor, significantly higher in unrelated donors ($p = 0.044$).

Conclusions: Our single-center experience suggests comparable outcomes of alloHCT post anti-PD1 to historical controls. Adoption of novel modalities, such as post-transplant cyclophosphamide, have led to encouraging results. Further studies are needed to determine the optimal tailored approach for chemo-refractory HL.

Clinical Trial Registry: NA

Disclosure: Nothing to declare

P143

Clofarabine followed by reduced intensity conditioning as a sequential concept prior to allogeneic HSCT in three patients with advanced staged cutaneous t cell lymphoma

E. Stauffer[1], A. Fraccaroli[1], H. Drolle[1], M. Flaig[1], L. Heinzerling[1], M. von Bergwelt[1], S. Theurich[1], J. Tischer[1]

[1]University Hospital Munich, Munich, Germany

Background: The prognosis of patients with refractory, advanced stage primary cutaneous T cell lymphoma remains poor particularly in patients with transformed mycosis fungoides (MF). In these cases, conventional cytotoxic regimens induce only short-lived responses and lymphoma relapses occur even more aggressively thereafter. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) provides a potentially curative treatment option for clinically suitable patients. However, the optimal approach to these patients including bridging treatment to conditioning and transplant remains undefined. Here, we report on three consecutive patients with high-risk MF that received tumor reduction and reduced intensity condition (RIC) in a sequential concept prior to allo-HSCT.

Methods: Three patients with advanced stage MF including one large-cell transformation were consecutively treated at our transplant center. All patients received multiple skin directed and systemic treatments including PUVA ($n = 2$), retinoids ($n = 3$), IFN-alpha ($n = 3$) and chemotherapy ($n = 2$) and brentuximab ($n = 3$) prior to allo-HSCT. All three patients were in PR prior to transplantation.

To reduce tumor burden, all patients received clofarabine shortly before RIC in terms of a sequential therapy concept. Conditioning consisted of fludarabine, cyclophosphamide and melphalan. Bone marrow ($n = 2$) and peripheral blood stem cells ($n = 1$) were used as graft source. Donor type was HLA-haploidentical in two and HLA-matched unrelated in one patient. In all cases, cyclosporine or tacrolimus and mycophenolate mofetil as well as post-transplantation cyclophosphamide (PTCY) were used for graft versus-host disease (GVHD) prophylaxis.

Results: Clofarabine induced rapid treatment responses in all patients and subsequent RIC could be performed without significantly increased toxicities. At day +30, lymphoma staging demonstrated profound remissions (PR in 2 cases) while complete donor chimerism was detectably in the peripheral blood and bone marrow in all patients. All patients engrafted, no primary graft rejection was seen. Acute GvHD > = Grade 2 was observed in 2 patients responding to the application of steroids in both. However, all three patients relapsed after a median time of 2.6 months but responded to subsequent treatments.

Conclusions: Using clofarabine as a salvage treatment prior to RIC in a sequential allo-HSCT concept may be a considerable strategy for patients with advanced cutaneous T cell lymphoma. However, as all patients relapsed within the first year after transplantation, further investigation is needed to determine the optimal post-transplant approach including early immunomodulatory maintenance treatments.

Disclosure: Nothing to declare

P144

Team versus beam conditioning regimen for autologous stem cell transplantation in malignant lymphomas. Retrospective comparison of toxicity

J. Stevkova[1], D. Belada[1], M. Lanska[1], B. Visek[1], A. Zavrelova[1], P. Zak[1], J. Radocha[1]

[1]University Hospital Hradec Kralove, Czech Republic and Charles University, Faculty of Medicine in Hradec Kralove, Hradec Kralove, Czech Republic

Background: Autologous stem cell transplantation (auto-SCT) is an important therapeutic approach for malignant lymphoma. Conditioning chemotherapy with alkylating agents such as BEAM and TEAM is the most commonly used in this indication. Our study compares the toxicity profiles of the BEAM and TEAM conditioning.

Methods: 48 patients (20 women, 28 men), mean age 53.5 years, who underwent auto-SCT for malignant lymphoma were retrospectively analyzed. BEAM (carmustine, etoposide, cytarabine, melphalan) was used in 24 patients between November 2015 and April 2019, TEAM (thiotepa, etoposide, cytarabine, melphalan) was used in 24 patients between June 2018 and September 2021.

Results: The indications for auto-SCT included: 16 patients with diffuse large B-cell lymphomas, 9 with mantle cell lymphomas, 10 with T-cell lymphomas, 4 with follicular lymphomas, and 9 with Hodgkin lymphoma. Grade 4 neutropenia was present in all patients in both groups. The median time to neutrophil engraftment for the TEAM and BEAM arm was 10.5 (9-15) days and 10 (5-15) days, respectively ($p = 0.322$). Grade 4 thrombocytopenia was present in all patients in both groups. The median time to platelet engraftment for TEAM and BEAM was 13 days (9-22) and 11 days (9-16), respectively ($p = 0.341$). Mucositis grade 4 was observed in 22/24 (91.7%) of patients receiving TEAM compared to 20/24 (83.3%) of patients receiving BEAM ($p = 0.383$). Mucositis grade 2-3 was observed in the 2/24 (8.3%) in TEAM cohort compared to 4/24 (12.5%) of patients in the BEAM cohort ($p = 0.383$). Febrile neutropenia developed in 15/24 (62.5%) of patients receiving TEAM compared to 12/24 (50%) of patients receiving BEAM ($p = 0.383$). Sepsis developed in 7/24 (29.1%) of patients after TEAM compared to 5/24 (20.8%) of patients after BEAM ($p = 0.505$). The infectious complications were as follows: 1/24 (4.2%) patient had colitis and 1/24 (4.2%) had pneumonia after TEAM ; 1/24 (4.2%) patient had urinary tract infection and 1/24 (4.2%) had soft tissue infection after BEAM. Transplant-related mortality on day 100 was 2/24 (8.3%) of patients receiving TEAM compared to 3/24 (12.5%) of patients receiving BEAM ($p = 0.637$). The reason for death was sepsis in all cases.

Conclusions: Our retrospective analysis documents a similar result regarding engraftment, toxicity profile, and transplant-related mortality between BEAM and TEAM conditioning prior to auto-SCT.

Disclosure: Nothing to declare.

P145

Haplo-identical hematopoietic stem cell transplantation using a combination of g-csf mobilized bone marrow and peripheral blood cells in high-risk hematological malignancies

D. Ait Ouali[1], M. Benakli[1], F. Mehdid[1], M. Baazizi[1], N. Rahmoune[1], S. Akhrouf[1], H. Bouarab[1], S. Zerkout[1], F. Louar[1], R. Benouattas[1], F. Harieche[1], R.-M. Hamladji[1], R. Ahmed Nacer[1]

[1]Pierre and Marie Curie Center, Algiers, Algeria

Background: Hematopoietic stem cell transplantation (HSCT) from an haplo-identical donor has been demonstrated to provide the best chances of a cure for many children in need of an allograft but who lack a sibling donor. We propose a retrospective study of 36 pts who benefited the "Beijing protocol" using myeloablative conditioning regimen with G-CSF mobilized/primed grafts

Methods: From May 2013 to January 2017, 36 haplo-identical HSCT were used in 36 pts with hematological malignancies (7 AML, 20 ALL, 5 CML, 2 AL biphenotypic, 2 MDS). Median age was 24 years (5-55) and sex-ratio (M/F):3. The diagnosis transplant delay was 29 months (6-138). At the time of the transplant, 7 pts were in first complete remission (CR), 20 pts in second CR and 4 pts in active disease. The donors used were parents (21), siblings (14) or offspring (1); with median age: 41 years (13-65). The degree of compatibility (HLA A, B and DR) was 3/6 (24 cases), 4/6 (10 cases) and 5/6 (2 cases). CMV status between donor/recipient was high risk in 36 cases. The ABO incompatibility is major in 8 cases, minor in 10 cases. The conditioning regimen used associated Busilvex 9.6 mg/kg, Aracytine 8 g/m^2, Cyclophosphamide 3.6 g/m^2 for 36 pts. The GVHD prophylaxis included the combination Ciclosporin Methotrexate, Mycophenolate mofetil and Thymoglobulin (10 mg/kg) and received an G-CSF mobilized/primed grafts: bone marrow and Peripheral blood stem cells. Median dose infused CD34 + cells: 4,42 10^6/kg (1,35-19,9), nuclear cells: 6,45 x 10^7/kg (0,59-21,53). At November 2021, the minimal follow-up delay was 58 months and maximal 102 months.

Results: Aplasia was observed in all pts with median duration of 15 days (13-34). The median day of neutrophils engraftment was 17 days (11-27). One pt presented transplant associated microangiopathy (MAT). Two pts presented an early rejection (5%). Acute GVHD grade II-IV occurred in 14 pts (43%) on average at day 42 (16-100). Chronic GVHD was seen in 9 pts (36%) with extensive form in 4 pts on average at day 210 (150-240). Sixteen pts (50%) showed CMV reactivation on average at day 45 (28-149). Seven cases of haemorrhagic cystitis (21%) (one grade 4) are observed . Ten pts (27%) relapsed, of which 4 pts were blast crisis at the time of the transplant. After follow-up of 42 months (58-102), 17 pts (47%) are alive and 19 pts (53%) died within 9 pts (25%) from TRM (acute GVHD:02, severe infection:4, haemorrhagic cystitis:1, TRALI syndrome:1, early rejection :1) And 10 from relapse (27%) and the overall survival (OS) and disease free survival (DFS) are 47% and 44% respectively.

Conclusions: Our study shows that haplo-identical HSCT using the Beijing is a well-validated approach and feasible in patients with advanced malignancies, associated with prompt engraftment, acceptable rates of GVHD, TRM and survivals.

Disclosure: Nothing to declare

P146

Single centre experience of efficacy and toxicity of reduced-dose melphalan conditioning (140 mg/m2 or 110 mg/m2) in autologous stem cell transplantation for multiple myeloma

E. Troy-Barnes[1], D. Melotti[1], M. Camilleri[1], J. Horder[1], F. Newrick[1], J. Marfil[1], L. Lee[2], A.S. Mahmood[3], B. Wisniowski[3], X. Papanikolaou[1], A. Wechalekar[3], J. Sive[1], R. Popat[4], K. Yong[2], N. Rabin[1], C. Kyriakou[1]

[1]University College London Hospitals NHS Foundation Trust, London, United Kingdom, [2]University College London Cancer Institute, London, United Kingdom, [3]University College London Centre for Amyloidosis & Acute Phase Proteins, London, United Kingdom, [4]National Institute for Health Research University College London Hospitals Clinical Research Facility, London, United Kingdom

Background: Autologous stem cell transplantation (ASCT) is a key component of treatment for multiple myeloma (MM) following induction therapy. The efficacy and safety of high-dose melphalan 200 mg/m2 conditioning is well-established in fit, non-elderly (<65-70 years) patients. Although historical data has demonstrated increased toxicity with

melphalan 200 mg/m2 in patients with renal failure, there is limited up-to-date literature demonstrating the safety and efficacy of low dose conditioning (140 mg/m2 or 110 mg/m2) in renal failure and other subgroups with high transplant comorbidity index.

Methods: A retrospective analysis was performed on 81 MM patients who underwent first ASCT with low-dose conditioning following induction therapy at a single centre between 2006-2020. The primary outcome was ASCT-related toxicity, and secondary outcomes were overall survival (OS); progression free survival (PFS), depth of response and renal function. Univariate and multivariate analysis was performed for age, renal function, co-morbidities, performance status, ISS/R-ISS, high-risk cytogenetics and depth of response prior to ASCT.

Results: Of 81 patients, 31 (38%) were female, 34 (42%) were >65 years (mean age 61.5, IQR 56-68). 76 (94%) patients had MM (34 (45%) light chain and 42 (55%) had IgG or IgA MM); the remainder (6%) had other conditions (AL amyloidosis, monoclonal gammopathy of renal significance, multifocal plasmacytoma). ISS was ≥2 in 46 (57%) at diagnosis; 18 (22%) had high-risk cytogenetics.

Prior to ASCT, mean GFR was 45 mL/min, IQR 61-27; mean left ventricular ejection fraction was 61%, IQR 66-55; 5 (6%) had poor performance status (Karnofsky < 80). Induction therapy included a PI in 66 (82%) and IMID in 45 (56%).

Mean duration of admission was 24.7 days, IQR 18-25; mean time to neutrophil engraftment was 11.4 days, IQR 11-12. 4 (5%) patients had worsening of renal function during their ASCT admission meeting definition of acute kidney injury by RIFLE criteria; mean creatinine clearance at 100 days was 69 mL/min, IQR 89-57. Mortality at 100 days was 1/81 (1%). Disease status as per IMWG criteria prior to ASCT was Very Good Partial Response (VGPR) or better in 57 (70%), Partial Response (PR) in 20 (25%) patients. Staging data at 3 month post-ASCT was available for 71 patients, of which 52 (73%) were in VGPR or CR, and 15 (21%) were in PR.

Mean follow-up period was 30 months, IQR 12-42. Median OS was 6.2 years. Median PFS was 2.3 years, with a significantly better median PFS (2.8 years vs 1.6 years) for patients <70 years old vs patients aged >70 (p-value 0.045); at latest review mean GFR was 67, IQR 89-50.

Early relapse/progression within <18 months was observed in 17/81 (21%) patients.

Conclusions: Our data suggest that autograft with low-dose melphalan conditioning is a feasible, safe and effective therapeutic option in patients deemed unfit for high-dose melphalan. This analysis provides real world data to support clinical decision making in MM that will be benefited from high-dose alkylating agent. The renal status did not significantly impact on toxicity or efficacy outcomes. In this cohort older patients had significantly inferior PFS.

Disclosure: Nothing to declare.

P147

Long-term follow-up of auto-hct with tbi-based conditioning regimen in patients with peripheral t-cell lymphomas: A single-center analysis

T. Czerw[1,2], A. Smagur[1,2], A. Chwieduk[1], M. Sadus-Wojciechowska[1], J. Najda[1], W. Mendrek[1], M. Sobczyk-Kruszelnicka[1], A. Frankiewicz[1], M. Ociepa-Wasilkowska[1], M. Dzierzak-Mietla[1], I. Mitrus[1], M. Krawczyk-Kulis[1], J. Holowiecki[1], S. Giebel[1]

[1]Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland, [2]These authors contributed equally to this work, Gliwice, Poland

Background: Peripheral T-cell lymphomas (PTCLs) are relatively rare and heterogeneous group of lymphoproliferative disorders accounting for 10%–15% of all non-Hodgkin lymphomas. High-dose consolidation therapy with autologous stem cell support (auto-HCT) is considered beneficial for transplant-eligible patients with newly diagnosed and relapsed disease. The evidence is based on retrospective analyses which included heterogeneity of mainly chemotherapy-based conditioning regimens. Achieving complete remission (CR) before auto-HCT is one of the strongest predictors of the outcome. We report on a retrospective, single institution analysis of auto-HCT with total body irradiation (TBI)-based conditioning regimen in patients with PTCLs in CR1.

Methods: Patient selection included all 23 consecutive adult patients with PTCLs in CR1 undergoing auto-HCT between 2010-2019 in the Department of Bone Marrow Transplantation and Onco-Hematology, National Research Institute of Oncology, Gliwice Branch, Poland. Eighteen of them were conditioned with 12Gy TBI (given in 3 fractions of 4Gy on 3 consecutive days) combined with 120mg/kg cyclophosphamide. Five patients (aged above 60 y.o. at transplantation) were conditioned with 8Gy TBI given in 2 fractions of 4Gy combined with bendamustine 160-200mg/m^2 given on 2 consecutive days. The group characteristics were as follows: median age at transplantation 52 years (range, 22-68); PTCL subtype (PTCL-not otherwise specified-8; angioimmunoblastic T-cell lymphoma-4; anaplastic large cell lymphoma ALK(-)-4, ALK(+)-6, enteropathy associated T-cell lymphoma -1); Ann Arbor stage at diagnosis (II-5; III-12; IV-6); median number of pre-transplant chemotherapy lines: 1 (1-2).

Results: All transplants were performed with use of peripheral blood as a source of stem cells. The median number of transplanted CD34+ cells was 8.6 (2.0-24.8) x 10^6 /kg b.w. of the recipient. All patients engrafted and the median time to neutrophil recovery was 10 days (9-13). With the median follow-up of 92 months (26-134) only 1 patient experienced relapse. Six patients died of other causes: one patient died 5 months after transplantation whereas the remaining 5 patients died at a time longer than 1 year after auto-HCT (median 64 months (17-91). The probability of overall survival at 5 and 8 years after auto-HCT was 87% (+/− 7%) and 68% (+/− 11%), respectively. The probability of progression-free survival at 5 and 8 years after auto-HCT was 82% (+/− 8%) and 63% (+/− 12%), respectively.

Conclusions: Our long-term follow-up analysis shows that TBI seems to be an effective part of conditioning regimen before auto-HCT for PTCLs allowing potentially to achieve good disease control.

Disclosure: Nothing to declare

P148

Reduced intensity conditioning regimen with treosulfan for second allogeneic stem cell transplantation in patients with acute myeloid leukemia or myelodysplastic syndrome. A single-centre experience

J. Stevkova[1], B. Visek[1], M. Lanska[1], A. Zavrelova[1], K. Doskocilova[1], J. Radocha[1], P. Zak[1]

[1]University Hospital Hradec Kralove, Czech Republic and Charles University, Faculty of Medicine in Hradec Kralove, Hradec Kralove, Czech Republic

Background: Second allogeneic stem cell transplantation (SCT2) is associated with a high risk of peri-transplant and post-transplant mortality. Reduced intensity conditioning regimens (RIC), usually based on busulfan and fludarabine (Bu-Flu), are usually chosen in these cases. The aim of our retrospective study was to evaluate the effect and toxicity of a conditioning regimen containing treosulfan (Treo) instead of busulfan.

Methods: In our retrospective analysis, 15 patients transplanted at our center between June 2012 and February 2019 were included (9 women, 6 men, mean age 50 years). There were 12 patients with acute myeloid leukemia (AML) (including 7 cases of secondary AML), 2 patients with myelodysplastic syndrome (MDS), and 1 patient with chronic myelomonocytic leukemia (CMML). Complete remission was achieved in 3/15 (20%) of the patients before aloSCT; In 9/15 (60%) of patients, sequential chemotherapy was used before SCT2 due to disease activity. All patients received peripheral stem cells from HLA-matched unrelated donors; RIC Thymoglobulin-Treo-Flu was used as a conditioning regimen. Graft versus host disease prophylaxis consisted of tacrolimus combined with mycophenolate mofetil. The HLA match was 10/10 in 13/15 (86%) of the patients and 9/10 in 2/15 (14%) of the patients. Fourteen patients had a comorbidity index (HCT-CI) 0; one patient had a HCT-CI 3.

Results: Neutrophil engraftment was achieved in 13/15 (86%) of patients, in platelets in all patients. The median time to neutrophil and platelet engraftment was 14 (11-21) days and 11 (10-20), respectively. Donor chimerism 99-100% on day +30 was achieved in all patients; on day +100 donor chimerism 100% was achieved in 13/15 (86%) of patients (2 patients had early relapse). Acute GvHD developed in 6/15 (40%) of patients (grade ≥ 3-4 in 13%) and extensive chronic GvHD (grade 4) in 1/15 (6%) of patients. At the median follow-up of 63 months, 10/15 (66,6%) of the patients have died: in 7 cases due to relapse, in 2 cases due to severe posttransplant lymphoproliferative disease, 1 patient died from acute GvHD. GRFS (GvHD-free, relapse-free survival) at 1 year was 33%. The median overall survival was 13.6 months.

Conclusions: Our data indicate a favorable safety profile and high efficacy of Treo-containing RIC in a selected group of patients undergoing SCT2. The advantages of this regimen are low peri-transplant and early post-transplant mortality and the ability to induce 100% chimerism early after transplantation.

Disclosure: Nothing to declare.

P149

Low dose anti-thymocyte globulin with posttransplant cyclophosphamide haploidentical stem cell transplantation for high risk hematologic malignancies – umc ljubljana, slovenia experience

P. Novak[1], M. Sever[1], K. Šlajpah[1], N. Gredelj[1]

[1]UMC Ljubljana, Ljubljana, Slovenia

Background: Haploidentical stem cell transplantation (haploSCT) rate is increasing worldwide, mostly due to its clinical efficiency and accessibility. Bone marrow used to be the preferred stem cell source in the haploSCT because it is less immunogenic and causes less graft versus host disease (GvHD) than peripheral blood stem cells (PBSC). To prevent relapse in high risk hematologic malignancies, at UMC Ljubljana, Slovenia we decided to use PBSC with low dose anti-thymocyte globulin (ATG) in combination with posttransplant cyclophosphamide (PTCy).

Methods: We analyzed six high risk leukemia patients who underwent haploSCT with low dose ATG (Grafalon) 5 mg/kg on day -3, -2, -1 (15 mg/kg total dose) and thiotepa -6, -5 (total dose 10 mg/kg), busulfan -4, -3, -2 (total dose 9,6 mg/kg), fludarabine -4, -3, -2 (total dose 150 mg/m^2), PTCy 50 mg/kg on day +3 and +5 conditioning regimen with cyclosporine and mycophenolate mofetil for GvHD prophylaxis since May 2020. At the time of haploSCT the median patient age was 64 years (26-67). 4/6 (67%) had secondary AML with MDS related changes, two of them resistant to primary induction but in CR after second induction, one (17%) had primary resistant AML, one (17%) patient had early T-ALL. 5/6 (83%) patients were in CR1 before the haploSCT.

Results: All patients received a myeloablative TBF protocol with ATG and PTCy and all received PBSC at median dose of 4 x10^6/kg CD34 + cells. Median time to neutrophil engraftment was 15 days. One patient died due to intracranial bleeding before engraftment. We did not observe acute or chronic GvHD. Two patients had CMV reactivation after letermovir prophylaxis discontinuation. All patients remain in remission. The mean survival time is 15 months (95% CI 9,6-20,3) with OS 83%.

Conclusions: For patients with high risk leukemia and no matched sibling or unrelated donor haploSCT with peripheral blood stem cells and low dose ATG combined with PTCy is an encouraging treatment option resulting in low GvHD and disease relapse rate.

Disclosure: Nothing to declare

P150

Determination of transplant conditioning intensity: A real-life data

İ. Yavaşoğlu[1], A.H. Eroğlu Küçükdiler[1], A.Z. Bolaman[1]

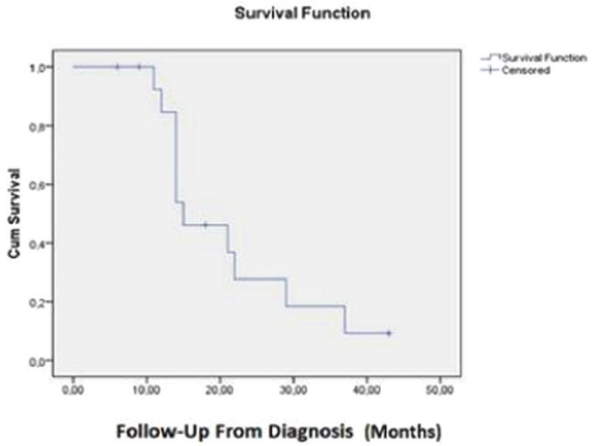
[1]Aydin Adnan Menderes University, Aydin, Turkey

Background: The pre-transplantation conditioning regimen in allogeneic hematopoietic stem cell transplantation (Allo-SCT) is important in early morbidity, non-relapse mortality, and long-term disease control. It is difficult to standardize the conditioning regimens in Allo-SCT. In this sense, the concept of 'transplant conditioning intensity (TCI) score', which has been developed recently, has become important [1].

Methods: Eighty-three patients with various diagnoses who underwent allo-SCT at the Hematology Department of Aydın Adnan Menderes University between the years of 2014-2020 were included in the study, which was designed to be single-center, retrospective. Regarding donor compatibility, we have included all allogeneic transplantation procedures, performed as related or unrelated 9-10/10, as well as haploidentical transplantations. Myeloablative, reduced intensity regimen (RIC), and non-myeloablative conditioning regimens were used in accordance with the diagnoses. Of the patients; the rates of myeloid malignancy, lymphoid malignancy, and aplastic anemia were 65%, 30%, and 5%, respectively.

Results: The distribution of conditioning regimens according to the TCI score group was as follows: 13 patients had a low, 44 patients an intermediate, and 30 patients a high TCI score. The mean age was 42 ± 3 in the low group, 48 ± 2 in the intermediate group, and 36 ± 2 in the high group, respectively. No statistical difference was found with Kaplan Meier between the three groups (Fig. 1). Low TCI had a mean survival of 42.1 ± 10.5 months, intermediate 61.3 ± 13.7, high 43.2 ± 8.9 months.

Figure - 1: Kaplan-Meier Survival Analysis



Conclusions: Although it is not statistically significant, the longer life expectancy may increase the interest in the RIC, although the mean age is higher in those with the intermediate TCI score. It is important to increase the use of TCI in practice.

Disclosure: Nothing to declare

EXPERIMENTAL TRANSPLANTATION AND GENE THERAPY

P151

Wolman cd34+ cells transduced with cd11blipa lentivirus drives lysosomal acid lipase enzyme expression

A. Guha[1], J. Potter[1], R. Wynn[1], B. Bigger[2]

[1]Manchester Foundation Trust, Manchester, United Kingdom, [2]University of Manchester, Manchester, United Kingdom

Background: Wolman disease (WD) is a lysosomal storage disorder (LSD) that is caused by complete deficiency of lysosomal acid lipase (LAL). There is a pathogenic variant in the LIPA gene which maps to chromosome 10q23. It is an infantile onset lethal disease characterised by lysosomal accumulation of cholesteryl esters (CE) and triglycerides (TG) predominantly in hepatocytes and macrophages.

Symptoms and signs develop due to large accumulation of CE and TG in the lysosomes of Kupffer cells and hepatocytes as well as in macrophages throughout the viscera. Untreated, infants do not survive beyond the first year of life.

Treatment includes enzyme replacement therapy (ERT) and haematopoietic stem cell transplant (HCT). The long-term use of ERT is limited by ongoing gastrointestinal symptoms, neutralising

anti-drug antibodies (ADA), the need for life long central venous access and the financial implications of treatment. HCT has a high transplant related morbidity and GvHD mortality. An engraftment defect has been reported with the majority of patients having a mixed chimerism.

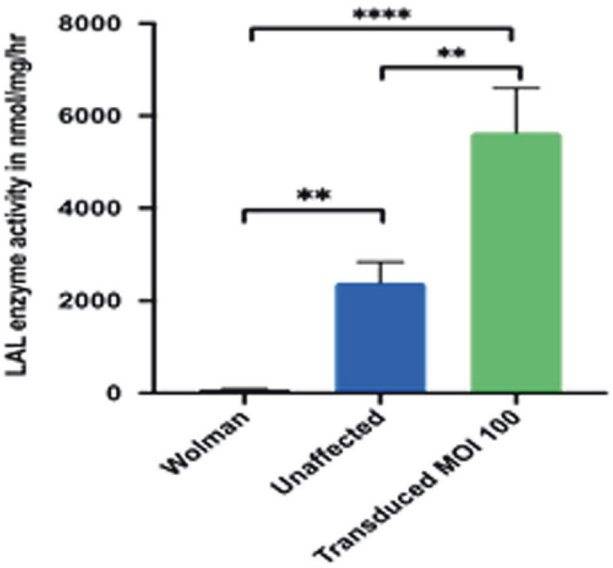
Autologous ex vivo haematopoietic stem cell gene therapy (HSC-GT) is an emerging treatment in LSD. HSC-GT eliminates the risk of GvHD and reduces the need for immunosuppression. By delivering a transgene that includes a promotor, there is the capacity to drive overexpression and achieve supra-physiological levels of enzyme.

Methods: Wolman CD34 + cells were transduced with a CD11bLIPA lentivirus at a multiplicity of infection (MOI) of 25,50 and 100 with and without transduction enhancers (TE). Transduction efficiency, vector copy number and enzyme levels were evaluated. Additionally Wolman CD34 + and unaffected CD34 + were compared, investigating colony forming unit (CFU) total, distribution and LAL enzyme level activity.

Results: As expected Wolman CD34 + cells had minimal LAL enzyme activity. After transduction of Wolman CD34 + cells with CD11bLIPA LV, the deficient CD34 + cells were able to achieve significantly higher levels of enzyme activity to that of unaffected controls (Figure 1).

Transduction without TEs achieved a vector copy number (VCN) between 1.5 and 3. With higher VCN (achieved with TEs) the enzyme activity is significantly higher than unaffected CD34 +; 'supraphysiological', however with MOI 100 there was reduction in overall colonies. There was no significant difference in the CFU distribution between Wolman and Unaffected. The transduction efficiency >90% in all CFU's.

Figure 1:



Conclusions: We have demonstrated ex vivo transduction of human Wolman CD34 + stem cells drives LAL activity and that the optimal MOI was reduced by transduction enhancers without associated toxicity.

To further demonstrate efficacy and to assess toxicity and safety, we aim to show direct macrophage correction and reduction of oxysterols in normal and Wolman macrophages derived from peripheral blood and transduce normal or Wolman CD34 + cells into NSG mice for biodistribution and toxicology outcomes.

Disclosure: Nothing to declare

P152

Eltrombopag in fanconi anemia patients infused with very low numbers of gene corrected cells

J. Iriondo[1], J. Zubicaray[1], P. Rio[2], L. Ugalde[2], E. Sebastian[1], S. Navarro[2], N. Garcia de Andoin[3], A. Catalá[4], M. Ivanova[1], J. Surralles[5], M. Garcia-Abos[3], J. Gonzalez de Pablo[1], J.J. Uriz[3], J. Schwartz[6], J. Soulier[7], J. Bueren[2], J. Sevilla[1]

[1]Fundación Biomédica Hospital Niño Jesús, Madrid, Spain, [2]CIEMAT/CIBERER/Fund. Jiménez Díaz, Madrid, Spain, [3]Hospital Universitario Donostia, Donostia/San Sebastian, Spain, [4]Hospital Sant Joan de Déu, Barcelona, Spain, [5]IIB Sant Pau - Fundació Institut de Recerca Hospital de Sant Pau, Barcelona, Spain, [6]Rocket Pharmaceuticals Inc., New York, United States, [7]Université de Paris, Institut de Recherche Saint-Louis, Paris, France

Background: Allogeneic HSCT currently constitutes the only available therapy which can revert the bone marrow failure (BMF) characteristic of Fanconi Anemia (FA). In the absence of a compatible donor, androgens may be used in FA patients, although other agents are being tested in clinical trials. In this respect, there are two ongoing clinical studies evaluating the safety and efficacy of eltrombopag in FA patients. From preclinical models, it has been postulated that this drug promotes DNA repair in FA HSCs through the non-homologous end joining repair mechanism, improving genome integrity, cell survival, and HSC functionality. In addition to these approaches, gene therapy has conferred preliminary evidence of safety and efficacy in phase I and II studies, in patients receiving autologous gene corrected CD34 + cells exceeding threshold levels and during early stages of BMF.

The aim of this study is to analyze the safety and efficacy of eltrombopag in FA patients who had been infused in the phase I clinical trial with very low numbers of corrected CD34 + cells.

Methods: We report the hematologic and molecular course of four patients initially included in the gene therapy clinical trial FANCOLEN-1 (NCT03157804) who had an evolution of BMF. Two of them were treated with eltrombopag under a "compassionate use program" and the other two were included in the clinical trial FANCREV (EUDRACT 2020-002703-18). During follow-up, peripheral blood counts (PBC), BM studies including cytogenetics, and vector copy number (VCN) analyses were carried out to assess the efficacy and safety of eltrombopag in these patients.

Results: Patients received treatment with eltrombopag for a duration between 3 and 12 months. No medication-related adverse events, including clonal evolution, were observed during their follow-up. One patient showed a modest increase in PBC counts after 3 months of treatment and remained free of transfusion requirements. In the remaining cases no sustained hematologic response was observed. In BM aspirations performed during the course of therapy, a decreasing trend in CD34 + cell numbers was observed. Strikingly, the analysis of VCNs in BM showed more marked increases in the proportion of gene corrected cells as compared to analyses performed prior to eltrompopag treatment.

Conclusions:

1. No relevant adverse effects, including clonal events, were observed during eltrombopag treatment in FA patients previously infused with very low numbers of gene corrected CD34 + cells.
2. The evolution of PBC counts during the treatment period does not allow us to conclude that eltrombopag mediated clinically relevant hematologic responses.
3. The proportion of gene-corrected cells in BM increased in all patients.

Although current data does not enable detection of a sustained eltrombopag-mediated benefit in the hematopoiesis of FA patients previously infused with very low numbers of gene corrected CD34 + cells, this drug promoted a more marked proliferative advantage of gene corrected cells compared to analyses performed prior to eltrombopag treatment. In order to evaluate the potential impact of eltrompopag in FA gene therapy, studies with a longer follow-up will be conducted in patients infused with autologous gene corrected cells, potentially at earlier stages of BMF.

Clinical Trial Registry: EudraCT 2020-002703-18

Disclosure: Julián Sevilla: Consultant/Advisor/Honorarium (Amgen, Novartis, Miltenyi, Sobi, Rocket Pharmaceuticals) and has licensed medicinal products from Rocket Pharmaceuticals.

Juan Bueren: Consultant/Advisor/Honorarium and has licensed medicinal products from Rocket Pharmaceuticals.

Jonathan D. Schwartz: employee and equity shareholder for Rocket Pharmaceuticals.

P153

Haploidentical stem-cell transplantation for children with acute leukemia, using αβ + t cell /cd19 + b-cell depletion, a single center experience

G. Dadi[1], E. Jacoby[1,2], B. Bielorai[1,2], A. Toren[1,2]

[1]Division of Pediatric Hematology and Oncology, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat Gan, Israel, [2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Background: HLA haploidentical stem cell transplantation using αβ + T Cell /CD19 + B-cell depletion (αβHaplo-SCT) has been utilized in the last decade as an alternative approach to matched donor allogeneic transplantation in children with hematological malignancies[1-4]. We report a single center experience using αβHaplo-SCT in children with acute leukemias between 2013-2020.

Methods: Data regarding donor/recipient, conditioning regimen, and graft characteristics were noted. Study endpoints were overall survival (OS), event free survival (EFS, relapse, death, or rejection), leukemia-free survival (LFS), non-relapse mortality (NRM), acute graft-versus-host disease (aGVHD), chronic graft-versus-host disease (cGVHD) and graft-versus-host disease, relapse-free survival (GRFS)[5].

Chi-square test or Fisher's exact test were used to compare categorical variables, and continuous variables were analyzed using Mann-Whitney non-parametric testing.

Cox proportional hazards regression models were constructed and analyzed using SPSS 25.

Results: Thirty-eight children with acute leukemia underwent αβHaplo-SCT, Most for advanced disease (≥CR2, or refractory) and third had prior HSCT. Patient's median age was 8.5 years. Conditioning regimen was total body irradiation (TBI) based in 55% of children and 45% were conditioned with combination of Fludarabine, Treosulfan or Melphalan and Thiotepa. Patients received serotherapy as part of the conditioning, using anti-thymocyte globulin. Eighteen patients had more than 3X10^4 /kg of αβ T cells in the graft and received GVHD prophylaxis with mycophenolate mofetil [2]. No patient had donor's HLA antibodies.

Thirty-four patients had primary engraftment and four had primary rejection. Median time for neutrophils engraftment was ten days and for platelets thirteen. Six patients had secondary rejection (median time 27 days). Using TBI was associated with higher engraftment and less rejection compared to chemotherapy only but did not reach a statistical significance (94% vs 82% $p = 0.3$ and 9% vs 23% $p = 0.37$, respectively).

Thirteen patients developed grade 1-2 aGVHD, age was a significant risk factor (11 Vs 6.5 $P = 0.023$). No patient developed grade 3-4 aGVHD and one developed extensive cGVHD.

Twenty-two patients were alive at last follow up with 5 years OS of 51%, and EFS of 42%. EFS was longer for patients with higher graft composition of γ/δ T cells (54% Vs 26%, $P = 0.04$).

Nine patients had relapse, all were males (34% vs 0%, $P = 0.026$). LFS probability was 72%. GRFS probability was 47.5%.

Eleven patients had NRM, mostly due to sepsis. CMV reactivation was common (50%) at a median time of 27 days, treated preemptively according to established guidelines.[6]

An expansion of NK cells was noted at day 30 of transplantation than reconstituted at three months. CD4/8 T cells and B cells recovered at six months. Immunoglobulins were supplemented as part of infection prophylaxis during immune recovery.

Conclusions: αβHaplo-SCT offers a cure for children with multiple relapses, or those who failed prior SCT with OS of 51%. Higher composition of γ/δ T cells had less rejections. Older age was a significant risk factor for grade 1-2 aGVHD. Chronic GVHD was rare. The role of prophylactic immunosuppression needs to be validated through a prospective trial. Immune reconstitution is slow, necessitating close follow up for viral reactivation, and preemptive prophylaxis is crucial for survival.

Disclosure: No conflict of interest

P154

Venetoclax added to sequential flamsa + alkylator based conditioning for allogeneic hematopoietic stem cell transplantation, a retrospective single center case series of the flamsaclax approach

G. Kobbe[1], E. Schuler[1], P. Jäger[1], B. Bärmann[1], R. Fenk[1], F. Schulz[1], S. Gehring[1], T. Ulrych[1], K. Nachtkamp[1], U. Germing[1]

[1]University Hospital Düsseldorf, Düsseldorf, Germany

Background: Relapse is the most common cause of treatment failure after allogeneic hematopoietic stem cell transplantation (aHSCT) in patients with high-risk myeloid malignancies. Increasing conditioning intensity before aHSCT has not been able to improve transplant results because of increased treatment related mortality (TRM) especially in elderly, comorbid patients. Venetoclax has been shown to greatly enhance efficacy of conventional chemotherapy as well as hypomethylating agents while increasing mainly hematologic toxicity. Experience in combining Venetoclax with intensive conditioning therapy, where hematotoxicity can be suspended by aHSCT so far is limited.

Methods: Starting in 2018, we added Venetoclax to Fludarabine/Amsacrine/Ara-C (FLAMSA) + alkylator based sequential conditioning regimen (FLAMSAClax) in individual patients with poor prognosis myeloid malignancies. All patients gave written informed consent for individualized treatment. We now retrospectively collected data on 11 patients (9 AML, 1 MDS, 1 CMML, 6 female, median age 57, range 20-66) who had a minimum follow up of 300 days after transplant. All patients had active disease at transplant (8 refractory, 3 untreated) and 10 had high-risk genetics. Various doses of Venetoclax (100-400mg/d) were given in addition to FLAMSA and stopped one day before alkylator treatment (8 Melphalan, 3 Treosulfan).

Results: No additional extrahematologic toxicity was observed. There was 1 laboratory TLS, but no TRM. WBC and PLT reconstitution occurred on day + 12 (median, range 8-19 for WBC > 1000/ul) and on day + 14 (median, range 10-31 for PLT > 20000/ul). aGvHD grade III/IV occurred in 2 and severe cGvHD in 1 patient. At day +30, ten patients were in CR or CRi, 1 with molecular disease persistence. One patient had blast persistence but achieved molecular CR after salvage with HMA + Venetoclax. After a median follow up of 600 days (range 304-1001) for surviving patients, 10 patients (91%) are alive, 8 in molecular CR and 2 currently receive salvage therapy for relapse. So far 3 patients relapsed (day + 175, +267 and +855) and 1 finally died after salvage and 2nd transplant from disease progression.

Conclusions: Venetoclax added to sequential FLAMSA + alkylator based conditioning seems to be feasible and highly effective in patients with poor risk myeloid malignancies. The FLAMSAClax approach should therefore be studied in a controlled prospective trial.

Clinical Trial Registry: NA

Disclosure: GK has received honoraria for an advisory role from Abbvie and Eurocept as well as travel support from Medac. All other authors have nothing to declare.

P155

Allogeneic hematopoietic stem cell transplantation in patients with adult onset leukoencephalopathy with axonal spheroids

G.-N. Franke[1], V. Vucinic[1], B. Schetschorke[1], J. Claßen[2], U. Platzbecker[1], W. Köhler[2]

[1]University of Leipzig Medical Center, Leipzig, Germany, [2]University of Leipzig Medical Center, Leukodystrophy Clinic, Leipzig, Germany

Background: Adult onset leukoencephalopathy with axonal spheroids (ALSP) is a very rare disease and belongs to the heterogenouos groups of leukodystrophies. ALSP is a hereditary disease caused by a mutation in the *CSF1R* gene, presenting with progressive neurological symptoms, usually in the 4th or 5th decade and death within 5-6 years after onset of symptoms. The *CSF1R* gene is associated with phosphatase and kinase proteins regulating the function of macrophages, microglia and neuronal pathways. Dysbalances and disturbances caused by the *CSF1R* mutation lead to progressive inflammation and white matter lesions. Patients (pts) with leukodystrophies might benefit from allogeneic hematopoietic stem cell transplantation (allo-HSCT) by exchanging part of the host's microglia through donor cells.

Methods: Two male patients with ALSP and *CSF1R* gene mutations and white matter lesions in the MRI underwent allo-HSCT at our center. Pt 1, a 49 year old male, was diagnosed in 2017, when he developed gait disturbances and a speech disorder, mainly due to a severe dyspraxia. Pt 2, a 47 year old male, underwent extensive neurological assessment in 2016 for left-sided sensomotor dysfunstions, visual disturbances and progressive cognitive deficits. He also had a family history with his mother, maternal grandmother, two maternal aunts and one older brother dying from early onset dementia and one younger, still asymptomatic, brother. The *CSF1R* mutation was also found in his two brothers. Due to the lack of material, no analyses are available from his mother, grandmother and aunts.

Results: Pt 1 was transplanted in 2019 from an HLA-identical sibling not carrying the mutation, while Pt 2 received a transplant from an unrelated HLA-identical male donor in 2020. Both pts were conditioned with busulfan (9.6 mg/kg BW) and fludarabine (180 mg/m^2). Immunosuppression (IS) consisted of anti-thymoglobulin, cyclosporine A (CsA) and short course methotrexate. Both pts promptly engrafted and IS could be tapered without signs of acute or chronic GvHD.

Transient deterioration of the neurological functions was seen in both pts in the first 6 months after HSCT, followed by improvement to pre-HSCT status. 2.5 years after allo-HSCT, the symptoms of dyspraxia and dysarthria of pt 1 have improved, he is walking without limitations and has stable cognition . Pt 2 presented with progressive MRI changes 6 months after transplantation and deterioration of gait and speech. In the last evaluation 1.25 years after allo-HSCT, he clearly improved in gait and speech, his MRI was stable.

Conclusions: ALSP is a usually fatal neurological disease caused by *CSF1R* gene mutations. Allo-HSCT has the potential to prevent further destruction of brain by replacing the recipient's microglia through donor cells and thus stabilization of the neurological functions after 6-12 months.

Disclosure: Nothing to declare

P156

Haploidentical stem cell transplant for haematological malignancies: Real world experience from a developing country

P. Mehta[1], N. Yadav[1], R. Halder[1], N. Agrawal[2], R. Ahmed[1], D. Bhurani[1]

[1]Rajiv Gandhi Cancer Institute & Research Centre, Delhi, India, [2]Rajiv Gandhi Cancer Institute & research Centre, Delhi, India

Background: Haploidentical peripheral blood hematopoietic cell transplantation(HaploSCT) has become the preferred alternative donor transplant program, owing to its logistic and cost advantages. However, the data from developing countries is not sufficient enough to hold this statement true for them.

Methods: It is a retrospective observational study hospital record based study where the outcome of Haplo-SCT was analysed using standard statistics.

Results: Between March 2015 and April 2021, 74 patients underwent 75 haploidentical transplantations at our institution. Median age was 31(9-60) years and indications included malignant disorders in majority (96%). Conditioning regimens included myeloablative (38.7%), nonmyeloablative regimens (44%) and reduced intensity (17.3%). GVHD prophylaxis was post-transplant cyclophosphamide on day+3,4 with Mycophenolate and Cyclosporine from day+5 onwards. Peripheral blood stem cells were the predominant graft source. Majority (92%) had CMV reactive donor and recipient combination. Median cell dose (CD34) was 5.26 (1.8-8.09) $x10^6$/kg. Median engraftment for neutrophils and platelets was 14 (11-32) and 15 (10-43) days respectively. Nine (12.1%) patients had rejection (primary = 8, secondary=1). CMV reactivation was observed in 52 (69.3%) patients. The cumulative incidence of acute GVHD was 37.3% with 32.1% incidence of grade III-IV acute GVHD and 14.2% patients were steroid refractory. Chronic GVHD was seen in 16% and one fourth patients had extensive chronic GVHD. Sixty-four(85.3%) culture positive bacterial infections (Gram positive= 14, Gram negative=50) were observed in 44 patients whereas 32.4% patients had fungal infection and 17.5% had viral infections. TRM within 30 days, 30-100days and >100days was 8(10.6%), 14(18.6%),16(21.3%) patients respectively. Common causes of death were sepsis and relapse.

Conclusions: We emphasize haploidentical SCT offers a reasonable hope of cure for patients with hematological malignancies, though infections, GVHD, relapse are still deal-breakers in our experience which we are striving to overcome in our prospective studies.

Clinical Trial Registry: Not Applicable

Disclosure: No conflict of interest.

GRAFT-VERSUS-HOST DISEASE – CLINICAL

P157

Real-world data on ruxolitinib in steroid-refractory acute intestinal graft-versus-host-disease

F. Biavasco[1], G. Ihorst[2], R. Wäsch[1], C. Wehr[1], H. Bertz[1], J. Finke[1], R. Zeiser[1]

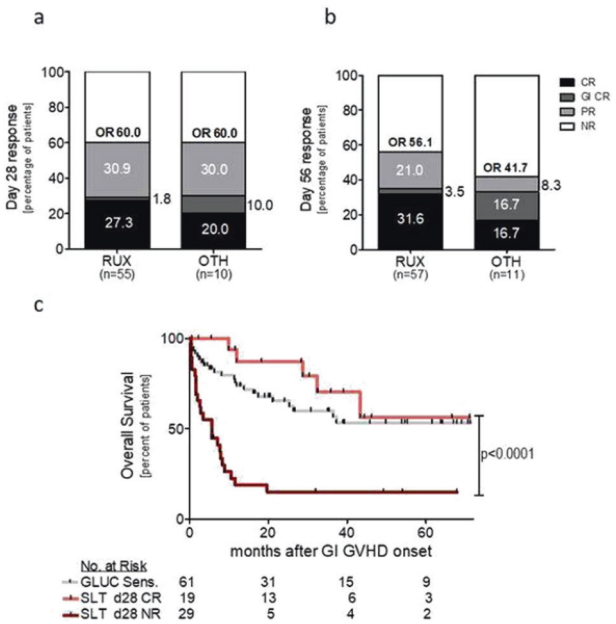
[1]University Medical Center Freiburg, Freiburg, Germany, [2]Clinical Trials Center Freiburg, Freiburg, Germany

Background: Acute graft-versus-host disease affecting the lower gastrointestinal tract (GI-GVHD) is a major life-threatening complication of allogeneic hematopoietic cell transplantation and is frequently resistant to glucocorticosteroid-therapy (SR). Higher overall response rates and failure-free survival of ruxolitinib compared to best available second-line therapy (SLT) was recently reported in a phase-III trial. However, real-world data and external validation of these promising results are lacking.

Methods: To determine the outcome of patients with GI-GVHD in the era of ruxolitinib, we retrospectively analyzed patients who developed GI-GVHD over a 6-year period to determine therapy-responsiveness and survival.

Results: A total of 144 patients developed GI-GVHD and 83 (58%) were SR. Ruxolitinib was most commonly used (74.3%) as SLT. Overall and complete response (CR) to ruxolitinib on day 28 were similar to what reported in REACH2 trial (60.0% and 27.3% respectively, Figure 1A). A durable CR was observed in ruxolitinib-treated patients at day 56 in 31.6% and in other single-agent SLT in 16.7% (Figure 1B). Around one fourth of patients could achieve a CR even after third-line (25.8%) and fourth-line therapy (25.0%). Moreover, SR-GVHD patients experienced a lower 5-year overall survival (OS) (34.8% vs 53.3%, p = 0.0014) and higher cumulative incidence of 12-months non-relapse-mortality (NRM) (39.2% vs 14.3%, p = 0.016) compared to glucocorticosteroid-sensitive patients. Interestingly, SR-GVHD patients who achieved CR on day 28 experienced higher 5-year OS (56.3% vs 14.9%, p < 0.0001) and lower 12-months NRM (13.8% vs 77.4%, p < 0.0001) compared to non-responders, having an outcome comparable to glucocorticoid-sensitive patients (Figure 1C).

Figure 1



Conclusions: These real-world unselected data confirm the response rate to ruxolitinib as SLT in SR-GI-GVHD obtained in REACH2 trial and the poor outcome of SR-GI-GVHD. Additionally they show improved OS of ruxolitinib-CR-responders and indicate that first-line therapy failure still allows for a considerable CR rate upon SLT.

Disclosure: Rober Zeiser received honoraria from Incyte, Novartis and Mallinckrodt, was supported by the Deutsche Forschungsgemeinschaft (DFG), Germany for the SFB 1479 OncoEscape P01, Project ID: 441891347 to RZ, SFB1160 to RZ, ZE 872/4-2, TRR167 to RZ, Deutsche Krebshilfe (grant number

70113473), the Jose-Carreras Leukemia foundation grant number DJCLS 01R/2019.

P158

Bortezomib maintenance after upfront allogeneic transplantation in myeloma patients: Less chronic GVHD and immunosuppression but still no impact on survival

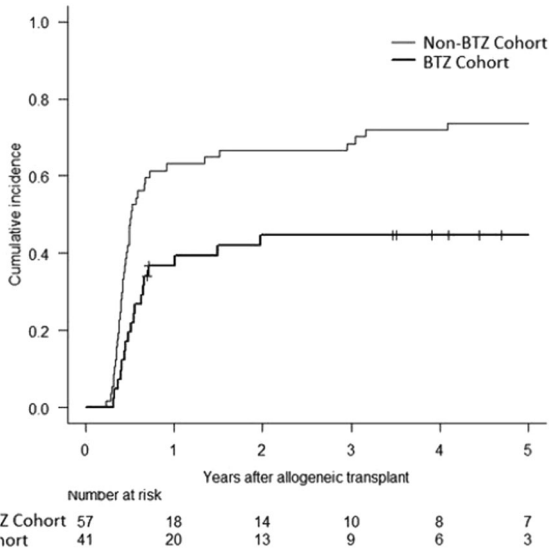
J.-S. Claveau[1,2], R. LeBlanc[2], I. Ahmad[2], J.-S. Delisle[2], J. Roy[2]

[1]Mayo Clinic, Rochester, United States, [2]Maisonneuve-Rosemont Hospital, Montreal, Canada

Background: Allogeneic (allo) hematopoietic stem cell transplant (HCT) has curative potential in multiple myeloma (MM) but remains hampered by high rates of relapse and chronic (c) GVHD. We recently completed a prospective phase II study (LeBlanc R, BMT 2021) in newly diagnosed MM using bortezomib (BTZ) maintenance after tandem autologous (auto) + alloHCT aimed at decreasing relapse. Based on previous clinical observations, we hypothesized that BTZ could also decrease incidence and severity of cGVHD.

Methods: Using the 2015 NIH criteria, we retrospectively reviewed the incidence and organ distribution of cGVHD, as well as duration of immunosuppression in 2 contemporaneous cohorts: patients receiving BTZ maintenance q2 weeks for 1 year after alloHCT, and tandem transplants without BTZ maintenance. After autologous HCT, patients from both cohorts received an outpatient nonmyeloablative conditioning followed by G-CSF mobilized donor stem cells. GVHD prophylaxis consisted of mycophenolate mofetil and tacrolimus tapered by D + 100 (sibling donors) or D + 180 (unrelated donors) in both groups. Cumulative incidences of cGVHD were estimated using competing-risk methods including relapse, second transplantation and death.

Results: Between 2014 and 2018, 41 patients received BTZ maintenance, whereas 57 patients did not. Myeloma subtypes were similar in both groups. Baseline characteristics showed no difference except that patients in the BTZ group had younger donors (40 years vs. 52 years) and more unrelated donors (59% vs. 12%). Incidences of grade II-IV acute GVHD at day+180 were similar in both cohorts (17.1% vs. 26.6%, $p = 0.518$). At 2 years, incidences of overall (61.0% vs. 84.2%, $p = 0.001$) and moderate/severe cGVHD (44.7% vs. 66.7%, $p = 0.003$, Fig. 1) were significantly lower in BTZ than in non-BTZ recipients. After univariate analysis, overall mouth (56% vs. 79%, $p = 0.025$), skin (34% vs. 56%, $p = 0.041$) and liver (32% vs. 54%, $p = 0.039$) involvement were less frequent in BTZ patients. We elected to choose donor age, sex, CD34 + cell dose, major ABO mismatch, recipients' CMV status and grade II-IV acute GVHD as variables to perform multivariable analysis. Following multivariate Fine-Gray regression, not receiving BTZ was associated with higher overall incidence of cGVHD (HR 2.38, $p = 0.002$) and moderate/severe cGVHD (HR 2.39, $p = 0.004$). The cumulative incidence of prednisone initiation at 5 years was 42.2% in BTZ and 78.3% in non-BTZ recipients ($p < 0.001$). The cumulative incidence of tacrolimus resumption at 5 years was also lower in BTZ than in non-BTZ recipients (30.1% vs. 73.6%, $p < 0.001$). Probability of being alive and off immunosuppressants at 3 years were 86% for BTZ patients vs. 47% for non-BTZ patients ($p < 0.001$). NRM at 2 and 5 years were 4.9% and 8.8% in BTZ recipients vs. 1.8% and 5.4% in non-BTZ recipients ($p = 0.575$). We observed no impact of BTZ on 5-year OS (82.9% vs. 83.4%, $p = 0.938$) and PFS (49.5% vs. 58.5%, $p = 0.277$) respectively in patients receiving or not BTZ.



Conclusions: Although it had no impact on survival, BTZ maintenance led to a significant reduction in incidence and severity of cGVHD with shorter duration of immunosuppressants. BTZ maintenance should be considered as a valid option in MM receiving upfront auto-alloHCT.

Clinical Trial Registry: N/A

Disclosure: The authors declare no conflicts of interest.

P159

Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of systemic therapy: Long-term safety follow-up of the pivotal phase 2 rockstar study (kd025-213)

C. Cutler[1], S. Lee[2], S. Pavletic[3], B. Blazar[4], L. Green[5], Z. Yang[5], D. Eiznhamer[5], J. Ieyoub[5]

[1]Dana Farber Cancer Institute, Boston, United States, [2]Fred Hutchinson Cancer Center, Seattle, United States, [3]Center for Cancer Research, National Cancer Institute, Bethesda, United States, [4]University of Minnesota, Minneapolis, United States, [5]Kadmon Corporation, New York, United States

Background: Belumosudil is a novel oral selective rho-associated coiled-coil–containing protein kinase-2 inhibitor designed for the treatment of cGVHD following an allogeneic hematopoietic cell transplant. We report the 2-year, long-term, follow-up safety results from the ROCKstar study.

Methods: This open-label, randomized, multicenter study evaluated belumosudil 200 mg QD ($n = 66$) and BID ($n = 66$) in patients with cGVHD (aged 21-77 years) who received 2 to 5 prior LOTs; cutoff date for the long-term follow-up was August 19, 2021.

Results: Median age was 56 years, median time from diagnosis to enrollment was 28 months, median prednisone dose was 0.19 mg/kg/d, 67% of patients had severe cGVHD, 52% had ≥4 organs involved, 73% had received ≥3 prior LOTs (including ibrutinib [34%] or ruxolitinib [29%]) and 73% were refractory to their last LOT. Median treatment duration was 10 months, with 29% of patients receiving belumosudil for ≥24 months. The ORR (95% CI) with belumosudil 200 mg QD and BID was 74% (62%-84%) and 77% (65%-87%), respectively. Belumosudil continued to be well tolerated (Table). The primary reasons for drug discontinuation were adverse events [AEs] ($n = 17$ [13%]; 7 experienced AEs that were not drug related), progression of underlying malignancy ($n = 5$ [4%]) and progression of cGVHD ($n = 16$ [20%]). Twenty

percent and 10% of patients experienced ≥1 drug-related AE that led to dose modification and interruption, respectively. Forty-eight percent and 32% of patients experienced ≥1 AE not drug related that led to dose modification and interruption, respectively.

AEs observed at all grades in ≥30% of patients included fatigue (39%), diarrhea (35%), nausea (31%) and cough (30%). Grade ≥3 AEs observed in ≥5% of patients included hypertension (8%), pneumonia (8%) and hyperglycemia (5%). Grade ≥3 cytopenias included anemia (4%), neutropenia (2%) and leukopenia (1%). At least 1 serious AE occurred in 44% of patients. There was 1 case of cytomegalovirus reactivation.

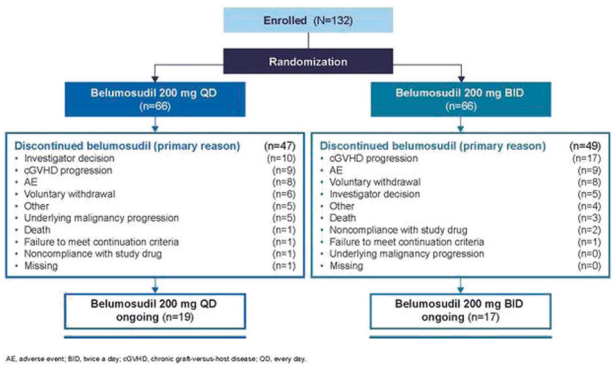
Of all patients, 5% had ≥1 grade ≥3 drug-related hepatic disorder, 14% had increased gamma-glutamyltransferase, 12% had increased aspartate aminotransferase, 10% had increased alanine aminotransferase and 1% had increased bilirubin.

The median corticosteroid dose reduction was 50%. Corticosteroid discontinuation was observed in 27% of patients. Calcineurin inhibitor dose reduction and discontinuation was observed in 54% and 27% of patients, respectively.

Table

Safety overview	Belumosudil 200 mg QD (n = 66)	Belumosudil 200 mg BID (n = 66)	Total (N = 132)
Median months of treatment	9	12	10
Any AE, n (%)	65 (99)	66 (100)	131 (99)
Grade ≥3 AEs, n (%)	41 (62)	38 (58)	79 (60)
Any serious AE, n (%)	30 (46)	28 (42)	58 (44)
Any drug-related AE, n (%)	50 (76)	42 (64)	92 (70)
Any drug-related grade ≥3 AE, n (%)	14 (21)	11 (17)	25 (19)
Any drug-related serious AE, n (%)	6 (9)	3 (5)	9 (7)
Any AE leading to death, n (%)	4 (6)	5 (8)	9 (7)

Figure



Conclusions: Belumosudil remained well tolerated, with low rates of cytopenias. AE and drug discontinuation rates were comparable to those reported in Cutler et al, 2021. Patients have continued to sustain belumosudil therapy and achieve clinically meaningful responses.

Clinical Trial Registry: NCT03640481

Disclosure: Corey Cutler is a consultant and advisor for Janssen, Mesoblast, Syndax Pharmaceuticals Inc, Omeros, Incyte Corporation, Jazz Pharmaceuticals, Mallinckrodt, CareDx and Pfizer; has been a pro bono consultant for Kadmon Corporation; and has not received any payment for consulting in the past year. Stephanie J. Lee is on a steering committee for Incyte Corporation and has received research funding from Amgen, AstraZeneca, Incyte Corporation, Kadmon Corporation, Novartis Pharmaceuticals Corporation, Pfizer, Syndax Pharmaceuticals Inc and Takeda. Steven Pavletic received research support from the Center for Cancer Research at the National Cancer Institute through the National Institutes of Health Intramural Research Program, which includes Clinical Research Development Agreements with Celgene, Actelion, Eli Lilly, Pharmacyclics and Kadmon Corporation. Bruce R. Blazar is a cofounder of Tmunity Therapeutics, is a consultant and advisor for Magenta Therapeutics and Blue Rock Therapeutics and has received research funding from Blue Rock Therapeutics, Children's Cancer Research Fund and Kids First Fund. Laurie Green, Zhongming Yang, David Eiznhamer and Jonathan Ieyoub have stock options in and are employees of Kadmon Corporation.

P161

Fecal microbiota transplantation in the treatment of acute gastrointestinal graft-versus-host disease: A retrospective survey of the transplant complications working party of EBMT

J. Bilinski[1], G.W. Basak[1], K. Halaburda[2], D. Wu[3], O. Goloshchapov[4], S. Maury[5], A. Tanase[6], G. Van Gorkom[7], A. Delie[8], T. Kerre[8], O. Penack[9], I. Moiseev[4], H. Schoemans[10], C. Koenecke[11], S. Corbacioglu[12], Z. Peric[13]

[1]Medical University of Warsaw, Warsaw, Poland, [2]Institute of Hematology and Transfusion Medicine, Warsaw, Poland, [3]China Suzhou, First Affiliated Hospital of Soochow University, Suzhou, China, [4]Pavlov University, St. Petersburg, Russian Federation, [5]Hôpital Henri Mondor, Creteil, France, [6]undeni Clinical Institute, Bucharest, Romania, [7]University Hospital Maastricht, Maastricht, Netherlands, [8]Ghent University Hospital, Ghent, Belgium, [9]Charité Universitätsmedizin Berlin, Berlin, Germany, [10]University Hospitals Leuven, Leuven, Belgium, [11]Hannover Medical School, Hannover, Germany, [12]University Hospital Regensburg, Regensburg, Germany, [13]University of Zagreb, Zagreb, Croatia

Background: Loss of intestinal bacterial diversity, a relative shift toward bacterial monocolonization (i.e. with *Enterococci)* and colonization with antibiotic-resistant bacteria (ARB) before allogeneic hematopoietic stem cell transplantation (alloHCT) are observed in gastrointestinal (GI) acute graft-versus-host disease (aGvHD) patients. Allogeneic gut microbiota may modulate systemic immune responses, which has been proven in many microbiota dependent diseases. Fecal microbiota transplantation (FMT) is able to restore gut microbiota diversity and has been successfully used for recurrent *Clostridioides difficile* infection as well as for the treatment of autoimmune diseases (i.e. ulcerative colitis). Recently, studies of the use of FMT to treat (steroid-refractory (SR) intestinal) aGvHD have shown promising results. Our aim was to identify EBMT centers who perform FMT in this indication and summarize procedure modalities, application regimens, indications and outcome.

Methods: The study was performed by Transplant Complications Working Party (TCWP) between May 2018 and May 2020 and used a 2-step approach. In the first step we conducted a survey among EBMT centers with >100 alloHCTs since 2010 to identify

cases, while in second, we retrospectively collected details of performed FMTs.

Results: A total of 10 centers reported 32 patients. Among these, 27 patients (25 adults and 2 children) met inclusion criteria and had undergone 52 FMTs. Most of the reported patients were already published elsewhere separately. 24/2/1 patients had steroid refractory/dependent/*de novo* GI aGvHD, respectively and concomitant indications to perform FMT were *C. difficile* infection in 3 and ARB colonization in 14 of subjects. 22 patients (81%) had grade III-IV gut aGvHD and 24 (89%) overall III-IV aGvHD. Almost all patients (25, 93%) had an unrelated stool microbiota donor and obtained FMT as an infusion (25, 93%) or capsules (1, 4%). Most of the patients received FMT through gastrointestinal/duodenal tube (23, 85%) and the procedure was performed as multiple administration regimen (FMT sessions; in 20 patients, 74%). Overall aGvHD response rate (ORR) at day 28 post-FMT reached 63% (17/27); with 12 patients achieving complete response (CR; 44%) and additional 5 patients achieving partial response (PR; 19%). Additionally, successful ARB decolonization was achieved in 8 out of 14 previously colonized patients (57%). It is also important to highlight that 20 patients (74%) were treated with antibiotics during the first two weeks after FMT, which could have negatively impacted the ORR. In total, 2 cases of sepsis as severe adverse events were reported.

Conclusions: In this one of the largest cohort of patients published to date, undergoing FMT after alloHCT, we found high response rates of aGVHD as well as decolonization of ARB. To enable a broader clinical use of this promising approach, more evidence from prospective clinical trials as well as a standardization of FMT modalities is needed.

Disclosure: OP has no COIs directly related to this manuscript. OP has received honoraria or travel support from Astellas, Gilead, Jazz, MSD, Neovii Biotech, Novartis, Pfizer and Therakos. He has received research support from Gilead, Incyte, Jazz, Neovii Biotech and Takeda. He is member of advisory boards to Jazz, Gilead, MSD, Omeros, Priothera, Shionogi and SOBI.

P162

Prospective multicenter non interventional observational study on the use of anti-human t-lymphocyte immunoglobulin (atlg) in unrelated donor transplantation in adults with haematological malignancies (atos study)

J. Finke[1], C. Schmoor[1], F. Ayuk[2], J. Hasenkamp[3], M. Verbeek[4], E.-M. Wagner[5], K. Schäfer-Eckart[6], J. Tischer[7], C. Schmid[8], M. Kaufmann[9], M. Eder[10], H. Bertz[1], O. Grichina[1]

[1]University of Freiburg Medical Center, Freiburg, Germany, [2]University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [3]University of Göttingen Medical Center, Göttingen, Germany, [4]Medical Center TU Univerity München, München, Germany, [5]Mainz University Medical Center, Mainz, Germany, [6]Medical Center Nürnberg Nord, Nürnberg, Germany, [7]Medical Center LMU University München, München, Germany, [8]University Medical Center Augsburg, Augsburg, Germany, [9]Robert Bosch Krankenhaus Stuttgart, Stuttgart, Germany, [10]University Medical School Hannover, Hannover, Germany

Background: Long-term follow-up from the prospective randomized phase III multicenter[PDJF1] trial (RCT) comparing a standard GvHD prophylaxis with cyclosporine A and methotrexate with or without additional pretransplant anti-human T-lymphocyte immunoglobulin (ATLG, Grafalon) (20mg/kg/day, days -3 to -1) in unrelated donor hematopoietic cell transplantation after myeloablative conditioning resulted in a significant reduction of acute and chronic GvHD without compromising relapse and survival (Finke et al., Lancet Hematol 2017).

Methods: ATOS is a subsequent prospective non-interventional observational study evaluating the outcome of patients receiving ATLG in unrelated donor transplantation in routine clinical practice without the selective measures of a clinical trial. No control group was included. Patients' characteristics and outcomes were compared to 103 patients in the ATLG treatment arm of our RCT. Primary endpoint was severe GvHD and relapse-free survival (SGRFS).

Results: Between May 2013 and March 2015, 13 transplant centers included 165 patients with haematological malignancies (age median 54, range 18-77 years) in early (45%), intermediate (18%) or advanced (37%) disease receiving marrow (N = 6) or PBSC (N = 159) from 10/10 matched (78%) or mismatched (22%) donors after myeloablative (51%) or reduced intensity conditioning (RIC) (49%).

GvHD prophylaxis consisted of calcineurin inhibitors, mainly CSA (93%) with MTX or MMF and ATLG. Different dosing regimens were allowed according to current center practice. Median total ATLG dose was 46 (IQR 32-60, range 15-91) mg/kg. Median follow-up was 70 months (range 11-91 months). ATLG dose differed strongly between centers, so dose effects cannot be separated from center effects.

As compared to our RCT, patients in ATOS were older, had a more advanced disease status, RIC, HLA 10/10 match and PBSC transplantation were more frequent, and given median ATLG dose was lower.

Incidences of aGvHD (0.56), aGvHD III-IV (0.13), relapse (0.33), relapse mortality (0.24), non-relapse mortality (0.24), and disease-free (0.43) and overall survival rates (0.52), (all 5-years), were similar to the results in the ATLG arm of our RCT. Five-year incidences of cGvHD (0.42), and severe cGvHD (0.27) were higher as compared to results in the ATLG arm of our RCT (any 0.31, severe 0.14), which may be due to different reporting procedures. As a result of these differences, also the 5-year rate of SGRFS was lower in ATOS (0.27) as compared to the ATLG arm in our RCT (0.34).

In general, the comparison of outcomes in ATOS and the RCT has to take into account the differences in patient characteristics and treatment procedures. In multiple regression models adjusting for these differences, the largest difference in outcome was seen with respect to severe cGvHD (ATOS vs ATLG arm RCT: hazard ratio 2.79, 95%-confidence interval [1.20,6.51], p = 0.017). All other adjusted comparisons resulted in 95%-confidence intervals of the hazard ratio overlapping the value of one.

Adverse drug reactions occurred at a rate and severity that are consistent with the known safety profile, and are clinically manageable.

Conclusions: The long-term experience in routine clinical practice confirms the results shown in our RCT, namely the GvHD protective effect of ATLG without compromising relapse and non-relapse mortality rates.

Clinical Trial Registry: German clinical trials register DRKS00004581

Disclosure: JF: Neovii, Medac Riemser

P163

Graft versus host disease related eosinophilic fasciitis

C. Hidalgo-Calleja[1], D. Martín-Hidalgo[2], C. Román Curto[1], L. Vázquez López[1], E. Pérez-López[1], M. Cabrero Calvo[1], A.Á. Martín-López[1], M.D. Caballero Barrigón[1], L. López-Corral[1]

[1]University Hospital, Salamanca, Spain, [2]Salamanca University, Salamanca, Spain

Background:

Chronic Graft Versus Host Disease (cGVHD) simulating eosinophilic fasciitis (EF) is a rare complication after allogeneic transplantation of hematopoietic progenitors (allo-TPH). EF related

cGVHD is an underdiagnosed and challenging complication due to the lack of knowledge about its pathogenesis, refractoriness to traditional immunosuppressive agents and their negative impact on physical function and quality of life.

The aim of this study is to describe the clinical-biological characteristics and response to treatment of a case series of EF related cGVHD.

Methods: Prospective observational study to describe the clinical and diagnostic evaluation characteristics of patients with EF-like follow-up in our multidisciplinary cGVHD consultations since March 2014 to present. 118 patients were evaluated, 39 of whom (33%) developed fasciitis. Joint and fascial cGVHD was diagnosed if the patient had NIH joint and fascia score ≥1. Clinical variables analyzed in the entire cohort were the baseline and transplant-related characteristics and clinical assessment of cGVHD including time from all-HCT to enrollment, cGVHD type, organs affected and NIH global score. In addition, in the fasciitis group, complementary laboratory and imaging tests as well as the therapeutic approach and response were detailed. Diagnosis and classification were performed according to 2015 NIH and treatment response in EF-like according to the response criteria redefined by Inamoto 2020.

Regarding statistical analysis, a descriptive analysis of frequencies was performed and nonparametric tests were used for comparisons (X^2 or Fisher's exact test for categorical variables or the Mann-Whitney test for continuous variables). The analyses were performed using the SPSS 25.0 statistical package (SPSS, Chicago, IL, USA).

Results: From March 2014 to present, 118 patients were evaluated in the multidisciplinary cGVHD consultation and 39 patients (33%) developed fasciitis. No differences regarding baseline and transplant-related characteristics neither clinical assessment of cGVHD was found between patients with or without fascial involvement. The clinical characteristic of EF related cGHVD are described in Table 1. After a 3 median lines of treatment, the vast majority of patients achieved some degree of response, with a complete response rate of 41%.

Table 1.- Clinical-biological characteristics and therapies administered in patients with fasciitis (n = 39).

Nonspecific prodromal symptoms	
• Absent	8 (20.5%)
• Stiffness	33 (84.6%)
• Arthromyalgias	24 (61.3%)
• Edemas	11 (28.2%)
• Cramps	9 (23.0%)
• Skin tightness	29 (74.4%)
Joint contracture	14 (35.8%)
Affected range of motion (ROM):Mild/ moderate / severe	23 (59.0%)/10 (25.6%)/ 1 (2.6%)
Limitation of upper limb mobility:	
• P-ROM shoulders	23 (58.9%)
• P-ROM elbows	13 (33.4%)
• P-ROM wrists/fingers	19 (50.0%)
Limitation of mobility of lower limbs:	
• P-ROM ankles	14 (35.9%)
Concomitant skin sclerosis	35 (89.7%)
Nonspecific prodromal symptoms	
Eosinophilia at diagnosis (>500/mm3)	21 (53.8%)
Positive autoantibodies	10 (25.7%)
Imaging tests performed: • Rx/MRI / Echo	2 (5.1%)/2 (5.1%)/ 3 (7.7%)
Median number of treatment lines (range)	3 (1-7)
First-line treatment	
• Corticosteroids	37 (94.4%)
Rescue treatment	
• Extracorporeal photopheresis	25 (64.1%)
• Ruxolitinib	8 (20.5%)
• Imatinib	10 (25.6%)
• Others	11 (28.2%)

Conclusions: Fascial/articular involvement needs to be recognized and evaluated early with validated scales. In our knowledge, our cohort is the second largest series reported. Literature addressing fascial/joints complications related to cGVHD are scarce. The search for new biomarkers, the use of advanced imaging techniques and multidisciplinary approach may help to improve the prognosis of patients with cGVHD.

Disclosure: This work was partially supported by the Education Council and Health Council of the Junta de Castilla y León (GRS 2183/A/20), Spain.

P164

Methotrexate or mycophenolate mofetil with cyclosporine and antithymocyte globulin in matched unrelated donor transplantation for acute myeloid leukemia with busulfan-fludarabine reduced-intensity conditioning: An alwp study

G. Battipaglia[1], J.-E. Galimard[2], M. Labopin[2], G. Socié[3], E. Forcade[4], C.E. Bulabois[5], U. Schanz[6], N. Fegueux[7], S. Mielke[8], K. Carlson[9], E. Deconinck[10], J. Maertens[11], G. Guillerm[12], P. Turlure[13], T. Gedde-Dahl[14], A. Nagler[15], M. Mohty[16]

[1]Federico II University of Naples, Naples, Italy, [2]EBMT Statistical Unit, Paris, France, [3]Hopital St. Louis, Dept.of Hematology – BMT, Paris, France, [4]Service d'Hématologie Clinique et Thérapie Cellulaire, CHU Bordeaux, Bordeaux, France, [5]CHU Grenoble Alpes - Université Grenoble Alpes, Service d`Hématologie, Grenoble, France, [6]University Hospital, Clinic of Hematology, Zurich, Switzerland, [7]CHU Lapeyronie, Département d`Hématologie Clinique, Montpellier, France, [8]Karolinska University Hospital, Dept. of Hematology, Stockholm, Sweden, [9]Dept of Hematology, University Hospital, Uppsala, Sweden, [10]Hopital Jean Minjoz, Service d`Hématologie, Besançon, France, [11]University Hospital Gasthuisberg, Dept. of Hematology, Leuven, Belgium, [12]C.H.R.U de Brest, Service Onco-Hematologie, Brest, France, [13]CHRU Limoges, Service d`Hématologie Clinique, Limoges, France, [14]Institute of clinical medicine, University of Oslo, Oslo, Norway, [15]Chaim Sheba Medical Center, Tel-Hashomer, Israel, [16]Sorbonne Universités, UPMC Univ Paris 06, INSERM, Centre de Recherche Saint-Antoine (CRSA), Paris, France

Background: Graft-versus-host disease (GVHD) prophylaxis in matched unrelated donor (MUD) allogeneic hematopoietic stem cell transplantation (allo-HSCT) is mainly based on the use of a calcineurin inhibitor with either short course methotrexate

(MTX) or mycophenolate mofetil (MMF). When using peripheral blood as stem cell source (PBSC), addition of antithymocyte globulin (ATG) significantly reduces the incidence of chronic GVHD (cGVHD). Reduced-intensity conditioning regimen (RIC) with fludarabine and busulfan (BuFlu) is largely used in this setting.

Methods: Included were adults ≥18 years undergoing first allo-HSCT for acute myeloid leukemia (AML) in complete remission (CR) from a MUD and receiving PBSC and a BuFlu-RIC with ATG, transplanted between 2010-2019. Patients receiving cyclosporine (CsA) with either MTX or MMF were included and transplant outcomes with these GVHD prophylaxis were compared.

Results: We identified a total of 1001 patients, including 517 receiving CsA+MMF (MMF group) and 484 receiving CsA+MTX (MTX group). Patients in the MMF group were younger (61 versus 63 years, $p < 0.01$) and less frequently seropositive for CMV (60% versus 72%). No imbalances were observed for other characteristics. Most patients were transplanted in first CR (85% versus 81% in MMF and MTX groups 1 and 2, respectively, $p = 0.12$). With a median follow-up of 3 years for both groups, 2-years (2y) relapse incidence (RI) was 26% versus 32% in MMF and MTX groups ($p = 0.20$) while non-relapse mortality (NRM) was lower in the MTX group (9% versus 15%, $p = 0.02$). No differences were observed in 2y-overall survival (OS, 64% versus 69% in MMF and MTX groups, respectively, $p = 0.10$) and 2y-leukemia-free survival (LFS, 59% in both groups, $p = 0.70$) while a higher 2y-GVHD/relapse-free survival (GRFS) was found in the MTX group (52% versus 46%, $p < 0.01$). Of note, both grade II-IV and III-IV acute GVHD (aGVHD) were lower in the MTX-group (18% and 4% compared to 37% and 11% in the MMF group, $p < 0.01$). Similarly, cGVHD of all grades and extensive cGVHD were lower in the MTX group (29% and 8% compared to 36% and 17% in the MMF group, $p < 0.05$ for all grades and $p < 0.01$ for extensive cGVHD). These results were confirmed in multivariate analysis with lower NRM (HR 0.63, 95% CI 0.44-0.92, $p = 0.01$) and higher GRFS (HR 0.80, 95% CI 0.65-0.99, $p = 0.04$) in the MTX group. Use of CsA+MTX was also associated to lower grade II-IV (HR 0.45, 95% CI 0.32-0.62, $p < 0.01$) and grade III-IV (HR 0.39, 95% CI 0.23-0.67, $p < 0.01$) aGVHD and lower cGVHD (HR 0.71, 95% CI 0.56-0.90, $p < 0.01$) and of extensive cGVHD (HR 0.39, 95% CI 0.22-0.68, $p < 0.01$). Neither RI (HR = 1.20, 95% CI 0.94-1.52), $p = 0.14$) or LFS (HR 0.99; 95% CI 0.81-1.21, $p = 0.93$) or OS (HR 0.85, 95% CI 0.69-1.05, $p = 0.13$) differed significantly between the two groups.

Conclusions: In MUD allo-HSCT GVHD prophylaxis containing CsA+MTX and CsA+MMF were not significantly different in term of LFS and OS. However, CsA+MTX better prevented both acute and chronic GVHD, subsequently reducing NRM and providing higher GRFS compared to CsA+MMF when a BuFlu RIC with ATG is used in MUD-PBSC allo-HSCT.

Disclosure: No COI to disclose

P165

Triple agents GVHD prophylaxis for HLA matched donor: Post-transplant cyclophosphamide versus thymoglobulines and methotrexate

E. Metafuni[1], S. Giammarco[1], M.A. Limongiello[1], F. Sorà[1], E. Galli[1], N. Piccirillo[1], L. Teofili[1], A. Bacigalupo[1], S. Sica[1], P. Chiusolo[1]

[1]Fondazione Policlinico Universitario Agostino Gemelli, Roma, Italy

Background: HLA matched donor has represented the most used stem cell source in last decades. The main graft-verus-host disease (GvHD) prophylaxis platform includes calcineurin inhibitors with methotrexate (MTX) or mycophenolate mofetil (MFA), but recently cyclophosphamide post-transplant (CY) emerged as reliable alternative, not only for haploidentical donors.

Methods: We retrospectively analyzed post-transplant outcomes in HLA matched allogeneic stem cell transplantation (HSCT) between March 2015 and May 2021, comparing two GvHD prophylaxis platforms. The first included cyclosporine A 3 mg/Kg from day 0 (CSA), MFA 30 mg/Kg from day +1 to day +36 and CY 50 mg/kg on day +3 and +5 (n = 91). The second one included CSA 3 mg/kg from day 0 to day 60 and then tapering until day +180, MTX 15 mg/m2 on day +1, 10 mg/m2 on day +3, +6 and +11, and rabbit thymoglobulines 2.5 mg/kg on day -1 (ATG) (n = 111).

Results: One year (1-yr) cumulative incidence of moderate/severe chronic GvHD (cGvHD) was of 14.7% (95% CI 8.7-24.9) in the CSA/MFA/CY group and 26% (95% CI 18.5-36.5) in the CSA/MTX/ATG group ($p = 0.04$). In multivariate analysis, CY-based prophylaxis (HR 0.45, $p = 0.02$), complete remission status of the underlying disease at transplant (HR 0.40, $p = 0.007$) and a previous acute GvHD (aGvHD) (HR 2.14, $p = 0.003$) resulted as independent variables for moderate/severe cGvHD occurrence. Moreover, 1-yr graft-relapse free survival (GRFS) was of 58.2% (95% CI 47.4-67.6) in the CSA/MFA/CY group and 43.2% (95% CI 33.9-52.2) in the CSA/MTX/ATG group ($p = 0.01$). In multivariate analysis, CY-based prophylaxis (HR 0.59, $p = 0.01$) complete remission status of the underlying disease at transplant (HR 0.65, $p = 0.03$) and the use of a female donor (HR 1.51, $p = 0.05$) emerged as independent variables for GRFS. Considering the occurrence of viral infections after transplant, 1-yr EBV viremia occurred in 22.6% (95% CI 15.2-33.7) in the CSA/MFA/CY group and in 64.3% (95% CI 55.5-74.7) of the CSA/MTX/ATG group ($p < 0.0001$). Multivariate analysis identified CY-based prophylaxis (HR 0.30, $p < 0.0001$), a previous aGvHD (HR 1.74, $p = 0.01$) and a previous CMV infection (HR 2.88, $p < 0.0001$) as independent variables for EBV infection. Finally, 1-yr cumulative incidence of CMV viremia was of 23.6% (95% CI 14.3-39) in the CSA/MFA/CY group and 57% (95% CI 48.4-67.2) in the CSA/MTX/ATG group ($p < 0.0001$). Multivariate analysis revealed CY-based prophylaxis (HR 0.41, $p = 0.007$), a diagnosis of acute leukemia or myelodysplasia (HR 2.10, $p = 0.02$), a familial donor (HR 0.22, $p = 0.0001$) and CMV seropositive recipient (HR 5.73, $p = 0.0008$) as independent variables for CMV infection.No differences among the two groups were identified for aGvHD occurrence, disease free survival, transplant-related mortality or overall survival.

Conclusions: Patients receiving HLA matched transplant experienced a low incidence of moderate/severe cGvHD, EBV viremia and CMV viremia and a better GRFS when GvHD prophylaxis is realized using CY with CSA and MFA.

Disclosure: Nothing to declare

P166

Ten years of steroid refractory acute graft-versus-host disease in pediatric allogeneic hematopoietic stem cell transplantation: What have we learned?

A.B Verbeek[1], S.A Jansen[2,3], E.GJ von Asmuth[1], A.C Lankester[1], C.A Lindemans[2,3], E.P Buddingh[1]

190

[1]Leiden University Medical Center, Leiden, Netherlands, [2]Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands, [3]University Medical Center, Utrecht, Netherlands

Background: Steroid refractory acute Graft-versus-Host Disease (SR-aGvHD) in children after allogeneic hematopoietic stem cell transplantation (alloHSCT) is associated with high morbidity and mortality. We aimed to assess clinical course and outcomes of pediatric SR-aGvHD.

Methods: We performed a retrospective nationwide multicenter cohort study in the Netherlands. All patients aged 0-18 transplanted between 2010 and 2020 with SR-aGvHD were included. For each patient, weekly clinical aGvHD grade and stage, immunosuppressive treatment and clinical outcomes were collected. The primary study endpoint was clinical course of SR-aGvHD over time, which was graphically analyzed. As a secondary outcome, factors influencing overall survival and remission were identified using a multistate Cox model.

Results: Between 2010 and 2020, 786 children received an alloHSCT. 158 patients (20%) suffered from grade II-IV aGvHD, which occurred after a median of 34.5 days. 81 patients (51%) required second line therapy after first line treatment with steroids (Table 1).

Second line therapy was started after a median of 8 days after aGvHD diagnosis. 42 patients (52%) required three or more lines of therapy. One year after start of second line therapy, 34 patients (42%) were alive and in remission of their SR-aGvHD and 33 patients (41%) had died. 14 patients (17%) had persistent GvHD. Figure 1 displays clinical course since start of second line therapy.

Cord blood (CB) grafts were associated with a significantly lower chance of achieving remission of SR-aGvHD than bone marrow (BM) or peripheral blood stem cell (PBSC) grafts (HR 0.51, 95% CI 0.28-0.94, $p = 0.032$). Older age was associated with higher mortality: children aged 13.9-17.9 (fourth quartile) had a significantly higher hazard of death compared to children aged 0.175-3.01 (first quartile) (HR 2.64, 95% CI 1.05-6.63, $p = 0.04$). When modelling the interaction between age and graft source, we found that in BM/PBSC grafts older age was also significantly associated with lower remission rates (HR 0.89, 95% IC 0.83-0.96, $p = 0.003$). Underlying diagnosis, donor matching or choice of second line therapy were not associated with outcome.

Pulmonary manifestation of GvHD leading to respiratory insufficiency was an important cause of death in our cohort, accounting for 10/38 deaths (26%).

Table 1. Highlight of patient and treatment characteristics.

		N = 81
Age	Median (range)	8.9 (0.2-17.9)
Diagnosis	Hematologic malignancy	40 (49%)
	Inborn errors of immunity	16 (20%)
	Bone marrow failure	10 (12%)
	Other	15 (19%)
Second line therapy	Mesenchymal stromal cells	39 (48%)
	Infliximab/Etanercept	27 (33%)
	Basiliximab	4 (4.9%)
	Combination therapy	11 (14%)

Figure 1. Clinical course after start of second line therapy

Conclusions: Our study demonstrates that SR-GvHD confers a high mortality risk in pediatric HSCT. Older age and use of CB grafts are associated with an unfavorable outcome. Novel treatment strategies to prevent SR-GvHD and timely initiation of second line interventions are pivotal to further reduce GvHD-related mortality.

Disclosure: Nothing to declare

P167

Ruxolitinib as an effective and steroid-sparing first-line treatment in newly-diagnosed bos patients after hematopoietic stem cell transplantation

X. Zhang[1], X. Zhao[1], S. Zhang[1], C. Liang[1], L. Zhang[1], M. Hao[1], J. Wei[1], R. Zhang[1], S. Feng[1], Y. He[1], E. Jiang[1], M. Han[1]

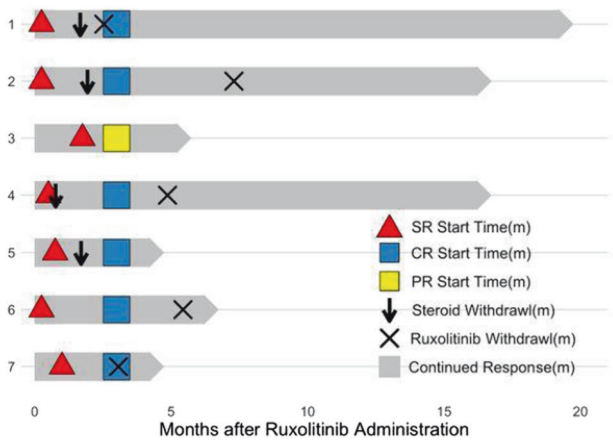
[1]Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China

Background: Bronchiolitis obliterans syndrome (BOS) is a life-threatening pulmonary complication of chronic graft versus host disease (cGVHD) after allogeneic hematopoietic stem cell transplantation (HSCT). The classic first-line therapy of BOS is systemic steroids to prevent progression. However, patients with steroid-refractory BOS did not get a significant improvement in pulmonary function. Furthermore, long-term systemic steroids usage may cause serious complications such as infection. In this study, we retrospectively investigated the outcome of ruxolitinib as first-line therapy in treating newly-diagnosed BOS patients.

Methods: All patients who underwent an allogeneic HSCT for a hematological malignancy between January 2019 and June 2021 at the Institute of Hematology and Blood Diseases Hospital, CAMS and PUMC were retrospectively screened. BOS diagnosis uses the criteria of the National Institute of Health (NIH) consensus. Ruxolitinib therapy was begun with an initial dosage of 5 mg twice daily (BID), then a maintenance dosage of 10 mg. The dose of ruxolitinib could be reduced if severe adverse events occurred. Steroids and other immune-suppression agents were added according to the clinical situation. All patients received anti-fungus prophylaxis and FAM therapy in addition to the ruxolitinib therapy. Treatment response included both symptoms response (SR) and disease responses (DR). Symptom response (SR), which was evaluated in the first two weeks after ruxolitinib administration, was defined as relieving respiratory symptoms, elevated

peripheral blood oxygen saturation ($SpO_2 \geq 96\%$), and significant improvements in CT scans. We evaluated ruxolitinib disease response (DR) in the 3rd month. The ruxolitinib administration to DR was defined as CR (Complete Response) when clinical symptoms significantly alleviated and FEV1% pred (FEV 1% prediction) increased by more than 75%; partial response (PR) was defined by FEV1% pred levels increased or symptoms improved with stabilization of FEV1% pred. Nonresponse (NR) was defined by worsened clinical status and PFTs, or FEV1% pred decreased to less than 5% with stable symptoms.

Results:



We identified seven BOS patients. A median time of 300 days (ranged from 103 to 489 days) elapsed between the time of HSCT and diagnosis of BOS. Five patients were treated with steroids at the same time. The average initial daily dose of methylprednisolone was 48.4 milligrams per day (ranged from 6–80 milligrams). It is inspiring that all patients achieved SR within only two weeks after ruxolitinib therapy. Concerning disease response, six patients (85.7%) achieved CR, and one (14.3%) achieved PR (Figure 1). The mean FEV1% pred at diagnosis of BOS was 58.05%, and increased to 79.47% three months after ruxolitinib therapy, suggesting the therapy was effective. At the same time, the steroid dose was reduced to 50% of the initial dose in about two weeks (ranged from 7 to 16 days) and ended within two months of ruxolitinib treatment (ranging from 23 to 58 days).

Conclusions: All patients taking ruxolitinib as first-line therapy achieved remarkable responses with a CR rate of 85.7%. It is also noteworthy that ruxolitinib as first-line therapy in BOS could significantly shorten steroid therapy duration and reduce total steroid dose. Additionally, ruxolitinib was well tolerated, no severe infection or relapse was reported.

Disclosure: The authors declare no conflicts of interest.

P168

Impact of timing of cyclosporine-a administration in graft-versus-host-disease and patient outcomes in haploidentical hematopoietic stem cell transplantation

A. Banet[1,2], N. Stocker[1,2], F. Malard[1,2], M. Labopin[1,2], E. Brissot[1,2], Z. Van de Wyngaert[1,2], V. Radici[1], A. Bonnin[1], M. Memoli[1], A. Genthon[1,2], O. Legrand[1,2], T. Leedra[1], R. Belhocine[1], S. Sestili[1], M. Mohty[1,2], R. Duléry[1,2]

[1]APHP, Hôpital Saint-Antoine, Service d'Hématologie Clinique et de Thérapie Cellulaire, Paris, France, [2]Sorbonne Université, INSERM UMR 938, Centre de Recherche Saint-Antoine (CRSA), Paris, France

Background: In a haploidentical setting, graft-versus-host disease (GVHD) prophylaxis is now widely based on the combination of post-transplantation cyclophosphamide (PTCY), cyclosporine-A (CsA), and mycophenolate mofetil (MMF). It has been shown that high concentration of CsA in the first week after haploidentical hematopoietic cell transplantation (HCT) is associated with a reduced incidence of acute GVHD. However, the optimal timing of CsA initiation remains controversial. We performed a single-center retrospective study comparing the incidence of GVHD and patient outcomes after haploidentical HCT according to the timing of CsA initiation.

Methods: All consecutive adult patients undergoing haploidentical HCT from November 2013 to December 2020 were included according to the following criteria: (1) peripheral blood stem cell graft, (2) hematological malignancy, and (3) thiotepa-based conditioning regimen with a total thiotepa dose of 5 mg/kg. GVHD prophylaxis consisted of a combination of CsA, MMF, anti-thymocyte globulin (ATG, 2.5 to 5 mg/kg) and PTCY in all patients. CsA was either initiated at day − 3 before HCT (group 1, from November 2013 until July 2017) or the day after last administration of PTCY (group 2, from August 2017 until December 2020).

Results: The study included 131 patients (57 in group 1, 74 in group 2). The median age was 58 years (range, 15-74) and 78 (60%) patients were male. Patients in group 1 were younger (median age 53 versus 60 years, $p = 0.007$) and received a graft with a lower number of CD34 + cells ($5.5x10^6$/kg versus $7.2x10^6$/kg, $p = 0.015$). The sequential conditioning regimen was the most used in group 1 (52.6%), whereas a reduced intensity conditioning was the most used in group 2 (47.3%) ($p = 0.042$). One hundred and twenty-six patients (96%) engrafted, with a median time for neutrophil recovery of 18 days (range, 9-30) in group 1 versus 17 days (range, 13-55) in group 2 ($p = 0.016$). At day + 180 after HCT, there was no difference in terms of incidence of grade II-IV acute GVHD (21% in group 1, 22% in group 2, $p = 0.83$) or grade III-IV acute GVHD (11% in group 1, 7% in group 2, $p = 0.29$) between the two groups. At 2 years, the incidence of chronic GVHD was also similar in both groups (32% in group 1, 21% in group 2, $p = 0.21$). With a median follow-up of 49 months (95% CI 48-59) for group 1 and 19 months (95% CI 15-27) for group 2, non-relapse mortality was 23% and 17%, relapse incidence 23% and 15 %, disease-free survival 56 % and 68%, overall survival 67% and 76%, GVHD-free, relapse-free survival 32% and 47% at 2 years in group 1 and group 2, respectively (p values are non-significant). In multivariable analysis, the timing of CsA initiation had no significant impact on survival outcomes and on the risk of acute or chronic GVHD.

Conclusions: These results suggest that in haploidentical HCT with peripheral blood stem cells, and GVHD prophylaxis combining CsA, MMF, ATG and PTCY, CsA can be initiated either at day-3 before HCT or the day after the last administration of PTCY, without impacting the risk of GVHD or survival outcomes.

Disclosure: nothing to declare

P169

Early results of phase i study of shr0302, a selective jak1 inhibitor, combined with prednisone in first-line treatment of cgvhd after allo-hsct

H. Qiu[1], J. Niu[1], X. Sun[1], H. Li[2], J. Yang[1], C. Huang[1], Y. Cai[1], K. Zhou[1], Y. Tong[1], L. Wan[1], X. Song[1]

[1]Shanghai General Hospital, Shanghai, China, [2]Jiangsu Hengrui pharmaceuticals Co., Ltd., Shanghai, China

Background: Chronic graft-versus-host-disease (cGVHD) is one of the major complications after allogeneic hematopoietic stem cell

transplantation (allo-HSCT) with an incidence of 40% to 70%. cGVHD is also the common cause of late non-relapse-related death in patients undergoing allo-HSCT, and seriously affects their quality of life. SHR0302 is a Janus kinase (JAK) 1 selective inhibitor that has demonstrated efficacy in preclinical models of GVHD. Herein, we reported the safety and efficacy of SHR0302 in combination with prednisone as first-line therapy for newly diagnosed cGVHD after allo-HSCT.

Methods: This was a single-center, open-label, and phase I study. The study enrolled patients who had a confirmed diagnosis of first-episode moderate/severe cGVHD requiring systemic immunosuppressive therapy after allo-HSCT with an age limitation of 18-70. cGVHD was defined according to national institutes of health (NIH) criteria. Patients were treated with SHR0302 plus prednisone daily. For every patient, prednisone was administered at an initial dose of 1 mg/kg/d, and was tapered according to patient's response after two weeks of treatment. Dose-escalation of SHR0302 was performed in a 3 + 3 design at doses of 1 mg/d, 2 mg/d, 4 mg/d, 6 mg/d, and 8 mg/d. Primary endpoints are safety and tolerability of SHR0302 and prednisone. Secondary endpoints include the overall response rate (ORR) at week 4 of treatment and the recommended Phase II dose (RP2D). Dose-limiting toxicities (DLTs) were defined as grade 4 hematologic toxicity or grade 3 non-hematologic toxicity related to SHR0302 that occurred in the first 28 days of study treatment.

Results: As of December 1st, 2021, 15 patients were enrolled in 5 dose levels with 3 patients in every dose level. The median age was 48 (31-64) years, and the median follow-up was 17 (4 -59) weeks. 5 patients (33%) had moderate cGVHD, 10 patients (67%) had severe cGVHD, and the median cGVHD NIH score was 4 (3-7). As of data cutoff, only 1 patient (7%) had discontinued therapy due to lack of efficacy.

Only one DLT, grade 4 hypercholesterolemia, was observed among 3 patients who received 8 mg/d of SHR0302. The patient who experienced DLT had preexisting hypercholesterolemia. 3 additional patients would be enrolled to receive 8 mg/d of SHR0302 plus prednisone to determine the maximum tolerated dose. 14 patients experienced adverse events (AEs) related to SHR0302 (93%), and 2 patients experienced grade ≥3 AEs related to SHR0302 (13%). The most common SHR0302-related AEs included hypercholesterolemia (67%), hypertriglyceridemia (33%) and platelet count decreased (27%). No SHR0302-related serious adverse event occurred.

At 4 weeks after being treated with SHR0302 and prednisone, 3 patients (20%) achieved complete response, and 11 patients (73%) achieved partial response among 15 evaluable patients. The ORR at week 4 was 93%, just 1 patient showed no response to treatment.

Conclusions: In summary, SHR0302 plus prednisone was well tolerated and demonstrated encouraging efficacy in patients with steroid-naive cGVHD, warranting continued clinical investigations.

Clinical Trial Registry: NCT04146207

Disclosure: Nothing to declare.

P171

Clinical and economic burden associated with graft-versus-host disease (GVHD) following allogeneic hematopoietic cell transplantation (allo-hsct) in france

D. Michonneau[1], N. Quignot[2], H. Jiang[2], D. Reichenbach[3], M. Kelly[4], A. Burrell[5], X. Zhang[3], K. Thiruvillakkat[3], M. Mohty[6]

[1]Hospital Saint-Louis, Paris, France, [2]Certara France, Paris, France, [3]CSL Behring, King of Prussia, United States, [4]CSL Behring, West Sussex, United Kingdom, [5]Anita Burrell Consulting, Flemington, United States, [6]Hospital Saint-Antoine, Paris, France

Background: There is a need for new therapies to prevent and treat GvHD following allo-HSCT; however, contemporary evidence on the burden of the disease in France is not available. This study aimed to investigate the clinical outcomes, healthcare resource utilization (HCRU), and costs associated with GvHD in France, by type – acute (aGvHD), chronic (cGvHD), or both (a + cGvHD).

Methods: A nationwide cohort study using administrative claims from the French Health Insurance database, SNDS, identified 6385 adult patients who received allo-HSCT for hematologic malignancies between January 2012 and December 2018. Relapse was explored using re-admission diagnoses and treatments. Propensity score matching was undertaken to compare patients who developed GvHD (by type) vs patients who did not develop GvHD ('noGvHD') for occurrence of severe infection during follow-up (defined using hospital discharge diagnosis codes), all-cause death, HCRU, and costs.

Results: The mean age of the cohort was 51.1 years; 58% were male; 2668 (42%) patients had no recorded diagnosis code for GvHD, 2002 (31%) experienced an aGvHD episode, 411 (7%) had cGvHD, and 1304 (20%) had a+cGvHD. Patients with GvHD had slightly lower rates of relapse, with 276 (14%), 61 (15%), and 220 (17%) patients with evidence of relapse in the aGvHD, cGvHD and a +cGvHD subgroups, respectively, vs 486 (18%) patients in the noGvHD subgroup. For comparisons, 1934, 408, and 1268 matched pairs were retained for the aGvHD, cGvHD and a+cGvHD subgroups, respectively. Patients with aGvHD and a+cGvHD had an increased rate of hospitalization for severe infection, with a rate ratio (RR) (95% CI) of 1.32 (1.23-1.41) and 1.14 (1.05-1.24), respectively vs noGvHD; rate of severe infection was similar for patients with cGvHD vs without GvHD. Patients with aGvHD had an increased mortality rate, (RR [95% CI], 1.55 [1.41-1.70] vs noGvHD); mortality rate was slightly higher (although not statistically significant) for a+cGvHD vs noGvHD and similar between patients with cGvHD and those without GvHD. Patients with aGvHD and a +cGvHD had significantly more overnight hospitalizations per patient-year (mean rates: 4.3 vs 3.3 and 4.2 vs 3.2 admissions, respectively; $p < 0.001$) than those without GvHD. Total direct costs (including hospitalizations, outpatient visits, drugs dispensed) were 1.18, 1.53, and 1.89 times higher ($p < 0.001$) for patients with aGvHD, cGvHD, and a+cGvHD, respectively, vs noGvHD. Inpatient care (including drugs dispensed during hospitalization) cost was the primary driver of increased HCRU and costs.

Conclusions: GvHD was associated with significant clinical and economic burden post-allo-HSCT. Patients with GvHD, and in particular, patients with aGvHD and a+cGvHD, had a higher rate of infection and higher mortality. This clinical burden translated into increased HCRU and costs, with patients with aGvHD, cGvHD, and a+cGvHD having a statistically significant higher total direct cost vs noGvHD patients. There is a continued need for effective prophylaxis and treatment options for GvHD, which could prevent clinical burden for patients, as well as the increased cost of allo-HSCT due to GvHD.

Disclosure: David Michonneau reports consultancy for Novartis and Incyte, and honoraria from Jazz Pharmaceuticals.

Nadia Quignot reports consulting fees paid to Certara contracted with CSL for implementing the analyses.

Heng Jiang reports consulting fees paid to Certara contracted with CSL for implementing the analyses, and stock ownership from Certara.

Dawn Reichenbach reports employment and stock options from CSL Behring.

Maebh Kelly reports employment from CSL Behring.

Anita Burrell reports consultancy for CSL Behring and Neumentum

Xiang Zhang reports employment from CSL Behring.

Kris Thiruvillakkat reports employment, stock options and salary from CSL Behring.

Mohamad Mohty reports honoraria from Adaptive Biotechnologies, Amgen, Astellas, BMS, Celgene, Gilead, GSK, Janssen, Novartis, Oncopeptides, Pfizer, Sanofi, and Takeda; and research funding from Celgene, Janssen, and Sanofi.

P173

Incidence and risk factors for hyponatremia induced by post-transplant cyclophosphamide in allogeneic hematopoietic cell transplantation

M. Gómez Hernando[1], A. Pedraza[1], L. Quintana[2], E. Carcelero[3], G. Riu[3], I. Monge[3], A. Domenech[1], M.T. Solano[1], M. Suárez-Lledo[1], N. Martinez-Cibrian[1], L. Rosiñol[1], G. Gutiérrez-Garcia[1], E. Carreras[4], J. Esteve[1], A. Urbano-Ispizua[1], F. Fernández Avilés[1], C. Martínez[1], M. Rovira[1], M.Q. Salas[1]

[1]*Institute of Hematology and Oncology, Hospital Clinic de Barcelona, IDIBAPS, Barcelona, Spain,* [2]*Institute of Nephrology and Urology, Hospital Clinic de Barcelona, IDIBAPS, Barcelona, Spain,* [3]*Pharmacology Unit, Hospital Clinic de Barcelona, IDIBAPS, Barcelona, Spain,* [4]*Fundació Josep Carreras, Barcelona, Spain*

Background: The use of post-transplant cyclophosphamide (PTCY) is becoming prevalent in alloHCT due to it efficacy for GVHD prevention. Intravenous cyclophosphamide-associated hyponatremia is an uncommon adverse effect attributed to an indirect inappropriate antidiuretic hormone release followed with a reduction in the ability of the kidney to excrete water. This study investigates the incidence and risk factors for hyponatremia in adults undergoing PTCY-based alloHCT.

Methods: Between January 2018 and December 2020, 90 adults with hematological disorders underwent first alloHCT combined with PTCY-based GVHD prophylaxis at our Institution. Intravenous PTCY was administered at a dose of 50 mg/kg/day IV on day +3 and +4 at 9 am and followed by tacrolimus from day +5, alone; for matched related and unrelated donor alloHCT (n = 79, 87.8%), and combined with tacrolimus and mycophenolate when haploidentical donors were selected (n = 11, 12.2%). Patients received intravenous fluid therapy with glucosaline 5% 1L/8h and bicarbonate 1/6M 500ml/12h from day +2 to +4. Following our standard Institutional protocols, sodium level was routinely monitored two hours before and 12 hours after every dose of cyclophosphamide.

Hyponatremia was defined as plasma sodium levels < 135 mEq/L), and severe hyponatremia was defined as plasma sodium levels < 125 mEq/L). Data was collected retrospectively and updated in November 2021. Risk factors for hyponatremia were explored using Regression Logistics Models.

Results: Overall, the median age was 51 years, 40 (44.4%) patients were females, and 49 (54.4%) underwent MAC alloHCT. Hyponatremia was diagnosed in 80% of patients, and in 5.6% of the cases was severe. The majority of episodes were diagnosed 12h after the first dose of cyclophosphamide (73.3%). Four patients (4.4%) had symptomatic hyponatremia, and in all these cases the sodium levels were inferior to 125 mEq/L.

Forty-one (45.6%) patients required specific treatment: all were started on oral sodium supplementation or fluid therapy with glucosaline 5% was replaced by normal saline. Hypertonic serum supplementation was given for symptomatic severe hyponatremia. The second dose of PTCY had to be reduced to 40 mg/kg in 1 patient and delayed in an additional one. Out of the overall 72 patients presenting with hyponatremia following PTCY, 57 (79.2%) successfully recovered in a median of 2 days from diagnosis. Hyponatremia did not result in non-reversible sequelae in any patient. Higher doses of cyclophosphamide (>5000mg and >7000 mg) were not associated with higher rates of hyponatremia (p = 0.32 and p = 0.346, respectively). Patient's age (>60 years) (p = 0.205), sex (p = 0.0.601) and the conditioning regimen intensity (p = 0.249) were not found to be predictors for hyponatremia.

Conclusions: This study reports for the first time the incidence of hyponatremia after PTCY administered for GVHD prevention. Hyponatremia was found to be a prevalent adverse effect after PTCY infusion, although the incidence of symptomatic hyponatremia was low.

Based on these results, sodium levels after PTCY infusion should be carefully monitored, and hyperhydration using intravenous normal saline may be prioritized to decrease the rates of this complication.

Disclosure: No conflict of interest to disclose.

P174

Host versus graft HLA-dpb1 mismatches promote clinical graft versus host disease

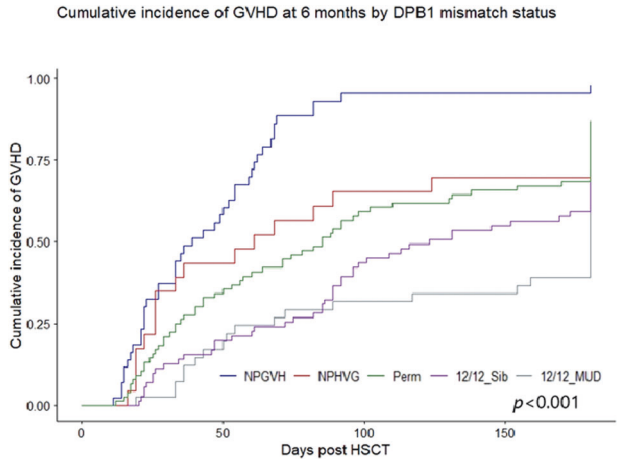
C. Wright[1], G. Reid[1], C. Lendrem[1], L. Duncan[2], R. Luke[2], E. Hurst[2], A. Publicover[1], V. Bigley[1], M. Collin[1]

[1]*Newcastle University, Newcastle upon Tyne, United Kingdom,* [2]*Northern Centre for Bone Marrow Transplantation, Newcastle upon Tyne, United Kingdom*

Background: HLA matching is crucial to donor selection in allo-HSCT. HLA-DPB1 mismatches between donor and recipient are known to increase GVHD and can be unidirectional in the Graft-versus-Host or Host-versus-Graft direction. Recent data highlight the potential of host resident T-cells to cause cutaneous inflammation in xenograft models. In this study we sought to determine whether unidirectional HVG mismatches could cause clinical manifestations of GVHD.

Methods: 183 patients transplanted at a single UK centre between 2013 and 2018 with 10/10 matched unrelated donor (MUD) PBSC transplants for malignant and non-malignant conditions were retrospectively scored for DP mismatch permissivity and directionality using the T-cell epitope (TCE) algorithm (https://www.ebi.ac.uk/ipd/imgt/hla/dpb.html), and compared with 71 12/12 sibling donor transplants (Sib) for onset of any acute-type GVHD within 6 months of transplant including classic acute, late onset and acute/chronic overlap. Conditioning regimens included MAC (n = 4), RIC (n = 175), Kroger (n = 15), FLAMSA (n = 38) and Seattle (n = 22) protocols. T cell depletion strategies included alemtuzumab (n = 180), ATG (n = 48) and T-replete (n = 26). Cumulative incidence of GVHD by DP mismatch status was adjusted for death from any cause as a competing risk. A multivariate regression was performed controlling for age, diagnosis, T-cell depletion, conditioning protocol and CMV status.

Results: With death from any cause as a competing risk, there was a significant difference in GVHD incidence according to DP mismatch group ($p < 0.001$) (Figure). Multivariable hazard ratios were calculated demonstrating 12/12 MUD and 12/12 sibling transplants had the lowest GVHD incidence, then permissive DP mismatch, then non-permissive HVG with the highest incidence of GVHD in the non-permissive GVH group (Table). 12/12 MUD transplants demonstrated no significant increase in GVHD incidence compared to 12/12 sibling transplants. 6 month overall survival was adverse for HVG HLA-DPB1 mismatches compared to the other groups ($p < 0.05$). The only co-variate predicting GVHD by multivariate competing risks regression was the permissivity and directionality of DP mismatch ($p = 3.2 \times 10^{-9}$), with age, diagnosis, T-cell depletion, conditioning protocol and CMV risk group failing to reach significance. The maximal grade of GVHD reached in the HVG group was grade I in 40% and grade II in 60%, with no grade III or above GVHD in the HVG group.



DP mismatch status	Multivariable Hazard Ratio GVHD (95%CI)	p
12/12 MUD (n = 41)	Reference	NA
12/12 Sib (n = 71)	1.53 (0.85-2.8)	0.16
Permissive (n = 76)	2.42 (1.36-4.3)	<0.01
Non-permissive HVG (n = 23)	3.88 (1.88-8.0)	<0.001
Non permissive GVH (n = 43)	6.41 (3.52-11.7)	<0.001

Conclusions: These data show that DP mismatching is the major cause of excess GVHD in patients receiving unrelated donor transplants in this cohort with mostly T-depleted transplant regimens. The surprising observation that HVG DPB1 mismatches are associated with a higher risk of GVHD supports recent findings that host resident T-cells may play a role in GVHD pathogenesis. The role of HVG reactions in the pathogenesis of GVHD or as a separate entity which is indistinguishable from clinical GVHD, requires further elucidation.

Disclosure: Nothing to declare

P176

The use of vedolizumab as second-line therapy for steroid-refractory gastrointestinal acute graft-versus host disease in children

G. Bronin[1], M. Zhuravel[1], A. Lifshits[1], G. Seregin[1], E. Zhuravel[1], B. Kurmanov[1], I. Taishikhina[1], E. Burtsev[1], E. Kumirova[1], M. Maschan[1,2]

[1]Morozov Children's Hospital, Moscow, Russian Federation, [2]Dmitriy Rogachev National Medical Researh Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation

Background: The gastrointestinal (GI) graft-versus host disease (GVHD) remains to be challenging and life-threatening complication of hematopoietic stem cell transplantation (HSCT) in children. Steroid based treatment of this condition remains a universal standard first-line therapy. Despite authorization of new agents for second-line therapy, steroid refractory GI GVHD awaits safer and more effective therapeutic approach.

Methods: Clinical and laboratory data from 9 children (5 boys and 4 girls) aged from 1 to 17 years treated with anti-α4β7 integrin monoclonal antibody (vedolizumab) for severe (grade 3-4) steroid-refractory GI GVHD were analyzed. The diagnosis of GVHD was proven by biopsy in all cases. The patients and their parents gave informed consent for the off-label use of the medication and publication of the results.

Results: The indications for HSCT were acute lymphoblastic leukemia (ALL) in 3 cases, acute myeloid leukemia in 4 cases, Diamond–Blackfan anemia (DBA) in 1 case and metachromatic leukodystrophy (MLD) in 1 case. HSCT from haploidentical family donors (haplo) were performed in all 7 cases of leukemia and HSCT from matched unrelated donor (MUD) were performed in DBA and MLD cases. Source of HSC were PBSC in cases of haplo and BM in cases of MUD. In all cases posttransplant cyclophosphamide (PtCy) on days+3, +4 at 50 mg/m^2/day, CNI and MMF with unmanipulated HSCs was used as GVHD prevention approach. Grade III-IV GI GVHD occurred between day +25 to day +320 (median time day +100). In 5 cases we used vedolizumab as a third line therapy after unsuccessful treatment with methylprednisone and ruxolitinib, and in 4 cases we started vedolizumab as a fourth line therapy (after methylprednisone, ruxolitinib and tumor necrosis factor inhibitors). Median time of start of vedolizumab therapy was 14 days after manifestation of GI GVHD. In all cases we continued ruxolitinib course and performed withdrawal of steroids with slow gradual dose reduction during vedolizumab treatment. In 2 cases we combined the course of anti-α4β7 integrin antibodies and extracorporeal photopheresis. We use vedolizumab as intravenous infusion 6 mg/kg and repeated this dose weekly until resolution of GI GVHD symptoms. The number of injections varied from 1 to 4. Four patients received 2 injections, 3 patients -3, 1 patient – 1 and 1 – 4 injections. The median time of response was 33 days after start of vedolizumab treatment. Eight patients survived with complete resolution of GI GVHD symptoms. Six of them during vedolizumab treatment and two demanded additional lines of immunosuppressive drugs after discontinuation of vedolizumab. One patient died from GI GVHD associated complications. We did not see any significant side effects of vedolizumab in any case, but it was quite difficult to assess in this heavily pretreated group of patients.

Conclusions: Targeted approach to the treatment of steroid-refractory grade 3-4 GI GVHD with the use of anti-α4β7 integrin monoclonal antibody (vedolizumab) can be promising curative option in pediatric HSCT patients. Further prospective evaluation of this approach is clearly warranted.

Disclosure: Nothing to declare

P177

Predictive value of st2, reg3a and magic algorithm in survival and complications related to haploidentical transplantation with post-trasplant cyclophosphamide: Single center experience

M. Fonseca Santos[1], M. Garcia Alvarez[1,2], L.A. Corchete Sanchez[1,2], M. Salinero[1], A. Rodriguez Rodriguez[1], D. Alonso Castronuño[1], E. Alejo Alonso[1], J.M. Navarro Garcia[1], A. Hernandez Sanchez[1], A.A. Martin[1], A. Avendaño Pita[1], M. Baile Gonzalez[1], A. Cabero Martinez[1], E. Perez Lopez[1], M. Cabrero Calvo[1], R. Garcia-Sanz[1], F. Sanchez-Guijo Martin[2,1], L. Vazquez Lopez[1], M.D. Caballero Barrigon[1,2], M. Alcoceba[2,1], L. Lopez Corral[2,1]

[1]Hospital Universitario de Salamanca, Salamanca, Spain, [2]CIBER-ONC, Madrid, Spain

Background: Recent studies describe protein biomarkers in peripheral blood associated to allogeneic-stem-cell transplantation (allo-SCT) outcomes. To date, two studies have focused on haploidentical allo-SCT with post-transplant cyclophosphamide (haplo-SCT). These works evaluate two and seven biomarkers - including ST2 and REG3α- in limited time-points (days + 15 and +30) but do not include the analysis of the MAGIC algorithm, validated with the combination of these 2 biomarkers as a predictor of higher Non Relapse Mortality (NRM).

We are analysing ST2, REG3a and MAGIC algorithm early weekly after haplo-SCT and its association with Graft-versus-host disease (GVHD) and transplant outcomes.

Methods: Prospective study with 151 consecutive patients who underwent haplo-SCT at University Hospital of Salamanca (2012-2020). The panel was analysed in serial serum samples collected on days 0, +3, +7, +14 and +21 in 81 patients.

ST2 and REG3α serum concentration was established by Lumynex X-MAP, comparing the median luminescence levels between groups using Wilcoxon-Mann-Whitney test. Cut-off points for each cytokine were estimated using Cutoff-Finder application in R. MAGIC algorithm was determined from the ST2 and REG3α values considering a threshold of =0.16. Log-rank was used to compare survival curves. Multivariable analyses were carried out with Cox regression, including the most significant clinical variables.

Results: Patients' and transplant characteristics are shown in table 1:

Characteristics	n (%)
Recipient/donor age; median (range)	50 (16-73)/39 (14-75)
Recipient/donor male sex	85 (56)/85 (56)
Male receptor/Female donor	37 (24)
Hematological disease	
AML / MDS	63 (42)/19 (13)
HL / NHL	22 (15)/24 (16)
ALL	9 (6)
CMML	5 (3)
Others	4 (5)
Previous treatments ≥2	93 (61)
Previous autologous transplantation	35 (23)
Previous allogenic transplantation	13 (8)
Disease risk index ≥ high and very high	27 (18)
Sorror, n (%) ≥3	44 (29)
Conditioning	
Myeloablative	35 (23)
Flu (150mg/m^2) + Bu (9,6mg/Kg) + Thio (10mg/Kg)	29 (19)
Flu(150mg/m2)+Bu (9,6 mg/kg) + Cy(29mg/kg)	6 (4)
Reduced intensity	112 (73)
Flu (150 mg/m^2) + Bu (3,2 ó 6,4mg/Kg) + Cy (29mg/Kg)	99 (65)
Flu (150 mg/m^2) + TBI (2Gy) + Cy (29 mg/kg)	5 (3)
Flu(150mg/m2)+Bu(6,4mg/kg)+Thio(10mg/kg)	8 (5)
Sequential	5 (4)
GVHD prophylaxis	
Tacro + MMF + Cy	148 (98)
CsA + MMF + Cy	3 (2)
CD34 + x10^8 infused dose, median (range)	6,26 (2.59-9,34)
Graft source: Peripheral blood	148 (98)
Median follow up months, n (range)	35 (9-87)
Overall Survival (OS) 2 years	66%
PFS 2 years	60%
NRM day 100 / 1 year	14% / 24%
Cumulative incidence of aGVHD II-IV day 180	57%
Cumulative incidence of aGVHD III-IV day 180	13%
GRFS (Graft versus host-free relapse-free survival) 2 years	49%

Table 1. Patients' and transplant characteristics

Higher levels of ST2 were associated with aGVHD (II-IV day +21, III-IV day +14), higher NRM 1-year (+0, +7, +14), lower OS 2-years (+7, +14) and GRFS 2-years (+14, +21). Higher levels of REG3α were associated with aGVHD III-IV (+ 14), higher NRM 1-year (0, 7, 14, 21), lower OS 2-years (0, +7, +14, +21) and lower GRFS-2y (+14). Similarly, the inclusion of MAGIC algorithm in multivariate analysis, distinguished two statistically significant risk groups for GRFS (+ 14), OS (0, +14) and NRM 1-year (0, +14) (Image 1). OS was independently associated with HCT-CI ≥ 3, ST2 (0, +7, 14, +21) and REG3α (0, +14, +21) levels, NRM with ST2 (0, +14), REG3α (14) levels and HCT-CI ≥ 3. ST2 (+ 7, +14, +21) REG3α (+14) levels and HCT-CI ≥ 3 were the only variables independently associated to GRFS.

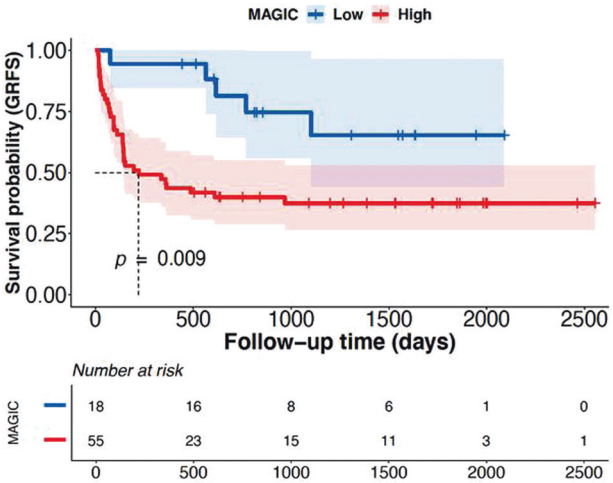


Image 1. GRFS according to MAGIC risk stratification at day 14

Multivariate analysis with the MAGIC algorithm revealed and independent association to GRFS (+14) and OS (0, +14) together with HCT-CI ≥ 3.

Conclusions: These results confirm the prognostic role of ST2, REG3α and MAGIC algorithm in haplo-SCT outcomes in the largest single-centre cohort to date of a homogeneous series of haplo-SCT. We also demonstrate, for the first time, the MAGIC algorithm prognostic impact in haplo-SCT on day +14.

Standarization in prospective and larger series is required before its incorporation into the clinical practice.

Disclosure: Nothing to declare

P178

Pancreatic atrophy and recovery after allogeneic hematopoietic cell transplantation: Predictive factors and prognosis

Y. Okada[1], H. Nakasone[1], Y. Nakamura[1], M. Kawamura[1], S. Kawamura[1], J. Takeshita[1], N. Yoshino[1], Y. Misaki[1], K. Yoshimura[1], S. Matsumi[1], A. Gomyo[1], A. Tanihara[1], M. Tamaki[1], M. Kusuda[1], K. Kameda[1], S.-i. Kimura[1], S. Kako[1], Y. Kanda[1]

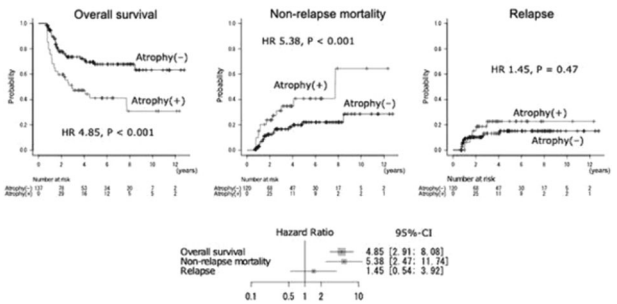
[1]Jichi Medical University Saitama Medical Center, Saitama, Japan

Background: Pancreatic atrophy after allogeneic hematopoietic cell transplantation (HCT) is one of symptoms associated with chronic graft-versus-host disease (GVHD). Although pancreatic atrophy has been considered to cause exocrine insufficiency and weight loss, it remains to be elucidated what kind of recipients could recover their body weight (BW) or pancreatic thickness. In

addition, the prognostic effect of pancreatic atrophy has not been clarified.

Methods: We retrospectively analyzed 171 recipients who received allogeneic bone marrow transplantation or peripheral blood stem cell transplantation at Jichi Medical University Saitama Medical Center between January 2008 and December 2018. The measurement of pancreas was performed every year after their transplantation if the recipients received CT scan. Pancreatic thickness was defined as a sum of the widths which were perpendicular lines to the long axis of pancreas in the following three regions of pancreas: the head, body, and tail of pancreas. We evaluated them using the closest CT scan images to the time-points of 1, 2, 3, and 4 years after HCT. Pancreatic atrophy was defined as 20% or more loss of thickness.

Results: Fifty-five recipients demonstrated pancreatic atrophy after HCT. While the BW of the recipients without pancreatic atrophy recovered gradually ($P < 0.001$), those with atrophy did not show that trend ($P = 0.12$) by linear mixed models. The 3-year simple cumulative incidence of pancreatic atrophy was 31.3%, while the 3-year current cumulative incidence of pancreatic atrophy, treating pancreatic atrophy as a reversible event, was 15.9%. Moderate and severe chronic GVHD tended to be slightly higher in the atrophy group (47.3% vs 37.9%), whereas these recipients tended to show the recovery of pancreatic thickness (30.8% vs 10.3%). HCT from female donor to male recipient showed superior pancreatic recovery than other donor and recipient sex combination. Although their pancreatic thickness seemed comparable between the recipients who continued and stopped immunosuppressant (IST) at one year ($P = 0.87$) and 2 years ($P = 0.11$) after HCT, that tended to decrease at 3 years ($P = 0.064$), and finally, the difference became significant at 4 years ($P = 0.027$).Pancreatic atrophy treated as a time-dependent covariate was significantly associated with inferior overall survival (OS) (HR 4.85, $P < 0.001$) and an increased risk of non-relapse mortality (NRM) (HR 5.38, $P < 0.001$), while it was not associated with disease relapse (HR 1.45, $P = 0.47$).



Conclusions: The recipients with pancreatic atrophy did not tend to recover their BW after HCT, and those who could stop IST demonstrated the recovery of pancreatic thickness. Moderate and severe chronic GVHD was associated with both pancreatic atrophy and recovery, which indicated that pancreatic atrophy might be mainly developed as a manifestation of chronic GVHD and could be reversible if the allogeneic response was controlled. Moreover, pancreatic atrophy was significantly associated with an increased risk of NRM, leading to inferior OS. These results suggest the importance of monitoring pancreatic thickness after HCT. Further prospective investigations are warranted to clarify the significance of pancreatic atrophy on clinical outcomes.

Disclosure: Nothing to declare.

P179

Safety of home care in patients with previous autologous stem cell transplant pursuing allogeneic stem cell transplantation

M. Garcia-Recio[1], A.C. Pedraza[1], C. Jimenez-Vicente[1], A. Martinez-Roca[1], C. Gallego[1], P. Ayora[1], T. Solano[1], M. Suárez-Lledó[1], L.G. Rodriguez-Lobato[1,2], C. Martínez[1], L. Rosiñol[1], M.Q. Salas[1], M. Rovira[1], G. Gutierrez-García[1], F. Fernandez-Avilés[1]

[1]Hospital Clinic of Barcelona, Barcelona, Spain, [2]Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain

Background: Home care has been associated with fewer infections, decreased acute GVHD, TRM, and improved survival in patients receiving allogeneic SCT (allo-SCT) (Gutiérrez-García et al., 2020; Svahn et al., 2008). The effect of previous autologous SCT (ASCT) on those advantages is unknown. We analyzed outcomes of home-cared allo-SCT patients with prior ASCT.

Methods: Since 2015, consecutive adult patients with hematological malignancies undergoing at-home allo-SCT with prior ASCT were included and classified considering GVHD prophylaxis: post-transplant cyclophosphamide (PTCy) (group 1) or tacrolimus plus mofetil mycophenolate (TK/MMF) (group 2). Groups 3 and 4 included matched hospitalized patients to groups 1 and 2, respectively.

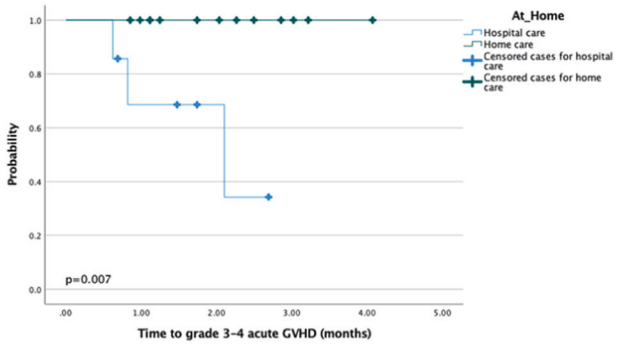
Results: Since 2015, 56 patients pursued home-cared allo-SCT in our center and, of those, 15 had previously received an ASCT. Baseline characteristics were comparable between home-cared and the respective matched hospitalized series (table 1). Median follow-up was 1.4 years (0.6-3.3). Similar mucositis, renal failure, and haemorrhagic cystitis incidence and grade distribution were observed across the 4 groups. Home care did not provide benefit in neutropenic fever, pathogen detection, multidrug-resistant microorganisms, aspergillosis, or viral reactivation. Similar time to engraftment and length of stay were observed between matched at-home and inpatient groups. Graft rejection was not observed. Acute and chronic GVHD incidence and grade distribution were homogeneous except for comparisons between groups 2 and 4 (grade 3-4 acute GVHD cumulative incidence of 0% vs 40%, $q = 0.003$) (figure 1). No differences in relapse, TRM, PFS, or OS were observed.

Table 1. Patient characteristics.

	At-home PTCy	At-home non-PTCy	In-patient PTCy	Inpatient non-PTCy	2-sided p value
Patients (n)	7	8	6	5	
Age (years)	31 (25-60)	53 (29-64)	45 (23-59)	50 (42-57)	0.58
Median HCT-CI	2 (0-4)	3 (0-4)	3 (0-3)	2 (0-3)	0.19
Diagnosis					0.99
AML/MDS	0 (0%)	1 (12.5%)	0 (0%)	1 (20%)	
Lymphoma	6 (85.7%)	5 (62.5%)	5 (83.3%)	2 (40%)	
MM	1 (14.3%)	2 (25%)	1 (16.7%)	2 (40%)	
Donor					0.414
*Related	4 (57.1%)	5 (62.5%)	4 (66.7%)	1 (20%)	
*Unrelated	3 (42.9%)	3 (37.5%)	2 (33.3%)	4 (80%)	
HLA compatibility					
*Identical	3 (42.9%)	8 (100%)	2 (33.3%)	5 (100%)	0.01[1]
*Mismatched 7/8	1 (14.3%)	0 (0%)	1 (16.7%)	0 (0%)	
*Haploidentical	3 (42.9%)	0 (0%)	3 (50%)	0 (0%)	
CMV risk					0.93
Low	2 (28.6%)	3 (37.5%)	2 (33.3%)	1 (20%)	
Intermediate	4 (57.1%)	4 (50%)	3 (50%)	3 (60%)	
High	1 (14.3%)	1 (12.5%)	1 (16.7%)	1 (20%)	
Conditioning regimen intensity					
*MAC	0 (0%)	3 (37.5%)	1 (16.7%)	1 (20%)	0.35

[1]Differences only observed between unmatched groups.
[o]Considering sample size, medians are given with their respective minimum and maximum values.

Figure 1. Cumulative probability of grade 3-4 acute GVHD for home-cared patients vs. controls.



Conclusions: Patients with previous ASCT can safely receive an allo-SCT in home care units regardless GVHD prophylaxis and without negative effect on toxicity or survival. Benefit in grade 3-4 acute GVHD incidence was observed in home-cared patients receiving TK/MMF compared with matched hospitalized patients. Other characteristic benefits associated with home care were not detected.

Disclosure: M.G.R. received honoraria from Janssen and Takeda. L.G.R.L. received honoraria from Janssen and travel grants from Janssen and Amgen. A.C.P., C.J.V, A.M.R., C.G., P.A., T.S., M.S.L., C.M., L.R., M.Q.S., M. R., G.G.G. and F.F.A. have nothing to declare.

P180

The ATG dose and tlc don't impact on the development of GVHD and viral reactivations in patients undergoing cd34+ selected allogeneic hematopoietic cell transplantation

Á. Sánchez Cayuela[1], V. Navarro[2], E. Roldan Galvan[1], M.L. Fox[1], O. Salamero García[1], I. Ruiz Camps[3], A. Pérez González[1], P. Barba Suñol[1], F. Bosch Albareda[1], D. Valcárcel Ferreiras[1], G. Ortí Pascual[1]

[1]Vall d'Hebron University Hospital, Barcelona, Spain, [2]Oncology Data Science Group, Vall d'Hebron Institute of Oncology, Barcelona, Spain, [3]Vall d'Hebron University Hospital, Barcelona, Spain

Background: A baseline total lymphocyte count (TLC) has been reported to correlate with the development of graft-versus-host disease (GvHD) in patients undergoing T-cell depleted (TCD) allogeneic hematopoietic cell transplant (allo-HCT) using antithymocyte globulin (ATG). We aimed to study the role of TLC and ATG on the development of GvHD and viral reactivations (VR) in patients undergoing ex vivo CD34 + selected allo-HCT.

Methods: We retrospectively analyzed data of patients undergoing a CD34 + selected allo-HCT between 2016 and 2021 at our institution. All patients signed a written inform consent. The CD34 + selection allo-HCT platform consisted on ex vivo CD34 + selection plus in vivo TCD with ATG 2.5 mg/Kg/day (2 days in HLA matched donors and 3 days in HLA mismatch donors). Primary endpoint was to study the association of the ATG dose and TLC with the development of acute GvHD (aGvHD) and VR. Secondary endpoints were NRM, RI, PFS and OS. Prognostic variables were: age, conditioning regimen, ATG, TLC, type of donor, disease diagnosis, disease status, HCT-CI, VR (CMV, Adenovirus and EBV), CD3 +, CD19 + and CD16 + CD56 + (NK) cells and CMV status. Associations between ATG, TLC with the number of VR and GvHD were calculated using the logistic model. Survival outcomes were calculated using Kaplan Meier method. The Proportional Hazards model was used to calculate HR and risk associations. We used R-software 4.1.1 for statistical analysis.

Results: A total of 51 patients were included, with complete data in 39 patients. The median follow up was 32.9 months (range, 20.2-42.3). The median dose of ATG per patient was 154.5 mg (range 121.5 – 189) and the mean of the TLC at allo-HCT was 161.5x10^6/L (SD ± 420.16).The cumulative incidence of aGvHD at 100 days was 15.8% (CI95%, 5.1%-25.2%).

We did not observe any associations between the ATG dose and the TLC with GvHD. Interestingly, we observed a trend towards an increased risk of adenoviremia in those patients with higher ATG exposure (p = 0.07). Nevertheless, we did not observe any further association between ATG, TLC with the number of viral reactivations.

The 2-year NRM was 26% (CI95%, 12%-37.7%), the 2-year RI was 22.5% (CI95%, 6.1%-36.1%), the 2-year PFS was 59.1% (CI95% 46.7%-74.8%) and the 2-year OS was 60.5% (CI95%, 48% -76.3%). RIC (p = 0.008) and older patient's age (p = 0.031) were associated with higher NRM. In contrast, a lower NK cell count at 3 months was associated with lower NRM (p = 0.004). RIC allo-HCT was associated with lower OS (p = 0.005). In MVA, a lower NK cell count at 3 months was associated with lower NRM (HR = 0, CI95% 0-0,21, p = 0.030) and RIC was associated with lower OS (HR = 8.57, CI95% 1.6 - 45.78, p = 0.012). RI and PFS MVA did not identify any prognostic variables.

Table 1: Patient's characteristics

Patient's characteristics n (%)	Median age	52.05 (Q1 41.18- Q3 61.15)
	Female gender	29 (55.77%)
	AML & MDS	27(67.5%)7(17.5%)
	ALL	6(15%)
Donor Type	Matched Sibling Donor	12(30.77%)
	Unrelated Donor	27(69.23%)
HLA Match	HLA Match	27(69.23%)
	HLA Mismatch (9/10)	12(30.77%)
CMV serostatus	Receptor IgG +/ Donor IgG +	14(34.15%)
	Receptor IgG+/Donor IgG -	14(34.15%)
	Receptor IgG -/Donor IgG +	5(12.19%)
	Receptor IgG -/Donor IgG-	8 (19.51%)
Conditioning regimen	CY-TBI-TT	23(57.5%)
	BU-MEL-FLU	17(42.5%)
ATG total dose (mg)	Median	386.2 (Q1 303.8- Q3 472.5)
TLC (x10^6/L)	Mean	161.5 (SD= +/-420.16)
Adenovirus infection		8(15.09%)
Epstein Barr infection		23(43.40%)
Cytomegalovirus infection		41(77.36%)

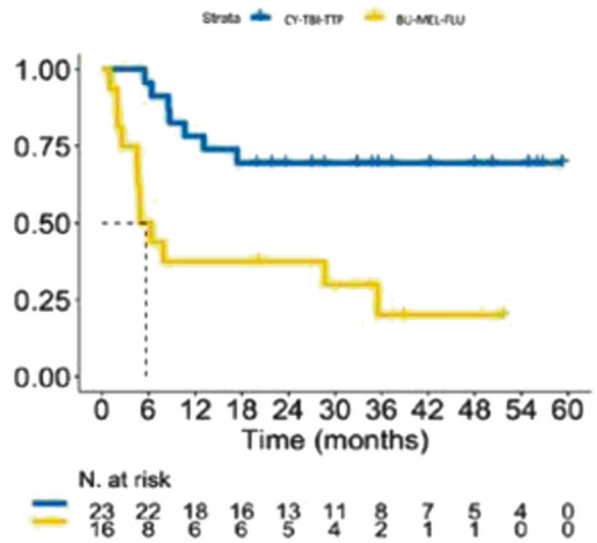


Figure 1: Overall Survival according to conditioning.

Conclusions: In this homogeneous cohort of CD34 + selected allo-HCT, ATG and TLC were not associated with GvHD or VR. However, the use of a RIC was associated with a lower OS. Further studies with a larger number of patients are warranted.

Disclosure: Guillermo Ortí Pascual: BMS, Incyte, Novartis, Pfizer.

P181

HLA molecular mismatch and its implication in the alloresponse and outcomes after hematopoietic stem cell transplantation

M. Gómez Hernando[1], J. Torres Canizales[2], C. Arnaldos-Pérez[2], J.L. Caro[2], C. Serra[2], E. Palou[2], M.Q. Salas[1], A. Pedraza[1], M. Rovira[1], C. Martínez Muñoz[1]

[1]Hematopoietic Stem Cell Transplantation Unit, Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain, [2]Hospital Clínic de Barcelona, Barcelona, Spain

Background: Higher HLA mismatch has been associated with worse clinical outcomes in the context of allogeneic stem cell transplantation (alloSCT). Traditionally, HLA disparity has been evaluated at the allele level. Recent in silico tools (PIRCHE and HLA-EMMA) are capable of assessing molecular mismatch (MM) differences. PIRCHE can predict the number of peptides presented by HLA molecules. On the other hand, HLA-EMMA compares HLA polymorphic amino acids between mismatches exposed on the surface of an HLA molecule. However, in the alloSCT the association of MM according to these tools and clinical outcomes has not been extensively investigated so far. The aim of this study is to analyze the relation between MM graft-versus-host disease (GvHD), relapse and early immune reconstitution.

Methods: We conducted a retrospective analysis of patients who underwent alloSCT in our center between 2018 and 2020 comparing those who received HLA-identical with HLA mismatched transplants from both related and unrelated donors . High resolution HLA typing was used to analyzed HLA genes and MM was evaluated with both PIRCHE and HLA-EMMA softwares in GvH and host-versus-graft (HvG) directions. PIRCHE and HLA-EMMA scores were divided in low or high categories according to the analysis of receiver operating characteristic (ROC) curves. The data of early immune reconstitution included the levels of lymphocytes and monocytes on day 15, 30, 45, 60 and 90 after transplant.

Results: 103 patients (10/10 HLA identical=67, HLA non-identical=36) had undergone alloSCT with a median age of 51 years (20-71). Patient characteristics are detailed in table 1. Median follow-up was 1.6 years. There were no differences in Overall Survival (OS) and Relapse-free survival at 3 years. Patients who developed acute GvHD obtained a significantly lower score in PIRCHE in class I in the HvG direction ($p = 0.033$). Non-relapsed patients presented significantly higher PIRCHE score (>5 MM) in HLA class I in HvG direction ($p = 0.047$). However, no differences were found in HLA-EMMA nor in GvH direction. Early immune reconstitution in patients with greater PIRCHE score (>5 MM) displayed higher levels of lymphocytes on day 60 after transplant in HvG direction ($p = 0.024$). Cumulative incidence of relapse was higher in >5 MM PIRCHE in this direction ($p = 0,0558$).

Factor	Group	HLA-Identical (n=67)	HLA-Mismatched (n=36)	P value
Sex (%)	Female	42 (62.7)	19 (52.8)	0.402
	Male	25 (37.3)	17 (47.2)	
Diagnosis (%)	ALL	10 (14.9)	4 (11.1)	
	AML	25 (37.3)	10 (27.8)	
	CLL	1 (1.5)	3 (8.3)	
	CML	1 (1.5)	3 (8.3)	
	HL	0 (0.0)	5 (13.9)	
	MDS	22 (32.8)	2 (5.6)	
	MM	0 (0.0)	1 (2.8)	
	NHL	8 (11.9)	7 (19.4)	
	PID	0 (0.0)	1 (2.8)	
aGvHD (%)		23 (34.3)	18 (50.0)	0.143
aGvHD Grade 2-4 (%)		22 (32.8)	14 (38.9)	0.665
aGvHD Grade 3-4 (%)		5 (7.5)	5 (13.9)	0.313
cGvHD (%)		22 (32.8)	9 (25.0)	0.502
Relapse (%)		26 (38.8)	8 (22.2)	0.124
Follow up days		589[60, 1185]	633 [91, 1307]	0.656
Time to relapse		163 [42, 1611]	237.00 [50, 729]	0.685

AML: acute myeloid leukemia, ALL: acute lymphoid leukemia, CLL: chronic lymphocytic leukemia, CML: chronic myeloid leukemia, HL: Hodgkin lymphoma, MDS: mylodisplastic syndrome, MM: multiple myeloma, NHL: non-Hodgkin lymphoma, PID: primary immunodeficiency, aGvHD: acute graft-versus-host disease, cGvHD: chronic graft-versus-host disease

Table 1. Patient characteristics and clinical outcomes.

Conclusions: HLA-MM in PIRCHE in the HvG direction is associated with a higher risk of acute GVHD and relapse and an improvement in early immune reconstitution. HLA molecular analysis could be useful for donor selection and management of patients post-transplant . The implications of HLA-MM according to these in silico tools in alloSCT outcomes deserve further investigation.

Disclosure: No conflicts of interest to disclose

P182

Post-transplant cyclophosphamide, abatacept, and short course of tacrolimus (cast) for graft-versus-host disease prevention following haploidentical hematopoietic stem cell transplantation

AS. Al-Homsi[1], F. Cirrone[1], K. Cole[1], K. Stocker[1], B. Bruno[1], JA. Suarez-Londono[1], S. Gardner[1], J. Goldberg[1], M. Abdul Hay[1]

[1]New York University, New York, United States

Background: Haploidentical (HI) hematopoietic stem cell transplant (HSCT) substantially expands the pool of available donors. However, a recent large registry study showed inferior outcomes of HI HSCT compared to MUD HSCT when both groups received identical post-transplant cyclophosphamide-based graft-versus-host-disease (GvHD). This was mainly due to higher rates of GvHD, underscoring the need for improved GvHD prophylaxis following HI HSCT. Abatacept (A) prevents T-cell co-stimulation by blocking the CD80I86-CD26 axis via its extracellular CTLA4 domain. Shortening the duration of tacrolimus may alleviate the burden of its unwanted effects.

Methods: We therefore initiated a clinical trial for patients with hematological malignancies undergoing HI HSCT. Patients received mobilized peripheral blood grafts from first-degree HI related donors. GvHD prevention consisted of PTCy (50mg/kg IV on day +3 and +4), A (10mg/kg IV on day +5, +14 and +28) and tacrolimus (T) (starting on day +5 at 0.02mg/kg/day, by continuous IV). The dose of T was adjusted to maintain a trough level of 5-12 ng/mL. Tacrolimus taper was started on day +60 over a period of 4 weeks.

Results: Since September 2020, 28 patients have been enrolled. Median age was 60 (18-73) years. There was 17 males and 11 females. Treated conditions included: AML (9), MDS (5), ALL (9), T-cell NHL (3), others (2). Disease risk index was intermediate in 18 and high in 9 patients. Nine patients had active disease at enrollment. Seventeen patients received myeloablative conditioning. CMV serology for recipients and donors were −/− (9), +/+ (14), −/+ (1,) and +/− (4). For the 27 patients already evaluable for engraftment, median time to ANC and platelet engraftment are 18 (14-30) and 27 (16-67) days. All 27 patients achieved full whole blood donor chimerism by day +30. Median follow-up was 6.6 months. Five patients developed grade II-IV acute GVHD and 2 patient developed grade III acute GvHD. There was no case of grade IV acute GvHD. Two patients developed chronic, 1 mild (skin only) and 1 severe (skin, eyes and oral cavity). There was no case of steroid-refractory GvHD. Only 3 patients did not complete the planned T taper by day +90. Six patients required systemic steroids. CMV reactivation rate was 33%. One patient had EBV reactivation and required preemptive therapy with 2 weekly rituximab doses. Seven patients developed BK reactivation. There were no cases of adenovirus or HHV-6 virus reactivation. Five patients developed transient renal insufficiency (4 in the setting of acute sepsis and 1 with thrombotic microangiopathy that resolved after tapering off T). One patient developed sinusoidal occlusive disease that resolved with therapy. Other toxicities included self-limiting rise in bilirubin. One patient with adult T-cell leukemia/lymphoma and 1 patient with ALL relapsed. All other patients remain disease-free.

Conclusions: Our ongoing study suggests that CAST with abbreviated course of T is safe and yields low rates of acute GvHD. Based on a planned interim analysis, the study continues to enroll patients. The results of a larger cohort with longer follow-up will be presented at the meeting.

Clinical Trial Registry: NCT04503616

Disclosure: A S Al-Homsi
Advisory Board: BMS and Celyad
Consultancy: Daiichi Sankyo

P183

Post transplantation cyclophosphamide based GVHD prophylaxis across donor types – a single center experience

J. Vydra[1], L. Nováková[1], M. Šťastná Marková[1], V. Válková[1], M. Koubová[1], B. Čemusová[1], R. Pytlík[1], A. Vítek[1], P. Cetkovský[1]

[1]Institute of Hematology and Blood Transfusion, Prague, Czech Republic

Background: Post transplant cyclophosphamide (ptCy) has been shown to improve outcomes of hematopoietic cell transplantation (HCT) from HLA mismatched related and unrelated donors. We analyzed retrospectively outomes of HCT from matched unrelated donors (MUD), mismached unrelated donors (MMUD) and haploidentical (HAPLO) donors using uniform GvHD prophylaxis with ptCy and compared these to a contemporary cohort of HCT from matched sibling donors (MSD) using standard prophylaxis.

Methods: Data on transplants performed at the Institute of Hematology and Blood Transfusion in Prague were retrieved from local transplant databases. All patients signed informed consent with data collection and anonymous analysis. Conditioning was either myeloablative (Bu/Flu or Bu/Cy) or reduced intensity (Flu/Mel). GvHD prophylaxis consisted of PtCy, cyclosporine and mycophenolate in MUD, MMUD and HAPLO groups. Standard prophylaxis in MSD group was tacrolimus and mycophenolate. Kaplan-Meier survival estimates, Cox proportional hazard models and competing risk cumulative incidence estimates were calculated.

Results: 218 patients were included in the analysis. Patient characteristics are summarised in Table.

OS at 2 years was 82% (95% CI 73-92%) in MSD group and 83% (95% CI 74-93%), 82% (95% CI 72-94%) and 73% (95% CI 62-86%) in HAPLO, MMUD and MUD groups (P = 0.4).

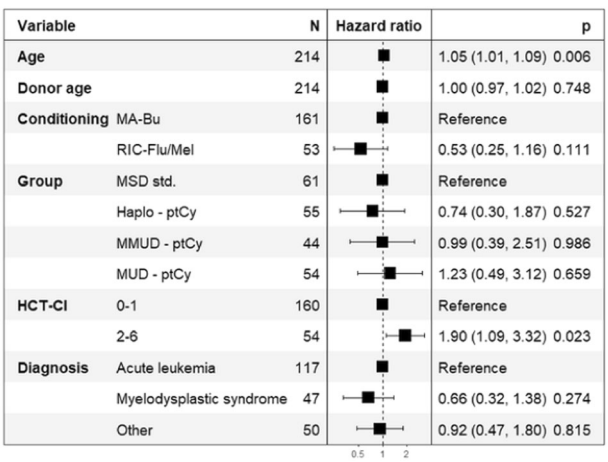
In multivariate analysis, only increasing age (HR 1.05, 95% CI 1.01-1.08 for each year) and commorbidities (HCT-CI > 1, HR 1.91 – 95% CI 1.09-3.33) were are associated with decreased overall survival (Figure). Non relapse mortality and incidence of relapse did not differ significantly between groups (P = 0.34) and were 10% and 27% for all patients, respectively. Acute GVHD grade III-IV was seen in 8% of patients in MSD group and 10%, 10% and 3.4% after HAPLO, MMUD and MUD HCT (P = 0.5). Chronic GVHD was seen in 69%, 62%, 64% and 31% of MSD, HAPLO, MMUD and MSD groups (P = 0.04).

Conclusions: GvHD prophylaxis with ptCy led to equivalent outcomes of HCT from MUD, MMUD and haploidentical donors when compared to a cohort of transplants from matched sibling donors without ptCy in a retrospective, single center analysis.

Table.

	MSD N = 62	HAPLO N = 55	MMUD N = 46	MUD N = 55	P
Age	49.0 [41.0;57.0]	53.0 [40.5;62.0]	45.0 [38.0;55.0]	54.0 [39.2;61.0]	0.073
HCT-CI > 1	12 (19.4%)	16 (29.1%)	7 (15.2%)	19 (34.5%)	0.086
MA-Bu	52 (83.9%)	36 (65.5%)	38 (82.6%)	39 (70.9%)	
RIC-Flu/Mel	10 (16.1%)	19 (34.5%)	8 (17.4%)	16 (29.1%)	
Bone marrow	2 (3.23%)	0 (0.00%)	5 (10.9%)	2 (3.64%)	
Peripheral blood prog. cells	60 (96.8%)	55 (100%)	41 (89.1%)	53 (96.4%)	0.05
Acute leukemia	32 (51.6%)	30 (54.5%)	26 (56.5%)	32 (58.2%)	0.250
Myelodysplastic syndrome	9 (14.5%)	13 (23.6%)	11 (23.9%)	15 (27.3%)	
Other	21 (33.9%)	12 (21.8%)	9 (19.6%)	8 (14.5%)	

Figure



Disclosure: Nothing to declare

P184

High expression of cd62l as a signature of steroid-refractory/resistant GVHD revealed by immune profiling and machine learning

Y. Ding[1], L. Wang[1], M. Ni[1,2], B. Neuber[1], M.-L. Schubert[1], T. Sauer[1], A. Krauss[1], T. Luft[1], U. Hegenbart[1], S. Schönland[1], V. Eckstein[1], W. Krueger[3], R. Yerushalmi[4], K. Beider[4], A. Nagler[4], C. Müller-Tidow[1], P. Dreger[1], M. Schmitt[1], A. Schmitt[1]

[1]University Clinic Heidelberg, Heidelberg, Germany, [2]Guizhou Medical University, Guizhou, China, [3]University Clinic Greifswald, Greifswald, Germany, [4]Chaim Sheba Medical Center, Tel Hashomer, Israel

Background: Steroid-refractory graft versus host disease (SR-GvHD) remains a major complication leading to a high morbidity and mortality post allogeneic hematopoietic stem cell transplantation (allo-HSCT), despite significant advances in the last few years. Therefore, an effective way to identify SR-GvHD as early as possible could provide an opportunity to start second-line therapy at an early stage. In our study, a comprehensive immune profiling was performed to analyze the phenotype of cell subsets in different GvHD and healthy donor models. Machine learning was used to find critical factors from the huge multidimensional immune profiling dataset and to construct an accurate prediction model for SR-GvHD.

Methods: Samples of ten patients without GvHD post allo-HSCT, eleven patients with steroid-sensitive aGvHD, 19 patients with SR-aGvHD ≥ II° and twelve with moderate to severe SR-cGvHD were included in this study. Glucksberg and NIH criteria were used for clinical staging of aGvHD and cGvHD. A comprehensive phenotypical analysis of monocytes, T cells, B cells, and NK cells was evaluated by multicolor flow cytometry. Unsupervised dimensional reduction and clustering algorithms were used to unearth the immunological and clinical data. Several different machine learning algorithms were used for the construction of prediction models.

Results: A pipeline for the discovery of biomarkers using machine learning was established for the FACS data analysis. Several distinct disease-specific subsets of monocytes, T cells and NK cells were discovered by unsupervised analysis strategies, and were further validated by manual analysis strategy. Clinical parameters had no influence on these disease-specific subsets. Moreover, the SR-GvHD groups, showed significant higher expression of CD62L on T, NK cells compared to the other two groups, $CD3^+CD62L^+$ T cells (no aGvHD vs. SR-aGvHD: 14.75% vs. 54.78%, $p < 0.001$; steroid-sensitive aGvHD vs. SR-aGvHD: 18.03% vs. 54.78%, $p < 0.001$), $CD56^+CD62L^+$ NK cells (no aGvHD vs. SR-aGvHD: 15.96% vs. 60.46%, $p < 0.001$; steroid-sensitive aGvHD vs. SR-aGvHD: 18.52% vs. 60.46%, $p < 0.001$),suggesting its important role in SR-GvHD. The groups of no aGvHD post allo-HSCT and steroid-sensitive aGvHD were similar in their immune profiling. Furthermore, lasso regression and random forest algorithms were used to screen potential predictors for SR-aGvHD. A prediction model was constructed based on the CD62L expression of CD3 + T, CD4 + T, NK and B cells. The specificity and sensitivity of the model was examined by ROC analysis showing a good prediction with an AUC of 0.867.

Conclusions: An effective algorithm for the definition of biomarkers was established using machine learning in our current study. The upregulation of CD62L on T and NK cells was defined as a robust predictor for SR-GvHD.

Disclosure: The authors declare no competing financial interests, except the following: Funding was provided by Mallinckrodt to AS and MS for the documentation of the clinical course and for the analysis of patient immune cells; MS received funding for collaborative research from Apogenix, Hexal and Novartis and travel grants from Hexal and Kite; he received financial support for educational activities and conferences from bluebird bio, Kite and Novartis; he is a board member for MSD and (co-)PI of clinical trials of MSD, GSK, Kite and BMS. AS received travel grants from Hexal and Jazz Pharmaceuticals. MS and AS are co-founders and shareholders of TolerogenixX Ltd. AS and LW are part-time and full-time employees, respectively, of TolerogenixX Ltd.

P185

Cytokine trajectories and risk of acute graft-versus-host disease after allogeneic hematopoietic cell transplantation

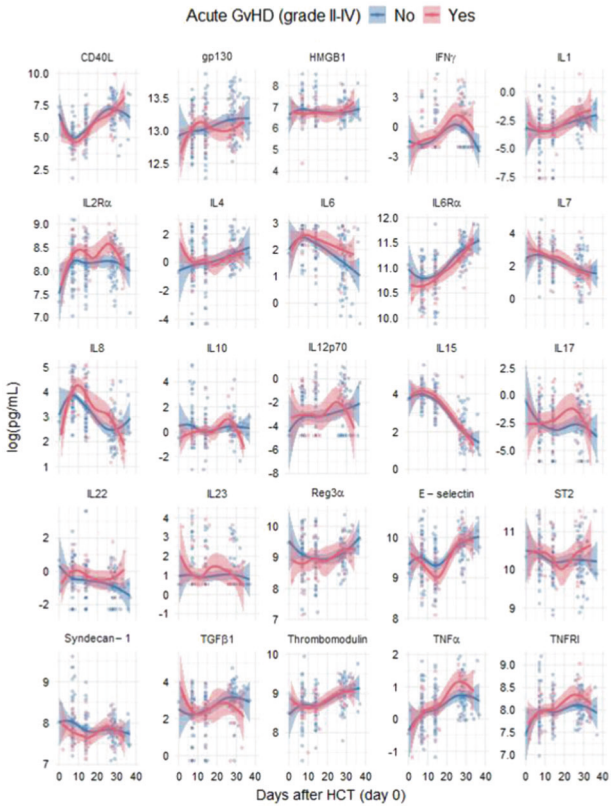
L.K. Gjærde[1,2], A.G. Zucco[3,2], J.H. von Stemann[1,2], L. Minculescu[1], J.A. Møller[1], P.T. Brooks[1,2], M.B. Hansen[1], J. Reekie[3], S.R. Ostrowski[1,2], H. Sengeløv[1,2]

[1]Rigshospitalet, Copenhagen, Denmark, [2]University of Copenhagen, Copenhagen, Denmark, [3]PERSIMUNE Center of Excellence, Copenhagen, Denmark

Background: Acute graft-versus-host disease (GvHD) remains a major cause of morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT). We aimed to investigate whether cytokine trajectories early post-HCT were associated with developing acute GvHD.

Methods: We measured 25 cytokines by ELISA or Luminex in 254 stored plasma samples obtained around day +7 (N = 92), +14 (N = 77) and +28 (N = 85) in 116 patients who underwent HCT with myeloablative conditioning between 2015 and 2018 (median age: 47 [min–max: 18–71] years, 52% transplanted for acute leukemia, 71% with a matched unrelated donor, 25% received anti-thymocyte globulin [ATG] and 41% received 12 Gy total-body irradiation [TBI]). All 254 plasma samples were obtained before an eventual diagnosis of grade II–IV acute GvHD. Longitudinal cytokine levels were smoothed using polynomial loess regression with 95% confidence interval (CI) bands. For each cytokine, a joint survival model was fitted, in which longitudinal mixed-effects model estimates of the cytokine level were used in a proportional hazards spline model to estimate hazard ratios (HR, all per log increase) of grade II–IV acute GvHD (adjusted for donor type, receipt of ATG and receipt of 12 Gy TBI).

Results: 35 (30%) patients developed grade II–IV acute GvHD at a median of 32 (Q1–Q3: 27–42) days after HCT. Stratified crude cytokine trajectories early post-HCT (Figure) revealed that patients who later developed acute GvHD had higher interferon-γ (IFNγ) levels from around day +20 to +35, higher interleukin-2-receptor-α (IL2Rα) levels from around day +10 to +35, a smaller decline in interleukin-6 (IL6) levels from around day +10 to +35, higher interleukin-17A (IL17) levels from around day +10 to +30, and more increasing tumor necrosis factor-α (TNFα) and suppression of tumorigenicity-2 (ST2) levels from around day +20 to +35. In the converging 22 joint survival models (the models for interleukin-1, interleukin-22, and E-selectin did not converge), we found that—after adjusting for donor type and receipt of ATG and TBI—higher levels of IL17 (HR: 1.22, CI: 1.00–1.49, p = 0.05) and lower levels of glycoprotein 130 (gp130, an interleukin-6 signal transducer, HR: 0.22, CI: 0.05–0.95, p = 0.04) and transforming growth factor-β1 (TGFβ1, HR: 0.37; CI: 0.15–0.94, p = 0.04) were associated with subsequent acute GvHD. Other cytokines associated with acute GvHD, albeit not with statistical significance at the 0.05 level, were TNFα (HR: 2.29, CI: 0.84–6.21, p = 0.11), IL2Rα (HR: 2.16, CI: 0.71–6.56, p = 0.17) and IL6 (HR: 1.40, CI: 0.95–2.07, p = 0.09).



Conclusions: Crude early post-HCT trajectories of IFNγ, IL2Rα, IL6, IL17, TNFα and ST2 differed according to later development of grade II–IV acute GvHD in adults undergoing myeloablative HCT. After adjustment for donor type and receipt of ATG and TBI, high levels of IL17 and low levels of gp130 and TGFβ1 were associated with increased risk of acute GvHD. Our findings warrant further prognostic and mechanistic research of the candidate cytokine trajectories to determine their role in predicting and causing or preventing acute GvHD.

Disclosure: Nothing to declare.

P186

Similar outcomes of ptcy and atg based GVHD prophylaxis in hematopoietic cell transplantation from matched unrelated donors

J. Vydra[1], P. Jindra[2], V. Válková[1], M. Karas[2], M. Šťastná Marková[1], D. Lysák[2], L. Nováková[1], J. Šrámek[2], M. Hrabětová[2], P. Cetkovský[1]

[1]Institute of Hematology and Blood Transfusion, Prague, Czech Republic, [2]University Hospital Pilsen, Pilsen, Czech Republic

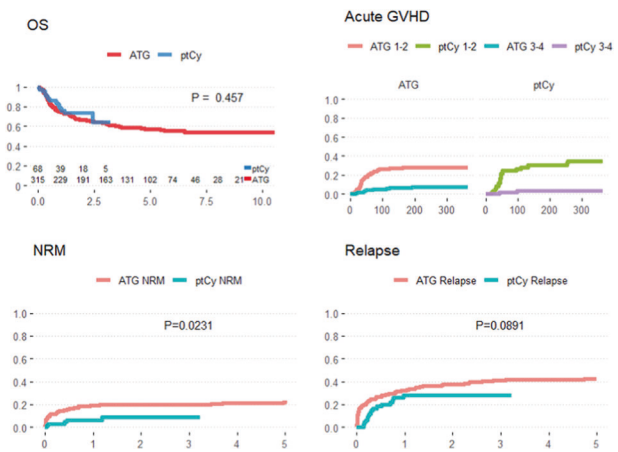
Background: Post transplant cyclophosphamide (ptCy) has been shown to improve outcomes of HLA mismatched hematopoietic stem cell transplantation (HCT). Role of ptCy in HLA matched unrelated donor HCT is less well established. We analyzed retrospectively outomes of transplantation from matched unrelated donors using ptCy based GVHD prophylaxis and compared these outcomes to standard ATG based prophylaxis.

Methods: Data on transplants performed at the Institute of Hematology and Blood Transfusion in Prague and in Pilsen Teaching Hospital were retrieved from local transplant databases. All patients signed informed consent with data collection and anonymous analysis. Conditioning was either myeloablative (Bu/Flu or Bu/Cy) or reduced intensity (Flu/Mel). GvHD prophylaxis consisted of PtCy, cyclosporine and mycophenolate (ptCy group) or ATG, cyclosporine and either mycophenolate or methothrexate (ATG group). Kaplan-Meier survival estimates and competing event cumulative incidence curves were calculated and compared using log-rank and Gray's tests.

Results: 383 patients were included, 315 in the standard ATG group and 68 in the ptCy group. Patient characteristics are summarized in Table 1. OS at 2 years was 75,6% (95% CI 63-90%) and 72,6% (95% CI 65,8-80%) after ptCy and ATG, respectively (Figure 1A). Cumulative incidence of NRM within 2 years was 9% after ptCy and 19% after ATG (P = 0,023); incidence of relapse was 28% after ptCy and 38% after ATG (P = 0,089). Incidence of acute GVHD grade 1-2 was 35% and 28% (P = 0,56); incidence of grade 3-4 aGVHD was 3,5% and 7,5% (P = 0,28) in ptCy and ATG groups, respectively. Incidence of moderate and severe chronic GvHD was 4,2% after ptCy and 18% after ATG (P = 0,03 for moderate and 0,3 for severe cGVHD); mild cGVHD was seen in 17% (ptCy) and 25% (ATG) of cases.

Table 1

	ATG (*N = 315*)	ptCy (*N = 68*)	P
Age	50.0 (13.1)	48.9 (11.6)	0.504
HCT-CI			0.547
0-1	174 (63.5%)	48 (70.6%)	
2-3	74 (27.0%)	15 (22.1%)	
>3	26 (9.49%)	5 (7.35%)	
Conditioning			0.002
MA-Bu	155 (49.2%)	48 (70.6%)	
RIC-FluMel	160 (50.8%)	20 (29.4%)	
Graft	266 (84.7%)	67 (98.5%)	0.001
PBPC	47 (15.0%)	1 (1.47%)	
Bone marrow			
Donor age	31.4 (8.30)	32.8 (8.41)	0.235



Conclusions: GvHD prophylaxis with ptCy and ATG led to similar outcomes after allogeneic hematopoietic cell transplantation from matched unrelated donors in this retrospective analysis of data from two centers.

Disclosure: Nothing to declare

P187

Anti-thymocyte globulin (atg) equalize the incidence of graft-versus-host disease (GVHD) among unrelated and identical sibling donor transplantation

A. Cia[1], N. Fernandez Escobar[1], A. Requejo[1], M. Castro[2], G. Bentolila[3], G. Jaimovich[1]

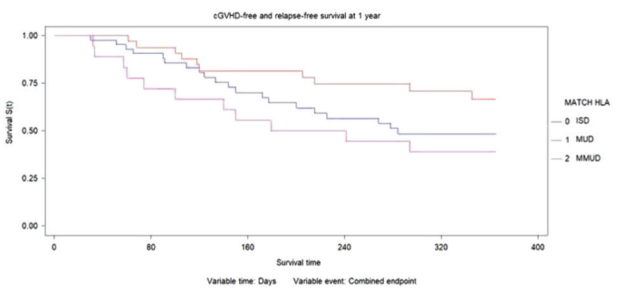
[1]Favaloro Foundation University Hospital, Capital Federal, Argentina, [2]Sanatorio Anchorena, Capital Federal, Argentina, [3]FUNDALEU, Capital Federal, Argentina

Background: GVHD is the main cause of morbidity and mortality associated with allogeneic hematopoietic stem cell transplantation (HSCT) with an incidence rate of 40-60%. Addition of ATG has shown to reduce its incidence. We report the results of the prophylactic use of ATG in a group of patients (pts) undergoing HSCT.

Methods: From March 2018 to June 2021 we conducted a prospective multicenter study including 95 consecutive pts.: 33 transplanted with an identical sibling donor(ISD), 33 with an HLA-matched unrelated donor(MUD) and 18 with an HLA 1 miss-matched donor (MMUD). Conditioning regimen was according to institutional protocol. GVHD prophylaxis included tacrolimus and methotrexate plus ATG (Timoglobulina®Sanofi) 2.25 mg/kg days -3 and -2. GVHD incidence, relapse and death were recorded. Acute GVHD (aGvHD) and chronicGVHD (cGVHD) were defined using Glucksberg criteria and NIH clinical grading respectively. Median and interquartile range (IQR) were used to describe non-parametric data, group comparison with X2, Kaplan Meyer curve and multi-sample log Rank test for survival analysis, considering a statistically significant p value of less than 0.05.

Results: 42 pts were male and donors were female in 56% (n:54). Conditioning regimen was myeloablative in 81% (n:77). Median time to neutrophil and platelet engraftment were 17 days (range 15-21) and 17 days (range 12-20) respectively. 6/95 pts presented graft failure. aGVHD incidence was 36% (n:34), grades I-II 19% (n:19) and III-IV 16% (n:15). Incidence of grades III-IV did not varied according to donor: 15% (n:7) for ISD, 9% (n:3) for MUD and 27% (n:5) for MMUD (X2 3.06, p0.21). Overall incidence of cGVHD was 23% (n:21): Grades mild 6% (n:6), moderate 11% (n:11) and severe 4% (n:4). According to donor type, severe cGVHD was 2% (n:1), 3% (n:1) and 11% (n:2) using ISD, MUD and MMUD respectively (X2 2.65, p0.26). At one year, 15/79 pts (19%) were under immunosuppressive treatment. Transplant related mortality at day 100 was 9% (n:9). Most frequent cause was sepsis (n:4). In 31 pts CMV reactivation was detected (more than one reactivation in 6 pts of which 5 had GVHD) and 7 reactivated EBV infection. None evolved to PTLD.

Median follow-up time was 524 days (IQR 168-833). cGVHD–free and relapse-free survival (combined endpoint) at 1 year was 57% (n:54) of 79 evaluables patients. cGVHD and relapse free survival at 1 year was 48% for IDS (33-63%CI), 66% for MUD (47-81%CI) and 38% for MMUD (21-60%CI). No significant difference was found according to donor type (X2 4.98; p0.083) Fig1



Conclusions: No difference was observed in the incidence of aGVHD, cGvHD and combined endpoint at 12 months between the different types of donor. This could suggest that ATG could equalize transplants results using different types of donor. To confirm these findings, studies with a higher level of evidence are required.

Disclosure: Nothing to declare

P188

First-line steroid-free systemic treatment of acute and chronic graft-versus-host disease after novel prophylaxis regimens in adults

I. Moiseev[1], M. Barabanshikova[1], A. Dotsenko[1], A. Smirnova[1], Y. Vlasova[1], E. Morozova[1], S. Bondarenko[1], A. Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, Saint-Petersburg, Russian Federation

Background: Since early studies of graft-versus-host disease (GVHD) (Sullivan et al., 1981 and Kennedy MS et al., 1985) no agent was randomized against corticosteroids (CS), but rather additional immunosuppressive agents in combination with CS were tested against CS alone. Nonetheless these early studies identified comparable efficacy of calcineurin inhibitor (CNI) cyclosporine A (CsA) to CS, which was subsequently abrogated by introduction of CNIs in GVHD prophylaxis. Recently several CNI-free protocols were introduced based on posttransplantation cyclophosphamide (PTCY) (NCT02294552, NCT02806375) and alpha/beta ex vivo depletion (NCT02337595). Under these protocols steroid-sparing regimens were evaluated. Here we report the outcome of first line GVHD treatment without CS in patients from these protocols.

Methods: The study comprised 74 patients, 44% were allografted from matched related donor (MRD), 42% from matched unrelated donor (MUD) and 14% from haploidentical donor. Underlying disease was acute myeloid leukemia in 21%, acute lymphoblastic leukemia in 27%, primary myelofibrosis in 15%, chronic myeloid leukemia in 11% and other malignant diseases in 26%. Twenty patients were treated for acute GVHD (aGVHD) after single-agent PTCY, 23 were treated for chronic GVHD (cGVHD) after single-agent PTCY, 11 patients were treated for de novo cGVHD after PTCY, tacrolimus and MMF combination, 13 – after PTCY and ruxolitinib combination and 7 after ex vivo depletion. Overall 34 patients were treated for aGVHD (grade II – 44%, grade III- 47% and grade IV – 9%) and 40 for cGVHD (60% moderate and 40% severe by NIH criteria). CNIs were used as the first line treatment in 80% of patients, sirolimus in 10%, and TKIs, rituximab and ruxolitinib in another 10%.

Results: Overall response rate (ORR) was significantly higher in chronic GVHD than in acute (80% vs 47%, $p = 0.031$). However the incidence of complete response (CR) was not different (43% vs 35%, $p = 0.53$). Median time to partial response (PR) was 35 days in aGVHD and 6 months in cGVHD. Median time to CR was 67 days in aGVHD and 16 months in cGVHD. 2-year failure-free survival was 21% in aGVHD and 81% in cGVHD ($p < 0.001$, figure A), while overall survival was 76% and 95% in these groups, respectively ($p = 0.017$). In refractory aGVHD the response to CS administration was 39%, and ORR to all lines in aGVHD was 94% (figure B). In refractory cGVHD 71% achieved a response after CS administration and ORR to all lines was 98%. Among aGVHD and cGVHD patients 47% and 63% did not receive systemic antibiotics, 79% and 90% systemic antimycotics, 35% and 73% systemic antivirals, 62% and 85% did not require hospital re-admission for complications or progressive disease during the course of treatment. GVHD severity in acute (HR 4.69, 95%CI 2.08-10.13, $p < 0.001$), in chronic

disease (HR 5.0, 95%CI 0.96-26.22, p = 0.057) was predictive for response.

Conclusions: An attempt to achieve a response without CS in the first line is justified for patients with cGVHD and grade II aGVHD in CNI-free patients after novel GVHD prophylaxis regimens. This approach does not compromise subsequent response to steroids or second-line agents and is associated with low incidence of complications and re-admissions.

Clinical Trial Registry: NCT02294552, NCT02806375, NCT02337595

Disclosure: Nothing to disclose

P189

Pembrolizumab and allotransplants for relapsed refractory classical hodgkin lymphoma

K. Halahleh[1], I. Muradi[2], D. Al-Rimawi[1], M. Ma'koseh[3]

[1]King Hussein Cancer Center and Foundation, Amman, Jordan, [2]Al-Ahliyya Amman University, Amman, Jordan, [3]King Hussein Cancer Center and foundation, Amman, Jordan

Background: Pembrolizumab is safe and effective in persons with rrHL and has been used as a bridge to allo-SCT. There is concern, prior to allo-SCT pembrolizumab use might increase the risk of graft-*versus*-host disease (GvHD) and other IRAE [2-3].

Methods: Retrospective comparative cohort study,22 subjects included(Jan,2017 to July, 2019). 2 cohorts(prior to SCT pembrolizumab use,n-9), and 13 with no prior pembrolizumab. All received RIC SCT and PBSC grafts. a*GvHD*, c*GvHD*, CRS, reported, compared, and survival outcomes calculated. All had similar baseline characteristics.

Subject-, disease- and transplant-related variables displayed in Table 1.

Results: Median follow up was 9mo (range:7.7-44.5mo). The median time from the last dose of pembrolizumab to SCT 67 d (range, 42- 135d). All subjects (n-9) in pembrolizumab cohort achieved CR after SCT, compared to 84.6%(n-11) in the no pembrolizumab cohort;

100-day grade 2-4 *aGvHD* was 63.6% (n-14), more in pembrolizumab (89%,46%; P = 0.04); and 75%(9) vs 37.5% (3),P = 0.062) had grade 3-4.1-year cumulative incidence of moderate-severe *cGvHD* was 41%(n-9), more in pembrolizumab cohort (55.5% vs 30.7%; P = 0.378). *GvHD* was not influenced by any variable, but with a trend toward higher *GvHD* with prior pembrolizumab use (P = 0.074; P = 0.08). No *VOD* in either cohort, however, there was 1 subject with TAM, 2 CRS reported in pembrolizumab cohort, within 14 days post-SCT. All treated with steroids (1mg/kg) within 14 days with a quick benefit.

2- year OS, PFS for the entire cohort were 76.7%(95% CI:56.9-91.8) and 51.3%(95%CI: 29.8-72.6) respectively. No difference in survival outcomes in univariate analysis. However, when we analyzed subjects, who attained CR, or PR before SCT, 2-year OS 92.3 vs 33.3%; P = 0.05) and 2-year PFS 57.0% vs 33.3%; P = 0.03) respectively.

2-year CIR was 27.3%(n-6/22).When we analyzed subjects according to prior pembrolizumab use, no significant difference was evident between 2 cohorts (33.3%, 23.1%; P = 0.807). Taking into account subjects in CR at SCT, 2-year CIR was 14.9%, with no significant difference between 2 cohorts (46.15%, 36.51%; P = 0.93). 2-year NRM 18%(n-4/22) for the entire cohort; more in no pembrolizumab (11% vs 23%; P = 0.0093).In the pembrolizumab cohort, deaths were attributed to *GvHD* of the gut and lung(n-2), recurrent pneumonia(n-2), compared with lung *cGvHD* and DP (n-1), CMV colitis and DP (n-2) in the no pembrolizumab cohort.

Conclusions: Pembrolizumab PRIOR to all-SCT results in favorable outcomes, enhanced PFS, in subjects who received

Variable(N,%)	Total:22(100%)	Characteristic	Pembrolizumab		Fisher Exact P-value	CHI Sq. P value
			Yes 9(41%)	No 13(59%)		
Gender	Female/Male	6 (27.3%)/16 (72.7%)	2 (22.2%)/7 (77.8%)	4 (30.8%)/9 (69.2%)	1.000	0.658
Age	Median, range	26.0 (15.0-44.0)	26.0 (15.0-44.0)	25.0 (15.0- 44.0)	–	0.663
Previous lines before pembrolizumab	Median, range	-----	5.0 (2-10)	6.0 (2-10)	–	0.097
Disease status before allo-SCT	CR	14 (63.6%)	4 (44.4%)	10 (76.9%)		
	PR	3 (13.6%)	1 (11.1%)	2 (15.4%)	0.194	0.128
	VGPR	5 (22.7%)	4 (44.4%)	1 (7.7%)		
Post Allo-SCT Relapse	No	12 (54.5%)	5 (55.6%)	7 (53.8%)	1.000	0.937
	Yes	10 (45.5%)	4 (44.4%)	7 (53.8%)		
aGVHD	No	8 (36.4%)	14 (63.6%)	7 (53.8%)	0.074	0.040
	Yes	14 (63.6%)	8 (88.9%)	6 (46.2%)		
cGVHD	No	11 (52.4%)	2 (25.0%)	9 (69.2%)		
	Yes	10 (47.6%)	6 (75.0%)	4 (30.8%)	0.080	0.049
	NK	1 (4.5%)	14.5 %)	–		
Disease status at Last encounter	CR	14 (63.6%)	5 (55.6%)	9 (69.2%)	0.819	0.807
	PR	2 (9.1%)	1 (11.1%)	1 (7.7%)		
	DP	6 (27.3%)	3 (33.3%)	3 (23.1%)		
Patient Status at last encounter	Alive	14 (63.6%)	8 (36.4%)	3 (33.3%)		
	Dead	8 (36.4%)	3 (33.3%)	–	1.000	0.806

SCT in CR, and decrease the risk of relapse, but at the cost of increased grade 2-4 aGvHD without increased NRM.

Clinical Trial Registry: NA

Disclosure: All authors has nothing to disclose

P190

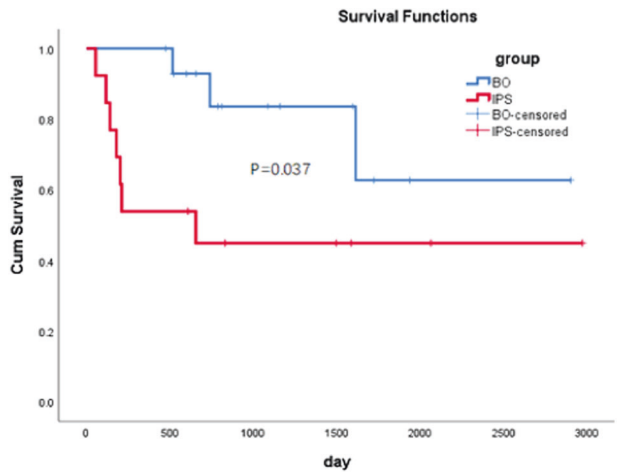
Clinical analysis of air-leak syndrome following allogeneic hematopoietic stem cell transplantation in pediatric patients

W. Zhao[1], M. Chen[1], Y. Zhao[2], H. Wang[2], P. Lu[2], M. Xiong[2]

[1]Beijing Lu Daopei Hospital, Beijing, China, [2]Hebei Yanda Lu Daopei Hospital, Langfang, Sanhe, China

Background: Air-leak syndrome (ALS) occurs when there is leakage of gas from the alveoli resulting in clinical symptoms that include cough, dyspnea and hypoxemia. ALS is an independent poor prognosis factor among adult patients who have received hematopoietic stem cell transplantation (HSCT), which the 5-year overall survival (OS) is less than 30%. However, the clinical features of ALS among post-transplant pediatric patients have rarely been explored.

Methods: We retrospectively reviewed 2,206 pediatric patients who received an allo-HSCT between January 2013 and December 2019 at the Hebei Yanda Lu Daopei Hospital and analyzed the role of ALS in their prognosis following HSCT.



Results: Twenty-eight pediatric patients (16 male and 12 female) were diagnosed with ALS: 16 patients with acute myeloid leukemia, 9 patients with acute lymphoblastic leukemia, and 3 patients with aplastic anemia. Twenty-one of the patients received a complete remission status prior to HSCT and 7 patients were in non-remission. The median patient age was 12 years (1-16) and the follow-up time was 871 days (55-2,973). The median OS time was 429 days (55-1614). The most frequent adverse event accompanying the ALS was hypoxemia which occurred in 92.8% of the patients, followed by wheezing and coughing, which occurred in 67.9% and 53.5% of the patients, respectively. Chest pain related to breathing occurred in 21.4% of the patients. ALS types included mediastinal emphysema, subcutaneous emphysema, pneumothorax, scrotal emphysema, peritoneal meteorism, pneumopericardium, intestinal wall and intraspinal emphysema. Following treatment of the ALS, 18 patients survived (18/28, 64.3%) and 10 patients died of respiratory failure or infection (10/28, 35.7%). We divided ALS into two categories: 15 cases of bronchiolitis obliterans syndrome (BOS) and 13 cases of idiopathic pneumonia syndrome (IPS). Patients with BOS-related ALS had a better prognosis compared to those with IPS, who were more likely to die in the early stage of ALS (80% versus 46% in the IPS and BOS groups, respective; $P = 0.037$). Logical regression analysis showed that, greater than 7 years of age ($P = 0.028$), non-remission prior to HSCT ($P = 0.022$), use of tacrolimus ($P = 0.005$), pulmonary graft-versus-host disease (GVHD) before +163 days ($P = 0.004$), Grade III-IV acute GVHD ($P = 0.001$), extensive chronic GVHD ($P < 0.001$), were independent risk factors for ALS. Primary GVHD before +23.5 days ($P = 0.021$) and IPS type ($P = 0.037$) were independent risk factors of poor prognosis following an ALS diagnosis. Disease state prior to HSCT, pulmonary infection, TBI pre-treatment, donor type did not have a statistically significant ($P > 0.05$) effect on patient survival. Additionally, we found that fluticasone, azithromycin, and montelukast (FAM) could significantly improve the prognosis following ALS in our patients ($P = 0.005$). Compared with IPS, patients with BOS appeared to benefit from imatinib ($P = 0.055$), ruxolitinib ($P = 0.009$), and pirfenidone ($P = 0.044$).

Conclusions: ALS is a rare and poor prognosis complication of HSCT, particularly IPS-related ALS. The OS of ALS in our hospital is significantly higher than that cited in previous reports which may be related to early diagnosis and timely FAM treatment.

Disclosure: Nothing to declare

P191

Comparison of regulatory t cell subpopulation between antithymocytic globulin and post-transplantcyclophosphamide for prevention of the GVHD in patients undergoing allogeneic hematopoietic stem cell transplantation

B.-Y. Heo[1], S. Choi[1], S.-H. Yeon[1], P.T.T. Doung[1], M.-W. Lee[1], D.-Y. Jo[1], J. Kwon[1], I.-C. Song[1]

[1]Chungnam National University, Daejeon, Korea, Republic of

Background: Antithymocytic globulin (ATG) and post-transplant cyclophosphamide (PTCy) are frequently used regimens for graft-versus-host disease (GVHD) prophylaxis. However, there is lack of data about the difference of regulatory

T cell (Treg) subpopulation between these two regimens.

Methods: We collected peripheral blood sample at day+21 after allogeneic hematopoietic stem cell transplantation (Allo-HSCT). We analyzed Treg subpopulation by flow-cytometer and classified Treg into 3 subgroups: naïve, effector and non-suppressive Treg. And, we compared overall survival (OS), the cumulative incidence of acute and chronic GVHD, relapse rate between ATG and PTCy group.

Results: We enrolled 39 patients (25 in ATG, 14 in PTCy) in total. In ATG group, 9 and 16 patients underwent human leukocyte antigen (HLA) matched-sibling donor and unrelated donor HSCT, respectively. In PTCy group, 9 patients underwent haplo-identical HSCT and 5 patients underwent HLA-matched unrelated donor HSCT. The conventional CD25 + FOXP3 + Treg count of CD4 + T cell was 6.49% in ATG and 13.34% in PTCy ($p = 0.0086$). The naïve Treg count of CD4 + T cell was 4.87% in ATG and 5.95% in PTCy ($p = 0.32$). The effector Treg count of CD4 + T cell was 3.89% in ATG and 6.31% in PTCy ($p = 0.16$). The non-suppressive Treg count of

CD4 + T cell was 23.67% in ATG and 19.00% in PTCy ($p = 0.25$). The cumulative incidence of Grade 2 to 4 acute GVHD was 16.2% in ATG and 36.5% in PTCy ($p = 0.15$) and extensive chronic GVHD was 19.1% in ATG and 16.7% in PTCy ($p = 0.955$) And, OS and relapse rate were not statistically different between two group.

Conclusions: There were more conventional CD25 + FOXP3 + Tregs in PTCy group than in ATG group, which

was a result of the fact that there were more naïve and effector Treg in PTCy group. PTCy showed similar clinical outcomes with ATG group, although there were more haplo-identical HSCT in PTCy group. This may be because there were more Tregs in the PTCy group, which effectively prevents GVHD.

Disclosure: Nothing to declare

P192

Treatment pattern characterization and outcomes in chronic graft versus host disease patients treated with extracorporeal photopheresis in clinical practise in Sweden

F. Schain[1], C. Boissin[2], T. Laczik[3], S. Fedeli[3], M. Remberger[4], O. Blennow[5], J. Dykes[6], T. Eich[7], C. Jones[1], J. Mattsson[8], G. Berlin[9]

[1]Schain Research, Bromma, Sweden, [2]Karolinska Institutet, Stockholm, Sweden, [3]KTH Royal Institute of Technology, Stockholm, Sweden, [4]Uppsala University and Uppsala University Hospital, Uppsala, Sweden, [5]Karolinska University Hospital, Stockholm, Sweden, [6]Clinical Immunology and Transfusion Medicine, Lund, Sweden, [7]Uppsala University, Uppsala, Sweden, [8]Princess Margaret Cancer Centre and University of Toronto, Toronto, Canada, [9]Linköping University, Linköping, Sweden

Background: Extracorporeal photopheresis (ECP) is frequently used in clinical practise to treat moderate to severe chronic Graft versus Host Disease (cGVHD), however there is limited data available to describe treatment patterns and outcomes associated with this treatment outside clinical trials.

Methods: Patients ³18 years with a record of an allogeneic hematopoietic stem cell transplantation (HSCT) in the Swedish Patient Register between January 2006 and July 2020 were identified (n = 2708). Among these, patients with ECP treatment from 3 months post HSCT (index) and onwards were included (n = 183). The data was linked to other nationwide longitudinal and population-based registers; the Prescribed Drug Register, the Cause of Death Register, the Cancer Register and the Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA) for follow-up until December 2020. The median follow-up time was 2.7 years.

Results: The median age at index was 58 years (interquartile range [iqr] 1-3; 38-61), and 65.6% (n = 120) were male. The median time from index date to the first ECP exposure was 7.8 months (iqr 1-3; 3.0-19.0) and the median number of ECP treatments given was 18 (iqr 1-3; 4-39). The average time spent in healthcare decreased over follow-up time; 68.9%, and 22.1% the first and fifth follow-up year, respectively. During the 3-month period before the first ECP treatment, 90.0% (n = 165) received cyclosporine, 9.8% (n = 18) received tacrolimus and 3.8% (n = 7) received ruxolitinib, respectively. During the same period 52.5% (n = 96) received prednisolone and/or prednisone. When comparing the 3-month period prior to the first ECP treatment [reference] with 3-month periods during the first year after ECP initiation, there was a decrease in the cumulative dose dispensed by pharmacies per patient-time for prednisone/prednisolone (1,381 mg [reference] versus 658 mg [9-12 months post ECP initiation], p = <0.001) and cyclosporin (12,242 mg [reference] versus 3,501 mg ([9-12 months post ECP initiation] p < 0.001). The incidence rate of infections during the 3-month period prior to ECP initiation was 79.2% and decreased over time to 59.1% ([9-12 months post ECP initiation] p < 0.001). The median overall survival time from index was 6.0 years. The direct medical cost per patient-year decreased from 27,719 euro to 1,981 euro when comparing the first versus fifth follow-up year from index. Similarly, among patients < 66 years at index (n = 130), illness-related time absent from work decreased from 73.2% to 31.9%, with a corresponding decrease in productivity loss from 20,358 euro to 7,211 euro per patient-year.

Conclusions: ECP treatment was associated with reduced use of corticosteroids, immunosuppressive agents, and fewer infections. Furthermore, cost and healthcare utilization decreased over time.

Disclosure: Frida Schain is an employee and own stocks in Schain Research AB. Christina Jones in an employee of Schain Research AB. Constance Boissin, Tamas Laczik and Stefano Fedeli were interns at Schain Research AB and have received payments for analytical work. Mallinckrodt has been the sponsor of the study and Schain Research AB has received payments from Mallinckrodt.

P193

Long-term follow-up of ruxolitinib for therapy in corticosteroid refractory chronic graft-versus-host disease: A single center-experience

N. Mandaci Şanli[1], E. Karakuş[1], M. Keklik[1], A. Unal[1]

[1]Erciyes University, Kayseri, Turkey

Background: Steroid–resistant graft-versus-host disease (GvHD) is a major challenge after allogeneic stem cell transplantation and associated with significant morbidity and mortality There is no therapeutic standard defined beyond calcineurin inhibitors (CNI) and steroids. Pre-clinical evidence indicates the potent anti-inflammatory properties of the ruxolitinib and efficacy of ruxolitinib against GVHD have been described recently.

Methods: In this retrospective study, 16 patients had received ruxolitinib as salvage therapy for corticosteroid–refractory chronic GVHD. All patients had moderate (9/16, 56.2%) to severe (7/16, 43.8%) cGVHD. The most frequent underlying diseases were: acute myeloid leukemia (8, 50%), acute lymphoblastic leukemia (5, 31.3%), Hodgkin's disease (1, 6.3%), myelodysplastic syndrome (1, 6.3%), or T-cell lymphoma (1, 6.3%). All of the patients received myeloablative conditioning regimens. Grading of cGVHD and response (complete and partial organ based on clinician assessments) was performed

Results: The median age was 48 years (range, 30-67). Median cGVHD time was 12 months (range: 2-44). Types of GVHD involvements: liver 7/16 (43.8%), lung 2/16 (12.5%), oral mucosa 1/11 (6.3%), oral mucosa and liver 1/11 (6.3%), skin 2/16 (12.5%), oral mucosa and skin 2/11 (12.6%), skin and gastrointestinal system 1/11 (6.3%). The median number of previous GVHD-therapies was 2.5 (range 1-5). The median dose administered was 20 mg (7 patients) and 10mg (9 patients) daily divided in two doses. Overall response rate was 75.1% (12/16) which was obtained after a median of 40 days of treatment, 43.8% (7/16) reached complete response, and 31.3% (5/16) partial response. cGVHD exacerbation developed in 4 patients during ruxolitinib therapy. Median follow-up and ruxolitinib-treatment was 15 months (range: 2-54). While 68.8% (11/16) of patients were alive, 30.2% (5/16) of patients died (2 of the 5 patients developed disease recurrence). Cytopenia, CMV-reactivation and infections were observed during ruxolitinib-treatment for cGVHD (respectively, 7/16, 43.9%; 6/16, 68.9%; and 11/16, 37.6%)

Conclusions: Ruxolitinib in the real-life setting is an effective and safe treatment option for cGVHD, with an overall response rate of 75.1% for chronic graft-versus-host disease, in heavily pretreated patients.

Disclosure: Nothing to declare

P194

Pharmacokinetics of different tacrolimus formulations for GVHD prevention after allogeneic hematopoietic stem cell transplantation

D.N. Marco[1], G. Gutiérrez-García[1,2], I. Monge[3], G. Riu[3], E. Carcelero[3], J.R. Roma[3], M. Suárez-Lledó[1,2], M.Q. Salas[1,2], N. Martínez-Cibrian[1,2], A. Pedraza[1], A. Doménech[1], L. Rosiñol[1,2], F. Fernández-Avilés[1,2], M. Rovira[1,2], C. Martínez[1,2]

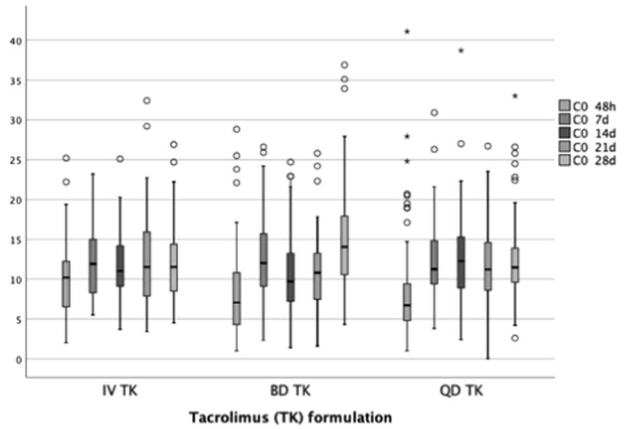
[1]*Institute of Hematology and Oncology, Hospital Clinic of Barcelona, Barcelona, Spain,* [2]*Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain,* [3]*Hospital Clinic of Barcelona, Barcelona, Spain*

Background: Tacrolimus (TK) is a pivotal immunosuppressant agent used for GVHD prevention after allogeneic hematopoietic stem cell transplantation (allo-HSCT). TK is usually given intravenously (IV) in the early phase after allo-HSCT and then switched to twice-daily (BID: *bis in die*) oral administration. In addition to IV and BID TK formulations, once-daily modified-release (QD: *quaque die*) formulation is available. In solid organ transplantation, BID and QD formulations have been shown to have the same efficacy and safety profile. However, in alloHSCT there is little experience with the use of QD. We analyzed pharmacokinetics of the classic IV TK vs. the oral (BID and QD) formulations used from the beginning of transplantation.

Methods: Two-hundred and thirty-eight patients were enrolled: 74 started immunosuppression with IV TK (Prograf®, 0.03mg/kg by continuous perfusion), 73 with BID (Tacni®, 0.6mg/kg/12h), and 91 with QD (Advagraf®, 0.12-0.18mg/kg/24h). The dose was subsequently modified in order to maintain a TK through level (C_0) of 5-15ng/mL. Those patients receiving IV formulation were switched to either of the two oral formulations as soon as they could tolerate oral administration. For the purpose of this analysis, C_0 at 48 hours, 7, 14, 21, and 28 days after d0 were recorded as well as acute GVHD and adverse effects of TK (acute kidney injury [AKI], thrombotic microangiopathy [TMA], and neurotoxicity within the first 3 months).

Results: With the exception of the first 48h, only a small percentage of patients had sub-therapeutic TK levels (23% at 48h, 3% at 7d, 6% at 14d, 3% at 21d, and 3% at 28d). Additionally, despite close C_0 monitoring and dose adjustments, a higher proportion of patients presented TK overdosing (>15ng/mL) at different timepoints after alloHCT (23% at 48h, 28% at 7d, 22% at 14d, 20% at 21d, and 26% at 28d) (Figure 1).At 48 hours, C_0 levels were significantly higher with IV TK than with oral formulations, resulting in lower proportion of patients with $C_0 < 5$ng/mL (IV TK 14% vs. BID 27%, $p = 0.037$; and vs. QD 28%, $p = 0.027$) and higher proportion with $C_0 > 15$ng/mL (IV TK 23% vs. BID 11%, $p = 0.027$; and QD 11%, $p = 0.042$). Sub-therapeutic TK levels at 48 hours and at 7d were associated to a higher incidence of grade II-IV GVHD (31% vs. 21% at 48h, $p = 0.088$; and 8% vs. 0.6% at 7d, $p = 0.001$). AKI was observed in 180 (76%) patients (grade 1 $n = 77$, grade 2 $n = 79$, and grade 3 $n = 24$) with no significant differences between IV TK, BID, and QD. Ten (4%) and 14 (6%) patients developed TMA and neurotoxicity, respectively, with no differences between groups.

Figure 1. TK C_0 levels according to different TK formulations (IV TK, intravenous; BID, twice-daily oral; QD, once-daily modified-release).



Conclusions: IV TK allows reaching therapeutic levels more quickly than oral formulations. Our results show that a quarter of the patients have supra-therapeutic TK levels regardless of the formulation used, and despite close monitoring. Considering that sub-therapeutic levels are associated with increased risk of GVHD, the use of TK IK subsequently switching to VO appears to be the best option.

Disclosure: All authors declare no conflicts of interest.

P195

Prophylactic defibrotide is effective for acute graft versus host disease as well as sinusoidal obstructive syndrome

E. Kircali[1], G. Cengiz Seval[1], S. Civriz Bozdag[1], M. Kurt Yuksel[1], P. Topcuoglu[1], O. Arslan[1], M. Ozcan[1], T. Demirer[1], G. Gurman[1], M. Beksac[1], O. Ilhan[1], S.K. Toprak[1]

[1]*Ankara University, Ankara, Turkey*

Background: Defibrotide is an antithrombotic, anti-inflammatory, profibrinolytic and antiischemic drug composed predominantly of single-stranded polydeoxy ribonucleotides. It is mainly used to prevent and treat sinusoidal endothelial cell damage in sinusoidal obstruction syndrome (SOS) after allogeneic stem cell transplantation (Allo-SCT), with acceptable toxicity. As the data showing that defibrotide may have a protective effect on activated endothelial cells become widespread, and it has been shown in preclinical studies that defibrotide suppresses heparanase gene expression, which is thought to have a great effect on acute graft versus host disease (aGvHD) the role of this drug in aGvHD has also become evident, the hypothesis that defibrotide may have a role in aGVHD has been developed. In this study, we investigated the relationship between defibrotid and aGvHD based on this hypothesis.

Methods: Between January 2014 and May 2021, 345 patients who underwent allogeneic stem cell transplantation (Allo-SCT) were included for this analysis in our center. In 116 (33.6%) of these patients, the risk of SOS was found to be high (busulfan will be used in the preparation regimen, gemtuzumab ozogamicin was used in the 3 months before the transplant, the abdominal region will be irradiated, in these patients with active hepatitis B or C infection, the preparation regimen will be started. Similarly, 25 mg/kg/dose prophylactic defibrotide was used in 4 equal doses for 21 days. Patients who used defibrotide for therapeutic purposes were not included in the study. The patients who

underwent ASCT from a fully matched sibling donor, fully matched unrelated, or a 9/10 HLA-matched unrelated donor were included whereas cord blood transplants were not.

Results: The female to male ratio was 143/202 and the median age was 43 (18-72). The distribution of ASCT indications according to defibrotide absent and present groups were as follows: acute myeloid leukemia(AML,n = 142) 88(62%)/54(38%), acute lymphoblastic leukemia(ALL,n = 64) 46(71,9 %)/18(28.1 %), myelodysplastic syndrome(MDS,n = 26) 17(65.4%)/9(34.6%), aplastic anemia(AA, n =18) 12(66.7%)/6(33.3%), mycosis fungoides(MF,n = 13) 9(69.2%)/4(30.8 %), chronic myeloid leukemia(CML,n = 13) 10(76.9%)/3(23.1%), primary myelofibrosis(PMF,n = 11) 6(54.5%)/5(45.5%), Hodgkin's lymphoma(HL,n = 7) 6(85.7 %)/1(14.3), peripheral T cell lymphoma(PTCL,n = 7) 7(100%)/0 and other(n = 44) 28(63.6%)/16(36.4 %), respectively. The distribution did not differ statistically between the groups (p = 0,537). We performed a multivariate analysis to examine the effect of defibrotide on the risk of developing aGvHD and the degree of aGvHD, and observed that prophylactic defibrotide significantly reduced the risk of developing aGvHD (p = 0.001). Similarly, in patients who have developed aGvHD, total Glucksberg degree of aGvHD is attenuated with prophylactic defibrotide, too (p = 0,049).

Table 1. Probability of developing aGvHD according to defibrotide use (p= 0.001)

	aGvHH		Total
	Absent	Present	
Defibrotide (+)	83 (% 71,6)	33 (% 28,4)	116
Defibrotide (-)	112 (% 48,9)	117 (% 51,1)	229
	195	150	345

Table 2. Relationship between defibrotide and aGvHD grade (p= 0.049)

			aGvHD Grade				
			0	1	2	3	Total
Defibrotide	(+)	N	112	104	8	5	229
		%	% 50,7	% 43,7	% 3,5	% 2,2	% 100,0
	(-)	N	83	30	1	2	116
		%	% 65,5	% 31,9	% 0,9	% 1,7	% 100,0
Total		N	195	134	9	7	345
		%	% 55,7	% 39,7	% 2,6	% 2,0	% 100,0

Conclusions: aGvHD is one of the life-threatening early complications of AKHN and is still the most important cause of non-recurrent mortality. Therefore, any approach that can reduce the risk and degree of aGvHH may be clinically important.To our knowledge, this is the largest study that evaluate the effectiveness of defirotide on GvHH, but prospective randomized controlled studies are warranted to verify our data.

Disclosure: Nothing to declare

P196

Prospective analysis of the incidence and outcome of late acute and chronic graft-versus-host disease from multiple transplant centers

R. Langer[1], A. Lelas[2], L. Desnica[2], M. Rittenschober[3], A. Piekarska[4], A. Sadowska-Klasa[4], I. Sabol[5], H. Greinix[6], A. Dickinson[7], M. Inngjerdingen[8], A. Lawitschka[3], R. Vrhovac[2], D. Pulanic[2], S. Klein[9], J.M. Middeke[10], M. Grube[1], E. Holler[1], M. Edinger[1], W. Herr[1], D. Wolff[1]

[1]University Hospital Regensburg, Regensburg, Germany, [2]University Hospital Centre Zagreb, Zagreb, Croatia, [3]St. Anna Children`s Hospital, Medical University of Vienna, Vienna, Austria, [4]Medical University of Gdansk, Gdansk, Poland, [5]Rudjer Boskovic Institute, Zagreb, Croatia, [6]Medical University of Graz, Graz, Austria, [7]Newcastle University Faculty of Medical Sciences, Newcastle upon Tyne, United Kingdom, [8]Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [9]University Medical Center Mannheim, Mannheim, Germany, [10]University Hospital Dresden, Dresden, Germany

Background: Chronic Graft-versus-Host Disease (cGvHD) is the most serious late complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Our aim was to capture the current incidence of cGvHD and late acute GvHD (laGvHD) based on the 2014 NIH consensus criteria and its impact on transplant related mortality (TRM), relapse (R), and overall survival (OS) within a multi-center analysis including transplant centers from Regensburg, Mannheim, Dresden, Vienna, Zagreb and Gdańsk.

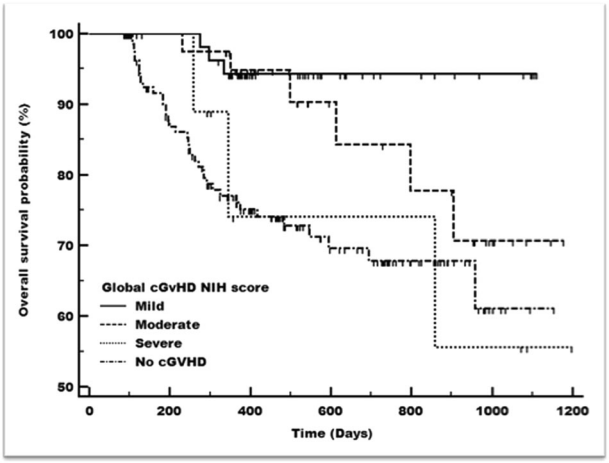
Methods: The analysis was performed on 317 consecutively transplanted patients, 296 adults and 21 pediatrics, who underwent first allo-HSCT in 2017. Endpoints were OS, TRM and R at last follow-up and second transplantation with the latter being censored. Patients with TRM or R before day 100 after allo-HSCT were excluded from cumulative incidence (CI) analysis of cGvHD.

Results: CI of laGvHD were 9.5% (adults) and 4.8% (pediatric) (median d onset 137, range 100-415), while CI of cGvHD of the patient cohort at risk was 43.6% (adults) (median d onset 198, range 68-1051) in a median observation time of 397 days. The type of onset of cGvHD was de novo in 45 (41.3%), quiescent in 54 (49.5%) and progressive in 10 (9.2%) patients, respectively. In adults, the use of ATG (n = 137) or post-transplant cyclophosphamide (n = 62) as prophylactic agents led to a significantly (p < 0.01) lower incidence of cGvHD compared to standard prophylaxis (n = 116) (33.3% and 31.9% vs. 61.5%).

	Adults with allo-HSCT (n = 296)	**Pediatrics with allo-HSCT (n = 21)**	**Adults at risk (n = 250)**	**Pediatrics at risk (n = 19)**
no GvHD	107 (36.1%)	15 (71.4%)	70 (28.0%)	13 (68.4%)
aGvHD	127 (42.9%)	6 (28.6%)	118 (47.2%)	6 (31.6%)
laGvHD	28 (9.5%)	1 (4.8%)	28 (11.2%)	1 (5.3%)
cGvHD	109 (37.2%)	2 (9.5%)	109 (43.6%)	2 (10.5%)
mild	56 (51.4%)	0 (0.0%)	56 (51.4%)	0 (0.0%)
moderate	43 (38.5%)	1 (50.0%)	43 (38.5%)	1 (50.0%)
severe	10 (8.3%)	1 (50.0%)	10 (8.3%)	1 (50.0%)

By exclusion of the early mortality (d 100: TRM 7.6%, R 6.3%, OS 91.2%) and start of CI on day 100 of the remaining 269 patients at risk for cGvHD or laGvHD TRM was significantly higher in patients with aGvHD and cGvHD compared to no cGvHD (19.3% and 9.0% vs. 5.4%; p = 0.0036). OS was significantly higher in patients with cGvHD compared to patients without cGvHD (77.7% vs. 61.1%; logrank test p = 0.0006; HR 0.3396, 95%CI 0.1939-0.5945) since diagnosis of cGvHD resulted in a significant lower relapse rate compared to patients without cGvHD (17.9% vs. 32.6%; logrank test p < 0.0001, HR 0.216, 95%CI 0.115-0.405). We didn't find a significant influence of onset type or maximum severity grade of cGvHD on TRM and R. We also found a significant better OS in patients with mild and moderate cGvHD compared to patients without cGvHD, but not for severe cGvHD forms (mild: 94.3%; moderate: 70.7%; severe: 55.6% vs. no cGvHD: 61.1%; p = 0.001; p = 0.0426 and p = 0.9645).

OS for adults after diagnosis of cGvHD



Conclusions: The analysis revealed an improved survival with mild and moderate GvHD compared to patients without cGvHD due to a reduced relapse rate. In contrast, severe cGvHD negatively affected OS and future aims should focus on prevention of severe forms to improve OS and quality of life. Interestingly, the prognosis of patients with cGvHD appeared to be better compared to past cohorts.

Disclosure:

Prof. Dr. med. Daniel Wolff received research funds from Novartis and honoraria from Amgen, Neovii, Novartis, Mallinckrodt, Incyte and Takeda.

Radovan Vrhovac received honoraria from Novartis, Pfizer, Abbvie and MSD.

Dr. Anita Lawitschka, MD received honoraria from Novartis.

Dr. med. Jan Moritz Middeke received honoraria from advisory board Novartis.

Univ.-Prof. Dr. med. univ. Greinix, Hildegard received honoraria for participation in advisory boards and speakers bureau from gilead, BMS/celgene, sanofi, takeda, Therakos.

Prof. Dr. med. Ernst Holler received honoraria from Advisory board MEDAC, Maatpharma, pharmabiome and Novartis, speakers bureau Neovii.

P197

Myeloid-derived suppressor cells predict response to ruxolitinib-corticosteroids therapy for acute graft versus host disease

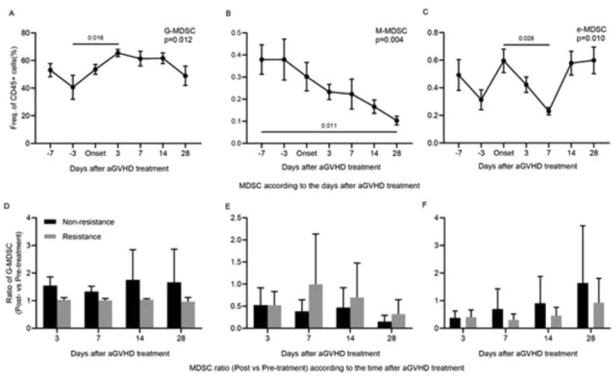
B. Peng[1,2], L. Dou[3,2,4], J. Yang[2], D. Liu[3,2]

[1]The Fifth Medical Center of Chinese PLA General Hospital, Beijing, China, [2]Medical School of Chinese PLA, Beijing, China, [3]the Fifth Medical Center of Chinese PLA General Hospital, Beijing, China, [4]The second School of Clinical Medicin, Southern Medical University, Guangzhou, China

Background: Acute graft versus host disease (aGVHD) remains one of the principal causes of nonrelapse mortality (NRM) following hematopoietic stem cell transplantation (HSCT). Systemic corticosteroids are often used as first-line therapy for aGVHD, but nearly 50% of the aGVHD patients are resistant to steroids. It has been reported that ruxolitinib combined with steroids was tolerable in patients with newly diagnosed aGVHD with improved overall response rate (ORR). However, the optimal predictor for predicting response to this novel first-line treatment has not been established clearly. Myeloid-derived suppressor cells (MDSC) are a group of myeloid cells with immunosuppressive activity, including granulocytic MDSCs (G-MDSC), monocytic MDSC (M-MDSC) and early-stage MDSC (e-MDSC). This study focused on the kinetics of MDSC during the treatment of ruxolitinib combined with steroids for aGVHD, and explored the relationship between MDSC and response to treatment.

Methods: Peripheral blood (PB) samples from patients who underwent HSCT were prospectively obtained for regular evaluation of MDSC reconstitution after transplantation. Flow cytometry was utilized to monitor MDSC recovery at different time points. And in cases with aGVHD, MDSC frequency before and after aGVHD treatment (+3 days, +7 days, +14 days and +28 days) were also monitored. MDSC suppression assay was performed to verify the inhibition of MDSC on T cell proliferation through the co-culture of purified CD8 + T cell and MDSC isolated from the PB of patients.

Results: Changes of G-MDSC kinetics observed during ruxolitinib-corticosteroids treatment are significant and showed an upward trend after initiation of therapy ($P = 0.012$). The ratio of G-MDSC to PB CD45 + cells on day 3 after aGVHD therapy was significantly higher than that of day 3 prior to aGVHD. In contrast to G-MDSC, M-MDSC showed a decreasing trend after aGVHD treatment ($P = 0.004$). Ratios of E-MDSC at different time points were also obviously different during aGVHD treatment ($P = 0.010$). The G-MDSC of the ruxolitinib-corticosteroids sensitive group increased significantly from baseline after treatment, while the G-MDSC of the combined treatment resistant group showed no noticeable change (Figure 1) . In the MDSC suppression assay, MDSC markedly inhibited T cell proliferation (proliferation index: no MDSC, 9.24 ± 8.10 vs. with MDSC, 5.45 ± 4.05; $P = 0.037$).



Conclusions: MDSC recovery is closely related to the response to ruxolitinib-corticosteroids as first-Line therapy for newly diagnosed aGVHD. Patients with lower G-MDSC levels at baseline and 7-21 days after HSCT were more likely to develop aGVHD resistance to ruxolitinib combined with corticosteroids than controls. The kinetics of MDSC subpopulations may be used to predict the duration of response to this novel first-line treatment.

Clinical Trial Registry: None

Disclosure: Nothing to declare

P198

Relationship within anaerobicidal antibiotics, clostridium difficile infection and the development and degree of digestive graft versus host disease

A. Borrero Borrego[1], L. González Pinedo[1], M.K. Torres Ochando[1], M.T. Borrero Borrego[2], G. Strigkos[2], M.D.M. Perera Álvarez[1]

[1]Hospital Universitario de Gran Canaria Doctor Negrin, Las Palmas de Gran Canaria, Spain, [2]University of Utrecht, Utrecht, Netherlands

Background: Severe digestive graft versus host disease (GVHD) is a topic of great importance after allogeneic Hematopoietic Stem Cell tTransplantation (allo-HSCT), since it is difficult to treat and the involvement of the digestive system is described in almost all cases of fatal acute GVHD. It is also known that the recruitment of inflammatory cells is dependent on bacterial translocations in the intestinal wall, leading to an increasing interest in factors that could take part in this process.

Methods: We performed an observational and retrospective analysis in a single-center study, of all patients that underwent to allo-HSCT from January/2019 to March/2021 (N = 71) and analyzed all the possible pre-transplant conditions and during it, which could determine the development of digestive GVHD, such as, antibiotics guided by multi-resistant bacteria isolated in rectal exudates, clostridium difficile infection and mucositis. The primary outcome was the risk of developing upper and lower acute GVHD. We adjusted logistic regression model included transplantation characteristics, GVHD risk factors and adjunctive antibiotic exposures as covariates.

Results: A total of 71 patients were included in the full cohort. There were no differences regarding the distribution by sex. The average age was 47. The main transplanted pathology was acute leukemia. The types of HSCT were: 56.3% (40/71) haploidentical, 24% (17/71) non related, 17% (12/71) HLA identical and 2 mismatch.

The standard prophylaxis of GVHD was High Dose Cyclophosphamide on days + 3/+ 4 followed by anticalcineurinic and Mycophenolate mofetil from day +5.

We used standard antibiotic prophylaxis with quinolones. Multiresistant (MR) bacterias were discovered in 20% (13/64) of patients at admission date, and from the rest, 15% acquired resistance during hospital stay; no relationship was observed between colonization with MR bacteria and the development of digestive GVHD.

Empirical antibiotic therapy in our center is with third generation cephalosporins (cefepime). 93% (66/71) suffered from febrile neutropenia and of these, 82% (54/66), were treated with cefepime combined or in monotherapy. 33% (21/66) used combined therapy, being the main group of antibiotics: glucopeptides (28), piperacilina tazobactam (15), carbapenems (20) and Ceftazidime-avibactam (4). None of them was associated, in adjusted models, with an increased risk of GVHD.

Mucositis grades II-IV was present in 41% (29/71) of patients, having received 76% (22/29) of those, a myeloablative conditioning regimen. Clostridium difficile infection was discovered in 18% (13/71) of patients.

20 patients developed digestive GVHD: 30% (6/20) grades III-IV and 75% (15/20) grades II-IV, and we observed an association between the infection with clostridium difficile and an increased risk of GVHD (adjusted odds ratio (aOR) 6.33; 95% confidence interval (CI) 1.7 – 23.5), as well as with an increased risk of grade II-IV GVHD (not statistically significant).

Conclusions: Clostridium difficile must be carefully studied in allo-HSCT patients and prevention strategies should be made, in order to control this entity; as it has been related to digestive GVHD according to the bibliography and as it has been shown in our study. No recommendations could be made about the antibiotic strategy and more studies should be performed in this way.

Disclosure: Nothing to declare.

P199

Low-dose antithymocyte globulin plus low-dose posttransplant cyclophosphamide could mitigate the risk of graft versus host disease after haploidentical transplantation from maternal/collateral donors

X. Song[1]

[1]Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Maternal and collateral donors were associated with higher incidence of acute graft-versus-host disease (aGvHD) after haploidentical hematopoietic stem cell transplantation (haplo-HSCT).

Methods: To improve the efficiency of GvHD prophylaxis in haplo-HSCT with maternal and collateral donors, a novel regimen which was composed of low-dose ATG and low-dose PTCy combined with CsA and MMF had been developed in our center. We performed a retrospective study on 50 patients diagnosed with hematological malignancies after maternal/collateral haplo-HSCT (20 with ATG-based regimen for GvHD prophylaxis and 30 with the low-dose ATG/PTCy-based regimen).

Results: The 180-day cumulative incidences (CIs) of grades II-IV and III-IV acute GvHD were 24.1% and 7.6% in the low-dose ATG/PTCy-based group, which were significantly lower than that in the ATG-based group (51.6% and 27.7%). In low-dose ATG/PTCy-based group, the 2-year probability of overall survival (OS) and relapse-free survival (RFS) were 70.9% and 71.1%, which were higher than that in ATG-based group with OS of 43.2% and RFS of 44.1%. Furthermore, according to multivariate analysis, the low-dose ATG/PTCy-based regimen significantly reduced the risk of grade II-IV (HR = 0.237, 95% CI 0.067-0.829; P = 0.024) and grade III-IV aGvHD (HR = 0.015, 95% CI 0.000-0.899; P = 0.044) as a positive risk factor.

Conclusions: The results suggested that low-dose ATG with low-dose PTCy could be a novel regimen to effectively prevent acute GvHD after maternal/collateral donor transplantation.

Disclosure: Nothing to declare.

P201

Exocrine pancreatic insufficiency as an atypical manifestation of chronic graft versus host disease following allogeneic hematopoietic stem cell transplantation

A. Puchol Crespo[1], I. Iturrate Basarán[1], C. Mayor Bastida[1], S. Díaz López[1], A. Alegre Amor[1], Á. Figuera Álvarez[1], B. Aguado Bueno[1]

[1]Hospital La Princesa, Madrid, Spain

Background: Graft-versus-host disease (GVHD) remains a major complication after allogeneic hematopoietic stem cell transplantation (HSCT). The diagnosis of chronic GVHD is complex, as it can potentially affect almost any organ/tissue[1]. Rare forms of GVHD have been described in the literature including neurological, myofascial and cardiac involvement among others[2,3]; to date, few reports have evaluated pancreas involvement in cGVHD. The major difficulty is to be suspicious in the face of the huge number of different clinical presentations of this postHSCT complication, as the one we show in our case report.

Methods: We report a case of pancreatic atrophy as a manifestation of cGVHD.

Results: A 42-year-old woman was diagnosed with AML in 2018 with NPM1 and FLT3/ITD +. Abnormal karyotype 47XX + mar, MLL negative. The patient had a morphologic complete remission after induction chemotherapy cytarabine and anthracycline, with positive minimal residual disease (MRD). It was followed by early consolidation with 2 cycles with high dose cytarabine and

Midostaurin, achieving MRD negative before transplantation. She received and allogeneic peripheral blood HSCT from a matched unrelated female donor, with Cyclophosphamide and Busulfan (CyBu) conditioning regimen. Prophylaxis for GVHD with standard course of methotrexate and cyclosporine. She experienced acute grade II skin GVHD and diarrhoea that cleared after 2 weeks of prednisolone therapy.

Six months after transplantation cyclosporine was discontinued. For the next three months she gradually presented with weight loss (4 kg), steatorrhea and abnormal liver function tests. Due to GVHD suspicion 0.5 mg/kg/day course of Prednisone was started. The stool examination was negative for infectious causes of diarrhoea. Faecal elastase level was 5 mcg/g (normal > 200mcg/g). Breath test with ^{13}C-mixed triglycerides was 20.75% (normal > 29% exhaled). Magnetic resonance imaging (MRI) showed remarkable diffuse pancreatic atrophy.

The clinical diagnosis was exocrine pancreatic insufficiency due to pancreatic atrophy, most likely as a form of cGVHD after allogenic stem cell transplantation. The patient received pancreatic enzyme supplement (Kreon 10.000 U, containing lipase 10.000U, protease 600U and amylase 8.000U) as required, starting on day +258, and nutritional support. After three months, steatorrhea was fully resolved, being able to taper prednisone without worsening, with progressive weight gain, stabilizing at her initial weight 6 months later.

Despite the clinical improvement, the pancreas atrophy persisted in the following MRIs. She didn't suffer GVHD relapse nor needed to restart immunosuppressive treatment at any point of the follow-up.

Conclusions: There are few cases of pancreatic insufficiency after HSCT reported in the literature, being the most common form of presentation weight loss and steatorrhea. The etiology of pancreatic atrophy after HSCT is not fully known, although it shows a significant association with cGVHD, with greater loss of pancreatic glandular tissue than patients without cGVHD. In this population, the presence of gastrointestinal (GI) cGVHD is significant, suggesting that pancreatic atrophy might be a part of GI cGVHD. HSCT receptors that develop persistent fat malabsorption symptoms should be tested for exocrine pancreatic insufficiency, liable to be treated with oral enzyme supplements. All cases should be reported in order to better define and diagnose this rare entity.

Disclosure: Nothing to declare.

P202

Assessment of efficacy and toxicity of methotrexate in the treatment of chronic graft-versus-host disease

I. Gonçalves Ramos[1], G. Fatobene[1], A. Costa Cordeiro[1], A. Ferreira Meneses[1], M. Fonseca[1], J. Manuel Carranza Jara[1], L. Netto Chaer[1], L. Carolina Barbosa Mariano[1], V. Rocha[1]

[1]University of São Paulo, São Paulo, Brazil

Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is associated with several complications, including chronic graft-versus-host disease (cGVHD) in 30-70% of HSCTs. Chronic GVHD has impact on quality of life and mortality, often requiring multiple therapeutic lines. Among available therapeutic options, methotrexate is an attractive one as it is a potentially low-cost, effective alternative associated with reduced toxicity. However, previous studies were relatively small or included heterogeneous groups of patients. The aim of this analysis was to assess the impact of methotrexate on the treatment of cGVHD in adult patients.

Methods: Retrospective evaluation of electronic medical charts of patients. Eligible patients were those with diagnosis of cGVHD according to the 2014 NIH consensus criteria treated with methotrexate in second line or beyond between January 2014 and November 2020. Additionally, patients were required to have received at least 4 doses of methotrexate and have a minimum follow-up time of 3 months after starting this therapy. Best overall response (BOR) at 6 months was the primary endpoint, whereas secondary endpoints included failure-free survival, cumulative incidence of steroid withdrawal, overall survival, and toxicity.

Results: Twenty-one patients receiving methotrexate for treatment of cGVHD were identified; two of whom were excluded for having less than 3 months of follow-up period. The analysis included 19 patients with a median follow-up of 18 months (range, 3 to71). The cumulative incidence of BOR at 6 months was 63% (11/19 patients), 16% of which (3/19 patients) corresponding to complete response, and 43% (8/19 patients) to partial response. Among patients with severe and moderate cGVHD, BOR were 37% (3/8 patients) and 45% (5/11 patients), respectively. The cumulative incidence of steroid discontinuation at 6 months was 60% (95% confidence interval [CI] 29-81%). Skin, mouth and liver were the most affected organs in evaluable patients; only two patients presented fascia/joint involvement. Failure-free survival at 6 months was 90% (95% CI 64-97%), and the overall survival at 1 year was 88% (95% CI 59-97%). Little methotrexate-attributable toxicity was observed, with only one case of renal toxicity and one case of liver toxicity, both at grade. One patient had disseminated adenoviral infection on methotrexate and other concomitant immunosuppressive drugs, which was not fatal. The median time between the start of methotrexate and BOR was 92 days (17-180, $n = 11$), and the maximum dose was 7.3 mg/m^2 (min-max3.2-13.4).

Conclusions: Patients receiving methotrexate for the treatment of cGVHD had an overall response rate comparable to previous studies in the literature and showed favorable toxicity and tolerance profiles. These advantages combined with its low cost make this medication an interesting option in resource-constrained countries. Apart from its retrospective nature, this analysis has relevant limitations: lack of a comparative group, organ-specific responses, and a formal evaluation of cost-effectiveness. Studies defining the ideal dose of methotrexate in cGVHD and encompassing a larger number of participants are necessary for a more accurate assessment of the role of this medication in the treatment of cGVHD.

Disclosure: Nothing to declare.

P203

Treatment of graft-versus-host disease with extracorporeal photopheresis. Experience in a center

P. López de Ugarriza[1], P.C. Tamayo Arroyo[1], E. Martínez Revuelta[1], J.M. García Gala[1], M.Á. Fernández Rodríguez[1]

[1]Hospital Universitario Central de Asturias, Oviedo, Spain

Background: Extracorporeal photopheresis (ECP) is an immunomodulatory therapy mainly indicated in cutaneous T lymphoma treatment, acute graft-versus-host disease (aGVHD) and chronic graft-versus-host disease (cGVHD) after allogeneic hematopoietic stem cell transplant (AHSCT), solid organ transplant rejection and conventional treatment resistant autoimmune disorders. Among its advantages, it stands out that it does not produce immunosuppression or drug interactions with complementary immunosuppressive treatment. Although it has been shown to be effective, safe and well tolerated, reported responses are highly variable. The objective of this study is to describe the experience

in our center in the treatment of graft-versus-host disease (GVHD) with ECP.

Methods: Medical histories of those patients who received treatment with ECP for both aGVHD and cGVHD in our center were retrospectively reviewed. The analysis period was from 2014 to 2021.

Results: 28 patients were included in the study. The average age was 41,21 years (5-68). For all of them, 20/28 (71,42%) were men. Related to type of AHSCT, patients who received an unrelated donor transplant, HLA-matched sibling donor transplant and haploidentical donor transplant were 17/28 (60,71%), 8/28 (28,57%) and 3/28 (10,71%) respectively. The diagnosis that motivated the transplant was Acute Lymphoblastic Leukemias in 8/28 (28,57%), Acute Myeloblastic Leukemias in 8/28 (28,57%), Chronic Myeloproliferative Neoplasms in 4/28 (14,28%), Non-Hodgkin Lymphomas in 4/28 (14,28%), and other diagnoses in 4/28 (14,28%). All patients (28/28; 100%) received at least one adjuvant immunosuppressant treatment and 17/28 (60,71%) received three. Many patients (24/28; 85,71%) had cGVHD. Clinical involvement related to GVHD that patients presented most frequently was cutaneous (25/28; 89,28%) followed by digestive (12/28; 42,85%), joint (5/28; 17,85%), hepatic (4/28; 14,28%) and respiratory (2/28; 7,14%). Most patients (25/28, 89,28%) required the placement of a central venous catheter. Mean number of procedures performed was 26,53 (2-51). 3/28 (10,71%) patients performed more than one cycle of procedures. The response to ECP was complete, partial and non-response in 8/28 (28,57%), 12/28 (42,85%) and 8/28 (28,57%) respectively. Of the 5/28 (17,85%) patients who died, the cause was aGVHD in 2/5 (40%) and intercurrent infection was the cause in 3/5 (60%). No complications were detected with ECP except catheter-related infection. It was detected in 8 episodes (28,57%) that involve 7/28 (25%) patients. A patient died because of catheter-related infection.

Conclusions: ECP is an immunomodulatory procedure, safe and excellently tolerated in patients with GVHD that offers the advantage of being able to be administered together with other immunosuppressive treatments without interactions. Two thirds of patients with GVHD experience a total or partial response so the treatment is effective and should be considered associated with immunosuppression.

Disclosure: Nothing to declare

P204

Apoptosis and cytokine secretion of t cells during ecp treatment for cgvhd using the amicus™ blue™ online ecp system

Y. Ventura-Carmenate[1], Y.M. Castillo-Aleman[1], C.A. Villegas-Valverde[1], A.A. Bencomo-Hernandez[1], M. Al Amin[1], M.A. Martinez[1], F.M. Al Kaabi[1]

[1]Abu Dhabi Stem Cells Center, Abu Dhabi, United Arab Emirates

Background: ECP is an immunomodulatory therapy for T-cell mediated diseases. Although the immunological mechanisms are not fully understood, it is known that the induction of apoptosis is a central mechanism of ECP. Following ECP, the cytokine profile is modified toward upregulation of immunosuppressive factors and downregulation of co-stimulatory molecules. These immune responses can help attenuate inflammatory conditions such as GvHD. We performed a prospective analysis of apoptosis and cytokine secretion by flow cytometry in ECP treated cells of steroid refractory cGvHD patients. ECP was performed with the Amicus Blue™ online system (Fresenius Kabi, Germany).

Methods: Seventy-five ECP procedures ($n = 75$) were performed in 3 female patients from May 2021 to December 2021. Samples (2mL) of the collected cells were taken before the addition of 8-methoxypsoralen (8-MOP) and after UVA photoactivation. The samples were re-suspended in 3mL of RPMI 1640 culture medium with 10% AB serum and incubated at 37°C in 5% CO2 for 24, 48, and 72 hours. Apoptosis measurement was performed by flow cytometry using the DxFlex flow cytometer (Beckman Coulter, USA) and the Beckman Coulter Annexin A5 FITC/7AAD kit (IM3614) according to the instructions, and with the additional use of reagents Beckman Coulter CD45-APC AF 750 (A79392) and CD3-APC (IM2467). The expression of two cytokines, TNFα and IFNγ, was assessed by flow cytometry using the DxFlex flow cytometer on CD4 + T and CD8 + T cells before and after 24hr in the culture at 37°C in 5% CO2. The samples were either stimulated with CytoStim™ (Miltenyi Biotec), or with PBS (negative control), and incubated at 37°C and 5% CO_2 for 2hr. Brefeldin A was added and incubated for 6hr, and fixation and permeabilization were performed. Staining was performed with monoclonal antibodies (Miltenyi Biotec): CD3-APC, CD4-Vio® Bright B515, CD8-VioGreen™, IFNγ-PE, TNFα-PE-Vio® 770 Fixed Dye and Viobility 405/452. Data were processed using Kaluza C Software v1.1 with a minimum of 150,000 acquired events. The one-way ANOVA test for paired samples was performed with GraphPad Prism v.8 (La Jolla, USA) and considered statistically significant for $p < 0.05$.

Results: We used simultaneous staining with annexin V-FITC and 7ADD to measure apoptosis. After in vitro culture of ECP treated cells, 13% (5-20%) of CD3 + T cells were apoptotic at 48hr compared to 31.3% (23-46%) at 72hr, with only 30.3% (24-40.1%) viable cells ($p = 0.03$). Untreated cells maintained up to 80% viability after 72hr. The number of TNFα-secreting TCD8 cells was significantly higher in pre-ECP stimulated samples ($p = 0.001$). A decrease in T cells secreting IFNγ was also observed in the post-ECP stimulated samples without statistical significance.

TCD3 apoptosis induced by ECP and (B) Intracellular flow cytometric enumeration of IFNγ/TNFα secreting CD4, CD8-T cells

Conclusions: Our results for ECP-induced apoptosis at 72hr with the Amicus Blue ECP system were comparable to published literature. Reduction of TNFα after ECP treatment may have a direct role in reducing the progress of cGvHD. ECP performed with the Amicus Blue system resulted in a reduction of TNFα and IFNγ levels in the treated cells, as expected.

Disclosure: Nothing to declare

P205

Routine use of anti-thymocyte globulin (atg) results in low incidence of severe graft-versus-host disease: A single center experience

F. Kovácsová[1], M. Krejčí[1], B. Weinbergerová[1], M. Tomíška[1], T. Kabut[1], F. Folber[1], J. Mayer[1]

[1]Masaryk University Hospital Brno, Brno, Czech Republic

Background: Anti-thymocyte globulin (ATG, Grafalon) is a mix of polyclonal rabbit anti T-cell antibodies used to reduce the risk of graft rejection and acute and chronic graft-versus-host disease (GVHD) in the setting of an allogeneic hematopoietic stem cell transplantation (alloHSCT). The aim of this study was to find out the cumulative incidence (CI) of GVHD while using ATG at our institution, and to compare this incidence among various patient subgroups.

Methods: From all the patients who underwent their first alloHSCT at our department between 2006 and 2020 we excluded those who did not receive ATG. We studied the cumulative incidence and severity of acute (100-day CI) and chronic GVHD (24-month CI), and differences depending on HLA matching, conditioning regimen intensity, and the underlying disease.

Results: We identified 481 patients in the defined time period. Eighty-three of them were excluded for not having received ATG due to heterogeneous reasons (e.g. obsolete conditioning regimens, non-malignant diseases, bone marrow stem cell source, high risk of relapse), making this subgroup unevaluable. A total number of 398 patients were included into this analysis, 203 with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), 69 with acute lymphoblastic leukemia (ALL), 44 with lymphoma, 40 with myeloproliferative neoplasms, 30 with chronic lymphocytic leukemia (CLL), and 12 others. Acute GVHD was observed in 44.7% patients (grade III and IV in 11.6%), chronic GVHD in 37.6% (extensive in 7.1%). Incidence of GVHD using an unrelated donor was higher than in related donor HSCT (acute GVHD 49.0% vs. 34.8%, respectively, $p = 0.01$; chronic GVHD 40.5% vs. 30.6%, respectively, $p = 0.02$). Higher incidence of both acute and chronic GVHD was observed in the case of HLA mismatch (53.0%, 44.6%, respectively) compared with the group of fully matched (10 out of 10) unrelated donor HSCT (45.1%, 34.9%, respectively). Myeloablative conditioning was administered in 27.6%, and reduced intensity in 72.4% patients. Incidence of acute GVHD was higher among the patients who received reduced intensity conditioning than in the subgroup with myeloablative conditioning regimen (48.9% vs. 34.0%; $p = 0.02$). The same was observed for chronic GVHD (42.0% vs. 26.0%; $p<0.01$). Incidence of GVHD was also higher in myeloid malignancies (statistically insignificant), but this can be explained by more frequent use of reduced intensity conditioning in this subgroup.

Conclusions: With the routine use of ATG the incidence of severe grades (III to IV) acute and chronic GVHD was as low as 11.6% and 7.1%, respectively. There were significant differences in the incidence according to conditioning regimen intensity and HLA matching.

Disclosure: Nothing to declare.

P206

JAK 1/2 inhibitor (ruxolitinib) might have a positive effect on MDSCS

J. Yang[1], B. Peng[1], S. Fang[1], K. Qian[1], H. Wang[1], Y. Wen[1], Y. Jiao[1], D. Liu[1], L. Dou[1]

[1]the Fifth Medical Center of Chinese PLA General Hospital, Beijing, China

Background: Graft-versus-host disease (GVHD) is the major cause of non-relapse mortality (NRM) after allogeneic hematopoietic stem-cell transplantation (HCT). The response rate to first-line corticosteroid therapy for aGVHD patients is approximately 50%. The overall survival of steroid-refractory aGVHD patients is only approximately 30%. A new first-line therapy to improve the efficacy of treatment for aGVHD is of great significance.

Methods: We performed a prospective, open-label trail (NCT04061876) in my transplantation center and prospectively observed the kinetic characteristics of lymphocyte subsets and MDSC were monitored, and then we compared them in steroids-ruxolitinib group ($n = 23$), free-aGVHD group ($n = 20$) and steroids group ($n = 23$). Healthy human PBMC was treated with different concentrations of JAK 1/2 inhibitor (Ruxolitinib) to detect the effects on differentiation and function of MDSC.

Results: In all aGVHD patients treated with Steroids-Ruxolitinib therapy, the Day 28 CR rate was 78.26% (18/23). On day 28 after treatment, patients had lower level of $CD4^+CD29^+$ T cells ($P = 0.08$) than that of pre-treatment, whereas levels of other lymphocyte subsets in this study were higher than that of pre-treatment; $CD8^+CD28^-$ T cells ($P = 0.03$) significantly increased in patients with aGVHD than that in patients without aGVHD, so did $CD8^+CD28^-$ T/$CD8^+CD28^+$ T cell ratio ($P = 0.03$). Compared with patients without aGVHD, patients with aGVHD had lower level of G-MDSC, especially on day 14 after allo-HSCT ($P = 0.04$). Compared with pre-treatment, M-MDSC was higher in CR patients on day 3 and 7 post-treatment($P_3 = 0.01$, $P_7 = 0.03$), e-MDSC was higher on day 28 post treatment ($P = 0.01$). Moreover, compared with CR patients, M-MDSC was lower in refractory aGVHD patients on day 3 post-treatment ($P = 0.01$) and e-MDSC was lower on day 28 post-treatment ($P = 0.01$). Compared with steroids group, MDSC in steroids-ruxolitinib group was higher, with the most significant difference in M-MDSC ($P_3 = 0.03$; $P_7 = 0.01$; $P_{14} = 0.04$). In the vitro differentiation model of peripheral blood mononuclear cell (PBMC), JAK 1/ 2 inhibitors can promote MDSC and Treg most ($P_{e\text{-}MDSC} = 0.01$; $P_{G\text{-}MDSC} = 0.05$; $P_{M\text{-}MDSC} = 0.02$; $P_{Treg} = 0.04$), at 1.0 μM JAK 1/2 inhibitor (Ruxolitinib) treated for 72 h; We also found JAK 1/ 2 inhibitor can increase the expression of S100A8($P = 0.004$), S100A9 ($P = 0.04$) and NO($P = 0.03$), at a concentration of 1.0 μM.

Conclusions: The response rate of the novel first-line therapy, Steroids-Ruxolitinib, for aGVHD was promising in patients with moderate and high "Minnesota and MAGIC" risk. Moreover, the novel first-line therapy has a small impact on the immune reconstitution of patients after allo-HSCT. Patients with a better response with novel aGVHD first line therapy have higher level of MDSCs, compared to refractory ones. JAK 1/2 inhibitor can promote the differentiation and function of MDSCs.

Disclosure: This work was partially supported by grants from the National Natural Science Foundation of China (Nos. 82070178, 81770203,81700122, 81270610), Military Translational Medicine Fund of Chinese PLA General Hospital (ZH19003). Medical big data and artificial intelligence development fund of Chinese PLA General Hospital (2019MBD-016, 2019MBD-008). Military medical support innovation and generate special program(21WQ034). Special Research Found for health protection(21BJZ30).

P207

Long-term outcome in patients receiving imatinib for steroid-refractory chronic GVHD/ for refractory chronic graft-versus-host disease with fibrotic features: A single-center experience

N. Mandaci Şanli[1], E. Karakuş[1], A. Unal[1], M. Keklik[1]

[1]Erciyes University, Kayseri, Turkey

Background: Pathogenesis of chronic graft-versus-host disease (cGVHD) is incompletely defined. Standard treatment is lacking for steroid-dependent/refractory cases; Recent insights suggest that several players and different pathways are involved, including imbalance of T and B cells and exaggerated collagen production. therefore, the potential usefulness of tyrosine kinase inhibitors (TKIs) has been suggested, based on their potent antifibrotic effect.

Methods: We performed in our clinic including 11 patients with refractory cGVHD, given imatinib at a starting dose of 100 mg per day. All patients had active cGVHD with measurable involvement of skin or other districts and had previously failed at least 2 treatment lines. The most frequent underlying diseases were: acute myeloid leukemia (7/11, 63.6%), acute lymphoblastic leukemia (3/11, 27.3%), and chronic myeloid leukemia (1/11, 9.1%). All of the patients received myeloablative conditioning regimens. Grading of cGVHD and response (complete and partial organ based on clinician assessments) was performed

Results: Patient median age was 42 years (range, 30-57 years), and median duration of cGVHD was 24 months (range, 2-300 months). All patients had moderate (37/11, (63.6%) to severe (4/11, 36.4%) cGVHD. Patients developed sclerotic skin lesions

(8/11, 72.1%), lichen planus-like lesions (1/11, 9.1%), gastrointestinal and sclerotic skin lesions (1/11, 9.1%), liver and skin lesions (1/11, 9.1%). The median number of previous GVHD-therapies was 2 (range 2-5). Median imatinib treatment was 54 months (range: 3-108). Median follow-up was 77 months (range: 3-107). Overall 10 patients achieved a partial response and 1 patient complete response (CR) at 6 months of treatment. 3 of the patients responding as a partial response in the first year turned into a complete response during their follow-up. 2 patients discontinued imatinib therapy at year 4 of CR. They have been followed for a year without cGVHD treatment. While 1 patient responding as a partial response discontinued imatinib treatment after two years, another 1 patient discontinued imatinib treatment after three years. However, these two patients stopped treatment by themselves and one has been followed for 2 years and the other for 6 years in partial remission. 1 patient responding as a partial response in the first year turned into a flare after two years of imatinib treatment. All of the patients included in the study are still alive and 6 of the patients are still in a partial response. Of those patients responding to imatinib, the rate of GVHD-relapse was 9% (1/11) for fibrotic cGVHD. Imatinib-related, grade 3 to 4 toxicity included fluid retention, infections, and anemia were observed during the cGVHD treatment (respectively 2/11, 18.2%; 1/11, 9.1%; and 1/11, 9.1%).

Conclusions: Our findings suggest that imatinib is a promising treatment for patients with refractory fibrotic cGVHD

Disclosure: Nothing to declare

P208

Escalating combinatory first-line treatment for severe acute GVHD after hematopoietic stem cell transplant

F. Saraceni[1], I. Scortechini[1], G. Mancini[1], A. Fiorentini[1], F.R. Colaneri[1], A.F. Lotito[1], S. Guerzoni[1], B. Puglisi[1], I. Federici[1], R. Bencivenga[1], B. Costantini[1], V. Bisraoui Huaman[1], S. Angeletti[1], M. Montanari[1], A. Olivieri[1]

[1]*Ancona University Hospital, Ancona, Italy*

Background: Acute graft-versus-host disease (aGVHD) is a major cause of morbidity and mortality after hematopoietic stem cell transplant (HSCT). High dose steroids remain the standard of care as first-line treatment for severe aGVHD, however less than 40% of patients show a long durable remission following such approach.

Methods: We retrospectively analyzed the outcome of 23 consecutive patients who developed grade 3-4 aGVHD and received an escalating combinatory first-line treatment at our institution.

Results: Donor was matched sibling (n = 1), matched unrelated (n = 12) or haploidentical (n = 10). Stem cell source was PBSC in 90% of the patients. Conditioning was myeloablative (MAC) or reduced-intensity (RIC) in 35% and 65% of the patients, respectively. aGVHD involved skin, GI, and liver in 87%, 83% and 17% of the patients, respectively. All patients received prednisone or methylprednisolone at a dose >= 1 mg/kg as first treatment. Response was evaluated at day 3 and 5 since start of steroids. In patients with symptoms progression at day 3 or stable disease at day 5 extracorporeal photopheresis (ECP) was added (n = 12 patients). In all patients with stage >=2 lower GI involvement, Ruxolitinib 10 mg twice daily was added within 5 days since start of steroids (n = 7 patients). ECP schedule included two treatments per week for 8 weeks with a subsequent individual reduction of treatment frequency. Response to first line treatment was evaluated at day 28 and day 56. In patients treated with steroids + ECP the overall response rate (ORR) at day 28 was 75% (n = 9), with 58% (n = 7) achieving CR. In patients treated with steroids + ECP + Ruxolitinib the ORR was 86% (n = 6), with 67% (n = 4) achieving CR (Figure 1). The durable ORR at day 56 was 58% (n = 7/12) in patients treated with steroids + ECP and 71% (n = 5/7) in patients treated with steroids + ECP + ruxolitinib. Median time on steroids was 12 days. ECP was well tolerated; the only adverse event recorded was mild thrombocitopenia in 4 patients. 5 patients receiving ruxolitinib experienced grade 2 anemia or thrombocytopenia, the latter leading to drug discontinuation in 2 patients. 13 patients received ECP and 3 patients received Ruxolitinib as second line treatment for steroid refractory or steroid dependent GVHD. 2 patients with lower GI involvement received vedolizumab as second line therapy. Median time to second line treatment was 24 days. 5 patients died; 4 due to infectious complications secondary to refractory GVHD, 1 of pulmonary embolism with GVHD in complete response. Median overall survival of the global population was 20 months.

Conclusions: In conclusion, an escalating combinatory first-line treatment with a backbone of steroids and ECP, and the addition of Ruxolitinb in patients with lower GI involvement seems feasible and associated with a promising response rate, allowing a rapid steroid taper.

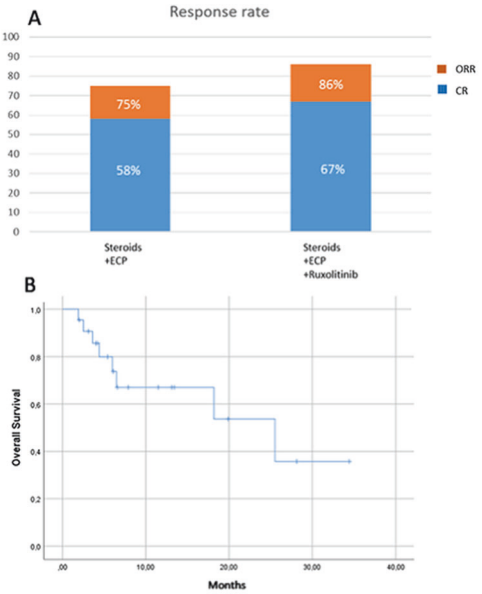


Figure 1. Response rate at day 28 according to first line treatment (A). Global overall survival (B).

Disclosure: Nothing to declare

P209

Retrospective single center analysis of alpha 1 antitrypsin for steroid-refractory acute graft-versus-host-disease of the gut after multiple lines of pretreatment

K. Nickel[1], K. Braitsch[1], R. Eichner[1], K. Koch[1], I. Miller[1], L. Oßwald[1], F. Bassermann[1], P. Herhaus[1], M. Verbeek[1]

[1]*Klinikum rechts der Isar der TU München, München, Germany*

Background: Steroid-refractory acute Graft-versus-Host-Disease (SR-aGvHD) after allogenic hematopoietic stem cell transplantation (allo-HSCT) is challenging and associated with high morbidity and mortality. So far, no standard second-line therapy for SR-aGvHD has been established. Response rates of second-line immunosuppressive drugs are often disappointing. Also toxicity and especially infective complications are common issues. Alpha 1

antitrypsin (AAT1) is a serine protease inhibitor with antiapoptotic, anti-inflammatory and immunomodulatory effects, which showed efficacy in animal models on inflammatory disorders and autoimmune diseases, as well as promising results in a prospective clinical trial as second-line therapy for SR-GvHD. Safety of long-term AAT1 substitution in patients with inherited AAT deficiency without increased rates of infection was previously shown.

Methods: In a single center retrospective analysis we investigated the use of AAT1 in patients with grade III-IV SR-aGvHD of the gut. Steroid-refractory was defined by missing clinical benefit after the administration of 2 mg /kg prednisolone over at least 5 days. All patients had previously received at least one off-label second-line treatment for SR-aGvHD. AAT1 was administered intravenously twice a week for 4 weeks with 60 mg/kg. We analysed overall response rate (ORR), drug related toxicity and overall survival (OS). The response was assessed clinically using MAGIC criteria for aGvHD.

Results: We retrospectively analysed 14 patients with a median age of 53 (36-69) years treated for SR-aGvHD after allo-HSCT at our center. 4 patients had grade III aGvHD and 10 patients had grade IV GvHD with at least grade III gut involvement in all 14 patients. Biopsies were performed to confirm a histological GvHD. One patient received a bone marrow graft while the other 13 patients received peripheral blood stem cell grafts. 12 patients had matched unrelated donors (MUD) and 2 patients had haploidentical sibling donors. GvHD prophylaxis after allo-HSCT consisted of anti-thymocyte globulin (ATG), ciclosporin A and mycophenolatmofetil (MMF) for MUD and post-transplant cyclophosphamide, tacrolimus and MMF for haploidentical donors. In median, patients previously received 3 (1-6) lines of GvHD treatment before AAT1 administration, including ruxolitinib, methotrexate, calcineurininhibitors, etanercept, extracorporal photopheresis and mesenchymal stromal cells. 12 patients received all 8 doses of AAT1. One patient died before treatment completion due to infective complications. One other patient even received 2 cycles of AAT1 (16 doses) after responding to the first cycle and relapsing 5 weeks after administering the 8th dose. GvHD manifestations improved in 8 of 14 (57%) patients by day 28 after first dose of AAT1. 3 patients achieved complete remission (CR) and 5 achieved partial remission (PR). AAT1 was well-tolerated and no toxicities attributable to AAT1 were observed. At the last follow-up 5 of the 14 patients were alive with a follow-up of up to 77 weeks after allo-HSCT. Causes of death were infections in 5 patients and progression of GvHD in 4 patients.

Conclusions: In this retrospective analysis, AAT1 showed good efficacy in heavily pre-treated patients with SR-GvHD and gut involvement with an ORR of 57% and a CR rate of 21% while having a well-tolerable safety profile.

Clinical Trial Registry:

Disclosure: Nothing to declare

P210

Mesenchymal stromal cells in patients with iii-iv grade steroid-refractory acute graft versus host disease: 8 years of experience

A. Bukauskas[1], A. Slobinas[1,2], R. Jucaitienė[1], I. Šlepikienė[1], A. Žučenka[1,2], V. Pečeliūnas[1,2], I. Trociukas[1], L. Griškevičius[1,2]

[1]Vilnus University Hospital Santaros Klinikos, Vilnius, Lithuania, [2]Faculty of Medicine, Institute of Clinical Medicine, Vilnius University, Vilnius, Lithuania

Background: Bone marrow-derived mesenchymal stromal cells (MSCs) are one of the salvage therapy options for steroid-refractory acute graft versus host disease (SR-aGVHD). Herein we present 8 years of experience in Vilnius University Hospital Santaros Klinikos.

Methods: All patients developed biopsy-proven grade III-IV SR-aGVHD after allogeneic hematopoietic stem cell transplantation (HSCT) or donor lymphocyte infusion (DLI). SR-aGVHD was managed with bone marrow-derived MSCs manufactured in a hospital setting. MSCs target dose was 1x10e6 cells/kg body weight administered intravenously once weekly. Treatment response was evaluated on day 7, day 14, and day 28. The patients were evaluated for overall survival. The data were collected prospectively.

Results: 45 adult SR-aGVHD (Grade III-41 and Grade IV-4) patients, with a median of 54 (19-66) years, received MSCs as salvage treatment. 34 patients (76%) were transplanted due to acute leukemia. Involvement of the gastrointestinal tract, skin, and liver were 93%, 44%, and 29 %, respectively. One organ was affected in 18 (40%) (gastrointestinal involvement in 94 % of the cases), two organs in 24 (53%), and three organs in 3 (7%) patients. The median time from HSCT/DLI to MSCs treatment was 11 (2-217) days and the median dose was 1x10e6/kg (0,68-1,33). 19 patients received ≤ 3 MSC doses and 26 patients > 3 doses. The median observation time was 2 months (range – 0-97) and the median observation time of surviving patients was 57 months (range – 7-97). Response rates and overall survival are represented in Table 1 and Figure 1.

Table 1. Response rate and overall survival.

Characteristics	SR-aGVHD patients (N = 45)
Day 7 response rate	CR-0 (0%)
	PR-7 (15,5%)
	SD-36 (80%)
	PD-2 (4,5%)
Day 14 response rate	CR-7 (15,5%)
	PR-10 (22%)
	SD-26 (58%)
	Dead-1 (2,25%)
	LFU-1 (2,25%)
Day 28 response rate	CR-12 (27%)
	PR-7 (15,5%)
	SD-13 (29%)
	PD–2 (4,5%)
	Dead–10 (22,25%)
	LFU-1 (2,25%)
Estimated OS	6 months – 31%
	1 year – 26%
	2 years – 26%
Day 7 CR/PR vs SD/PD OS, p value	3 months vs 2 months, p = 0.845
Day 14 CR/PR vs SD/PD OS, p value	Not reached vs 1 month, p = 0.000
Day 28 CR/PR vs SD/PD OS, p value	Not reached vs 1 month, p = 0.001

OS – overall survival, CR-complete response, PR-partial response, SD-stable disease, PD-progressive disease, LFU-lost to follow up

The next line treatment was initiated in 27 (60%) patients who failed to respond to MSCs: R-ECP 15, Tocilizumab 7, Vedolizumab 3, Ruxolitinib 1, Methylprednisolone re-initiation 1. Regardless of additional therapy, 21 (78%) patients died, all due to infectious complications alone or together with concomitant GVHD. At the last follow-up, 12 of 45 patients were alive. Causes of death were infectious complications alone or with concomitant GVHD – 25 (76%), primary disease relapse – 7 (21%), asystole – 1 (3%). No adverse events that would be clearly attributed to MSCs infusion were observed.

Conclusions: The day 14 and day 28 III/IV grade SR-aGVHD responders have a significantly better prognosis, therefore we suggest considering salvage treatment in non-responders on day 14. Novel therapies for refractory SR-aGVHD patients are in urgent need.

Clinical Trial Registry: ISRCTN18091201.
https://www.isrctn.com.

Disclosure: Nothing to declare.

P211

A single centre experience of ruxolitinib for treatment of steroid refractory chronic graft versus host disease

Z. Kirkham[1], M. Ethell[1], M. Potter[1], C. Gonzalez Arias[1], K. Davis[1], F. Dallas[1], C. Salmen[1], C. Anthias[1], E. Nicholson[1], S. Easdale[1]

[1]*The Royal Marsden NHS Trust, Sutton, London, United Kingdom*

Background: Chronic graft versus host disease (GvHD) is common side effect of allogeneic stem cell transplants and can cause a significant reduction in patients quality of life and a leading cause of transplant related mortality. Severe GvHD can be very difficult to manage with second line treatment options being associated with significant risk of infectious complications. There is emerging evidence that Ruxolitinib, an oral JAK-1 and JAK-2 inhibitor, can improve response rates in terms of improvement in symptoms and severity of GVHD by NIH score and reduction of steroid doses and has impact on GvHD severity in both the acute and chronic settings. Here we share the experience of 15 patients who have been prescribed Ruxolitinib for chronic GvHD at The Royal Marsden hospital NHS Trust, London.

Methods: We retrospectively collected data on 15 patients (aged over 18 years) who were commenced on Ruxolitinib for chronic GvHD over the preceding 4 years. Haemoglobin, lymphocyte, neutrophil and platelet counts were assessed at day 1, day 30 and day 90 from starting treatment. In addition, the ALT level and CMV reactivation were also measured. The degree of GvHD at day 1 and day 90 was assessed and graded in terms of mild, moderate or severe disease by NIH criteria.

Results: From our cohort of patients, 2 (13.3%) patients required the Ruxolitinib to be withdrawn within 30 days of starting due to toxicity. One patient experienced pulmonary oedema and shortness of breath. The second patient developed acute reversible kidney injury. Of the 13 remaining patients, all tolerated Ruxolitinib with no reported significant side effects.

The patients all had steroid refractory chronic GvHD which affected a combination of organs including skin, liver, eyes, mouth and joints. 12/13 (92.3%) patients had an improvement in their GvHD symptoms by at least 1 grade, 3 (23.1%) patients had complete resolution of their symptoms. 4 (26.6%) patients have been able to stop all other immune suppression including steroids following commencement of Ruxolitinib. There was no significant change in the patients full blood count or liver function tests within the 3 months of starting Ruxolitinib. CMV reactivation was noted in 2 patients (13.3%) within 3 months of starting. Both were recipient/donor CMV IgG positive.

Conclusions: From this small study, it can be seen that Ruxolitinib is a safe and effective treatment for chronic GvHD which is well tolerated and does not appear to have significant side effects. Only 2 patients (13.3%) required cessation of the treatment due to toxicity. The remainder of the patients either experienced significant improvement in their symptoms or had stabilisation of disease. There was no evidence of significant bone marrow suppression, liver dysfunction or CMV reactivation in patients assessed. This study demonstrates both clinical efficacy and tolerability of Ruxolitinib for the management of chronic GvHD.

Disclosure: Nothing to declare

P212

A prospective analysis of the changes in the immune profile of sr-cgvhd patients undergoing ecp treatment with the amicus blue™ online ecp system

Y. Ventura-Carmenate[1], Y.M. Castillo-Aleman[1], C.A. Villegas-Valverde[1], A.A. Bencomo-Hernandez[1], M. Thabet Al Amin[1], M.A. Martinez[1], F.M. Al Kaabi[1]

[1]*Abu Dhabi Stem Cells Center, Abu Dhabi, United Arab Emirates*

Background: The pathophysiology of GvHD describes the activation of antigen-presenting cells (APC) and the activation, differentiation, and migration of T cells. Dendritic cells (DC) are professional APCs promoting antigen-specific T cell responses. Tolerogenic DCs can play a fundamental role in GvHD by exerting an immunomodulatory or even immunosuppressive effect on T cells. We performed a prospective analysis of the immune profile of peripheral blood (PB) and ECP treated cells (ETC) of steroid refractory cGvHD patients undergoing treatment exclusively with the Amicus Blue™ online ECP system (Fresenius Kabi, Germany).

Methods: ECP was given for a minimum of 24 of 28 planned procedures between May and December 2021, with an accelerated treatment plan consisting of three 8-week blocks: 2 sessions/week, 1 session/week, and finally tapered to 1 session every 2 weeks. Immune profiles were measured for PB and the ETC for procedures 1, 6 (21 days) and 16 (2 months). Samples were analyzed within 24 hours of collection, by flow cytometry using the Navios EX flow cytometer (Beckman Coulter, USA) and the Beckman Coulter Duraclone, IM Phenotyping Basic (B53309), IM Treg (B53346), IM T cells subsets (B53328), and IM TCR (B53340) kits. For mass cytometry immunophenotyping, Helios™ (Fluidigm) was used with the Maxpar® Direct™ Immune Profiling Assay™ kit. Statistical analyses were performed with GraphPad Prism v.8 (La Jolla, US). The one-way ANOVA test for paired samples was used to compare immune profiles in PB and ETC over time and considered statistically significant $p < 0.05$.

Results: Three female patients completing at least 24 ECP sessions were included in the analysis. Patients received out-patient treatment and reported only mild adverse events (AEs) typical of apheresis procedures. All patients had received HLA–identical sibling grafts and were classified as severe cGvHD. Comparison of the PB immunophenotypes did not show statistically significant differences, however, the relative count of FoxP3 + /Helios+ Treg cells and TCD8 naive increased over time when compared with baseline. A decrease of TCD8 terminal effector cells was observed, and there was no change in the dendritic cell subsets. In the ETC, a statistically significant increase ($p = 0.012$) of relative frequency of FoxP3 + /Helios+ Treg cells was observed compared to the baseline. We also saw the same

tendency of TCD8 terminal effector decrease. The ratio of myeloid dendritic cells (mDC)/plasmacytoid dendritic cells (pDC) increased. The reduction of effector cells is beneficial because CD8 + T cells are a mechanism by which cGvHD is sustained and persists. Still, there has been little information about the action of ECP on these subsets. Shiue, et al. have reported that the ratio mDC/pDC in GvHD patients is favorably altered after ECP (increase).

Conclusions: Our findings align with the previously reported increase in the relative frequency of FoxP3 + /Helios+ Treg cells, a non-significant decrease in the TCD8 end effector, and the increased mDC/pDC ratios in the ECP treated cells. Further research is needed in larger cohorts of patients.

Disclosure: Nothing to declare

P213

Association between vitamin d and GVHD biomarkers with response to immunosuppression and survival in acute GVHD: An exploratory study

J. Ros-Soto[1], N.C. Matthews[2], C. Burton[2], R. Szydlo[1], A. Alfred[2], R. Andrews[3], C. Anthias[4], V. Mehra[5], V. Potter[5], A. Madrigal[6], J.A. Snowden[3]

[1]Imperial College Healthcare Trust, London, United Kingdom, [2]Rotherham NHS Foundation Trust, Rotherham, United Kingdom, [3]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom, [4]The Royal Marsden NHS Foundation Trust, London, United Kingdom, [5]King's College Hospital NHS Foundation Trust, London, United Kingdom, [6]Anthony Nolan Research Institute, London, United Kingdom

Background: Vitamin D (VD) may influence outcomes following allogeneic HSCT due to its impact on immunity, including GvHD. In some inflammatory diseases, VD levels correlate with steroid response. Elafin, ST2 and REG3α are GvHD biomarkers that predict therapeutic response and disease prognosis. The association between VD, GvHD biomarkers and response to immunosuppression (steroids) in the acute GvHD (aGvHD) setting has never been explored.

Methods: This exploratory, observational study obtained research ethics approval for sampling and analysis. Serum from 16 patients with clinical diagnosis of aGvHD following allogeneic HSCT/DLI was taken at diagnosis and 1 month later. GvHD biomarkers and 25(OH)D^3 were measured by ELISA. Vitamin D deficiency (VDD) was defined as 25(OH)D^3 serum levels <50 nmol/L . *Modified Seattle Glucksberg criteria* were used to grade aGvHD. Complete remission (CR) was defined as complete resolution of aGvHD-derived signs/symptoms. Statistical tests performed were *Chi-square* and *Mann-Whitney U tests* (SPSS), and *Kaplan-Meier method* (R).

Results: *Baseline*

Twelve patients (75%) had VDD at diagnosis of aGvHD (14 skin, 7 gut and 5 liver, individually or in combination). Ten patients (63%) had grade I-II and 6 (37%) III-IV aGvHD.

At diagnosis, there was a trend in ST2 levels, higher in patients with grade III-IV aGvHD compared to those with grade I-II (180.4 *vs* 47.3 ng/ml; $p = 0.051$). There was an association between skin involvement and elafin, higher in stage II-IV compared to stage 0-I (32.2 *vs* 19.9 ng/ml; $p = 0.029$). No other significant differences were identified. At this time point, none of the variables could predict GvHD grade at 1-month.

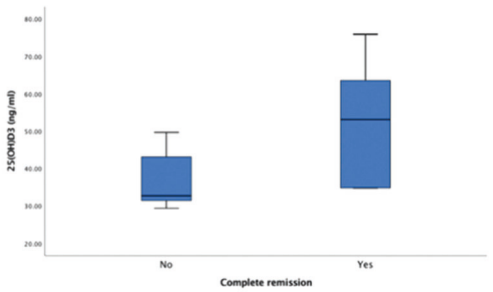
1 month response

Response 1-month after starting on steroids was assessed in 12 patients (75%). Six patients (50%) achieved CR (*responders*) whereas 6 did not (*non-responders)*. Two responders (33%) were on systemic and 4 (67%) on topical steroids. Three non-responders (50%) were on systemic and 3 (50%) on topical steroids.

There was no significant difference in the median baseline levels of elafin, ST2 and REG3α between the 1-month responders *vs* non-responders. However, baseline 25(OH)D^3 was significantly higher in responders *vs* non-responders (53.1 *vs* 32.7 nmol/L; $p = 0.037$) (Graph 1). Patients with grade 0-II had a higher concentration of 25(OH)D^3 compared to those with grade III-IV (41.6 *vs* 23.3 nmol/L; $p = 0.032$).

Twelve-month survival from diagnosis was 52%. In the deceased cohort, REG3α levels at diagnosis were significantly higher (287.6 *vs* 23.4 ng/ml; $p = 0.007$), with significantly higher ST2 levels at 1-month (82.9 *vs* 24.3 ng/ml; $p = 0.019$) and REG3α levels also at 1-month (117.9 *vs* 61 ng/ml; $p = 0.008$) compared to those alive at 12 months.

Conclusions: VDD is common following allogeneic HSCT in reflection of patient-related factors (sunlight exposure, malnourishment). Our small exploratory study provides some support for the association of VD and steroids response in aGvHD. We also found that ST2 correlates with GvHD severity and elafin with organ involvement, and REG3α and ST2 may have prognostic value at early stages of aGvHD. Routinely monitoring and early management of VDD after HSCT is inexpensive and may benefit GVHD outcomes. However, our small exploratory study cannot provide definitive conclusions thus larger observational studies are warranted.



Graph 1: 25(OH)D^3 levels at diagnosis and response to steroids at 1-month post-treatment

Disclosure: Nothing to declare

P214

Anti-thymocyte globulin to prevent graft versus host disease after HLA matched related allogeneic hematopoietic cell transplantation in acute leukemia patients

N. Yafour[1], F. Serradj[1], S. Osmani[1], F. Bouamama[1], M. Brahimi[1], M. Chekkal[2], K. Bouhafs[1], A. Baki[1], A. Arabi[1], R. Bouhass[1], M.A. Bekadja[1]

[1]Service d'hématologie et de Thérapie Cellulaire, Ètablissement Hospitalier et Universitaire 1er Novembre 1954, Université d'Oran 1, Ahmed Ben Bella, Faculté de Médecine, Oran, Algeria, [2]Service d'hémobiologie et transfusion sanguine. Etablissement hospitalier et UNIVERSITAIRE 1er NOVEMBRE d'ORAN, Oran, Algeria

Background: Allogeneic hematopoietic cell transplantation (allo-HCT) with a myeloablative conditioning (MAC) is a curative option in acute leukemia (AL) patients, However GVHD (graft versus host disease), and recurrence of diseases remains the main causes of morbidity and mortality. Objective of this study was to evaluate the impact of addition of anti-thymocyte globulin (ATG) in the prevention of graft versus host disease (GVHD) after HLA matched related allo-HCT.

Methods: We retrospectively evaluated all consecutive acute leukemia patients undergoing allo-HCT from matched related donors who were received ATG (5 mg/kg) as part as conditioning regimen. Primary endpoints were grade III/IV acute GVHD rate, moderate/severe chronic GVHD rate and cumulative incidence of relapse

Results: Between February 2013 and November 2020, 62 patients (AML = 54, ALL = 8) were included. Median age was 37 years (18- 62). At time of transplant, all patients were in complete remission. Conditioning regimen was FB4 in 57 patients including; Fludarabine 40 mg/ m3/day for 4 days, iv Busulfan (Bu)130 mg/ m3/day for 4 days, and busulfan /melphalan 140 for 5 patients. GVHD prophylaxis consisted of rabbit ATG (Thymoglobulin 1, Genzyme) iv.5 mg/kg/day (days -2, -1), cyclosporine (CsA) and methotrexate 15 mg /m^3 day +1, and 10 mg/m^3 (days + 3, +6,+ 11). In the absence of GVHD, CsA was tapered from day 100–180. All patients achieved hematopoietic reconstitution except one patient who died before engraftment. The median time to neutrophil engraftment was 12 days (range 5–25 days), and the median time to platelet engraftment was 14 days (range 10–43 days). CMV reactivation occurred in 15 patients (24 %). One patient died from CMV infection. At the end of follow up, incidence of overall acute GVHD was 44 % including 17 patients (27 %) grade II-IV and 5 patients (8 %) grade III-IV. Chronic GVHD occurred in 34 % of patients; including 11 patients (18%) moderate grade and only 4 patients (6 %) presented a severe grade. Relapse occurred in 16 patients (26 %). With a median follow up of 63 months (15-104 months) overall survival rate was 53% (33 patients).

Conclusions: Incorporation of an intermediate dose of ATG in the context of HLA matched related allo-HCT reduces severe acute and chronic GVHD without impact graft versus leukemia effects in acute leukemia patients.

Disclosure: no conflict of interest

P215

Safety and effectiveness of the amicus blue™ online ecp system in sr-cgvhd patients during a 6-month treatment regimen

Y. Ventura-Carmenate[1], Y.M. Castillo-Aleman[1], C.A. Villegas-Valverde[1], A.A. Bencomo-Hernandez[1], M. Al Amin[1], M.A. Martinez[1], F.M. Al Kaabi[1]

[1]Abu Dhabi Stem Cells Center, Abu Dhabi, United Arab Emirates

Background: Although the Amicus Blue™ ECP system (Fresenius Kabi, Germany) has received marketing authorization in Europe for treatment of CTCL, there is evidence supporting its benefits for treatment of cGVHD. This system includes the Amicus Separator®, the Phelix photoactivation device, a functionally closed disposable kit, and 8-MOP (20 µg/mL) to perform ECP therapy. We evaluated the characteristics and outcomes of steroid-refractory cGvHD (SR-cGVHD) patients, aiming to characterize the safety and effectiveness profile of the Amicus Blue™ ECP system with the implemented regimen.

Methods: All patients were evaluated before starting ECP therapy against inclusion/exclusion criteria. The U.S. NIH severity scoring was performed at baseline and after cycle 2, and classified as mild, moderate, or severe global GvHD disease. ECP standard intensity was performed within 6 months between May and December 2021, with an accelerated treatment plan consisting of 2 sessions/week for 8 weeks, followed by 1 session/week for 8 weeks, and tapered to 1 session every 2 weeks for the last 8 weeks. Amicus v6.0, Phelix v2.0 and double-needle disposable kits were used with central access for all patients. A 12:1 whole blood (WB) to ACD-A anticoagulant ratio was used, 1.24 mg/kg/min citrate infusion rate. We intended to process 1.0 total blood volume (TBV), with minimum of 0.5 TBV and maximum of 1.2 TBV. Haematology counts were performed on patient WB and the treated MNCs, and lymphocyte apoptosis was measured at 72hr.

Results: Three female patients age 24-35 years with severe cGvHD (2 *de novo*, 1 progressive) received ECP treatment. The patients had received HLA–identical sibling peripheral blood transplants for sickle cell anemia/β-thalassemia, blastic plasmacytoid dendritic cell neoplasm, and hypogammaglobulinemia approximately 3-4 years prior to treatment. Cutaneous cGvHD with significant sclerodermal changes was the leading indication for ECP. Two patients received concomitant corticosteroids, and 1 patient received ruxolitinib. No procedure-related severe adverse events (AEs) were reported, only mild AEs typical of apheresis procedures. Median (range) total procedure time including collection, photoactivation and reinfusion was 103 (76-240) minutes. WB processed was 3001 (1830-4044)mL. The yield Hct was 2.84 (2.3-4.1)%. Median treated cell doses (x10^9) were: WBCs 19.94 (8.7-31.3), lymphocytes 15.7 (3.3-28.9), monocytes 3.5 (0.5-7.2) neutrophils 0.6 (0.1-0.63). MNC collection efficiency was 51.2 (23.4-83.6)%. Lymphocyte apoptosis was 31.3% (23-46%) at 72hr. All 3 patients showed partial response after 2 cycles (24-28 procedures), detailed outcome data is presented in table 1.

Table 1. Clinical outcome of SR-cGVHD Patients Undergoing ECP.

Organ Involvement	Baseline; n (%)	After cycle 2; n (%)
Skin	3 (100) Severe	2 (66.66) Moderate/1 (33.33) Severe
Mouth	2 (66.66) None/1 (33.33) Mild	3 (100) None
Gastrointestinal	2 (66.66) None/1 (33.33) Mild	3 (100) None
Liver	2 (66.66) None/1 (33.33) Mild	2 (66.66) None/1 (33.33) Mild
Lung	2 (66.66) None/1 (33.33) Mild	3 (100) None
Joint	3 (100) Moderate	2 (66.66) None/1 (33.33) Mild
NIH global severity scale	3 (100) Severe	2 (66.66) Moderate/1 (33.33) Severe

Conclusions: Our pilot experience confirms that the use of the Amicus Blue™ ECP system was safe and efficacious for treating SR-cGVHD patients with the reported regimen.

Disclosure: Nothing to declare

P216

A randomized, open label, multicentre, phase 3 trial of first line treatment with msc versus bat in patients with steroid refractory acute GVHD (idunn trial)

R. Zeiser[1], E. Osswald[2], A.-K. Moeller[2], P. Bader[3]

[1]University of Freiburg Medical Center, Freiburg, Germany, [2]medac GmbH, Wedel, Germany, [3]University Children's Hospital, Frankfurt/Main, Frankfurt, Germany

Background: Acute graft-versus-host disease (aGVHD) that is refractory to glucocorticoids (SR) is a major cause of death after

allogeneic hematopoietic cell transplantation (allo-HCT). Human bone marrow -derived mesenchymal stromal cell (MSC) have shown activity in patients with SR-aGVHD in retrospective patient series indicating safety of this approach. Prospective data on the efficacy of the MSC product MC0518 for SR-aGVHD are lacking.

Methods: The IDUNN-study is a randomized, open label, multicentre, phase 3 trial comparing MSCs MC0518 with Best available therapy (BAT) in patients with SR-aGVHD. Adult and adolescent patients with acute skin, intestinal or liver GvHD > grade 1 and failure of previous steroid treatment are eligible. The trial aims to include 210 patients who will be randomized in a 1:1 ratio and stratified by GvHD grade (grade 2 versus grades 3/4), underlying disease (malignant versus non-malignant), and age group (<18 years of age versus ≥ 18 years of age).

Results: The primary endpoint is the overall response rate (ORR) at day 28, defined as: Partial Response (improvement of at least one stage in the severity of aGvHD in one organ without deterioration in any other organ), or Complete Response (disappearance of any GvHD signs from all organs without requirement for new systemic immunosuppressive treatment). Secondary objectives include freedom from treatment failure until 6 months, overall survival until visit month 24, aGVHD response at visit days 60, 100 and 180, change of aGvHD grade at visit days 8, 15, 22, 28, 60, 100 and 180, time to response, duration of response, best OR until and at day 28, cumulative dose of steroids from baseline until visit days 28, 60, and month 24, incidence of and time to cGVHD and graft failure, relapse or progression in subjects with underlying malignant disease, event-free survival, non-relapse mortality, incidence and severity of adverse events and adverse reactions, performance score, and quality of life. In addition, changes in serum levels of pro-inflammatory cytokines and aGvHD-related biomarkers soluble suppression of tumorigenicity 2 (sST2) and regenerating islet-derived 3α (Reg3α) will be assessed. The trial will be conducted across approximately 40 trial sites in approximately 7 European countries.

Conclusions: This randomized prospective trial will provide evidence if the retrospectively collected data demonstrating activity of MSC for SR-aGvHD can be reproduced in a prospective trial setting and if MSC show higher efficacy compared to BAT. A major advantage of MSC could be the limited toxicity profile observed in previous applications of MSC in SR-aGVHD patients. This trial will investigate candidate biomarkers to predict and monitor responses to MSC.

Clinical Trial Registry: ClinicalTrials.gov Identifier: NCT04629833.

Disclosure: R.Z. received honoraria from Novartis, Incyte and Mallinckrodt.

P217

Extracorporeal photopheresis- a case based new experience in treating chronic GVHD

L. Chadievski[1], I. Panovska Stavridis[1], B. Georgievski[1], L. Chevreska[1], S. Stojanovska[1], M. Cvetanovski[1], B. Kochoski[1], A. Pivkova Veljanovska[1]

[1]University clinic for hematology, Skopje, North Macedonia, The Republic of

Background: Extracorporeal photopheresis (ECP) is an apheresis based immunomodulatory therapeutic procedure. It utilizes separated white blood cells from the patient, threated with a photoactivated agent – methoxypsoralen, exposed to UVA and then reinfused back, to make an immunosuppressive effect as a addition to the therapeutic activities against chronic GvHD.In our bone marrow transplant unit, we perform hematopoietic stem cell (HSC) transplants from year 2000, and so far have made over 600 interventions. We recognized the therapeutic potential of ECP and have implemented it in 2021. So far we have made 38 procedures. We used peripheral venous access in 22(58%) and had to use central venous access in 16 (42%). So far no serious adverse events were noted. We have treated 3 patients with chronic GvHD and had an attempt in treating 1 patient with Non Hodgkin lymphoma – PTCL.

Methods: Unfortunately, in only 1 patient with chronic GvHD we performed the whole treatment protocol. It`s a male, 24 years old, diagnosed with Severe Aplastic Anaemia in 2017. Allogeneic unrelated matched HSC transplant was done in 2018 with successful engraftment. But in may 2019, he complained of stomach ache and yellow skin. The CBC Hgb 119 g/L WBC 11.2 x 10^9/L PLT 247 x 10^9/L AST 238 U/L ALT 178 U/L AP 800 U/L GGT 1996 U/L LDH 691 U/L Total Bilirubin 209 μmol/L Direct 126 μmol/L Indirect 83 μmol/L. There was a complete chimerism of the graft. HBV and HCV excluded. The liver biopsy showed chronic GvHD of the liver. We started as first line treatment Methylprednisolone + Cyclosporin A. Only partial response was met, AST 137 U/L ALT 280 U/L AP 588 U/L GGT 1756 U/L Total bilirubin 53 μmol/L Direct 25 μmol/L Indirect 28 μmol/L. As second line we used Rituximab for four doses, and as third line mycophenolate mophetil, but still the results were similar (AST 146 U/L ALT 238 U/L AP 880 U/L GGT 1200 U/L LDH 390 U/L T.Bil 92 μmol/L Direct 87 μmol/L Indirect 5μmol/L).

Results: As fourth line we started ECP alone. Treatment plan was 2 procedures on 2 consecutive days equals 1 cycle, and 1 cycle every 2 weeks for 4 months, then 1 cycle a month. All procedures were done successfully, with no adverse events. We used only peripheral venous access. The patient now has normal CBC, AST 51 U/L ALT 55 U/L AP 400 U/L GGT 250 U/L Total Bilirubin 22 μmol/L Direct 12 μmol/L Indirect 10 μmol/L and stabilization and a slight regression of the skin changes that accompanied the chronic GvHD spectrum.

Conclusions: This successful treatment story encourages us to maintain on this course and utilize the therapeutic potentials of ECP and implementing it in a number of our patients, even earlier in the treatment plan, mainly for chronic GVHD

Disclosure: No disclosures

GRAFT-VERSUS-HOST DISEASE – PRECLINICAL AND ANIMAL MODELS

P218

SER-155, an investigational cultivated microbiome therapeutic, rationally designed to reduce gastrointestinal inflammation and promote epithelial barrier integrity in patients undergoing hematopoietic stem cell transplantation

E. Halvorsen[1], A. Martinez[1], D. Balasubramanian[1], A. Pina[1], M. Vulic[1], T. Nelson[1], S. Pandian[1], K. Cieciuch[1], J. Black[1], K. Halley[1], M.-J. Lombardo[1], C. Ford[1], M. Henn[1]

[1]Seres Therapeutics, Cambridge, United States

Background: SER-155, an oral investigational microbiome therapeutic composed of cultivated human-commensal bacterial strains, is being developed to reduce the risk of bloodstream infection and graft-versus-host disease (GvHD) in allogeneic hematopoietic stem cell transplant (HSCT) recipients. SER-155 was rationally designed to restore gastrointestinal homeostasis by restoring colonization resistance, reducing gastrointestinal inflammation and improving epithelial barrier integrity.

Methods: SER-155 was evaluated in vitro and in vivo for specific pharmacological properties to mitigate drivers of morbidity and mortality following HSCT. In vitro, functional properties of SER-155 were assessed utilizing culture supernatants to test for a)

production of anti-inflammatory metabolites, b) anti-inflammatory activity measured by suppression of IL-8 secretion by TNF-α treated HT29 cells and modulation of inflammatory pathways in IFN-ɣ treated primary colonic epithelial organoids, and c) protection of epithelial barrier integrity in a trans-well culture system of differentiated primary human colonic epithelial cells treated with IFN-ɣ. In vivo, germ-free mice were used to assess the ability of SER-155 colonization to modulate gut immune cell populations towards a noninflammatory phenotype; specifically the ratios of regulatory T cells (Tregs) to Th1 and Th17 effector T cells in the colonic lamina propria.

Results: Development of SER-155 included preclinical screening in vitro and in vivo of over 50 designed candidate consortia containing combinations of >150 species. Analysis of culture supernatants showed that SER-155 produces diverse anti-inflammatory metabolites including short- and medium-chain fatty acids and a variety of tryptophan and bile acid metabolites. In vitro, SER-155 supernatants inhibited IL-8 secretion in TNF-α stimulated HT29 cells and induced transcriptional changes in colonic organoids that reduced IFN-ɣ driven inflammatory gene and pathway expression. In an in vitro intestinal epithelial barrier model, SER-155 supernatants protected barrier integrity as shown by a significant reduction in IFN-ɣ mediated barrier permeability. In vivo, SER-155 colonization led to a significant expansion of regulatory T cells (Tregs) and an increased ratio of Tregs to Th1 and Th17 effector T cells.

Conclusions: Preclinical assessments in vitro and in vivo support the ability of SER-155, an investigational cultivated microbiome therapeutic, to promote epithelial barrier integrity and reduce local inflammation to restore immune homeostasis in the gut. These data support the ability of microbiome therapeutics to affect diverse pathways important to disease pathogenesis. A phase 1b study evaluating SER-155 in allogeneic HSCT patients is currently enrolling (NCT04995653).

Disclosure: This research was sponsored by Seres Therapeutics. Elizabeth Halvorsen, Asuncion Martinez, Marin Vulic, Swarna Pandian, Kathleen Cieciuch, Jennifer Black, Keith Halley, Mary-Jane Lombardo, Christopher Ford, and Matthew Henn are current employees and shareholders of Seres Therapeutics. Divya Balasubramanian, Ambar Pina, and Tim Nelson were past employees and shareholders of Seres Therapeutics.

P220

JAK1/2 inhibitor ruxolitinib induce polymorphonuclear myeloid-derived suppressor cells mobilization and function via jak/stat and mapk/nf-κb dependent manner in protecting against acute graft-versus-host disease

Y. Cao[1], J. Wang[1], Y. Xu[1], E. Jiang[1], M. Han[1]

[1]Center for Blood Diseases, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China

Background: Ruxolitinib has been demonstrated to be effective in the treatment of steroid-resistant acute graft-versus-host disease (aGVHD) as a JAK1/JAK2 inhibitor. MDSCs represent a heterogenic population of immature myeloid cells to have a protective effect on aGVHD via suppressing T cell functions. Ruxolitinib's effect on inflammatory cells such as regulatory T cells, dendritic cells and natural killer cells is known. However, its effect on myeloid derived suppressor cells (MDSCs) competency plausibly involved in pathogenesis of GVHD has not been explored.

Methods: We aimed to define the effect of ruxolitinib on the immunobiology of MDSCs in the pathogenesis of aGVHD. The ratios and functions of MDSCs were analyzed after ruxolitinib administration compared with controls in vivo and in vitro. Meanwhile, its downstream effector molecules were tested by flow cytometry, western blot and phosflow techniques.

Results: In this study, we demonstrate that in vivo administration of ruxolitinib results in the expansion and functional enhancement of polymorphonuclear MDSCs (PMN-MDSCs) in a murine model of aGVHD and the effects could be partially reversed by anti-Gr1 antibody. Ruxolitinib treatment can enhance the suppressive function of PMN-MDSCs via up-regulation of reactive oxygen species (ROS) and activated MAPK/NF-κB signaling pathway. Ex vivo experiments demonstrated that ruoxlitinib can prevent differentiation of mature myeloid cells and promote accumulation of MDSCs via inhibiting STAT5. Moreover, ruxolitinib can also induce a strong immunosuppressive function in PMN-MDSCs utilizing the NF-κB transcription factors as well as NOX2 upregulation.

Conclusions: In summary, impaired MDSCs are involved in the pathogenesis of aGVHD, and ruxolitinib corrected PMN-MDSC functions via a mechanism underlying JAK/STAT and MAPK/NF-κB signaling pathways. Our findings may also explain the outstanding immunomodulating activity of ruxolitinib currently used in the treatment of aGVHD and other autoimmune diseases.

Disclosure: Nothing to declare

P221

Single cell transcriptomic survey of the human GVHD landscape

J. Lam[1], P. Milne[1], A. Resteu[1], C. Wright[1,2], S. Pagan[1], R. Hussain[3], J. Coxhead[3], M. McCorkindale[3], M. Hasoon[3], R. Queen[3], E. Hurst[2], A. Publicover[2], V. Bigley[1,2], M. Collin[1,2]

[1]The Medical School, Newcastle University, Newcastle upon Tyne, United Kingdom, [2]Northern centre for bone marrow transplantation, Freeman Hospital, Newcastle upon Tyne, United Kingdom, [3]Biosciences Institute, Newcastle University, Newcastle upon Tyne, United Kingdom

Background: Graft versus host disease (GVHD) remains a major obstacle to successful haematopoietic stem cell transplant. Although donor T cells are necessary in animal models, recent data indicate that the full expression of tissue inflammation in transplanted humans may depend upon myeloid cells, and even recipient T cells. Furthermore, the signals that drive recruitment from blood and the circuits that exist between immune cells, targets and supporting stroma, are not well defined. In this study we sought to understand these mechanisms in detail by defining the landscape of GVHD in human skin and blood at single cell transcriptomic resolution.

Methods: We collected paired skin biopsy and blood samples from five patients at the onset of acute GVHD, two transplant recipients without acute GVHD at day 100 post-transplant and samples from healthy untransplanted donors as controls.

Skin biopsies were split into epidermis and dermis by enzymatic digestion. Separated tissues were then digested into single cell suspensions. Peripheral blood mononuclear cells were isolated from whole blood by density gradient separation. Samples were then loaded onto 10x genomics single cell 5′ platform to generate gene expression and T-cell receptor libraries.

Data was processed using Seurat R package (v4.0.3). Poor quality cells and multiplets were first removed. Samples were then normalized, dimensionally reduced and clustered using the SCTransform approach.

To identify the donor or recipient origin of cells, germline single nucleotide polymorphisms were defined by exome sequencing of DNA samples from each donor and recipient. The output was then

passed into Demuxlet, a computational tool that calls the origin of each cell base on its genetic identity.

Results: It was possible to identify various cell types in each anatomical location. In the epidermis without GVHD, we identified Langerhans cells, keratinocytes and melanocytes. In dermis, there were cells from the non-immune compartment (fibroblasts, Schwann cells, pericytes and endothelial cells) and the immune compartment (T cells, NK cells, innate lymphoid cells, macrophages, dendritic cells, etc). Additionally, we identified the leukocyte subsets in blood.

Skin with acute GVHD contained a vastly altered cellular composition, compared to skin unaffected by GVHD. Most notably there was an influx of donor myeloid cells and lymphocyte. Myeloid cells were mainly of donor origin, while a mixed population of donor and recipient T cells were found in both epidermal and dermal compartments. There was an elevated proportion of monocytes in the blood of GVHD patients compared to controls. Populations of monocytes expressing activation markers were also identified.

T cell receptor analysis revealed that T cell clones were less diverse and highly shared between skin and blood of each patient with GVHD, consistent with a systemic distribution of T cells mediating GVHD.

Conclusions: Single cell RNA sequencing allowed detailed information to be obtained from small clinical biopsies of GVHD-affected tissue. There was a vast difference in cellular composition and gene expression between GVHD-affected tissues compared to controls. By simultaneously profiling the landscape of GVHD in human skin and blood at single cell resolution, we aim to obtain new insights of classical and novel mechanisms of GVHD.

Disclosure: Nothing to declare

P222

Apraglutide decreases severity of intestinal damage from acute gastrointestinal graft versus host disease (gi-GVHD) following allogeneic transplantation without impacting engraftment

V. Dimitriadou[1], G. Chabot-Roy[2], C. Audiger[2], I. Banu[2], J.-S. Delisle[3], S. Lesage[2]

[1]VectivBio, AG, Basel, Switzerland, [2]Maisonneuve-Rosemont Hospital Research Center, Montréal, Canada, [3]Maisonneuve-Rosemont Hospital Division of Hematology, Oncology and Transplantation, Montréal, Canada

Background: The GI tract is a primary tissue system damaged by GvHD, leading to a compromised mucosal barrier, mucosal protein loss, and nutrient/fluid absorption failure. Glucagon-like peptide-2 (GLP-2) has demonstrated intestinotrophic effects, enhanced barrier function, and decreased intestinal permeability. Apraglutide, a novel, long-acting synthetic GLP-2 analog, represents a potential regenerative approach to GI-GvHD prevention and treatment. Using two mice models of GvHD, we assessed the effects of apraglutide on engraftment and GI protection following irradiation and allogeneic transplantation.

Methods: In Study 1, total-body-irradiated (TBI) immunodeficient (NOG) mice (Day 0) were injected with human peripheral blood mononuclear cell (hPBMC; $3x10^7$; Day 2) and treated with apraglutide 3.3 mg/kg or vehicle (Days -6 to 18). Engraftment rate was determined through CD45 expression (human vs. mouse) in blood, bone marrow, and spleen. In Study 2, TBI-induced intestinal damaged BALB/cJ mice received allogeneic transplantation from C57BL/6 strain and were treated with apraglutide (3.3 mg/kg) or vehicle (Days -9, -7, -5, -3 -1, +1, +3, +5, +7). Intestinal damage indicative of GvHD (histological changes, length, hemorrhage, inflammation), body weight, and survival were assessed.

Results: In study 1, hPBMC were successfully engrafted. The engraftment rate in blood, spleen, and bone marrow was not affected by apraglutide (range 22.2-47.6% at D20 in blood). hCD45+ cell infiltration was observed in the intestinal wall with no difference between apraglutide vs. vehicle. In study 2, lymphocyte engraftment was successfully achieved in both apraglutide- and vehicle-treated mice. Weight loss and median survival were similar in both groups, but apraglutide-treated mice had significantly higher overall survival vs. vehicle on Day +9 (40% vs. 0%, respectively; $p = 0.0134$). Post-mortem histological examination revealed less mucosal degenerative/inflammatory changes (villous atrophy, mononuclear/neutrophilic cell infiltrate in the lamina propria/intra-cryptal epithelium, crypt necrosis) in apraglutide-treated mice vs. vehicle. Mean colon length in the apraglutide group (8.6 ± 0.35 cm) was comparable to mice that did not undergo irradiation or transplantation (9.6 ± 0.33 cm), whereas a significant reduction was apparent in the vehicle group (7.19 ± 0.10 cm; $p < 0.05$).

Conclusions: These results suggest that apraglutide treatment before allogeneic transplantation in immunodeficient mice does not affect engraftment rate. Furthermore, apraglutide showed a significant protective effect in TBI- and allogeneic-transplant-induced GvHD with reduced villi atrophy, less colon shortening, less severe intestinal damage, and showed a survival advantage. These findings support the beneficial role of apraglutide in reducing GI damage and limiting mortality from GvHD.

Disclosure: Violetta Dimitriadou is an employee of VectivBio, AG.; Geneviève Chabot-Roy, Cindy Audiger, Ianula Banu, Jean-Sébastien De, and Sylvie Lesage have no relevant disclosures.

P223

Apraglutide treatment reduces chemotherapy-induced gastrointestinal (gi) damage in mice and preserves cellular integrity during chemotherapy

V. Dimitriadou[1], M. Minden[2]

[1]VectivBio, AG, Basel, Switzerland, [2]University of Toronto, Toronto, Canada

Background: Chemotherapy-induced mucositis is a common condition caused by the breakdown of the mucosal barrier. Administration of exogenous glucagon-like peptide 2 (GLP-2) has been associated with reduced epithelial damage, decreased bacterial infection, and decreased mortality or gut injury in rodents with chemically induced enteritis. GLP-2 decreases chemotherapy-induced mucositis via inhibition of drug-induced apoptosis in the small and large bowel. Apraglutide is a novel, long-acting synthetic GLP-2 agonist that has been shown to promote intestinal growth and repair. Two preclinical studies aim to evaluate the efficacy of apraglutide (3.3 mg/kg) as pre-treatment or concomitant treatment in models of chemotherapy-induced intestinal damage with cytarabine or melphalan; both extensively used in hemato-oncology.

Methods: Study 1 included four groups of Balb/c mice: (A) vehicle only; (B) cytarabine on Days 5-9, no apraglutide given; (C) cytarabine on Days 5-9; concomitant apraglutide on Days 5-18; (D) cytarabine on Days 5-9; pre-treatment apraglutide on Days 1, 3, and continued as a concomitant treatment on Days 5, 8, 11, 14, and 17.

Study 2 included three treatment groups of Balb/c mice: (A) vehicle only; (B) melphalan on Day 9, no apraglutide; (C) melphalan on Day 9; pre-treatment apraglutide on Days 1, 3, 5, 7 and continued as a concomitant treatment on Days 9, 11, and

13. In both models, mice that received the vehicle without any treatment served as controls. Intestinal tissue histology, body weight, survival, and plasma citrulline, a marker of total mucosal mass and intestinal growth, were assessed in both models.

Results: Histological examination showed that the degenerative intestinal changes (villi and crypt atrophy) caused by cytarabine or melphalan were reduced by apraglutide co-administration, as demonstrated by similarities in tissue morphology between vehicle-treated and apraglutide-treated mice. In addition, the duodenum, ileum, and jejunum increased in weight with apraglutide. The intestinal protective effects of apraglutide were further supported by preserving plasma citrulline levels (a biomarker of intestinal mass): apraglutide-treated mice had similar levels to animals that did not receive chemotherapy. Apraglutide attenuated chemotherapy-induced weight loss and improved overall survival vs. vehicle-only or chemotherapy-only groups. The effects of apraglutide were optimal when it was administered as pre-treatment before chemotherapy.

Conclusions: Microscopic examination showed apraglutide protected GI epithelium structure from chemotherapy-induced injury, improved survival, and prevented severe body weight loss in mice undergoing chemotherapy. Apraglutide also maintained plasma citrulline levels, a marker of intestinal mass, comparable to that in mice who did not undergo chemotherapy.

Disclosure: Violetta Dimitriadou is an employee of VectivBio, AG.; Mark Minden has no relevant disclosure.

P224

Treatment with apraglutide preserves the global homeostatic environment of intestinal microbiota during chemotherapy in mice

***V. Dimitriadou*[1]**

[1]*VectivBio, AG, Basel, Switzerland*

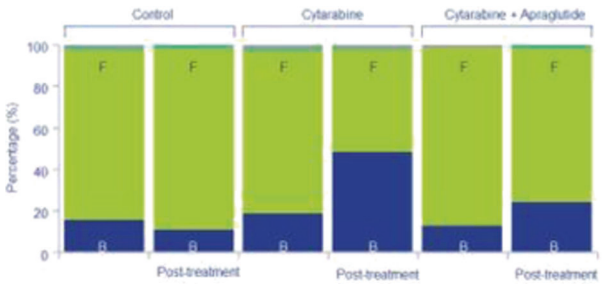
Background: Hematopoietic stem cell transplantation patients experience profoundly altered gut microbiota composition due to dysregulation of intestinal homeostasis by conditioning regimens, broad-spectrum antibiotics, immunosuppressants, and the introduction of foreign lymphocytes from the donor. A growing body of evidence shows reduced microbiome diversity increases the incidence and seriousness of graft versus host disease (GvHD) and bacteremia. Apraglutide, a novel long-acting synthetic glucagon-like peptide 2 (GLP-2), has been shown to protect gastrointestinal (GI) epithelium structure from chemotherapy-induced injury, improve survival, and allowed better body weight maintenance in mice undergoing chemotherapy. The study aimed to evaluate the protective effect of apraglutide on gut microbiota during chemotherapy with cytarabine.

Methods: Balb/c mice received 30 mg/kg of cytarabine on Days 5-9 and apraglutide 3.3 mg/kg on Days 1-18. Control mice received the vehicle on Days 1-18. Fecal samples were collected over 24 hours for bacterial phenotyping at pre-treatment and the day before scheduled termination and for found dead or pre-terminally euthanized animals. Microbiota composition was determined by 16S taxonomical meta-sequencing.

Results: *Bacteroidetes* and *Firmicutes* were the two leading bacterial phyla identified. Chemotherapy with cytarabine caused significant changes in the composition of bacterial species, increasing the *Bacteroidetes* population and decreasing the proportion of *Firmicutes* bacteria.

The change in *Bacteroidetes* and *Firmicutes* bacteria levels from Days 0 to 18 was significantly greater in the cytarabine-only and cytarabine + apraglutide mice vs. vehicle. However, this effect was reduced by apraglutide co-administration. The difference in the change between cytarabine-only and cytarabine + apraglutide groups reached statistical significance for both *Bacteroidetes* (0.2486; $p < 0.0001$) and *Firmicutes* (0.2037; $p < 0.0001$). In addition, the ratio of *Bacteroidetes* to *Firmicutes* bacteria present remained more constant in cytarabine + apraglutide than in the cytarabine-only group.

Conclusions: Chemotherapy profoundly impacted bacterial homeostasis in the mouse intestine, with a notable increase in opportunistic pathogenic bacteria populations. The proportions of different bacterial phyla in feces remained closer to normal when apraglutide was co-administered with chemotherapy. Treatment with apraglutide resulted in the preservation of the global homeostatic environment of the intestinal microbiota. Prevention of intestinal dysbiosis may contribute to the improved outcomes (reduced body weight loss, increased survival) observed in mice when apraglutide is administered concomitantly with chemotherapy agents.



	Mean % of taxa at the Phylum level					
	Bacteroidetes			*Firmicutes*		
	Day 0	Day 18	P-value for change Day 0 – Day 18	Day 0	Day 18	P-value for change Day 0 – Day 18
Vehicle only	15.2	10.5	0.01723	82.6	88.2	0.1374
Cytarabine only	16.3	48.7	<0.0001	78.7	49.5	<0.0001
Cytarabine + apraglutide	12.2	24.0	0.0057	85.3	73.7	0.0107

Disclosure: Violetta Dimitriadou is an employee of VectivBio, AG.

P225

Apraglutide does not impact anti-tumor and immunosuppressive efficacy of conditioning chemotherapy in mice

***V. Dimitriadou*[1], *M. Minden*[2]**

[1]*VectivBio, AG, Basel, Switzerland,* [2]*University of Toronto, Toronto, Canada*

Background: Conditioning chemotherapy reduces tumor burden and provides immunoablation to prevent graft rejection with hematopoietic cell transplantation, but often induces mucosal barrier breakdown and mucositis. Apraglutide is a novel, long-acting synthetic glucagon-like peptide-2 (GLP-2) analog that protects the GI epithelium from chemotherapy-induced injury, improves survival, and allows better weight maintenance in mice undergoing chemotherapy. Preclinical studies aim to evaluate the impact of apraglutide on chemotherapy's efficacy in reducing tumor load and inducing immunosuppression.

Methods: Study 1 assessed cytarabine's antitumor effects in leukemic NOD/SCID mice. Apraglutide or vehicle was administered on Days -4 to 4. Cytarabine or vehicle was administered on Days 0-4. Bone marrow and spleen samples were collected on Day 7, and the percentage of hCD45+ cells was determined. Study 2

assessed the effect of apraglutide on cytarabine-induced immunosuppression and included three groups of Balb/c mice:

(A) vehicle;
(B) cytarabine on Days 5-9;
(C) cytarabine on Days 5-9,

concomitant apraglutide on Days 5-18. RBC, platelets, WBC, NEU, and LYMPH, were assessed. A cohort was allowed to survive for four weeks to evaluate the effect of apraglutide on immunosuppression recovery. Study 3 assessed the effect of apraglutide on melphalan-induced immunosuppression. Three groups of Balb/c mice were included:

(A) vehicle;
(B) melphalan on Day 9;
(C) melphalan on Day 9,

apraglutide pre-treatment on Days 1, 3, 5, 7 and continued as co-administration on Days 9, 11, and 13. WBC, NEU, and LYMPH were assessed.

Results: Study 1 showed that human leukemia cells reduction did not differ significantly between cytarabine-only and cytarabine + apraglutide and were significantly greater than in the vehicle-only group. The percentage of hCD45 in bone marrow after chemotherapy was 35.5 ± 4 with cytarabine-only and 33.9 ± 4.2 with cytarabine + apraglutide. A dramatic decrease in leukocytes at the end of the treatment period in Study 2 indicated that cytarabine-induced immunosuppression was not impaired by apraglutide co-administration (91% reduction in lymphocytes with both cytarabine + apraglutide and cytarabine-only). Apraglutide did not impact the recovery of hematological parameters four weeks after the end of treatment. Study 3 showed that melphalan elicited immunosuppression as evidenced by leukocyte decrease. Mice treated with melphalan, with or without apraglutide, had severe reductions in WBC and LYMPH vs. vehicle.

Conclusions: Pre- and concomitant apraglutide did not impair the efficacy of cytarabine in destroying human leukemia cells in vivo. Moreover, combination with apraglutide had no negative impact on cytarabine- or melphalan-induced immunosuppression. Apraglutide did not negatively impact the antitumor or immunosuppressive effects of cytarabine or melphalan.

Disclosure: Violetta Dimitriadou is an employee of VectivBio, AG.; Mark Minden has no relevant disclosures.

HAEMATOPOIETIC STEM CELLS

P227

Antibody response to sars-cov-2 vaccination in patients following allogeneic hematopoietic cell transplantation

A. Huang[1], C. Cicin-Sain[1], C. Pasin[2,3], S. Epp[2], A. Audige[2], N.J. Mueller[3], J. Nilsson[4], A. Bankova[1], O. Vilinovszki[1], G. Nair[1], N. Wolfensberger[1], P. Hockl[1], U. Schanz[1], A. Trkola[2], R. Kouyos[3,2], B. Hasse[3], A. Zinkernagel[3], M.G. Manz[1], I.A. Abela[3,2], A.M. Müller[1]

[1]University Hospital Zurich, Zurich, Switzerland, [2]University Hospital Zurich/ Institute of Medical Virology, Zurich, Switzerland, [3]University Hospital Zurich/ Division of Infectious Deseases and Hospital Epidemiology, Zurich, Switzerland, [4]University Hospital Zurich, Zurich, Switzerland

Background: Vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been approved rapidly. Long-term data in recipients of allogeneic hematopoietic cell transplantations (allo-HCT) after SARS-CoV-2 vaccination are lacking.

Methods: We examined longitudinal antibody responses to SARS-CoV-2 vaccination with BNT162b2 (BioNTech/Pfizer) or mRNA-1273 (Moderna) in allo-HCT recipients and healthy controls. Seroprofiling recording IgG, IgA, and IgM reactivities against SARS-CoV-2 antigens (receptor-binding domain (RBD), spike glycoprotein subunits S1 and S2, and nucleocapsid protein (N)) was performed prior to vaccination (T0), prior to the 2nd dose (T1), and 1 (T2), 3 (T3), and 6 (T4) months (m) after the 2nd dose by using the immunoassay ABCORA, an in-house developed assay that allows differentiating immunity after vaccination versus immunity after infection. Based on computational methods high neutralization potency was predicted above a sum of S1 threshold of 17.

Results: We enrolled 110 allo-HCT patients (median age 57y (interquartile range (IQR: 46-65 y)) between March 2021 and May 2021 at the University Hospital Zurich. AB responses are available for 101 (T1), 101 (T2), 96 (T3) and 78 (T4) patients, respectively. Patients were stratified to three groups (A) 3-6m post-HCT, (B) 6-12m post-HCT and (C) > 12m post-HCT. In addition, AB responses are available for $n = 72$ healthy controls (median age 35.5y (IQR 23-64 y)). The study cohort includes 10 patients and 5 healthy controls with a reported preinfection. Individuals early post allo-HCT (3-6m and 6-12m post HCT) developed statistically significant lower antibody titers after vaccination compared to patients >12m post allo-HCT and healthy controls ($p < 0.001$, Fig 1A-D). Antibody titers achieved the highest levels 1m after the 2nd dose but declined substantially in all transplanted and the healthy group over time: At 6m after the 2nd dose only in 3/15 (20%) of group A, 3/9 (33%) of group B, 29/54 (54%) of group C and 42/66 (64%) of the healthy controls protective neutralization titers were measurable.

In a multivariate linear regression analysis on factors associated with antibody response in allo-HCT patients at 1m after the 2nd dose, we found consistently lower immune response in the group 3-12m post-HCT (coefficient = -0.66, 95% CI [-1.06, -0.25], $p = 0.002$); age >65 years (coefficient = -0.59, 95% CI [-1.11, -0.07], $p = 0.030$); patients under immunosuppressive treatment (IST) (coefficient = -0.44, 95% CI [-0.84, -0.04], $p = 0.033$); and whether patients suffered from relapse of the underlying disease (coefficient = -0.55, 95% CI [-0.98, -0.12], $p = 0.014$), (Fig 1E). Statistically significant higher antibody levels were seen in preinfected patients (coefficient = 0.78, 95% CI [0.21, 1.35], $p = 0.009$). In contrast, presence of moderate or severe chronic GVHD was not found to directly influence AB levels.

Conclusions: Allo-HCT patients early post-HCT displayed impaired antibody formation to vaccination against SARS-CoV-2. A remarkable decline of protective antibody levels has been observed in all groups of patients as well as healthy control in the follow-up until 6m. This analysis of long-term vaccine antibody response is of critical importance to allo-HCT patients and transplant physicians to guide treatment decisions regarding re-vaccination and social behavior during this pandemic.

Clinical Trial Registry: The study was conducted according to the Declaration of Helsinki and was approved by the Cantonal Ethics Committee Zurich, Switzerland (BASEC No 2021-00261).

Disclosure: Nothing to declare.

P228

Influence of c-kit mutations on prognosis following allogeneic hematopoietic stem cell transplantation in pediatric patients with core binding factor AML with runx1-runx1t1 fusion gene

H. He[1], R. Sun[1], D. Liu[1], Z. Wei[1], M. Xiong[1], Y. Lu[1], J. Zhang[1], Y. Zhao[1], X. Cao[1], J. Zhou[1], P. Lu[1], D. Lu[1]

[1]Department of Bone Marrow Transplantation, Langfang, China

Background: Pediatric core binding factor acute myeloid leukemia (CBF-AML) positive for the RUNX1-RUNX1T1 fusion gene is generally associated with favorable outcomes. However,

outcomes for patients who also harbor an additional c-KIT gene mutation remain unclear. This study explored the impact of an additional c-KIT gene mutation on the prognosis of CBF-AML pediatric patients with a positive RUNX1-RUNX1T1 fusion gene and who underwent an allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Methods: We retrospectively analyzed 119 patients with RUNX1-RUNX1T1 fusion gene positive CBF-AML who received an allo-HSCT and achieved first complete remission (CR1) between February 2012 and August 2021. The median age of patients was 8 years old (range: 2-14 years old). The male to female ratio was 74 to 45. Prior to transplant, 54 of the 119 patients harbored a c-KIT gene mutation and 21 of 54 c-KIT-positive patients harbored a D816 mutation in the c-KIT gene. Ten of the transplant donors were matched siblings, 13 were matched-unrelated, and the remaining 96 were haploidentical. 117 patients received conditioning regimens with busulphan (Bu), cyclophosphamide (CTX) and antilymphocyte globulin (ATG). The other two patients underwent total body irradiation (TBI) and received cyclophosphamide (CTX) and antilymphocyte globulin (ATG) regimens. Cyclosporine or tacrolimus, mycophenolate mofeil and short-course methorexate were the most frequently administrated graft versus-host disease (GVHD) prophylaxis regimens.

Results: After a median follow-up of 32 months (range: 1-93 months) after transplant, all patients were successfully engrafted and had 100% donor chimerism. Following the allo-HSCT, 45 of 119 patients (37.8%) developed Grade II-IV acute GVHD and 20 of 119 patients (16.8%) had Grade III-IV acute GVHD. The 3-year overall survival (OS) after allo-HSCT was 81.5%. Eighteen patients died (15.1%) after a median of 10 months (range 2-36 months) post-transplant. Compared with patients without c-KIT mutations ($N = 65$), patients who harbored c-KIT mutations ($N = 54$) exhibited a lower OS, although the difference was not statistically significant (72.4% 3-year OS and 89.5% 3-year OS in the c-KIT positive and negative, respectively; $p = 0.061$). Of the 54 patients with c-KIT gene mutations, 21 had a D816 mutation and the remaining 33 patients had other c-KIT mutations. We observed a worse outcome among those c-KIT mutation-positive patients who harbored the D816 mutation compared to the other c-KIT mutations (3-year OS of 54.7% compared to 83.9%, respectively; $p = 0.024$). Patients without c-KIT mutations had a prognosis comparable to those patients who harbored a non-D816 c-KIT mutation (3-year OS of 83.9% compared to 89.5% respectively; $p = 0.701$).

Conclusions: Allo-HSCT is an effective therapy among high-risk CBF-AML pediatric patients positive for the RUNX1-RUNX1T1 fusion gene. However, we found that an additional D816 c-KIT mutation is strongly associated with a poor prognosis among these pediatric AML patients.

Disclosure: Nothing to declare

P230

Validation of the revised pretransplant assessment of mortality score after allogeneic hematopoietic transplantation using post-transplant cyclophosphamide

S. Piemontese[1], C.A. Fidanza[2], A. Ruggeri[1], M. Marcatti[1], A. Acerbis[1], M.T. Lupo Stanghellini[1], F. Giglio[1], R. Greco[1], F. Lorentino[1], F. Farina[1], A.A. Assanelli[1], C. Corti[1], J. Peccatori[1], F. Ciceri[1,3]

[1]IRCCS San Raffaele Scientific Institute, Milan, Italy, [2]Università degli studi di Milano Statale, Milan, Italy, [3]Vita-Salute San Raffaele University, Milan, Italy

Background: Despite trends showing improved outcomes after allogenic hematopoietic cell transplantation (allo-HCT), non-relapse mortality remains a major concern. The prediction of survival is therefore crucial. Large cohorts of patients are needed to develop and validate prognostic scores and the same must be periodically revised in response to changes in clinical practice. The aim of this study was to evaluate the ability of the revised pre-transplant assessment of mortality (PAM) score in predicting survival in an independent large cohort of patients receiving allo-HCT using post-transplant Cyclophosphamide (PTCy) as graft-versus host disease prophylaxis.

Methods: All consecutive adult patients with hematological malignancies who underwent a first allo-HCT with PTCy regardless the type of donors at San Raffaele Hospital in Milan between January 2013 and June 2020 were included. Patients with missing PAM score were excluded.

Results: A total of 373 patients met the inclusion criteria and were retrospectively analyzed. Median patient age was 54.97 (IQR 41.32-64.64) years. Median follow-up among survivals of 30.49 (range, 2.98-80.13) months. The 2-year overall survival (OS) was $66 +/- 4\%$. Median PAM score was 18.60 (IQR 15.80-24.00). Patients were analyzed according to the PAM score into 4 groups, using the cut-points of the original study. The 2-year OS was $78 +/- 4\%$ for group 0 (PAM < 17), $71 +/- 5\%$ for group 1 (PAM 17-23), $52 +/- 6\%$ for group 2 (PAM 24-30) and $30 +/- 8\%$ for patients in group 3 (PAM > 30) ($p < 0.0001$) As OS for group 0 and 1 were superimposable, we identified a novel cut-point of 25 that allowed us to better stratify overall survival of our patients ($p < 0.0001$). Matched donors (related or unrelated) were similarly represented in group 0 and 1 (group 0: 65.6% vs group 1: 52.4%; $p = 1$) but they were less represented in group 2 and 3 (group 0-1: 60.1% vs group 2-3: 16%, $p < 0.0001$). Haploidentical donors was more frequent in group 2 and 3 (group 0-1: 29.2% vs group 2-3: 69.7%, $p < 0.0001$). Analyzing OS by donor type (matched vs non-matched) we were able to confirm the ability of PAM score to predict OS for patients receiving a mismatched donor ($p < 0.0001$) but not for patients receiving a matched one ($p = 0.125$). In multivariate analysis risk factors for lower OS were PAM (as continuous variable for each point increase: HR: 1.068, CI: 1.041-1.096; $p < 0.0001$) and HCT-CI ≥ 4 (HR 2.055, CI: 1.380-3.059; $p = 0.001$).

Conclusions: Based on our result, PAM score confirmed to be a useful tool for predicting survival especially in high risk patients (PAM group 2 and 3) and in particular in patients receiving a mismatched donor. Recipients of matched donor showed increased OS but PAM score could not identify patients with different outcome. These results could be likely addressed to the beneficial effects of PTCy use in the matched donor setting. Further validation of our results in different transplant centers and cohorts of patients are needed. Integration of PAM with other pre-transplant scores, in particular with HCT-CI, remains crucial to better define the main outcomes of each individual patient.

Disclosure: Nothing to disclose

P231

Excellent results of allogeneic hematopoietic stem cell transplantation for relapsed/refractory ph-positive b-cell acute lymphoblastic leukemia

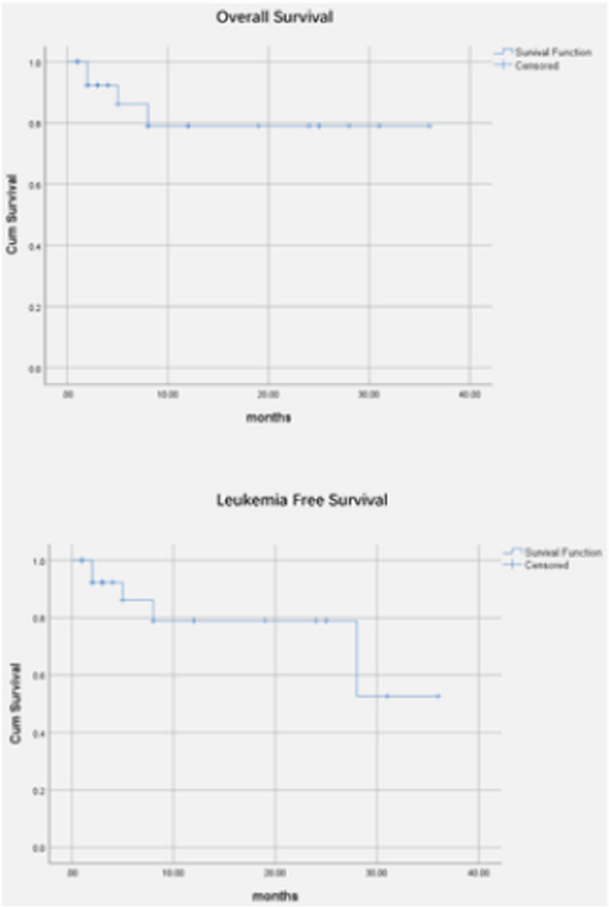
Y. Song[1], Z. Li[1], Y. Zhao[1], E. Yuan[1], Q. Qin[1], K. Gao[1], Q. Wang[1], T. Wu[1]

[1]Beijing Boren Hospital, Beijing, China

Background: The introduction of tyrosine kinase inhibitors (TKIs) has significantly improved the prognosis of Ph-positive (Ph +)

B-cell acute lymphoblastic leukemia (B-ALL). However, there are still a significant proportion of patients will relapse and allogeneic hematopoietic stem cell transplantation (allo-HSCT) are the most effective treatment for them. In current study, the efficacy and safety of allo-HSCT for the patients with relapsed/refractory (r/r) Ph + B-ALL were evaluated.

Methods: Between November 2018 and November 2021, 29 consecutive patients with r/r Ph+ B-ALL who received allo-HSCT in our hospital were included. The median age was 28 (3-59) years old. The median disease course was 21 (5-59) months. All patients were in complete remission and eight patients (27.6%) were MRD positive (2 detected by flow cytometry, and 6 detected by RT-PCR) before HSCT. 21 (72.4%) get remission by chimeric antigen receptor T-cell (CART) therapy. Eleven patients (37.9%) had T315I mutation. Five patents (17.2%) underwent the second transplantation. Two patients (6.9%) received allo-HSCT from sibling matched donrs, nineteen patients (65.5%) from haploidentical donors and eight patients (27.6%) from unrelated donors (HLA 10/10 or 9/10 matched). Myeloablative conditioning regimens with total body irradiation (fractionated, total 10 Gy) /etoposide (200mg/m^2 x 3) /fludarabine (30mg/m^2 x 5) or cyclophosphamide (1.8g/m^2 x 2) /rabbit anti-T-cell globulin were used. Cyclosporine, mycophenolate mofetil and short-term methotrexate were employed for graft-versus-host disease (GVHD) prophylaxis. All patients received maintenance regimens with sensitive TKIs based on their ABL1 gene mutations up to 2 years post-transplantation.



Results:

The two-year OS and LFS of all included patients.

All patients achieved durable engraftment. the median follow-up time was 8 (1-36) months and two-year OS and LFS were both 79%. Only two patients relapsed, one patient died of relapse and the other one is receiving post-transplantation CART therapy. Three patients developed grade III~IV aGVHD and two patients had extensive cGVHD. All of them were resolved with immune-suppressants except two patients died from grade IV aGVHD. One patient died of severe viral pneumonia seven months after HSCT. Seven patients had CMV reactivation and no patient had EBV reactivation. Five patients had mild hemorrhagic cystitis. One patient occurred severe bacterial pneumonia and was cured with antibiotics. The non-relapse mortality (NRM) was 10.3% (3/29). For the eleven patients with T315I mutation, only one patient relapsed and died of relapse. The two-year OS and LFS were both 87.5%. There was no patient with T315I mutation died of transplant-related adverse events. For the 21 patients who got remission by CART therapy, the two-year OS, LFS and NRM were 85.3%, 85.3% and 9.5% (2/21), respectively. For the 8 patients with MRD positive before HSCT only one patient relapsed 28 months after HSCT and there was no transplant-related death.

Conclusions: Our results indicate that allo-HSCT is an excellent therapeutic method for r/r Ph+ B-ALL. The two-year OS and LFS can reach to 79%, in addition, NRM is quite low 10.3% (3/29). Even for patients with T315I mutation or MRD positive before HSCT, survival was also remarkedly good with the two-year OS and LFS both more than 70%.

Disclosure: There is on conflicts of interesting to disclosure.

P232

a comparison between atg and pt-cy graft-versus-host-disease prophylaxis in patients with lymphoma undergoing reduced intensity conditioning regimen HSCT from 1 antigen mmud

A. Paviglianiti[1,2], A. Mussetti[1,2], M. Ngoya[3], A. Boumendil[3], N. Fegueux[4], F. Bonifazi[5], Z. Gülbas[6], F. Ciceri[7], D. Russo[8], G. Socié[9], M. Bornhäuser[10], H. Finel[3], S. Robinson[3], S. Montoto[11], B. Glass[3]

[1]Institut Català d'Oncologia-Hospitalet, Barcelona, Spain, [2]Institut d'Investigacio Biomèdica de Bellvitge, Barcelona, Spain, [3]Lymphoma Working Party, EBMT, Paris, France, [4]Lapeyronie, Montpellier, France, [5]IRCCS Azienda Ospedaliero-Universitaria di Bologna, University of Bologna, Bologna, Italy, [6]Anadolu Medical Center Hospital, Kocaeli, Turkey, [7]Hematology and Bone Marrow Transplant Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy, [8]USD Trapianti di Midollo Adulti, Università di Brescia, Brescia, Italy, [9]Hopital Saint Louis, Paris, France, [10]Universitaetsklinikum Dresden, Medizinische Klinik und Poliklinik I, Dresden, Germany, [11]St.Bartholomew's Hospital, Barts Health NHS Trust, London, United Kingdom

Background: The use of post-transplant cyclophosphamide (PTCY) as a graft-versus-host disease (GvHD) prophylaxis has led to important improvements in the haploidentical setting. Following this, PTCY was introduced as a safe and feasible option in the mismatched and matched unrelated donor settings. Nevertheless, the main GVHD strategy to date remains T-cell depletion with ATG in one antigen HLA-MMUD (9/10 MMUD). Data comparing the two GVHD strategies in patients undergoing MMUD 9/10 for lymphoproliferative disease are limited.

Methods: We compared PTCY versus ATG as GvHD prophylaxis in patients with lymphoproliferative diseases undergoing a first 9/10 MMUD HSCT with a reduced intensity conditioning regimen from 2009 to 2019. Adult patients in all disease status for which high-resolution HLA-allele typing was available in the LWP/EBMT data registry were included. Patient receiving PTCY were matched to patients receiving ATG for age, disease status at transplant, source of stem cells, CMV serology and gender.

Results: A total of 322 patients were identified (n = 287 for ATG group and n = 35 for PTCY group). According to the above

mentioned variables, 56 patients receiving ATG were identified and matched with 31 patients receiving PTCY. Among the group of 87 patients paired up, diagnosis was Hodgkin Lymphoma in most of the cases (27% and 40% in the ATG and PTCY group, respectively). The majority of patients had received a previous autologous HSCT (62% in the ATG and 68% in the PTCY group, respectively). Graft stem cell source was peripheral blood in all patients of both matched groups. The majority of patients were in complete remission at HSCT (67% and 66% in the ATG and PTCY group, respectively). The most frequent GvHD prophylaxis in the ATG group was cyclosporine A (CsA) and methotrexate (MTX) (n = 24; 43%), followed by CsA and mycophenolate mofetil (MMF) in 29% of the cases. In the PTCY group, the majority of patients (n = 18; 58%) received CsA and MMF, while tacrolimus and MMF (19%) were the second most used associated immunosuppressive agents. The median follow-up was 5 (3.6-6.8 IQR) years for the ATG group and 2.6 (2-4.1 IQR) years in the PTCY group. No significant differences were detected across the two groups. Karnofsky performance status was > = 80% in 100% and 90% of the ATG and PTCY groups, respectively (p = 0.04).

A similar engraftment rate was observed for both groups (98% and 100% in ATG and PTCY groups, respectively). The two year-progression free survival was 48% in patients receiving ATG and 41% in those receiving PTCY (NS). Grade III-IV acute GVHD and GRFS were not significantly different in patients receiving ATG or PTCY. No differences were observed in relapse incidence (35% versus 26%, p = 0.14), non-relapse mortality (17% versus 33%, p = 0.39) and overall survival (64% versus 51%, p = 0.25).

Conclusions: In patients with lymphoproliferative diseases undergoing 9/10 MMUD HSCT, PTCY as GVHD prophylaxis could be a safe and feasible option. Prospective randomized trial will help to better understand the effectiveness of adding PTCY into different platforms, comprising MMUD 9/10 HSCT.

Clinical Trial Registry: not applicable

Disclosure: Nothing to declare

P233

Preceding proteinuria as a risk and prognostic factor for transplant-associated thrombotic microangiopathy in adult acute myeloid leukemia cohorts

G.J. Min[1], D. Kwag[1], T.Y. Kim[1], J.H. Lee[1], J. Lee[1], S.-S. Park[1], S. Park[1], J.-H. Yoon[1], S.-E. Lee[1], K.-S. Eom[1], Y.-J. Kim[1], S. Lee[1], H.-J. Kim[1], C.-K. Min[1], S.-G. Cho[1], J.W. Lee[1], B.-S. Cho[1]

[1]Leukemia Research Institute, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea, Republic of

Background: Transplant-associated thrombotic microangiopathy (TA-TMA) is an endothelial injury syndrome with a wide range of presentations that could lead to multiorgan injury after allogeneic hematopoietic stem cell transplantation (HSCT). Morbidity and mortality from TA-TMA remain high. Therefore, identifying patients at the highest risk for severe disease and proper management is critical. Recently, a prospective study with children and young adults (*Jodele et al*, Blood 2014) has proposed new diagnostic criteria, including preceding proteinuria (>30 mg/dL) and elevated sC5b-9 levels, and risk/prognostic factors for TA-TMA, which needs to be validated in adult population. Thus, we investigated risk and prognostic factors for TA-TMA in recent large adult cohorts with acute myeloid leukemia (AML).

Methods: We used Cho's criteria for TA-TMA diagnosis previously published by our group (Cho *et al*., Transplantation 2010) and analyzed the incidence, risk, and prognostic factors in two independent cohorts of training (n = 382, 2012 to 2015, retrospective) and validation (n = 231, 2016 to 2017, prospective). A total of 613 patients with AML who received allogeneic HSCT from matched siblings (n = 260), unrelated donors (n = 167), or haploidentical family donors (n = 186) was analyzed.

Results: TA-TMA developed in 72 patients, and the cumulative incidence was 12.6% (95% confidence interval (CI) 10.0 – 15.5). The validation cohort presented with higher TA-TMA incidence than the training cohort (18.8% vs. 8.9%, p < 0.001). Both cohorts had no significant difference in pre-transplant characteristics with an exception of the higher number of haploidentical transplantation in the validation cohort. In terms of risk factors for TA-TMA, multivariate analysis revealed that preceding proteinuria (≥30 mg/dL) was a significant factor for TA-TMA in both the training cohort (HR 5.94, 95% CI 2.77 – 12.77, p < 0.001) and validation cohort (hazard risk (HR) 5.29, 95% CI 2.51 – 11.16, p < 0.001). Preceding hemorrhagic cystitis was a significant risk factor only in the validation cohort (HR 1.99, 95% CI, 1.07 – 3.71, p = 0.003). In entire cohort, elevated LDH x1.5 above normal (HR 1.66, 95% CI, 1.04 – 2.64, p = 0.034), proteinuria (≥30 mg/dL, HR 5.69, 95% CI 3.30 – 9.82, p < 0.001), and CMV disease (HR 1.99, 95% CI, 1.18 – 3.37, p = 0.010) were significant risk factors. In terms of prognostic factors, preceding proteinuria (≥300 mg/dL), concurrent hemorrhagic cystitis in any grades, acute GVHD grade II to IV, and bacterial and/or fungal infections were associated with poor overall survival (OS) and non-relapse mortality (NRM), but only preceding proteinuria (≥300 mg/dL) remained significant in the multivariate model (OS; HR 2.54, 95% CI 1.45 – 4.43, p = 0.001 and NRM; HR 2.98, 95% CI 1.57 – 5.66, p < 0.001).

Conclusions: This study found out potential risk and prognostic factors for TM-TMA in a recent adult retrospective cohort and validated them in an independent prospective cohort. Our data highlight that the preceding proteinuria as a marker for renal involvement of TA-TMA would be an important risk and prognostic factor for TA-TMA in adults. Prospective multicenter studies are warranted to confirm our findings in an adult population.

Clinical Trial Registry: CRIS KCT0002261 https://cris.nih.go.kr/cris/search/listDetail.do

Disclosure: Nothing to declare

P234

Covid19 vaccine responses in patients post stem cell transplant

F. Alroqi[1,2,3], B. Alahmari[1,2,4], M. Alzahrani[1,2,4], M. Damlaj[1,2,4], M. Saud[1], R. Jaha[1], A. Al Harbi[1], M.-A. Mendoza[1], M. Abdoh[5], A. alaskar[1,2,4]

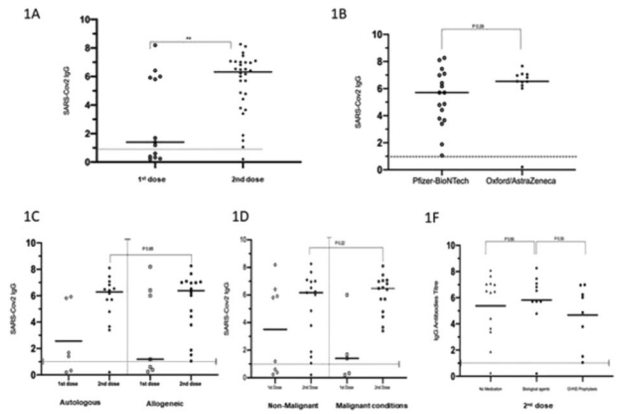
[1]King Abdullah International Medical Research Centre (KAIMRC), Riyadh, Saudi Arabia, [2]King Saud Bin Abdul-Aziz University for Health Sciences, Riyadh, Saudi Arabia, [3]King Abdullah Specialized Children's Hospital (KASCH), Ministry of National Guard - Health Affairs, Riyadh, Saudi Arabia, [4]King Abdullah Specialized Children's Hospital (KASCH), Ministry of National Guard - Health Affairs, Riyadh, Saudi Arabia, [5]College of Applied Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Background: Patients status post stem cell transplant (SCT) are at high risk for severe COVID-19 infections (1). During this pandemic, SARS-CoV2 vaccines have been considered as the priorities for this vulnerable population. Previous reports shed light on the poor immune response after SARS-CoV2 vaccines in recipients of SCT especially in those patients on immunosuppressive medications(2). In this study, we report SARS-CoV2 IgG after COVID19 vaccinations in patients post autologous and allogeneic SCT.

Methods: This is a cross-sectional study enrolling 43 patients post SCT (autologous 20, allogeneic 23).

who received COVID-19 vaccination (Pfizer-BioNTech or Oxford/AstraZeneca). The participants were recruited between 1st of May to the end of November 2021. The blood samples were collected and tested for the presence of IgG antibodies against SARS-CoV2 spike protein using enzyme-linked immunosorbent assay (ELISA).

Results: Around 60% of post SCT patients have COVID19 protective humoral immunity after 1st dose of COVID19 vaccination(1A). This immune response has increased dramatically after the second dose regardless of the type of the vaccine (1A,B). No observed significant differences in immune responses in patients post autologous or allogeneic SCT (1C). A similar response was observed in patients with Non-malignant and malignant conditions (1D). Most of post SCT patients have good immune response after the 2nd dose of COVID19 vaccinations apart from one patient who had poor T cell engraftment despite holding immunosuppressive medications and another patient who is currently on B cell ablative therapy (1F). No major concerns regarding immune protection was observed in patients either on GVHD prophylactic medications (Cyclosporine, Tacrolimus, Sirolimus and Ruxilitinib) or biologics (Nivolumab, Bortezomib, Ixazomib) apart from B cell ablative medications.



Conclusions: Post SCT patients have good response to SARS-CoV2 vaccination. This response was observed to be increasing after subsequent dosing regardless of the original diagnosis. Our results provide evidence that the SARS-CoV2 vaccination generates protective immunity in this high risk population even if they are on immunosuppressive medications.

References:

1- Q. Wang, N.A. Berger, R. Xu, Analyses of risk, racial disparity, and outcomes among US patients with cancer and COVID-19 infection, JAMA Oncol. 7 (2) (2021) 220–227.

2- Oluwafeyi Adedoyin, Sharmela Brijmohan, Ross Lavine, Fausto Gabriel Lisung. Undetectable SARS-CoV-2 active adaptive immunity-post-vaccination or post-COVID-19 severe disease-after immunosuppressants use. BMJ Case Rep. 2021 Nov 29;14(11).

Disclosure: No conflict of interest

P235

Multiple myeloma: Home treatment is possible in a tertiary hospital. From autologous stem cell transplantation to oral therapy

L. Solán[1], A. Domingo[1], J.I. Merlo[1], A. Sánchez Donaire[1], A. López García[1], C. Élez[1], E. González[1], J. Cornago[1], J.L. López Lorenzo[1], P. Llamas[1]

[1]University Hospital Fundación Jiménez Díaz, Madrid, Spain

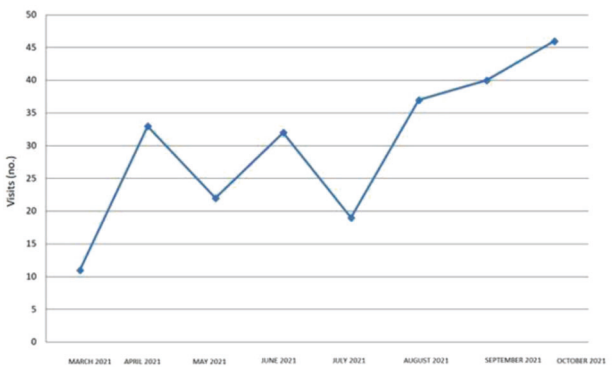
Background: Multiple myeloma (MM) is the most common indication for autologous stem cell transplantation (ASCT), and outpatient models have been widely developed in this setting. In addition, the use of oral and subcutaneous treatments both in induction and maintenance, as well as the development of new technologies, has allowed these patients to continue their treatment without going to the hospital, thus improving their quality of life.

Methods: Since March 2021, we have put in place a comprehensive home-care program for patients with multiple myeloma in a tertiary hospital. It is a multidisciplinary project in which nutrition, rehabilitation, psychology, pharmacy, hematology and nursing services collaborate to offer the patient individualized and quality care.

Results: A total of 59 patients with MM have benefited from our program (Figure 1). Two patients have received an ASCT, going from a hospital stay of about 3 weeks to just 4 days (none of the patients had to be readmitted, completing the treatment at home).A total of 276 analytical extractions have been carried out at home, 427 calls by nurses, and an approximate saving of 30 face-to-face medical consultations per month, doing them virtually (videoconference or phone call).The entire program is coordinated by two hematologists specializing in multiple myeloma and transplantation. 2 nurses are in charge of the analytical extraction and assessment of the patients at home. There is 1 pharmacist who sends the medication to the home.

It is a program where the optimization of resources and the use of new technological tools have made it possible to offer the patient with MM a personalized and quality treatment.

Figure 1. Number of home visits since the beginning of the home program for patients with multiple myeloma.



Furthermore, external companies have collaborated in this innovation project (the car company "KIA" donated the car with which we make home visits) and the Spanish Association Against Cancer (AECC) has given the use of two homes close to the hospital for patients who live outside the hospital area can undergo ASCT and have all the benefits adhered to the program.The implementation of this program has allowed, on the one hand, to carry out multidisciplinary work (hematologists, specialist nurses, nutritionists, pharmacists and psychologists) focused on the patient with MM. On the other hand, the MM patient continues their treatment outside the hospital, thus improving their quality of life and having more self-control of the treatment they receive.

Conclusions: The implementation of a home program for patients with MM (ASCT and oral treatment) is possible in a tertiary hospital with availability of digital technology. The multidisciplinary work and the personalization of the treatments

in our patients increases their quality of life and even reduces the associated complications.

Disclosure: No conflict of interest

P236

Haploidentical transplant from PBSC with post-transplantation cyclophosphamide and controlled number of t lymphocytes

S. Rossi[1], V. Pintabona[1], E. Soncini[1], M. Comini[2], M. Maffeis[1], G. Baresi[1], F. Bolda[2], A. Beghin[2], A. Lanfranchi[2], F. Porta[1]

[1]Pediatric Oncohematology Unit and Pediatric Bone Marrow Transplant Center - ASST Spedali Civili, Brescia, Italy, [2]Stem Cell Laboratory, Section of Hematology and Blood Coagulation, Clinical Chemistry Laboratory, ASST Spedali Civili, Brescia, Italy

Background: The use of post-transplantation cyclophosphamide (PT/Cy) is a well-established strategy that has been proved to achieve excellent results in haploidentical transplants with donor bone marrow cells. On the other hand, the use of PBSC in this setting is limited by the risk of an increased incidence and severity of GVHD compared to the use of bone marrow cells. Recently, new data have been reported describing the use of PT/Cy both in combination and without traditional immunosuppression, also in MFD and MUD donor transplants with promising data, such as reduced risk of GVHD and fewer viral reactivations. At our center, the use of PBSC has been consolidated for several years by performing a procedure that provides the selection of CD34 + and later addback of a controlled number of T lymphocytes ($30x10^6$/kg/recipient). This technique leads to rapid engraftment, rapid immunological reconstitution and low incidence of acute and chronic GVHD.

Methods: In recent years, 4 transplant procedures have been carried out at our center using peripheral cells as a source of haploidentical donor stem cells and performing product manipulation with CD34 + selection and CD3 + addback with controlled number and subsequent post-transplant Cyclophosphamide.

Results: Average neutrophil engraftment was reported on day +18, while that of platelets on day +30. There was no documented presence of significant acute GVHD or chronic GVHD. Only one case of invasive infection (Adenovirus pneumonia), resolved after targeted therapy.

Conclusions: In our opinion this technique represents a promising alternative in the setting of haploidentical donor transplantation as it guarantees rapid engraftment, accordingly to the greater number of CD34 + cells (>10 x 10^6/kg), while not causing an increase in the incidence and severity of GVHD. Indeed, it combines the advantages of administering a high number of CD34 + cells, obtainable through PBSC, and those of the reduced number of lymphocytes T of the donor with the lowest risk of GVHD. Certainly, further data and research will be needed to consolidate this procedure.

Disclosure: Nothing to declare

P237

Predictors of outcomes in hematopoietic cell transplantation for fanconi anemia: A multicenter analysis

M. Cancio[1], A. Troullioud[1,2], K. Elizabeth[1], M. de Witte[3], F. Smiers[4], D. Bresters[2], J.J. Boelens[1], M. Bierings[2], S. Smetsers[2]

[1]Memorial Sloan Kettering, New York, United States, [2]Princess Maxima Center, Utrecht, Netherlands, [3]University Medical Center Utrecht, Utrecht, Netherlands, [4]Leiden University Medical Center, Leiden, Netherlands

Background: Hematopoietic cell transplantation (HCT) remains the only curative option for aplastic anemia or MDS/AML in Fanconi anemia (FA) patients. We were interested in performing a predictor analysis for outcomes of HCT for FA patients across four large FA referral institutions using different transplant platforms.

Methods: We conducted a retrospective analysis of prospectively collected data of FA patients undergoing their first HCT at Memorial Sloan Kettering Cancer Center (New York, USA), Princess Maxima Center, University Medical Center Utrecht, and Leiden University Medical Center (the Netherlands) between 2007 and 2019. No restrictions applied in terms of age, gender, indication (SAA, MDS/AML), HLA matching, conditioning regimen, and graft source or manipulation. These variables were also considered in analyses. Main outcomes of interest were event free survival (EFS) (events: relapse, graft failure (GF), treatment related mortality) and overall survival (OS). Other outcomes of interest were treatment related mortality (TRM), acute graft vs. host disease (aGvHD) grade II-IV, extensive chronic GvHD, and posttransplant malignancies. COX proportional hazard models and Fine and Gray models for competing risk were used for analyses.

Results: 89 patients were included: 64 SAA +/− cytogenetic abnormalities and 25 MDS/AML. Median age at transplant was 9.2 years (1.7 - 44.0 years). 52 (58.4%) received a T-replete HCT: 40 (77%) from bone marrow and 12 (23%) from cord blood (10 HLA-mismatched; 19.2%). 37 (41.6%) underwent a TCD-HCT of whom 20 (54.0%) were HLA-mismatched. Conditioning regimens included Cyclophosphamide (Cy) and Fludarabine (Flu) ($n = 52$), Total Body Irradiation (TBI) /Cy/Flu ($n = 11$) and Busulfan/Cy/Flu ($n = 26$). The 5-year OS and EFS were 83.2% (75.3-91.9%) and 74% (65-84.2%), respectively. Age >18 was found to be the only multivariate (MV) predictor for OS (HR 9.1, 95%-CI 1.3– 61.7, $p = 0.024$), while for EFS, in addition to age >18 (HR 8.9, CI 2.2 – 36.7, $p = 0.002$), HLA-matching was a MV predictor (HR 4.7, 95%-CI 1.7–12.6, $p = 0.002$). In the pediatric group (age < 18, $n = 73$), TCD was a borderline MV predictor (HR 8.4, CI 0.9–76.6 $p = 0.059$) with 5-year OS of 73.0% (54.7 – 97.4%) in TCD vs 100% for T-replete HCT. For TRM the only MV predictor was age >18 (HR 20.1, CI 1.7 – 236.5, $p = 0.017$). Age above or below the median within the pediatric cohort was not a predictor for OS, EFS and TRM. The cumulative incidence of day100 grade II-IV aGvHD and 5-year cGvHD was 6.7 % and 4.5%, respectively. Relapse in the MDS/AML subgroup was only seen in 4 (16%). GF was seen in 9 patients (TCD 6/37; 16%; T-replete 3/52; 5.7%). Six patients developed malignancy after HCT; of these, two had preceding GvHD.

Conclusions: Survival chances after HCT for FA are excellent and associated with low toxicity. Age above 18 is the main predictor for inferior survival (driven by TRM). For pediatric patients undergoing a T-replete transplant with an HLA-matched donor (or HLA-mismatched cord blood) survival was excellent (100% survival at 5yrs). For patients without a good matching donor, TCD offers a very good alternative.

Clinical Trial Registry: None

Disclosure: Nothing to declare

P238

Adverse events of mrna-1273 sars-cov-2 vaccine in recent allogeneic hematopoietic stem cell transplant recipients

N. Albiol[1,2], O. Aso[1], L. Gómez-Pérez[1], M. Triquell[1], N. Roch[1], E. Lázaro[1], A. Esquirol[1,2,3,4], I. González[1], J. Sierra[1,2,3,4], R. Martino[1,2,3,4], I. García-Cadenas[1,2,3,4]

[1]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [2]Institut d'Investigació Biomèdica, Barcelona, Spain, [3]Autonomous University of Barcelona, Barcelona, Spain, [4]Josep Carreras Leukaemia Research Institute, Barcelona, Spain

Background: Allogeneic hematopoietic cell transplant (HCT) recipients are highly susceptible to COVID-19 and related complications. This vulnerable population has been prioritized for vaccination despite limited safety data. Preliminary studies including heterogeneous series of HCT recipients reported variable frequency of adverse events (AE) including GVHD flares and vaccine-related cytopenias.

Methods: This single center prospective study describes frequency and severity of mRNA-1273 SARS-COV2 vaccine AE in 54 alloHCT recipients less than two years away from transplantation date.

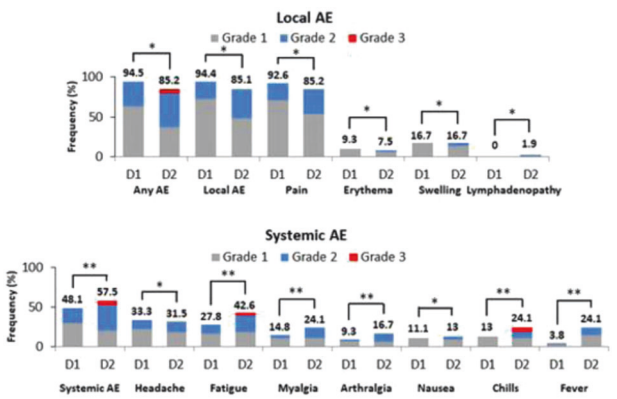
AE were assessed through calls during the seven days after each dose and graded from 0 to 4 according to the original phase III study (Baden. N Engl J Med 2021).

Results: Patients' characteristics are exposed in Table 1. Median age was 53.5 years (25-73) and 48.1% were females. Median time from HCT to first vaccine dose was 13 months (3-26).

Donor, n (%)		**GVHD, n (%)**	
MSD	11 (20.4)	Acute	19 (35.2)
MUD	21 (38.9)	*Grade 2-4*	*11 (20.4)*
MMUD	12 (22.2)	Chronic	10 (18.5)
Haploidentical	10 (18.5)	*Moderate-severe*	*2 (3.8)*
GVHD prophylaxis, n (%)		Active immunosuppression, n (%)	**40 (74.1)**
PTCy-based	36 (66.7)	Ongoing prophylaxis	27 (50)
Sirolimus-Tacrolimus	12 (22.2)	Corticosteroids	7 (13)
Other	6 (11.1)	Second-line treatment	6 (11.1)

AE incidence of any kind (94.4% at dose 1 and 85.2% at dose 2) was similar to that reported in the pilot study. Local AE were the most common, pain at site of injection being the most frequent one (92.6% and 85.2%, dose 1 and 2, respectively). Systemic AEs were rarer, affecting 48.1% and 57.4% (1st and 2nd dose respectively) of patients. Figure 1 shows incidence and grade for every AE. Systemic AEs were more common and severe after the second dose ($p = 0.007$).

Only 5.6% of patients presented grade ³3 AE, none requiring hospitalization. Neither vaccine-related deaths nor cytopenia or GVHD flares were observed.



Female sex was significantly associated with a higher degree of AEs at the first dose (OR 3.94, 95% CI 1.14-13.58, $p = 0.03$). Time from HCT was associated with a higher degree of systemic AEs at the second dose (OR 1.09, 95% CI 1.01-1.18, $p = 0.04$), specifically with higher degree of chills (OR 1.15, 95% CI 1.01-1.31, $p = 0.04$). Prior COVID-19 infection correlated with fever at the second dose (OR 10.22, 95% CI 1.21-86.59, $p = 0.03$), though only five patients had had COVID-19.

Age, graft source, donor type, donor age, number of CD34 + cells infused, conditioning type, GVHD prophylaxis, disease type and status, GVHD (either past or active), immunosuppression (neither active/inactive nor its type), living with vaccinated people, T-cell chimerism and some other lab values (lymphocyte, IgG, $CD4^+$, $CD8^+$, and $CD19^+$ counts) had no relation to any type of AE severity.

Conclusions: mRNA-1273-related AE in early alloHCT recipients were comparable to the general population. None presented new-onset cytopenias or GvHD flares. Female sex, prior COVID-19 infection and longer time from HCT were associated with a higher rate of AE.

Disclosure: Nothing to declare.

P239

Quality of life related-factors in long-term survivors following allogenic stem cell transplantation

J.J. Domínguez-García[1], M. Sánchez-Escamilla[1], L. Yáñez San Segundo[1], G. Martín Sánchez[1], M.Á. Cortés Vázquez[1], J.Á. Calvo Sánchez[1], S. Fernández García[1], L.P. Vega Suárez[1], E.M. Ocio San Miguel[1], M.A. Bermúdez Rodríguez[1]

[1]Hospital Universitario Marqués de Valdecilla, Santander, Spain

Background: Despite offering an opportunity of cure to patients with hematologic diseases, allogeneic stem cell transplantation (aSCT) and their related complications significantly affect quality of life (QoL). The purpose of this study was to evaluate QoL of aSCT long-term survivors (five-years from the aSCT) and determine those factors that could have an impact in it.

Methods: This is an observation study of sixty-seven patients who had undergone a single aSCT in our institution during January 2011 to December 2015. Participants answered in a telephone interview two validated aSCT-QoL questionnaires (FACT-BMT (score from 0 to 148) and EQ-5D-5L (score from 0 to 100)), and questions about employment, medications and comorbidities after transplantation.

Results: Long-term survivors' characteristics are shown in Table 1. Median time from aSCT to interview was 7 years (IQR 6-9). FACT-BMT and EQ-5D-5L mean scores were 115 to 148 and 73 to 100 respectively.

FACT-BMT score seemed higher in allogenic bone marrow stem cell transplantation (SCT) compared to allogenic peripherical blood SCT – 118 versus 107 points respectively (p-value 0.022). An association between QoL-working status and QoL-drugs intake was also observed. Statistically significant higher QoL FACT-BMT scores were present in patients who were working (123 vs. 111, p-value 0.002) and who were not taking drugs (125 vs. 113, p-value 0.026) as is summarized in Image 1. Patients with active graft-versus-host disease (GVHD) had worse EQ-5D-5L score (78 vs. 65, p-value 0.002). We did not find differences in QoL regarding age and gender of patients and donors, previous autologous SCT, disease status at aSCT or previous acute/chronic GVHD.

Patients with current pulmonary complications (mainly obliterative bronchiolitis and recurrent infections) have worse FACT-BMT score (102 vs. 117, p-value 0.010). By contrast, cardiovascular, hormonal, and neoplastic comorbidities do not impact FACT-BMT score.

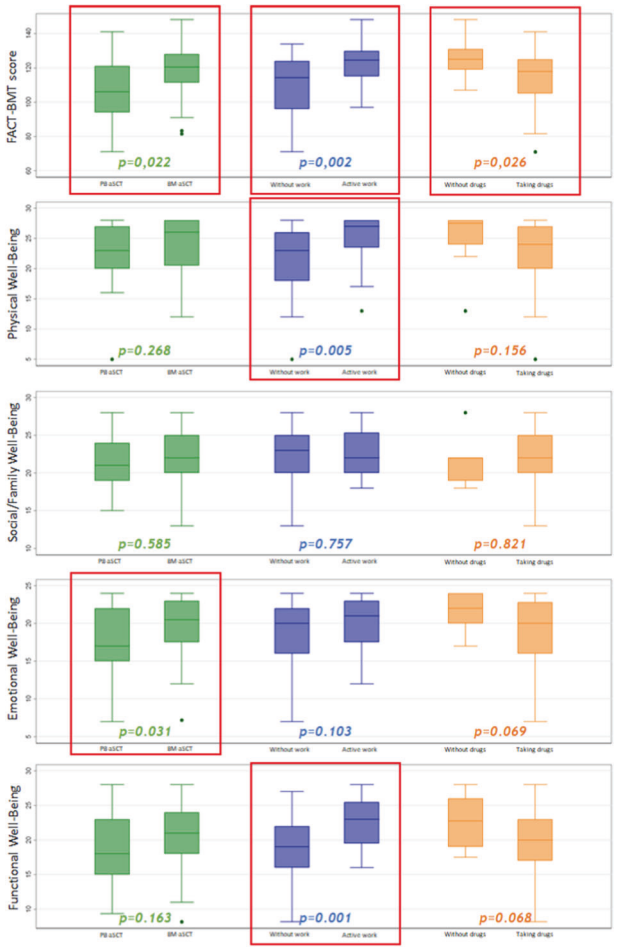
Factors associated with a worse QoL score in the multivariate analysis were drug-intake, active GVHD and SCT source. Having an

active GVHD at the time of the interview increased the risk of a worse QoL (defined as having under a 75th percentile score on one or both scores) by 1,7 (95%CI 1,1-9,4 p = 0,029) and using PB as stem cell source by 2,4 (95%CI 1,1-5,8 p = 0,042).

Table 1.

VARIABLES	SAMPLE (n = 67)
Age (yr), median (IQR)	48 (36-56)
Gender (male), n (%)	38 (56,7)
HLA-matched related donor aSCT, n (%)	22 (32,84)
Haploidentical related donor aSCT,n (%)	8 (11,94)
HLA-identical unrelated donor aSCT, n (%)	22 (32,84)
HLA-nonidentical unrelated donor aSCT, n (%)	15 (22,39)
BM-aSCT, n (%)	52 (77,6)
Active GVHD, n (%)	28 (41,8)

Image 1.



Conclusions: QoL for adult long-term aSCT survivors is close to the 75th percentile in our study. Drug-intake, previous chronic or active GVHD and not having reincorporated to active work are associated with a worse QoL. Among factors related with the procedure, just the use of peripheral blood seems to influence the aSCT QoL scores.

Disclosure: Nothing to declare.

P240

Hematopoietic stem cell transplant (HSCT) international cooperative project in iraqi kurdistan: A 3 year follow up on thalassemia patients and impact of sarscov2 infection

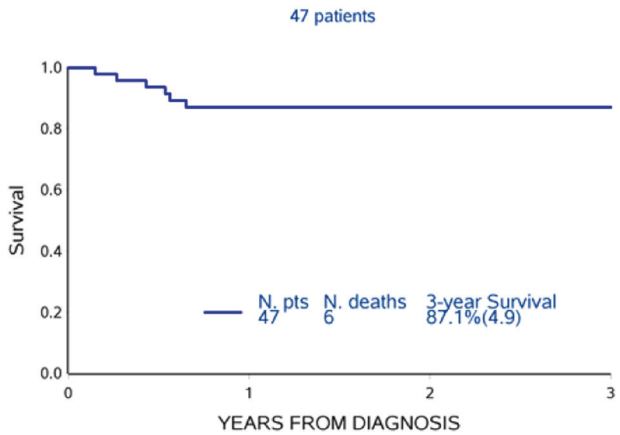
M. Verna[1], A.M. Rovelli[1], V. Conter[1], D. Silvestri[1], D. Hotman[2], D. Ahmed[2], C.N. Abdullah[2], R. Mohammed[2], S. Sozan[2], V. Faeq[2]

[1]Pediatric Hematology, Fondazione MBBM, University of Milano Bicocca, Monza, Italy, [2]Pediatric Hematology, Hiwa Cancer Hospital, Sulaymaniah, Iraq

Background: The spectrum of indications to HSCT in the pediatric age group is wide, starting from hemoglobinopathies, which are the most frequent life-threatening non-communicable disease of children. Transplantation can cure over 85% of low risk children with severe thalassemia directly in middle income countries and is highly cost-effective.

Methods: In 2016 the first HSCT Unit both for adult and children was developed in Iraqi Kurdistan at Hiwa Cancer Hospital of Sulaymaniyah, thanks to a capacity building project funded by the Italian Agency for Development Cooperation. Here we present a 3 years follow up on 47 thalassemia pediatric patients transplanted from matched sibling donors from Oct 2016 to July 2021 with granulocyte colony stimulating factor priming. Follow-up was updated in Nov 2021.

Results: Mean age was 6.6 years; mean total nucleated cells (TNC) received was 17.2 x 108/Kg; mean time to engraftment of neutrophil > 500 x 109/L was 17 days and of platelets >50 x 109/L was 19 days. With a median follow-up of 2.6 years, the 3-years event free survival (EFS) and survival (OS) were 82.8% (SE 5.5) and 87.1% (4.9); the 3-yrs cumulative incidence risk of rejection was 4.3% (2.9). Treatment related mortality (TRM) was 12.9% (4.9); 3/6 patients died due to SarsCov2 infection. 10 patients (21%) presented acute graft-versus-host-disease (GVHD) grade III-IV and 14 (30%) moderate/severe chronic one. No statistically significant correlation was found between incidence of aGVHD grade III-IV and median count of white blood cells of the marrow (p = 0.84), white blood cells of the peripheral blood of the donor at the time of the donation (p = 0.98) and CD3 + cells in the marrow (p = 0.81). The same analysis was done for moderate/severe cGVHD (p = 0.55, 0.82 and 0.57 respectively). Even looking to mean values of plasma cyclosporine before the onset of the GVHD (week 1-2-3-4-8-12-16-20) there was no statistical difference between patients with/without aGVHD grade III-IV (p = 0.44) and moderate/severe cGVHD (p = 0.97).



Conclusions: Based on our experience HSCT is a feasible and safe procedure in MICs.The incidence of both acute and chronic

GVHD was not correlated to donor's marrow WBC and CD3 + counts or peripheral WBC count at the moment of donation or recipient's mean values of cyclosporine levels. However GvHD resolved in the vast majority of patients who are now free of any immunosuppression. Compared with our previous analysis on 35 patients, TRM was higher than expected due to SarsCov2 infection; for this reason the BMT program has been temporarily discontinued.

Disclosure: No disclosure

P241

Use of abatacept as GVHD prophylaxis in pediatric patients undergoing HSCT from matched or mismatched unrelated donor

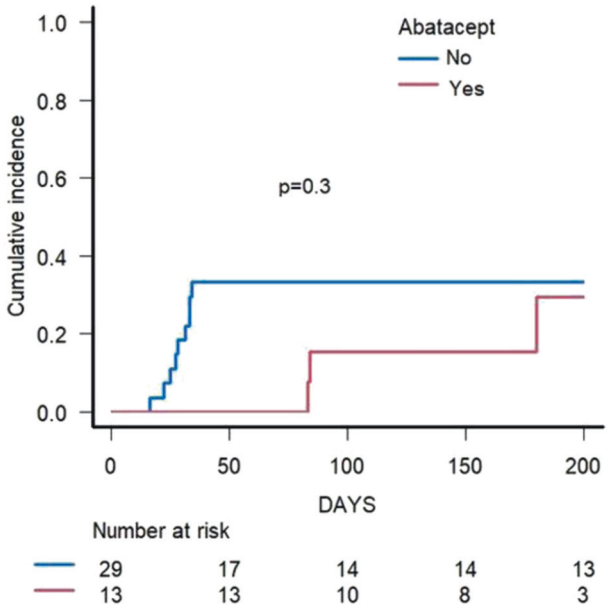
E. Boccieri[1], F. Quagliarella[1], M. Algeri[1], D. Pagliara[1], F. Galaverna[1], M. Becilli[1], R. Carta[1], M. Catanoso[1], G. Ceglie[1], F. Gottardi[2], F. Del Bufalo[1], T. Corsetti[1], P. Merli[1], F. Locatelli[1,3]

[1]IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, [2]IRCCS Ospedale Sant'Orsola Malpighi, Bologna, Italy, [3]Sapienza, Rome, Italy

Background: Hematopoietic stem cell transplantation (HSCT) is the only curative treatment for a number of malignant and non-malignant disorders. However, only in the 25% of cases is possible to identify a matched family donor. In lack of this, the probability to find a fully matched unrelated donor (MUD) is about 30-70% of cases. Patients given an allograft from a donor with a single antigenic or allelic disparity (mismatch, MM) had an increased risk of both acute GVHD and TRM as compared to patients receiving the transplant from fully matched donors; moreover, disparities at two or more loci further increase this risk. A possible strategy to minimize risks associated with HLA-mismatch is to add Abatacept to standard GVHD prophylaxis [Watkins, 2021]. Abatacept is a fusion protein that selectively inhibits T-cell co-stimulation by binding to CD80/CD86 on antigen-presenting cells and blocking CD28-mediated signaling.

Methods: From February 2021 to October 2021, Abatacept was administered to 12 pediatric patients (age 2-20 years) who received a transplant from a mismatched unrelated donor (mMUD) or PBSCs from a 10/10 MUD. The drug was administered intravenously at the dose of 10 mg/kg on days -1,+5,+14 and +28; moreover, one patient received an additional infusion on day +42 and two children two administrations on days +42 and +60 (see below for details).

Results: Seven patients were affected by malignant disorders and five by non-malignant diseases. Ten patients out of 12 were transplanted from mMUD, while 2 received the transplant from 10/10 MUD. The source of stem cells was peripheral blood in 4 cases(2 patients received PBSCs from fully matched donor). With a median follow up of 6 months, 3 of 12 patients developed grade III-IV aGVHD. In details, one patient presented acute grade IV GVHD on day +70 (gut stage 4); the second one developed acute grade IV GVHD on day +85 (gut stage 3 ed hepatic stage 4) and the last late acute grade IV GVHD on day +200 (gastrointestinal stage 4). The first two patients received PBSCs from 9/10 mMUD with a MM in locus A; the last one underwent HSCT from mMUD with MM in locus B and stem cell source was represented by bone marrow. After the occurrence of these cases of GVHD, we decided to administer additional doses of abatacept to the following patients; none of these additional 3 patients developed acute GVHD. No adverse events was related to the infusion of Abatacept. The comparison with an historical cohort of 29 patients treated with standard prophylaxis showed comparable cumulative incidence of aGVHD; however, GVHD occurred later in patients receiving Abatacept (Figure 1).



Conclusions: Our data confirm the efficacy and safety of Abatacept in the prevention of aGVHD in the context of HSCT from mMUD and/or using PBSCs as source of stem cells. Notably, the administration of additional doses (on days +42 and + 60), could further extend the protective effect of this treatment strategy.

Disclosure: No disclosure

P242

Early absolute lymphocyte recovery predicts better survival after autologous stem cell transplantation in patients with multiple myeloma and non-hodgkin lymphoma: A retrospective single-center study

C. Tolosa[1], A. Jaramillo[2], M. Santaliestra[1], F. Vall-llovera[1], J.M. Marti[1], C. Palafox[2], E. Fuste[2], R. Cortadellas[2], R.M. Claret[2], B. Calle[2], M. Garcia[1], J. Fernandez[2], S. Querol[2], N. Castillo[2]

[1]Hospital Universitari Mutua de Terrassa, Terrassa, Spain, [2]Banc de Sang i Teixits, Terrassa, Spain

Background: Clinical efficacy of autologous stem cell transplantation (ASCT) in treating malignancies has been attributed to high-dose chemotherapy. However, ASCT is not curative for a number of patients with malignant diseases. Many hypothesis for the high relapse rate after ASCT have been proposed. In brief, an early posttrasplant lymphocyte recovery could play a critical role for general outcomes. Some previous reports demonstrated that early lymphocyte recovery at day 15 after ASCT (ALC-15) had an impact on overall survival (OS) and disease-free survival (DFS).

Methods: Between January 2015 and December 2020, all consecutive patients diagnosed with multiple myeloma (MM) and non-Hodgkin lymphoma (NHL) who underwent an ASCT in the Hospital Universitari Mutua Terrassa were retrospetively enrolled in our study. All the stem cell products collected were processed in the same cell therapy laboratory at Banc de Sang i Teixits. Median (range) follow-up for the entire cohort was 35 (0-81) months. The schema for stem cells mobilization was granulocyte-colony stimulating factor (G-CSF) alone for patients diagnosed with MM or G-CSF plus chemotherapy for patients diagnosed with NHL. Additionally, plerixafor was administered in poor mobilizers with the aim to collect a sufficient cell dose required for an ASCT.

We considered an ALC-15 as predict factor for OS and DFS as primary endpoint. We registered demographic, clinical and blood test data to perform the analysis.

Results: A total of 142 patients underwent an ASCT during the period of study. Median (range) age was 60 years (23-71) and 86 (61%) patients were male. Underlying diseases were MM (n = 81, 57%), diffuse-large B-cell lymphoma (n = 32, 23%), primary central nervous system lymphoma (n = 7, 5%), follicular lymphoma (n = 9, 6%) and mantle cell lymphoma (n = 13, 9%). A total of 75 patients (53%) achieved a complete response (CR) and 67 patients (43%) achieved a partial response (PR) at time of transplantation. Median (range) for neutrophil and platelet engraftment was 13 days (range 8-27) and 18 days (range 8-57), respectively. Median (range) cell count for ALC-15 recovery was .55/μL (range 0-2.7). Univariate analysis for survival at 80 months after ASCT demonstrated that disease status (CR vs. PR) at time of transplantation [(OS 72% vs. 60% ($P = .04$) and DFS 73% vs. 48% ($P = .05$)], infused CD34 + cell dose ($\geq$ 3 x 10^6/kg vs. < 3 x 10^6/kg) [OS 79% vs. 62%, ($P = .03$) and DFS 69% vs. 58%, ($P = .02$)], absolute neutrophil engraftment ($\geq$ 500 cells/μL vs. < 500 cells/μL), [OS 79% vs. 67%, ($P = .02$) and DFS 72% vs. 61%, ($P = .015$)] and ALC-15 ($\geq$ 500 cells/μL vs. < 500 cells/μL) [OS 73% vs. 56%, ($P = .001$) and DFS 65% vs. 36%, ($P = .001$), were predictors of higher OS and DFS (Figure 1).

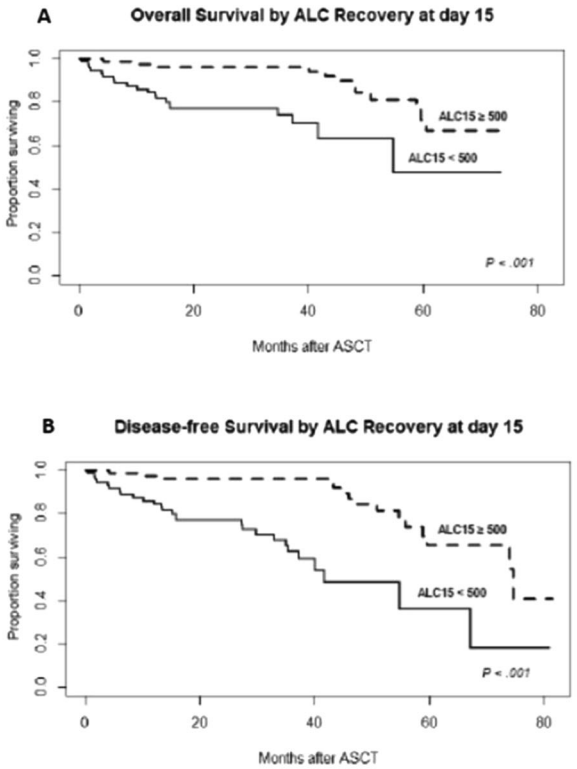


Figure 1. a) OS of patients with ALC-15 ≥ 500 cells/μL versus patients with an ALC-15 < 500 cells/μL. The median OS was 45 months in the group of patients with ALC-15 ≥ 500 cells/μL and 27 months in the group of patients with < 500 cells/μL ($P < .001$). **b)** DFS of patients with ALC-15 ≥ 500 cells/μL versus patients with an ALC-15 < 500 cells/μL. The median DFS was 42 months in the group of patients with ALC-15 ≥ 500 cells/μL and 25 months in the group of patients with < 500 cells/ μL ($P < 0.001$).

Conclusions: We concluded that patients who achieve an ALC-15 $\geq$ 500/μL after ASCT have a superior OS and DFS than patients who have < 500 lymphocyte/μL. ALC-15 is correlated with clinical outcomes and requires further study to demonstrate its impact as an independent prognostic factor in a multivariate analysis.

Disclosure: Nothing to declare

P243

Efficacy and safety of venetoclax in the treatment of recrudescence after allogeneic hematopoietic stem cell transplantation

X. Chen[1], Z. Liu[2], R. Zhang[1], W. Zhai[1], Q. Ma[1], A. Pang[1], D. Yang[1], Y. He[1], J. Wei[1], E. Jiang[1], S. Feng[1], M. Han[1]

[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China, [2]Binzhou Medical University Hospital, Shandong, China

Background: To investigate the efficacy and safety of preemptive/salvage therapy with venetoclax (Ven) in patients with recurrence after allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Methods: Retrospective analysis the clinical data of 25 patients with molecular biology or morphological recurrence after allo-HSCT treated with Ven in our center from 2021.2 to 2021.11, 15 patients were treated preemptive (P-group) and 10 patients were salvage (S-group). In the P-group, the median time from recurrence to the application of Ven was 2.5 (0-12.5) months. The median course of treatment was 2 (1-4). On the 7th day of the first course of treatment, the median concentration of Ven was 1945 (688-5383) ng/ml.

In the S-group,the median time from recurrence to the application of Ven was 0 (0-1) months. The median course of treatment was 1 (1-2). On the 7th day of the first course of treatment, the median concentration of Ven was 2419 (1200-6155) ng/ml.

Results: In the P-group, after one course of Ven treatment, 8 cases of minimal residual disease (MRD) turned negative, 4 cases of MRD decreased by 50% compared with that before treatment, 3 cases were ineffective, and the overall response rate (ORR) was 80%. The concentration of Ven < 1000 ng/ml or > 3000 ng/ml was 33.3%, and the concentration > 1000 ng/ml and < 3000 ng/ml was 83.3%. Two patients with TP53 mutation before transplantation turned negative after treatment. Grade 3/4 neutropenia occurred in 5 patients (33%) and grade 3/4 thrombocytopenia occurred in 5 patients (33%). No fatal cases of severe infection occurred.

In the S-group, after one course of Ven treatment, 1 case was in complete remission (CR) and MRD turned negative, 2 cases were CR but MRD was still positive, 3 cases were in partial remission (PR), 4 cases were ineffective, and the oRR was 60%. The concentration of Ven >3000 ng/ml was 25%, and the concentration > 1000 ng/ml and <3000 ng/ml was 33.3%. One patient with TP53 mutation before transplantation reached CR after ven salvage treatment. Grade 3/4 neutropenia and grade 3/4 thrombocytopenia occurred in 10 patients (100%). One patient died of severe pulmonary infection.

The median follow-up was 4.5 (1-8.5) months. No acute graft-versus-host disease (aGVHD) occurred after Ven treatment; There was no obvious abnormality in liver and kidney function. The overall survival rate (OS) of the P-group was (70.2 ± 12.7)%, and that of the S-group was (50.0 ± 15.8)%, P = 0.171.

Conclusions: The preemptive therapy with Ven after all-HSCT in patients with hematological malignancies is a promising treatment method. The early application and monitoring of drug concentration is expected to improve the curative effect, and the toxic and side effects can be tolerated.

Ven can achieve short-term curative effect in the salvage therapy of allo-HSCT. Monitoring the drug concentration is expected to improve the curative effect, but other treatments

still need to be bridged in the follow-up to maintain the curative effect.

Disclosure: Nothing to declare

P244

Efficacy of hematopoietic stem cell boost for patients presenting poor graft function (PGF) after hematopoietic stem cell transplantation (HSCT): A multicenter retrospective study

M. Gaffet[1], A. Wiedemann-Fode[1], B. Neven[2], J.H. Dalle[3], K. Bilger[4], C. Botella Garcia[5], M. Robin[6], J. Cornillon[7], H. Labussière-Wallet[8], P. Ceballos[9], C.E. Bulabois[10], M. Loschi[11], S. François[12], M.T. Rubio[1], C. Pochon[1]

[1]*CHRU Nancy, Vandoeuvre-lès-Nancy, France,* [2]*APHP Hopital Necker, Paris, France,* [3]*APHP Hopital Robert Debré, Paris, France,* [4]*CHU Strasbourg Hautepierre, Strasbourg, France,* [5]*CHU Bordeaux Hopital Haut l'Eveque, Pessac Cedex, France,* [6]*APHP Saint Louis, Paris, France,* [7]*CHU Saint Etienne, Saint-Priest-en-Jarez, France,* [8]*CHU Hopital Lyon Sud, Pierre Bénite, France,* [9]*CHU Montpellier, Montpellier, France,* [10]*CHU Grenoble, La Tronche, France,* [11]*CHU Nice, Nice, France,* [12]*CHU Angers, Angers, France*

Background: PGF is a severe complication of HSCT occurring in 5 to 27% of patients. We aimed to determine administration modalities of hematopoietic stem cell boost for patients with PGF, hematological response and tolerance.

Methods: We realized a retrospective, multicenter, observational study from 2013 to 2019. The data were collected from the registry of the French Society SFGM-TC to evaluate the outcome of patients with PGF who received a stem cell boost.

Results: Fifty-five patients were included, with a median follow-up of 346 days. Data from 12 HSCT centers in France were analyzed. Median age was 14 years (0 – 66), with 28 children, 5 adolescents and young adults and 22 adults. Thirty-three patients were transplanted for non-malignant diseases. Thirty-two patients had received a myeloablative conditioning. Grafts were from 16 matched related, 14 matched unrelated, 10 mismatched unrelated and 15 haploidentical donors. Eleven patients had a major ABO mismatch.

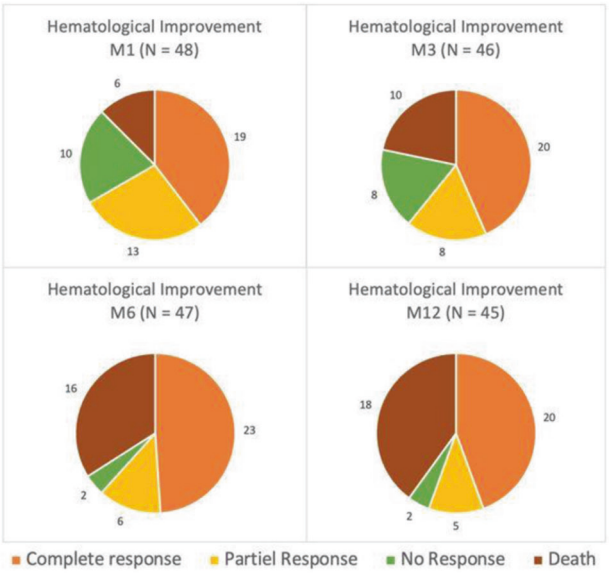
Twenty five patients experienced acute Graft Versus Host Disease (GvHD) and 15 experienced chronic GvHD after HSCT. Forty-eight patients had a complete donor chimerism post HSCT, and 7 patients a mixed chimerism.

There were 45 thrombocytopenia (<30G/L), 28 neutropenia (<0.5G/L) and 19 anemia (Hb < 8g/dl). Sixteen patients had a monocytopenia, 23 a bicytopenia and 10 a pancytopenia. The median delay between allo-HSCT and boost was 119 days (9-1949). Among 55 patients, 43 received a stem cell boost with CD34 positive selection.

For the CD34 positive selected boosts, median cell number reinjected was of $5.91.10^6$ CD34/kg (IQR 3.22 – 9.15) and of $3.14.10^3$ CD3/kg (IQR 0 - 62.5).

Complete response (CR) at 1 month, defined as platelets counts above 50 G/L, hemoglobin above 10 g/dL and neutrophils above 1.5 G/L, without death, was of 39.58%. Hematological response was stable during 12 months following boost, regardless of the hematopoietic lineage initially involved, as shown by Figure 1. Very few patients with no response or partial response at 1 month experienced a later response. A longer delay between HSCT and HSC boost was associated with a lower rate of complete response at 1 month ($p = 0.004$). Only 2 patients experimented GvHD *de novo* after CD34 + selected stem cells boosts.

Overall mortality was of 47.2%. Sixteen patients (29%) died from infections. All patients who died from infections were non responders at 1 month.



Conclusions: Hematopoietic stem cells boosts (mainly CD34 + selected) were effective for nearly 40% of patients with PGF after HSCT, and safe. However, mortality rate was very high in this cohort of patients and mostly caused by infections, occurring in patients with no CR at one month post boost. Therefore, another treatment should be considered for patients without CR at 1 month.

Disclosure: Nothing to declare

P245

Adverse reactions during infusion of allogeneic haematopoietic stem cells grafts

N. Friščić[1], I. Bojanić[1], S. Mazić[1], N. Duraković[1], R. Serventi Seiwerth[1], R. Vrhovac[1], B. Golubić Ćepulić[1]

[1]*University Hospital Centre Zagreb, Zagreb, Croatia*

Background: Incidence of adverse reactions (ARs) during the infusion of peripheral blood stem cells (PBSC) and bone marrow (BM) products depends, not only on patient's characteristics, but also on cellular and non-cellular elements of the product. Aim is to evaluate ARs reported in recipients of allogeneic haematopoietic stem cells (HPC) grafts.

Methods: A retrospective analysis of infusion-related toxicity of allogeneic PBSCs and BMs was conducted on paediatric and adult patients. The study included a data analysis of infusion reports for patients transplanted from July 2013 to July 2021. Allogeneic PBSC and BM grafts were usually infused fresh, but during COVID-19 pandemic due to logistic reasons PBSC were cryopreserved using dimethyl sulfoxide (DMSO) as a cryoprotective agent. According to institutional standard operating procedure, all patients received intravenous premedication before graft infusion consisting of chloropyramine-chloride, and in the case of ABO incompatible graft also methylprednisolone. Patients were monitored for vital signs and symptoms of the toxicity during and after infusion. ARs were classified according to *Common Terminology Criteria for Adverse Events* (CTCAE) version 5.0.

Results: Total number of patients included in the study was 507: 265 males (52,3%) and 242 females (47,7%), median of age 47 years (range 0-70). They were divided into three groups according to HPC source: 110 (21,7%) patients received BM, 298 (58,8%) fresh PBSCs and 99 (19,5%) cryopreserved PBSCs. The incidence of ARs was 14,5% in BM group, 13,5% in fresh PBSC group, and 23,2% in

the group that received cryopreserved PBSC. Patients' characteristics including gender, ABO incompatibility and diagnosis were not significant predictors for ARs occurrence in either group. However, younger age was significant predictor for occurrence of ARs during infusion in the patients that received cryopreserved PBSC (p = 0,03). According to CTCAE classification, grade 1 ARs were the most common in all three groups (59%). In BM group, febrile reactions (25%) and blood pressure rise (35,7%) were the most common. One case of Takotsubo cardiomyopathy after infusion of BM was reported and confirmed by echocardiography with asymmetry of regional function and positive enzymes. According to our knowledge it is the first case of Takotsubo cardiomyopathy reported after HSCT so far. Febrile reactions were the most common (59%) ARs reported in fresh PBSC group. Cytokine release syndrome was reported in two patients during infusion of fresh PBSC, and both patients required monitoring in the intensive care unit. One patient recovered successfully, but the other one deceased due to infectious complications. In cryopreserved PBSC group, ARs were mostly related to DMSO toxicity, such as nausea/vomiting (34,8%), rash (13%), hot flushes (13%), and cough (13%). Grade 5 ARs were not reported in any group of patients.

Conclusions: The highest incidence of ARs was observed in patients that received cryopreserved PBSCs. ARs were mostly mild, classified as grade 1, and they resolved spontaneously or after symptomatic treatment. However, considering that severe, life–threating ARs were reported, we strongly recommend careful patient monitoring during the graft infusion to recognise potential ARs and prevent possible further complications.

Disclosure: Nothing to declare.

P246

Total body irradiation based conditioning regimen improve the survival of patients with t-cell lymphoblastic lymphoma after allogeneic peripheral blood stem cell transplantation

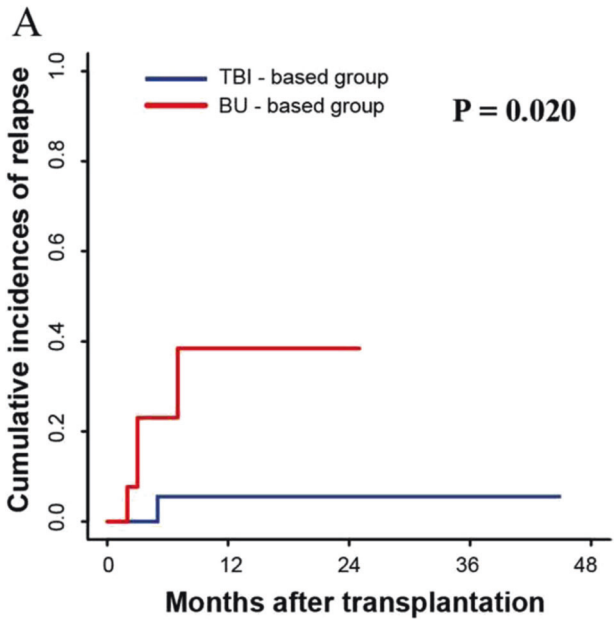
J. Niu[1], Z. Chen[1], H. Qiu[1], L. Wan[1], Y. Wang[1], W. Wang[1], Y. Tong[1], C. Huang[1], J. Gao[1], Y. Cai[1], X. Xu[1], K. Zhou[1], Y. Zhang[1], X. Xia[1], C. Shen[1], Y. Wei[1], T. Chen[1], X. Song[1], J. Yang[1]

[1]Shanghai General Hospital, Shanghai Jiao Tong University, Shanghai, China

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is one of the consolidation modalities for patients with T-cell lymphoblastic lymphoma (T-LBL), however, the best conditioning regimen needs to be explored to decrease the relapse risk and improve the survival of patients with T-LBL

Methods: 40 patients with T-LBL undergoing allo-HSCT in our center were retrospectively analyzed.

Results: 40 patients with T-LBL undergoing allo-HSCT in our center were retrospectively analyzed. 23/40(57.5%) received total body irradiation (TBI)-based conditioning regimen, while 17/40(42.5) received busulfan(BU)-based conditioning regimen. All patients achieved donor engraftment and neutrophil and platelet engraftment time were similar between TBI- and BU-based groups (P = 0.283andP = 0.368, respectively).TBI-based conditioning regimen significantly increased the cumulative incidence (CI) of grade II-IV aGvHD as compared with BU-based regimen (13.04%*vs* 0%, P = 0.000). TBI-based regimen significantly decreased the CI of relapse (CIR) after transplantation, the 1-year and 2-year CIRs were 9.11% and 9.11% in TBI-based group respectively, which were significantly lower than that of 41.18% and 49.58% in BU-based group (P = 0.006). The 2-year probabilities of over survival (OS) and relapse-free survival (RFS) were 83.0% (95%CI, 63.4-–100%) and 74% (95% CI, 54.4-93.6%) in TBI-based group respectively, which were both higher than that of 35.0%(95%CI,0.0%-72.2%) and 50.0% (95%CI,24.5-75.4%) (P = 0.020; P = 0.081, respectively) in BU-based group.In multivariate analysis, The presence of B symptoms at diagnosis and BU-based conditioning regimen significantly increased the risk of relapse (HR7.662, 95% CI, 1.056-55.593, P = 0.040; HR 33.32, 95% CI, 6.662-166.67, P = 0.000).



Conclusions: These results suggested that TBI-based regimen was an optimal conditioning regimen for patients with T-LBL receiving allo-HSCT with a decreased risk of relapse and an improved OS.

Disclosure: The authors declare no conflicts of interest

P247

Survival efficacy of MDS/AML patients with tp53 gene alteration received allo-geneic hematopoietic stem cell transplantation

D. Feng[1], E. Jiang[1]

[1]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China

Background: To investigate the survival efficacy of allo-geneic hematopoietic stem cells in patients with MDS/AML with TP53 state changes (deletion, mono-mutation, multi-hit). Analyzing the clinical characteristics in patients with different TP53 gene alterations, and further exploring the influencing factors of clinical prognosis of TP53-change MDS/AML after allo-HSCT.

Methods: A retrospective analysis was conducted on 42 patients with TP53-MDS/AML who underwent allo-HSCT from 2006.1 to 2021.7.These patients may have deletion of the TP53 gene and/or mutations in the TP53 gene.The 42 patients were divided into 3 groups,TP53 deletion MDS/AML group (group A), TP53 mono-mutation MDS/AML group (group B), and TP53 multiple-hit group (group C), and the differences in clinical features and the effect on the prognosis of inhibition were analyzed.The changes in the characteristics of second-generation sequencing of 137 genes in bone marrow specimens of 29 patients with mutations were also discussed.

Results: There were 42 MDS/AML patients, 30 males (71.4%), 12 females (28.6%), 21 MDS patients, 1 MDS-AML patient, and 20 AML patients. The average age of patients at the time of transplantation was 42 years, of which 11 patients with only TP53 deficiency (26.1%), 25 patients with TP53 single mutation (59.5%), and 6 patients with TP53 multiple hits (14.2%). Among the 42 patients, 14 (33.3%) died, 10 cases relapsed (23.8%), and the overall patients who received hematopoietic stem cell transplantation had 3 years OSå 40%, and there was no statistical difference in 3 years OS in group A, B and C. Univariate analysis shows,hemoglobin、age of HSCT、complex karyotype、pre-HSCT MRD were risk factors for survival ($p = 0.003$,$p = 0.042$,$p = 0.009$, $p = 0.004$), and TP53 stage、co-mutation、treatment before HSCT、type of Diseases not. Complex karyotype、hemoglobin、pre-HSCT MRD were also risk factors for relapse ($p = 0.038$, $p = 0.02$, $p = 0.023$),besides,pre-HSCT BM blast% also have an impact on relapse, $p = 0.027$.Among the 42 patients, 12 patients (28.5%) with complex karyotype, including 2 patients with TP53 deletion alone (16.6%), 5 patients with TP53 single mutation (41.6%), and 5 patients with TP53 multiple hit (41.6%). Of the 12 patients with complex karyotypes, 7 died, 5 relapsed, and 4 of the 7 deaths were patients with TP53 multi-hits. Survival and relapse of TP53 mutations may be associated with complex karyotype ($p = 0.009$,$p = 0.038$).

Conclusions: Allo-hematopoietic stem cell transplantation can overcome the poor changes of MDS/AML patients with TP53 mutation/deletion, but complex karyotype is still a poor prognostic factor for TP53-MDS/AML patients receiving allo-HSCT.

Disclosure: Nothing to declare

P248

Outcomes of reduced dose team (thiotepa, etoposide, cytarabine, melphalan) prior to autologous stem cell transplantation for hodgkin and non-hodgkin lymphoma: A monocentric experience

V. Marafioti[1], S. Barbato[1], S. Di Folca[1], S. Avilia[1], F. Grimaldi[1], A. Severino[1], M. Picardi[1], L. Luciano[1], G. Battipaglia[1], F. Pane[1]

[1]Federico II University of Naples, Naples, Italy

Background: Combination of carmustine, etoposide, cytarabine, melphalan (BEAM) is a commonly used regimen for autologous stem cell transplantation (auto-SCT) in patients with Hodgkin (HL) or non-Hodgkin lymphoma. Due to both a shortage of carmustine in the past decade and to reduce its pulmonary toxicity, this agent has been replaced in several centers by thiotepa (TEAM).

In our center, to further reduce gut toxicity, namely mucositis, since 2015 we use a reduced TEAM (dose reduction of etoposide and cytarabine).

Methods: We retrospectively analyzed transplant outcomes of adult patients undergoing auto-SCT conditioned with reduced TEAM (thiotepa 5mg/kg/12h on day −7; etoposide 100 mg/m^2/12h and cytarabine 100 mg/m^2/12h on days −6 to −3 (instead of the commonly used 200 mg/m^2/12h); melphalan 140 mg/m^2 on day -1).

Results: Included were thirty-nine patients (males, $n = 24$; females, $n = 15$) transplanted during the period 2015-2021. Median age was 43 (range 22-65) years. Most patients were transplanted for refractory ($n = 10$) or relapsed ($n = 15$) disease, while 12 patients were transplanted after first line treatment. The most frequent histology was diffuse large B-cell lymphoma ($n = 15$) followed by HL ($n = 10$), follicular lymphoma ($n = 5$), mantle cell lymphoma ($n = 5$) and primary mediastinal B-cell lymphoma ($n = 4$). The median number of chemotherapy lines prior to transplant was 2 (range 1-5), with a median interval from diagnosis to transplant of 16 months (range 5-218). Disease status at auto-SCT was complete response (CR) in 37 (CR1 = 22, CR2 = 14, >CR2 = 1) and partial response (PR) in 2 patients. Eight patients needed plerixafor for CD34 mobilization, with a median dose of CD34 + collected of 3.36 (range 0.70-17.00) x 10^6 /kg.

All but 1 patient engrafted, with a median time to neutrophil and platelet engraftment of 11 (range 8-16) and 19 (range 9-40) days, respectively. The median duration of hospitalization was 19 days (range 15-27). Regimen related toxicities included mucositis in 32 patients (82%) (grade 1-2, $n = 29$; grade 3, $n = 3$; no grade 4 mucositis) and febrile neutropenia in 26 patients (67%). Blood cultures were positive for Gram-positive or Gram-negative bacteria in 3 and 8 patients, respectively. One patient developed resolutive pneumonia.

Five patients (13%) underwent maintenance therapy after transplantation (brentuximab, $n = 3$; rituximab, $n = 1$; ibrutinib, $n = 1$) while twelve patients relapsed with a median time after auto-SCT of 5.5 (range 3-19) months, with a 1-year cumulative incidence of relapse of 38% [95% CI 20-56]. Two patients underwent allogeneic SCT with a median time after auto-SCT of 11 and 23 months, respectively. The 100-day and one-year non-relapse-mortality (NRM) was 2.5% [95% CI 0.2-11]. Eight patients died: one 5 days after auto-SCT due to septic shock; 5 due to disease progression and 2, after disease relapse, due to suicide and cerebral hemorrhage, respectively. At last follow-up, 29 patients (81%) were in CR. With a median follow-up of 18 (range 3-77) months, 2-year progression-free and overall survival were 59% [95% CI 38-75] and 81% [95% CI 74-88].

Conclusions: Reduced TEAM is a feasible and valid regimen prior to auto-SCT, with low toxicity and NRM and acceptable survival rates.

Disclosure: Nothing to declare

P250

DEGREE OF CELL PACKING OF CRYOPRESERVED AT -80ºC HEMATOPOIETIC STEM CELLS DOES NOT AFFECT THEIR VIABILITY AND HEMATOLOGIC RECOVERY OF TRANSPLANTED MYELOMA PATIENTS

I. Tonev[1], S. Simeonov[1], K. Milcheva[1], K. Venkov[1], P. Ganeva[1], G. Arnaudov[1], M. Mincheff[1]

[1]Specialized Hospital for Active Treatment of Hematological Diseases, Sofia, Bulgaria

Background: Dimethylsulfoxide (DMSO) is toxic to both cryopreserved cells and patients. We are using a method for freezing at -80ºC with 5% final DMSO concentration. In an attempt to further decrease the amount of infused DMSO we tested viability of cells and hematologic recovery of patients following cryopreservation with different degree of cell packing.

Methods: We compared two groups of myeloma patients with low and high cryopreserved cells concentration. Cell suspension in the first group of 88 patients contained average 175 x 10^6 cells/ml (maximum 250 x 10^6 cells/ml) and in the second group of 175 patients the cells were completely packed by total plasma removal (average 391 x 10^6 cells/ml and maximum 597 x 10^6 cells/ml) before adding the cryoprotectants resulting in a 60% decrease of the volume to be frozen. Cells were non-programmed frozen and stored at −80 °C in a solution with final concentrations of 5% DMSO, 3.6% hydroxyethyl starch (HES 450 000 mw) and 3% of human serum albumin.

Stem cell viability was evaluated by trypan blue exclusion test. Cell dose in the first patient group was 2,62 x 10^6/kg (0,8–6,6), while in the second group it was 2,67 x 10^6/kg (1,5-6,8).

Results: There was no statistically significant difference between the two myeloma patient groups. Viability was 97,0% (85-99) and 96,5 % (70-99) respectively. The neutrophil recovery was on day 11 (9-19) for the first and on day 11 (9-18) for the second group. Platelets recovered after 12 days for the first and the second group.

Conclusions: Dimethylsulfoxide is toxic and induces many side effects following transplant (cardiac, neurologic, respiratory, etc.), which are dose dependent. Reducing them could be achieved by lowering the final DMSO concentration (5%) and by decreasing the volume of the frozen suspension. Our approach does not affect the cellular viability or the hematologic recovery of the patients following transplantation.

Disclosure: Nothing to declare

P251

Lymphocyte dose in graft, clonogenic efficiency and male sex as predictive factors of early lymphocyte recovery following autologous stem cell transplantation

J. Fernandez-Sojo[1], J. Cid[2], C. Azqueta[1], E. Valdivia[1], L. Martorell[1], M. Codinach[1], J. Marsal[3], A. Mussetti[4], A. Esquirol[5], M. Trabazo[3], I. Benitez[6], C. Ferra[7], L. Fox[6], M. Linares[1], E. Alonso[1], E. Garcia-Rey[1], N. Garcia-Munoz[1], L. Medina-Marrero[1], N. Castillo-Flores[1], F. Vall-Llovera[8], A. Garcia[9], A. Pinacho[1], C. Talarn[10], J. Garcia-Arroba[1], R. Coll[11], M. Santos[1], O. Valero[12], E. Carreras[13], M. Lozano[2], S. Querol[1]

[1]Banc de Sang i Teixits, Barcelona, Spain, [2]Hospital Clinic de Barcelona, Barcelona, Spain, [3]Hospital Sant Joan de Déu, Barcelona, Spain, [4]Institut Catala d'Oncologia-Hospitalet, Hospitalet de Llobregat, Spain, [5]Hospital de Sant Pau i de la Santa Creu, Barcelona, Spain, [6]Hospital Universitari Vall d'Hebron, Barcelona, Spain, [7]Institut Català d'Oncologia-Badalona, Badalona, Spain, [8]Hospital Mutua de Terrassa, Terrassa, Spain, [9]Hospital Universitari Arnau de Vilanova, Lleida, Spain, [10]Institut Català d'Oncologia-Tarragona, Tarragona, Spain, [11]Institut Catala d'Oncologia-Girona, Girona, Spain, [12]Universitat Autonoma de Barcelona, Barcelona, Spain, [13]Spanish Bone Marrow Donor Registry, Barcelona, Spain

Background: Early lymphocyte recovery (ELR), defined as an absolute lymphocyte count (ALC) ≥ 500 cells/μL at day 15 after autologous stem cell transplantation (ASCT), impacts on overall survival and progression-free survival in patients with hematological and non-hematological diseases. However, limited data are available to predict immune recovery after ASCT.

Methods: To investigate which factors determine ELR following ASCT, we conducted a multicenter retrospective study in adult and pediatric patients who underwent ASCT with grafts provided by a single-cell processing laboratory during the period 2014 to 2016. Patients were divided in two groups according to whether ELR was achieved (ELR +) or not (ELR-). Patient demographic and transplant characteristics, and cell collection and quality control parameters of the stored cell product (purity, viability and potency tests) were compared between the two groups. A receiver operating characteristic (ROC) curve was constructed to predict ELR with statistical variables.

Results: We included 379 patients, of whom 278 (73%) achieved ELR + . Male sex (63% in the ELR + group versus 48% in the ELR- group) showed a statistical difference in the bivariate analysis that remained in the multivariate analysis (odds ratio [OR], 1.92; 95% confidence interval [95% CI], 1.19-3.10; $P = .008$). Regarding the cell graft, the median total lymphocyte dose (2.7 versus 1.6 × 10^8/kg in the ELR + and ELR- groups, respectively) was associated with ELR + in both the bivariate and multivariate analyses (OR, 1.34; 95% CI, 1.15-1.57; $P < .001$). Higher median clonogenic efficiency (CLONE), measured as the number of colony-forming units (CFU) scored per CD34 seeded, was also associated with a higher likelihood of ELR + in the bivariate and multivariate analyses (42% versus 38%) (OR, 1.02; 95% CI, 1.00-1.03; $P = .040$). ROC curves showed that infusion of more than 2.2 total lymphocytes × 10^8/kg (OR, 2.77; 95% CI, 1.72-4.48; $P < .001$) and CLONE values higher than 42% (OR, 1.75; 95% CI, 1.07-2.87; $P = .026$) were the best cut-off values for predicting patients who will achieve ELR + (area under the curve [AUC], 0.68; 95% CI, 0.63-0.74). No statistically significant differences in ELR were found for the transplant conditioning regimen, number of chemotherapy treatments prior to ASCT, medical device used during collection, or $CD34^+$ cells/kg in graft.

Conclusions: In summary, our study shows that the total lymphocyte content of the graft, CLONE and male sex may be used as predictors for ELR after ASCT. These data suggest that not only the $CD34^+$ cell dose per kg should be considered the target of peripheral blood cell collection, but the lymphocyte dose should be taken into account as well. Routine potency tests might help to predict not only myeloid engraftment, but also lymphocyte reconstitution. Further studies are needed to corroborate these findings not only in the autologous, but also in the allogeneic setting.

Disclosure: The authors state that they have no conflict of interest.

P252

Improvement in acute neurological complications related to stem cell transplant in sickle cell disease: Lessons from our experience

J.M. Marco Sánchez[1], M. García Morín[2], C. Beléndez Bieler[2], S. Otero[2], E. Bardón Cancho[2], J. Huerta Aragonés[2], C. Garrido Colino[2], O. Alvarez[2], A. Martinez[2], A. Perez[2], C. Muñoz[2], A. Aguado[2], E. Cela de Julián[2]

[1]Universidad CEU Cardenal Herrera, Castellón, Spain, [2]Universidad Complutense de Madrid, Madrid, Spain

Background: Central nervous system (CNS) complications during hematopoietic stem cell transplantation (HSCT) in sickle cell disease (SCD) patients are a major cause of morbidity, as: posterior reversible encephalopathy syndrome (PRES), seizures, strokes or subarachnoid haemorrhage (HSA). These complications can appear for several causes, but mostly due to variations on hemodynamic status of the patient. Conditioning regimen-related toxicity, graft-versus-host disease (GvHD) and the use of calcineurin inhibitors also play an important role.

Methods: A retrospective single center study was conducted in children with SCD, who underwent allogeneic HSCT from an HLA-identical sibling donor since January 2010 to December 2021. Implementation of arterial blood pressure (ABP) Holter, few weeks prior to HSCT, was established in December 2017 providing a better understanding of patient's hemodynamic status and easing early treatment of arterial hypertension prior to HSCT. We analyze CNS transplant complications between two different periods: May 2010 to November 2017, and December 2017 to June 2021.

Besides that, a change on conditioning regimen was established. Until June 2015 we used busulfan, cyclophosphamide and alemtuzumab. Afterwards, we changed to myeloablative but reduced toxicity conditioning: thiotepa, treosulfan, fludarabine, antithymocyte globulin. Also, GvHD prophylaxis used until 2019 was CsA and MTX, changing later to tacrolimus and mycophenolate mofetile (MMF).

Seizure prophylaxis was provided during calcineurin inhibitors treatment, as well as maintenance of platelet threshold above 50.000/mcL, hemoglobin 11 g/dL and avoid hypomagnesemia.

Epidemiological and clinical parameters were collected. Data are presented as percentages and quartiles. For the comparison of the variables under study, a bivariate analysis with non-parametric Fisher test was used. R Statistical Software was used for the numerical analysis and Survminer to represent Kaplan-Meier curves.

Results: 48 allo-HCST were performed in 47 patients, median age 6.0 years (p25 2;p75 9). 22 patients in first period, 10 males (55%); and 26 patients in second, 13 males (50%).

Prior to HSCT, 14/48 of HSCT had cerebrovascular disease (Moya-moya vasculopathy, silenct infarction, stroke or leukoencephalopathy); 64% (9/14) on first period and 36% (5/14) on second.

During transplant, 11/48 had acute CNS complications: 91% (10/11) on first period (9/10 seizures, 5/10 HSA, 5/10 PRES and 1/10 other complications), and 9% (1/11) on second (mild toxicity to tacrolimus). HTA is present in 89% of total HSCT and in 100% with post-HSCT neurological complications, suggesting his major role in these type of situations.

Global event-free survival of post-HSCT CNS complications at the end of follow-up period (10.69 years) was 77% (0.65-0.89). Statistically significant decrease on post-HSCT neurological complications on second period was observed compared to the first (seizures $p < 0.001$; HSA p0.02; PRES p0.049), after the implementation of ABP Holter. Also, we couldn't observe a statistically significant predisposition to have post-HSCT CNS complications according to their pre-neurological history.

Conclusions: Even with reduced-toxicity conditioning and the switch to tacrolimus, neurological events still happen. Recent modifications in our center, mainly since the implementation of ABPH, have decreased acute CSN complications and improved SCD event-free survival rates during transplant, with less toxicity, morbidity and mortality.

Disclosure: Nothing to declare.

P253

Thiotepa-treosulfan-fludarabine (ttf) as conditioning regimen in patients undergoing allogeneic hematopoietic stem cell transplantation (allohsct) for myelofibrosis or myelodysplastic syndrome: A single center experience

F.A. Canale[1], G. Porto[1], P.F. Provenzano[1], V. Naso[1], T. Moscato[1], M. Pugliese[1], B. Loteta[1], G. Irrera[1], G. Console[1], A. Ferreri[1], M. Martino[1]

[1]Stem Cell Transplantation and Cellular Therapies Unit (CTMO), Reggio Calabria, Italy

Background: AlloHSCT remains the only potentially curative treatment for myelofibrosis (MF) and myelodysplastic syndromes (MDS), but there is no consensus on the best conditioning treatment. The use of treosulfan as alkylating agent in a RIC (fludarabine-treosulfan) regimen demonstrated low toxic profile associated with excellent disease eradication in patients with acute myeloid leukaemia (AML) and MDS. On the other hand, the combination of two alkylating agents with the addiction of thiotepa seems to increase the chance of achieving engraftment with full donor chimerism in MF patients. Therefore, the replacement of busulfan by treosulfan in a dual alkylator regimen with thiotepa and fludarabine (TTF) could be a promising toxicity-reduced but myeloablative conditioning regimen for a setting of patients characterized by an advanced median age and usually with high comorbidity index (HCTI), therefore at high risk for relapse and transplant-related mortality.To date no data about the use of a dual-alkylator treosulfan-based regimen are reported in this setting.

Methods: We analyzed retrospectively 10 patients (median age: 61, range 44-69, 60% male) affected by MF (50%) or MDS (50%) who underwent alloHSCT (between December 2020 and November 2021) with TTF (9 pts) or TF (1 pts) as conditioning regimen. Seven patients had primary disease, 2 patients had MF secondary to essential trombocythemia (ET) and one patient had a MDS after autologous HSCT for mantle-cell lymphoma. Patients median EBMT-risk-score (for MDS) and MTSS (for MF) were 4 and 6, respectively.

Results: The median time from diagnosis to alloHSCT was 11.5 months (range, 6-158). Graft source was peripheral blood stem cells in all patients. Donor type was HLA-matched related ($n = 3$), matched unrelated ($n = 5$) and mismatched unrelated ($n = 2$). Treosulfan cumulative dose was 30g/m^2 in 60% and 36g/m^2 in 40% of patients. Graft-versus-host disease (GVHD) prophylaxis consisted of a calcineurin inhibitor (8 pts cyclosporine, 1 pt tacrolimus) plus methotrexate and ATG for 9 patients, while combination of cyclosporine with micophenolate mofetil and post-transplant cyclophosphamide was used in a patient who underwent HSCT from a mismatched unrelated donor. Full donor early engraftment was achieved in all patients except 2, who died during aplasia. The median time to neutrophil recovery was 16 days (range, 16-21). The median time to achieve platelet engraftment >20 G/L was 22 (range, 15-40) days. The median follow-up was 5.6 (range, 1-12) months. Complications after HSCT included mucositis grade 3-4 in 3 patients, one diarrhea grade 3, one grade 3 systolic disfunction, neutropenic fever. Two patients died: 1 for cerebral hemorrhage (at day 12) and 1 due to acute kidney disease and subsequent multi-organ failure (at day 32). One patient experienced grade II acute GVHD at day 35 while mild chronic GVHD occurred in another patient. No relapse was seen. A trend towards better survival was observed for patients who underwent alloHSCT before the median time period of 24 months (OS 100% versus 33.3%, $p = 0.06$).

Conclusions: These data suggest feasibility, safeness and efficacy of TTF myeloablative regimen for MF/MDS patients, with excellent early full donor engraftment and manageable transplant related toxicity. Larger cohort and longer FU are needed for survival analysis.

Disclosure: Nothing to declare

P254

Non-cryopreserved peripheral blood stem cell graft for autologous hematopoietic stem cell transplantation in multiple myeloma and lymphoma

P. Noiperm[1], J. Julamanee[1], P. Viboonjuntra[1], A. Lekhakula[1]

[1]Prince of Songkla University, Hatyai, Thailand

Background: Hematopoietic stem cell transplantation is a curative treatment option for various hematologic malignancies. The conventional cryopreserved stem cell grafts are time-consuming, expensive, and may be associated with dimethyl sulfoxide toxicity. Several studies demonstrated the successfulness of non-cryopreserved hematopoietic stem cell transplantation in the resource limited centers. The objective of this study is to evaluate the feasibility, efficacy, and safety of non-cryopreserved autologous stem cell transplantation (ASCT) in patients with multiple myeloma and lymphoma.

Methods: A retrospective study conducted in Songklanagarind Hospital, a tertiary university hospital in southern Thailand. The medical data of consecutive patients aged 18 years old or older diagnosed as multiple myeloma or lymphoma who underwent

ASCT using non-cryopreserved stem cell graft during January 1996 to March 2021 were enrolled. Mobilization was performed mainly with cyclophosphamide and granulocyte colony stimulating factor (G-CSF) and the collected stem cells were stored for 1–7 days in a blood bank refrigerator at a temperature 4°C. Stem cells were reinfused into patients after complete conditioning regimen infusion for 24 hours. All aphesis products were assessed for stem cell viability at the time of infusion.

Results: A total of 62 non-cryopreserved ASCT was performed (40 myeloma and 18 lymphoma cases). The median total $CD34^+$ cell count was 7.59 million/kg in myeloma and 6.9 million/kg in lymphoma with the stem cell viability before infusion was greater than 99% and 97% in myeloma and lymphoma, respectively. All myeloma patients were engrafted, whereas, 2 cases of lymphoma were failure to engraft. The median time of neutrophil engraftment was 9 (range; 7–19) and 13 (range; 8–53) days and platelet engraftment was 11 (range; 7–18) and 14 (range; 8–61) days in myeloma and lymphoma, sequentially. Regarding extra-hematopoietic toxicities, 65% of myeloma and 83% of lymphoma patients had mucositis. All patients experienced any grade of nausea or vomiting, while the diarrhea occurred in two-third of myeloma and half of lymphoma patients. More than 95% of patients developed febrile neutropenia, mostly were grade 1–2. Severe complication such as septic shock and respiratory failure was observed in only one myeloma and four lymphoma patients. With the median follow up time of 60 months, the median progression free survival (PFS) was not reached and overall survival (OS) was 130 months in lymphoma patients. For myeloma, the median PFS was 99.5 months and OS was 157 months, with the median follow up time of 38.6 months. The 100-day transplant-related mortality was 2.5% and 11.1% in myeloma and lymphoma, consequently. Cancer-related was the cause of death in half of myeloma and 14% of lymphoma patients, whereas, 28% of lymphoma patients were died from therapy-related complication. None of any factors were significant predicted PFS and OS in this study.

Conclusions: Non-cryopreserved ASCT was effectively and safely performed in multiple myeloma and lymphoma patients which resulted in a short duration of neutrophil and platelet engraftments, acceptable complications, and long-term survival outcomes.

Disclosure: Nothing to declare.

P255

Feasibility of daratumumab for adult patients with cd38 positive acute myeloid leukemia relapsed after allogenic stem cell transplantation

R. Zhang[1], E. Jiang[1], X. Chen[1], Q. Liu[1], J. Yao[1], Y. Cao[1], Y. Shi[1]

[1]Chinese Academy of Medical Sciences & Peking Union Medical College,Institute of Hematology & Blood Diseases Hospital, Tianjin, China

Background: Patients with acute myeloid leukemia (AML) relapsed after allogenic hematopoietic stem cell transplantation(allo-HSCT) have poor prognosis although some therapeutic options including hypomethylating agents, chemotherapy, donor lymphocyte infusion (DLI), or a second allo-HSCT could be adopted. Daratumumab, which is a therapeutic targeted drug to CD38 antigen for multiple myeloma, might be a new way for relapsed AML with CD38-positive after allo-HSCT.

Methods: Between January 2021 and October 2021, 4 adult patients (2 patients were hematologic relapsed, 2 patients were bone marrow minimal residual disease(MRD)-positive) with CD38 + AML relapsed after allo-HSCT were enrolled, including 2 sibling-matched stem cell transplantation and 2 haploidentical transplantation. Two out of the patients had received chemotherapy followed by DLI before the treatment of Daratumumab (Table). The dosage of Daratumumab was 8mg/kg/d, on day1, day2, day15 and day16; 4-weeks was one cycle. Clinical manifest, routine blood tests, Liver and kidney functions were recorded and evaluated. The bone marrow examinations were performed to assess the response 2 or 4 weeks after the Daratumumab treatment including bone marrow smear, MRD detection by flow cytometry, donor chimera rate by short tandem repeat (STR).

Results: The 4 patients did not show serious adverse reactions such as shiver or dyspnea during Daratumumab infusion. After Daratumumab infusion, Patient 2 occurred fever due to agranulocytosis which was cured by antibiotics and the number of neutrophils recovered 2 weeks later. No serious abnormal liver and kidney function were recorded for the 4 patients. Patient 1, who was hematological relapse before Daratumumab treatment, achieved complete remission and complete donor chimerism, but MRD was positive with CD38 negative after one cycle of Daratumumab. Then she received Desitabine maintenance treatment. Patient 2 and Patient 3 achieved MRD negative remission and complete donor chimerism after one cycle. Subsequently, Patient 2 received two cycles of venetoclax maintenance treatment and MRD was persistent negative. Patient 3 did not achieved maintenance treatment after Daratumumab due to cytomegaloviremia and acute graft versus host disease. Patient 4 showed no response to Daratumumab and refused further treatment because of economic reasons. She passed away at the 12th-month after relapsed.

Conclusions: Daratumumab treatment seems to be an effective and safe treatment for AML with CD38-positive relapsed after allo-HSCT, especially for the MRD(+)-relapse, which may be confirmed with more clinical studies.

Disclosure: Nothing to declare.

P256

The effect of delayed cord clamping on the quality of collected cord blood units for banking

M.R. Bassiouny[1], A. Zaghloul[2], K. Samir[3], A. Darwish[4,5]

[1]Mansoura University, Mansoura, Egypt, [2]Mansoura University, Mansoura, Egypt, [3]Faculty of Medicine, Mansoura University, Mansoura, Egypt, [4]Mansoura University, Mansoura, Egypt, [5]Mansoura University Research Center for Cord Stem Cells (MARC-CSC), Faculty of Medicine, Mansoura University, Mansoura, Egypt

Background: Umbilical cord blood (UCB) has been used as an alternative to bone marrow for transplantation of hematopoietic stem cell purposes. Cord blood transplantation (CBT) can be used successfully in patients with marrow failure, immunologic deficiencies, malignancies, inborn errors of metabolism, and other genetic diseases. Cord blood transplantation in children show similar outcome data compared to transplantation of stem cells from other sources. The primary confinement factor for the wide utilization of UCB for hematopoietic progenitors for transplantation is cell dose. Though it is assumed that delayed cord clamping would reduce the volume of placental blood that could be gathered for banking, the extent to which delayed cord clamping decreases total nucleated cells (TNCs) counts and as such impacts cord banking activities remains unknown. The current study aimed to investigate the duration of delayed umbilical cord clamping that impacts cord blood units (CBUs) volume, TNCs and CD34 + cells counts that can affect the quality of CBUs and banking efficiency.

Methods: Cord blood units collected at Mansoura University Hospitals from January 2020 to May 2021 were analyzed. The delay in cord clamping after birth was timed and classified as group 1 (30 to 60 seconds), and group 2 (61 to 90 seconds). The collected CBUs were evaluated as regard volume, TNCs and CD34 + cells count.

Results: Out of 252 attended deliveries, only 98 cord blood units were collected excluding 61% of donors that didn't achieve requirements of inclusion in the study. Group 1 was conducted on 52 donors and group 2 was 46 donors. The mean volume, TNCs and CD34 + cells counts in units among group1 were significantly greater than these among group 2 ($p < 0.05$).

Conclusions: Delayed cord clamping greatly diminishes the volume and TNCs and CD34 + cells counts of CBUs collected for a public cord blood bank. Aiming for good quality of collected cord blood units, our results suggest that better stem cell yield is obtained with a practice of delay in cord clamping after 30-60 seconds.

Disclosure: Nothing to declare

P257

Covid-19 risk perception in allogeneic hematopoietic cell transplant receptors following mrna-1273 sars-cov-2 vaccination

N. Albiol[1,2], A. Barata[3], O. Aso[1], L. Gómez-Pérez[1], M. Triquell[1], N. Roch[1], E. Lázaro[1], A. Esquirol[1,2,4,5], I. González[1], J. Sierra[1,2,4,5], R. Martino[1,2,4,5], I. García-Cadenas[1,2,4,5]

[1]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [2]Institut d'Investigació Biomèdica, Barcelona, Spain, [3]Moffitt Cancer Center, Tampa, United States, [4]Autonomous University of Barcelona, Barcelona, Spain, [5]Josep Carreras Leukaemia Research Institute, Barcelona, Spain

Background: Anxiety and depression represent a relevant problem for allogeneic hematopoietic stem cell recipients (HCT). Recent studies found that the COVID-19 risk perception is associated with emotional distress. Identification of predictors associated with higher COVID-19 risk perception among HCT recipients would enable provision of tailored psychological support following HCT.

Methods: The main aim of the study was to assess changes in COVID19's risk perception after vaccination in recent HCT recipients. We measured risk perception using the shortened Brief Illness Perception Questionnaire (BIP-Q5) in 54 HCT recipients after dose 1 and 2 of the mRNA-1273 SARS-CoV-2 vaccine through phone calls. This test consists of five items (consequences, timeline, identity, concern and emotional response; see Table 1) with a score from 0 (none) to 10 (a lot).

Results: Participants' median age was 53.5 (25-73) and 48.1% were females. Five out of 54 (9.3%) had suffered from COVID-19 prior to vaccination. Median time from infusion date at first vaccine dose was 13 months (range 3-26).

COVID-19 risk perception tended to decrease over time ($p = 0.077$) to an extent that it was clinically meaningful ($p < 0.05$), see Table 1.

Questionnaire item	Mean (SD) after D1	Mean (SD) after D2	*p*-value (Wilcoxon)
Total score	29.43 (9.35)	28.09 (10.07)	0.077
1. How much does COVID-19 affect your life?	6.61 (2.92)	6.57 (2.67)	0.706
2. How long do you think COVID-19 will last?	7.07 (2.06)	6.11 (2.67)	0.000*
3. How much do you experience symptoms from COVID-19?	1.74 (2.94)	2.17 (3.23)	0.13
4. How concerned are you about COVID-19?	7.91 (2.16)	7.11 (2.69)	0.012*
5. How much does COVID-19 affect you emotionally?	6.09 (3.10)	6.13 (3.23)	0.89

*Statistically significant ($p < 0.05$)

A *post hoc* exploratory analysis of the BIP-Q5 items (consequences, timeline, identity, concern and emotional response) revealed that, at time of the second dose, participants expected COVID-19 would last less over time and reported being less concerned about COVID-19 relative to prior to vaccination, with these differences being both statistically and clinically significant ($p < 0.05$). Females ($r = 0.42$, $p < .001$), patients receiving myeloablative conditioning -MAC- ($r = -0.300$, $p = 0.027$), post-transplant cyclophosphamide-based GVHD prophylaxis -PTCy- ($r = -0.371$, $p = 0.006$), having lower absolute neutrophil count ($r = -0.288$, $p = 0.034$), development of acute GVHD ($r = -0.355$, $p = 0.008$) and having a relative who suffered from COVID-19 ($r = 0.285$, $p = 0.036$) were significantly associated with greater disease risk perception in the univariable analysis.

Conclusions: Vaccination led to decreased COVID19-risk perception over time in HSCT recipients. Despite several characteristics seem associated with increased risk perception (i.e., females, myeloablative conditioning, PTCy, lower absolute neutrophil count, aGVHD, knowing a relative diagnosed with COVID-19), additional factors, such as patients' psychological symptoms, should be considered to further understand COVID-19 long-term effects on HCT recipients' mental health.

Disclosure: Nothing to declare.

P258

Acute graft versus host disease is common in patients who develop engraftment syndrome after allogeneic hematopoietic stem cell transplantation in children

M. Wright[1], V. Pai[1], R. Abu-Arja[1], H.G Rangarajan[1], J. Stanek[1], R.P. Bajwa[1]

[1]Nationwide Children's Hospital, Columbus, United States

Background: Engraftment syndrome (ES) is an inflammatory response that occurs during neutrophil recovery after hematopoietic stem cell transplantation (HSCT). The reported incidence of ES has been variable due to the lack of universal diagnostic criteria and its similar presentation to acute graft versus host disease (aGvHD). Several studies have shown an increased risk of aGvHD in patients who were treated for ES. Our primary objective is to determine the incidence of ES in pediatric patients who underwent allogeneic HSCT at a large pediatric institution. Secondary outcomes include determining the characteristics of ES, duration and dose of steroid treatment, and relationship between ES and aGvHD.

Methods: This is a retrospective chart review of pediatric patients who underwent allogeneic HSCT at Nationwide Children's

Hospital from 01/2009-09/2020 and were diagnosed and treated for ES. Patients who received HSCT or post-transplantation care at other institutions were excluded. Data collection included patient demographics, details of HSCT, symptoms of ES, staging of GvHD, and treatment characteristics. Univariate analyses were performed using nonparametric methods.

Results: There were a total of 261 allogeneic transplants from 01/2009-09/2020; 29/261 (11.1%) developed ES, aGvHD observed in 105 (40.2%), and 17/261 (6.5%) had both ES and aGvHD. Among the 29 patients with ES, 17 (58.6%) developed aGvHD, whereas 88 (37.9%) patients without ES developed aGvHD ($p = 0.052$). The median (interquartile range; IQR) time to development of ES was 15 days (IQR: 12-19), median duration of treatment with steroids for ES was 3 days (IQR: 3-5), and median steroid dose was 2 mg/kg/day of methylprednisolone or equivalent (IQR: 1-2). Patients presented with a median number of 3 clinical features at time of diagnosis (IQR: 2-3); rash: 75.9%, fever: 62.1%, respiratory symptoms: 62.1%, gastrointestinal symptoms: 37.9%, capillary leak: 41.4%, and liver dysfunction: 10.3%. Patients presenting with rash more often developed aGvHD compared to those who did not present with a rash (82.4% vs 33.3%; $p = 0.018$). A steroid wean was done in 9/29 (31%) of the patients with ES and did not differ among those who did and did not develop aGvHD (35.3% vs 25%; $p = 0.7$). Systemic steroids were required in 15/17 (88.2%) of the patients who developed aGvHD after ES. Of the 17 patients with ES and aGvHD, 6 (35.3%) developed steroid refractory (SR) aGvHD and 8 (28.6%) developed chronic GvHD.

Conclusions: In conclusion, 11.1% of patients who underwent allogeneic HSCT at our institution developed ES. Most patients with ES developed aGvHD and required systemic steroids. Approximately one third of patients with ES, developed steroid refractory or chronic GvHD. A steroid wean for ES treatment was not found to be associated with the development of aGvHD. Fever, rash and respiratory dysfunction were the most common presenting symptoms of ES. Future studies should examine the associations between ES and other endotheliopathies after HSCT in pediatric patients and further characterize the relationship between steroid duration and dosage used in treatment of ES and aGvHD.

Disclosure: Nothing to declare.

P259

Review of occurrences at a haematopoetic stem cell transplant collection and processing facility in South Africa

L. Anderson[1], T.N. Glatt[1]

[1]South African National Blood Service, Johannesburg, South Africa

Background: The South African National Blood Service (SANBS) provides haematopoietic stem cell transplant (HSCT) collection and processing facilities to 18 public and private clinical institutions across South Africa. The SANBS JACIE Quality Department (JQD) is responsible for overall quality of these two facilities and has implemented a quality management system in line with JACIE standards. In addition to annual mandatory audits, additional scheduled audits and staff competency audits, the JQD reviews and reports on occurrences on a 6 monthly basis. The findings of this report allow for continuous quality improvement.

Methods: During the period of 1st March 2021 to the 30th September 2021 all occurrences that were logged by the collections and processing facilities onto a Systems Applications and Products (SAP) platform, an enterprise resource planning (ERP) centralised software system, were reviewed. The number, type, risk rating, problem description and cause of each occurrence per facility were documented. The number of occurrences in this reporting period were compared to the previous 6 month reporting period.

Results: Collections facility: During this 6 month period 97 occurrences were logged: the top 3 occurrences were as follows: 63.94% ($n = 62$) due to delay in starting the procedure (documentation incomplete, access flow problems, blood results not available), 15.5% ($n = 15$) due to incorrect or incomplete records and 15.5% ($n = 15$) due to an adverse event. There were no serious adverse events, 66.7% ($n = 60$) were due to citrate reactions and 25.6% ($n = 23$) due to hypotension.

Processing facility: During the 6 month period 63 HSCT reinfusions were performed with no reinfusion related adverse events. A total of 28 occurrences were logged. Significant occurrences included: bacterial contamination due to patient source ($n = 2$), not following procedure ($n = 7$) and incomplete/unavailable/inadequate records ($n = 7$). 42.9% ($n = 12$) of the notifications were risk rated as major, followed by 21.4% ($n = 6$) that were risk rated as moderate. In comparison to the previous 6 months, bacterial contamination occurrences increased due to the patients' medical condition and recording keeping occurrences decreased.

Conclusions: Evaluation of all occurrences on a six monthly basis is a critical part of assessing the implementation and effectiveness of a quality management system and a useful tool to identify trends in a HSCT collections and processing facility.

Clinical Trial Registry: N/A

Disclosure: Nothing to declare

P260

Allogeneic transplantation (allohct) in acute myeloid leukemia (AML) with flt3 mutations: Study of outcome at the era of targeted therapy

N.-E. Loutsidi[1], E.-K. Dimitraki[1], I. Tsonis[1], F. Karaolidou[1], A. Roumelioti[1], A. Apsemidou[1], D. Gardeli[1], M. Dellatola[1], V. Babali[1], K. Kaouranis[1], L. Ligdi[1], P. Christoforou[1], M. Garofalaki[1], I. Tziotziou[1], Z. Mellios[1], C. Giatra[1], T. Tzenou[1], I. Tzannou[1], M. Bouzani[1], S. Delimbasi[1], M. Pagoni[1], I. Baltadakis[1], S. Gigantes[1], D. Karakasis[1]

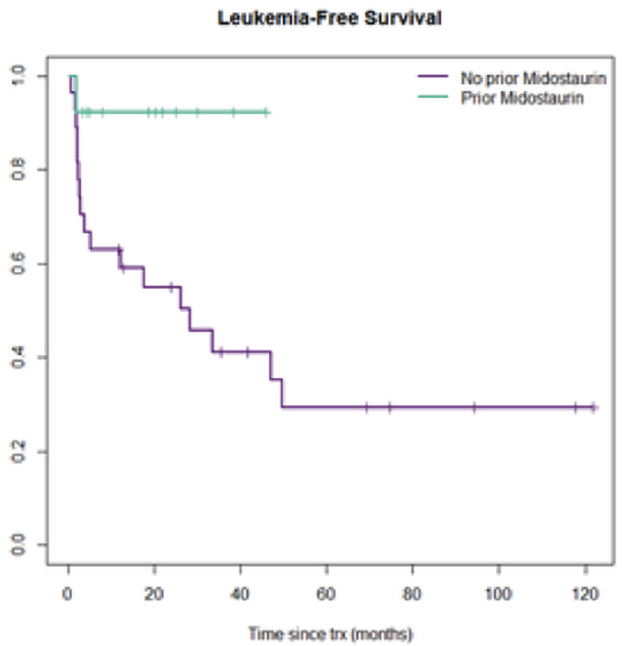
[1]Evaggelismos General Hospital, Athens, Greece

Background: FLT3 mutations concern 30% of patients with newly diagnosed AML. They are associated with lower rates of remission, high recurrence rates and unfavorable prognosis. The recent use of tyrosine kinase inhibitors against FLT3 mutations has altered outcome. The present study analyzed the outcome of alloHCT in patients with FLT3-AML and the factors affecting it.

Methods: 41 patients (18 men, 23 women) underwent alloHCT from 01/01/2010 to 05/15/2021 and were retrospectively studied. Median age was 52 years (range 33-65) and median follow-up duration 32.8 months (range 5-122). 36/41 (83%) patients were FLT3-ITD + while 5/41 (12%) TKD + . Six patients had high allelic load (>0.5) and 15 low. Data was not available for the remaining 20. 27/41 (66%) patients had normal karyotype while 13/41 (32%) had various karyotypic abnormalities. Median time from diagnosis to alloHCT was 8.7 months (range 2.6-25.5). 25/41 (61%) were transplanted in CR1, 11/41 (27%) in CR2 and 5/41 (12%) had refractory disease. 90% received myeloablative conditioning regimen while 10% reduced intensity. In 33/41 patients (80%) the graft source was peripheral blood, in 4/41 bone marrow and in 4/41 double umbilical cord blood. 21/41 (51%), 14/41 (34%) and 2/41 patients were transplanted from matched unrelated donor, histocompatible sibling and haploidentical donor respectively. 12/41 (29%) with FLT3-ITD relapsed, 17/41 (41%) died, 7 from disease and 10 (24%) from TRM. 7/41 (17%) received sorafenib, 6 as

prophylaxis and 1 for relapse after alloHCT. The following factors were studied: coexistence of NPM1 mutation, type of FLT3 mutation, allele load, age, karyotype, donor type, presence of MRD at transplantation, number of white blood cells at diagnosis, ELN risk classification, conditioning regimen and pre-treatment with midostaurin. LFS and OS were determined by Kaplan - Meyer and multifactorial analysis was performed by CoxRegression analysis. RStatistics (Rcran) software was used.

Results: 2-year CIR was 22.5% (95% CI12.4-40.1%), 2-year NRM 13.6% (95% CI5.9-31.3%), the estimated 2-year OS 66% (95% CI52.4-3.1%) and the estimated 2-year LFS 64.2% (95% CI35.8-72.6%). In unifactorial analysis, statistically important factors for LFS were age >60 years ($p = 0.006$), disease phase in alloHCT ($p = 0.017$) and previous administration of midostaurin ($p = 0.01$). Multifactorial analysis for LFS revealed age> 60 ($p = 0.017$) and disease phase in alloHCT ($p = 0.03$) as significant factors. Only age >60 years ($p = 0.005$) was statistically significant for OS. Midostaurin administration tends to favorably affect LFS ($p = 0.07$) and allthough statistically insignificant, it decreased CIR to 7.7% (95% CI 1.1 -54.6) versus 29.6% (95% CI 16.3 -53.8, p = ns) and to NRM 0% versus 15.6% (95% CI6.1-39.4).



Conclusions: AlloHCT is the treatment of choice for patients with AML-FLT3 + in CR1 regardless of other factors. The best outcome seems to be achieved in younger patients, possibly due to the ability of receiving myeloablative conditioning regimens. The addition of midostaurin, despite the small number of patients, tends to improve the outcome of alloHCT. Larger number of patients and longer follow-up time are required to evaluate the effectiveness of maintenance with sorafenib.

Disclosure: There are no disclosures

P261

Unrelated donor transplantation in aplastic anemia with a quadruple GVHD prophylaxis

S. Giammarco[1], N. Mordini[2], F. Zallio[3], I. Cavattoni[4], L. Castagna[5], E. Terruzzi[6], A. Iori[7], P. Chiusolo[8], E. Metafuni[1], F. Sorá[9], L. Luca[9], M.A. Limongiello[1], I. Innocenti[1], F. Autore[1], E. Galli[1], S. Sica[8], A. Bacigalupo[9]

[1]Fondazione Policlinico Universitario A. Gemelli IRCCS Rome, Italy, [2]Ospedale di Alessandria, Alessandria, Italy, [3]AO S Croce e Carlo, Cuneo, Italy, [4]Ospedale di Bolzano, Bolzano, Italy, [5]Ospedale Cervello, Palermo, Italy, [6]Ospedale San Gerardo, Monza, Italy, [7]Policlinico Umberto 1, Roma, Italy, [8]Università Cattolica del Sacro Cuore, Roma, Italy, [9]Università Cattolica del Sacro Cuore, Rome, Italy

Background: The Baltimore group has recently reported a transplant platform in patients with aplastic anemia (AA) undergoing a haploidentical transplantation (HAPLO) **(De Zern et al. 2020); t**he conditioning regimen is based on fludarabine cyclophosphamide (FLU-CY) TBI 2 Gy GvHD prophylaxis is based on 4 drugs : ATG on day -9-8-7, post transplant CY (PTCY) 50 mg/kg on days +3 + 4 and tacrolimus mycophenolate. The Baltimore group reports 37 patients, with 35 surviving without GvHD. The Brasilian group has confirmed these results in a multicenter study on 87 AA patients, with survival in excess of 90%, especially for those receiving an intensified TBI dose of 4Gy (instead of 2 Gy) and an increased dose of CY pre transplant (50 instead of 30 mg/kg) (BBMT, 2020; e222-e226).

Methods: If this platform allows the engraftment of an HLA HAPLO mismatched marrow, with little or no GvHD, then the same platform should be successful in patients with AA undergoing an unrelated donor (UD) transplant, or in elderly patients grafted from matched siblings.We have grafted 11 patients with AA with this platform.The conditioning was as follows: CY 14.5 mg/kg days -6-5, Fludarabine 30 mg/m^2 days -6-5-4-3-2, TBI 2 Gy day -1 and unmanipulated bone marrow on day 0 (1 patient was grafted with PB cells from a HAPLO donor). GvHD prophylaxis was ATG 0.5, 2 and 2 mg/kg days -9-8-7, PTCY 50 mg/kg day +3 + 4, cyclosporine (CSA) on day +5 onward and mycophenolated (MMF) day 5-day 35. The median age was 30 years (range 20-60). The donor was unrelated, matched (8/8, n = 5), or mismatched (7/8, n = 4), HAPLO (n = 1), or a matched sibling (n = 1). In the latter this transplant platform was chosen because of the patients age (60 years).

Results: All patients had 100% donor chimerism within 30 days from transplant. One patients died of a septic shock on day+34. One patient (UD 7/8 matched donor) (9%) experienced a rejection on day +88; underwent a second transplant from the same UD with peripheral blood as a stem cell source, on day +152 from the first transplant; the patient is currently alive and well with trilineage recovery on day +423. The median time to a neutrophil count of 0.5 x 10^9/L was 20 days (15-26) and for 20 x 10^9/L platelets, it was 24 days (13-30). Acute GvHD grade I was recorded in 1 patient (9%), minimal chronic GvHD was reported in 2 patients (18%); moderate severe chronic GvHD was not reported. EBV reactivation was seen in 5 patients (45%) and was treated in 2 patients with rituximab. CMV reactivation was seen in 3 patients (27%). With a median follow up of 323 days, the one year actuarial survival is 95%.

Conclusions: This small experience with the Baltimore quadruple GvHD prophylaxis, in patients undergoing unrelated donor transplants, confirms a very high degree of engraftment, low early mortality, low rate of rejection, and little or no GvHD. Whether the dose of CY in the conditioning should be increased from 29 mg/kg to 50 mg/kg, as suggested by the Brazilian group remains to be determined.

Disclosure: No disclosure to declare

P262

Evaluation of disease progression/relapse in patients with multiple myeloma waiting for autologous hematopoietic cell transplant in Brazil

G. Fatobene[1,2], F. Moreira[1], M. Jacomassi[1], B. Carvalho[1], L. Otuyama[1], L. Mariano[1], A. Cordeiro[1], G. Martinez[1], V. Rocha[1,2]

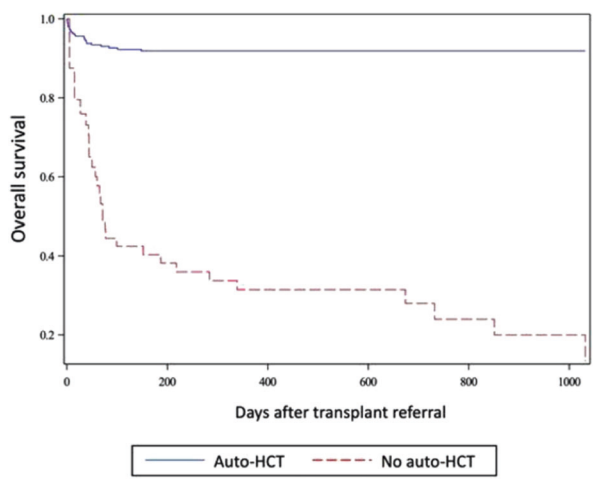
[1]University of São Paulo, São Paulo, Brazil, [2]Hospital Vila Nova Star, São Paulo, Brazil

Background: Autologous hematopoietic cell transplant (auto-HCT) is standard of care in multiple myeloma (MM) and should be performed within 4-6 months after the start of induction therapy in eligible patients. Unfortunately, in resource-constrained countries, the waiting time for auto-HCT is longer due to the small number of HCT beds and difficulties in completing the pre-HCT process. Our objective was to evaluate the incidence, risk factors and impact of progression/relapse (P/R) in transplant waiting list among patients with MM.

Methods: Patients with MM referred to auto-HCT at our public institution between 2010 to 2018 were included. The primary outcome was cumulative incidence (CI) of P/R in waiting list, defined as P/R requiring or not treatment after 4 months from the start of the most recent line of systemic treatment. Secondary outcomes were time in waiting list, disease-free survival (DFS) after auto-HCT, % of referred patients actually proceeding to auto-HCT, and overall survival (OS).

Results: 304 patients deemed eligible for auto-HCT were included in the analysis. Of these, 70 patients progressed or relapsed while waiting for transplant. Baseline characteristics were similar between patients with P/R or not in waiting list, except that the former were more likely to have non-IgG MM. The CIs of P/R in transplant waiting list at 3, 6 and 12 months were 5, 11 and 17%, respectively. In a univariate analysis, ECOG 2-4, non-IgG MM, serum monoclonal protein ≥1.7g/dL, having high school (vs. elementary school) and no prior use of immunomodulator were significantly associated with higher risk of P/R. In multivariate analysis, non-IgG MM was the only risk factor for P/R in waiting list (HR 1.74 [1.08-2.82], $p = .02$). Median waiting time was 231 days (IQR 131-429) for patients with P/R in waiting list compared to 149 days (95-213) for their counterparts ($p < 0.001$). Only 10% of patients were autografted within 6 months after the start of systemic therapy. Of the 70 patients with P/R in waiting list, 20 (29%) subsequently proceeded to auto-HCT compared to 214/234 (92%) of patients without P/R ($p < .001$). Post-transplant DFS of the 20 patients receiving auto-HCT after P/R in waiting list did not significantly differ from those proceeding directly to auto-HCT ($p = .10$). OS was significantly inferior for those not receiving auto-HCT (Fig. 1).

Figure 1 – Simon-Makuch curve of overall survival by autologous HCT group after transplant referral



Conclusions: Patients with P/R in waiting list waited longer for auto-HCT than their counterparts and were less likely to be autografted after P/R. This finding suggests that waiting longer may increase the risk of P/R, making these patients lose performance status to undergo auto-HCT subsequently. Prioritizing patients with non-IgG MM and expanding outpatient transplantation may be strategies to avoid P/R in waiting list. These data may also help stakeholders address hindrances in the pre-HCT process and increase the number of HCT beds in the public setting.

Disclosure: none to declare

P263

Feasibility of transplantation for myeloma in resource constrained stetting: Real-world data on survival and cost of treatment from the first haemato-oncology centre in Sri Lanka

S. Hewamana[1,2], C. Jayasinghe[3], P. Gunasena[1], M. Harischandra[1], T. Skandarajah[4], S. Abeyaratne[1], L. Ekanayake[1], G. Somasundaram[1], S. Somiah[1], V. Srinivasan[1], G. Arseculeratne[1], A. Mowlana[5], T. Niwanthika[1], H. Weerasekara[1], N. Ruwanika[1], S. Deshapriya1[1], C. Wickramarathna[6], A. Wijewickrama[7], P. Jayawardena[8], N. Pieris[2], E. Perera[2], S. Paranawithane[1], C. Perera[9], C. Kariyawasam[10], S. Munasinghe[11], C. De Silva[12], R. Wadanamby[5], G. Galagoda[5], T.T. Lin[13], B. Wijesiriwardena[9], J. Balawardena[14]

[1]Lanka Hospitals, Colombo, Sri Lanka, [2]Asiri Surgical Hospital, Colombo, Sri Lanka, [3]University of Sri Jayewardenepura, Colombo, Sri Lanka, [4]National Cancer Institute, Colombo, Sri Lanka, [5]Lanka Hospital Diagnostics, Colombo, Sri Lanka, [6]University of Ruhuna, Galle, Sri Lanka, [7]National Institute of Infectious Diseases, Colombo, Sri Lanka, [8]National Hospital of Sri Lanka, Colombo, Sri Lanka, [9]Durdens Hospital, Colombo, Sri Lanka, [10]Sri Jayewardenepura General Hospital, Colombo, Sri Lanka, [11]Military Hospital, Colombo, Sri Lanka, [12]University of Colombo, Colombo, Sri Lanka, [13]Coventry University, Coventry, United Kingdom, [14]General Sir John Kotelawala Defence University, Colombo, Sri Lanka

Background: Plasma cell myeloma (PCM) is the second commonest haematological malignancy. Poorer countries have several folds higher mortality in some cancers compared to those in affluent countries. However, data related to geographical differences, clinicopathological and global survival variability are not well documented and there is a correlation between poverty and lack of accessibility to health care and vice versa in low-income countries.

Methods: Sri Lanka is a developing country with a diverse healthcare structure with no dedicated Haemato-Oncology/ Clinical Haematology centres, transplant facilities or access to novel anti-cancer agents at the time the first 'blood cancer centre' was established in the Island nation in 2013. We have previously published data related to survival of patients treated in the centre. The aim of the study was to analyse patient and disease characteristics and evaluate survival parameters of patients who had peripheral blood stem cell transplant (PBSCT) in the first Haemato-Oncology centre in Sri Lanka.

Results: A total of 20 patients received PBSCT during study period. However, one each had the diagnosis of plasmablastic lymphoma and plasma cell leukaemia and one with creatinine clearance of less than 30ml/min at presentation were not included in the final analysis. The median age of the study population was 57 years (range 41,66). There were 9 (53%) males and 8 (47%) females. Melphalan 100mg/m^2 was used for conditioning. The median infused haematopoietic stem cells (HSC) per Kg was 4.25 x $10^{6.}$ Median duration for neutrophil and platelet engraftment was

11 days and the median in-patient hospital stay was 18 days. The average cost of PBSCT for PCM was US$ 7500. After a median follow up of 38.33 months, the median overall survival (OS) was not reached (restricted mean was 77.42 with s.e. 8.12) and the estimated 3-year OS rate was 0.9. There was no difference in the survival according to remission status, dose of HSC, age or gender. In comparison, three year over survival (OS) rate of the entire cohort of PCM patients (n = 79) treated in LHBCC was 0.760 (95% CI (0.662,0.873).

Table 1.

Variable and summary measure(s)	Summary statistics
OS (in months):	
Median (95% CI)	Not reached
Restricted mean (Restricted mean s.e.)	77.42 (8.12)
3-year Survival rate	0.900 (0.732, 1.000)
5-year Survival rate	0.750 (0.496, 1.000)
follow up (in months): Median (95% CI)	38.33 (30.30, NA)
Age (in years): Median (IQR, Range)	57.0 (11.5, (41, 66))
HSC dose (per Kg): Median (IQR, Range)	4.25 (4.21, (1.64, 17.22))
Time for neutrophil recovery (in days): Median (IQR, Range)	11.00 (1.50 (9.00, 14.00))
Time for platelet recovery (in days): Median (IQR, Range)	11.00 (4.00, (10.00, 23.00))
Hospital Stay (in days) : Median (IQR, Range)	18.00 (4.50, (14.00, 31.00))
Cost (in US$): Median (IQR, Range)	7500.00 (2367.00, (5160.00, 11429.00))

Conclusions: Our study has shown comparable survival parameters as reported in high-income countries using 100 mg/m^2 dose of melphalan and non-cryopreserved HSC. This is the only documented study related to PBSCT in any type of blood cancer in Sri Lanka.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare

P264

Results of allogeneic stem cell transplantation in bone marrow failures: A single-center experience

T. Ersal[1], V. Özkocaman[1], F. Özkalemkaş[1], İ.E. Pınar[1], C. Yalçın[1], B. Orhan[1], Ö. Candar[1], R. Ali[1]

[1]Uludag University, Bursa, Turkey

Background: Bone marrow deficiencies ıs a group of dıseases wıth dıfferent etıologıes. Supportive therapy, immunosuppressive therapy (IST), and allogeneic hematopoietic stem cell transplantation (SCT) are among the treatment options. This study aimed to retrospectively evaluate the demographic characteristics, treatment, and transplantation results of patients who underwent allogeneic SCT due to bone marrow failure in the Uludağ University Hematology Department and review HSCT in bone marrow failures.

Methods: Of the seven patients who underwent SCT, 6 had SAA, and 1 had unclassifiable MDS. Transplantation was performed from a fully HLA-matched sibling donor in 5 cases, syngeneic in one and 9/10 compatible in one. Peripheral blood was used as a stem cell source in only 2 of the patients, while bone marrow was used in the other four patients. Fludarabine/cyclophosphamide/anti-thymocyte globulin (Flu/Cy/ATG) was used as the conditioning regimen.

Results: 513 SCT were performed in our center between 2009 and 2021. Of these, 140 (27.2%) were allogeneic SCT, and the remaining 373 were autologous SCT. The 140 patients who underwent allogeneic SCT 7 (5%) were diagnosed with bone marrow failure. The median age was 37 (21-47). Four patients were <40 years old at the time of transplantation. Six of the patients received cyclosporine as IST, and one patient received ATG. The median time to transplantation was five months (3-34). Flu/Cy/ATG conditioning regimen was used in all patients. The median time for neutrophil engraftment was 25 days (14-31) and platelet engraftment>20,000 was 18 days (11-21). No correlation was found between the number of cells administered and the ferritin level, and the engraftment time. The patients were discharged on the mean of 29 days (23-39). The chimerism rates at the 1st month of transplantation were 100% in 2 patients, 98% in 1, and 86% in 1 (increased to 99.7% at three months) donor profile. Graft failure, acute or chronic GVHD, was not observed in any of the patients. Cytomegalovirus (CMV) reactivation was observed in two of our patients. One of them is the 4.5 of the transplant. The other was on the 50th day and 5th month. In both patients, CMV-DNA negativity was obtained after four weeks of oral valganciclovir treatment. During the five-year follow-up, the survival rate of the patients was 100%. The median overall survival was 39.5 months (25.5-75). The median survival time after transplantation was 35 months (10-71). All of the patients are still under follow-up, and their complete hematological responses continue.

Conclusions: All seven patients who underwent allogeneic SCT are alive and have complete hematological responses. There was no increase in mortality and morbidity in those over 40 years of age. Although the number of our patients is small, it was concluded that allogeneic SCT should be considered as the first-line treatment in the patient group with a fully compatible sibling donor with severe aplastic anemia and between the ages of 40-50 and without comorbidity.

Disclosure: Authors declare no conflict of interest.

P265

Strategic cost analysis of hematopoietic stem cell banking from cord blood: An egyptian model

S. Abdelhak[1], A. Darwish[2,3], S.A.E.-F. Saleh[1]

[1]Mansoura University, Mansoura, Egypt, [2]Mansoura University, Mansoura, Egypt, [3]Mansoura University Research Center for Cord Stem Cells (MARC-CSC), Faculty of Medicine, Mansoura University, Mansoura, Egypt

Background: Umbilical cord blood (UCB) has been used as an alternative source of hematopoietic stem cells for bone marrow transplantation (BMT). The advantages of cord blood include ready availability, no risk to the donor, low rate of viral contamination and low risk of GVHD. Egypt suffers from a large unmet need for BMT, especially for thalassemia being the most common chronic hemolytic anemia in Egypt. This need for BMT could be lessened by establishing a public cord blood bank (CBB). Public banks are about 53 banks in 37 countries around the world not including Egypt. However, many public cord blood banks have stated that they are struggling to maintain their financial sustainability.

Methods: The aim of this study is to prove the possibility of providing a cord blood unit (CBU) with the least cost that can

ensure the sustainability of a public CBB in a developing country. The study adopts an Activity Based Costing (ABC) system using a model of six steps in the first public cord blood bank in Egypt which is located in Mansoura University (the largest university in the Nile Delta) and comparing it with the traditional method. This is done through the measurement of the cost of each step in the banking process separately (collection, processing and cell enumeration, cryopreservation). Where there are common activities between those stages and therefore indirect costs.

Results: The cost of producing a unit of umbilical cord blood using the traditional method was about 17,704 pounds. While its cost was about 16,505 pounds using the ABC method, a difference of 1199 pounds per unit. Thus, the ABC method has contributed to reducing the cost of producing a stem cell unit derived from cord blood by up to 7%. In addition, on separating stem cells from UCB, the processing step produces by-products such as platelet-rich plasma and red blood cells, which are considered an indirect return.

Conclusions: This study concludes that using an activity-based costing method can reduce the cost of production of a CBU without sacrificing the value. The pooling of costs by activities or activity areas provides information that may help managers to better plan and control costs.

Disclosure: There are no conflicts of interest

P267

TRYPAN BLUE AND FLOW CYTOMETRY CELL VIABILITY TESTING OF PACKED OR DILUTED CRYOPRESERVED AT -80ºC HEMATOPOIETIC STEM CELLS SHOW SIMILAR RESULTS

I. Tonev[1], S. Simeonov[1], M. Ilieva[1], M. Muhtarova[1], R. Vladimirova[1], N. Andreinski[1], T. Yancheva[1], M. Guenova[1], M. Mincheff[1]

[1]Specialized Hospital for Active Treatment of Hematological Diseases, Sofia, Bulgaria

Background: Trypan blue exclusion and flow cytometry were compared for testing of cell viability of hemopoietic stem cells (HSCs) cryopreserved at -80ºC. Stem cells were frozen and stored with 5% final DMSO concentration with different degree of cell packing.

Methods: We analyzed 47 samples stored at -80ºC in a cryoprotectant solution with final concentrations of 5% DMSO, 3.6% hydroxyethyl starch (HES 450 000 mw) and 3% of human serum albumin. The cell concentration in the frozen suspension ranged between $69x10^6$/ml and $665x10^6$/ml (median $310,25x10^6$/ml). The cell viability was tested simultaneously by trypan blue exclusion test and by flow cytometry with 7 -aminoactinomycin D (7-AAD) without lysing solution.

Results: Both viability tests gave similar results. When tested by trypan blue, the viability was 95,5% (80-99%), and by flow cytometry was 95,92% (89,1-98,4%). The additional statistical Spearman's Rho analysis does not show statistically significant correlation between viability results, performed with either test, and the degree of cell packing.

Conclusions: Flow cytometry and trypan blue tests show similar viability results. Since trypan blue testing is well established, has lower cost, and can be performed faster, we accepted it as a routine for our further analyses of cell viability of packed prior to freezing stem cell concentrates. HSC viability after storage at -80ºC with 5% final DMSO concentration is very good and is not affected by higher cell packing thus allowing the reduction of infused DMSO and the side effects (cardiac, neurologic, respiratory, etc.) during transplantation.

Disclosure: Nothing to declare

P268

Allogenic hematopoietic stem cell transplantation in iranian patients with congenital sideroblastic anemia: A single-center experience

B.S. Shamsian[1], H. Abolghasemi[1], P. Eshghi[1], M.A. Ehsani[2], Z. Khafafpour[1], A. Latifi[1], M. Kazemi Aghdam[3], M. Jamee[4]

[1]Pediatric Congenital Hematologic Disorders Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran, Islamic Republic of, [2]Tehran University of Medical Sciences, Tehran, Iran, Islamic Republic of, [3]Pediatric Pathology Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran, Islamic Republic of, [4]Pediatric Nephrology Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran, Islamic Republic of

Background: Congenital sideroblastic anemia (CSA) is characterized by anemia and intramitochondrial iron accumulation in erythroid precursors (Ring sideroblasts). The most common recessive form is caused by mutations in *SLC25A38*.

Methods: We described the clinical course and outcomes of CSA patients receiving allogeneic hematopoietic stem cell transplantation (allo-HSCT) from 2016 to 2021 in Mofid Children's Hospital, Tehran, Iran.

Results: Case 1 was a 3-year-old female, the second child of close-relative parents. She presented at 2 months with severe anemia and later developed splenomegaly, large head, and frontal bossing. The blood tests and bone marrow aspiration (BMA) indicated CSA. Due to the transfusion-dependency and lack of response to pyridoxin, at 3 years of age, she received allo-HSCT from HLA-identical matched sibling donor (MSD). The conditioning regimen (CR) included busulfan (Bu), cyclophosphamide (CY), and anti-thymocyte globulin (ATG) with graft-versus-host-disease (GvHD) prophylaxis by cyclosporine (CS) and methotrexate (MTX). She was engrafted on day +21 but later developed GvHD in gastro-intestine (GI) and skin, cytomegalovirus (CMV) reactivation, and posterior reversible encephalopathy syndrome (PRES). Now five years post-transplant, she is drug-free with > 95% donor chimerism.

Case 2 was a 2.5-year-old female with first-degree consanguineous parents. She was found to suffer from severe anemia and head deformity at 1.5 months. Her blood tests and BMA indicated CSA, confirmed by a homozygous variant in *SLC25A38*. She underwent allo-HSCT at the age of 2.5years, from her HLA-identical matched related donor (MRD) with a CR consisting of BU, CY, and ATG and GvHD prophylaxis by CS and mycophenolate mofetil. She engrafted on day +18, however, was later complicated by skin GvHD. She is now, 3 years post-HSCT, stable, without blood transfusion, with 100% donor chimerism.

Case 3 was a 3.5-year-old male born to close-relative parents. He manifested with severe pallor at 2 months old and then splenomegaly. His blood tests and BMA suggested CSA. He showed transfusion-related complications (Anti IgG C3d) requiring IVIG, corticosteroids, and four courses of rituximab. At the age of 3.9 years, he received allo-HSCT from his HLA-identical MSD. The CR included Bu, CY, and ATG, and CS, MTX, and then methylprednisolone as GvHD prophylaxis. He engrafted on day +16. Although later developed CMV reactivation (day + 26), PRES, and high ferritin level, he is now 5 years post-HSCT stable with 75% donor chimerism.

Case 4 was a 2.6-year-old male born to first-degree relative parents. He was initially presented with severe anemia at 2.5 months old. Following blood and bone marrow analysis, he was diagnosed with CSA, later confirmed by homozygote

mutation in *SLC25A38*. He received allo-HSCT from HLA-identical MRD with a CR consisting of BU, CY, and ATG and GvHD prophylaxis by CS and MTX. He engrafted on day +12 with a 96% chimerism. He later developed bacteremia, GI complications, and thrombotic microangiopathy. He has now mild GI GvHD on day +45 and is on GvHD treatment with corticosteroids and CS.

Conclusions: In patients with transfusion-dependent and pyridoxine-resistant severe CSA, HSCT is the only curative option and can result in favorable outcomes particularly when used in a timely manner.

Disclosure: Nothing to declare.

HAEMOGLOBINOPATHY

P269

Sickle cell disease and thalassemia in pediatric hematopoietic stem cell transplantation: Evaluation of pulmonary risk factors and manifestations

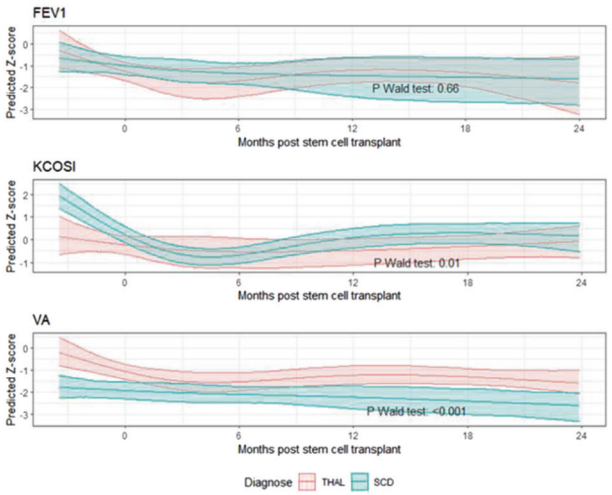
A. Tulling[1], A. Verbeek[1], E. von Asmuth[1], I. de Vreede[1], E. Rikkers-Mutsaerts[1], M. Los[1], I. Dekkers[1], A. ten Harkel[1], A. Lankester[1], F. Smiers[1], A. Mohseny[1], E. Buddingh[1]

[1]Leiden University, Leiden, Netherlands

Background: Pulmonary complications following allogeneic hematopoietic stem cell transplantation (HSCT) have been reported to occur in 12% of stem cell recipients. The aim of this study was to investigate whether pre-HSCT pulmonary comorbidity and pulmonary function test (PFT) abnormalities in children with hemoglobinopathies are associated with pulmonary complications after HSCT.

Methods: We performed a retrospective chart review in eighty-five children (35 SCD and 50 THAL) who were transplanted between 01-01-2010 and 31-12-2020. The primary determinants were pre-transplantation PFT results, radiographic imaging of the lungs, sonographic imaging of the heart and a history of pulmonary disease. PFTs were performed in children from 4 years and up and included spirometry, carbon monoxide (CO) diffusion capacity and lung voluminal tests. PFTs 120 days before up to 2 years after HSCT were modeled using a mixed effects model with splines. Z-scores for PFT measurements were calculated based on reference values corrected for age, height, gender and ethnicity. A multistate cox model was applied to determine the association between pre-HSCT covariates and pulmonary complications post-HSCT.

Results: Pre-existing pulmonary abnormalities during pulmonary screening tests were more prevalent in children with SCD than with THAL (74% vs 20%, p-value: < 0.001). Forty-eight percent of SCD patients had restrictive lung disease, 40% had a history of pulmonary disease (acute chest syndrome, pneumonia or asthma) and 17% had abnormal findings during radiographic imaging pre-HSCT. Pulmonary complications occurred in 21 (25%) patients in the first two years after HSCT. This rate was not significantly different between SCD and THAL patients (23% vs 26%). Moreover, 14 out of these 21 patients had an infectious pulmonary complication and 13 patients developed a non-infectious complications (8 bronchiolitis obliterans, 2 peri-engraftment respiratory distress syndrome, 2 idiopathic pneumonia syndrome and one case of cryptogenic organizing pneumonia). Pre-transplantation pulmonary screening abnormalities, including PFT results, radiographic imaging results and history for pulmonary disease, were not significantly associated with the occurrence of pulmonary complications after HSCT. However, the occurrence of acute graft versus host disease (GVHD) as a time-dependent covariate was associated with subsequent pulmonary complications (HR 2.85 (1.18 – 6.88), p-value = 0.02). Furthermore, the usage of Busulfan based conditioning and a matched unrelated donor showed an increased risk of pulmonary complications up to 2 years post-HSCT. Lastly, lung function tests before and up to 2 years after HSCT showed significantly lower levels of alveolar volume (VA) (p-value < 0.001) in patients with SCD as compared to THAL patients.



Determinant	Hazard ratio	95% Confidence interval	P-value
Diagnose (SCD)	0.79	0.33 - 1.89	0.6
Acute GVHD (>stage I)	**2.85**	**1.18 - 6.88**	**0.02**
Age at HSCT	1.02	0.94 - 1.10	0.6
Busulfan based conditioning	**2.97**	**1.23 - 7.18**	**0.016**
Matched unrelated donor (vs identical related donor)	**3.67**	**1.34 - 10.1**	**0.011**

Conclusions: SCD patients had more frequent pulmonary abnormalities pre-HSCT and worse pulmonary function tests post-HSCT than THAL patients. The development of acute GVHD is associated with subsequent pulmonary complications post-HSCT in hemoglobinopathy patients.

Disclosure: Nothing to declare

P270

Thiotepa and suppression of endogenous haemopoiesis with hydroxycarbamide and hypertransfusions abrogates risk of graft failure in haploidentical ric hct for paediatric patients with scd

D. Dexter[1], F. O'Boyle[2], S. Loaiza[2], R. Szydlo[2], K. Lund[1], L. Karnik[1], T. Petterson[1], A. Gassas[1], J. de la Fuente[1]

[1]St Marys Hospital, Imperial College London, London, United Kingdom, [2]Imperial College London, London, United Kingdom

Background: Haploidentical HCT allows universal availability of HCT to achieve long-term cure of sickle cell disease. The main barrier to this approach is graft failure. To minimise this risk, we

introduced pre-HCT suppression of haemopoiesis with hydroxycarbamide 30 mg/kg (HU) and hypertransfusions. We present a case series of 10 patients who underwent haploidentical HCT with reduced intensity conditioning and this pre-transplant approach.

Methods: Between August 2017 and May 2021, ten consecutive haploidentical related (4 maternal, 3 paternal, 3 sibling) HCT were performed at St. Mary's Hospital, London. Patients were transplanted for stroke or recurrent vaso-occlusive crises and/or acute chest syndrome not responding to hydroxycarbamide. After 8 weeks suppression of haemopoiesis with hydroxycarbamide and hypertransfusions, patients were conditioned with fludarabine 150 mg/m^2, thiotepa 10 mg/kg, cyclophosphamide 29 mg/kg, TBI 2Gy and ATG (Thymoglobulin) 4.5 mg/kg. GvHD prophylaxis was provided with post-transplant cyclophosphamide (PTCy) 50 mg/kg on day +3 and day +4, sirolimus and MMF. MMF was weaned over two weeks after day +35 once evidence of molecular haemopoiesis was available. Stem cells were harvested from the bone marrow for all transplants.

Results: The median age was 12 years (3 – 19). The median cell dose was 4.04 x 10^8 TNC/kg (range 1.85 – 10.26), 4.78 x 10^6 CD34/kg (range 2.1 – 13.71) and 39.7 x 10^6 CD3 + /kg (range 15.3 – 81). The median survival was 11.5 months (5.7 – 45.1).

No patient suffered transplant related mortality although one patient died on day +361 from Pneumococcal sepsis at a time where there was good donor haemopoiesis, no GvHD or immunosuppression. Primary or secondary graft failure was not seen. Median neutrophil engraftment was 19 days (range 15 to 22). The median platelet engraftment >50 x 10^9/L was 35 days (range 30 to 52). One patient required a top-up CD34 + selected PBSC on day +725. All patients achieved donor chimerism in T cells >50% by day +90 and were 100% donor in whole blood at day +180.

There was no incidence of VOD or idiopathic pneumonia syndrome. One patient suffered transplant associated microangiopathy and two macrophage activation syndrome. Five patients had ≥grade 2 aGvHD (50%), two patients had limited cGvHD (20%) and four patients extensive cGvHD (40%), although no patient had GvHD at 18 months post HCT. The median duration of immunosuppression was 191 days (range 160-525 days). The overall survival and disease free survival in this cohort of children is 90%.

Conclusions: In conclusion, haploidentical RIC HCT with thiotepa and PTCy in conjunction with pre-HCT suppression of haemopoiesis with HU and hypertransfusions abrogates the risk of graft failure in paediatric patients and leads to long-term donor haemopoiesis with low risk of mixed chimerism. The incidence of alloreactive complications was low. Although the incidence of GvHD during the treatment period was not insignificant, it responded to standard treatment in all patients with no patients suffering cGvHD long-term or requiring prolonged courses of immunosuppression. Haploidentical RIC HCT with PTCy using thiotepa and pre-HCT suppression with HU and hypertransfusions is effective and represents a feasible curative therapy for children with severe SCD.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare

P271

48 HLA-identical related hematopoietic stem cell transplants in sickle cell disease: Improving results during the last decade

M. García Morin[1], E. Cela[1], J.M. Marco Sánchez[1], E. Bardón Chanco[1], J. Huerta Aragonés[1], B. Ponce Salas[1], S. Otero Alambillaga[2], Y. Aguilar de la Red[3], M.d.C. Pérez Peñate[4], I. Astigarraga Aguirre[5], A. Gondra Sangroniz[6], A. Pérez Corral[7], C. Villegas Da Ros[7], J. Anguita[7], C. Beléndez Bieler[1]

[1]Pediatric Hematology Unit. Hospital General Universitario Gregorio Marañón. Universidad Complutense de Madrid, Madrid, Spain, [2]School of Medicine. Universidad Complutense de Madrid, Madrid, Spain, [3]Pediatric Hematology. Hospital Universitario Miguel Servet, Zaragoza, Spain, [4]Pediatric Hematology. Hospital Universitario Materno Infantil Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain, [5]Hospital Univesitario de Cruces, Bilbao, Spain, [6]Hospital Universitario de Basurto, Bilbao, Spain, [7]Hospital Universitario Gregorio Marañón. Universidad Complutense de Madrid, Madrid, Spain

Background: Despite the progress in medical management, sickle cell disease (SCD) is still associated with severe morbidity and early mortality in adults. Waiting for further development in gene therapy, allogeneic haematopoietic stem cell transplantation (HSCT) is currently the only curative therapy.

Methods: A single center descriptive study was conducted on patients with SCD who underwent HSCT from an HLA-identical sibling donor between May 2010 and December 2021. Stem cells source: bone marrow in all patients. Transfusion therapy was started 3 months before HSCT and since 2015 hydroxyurea was increased or started one month before HSCT in order to maintain reticulocyte count under 100 000/mm^3. Conditioning regimen:

- Until January 2015: Busulfan, cyclophosphamide, alemtuzumab. Graft versus host disease (GVHD) prophylaxis with cyclosporine and methotrexate.
- After January 2015: Thiotepa, Treosulfan, Fludarabine, antithymocyte globulin (myeloablative conditioning but reduced toxicity). GvHD prophylaxis with cyclosporine and mycophenolate mofetil (MMF) (January 2015 – February 2019) or tacrolimus and MMF (February 2019 – December 2021).

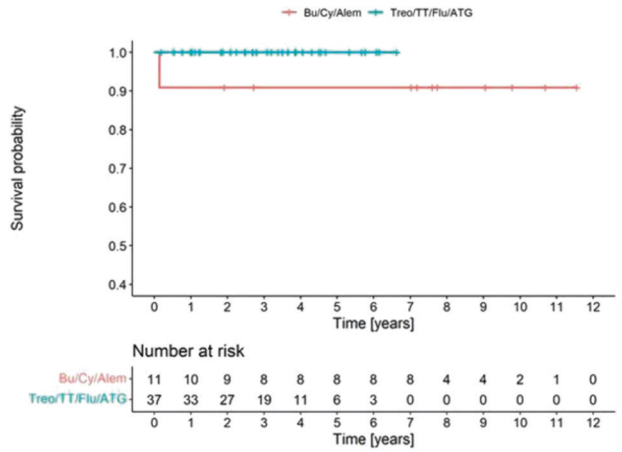
Seizure prophylaxis during immunosuppression: phenytoin until January 2015, afterwards levetiracetam. To decrease neurological complications: platelet threshold 50 000/mm^3, hemoglobin level 11 g/dL, avoid hypertension and hypomagnesemia. Ovarian tissue cryopreserved since 2015.

Epidemiological, clinical, and analytical parameters were collected. Data are presented as percentages and medians (p25-p75).

Results: 48 HSCT was performed in 47 patients (24 females), median age of 6.3 years (2.9-9.8); 11 of them with the first conditioning, 37 with the second one (GVHD prophylaxis with cyclosporine/MMF in 10/37 and tacrolimus/MMF in 17/37). Donor median age: 6.5 years (4.5-9.2), 48.9% sickle cell trait, 19% with major group and 19% with minor group incompatibility. All patients grafted but 3 patients experienced autologous recovery: 2 patients without symptoms (87% and 79% of receptor cells respectively); 1 patient suffered a vaso-occlusive crisis on day +180 but achieved complete donor chimerism after a second HSCT from the same sibling donor with the second conditioning regiment. Complete chimerism in 40/48 HSCT and stable mixed chimerism in 5/48. The overall survival (OS) and event-free survival (EFS) considering dead, or graft failure were 97.2% and 90.5%, respectively, with a median follow-up of 3.4 years (2.0-5.7). First conditioning: OS 90.9% and EFS 81.8%. Second conditioning: OS 100% and EFS 93.3%.

Median time to neutrophil and platelets recovery were 18.5 days (17-22) and 23 (19.7-22.2) respectively. Complications of HSCT were: arterial hypertension 42/48 (87.5%), CMV reactivation 34/48 (71%), acute renal failure 11/48 (23%), neurological complications 11/48 (23%) (subarachnoid haemorrhage, seizure, posterior reversible encephalopathy syndrome or toxicity related with drugs), and acute GVHD 20/48 (41.7%): 55% with stage I (10 patients), 35% with stage II (7 patients), one patients with stage III but good response to treatment and only one patient

developed refractory grade IV causing his death on day 51. None of the patients developed chronic GVHD.



Conclusions: The outcome of our center, the larger HSCT series in Spain is similar to the international cohort and confirms the role of HSCT for children with SCD. Since 2015 we have improved our results, with less toxicity and without mortality.

Disclosure: "Nothing to declare".

P272

Hemoglobin, lactate dehydrogenase, and facit-fatigue normalization rates in patients treated with pegcetacoplan: Results from the pegasus and prince phase 3 clinical trials

B. Mulherin[1,2], M. Yeh[3], M. Al-Adhami[3], J. Savage[3], D. Dingli[4]

[1]Hematology Oncology of Indiana, Indianapolis, United States, [2]Ascension St. Vincent Carmel, Carmel, United States, [3]Apellis Pharmaceuticals, Waltham, United States, [4]Mayo Clinic, Rochester, United States

Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, potentially life-threatening hematologic disease characterized by complement-mediated hemolysis and thrombosis. Pegcetacoplan, an FDA-approved C3-targeted therapy for PNH, controls both intravascular and extravascular hemolysis. This analysis reports hemoglobin, lactate dehydrogenase (LDH), and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue normalization rates in patients from the PEGASUS (NCT03500549) and PRINCE (NCT04085601) phase 3 trials.

Methods: PEGASUS enrolled patients with hemoglobin levels <10.5 g/dL at screening, despite stable eculizumab treatment ≥3 months. Patients were randomized 1:1 to eculizumab or pegcetacoplan (1080 mg subcutaneously twice weekly) during the randomized controlled period (RCP) through Week 16. Patients who received pegcetacoplan (PEG) during the RCP continued with pegcetacoplan monotherapy (PEG-to-PEG) and eculizumab (ECU) patients switched to pegcetacoplan monotherapy (ECU-to-PEG) during the open-label period (OLP) through Week 48. PRINCE compared pegcetacoplan treatment (1080 mg subcutaneously twice weekly) in complement-inhibitor naïve patients (i.e., no eculizumab/ravulizumab within 3 months prior to screening) to standard of care (SoC; excluding complement-inhibitors). SoC patients could escape to the pegcetacoplan group if hemoglobin levels decreased ≥2 g/dL from baseline.

Hemoglobin normalization (≥the lower limit of the gender-specific normal range in the absence of transfusions), LDH normalization (≤the upper limit of normal in the absence of transfusions), and FACIT-Fatigue normalization (≥population norm [43.6]) were determined at Week 16 and 48 (PEGASUS) and Week 26 (PRINCE). Patients who withdrew, were lost to follow-up without providing efficacy data at the specified timepoints, or escaped from SoC to the pegcetacoplan group in PRINCE were classified as non-responders. Safety endpoints included incidences of adverse events (AEs).

Results: At Week 16 (PEGASUS) and Week 26 (PRINCE), pegcetacoplan groups achieved significantly higher rates of hemoglobin, LDH, and FACIT-Fatigue normalization compared to eculizumab and SoC groups (Table). At Week 48, PEGASUS patients who received eculizumab during the RCP achieved similar results to the pegcetacoplan group at Week 16 after switching to pegcetacoplan monotherapy during the OLP (Table). The most common AEs for pegcetacoplan in PRINCE were hypokalemia (11.4%) and dizziness (11.4%). In ≥12.0% of PEGASUS patients, diarrhea (RCP, 22.0%; OLP, 13.2%), abdominal pain (RCP, 12.2%), nasopharyngitis (OLP, 15.8%), upper respiratory tract infection (OLP, 13.2%), hemolysis (OLP, 18.4%), cough (OLP, 13.2%), and headache (OLP, 13.2%) were commonly reported. Injection site reactions were experienced during both trials (PEGASUS: RCP, 36.6%; PEGASUS: OLP, 18.4%; PRINCE, 31.4%).

Conclusions: Overall, pegcetacoplan treatment leads to higher rates of normalization in hemoglobin and LDH, as well as improvements in FACIT-Fatigue in patients with PNH compared to SoC or eculizumab. This further supports the efficacy of pegcetacoplan in improving clinical parameters and quality of life while also demonstrating a favorable safety profile.

[a]Patients with missing data at the specified timepoint were classified as non-responders

Clinical Trial Registry: PEGASUS (NCT03500549): https://clinicaltrials.gov/ct2/show/NCT03500549

	PEGASUS						PRINCE			
	Baseline		Week 16		Week 48		Baseline		Week 26	
	PEG	ECU	PEG	ECU	PEG-to-PEG	ECU-to-PEG	PEG	SoC	PEG	SoC
	N = 41	N = 39	N = 41	N = 39	N = 41	N = 39	N = 35	N = 18	N = 35	N = 18
Hemoglobin Normalization, n (%)	0 (0)	0 (0)	14 (34.1)	0 (0)	10 (24.4)	12 (30.8)	1 (2.9)	0 (0)	16 (45.7)	0 (0)
Lactate Dehydrogenase Normalization, n (%)	17 (41.5)	24 (61.5)	29 (70.7)	6 (15.4)	23 (56.1)	20 (51.3)	0 (0)	0 (0)	23 (65.7)	0 (0)
FACIT-Fatigue Normalizationa, n (%)	9 (22.0)	7 (17.9)	20 (48.8)	4 (10.3)	13 (31.7)	18 (46.2)	10 (28.6)	5 (27.8)	21 (60.0)	2 (11.1)

PRINCE (NCT04085601): https://clinicaltrials.gov/ct2/show/NCT04085601

Disclosure:

1. Brian Mulherin: "nothing to declare".
2. Michael Yeh reports current employment and current equity holder in publicly-traded company for Apellis Pharmaceuticals.
3. Mohammed Al-Adhami and Jessica Savage report current employment with Apellis Pharmaceuticals.
4. David Dingli reports consultancy and advisory board with Alexion, Apellis, Janssen, Milleneum/Takeda, Novartis, R-Pharm, and Rigel and Sanofi; and research grant with Juno and Karyopharm.

P273

Pegcetacoplan treatment in patients with paroxysmal nocturnal hemoglobinuria and baseline hemoglobin levels at or above 10 grams per deciliter: A post hoc analysis

J. Panse[1], N. Daguindau[2], S. Okuyama[3], R. Peffault de Latour[4], P. Schafhausen[5], N. Straetmans[6], M. Al-Adhami[7], T. Ajayi[7], M. Yeh[7]

[1]University Hospital RWTH Aachen, Aachen, Germany, [2]Centre Hospitalier Annecy Genevois, Épagny-Metz-Tessy, France, [3]Denver Health and Hospital Authority, Denver, United States, [4]Hôpitaux de Paris, Université de Paris, Paris, France, [5]University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [6]Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, [7]Apellis Pharmaceuticals, Waltham, United States

Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare and potentially life-threatening disease characterized by chronic complement-mediated hemolysis, thrombosis, and some degree of bone marrow dysfunction. In May 2021, pegcetacoplan, a C3 complement-inhibitor, was approved by the FDA for the treatment of adults with PNH. This post hoc analysis evaluated the efficacy and safety of pegcetacoplan in a subgroup of patients with PNH with baseline hemoglobin levels ≥10.0 g/dL at 16 and 48 weeks from the PADDOCK (NCT02588833) Phase 1b and PEGASUS (NCT03500549) Phase 3 studies.

Methods: PADDOCK evaluated pegcetacoplan therapy (270-360 mg/day subcutaneously) in complement-inhibitor naïve patients. PEGASUS enrolled patients that remained anemic despite stable eculizumab treatment (≥3 months) with hemoglobin levels <10.5 g/dL at the screening visit. Patients were randomized 1:1 to eculizumab or pegcetacoplan (1080 mg subcutaneously twice weekly) during the randomized controlled period (RCP) through Week 16. Patients who received pegcetacoplan during the RCP continued with pegcetacoplan monotherapy through Week 48 of the open-label period.

The post hoc analysis included adult patients with PNH with baseline hemoglobin levels ≥10.0 g/dL and no transfusions within 14 days of the baseline measurement. For PEGASUS, only patients treated with pegcetacoplan in the RCP were included. Mean hemoglobin levels, absolute reticulocyte count (ARC), lactate dehydrogenase (LDH) levels, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores, and percentage of patients with hemoglobin response (≥1 g/dL hemoglobin increase without transfusion) were evaluated at Week 16 and Week 48.

Results: Overall, 12 patients were included in the post hoc analysis: six PADDOCK and six PEGASUS patients (baseline hemoglobin range: PADDOCK, 10.0-11.0 g/dL; PEGASUS, 10.0-10.8 g/dL). In this subgroup of patients treated with pegcetacoplan, improvements from baseline to Week 16 were seen in mean hemoglobin levels, ARC, LDH levels, and FACIT-Fatigue scores (Table). Similar results were also seen at Week 48 in both trials (Table), demonstrating the sustained effect of pegcetacoplan. A majority of patients in this subgroup also achieved a hemoglobin response at Week 16 and Week 48 (Table). Clinically significant increases (≥ 3-points) in mean FACIT-Fatigue scores were observed at both Week 16 and Week 48 (Table) and no thrombotic incidents occurred in this post hoc patient population.

Conclusions: Overall, these results suggest pegcetacoplan can be efficacious long-term in patients with PNH with less severe anemia regardless of prior complement-inhibitor treatment, which results in further clinical improvements in markers of hemolysis and quality of life. The safety profile of pegcetacoplan was similar to results from previous studies.

	PADDOCK			PEGASUS		
	Baseline	Week 16*	Week 48*	Baseline	Week 16	Week 48
	N = 6	N = 5	N = 5	N = 6	N = 6	N = 6
Mean Hemoglobin Levels, g/dL (Normal Reference Range, 12.0-18.0 g/dL)	10.5	12.7	12.0	10.3	12.4	12.6
Hemoglobin Response, n (%)	--	5 (100%)	3 (60.0%)	--	5 (83.3%)	4 (66.7%)
Mean Absolute Reticulocyte Count, x109 cells/L (Normal Reference Range, 30-120x10^9 cells/L)	198.8	115.6	121.4	252.5	70.0	99.8
Mean Lactate Dehydrogenase Levels, U/L (Normal Reference Range, 113-226 U/L)	1,935.8	242.8	241.6	211.6	149.0	220.5
Mean FACIT-Fatigue Scores (General Population Norm, 43.6; Cella D, et al., *Cancer*, 2002;94 (2):528-538)	36.7	45.2	44.0	24.3	38.8	34.0

**One PADDOCK patient stopped dosing at Day 29 and left the study due to physician decision; therefore Week 16 and Week 48 data are out of a total N = 5.*

Clinical Trial Registry: PADDOCK (NCT02588833): https://clinicaltrials.gov/ct2/show/NCT02588833.

PEGASUS (NCT03500549): https://clinicaltrials.gov/ct2/show/NCT03500549.

Disclosure:

1. Jens Panse reports consultancy, honoraria, membership on an entity's Board of Directors or advisory committees with Blueprint Medicines, MSD, Grunenthal, Bristol Myers Squibb, Apellis Pharmaceuticals, and F. Hoffmann-La Roche Ltd; consultancy, membership on an entity's Board of Directors or advisory committees with Amgen; speakers bureau with Chugai and Pfizer; and membership on an entity's Board of Directors or advisory committees, speakers bureau with Novartis, Alexion, and Boehringer Ingelheim.
2. Nicolas Daguindau and Sonia Okuyama: "nothing to declare".
3. Régis Peffault de Latour reports consultancy, honoraria, research funding with Novartis, Pfizer, and Alexion

Pharmaceuticals Inc.; research funding with Amgen; and consultancy and honoraria with Apellis Pharmaceuticals Inc. and Swedish Oprhan Biovitrum AB.
4. Philippe Schafhausen reports membership on an entity's Board of Directors or advisory committees with Blueprint Medicines and Swedish Orphan Biovitrum AB; Honoraria, Membership on an entity's Board of Directors or advisory committees and Speakers Bureau with Alexion and Bristol Myers Squibb; Honoraria and Membership on an entity's Board of Directors or advisory committees with MSD and Novartis.
5. Nicole Straetmans reports membership of advisory committee with Alexion.
6. Mohammed Al-Adhami reports current employment with Apellis Pharmaceuticals.
7. Temitayo Ajayi and Michael Yeh report current employment and equity holder in publicly-traded company with Apellis Pharmaceuticals.

P274

Matched-related bone marrow transplantation for low-risk children with sickle cell disease is an appropriate starting point for allogeneic bmt programs

M.S. Gizhlaryan[1], L.M. Krmoyan[2], I.V. Khalatyan[3], M.G. Anastasiadi[1], Y. K. Hakobyan[1,4], A. H. Farmazyan[1], M. V. Saaryan[1], T. J. Hovhannisyan[1], G.N. Tamamyan[1,5], S.H. Danielyan[1], K.H. Meliksetyan[1], L. Faulkner[6,7]

[1]Hematology Center after Prof. R.H. Yeolyan, Yerevan, Armenia, [2]Hematology Center after Prof R. H. yeolyan, Yerevan, Armenia, [3]Hematology center after prof. R. H. Yeolyan, Yerevan, Armenia, [4]National Institute of Health of the MOH RA, Yerevan, Armenia, [5]Yerevan State Medical University after M. Heratsi, Yerevan, Armenia, [6]Cure2Children Foundation, Florence, Italy, [7]European Blood and Marrow Transplantation Group, Florence, Italy

Background: Both from an ethical and sustainability perspective, centers initiating allogeneic transplantation should start with cases least likely to develop severe transplant-related complications. In countries with a population in the 2-5 million range, e.g. Armenia, having an allogeneic transplantation program is justified but the availability of appropriate start-up candidates at low transplant risk may be limited. On the other hand, children with severe sickle cell disease (SCD) have one of the highest success rates after BMT (*Iqbal et al. TCT 2020*) and may have a very poor quality of life and life expectancy (*Nnodu et al. Lancet Haematol 2021*).

Methods: Suitable initial candidates for allo HCT were defined as children < 10 years at low risk of pre-BMT active infections, poor prognosis with standard care, established indication for BMT, and full understanding and cooperation from their families. Free buccal swab DNA-based HLA typing was offered to families of children with SCD living in Sub-Saharan Africa and the implications of BMT were thoroughly explained. The start-up phase was carried out in collaboration with the Cure2Childen Foundation (C2C) which has been involved in the start-up of 10 HCT units across the Indian subcontinent and the Middle East, were more than 800 allogeneic transplants have been performed over the past 12 years. Intensive and structured collaborations with condition-specific experts combining both online and on-site training was implemented (*Faulkner et al. BMT. 2021*). A total of 4 children aged 1.9 to 10.6 years, three from Nigeria and one from Cameroon, were offered free HCT at the Haematology center after prof. R.H.Yeolyan, Yerevan – Armenia equipped with a state-of-the-art HCT unit used for autologous HCT in adults, and an active pediatric hematology-oncology unit treating high-risk patients with intensive chemotherapy. Families were fully informed that their child would be the initial allo HCT patient of that center but also that he/she would be followed by highly experienced HCT specialists.

Results: All 4 patients are doing well at 164, 158, 39 and 12 days post BMT. Two patients had steroid-responsive acute GVHD grade II and III, one patient had a CVL-associated infection with *staphylococcus aureus*. The initial 2 patients have over 95% donor chimerism and hemoglobin electrophoresis consistent with a sickle cell carrier as their donors, they returned to their home country on days +100 and +106.

Conclusions: This limited experience suggests that within structured cooperation with experienced professionals and organizations, offering BMT to children with SCD may facilitate BMT start-up and create a win-win situation for families whom otherwise would have not had the opportunity to cure their children from a life-threatening disease.

Disclosure: Nothing to declare

P275

t-haplo for SCD: A phase ii trial to assess haploidentical ab t-depleted stem cell transplantation in patients with scd with no available msd, un update

J. Föll[1], K. Kleinschmidt[1], A. Tröger[1], S. Ellinger[1], R. Spachtholz[1], S. Kramer[1], M. Jakob[1], T. Hanafee[1], R. Offner[1], A.-M. Brosig[1], R. Schmidt[2], M. Eyrich[3], D. Wolff[1], S. Corbacioglu[1]

[1]University of Regensburg, Regensburg, Germany, [2]University of Münster, Münster, Germany, [3]University Children's Hospital Würzburg, Würzburg, Germany

Background: Sickle cell disease (SCD) is the most common, inherited red blood cell disorder (RBC) worldwide with significant debilitating and life-threatening complications such as stroke, acute chest syndrome and multiorgan failure. Conventional care has not demonstrated to match long-term survival of healthy peers.

Hematopoietic stem cell transplantation (HSCT) is currently the only curative option for SCD and is the standard of care for the 20% of patients with a matched sibling (MSD) or matched unrelated donor (MUD). For the remaining 80% of patients, alternative curative options are a significant unmet need.

T cell depleted haploidentical HSCT (T-haplo-SCT) is an established transplant modality with major advantages for SCD patients. T-haplo-SCT at least doubles the donor pool, provides an accelerated engraftment, and is associated with a low incidence of acute and chronic graft-versus-host disease (GvHD).

In a pilot series feasibility, efficacy, and low toxicity of ab T cell depleted haplo-SCT for SCD has been shown. In order to provide prospective evidence for non-inferiority of T-haplo-SCT compared to MSD HSCT, a large international, controlled trial has been set up, the T-Haplo for SCD (T-haplo-SCT, EudraCT number: 2018–002652-33).

Methods: The control arm of this stratified trial consists of eligible SCD patients with a MSD. For patients with no MSD, haploidentical relatives will be identified as potential donors according to established criteria and will be enrolled in the T-haplo-SCT experimental arm.

The myeloablative conditioning for both arms consists of Fludarabin-Treosulfan-Thiotepa (FTT) with an ATG-Grafalon based in-vivo immunotherapy upfront in T-haplo-SCT versus prior to day 0 in MSD. Post-transplant immunosuppression consists of MMF and Tacrolimus. The primary endpoint is disease-free (DFS)/GvHD free survival (acute/chronic GvHD 12 months after omission of

immunosuppression). Key secondary endpoint(s) are graft failure, hematological and immune-reconstitution, quality of life (QOL) and fertility.

Results: The trial intends to enroll 212 patients in both arms and started recruitment in June 2021 in Germany. So far nine patients have been enrolled in three active centres. In total 27 centres in Germany, Austria, Italy, UK, Finland, Sweden and other European countries will be activated.

Conclusions: Alternative curative approaches are needed in SCD. This trial intends to analyze in a large group of patients the efficacy and safety of T-Haplo-SCT with standard MSD-HSCT in a direct comparative design. A successful trial will offer a curative option for the majority of patients with no MSD, available at young age prior to development of SCD related irreversible damage and low transplant-related morbidity.

Clinical Trial Registry: ClinicalTrials.gov: NCT04201210, https://clinicaltrials.gov/ct2/show/NCT04201210

EudraCT number: 2018–002652-33,

Disclosure: Nothing to declare

P276

Pre-transplant immunosuppression and related haploidentical hematopoietic cell transplantation in pediatric patients with hemoglobinopathies: Successful engraftment and no severe GVHD

B. Brown[1], D. Ragoonanan[1], M. Waseemuddin[1], B. Shoberu[1], J. Kawedia[1], S. Khazal[1], P. Tewari[1], D. Petropoulos[1], K. Mahadeo[1]

[1]The University of Texas MD Anderson Cancer Center, Houston, United States

Background: Hematopoietic cell transplant (HCT), the only standard curative option for patients with hemoglobinopathies, is limited by lack of unaffected HLA-matched donors, graft failure (GF), and graft-versus-host-disease (GVHD). Pre-transplant immunosuppression (PTIS), reduced toxicity conditioning (RTC) with related haploidentical (r-haplo) HCT has been associated with favorable outcomes among beta thalassemia (B thal) patients; Reports in sickle cell anemia (SCA) are evolving.

Methods: Retrospective study of pediatric patients with severe SCA and B thal who underwent HCT from 2019-2021 at our institution.

Results: Five patients (SCA n = 3, B thal n = 2; Table 1) with median age of 12 (2-16) years received 2 cycles of PTIS with fludarabine/dexamethasone followed by myeloablative r-haplo HCT with busulfan [AUC 18,000 μM.min with median clearance 108 (88-122) ml/min/m^2, and median marrow total nucleated cell dose was 4.65 (1.72-5) x10^8/kg](Figure 1). Median time to neutrophil and platelet engraftment of 50,000/uL was 16 (15-17) and 32 (25-54) days respectively. DFS within 100 days was 100%. No GF, seizures, PRES, >grade II acute or any chronic GVHD were observed. PTIS cycles were well tolerated with asymptomatic viral detection noted upon routine surveillance.

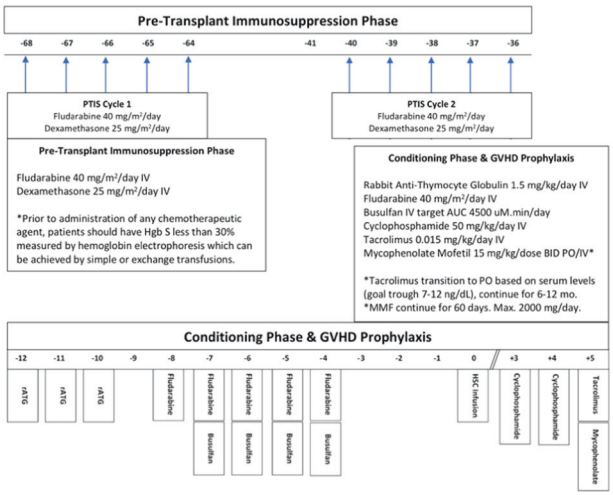
Patient 1 developed post-HCT hemolysis and decreasing chimerism on day 234, received rituximab and bortezomib (1125 mg/m^2 and 5.2 mg/m^2), required no further PRBC transfusions and was 100% donor on follow-up.

Patient 3 had CMV viremia pre-PTIS, developed early CMV reactivation, severe sinusoidal obstruction syndrome, pulmonary fibrosis and subsequently died.

No other patients required ICU admission and median hospitalization was 46 (42-113) days. Median absolute CD19, CD3/4, CD3/8, CD3/56 around 100 days post-HCT were 252 (64-415), 199 (96-282), 158 (50-465), and 5 (1-90) cells/uL, respectively. Neurocognitive testing and neuroimaging in two patients > 1-year post-HCT were unchanged from prior with no evidence of stroke. At median follow-up of 174 (95-898) days, all patients were 100% donor on most recent chimerism.

CMV = cytomegalovirus, Rh = Rhesus antigen, R = recipient, D = donor, TBI = total body iron, LIC = liver iron concentration

Figure 1. Treatment Schema for pre-transplant immunosuppression, reduced toxicity conditioning, and GVHD prophylaxis received by all 5 patients in this report.



Conclusions: We report 100% DFS within 100 days of r-haplo HCT among patients with SCA and B thal. Significantly, there was no GF, severe acute or any chronic GVHD associated with this regimen. Vigilant viral monitoring and mitigation strategies may further improve outcomes.

Disclosure: Nothing to declare.

IMMUNODEFICIENCY DISEASES AND MACROPHAGES

P277

Clinical and immunological outcomes of hematopoietic stem cell transplantation for inborn errors of immunity: 20 years' experience from a monocentric cohort of 220 patients

G. Baresi[1], E. Soncini[1], S. Rossi[1], M. Comini[2], A. Beghin[2], F. Bolda[2], A. Lanfranchi[2], F. Porta[1]

[1]Pediatric Oncohematology and Bone Marrow Transplant (BMT) Unit, Children's Hospital, Spedali Civili of Brescia, Brescia, Italy, [2]Stem Cell Laboratory, Section of Hematology and Blood Coagulation, ASST Spedali Civili of Brescia, Brescia, Italy

Background: Inborn errors of immunity (IEIs) are a heterogeneous group of monogenic defects that manifest as increased susceptibility to infectious diseases, immune dysregulation (autoinflammatory or autoimmune conditions, atopic manifestations), and hematopoietic or solid tissue malignancies. Although conservative treatment may be effective for some IEIs, hematopoietic stem cell transplantation (HSCT) still remains the only curative approach for the vast majority

Methods: Monocentric retrospective analysis of 220 patients treated with HSCT for IEIs at the Pediatric Bone Marrow Transplant Unit of Brescia between year 2000 and 2020. We report post-HSCT complications, evaluating their incidences according to conditioning strategies, use of graft source and donor. The incidence of viral reactivations and their correlation with long-term immunological outcome were also assessed. HSCT immunological outcome has

been evaluated as donor engraftment and lymphocytes' proliferative responses.

Results: On a 20-year experience on 220 IEIs patients, overall survival was 73,2%, with lower survival rate in patients treated with non-myeloablative regimens ($p < 0,001$) or receiving HSCT without preconditioning regimen ($p = 0,047$) rather than those treated with myeloablative conditioning with Busulfan ($p < 0,001$) and Treosulfan ($p = 0,003$) or Reduced Intensity Conditioning (RIC) ($p = 0,004$).

Graft failure occurred mostly in severe combined immune deficiency (SCID) patients, both T-B- and T-B + (31,8% and 22,8% respectively), followed by combined immune deficiency (CID) patients (18,2%) and congenital defects of phagocyte and osteopetrosis (13,6%). Median time of graft failure after first HSCT was 1,8 months.

Overall, immunological reconstitution showed T-cell restoration in 93,7% of patients and B-cell restoration in 87,17% of patients, with median time of replacement therapy of 20,32 months. Use of anti-thymocyte globulin for graft versus host disease (GvHD) prophylaxis resulted also in an higher incidence of immune reconstitution on CD4 + ($p < 0,05$) and CD19 + ($p < 0,05$) cells and a lower median time of immunoglobulin replacement treatment ($p < 0,005$). Patients with mixed chimerism on long-term follow-up were mainly treated for SCID and CID. Patients with previous EBV infection showed a reduced number of CD3 + ($p < 0,001$), CD8 + ($p = 0,005$) and CD19 + ($p = 0,014$) when compared to all the patients who suffered from post-HSCT infectious episodes.

GvHD occurred in 53,3% of all cases, with major prevalence in Wiskott-Aldrich syndrome patients; hepatic veno-occlusive disease occurred in 3,4% of the patients; transplant-associated microangiopathy was witnessed in 2,7% of all patients. Malignancies occurred in 4,7% of patients, lymphoproliferative disorders in 1,35%. Mean age from HSCT in patients presenting malignancy was 5,7 years. Cases of infection at HSCT or viral reactivation as post-HSCT complication mainly affected patients transplanted from cord blood units and treated with RIC conditioning ($p = 0,002$). Using human leukocyte antigens-mismatched donor was associated with a reduction of the average time of reactivation compared to other donors ($p = 0,006$) related to an increased use of immunosuppressive therapies in this subgroup.

Conclusions: Our results confirm the effectiveness of HSCT as a curative treatment for IEIs, with excellent long-term survival rate and effective immunological reconstitution.

Disclosure: No conflict of interest to declare

P278

Machine learning-based approach to predict prognosis of allogeneic hematopoietic stem cell transplantation in primary immunodeficiency disorders

X. Zhai[1], P. Wang[1], X. Qian[1], W. Jiang[1], C. Shen[1], H. Wang[1]

[1]Children's Hospital of Fudan University, Shanghai, China

Background: Allogeneic hematopoietic stem cell transplantation (HSCT) provides an option as life-saving and curative treatment for a subset of primary immunodeficiency disorders (PIDs). However, allogeneic HSCT is accompanied by high rate of morbidity and mortality.To establish and evaluate a model that can predict prognosis of patients with PIDs who received allogeneic HSCT by machine learning.

Methods: Clinical and lab data from 194 pediatric patients with PIDs who received allogeneic HSCT between February 2014 and June 2020 at the Children's Hospital of Fudan University were retrospectively analyzed. Random forest was employed for constructing prediction models with Leave-one-person-out cross-validation. Model performance was evaluated by area under the receiver operating characteristic curve (AUC).

Results: With a median follow-up of 32 months (range 0 to 92 months), estimated overall survival (OS) and disease-free survival (DFS) for the whole cohort at 3 years were 76.3% and 71.6%, respectively. We developed 3 models to predict patients' prognosis after HSCT. The first model was to predict the mortality within about 2 months (early mortality) by 4 variables which achieved an AUC of 0.63 (95% confidence interval [CI], 0.53-0.74). The second model was built to explore the relationship between factors and DFS by cox proportional hazards regression with all variables, significant factors including patients' height and transplantation age. The third model was built for risk event prediction model, consisting of all variables, demonstrated an AUC of 0.68 (95% CI, 0.58-0.78).

Conclusions: The machine learning approach provided clinically reasonable and robust model to predict prognosis of PIDs patients who received HSCT. Our findings may be helpful for transplantation window selection, stem cells selection and supportive care adjustment.

Clinical Trial Registry: No

Disclosure: Nothing to declare

P279

An international multi-centre review of haematopoietic cell transplantation for ripk1 deficiency

R.B Walsh[1,2], P. McNaughton[3], S.H. Lum[3,4], A. Laberko[4,5], D. Balashov[6], H. Al-Mousa[7], Z. Nademi[3,4], T. Flood[3], E. Williams[3], A. Cant[3,4], M. Abinun[3,4], S. Hambleton[3,4], M. Slatter[3,4], A.R Gennery[3,4], S. Owens[3,2]

[1]Royal Victoria Infirmary, Newcastle-Upon-Tyne, United Kingdom, [2]Population Health Sciences Institute, Newcastle-Upon-Tyne, United Kingdom, [3]Great North Children's Hospital, Newcastle-Upon-Tyne, United Kingdom, [4]Translational and Clinical Research Institute, Newcastle-Upon-Tyne, United Kingdom, [5]Immunology, Dmitry Rogachev National Medical Research Center of Paediatric Haematology, Oncology and Immunology, Moscow, Russian Federation, [6]Hematopoietic Stem Cell Transplantation, Dmitry Rogachev National Medical Reserch Center of Paediatric Haematology, Oncology and Immunology, Moscow, Russian Federation, [7]King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia The King Faisal Specialist hospital & Research Centre Shamali, Saudi Arabia

Background: Receptor Interacting Serine/Threonine Kinase 1 (RIPK1) is a widely expressed protein kinase, crucial in inflammatory and cell death signalling. *RIPK1*-knockout mice die perinatally secondary to tissue-wide apoptosis. Recently described in humans, RIPK1-deficiency results in impaired MAPK activation and reduced NF-κB activity causing uncontrolled necroptosis, and cytokine dysregulation, principally raised IL-1β and reduced IL-10. The phenotype includes lymphopenia, severe very-early-onset inflammatory bowel disease (VEOIBD) and arthritis. Haematopoietic cell transplantation (HCT) has been suggested as a potential curative therapy. We previously reported four children that were transplanted in the Great North Children's Hospital (GNCH). To expand upon the role of HCT as a curative option we performed a multi-centre international review of the presenting characteristics and clinical outcomes of transplanted RIPK1-deficient patients.

Methods: A retrospective case review of HCT for 7 children RIPK1-deficiency between 2011-2021 in: GNCH, UK; The King Faisal Specialist hospital & Research Centre (KFSH&RC), Saudi Arabia; Dmitry Rogachev Medical Research Centre of Paediatric Haematology, Oncology and Immunology (DRMRCPHOI), Russia.

Table 1: Abbreviations: Bu: Busulfan; Cy: cyclophosphamide; FT: Fludarabine, treosulfan; FTT: Fludarabine, treosulfan; Flu: Fludarabine; HID: haploidentical donor; MUD: matched unrelated donor; MMUD: mismatched unrelated donor; MSD: matched sibling donor; WB: whole blood.

Patient/ Centre/Year	Age at HCT (years)	Donor and stem cell source	Conditioning and GvHD prophylaxis	Engraftment	Latest donor Chimerism	Outcome
P1- GNCH 2011	12.0	MMUD PBSC	FTT Alemtuzumab CSA/MMF	Neutrophil D + 10 Platelet N/A	WB: 100%	Death D + 46 Multi-organ failure
P2- GNCH 2012	2.9	MUD PBSC	FT Alemtuzumab CSA/MMF	Neutrophil D + 15 Platelet D + 13	WB: 100%	Alive and well
P3- GNCH 2019	5.0	MUD PBSC	FT Alemtuzumab CSA/MMF	Neutrophil D + 12 Platelet D + 14	WB: 100% CD15:100% CD3 + 96%	Alive and well
P4- GNCH 2019	2.6	Maternal HID TCRab/CD19 depleted PBSC	FTT ATG Rituximab No GvHD prophylaxis	Neutrophil D + 10 Platelet D + 16	CD15 + 100% CD3 + 100%	Fed via Percutaneous endoscopic gastrostomy, on immunoglobulin
P5- GNCH 2021	0.4	Maternal HID TCRab-CD19 depleted PBSC	FTT ATG Rituximab No GvHD prophylaxis	Neutrophil D + 14 Platelet D + 18	WB:100%	Death D + 61 Multi-organ failure
P6- KFSH&RC 2020	1.2	MSD Marrow	BuFlu ATG CSA Methotrexate	Neutrophil +13 Platelet D + 31	CD15: 100% CD3: 100%	Alive and well
P7- DRMRCPHOI 2020	1.2	MMUD TCRab/CD19 depleted PBSC	FT + Cy ATG Rituximab Anakinra	Neutrophil D + 10 Platelet D + 10	Graft rejection at 6 months post-HSCT	Second transplant

Results: Table 1 summaries the transplant characteristics and outcomes. P1-P5 presented with lymphopenia, VEOIBD, and arthritis, P6-P7 had VEOIBD alone.

All except one received treosulfan-based conditioning and one had busulfan-fludarabine. Median CD34 + cell dose 17.09 x 10^6/kg (range 6.73-38.2). One event of Grade-I Acute Graft versus Host Disease. Viraemia post-HCT in P3: adenovirus, and P6: adenovirus, rhinovirus, and cytomegalovirus.

Overall survival was 71%. One had secondary autologous reconstitution and underwent a successful second HCT. Most have led relatively disease-free lives. All are free of arthritis and only one has residual effects from IBD; at the most recent follow up P4 continues regular immunoglobulin replacement.

Conclusions: Within the limitations of a retrospective small case series, the findings from this international, multi-centre review support the safety and efficacy of HSCT for RIPK1-deficiency, even with significant pre-transplant comorbidities.

Disclosure: The authors certify they have no relevant financial or non-financial interests to disclose.

P280

Targeted busulfan-based reduced-intensity regimen in mhc class ii deficiency and chronic granulomatous disease: Single center study

M. Essa[1], F. Alrogi[1], R. Abujoub[2], E. Elbashir[2], M. Alsalamah[1], S. Memon[2], A. Alsultan[3]

[1]King Abdullah Specialist Children's Hospital, King Saud bin Abdulaziz University for Health Sciences,King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, [2]King Abdullah Specialist Children's Hospital, Riyadh, Saudi Arabia, [3]King Saud University, Riyadh, Saudi Arabia

Background: Targeted busulfan (45-65 mg/L.h)-based reduced intensity conditioning (RIC) HSCT has been used successfully in chronic granulomatous disease (CGD) (Gungor et al. Lancet 2014). The use of this approach in MHC-class II deficiency (MHC-II-D) has not been reported. We describe our experience using this regimen in MHC-II-D and CGD.

Methods: All patients underwent HLA matched HSCT using the following conditioning regimen: busulfan to target a cumulative dose of 50-70 mg/L.h, fludarabine (180mg/m^2) and serotherapy (ATG for MRD and Alemtuzumab for MUD). GVHD prophylaxis included calcineurin inhibitor till at least day +180 and mycophenolate mofetil till day +100 if no GVHD. Bone marrow was the source of stem cells. Supportive care was consistent among all patients.

Results: A total of 16 patients (8 MHC-II-D and 8 CGD) underwent HSCT at our institution. Patient and transplant characteristics are shown in the Table. All patients engrafted successfully. All CGD patients had normal oxidative burst oxidative test post-transplant without developing infections. All MHC-II-D patients expressed HLA-DR on lymphocytes with no history of post HSCT infections except for one patient who underwent MRD and had secondary graft failure associated with multiple viral infections and the cumulative busulfan AUC was 52 mg/L.h. Acute

GVHD was reported in 2 patients, both of grade II and none had chronic GVHD. There was no mortality reported among our patients. Median whole donor chimerism at day 30-60, 100, 365 post HSCT were 88 (57-100), 78(0-100), 80 (0-100) respectively in MHC-II-D patients and were 94 (53-100), 97 (48-100), 88 (57-100) in patients with CGD. Median lymphocyte donor chimerism at day 30-60, 100, 365 post HSCT were 96(47-99), 84(0-100), 96 (0-100) respectively in MHC-II-D patients and 76 (53-100), 99(53-100), 82(60-100) in CGD patients. Median follow up duration was 1112 days (49-1839) in MHC-II-D patients and 409 days (111-1730) in patients with CGD.

Feature	MHC Class II Deficiency (n = 8) Median (range) or N	CGD (n = 8) Median(range) or N
Age (years)	1.71 (0.5-5.1)	7.14 (5.1-11)
Gender (F/M)	4/4	2/6
MRD/MUD	7/1	7/1
Cumulative Busulfan level (mg/L.h)	57 (50-70)	52.7 (46-62)
Time to Neutrophil engraftment (days)	24(16-30)	20 (17-26)
Time to Platelet engraftment (days)	33(25-65)	18(17-47)
Infused nucleated cell dose (X 10^8/kg)	5.7 (4-14)	4.2 (1.1-7.5)
Infused CD34 cell dose (X 10^6/kg)	12 (2.51-21.9)	7.6 (3.3-10.7)
Acute GVHD Grade II-IV	1 (grade II)	1 (grade II)

Conclusions: HSCT using targeted busulfan conditioning regimen was safe and effective in MHC-II-D and CGD patients. Larger sample size and longer follow up is warranted.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to Disclose in relation to this abstract

P281

Autoinflammatory periodic fever, immunodeficiency and thrombocytopenia (pfti) wdr1-linked. Case report of a successful second haematopoietic stem cell transplantion

L. Garcia Marzo[1], S. Redondo[2], L. Català[1], M. Torrent[1], S. Boronat[1], L. Alsina[3], I. Badell[1]

[1]Hospital de la Santa Creu I Sant Pau, IIB-Sant Pau and Universitat Autónoma de Barcelona, Barcelona, Spain, [2]Hospital de la Santa Creu i Sant Pau. IIB-Sant Pau and José Carreras Leukemia Research Institutes. Universitat Autónoma de Barcelona, Barcelona, Spain, [3]Hospital Sant Joan de Déu, Barcelona, Spain

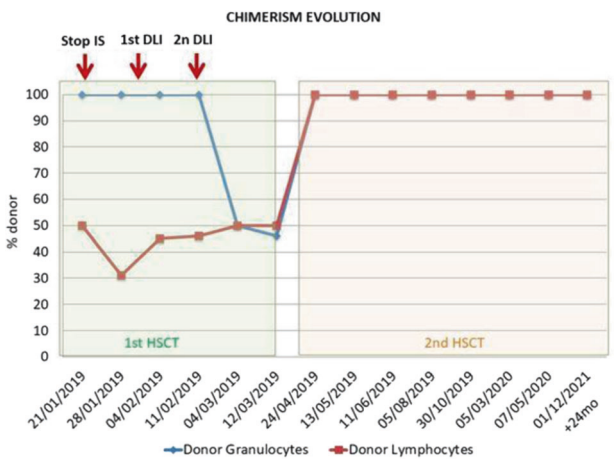
Background: Allogeneic haematopoietic stem cell transplant is currently the only curative treatment for the recently described Autoinflammatory Periodic Fever, Immunodeficiency and Thrombocytopenia disease (PFTI) caused by mutations in WD repeat domain-1 (WDR1). This mutation inherited in an autosomal recessive manner causes abnormalities in actin-interacting protein-1 affecting neutrophil morphology, motility and function.

Methods: We describe the case of a Pakistani 10 years old female from consanguineous parents diagnosed of PFTI from a Spanish tertiary University Hospital. She presented periodic fevers, thrombocytopenia (≤16 x 10^9/mm^3), pyoderma gangrenosum and chronic multifocal osteomyelitis requiring steroids and Adalimumab; accompanied of multiple recurrent infections despite antibiotic prophylactic treatment. A mutation in WDR1 was identified through whole exome sequencing. The family study revealed both parents carried the mutation.

Due to the lack of response to standard treatment she got an allogeneic stem cell transplant from an unrelated identical donor. She received a myeloablative conditioning regimen based on busulfan, fludarabine and rabbit antithymocyte globulin (ATG); and GVHD prophylaxis with cyclosporine and mycophenolate. Four months later she lost the engraftment requiring a second transplant this time from a related identical donor (mother). She received a reduced intensity myeloablative conditioning based on tiotepa, fludarabine, treosulfan and ATG. Cyclosporine was used as GVHD prophylaxis.

	1st HSCT	2nd HSCT
Donor	Identical unrelated donor	Related donor (mother, identical HLA)
Source	Peripheral blood	Peripheral blood
Conditioning regimen	Busulfan, Fludarabine, ATG	Tiotepa, Fludarabine, Treosulfan, ATG
GVHD prophylaxis	Cyclosporine, mycophenolate	Cyclosporine
CD34/kg of receptor	5.98 x 10^6	7.51 x 10^6

Results: After the first transplant, the patient had mixed chimerism (figure 1) progressively decreasing until final rejection of the graft, not improving despite immunosuppression suspension and two donor lymphocytes infusions. After the second transplant she achieved total chimerism and maintains it three years later. Clinically the thrombocytopenia resolved and has not presented new infectious complications or any other symptom of her autoinflammatory disease.



Conclusions: PFTI is a rare recently described disease and there is still not enough data to decide the best treatment for these patients. HSCT may be a valid therapeutic option, allowing restoring the immune system and decreasing their risk of fatal infection episodes. In cases where a related non carrier donor is

not available, a heterozygous donor could be suitable as seen in our patient.

Disclosure: Nothing to declare

P282

Allogeneic HSCT in children with severe treatment-refractory inflammatory bowel disease (IBD)

T. Vallée[1], T. Schwerd[1], S. Immler[2], J. Hubertus[3], I. Meyts[4], D. Kotlarz[1], K. Krohn[5], E. Klucker[1], M.S. Hajji[1], P. Bufler[6], F. Hauck[1], S. Koletzko[1,7], C. Klein[1], E. Lurz[1], M. Albert[1]

[1]Dr. von Hauner Children's Hospital, University Hospital, LMU, Munich, Germany, [2]Klinikum Rechts der Isar, TU Munich, Munich, Germany, [3]Marien Hospital Witten, Katholische Kliniken Rhein-Ruhr, Witten, Germany, [4]University Hospitals Leuven, KU Leuven, Leuven, Belgium, [5]Integrated Social Pediatric Center at the Dr. von Hauner Children's Hospital, LMU, Munich, Germany, [6]Charité Universitätsmedizin Berlin, Berlin, Germany, [7]School of Medicine Collegium Medicum University of Warmia and Mazury, Olsztyn, Poland

Background: Results of a randomized trial suggest that autologous HSCT is effective in adult patients with severe, therapy-refractory Crohn's disease (CD). However, relapse of the disease is frequent. In contrast, allogeneic (allo) HSCT has resulted in long-term cure of CD in few affected patients who underwent HSCT to treat life-threatening haematological malignancy. AlloHSCT is curative for many patients with inflammatory bowel disease (IBD)-like conditions due to monogenic inborn errors of immunity (IEI). Here, we describe alloHSCT in 3 children with severe treatment-refractory IBD in whom no genetic etiology could be found.

Methods: Retrospective analysis of 3 pediatric IBD patients receiving alloHSCT at our institution.

Results: All patients shared the following clinical features: disease manifestation at young age (1-7 years), severe systemic disease including failure to thrive, as well as refractoriness to various anti-inflammatory and immunosuppressive agents and/or steroid-dependency, requirement of surgical intervention, and failure to identify a genetic cause of IEI despite extensive immunophenotyping and whole exome sequencing including parents (trio-approach).

Patient 1 presented at the age of 7 with severe CD-like disease, refractory to anti TNF, 5-aminosalicylic acid (ASA), azathioprine (AZA) and methotrexate (MTX). Rectal stenosis required partial colectomy and permanent ileostomy. At age 18 she underwent alloHSCT (Table). 6 months post HSCT she developed a toxic megacolon of the stenotic and unused colon requiring colostomy. After 6 years of follow-up, she remains in excellent clinical condition, has regained normal weight and is off all medication, but required colectomy 2 years post HSCT.

Patient 2 presented at the age of 15 months with unclassified IBD, refractory to AZA, anti-TNF, MTX, 5-ASA, ustekinumab and ruxolitinib. Ileostomy was performed at the age of 8, followed by alloHSCT at the age of 9. At 1.5 years post HSCT she is in clinical remission, shows good catch-up growth and is off all medication. Endoscopy 6 months post HSCT showed colonic fibrosis with residual stenosis and mild inflammation.

Patient 3 presented at the age of 2 with CD-like disease, requiring ileostomy until the age of 7, refractory to anti-TNF, AZA, MTX, vedolizumab, ustekinumab and cyclosporine A. At age 12, steroid dependency required re-ileostomy, followed by alloHSCT. 1 year post HSCT he is well without clinical signs of intestinal inflammation, shows good catch-up growth and is off all medication.

Conclusions: While it is desirable to define the genetic etiology and immune-mediated pathomechanisms in greater detail, our experience shows that selected patients may benefit even in the absence of a molecular diagnosis. Early alloHSCT may avoid excessive morbidity caused by refractory disease and ineffective treatment.

Table:

Patient	Donor and graft	conditioning	GVHD prophylaxis	GVHD	donor chimerism at last f/u
1	MUD (10/10)	Fludarabine 6x30 mg/m^2 Busulfan tAUC 53770 ng x h/ml Alemtuzumab 3x0.2 mg/kg	CSA/MMF	aGVHD °I (skin)	>95%
2	MUD (9/10)	Fludarabine 5x30 mg/m^2 Treosulfan 3x14.000 mg/m^2 Thiotepa 2x5 mg/kg Alemtuzumab 4x0.2 mg/kg	CSA/MMF	aGVHD °I (skin)	100%
3	MSD (10/10)	Fludarabine 5x30 mg/m^2 Treosulfan 3x14.000 mg/m^2 Thiotepa 2x5mg/kg ATG 3x10mg/kg	CSA/MMF	aGVHD °I (skin)	100%

Disclosure: Nothing to declare.

P283

Wiskott aldrich syndrome caused by novel wasp interacting protein(wip) mutation is associated with juvenile myelomonocytic leukemia - a case report

S. Senthil[1], D. Bonney[2], S. Hughes[2], K. Gilmour[3], A. Thrasher[3], H. Campbell[2], R. Wynn[2]

[1]Royal Manchester Children's hospital, Manchester, United Kingdom, [2]Royal Manchester Children's Hospital, Manchester, United Kingdom, [3]Great Ormond Street Hospital, London, United Kingdom

Background: WASp interacting protein(WIP) mutation is an autosomal recessive disorder, molecularly characterised by premature degradation of Wiskott Aldrich syndrome protein (WASp), since WIP is a stabilising chaperone protein to WASp. It is a rare mutation which has been reported only in three kindreds and 6 patients. WIP deficiency, though expected to classically recapitulate classic Wiskott Aldrich Syndrome(WAS), confers a phenotype with slight differences. We report the clinical features of a seventh case of WIP deficiency. We extend the phenotype of WIP to include transient, Juvenile myelomonocytic leukemia (JMML), which has also previously been reported rarely in WAS.

Methods: Retrospective review of the patient records and laboratory investigations were undertaken.

Results: A 4 weeks old male infant born to consanguineous parents of Libyan ethnicity, was referred with bloody vomiting and was found to have isolated thrombocytopenia. The blood smear confirmed thrombocytopenia, and the platelets were small. Since there was also history of an earlier male sibling death with infection and bleeding tendency, a diagnosis of classical WAS was considered. Flow cytometric studies showed absent WASp but no genetic mutation within the WAS gene was identified, and

immunoblot revealed the presence of severely reduced amount of WASp in the cytoplasm. Panel sequencing showed a novel mutation in WIP, which is a chaperone protein for the WASP. On follow up, at 60 days of life, he developed signs of myeloproliferative disorder with gross hepatosplenomegaly, leucocytosis with monocytosis and a leukoerythoblastic blood picture with circulating myelocytes and erythroid precursors, qualifying for a diagnosis of Juvenile myelomonocytic leukemia according to 2016 WHO criteria. The HbF wasraised for age. The bone marrow-showed expanded left shifted myelopoiesis. The karyotype was normal. The molecular mutations for JMML including NRAS, KRAS, CBL, PTPN11, and NF1 were negative. In view of the underlying life limiting condition, he was worked up for a stem cell transplant.

He had a matched sibling donor transplant with Fludarabine, Treosulfan, Alemtuzumab and Thiotepa conditioning, and with Ciclosporin alone as GVHD prophylaxis at 7 months of age and engrafted after 11 days and became transfusion independent from D25 of transplant. He had a mild steroid responsive gut GVHD which settled down quickly. He remains GVHD free and donor cell engrafted, now several years after HCT, and is fully donor immune-reconstituted and all infection and GVHD prophylaxis has been stopped.

Conclusions: The dysregulation in RAS signalling caused by mutations of NRAS, KRAS, PTPN11 and CBL and NF1 can be found in 90% of the cases of JMML.However, in the remaining 10% of patients without a molecular mutation, the diagnosis is largely reliant on a combination of clinical and laboratory observations, as stringently laid by the 2016 WHO criteria.It has been well recommended to consider Wiskott-Aldrich syndrome in male infants with JMML where none of the 5 canonical molecular mutations of JMML can be identified. Certainly, a strong degree of suspicion should be exercised and investigations for WAS-WIP complex mutations should be actively looked for, particularly in children in JMML where the classic driver mutation cannot be identified.

Disclosure: Nothing to declare.

INBORN ERRORS, GRANULOCYTE AND OSTEOCLAST DISORDERS

P284

Neurological outcome after haematopoietic stem cell transplantation in patients with malignant infantile osteopetrosis

S. Amin-Salehi[1], A. Schulz[1], B. Winter[1]

[1]Universität Ulm, Ulm, Germany

Background: Autosomal recessive osteopetrosis is a rare disease caused by osteoclast malfunction. This results in a lack of bone resorption, thus leading to bone marrow suppression, extramedullary haematopoiesis, and compression of the cranial nerves, foremost the optic and vestibulocochlear nerve. As the disease proceeds, this causes visual and hearing impairment, as well as psychomotor developmental delay. Untreated it leads to death within the first decade of life. For most forms of autosomal recessive osteopetrosis haematopoietic stem cell transplantation is an option for curative treatment.

Methods: We present data from 62 patients with malignant infantile osteopetrosis, transplanted at Ulm University paediatric clinic between 03/1984 and 02/2019. We analyse the relationship between neurological level prior to transplantation and short as well as long term neurological outcomes. We created a questionnaire and a corresponding ranking score scheme to collect longitudinal neurologic data on the following six topics: visual function, optic atrophy, auditory function, cognition, autism spectrum disorder, motor function. Data were gathered during pre- and follow-up appointments at Ulm University paediatric clinic.

Results: Under 62 patients the share of females is slightly elevated. We find no evidence that the age of patients at the beginning of transplantation correlates with the occurrence of an autism spectrum disorder, diminished cognitive abilities, or motor function. There is a strong correlation between age and the occurrence of visual impairment, in particular the atrophy of the optic nerve. By exceeding the age of 12 months, we observe that optic atrophy occurs among all patients in our study. Furthermore, we find that patient's age correlates negatively with auditory function.

Conclusions: We conclude that the earlier beginning of the transplantation affects the neurological outcome of patients positively, especially concerning visual and auditory function. Hence, a precocious diagnosis and early treatment are of high prognostic relevance.

Disclosure: Nothing to declare

P285

Early allogeneic HSCT for mitochondrial neurogastrointestinal encephalomyopathy

A.E. Myhre[1], M. Hovland[1], T. Gedde-Dahl[1]

[1]Oslo University Hospital, Oslo, Norway

Background: Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disease due to TYMP mutations that result in thymidine phosphorylase (TP) deficiency, leading to accumulation of nucleosides thymidine and deoxyuridine and subsequent mitochondrial dysfunction. Patients develop clinical manifestations of peripheral and autonomous neuropathy and myopathy. MNGIE is uniformly progressive and fatal, leading to premature death due to cachexia and infections. Normal leukocytes and thrombocytes have abundant TP, and it can therefore be permanently replaced through allogeneic HSCT.

Methods: We present the case of a 23 years old man who presented with peripheral neuropathy. Diagnostic work-up revealed ptosis, ophtalmoplegy, leukencephalopathy and exercise-induced rhabdomyolysis. He was functioning normally, but was severely underweight (BMI 14.2 kg/m2) with evidence of malabsorption, but no gastrointestinal autonomous dysfunction, and intestinal biopsies were normal, consistent with an early stage of disease. He was homozygous for TYMP-mutation (c.866A > C) with complete TP deficiency and increased urine excretion of thymidine.

He was transplanted with a BMSC graft from an unrelated male 10/10 HLA-matched donor after RIC (fludarabine 160 mg/m2 and busulfan 6,4 mg/kg intravenously). GvHD prophylaxis was antithymocyte globuline 4 mg/kg, cyclosporine and methotrexate. Medications with potential toxic effects on mitochondria were avoided if possible.

Results: Post-transplantation follow-up was uneventful. Urine excretion of thymidine immediately fell to physiological levels, where it has remained. Neutrophil engraftment occurred on day +10, and by 3 months he achieved full unfractioned donor chimerism (>95%), but persistent mixed T-cell chimerism, which has been steadily improving after tapering of cyclosporine and subsequent removal at 10 months.

At 17 months after transplantation he is well, has resumed full-time studies and working part-time. His body weight has increased slightly. Peripheral polyneuropathy and leukencephalopathy are unaltered and does not interfere with his everyday life. He has not experienced acute or chronic GvHD or other significant transplant related complications.

Conclusions: Allogeneic HSCT was successfully performed in an adult MNGIE patient with malabsorption but no evidence of severe gastrointestinal involvement.

Restoring TP through HSCT may repair mitochondrial function in MNGIE and improve clinical symptoms over time. However, there is conflicting data to support whether symptoms of progressive disease can be improved or not, and irreversible gastrointestinal changes, such as loss of interstitial Cajal cells, cannot be amended.

Mortality after HSCT is reported in the literature as high as 62,5%, either due to TRM or progression of disease. Therefore, HSCT should be performed early, before irreversible gastrointestinal manifestations occur, to minimize risk and maximize recovery potential.

Disclosure: Anders Myhre: Advisory board Takeda.

Tobias Gedde-Dahl: Advisory board Takeda, Novartis, Incyte.

INFECTIOUS COMPLICATIONS

P286

The management of cytomegalovirus infection among ebmt centers: A survey from infectious diseases working party of ebmt

S. Cesaro[1], G. Tridello[1], L. Wendel[2], N. Knelange[2], D. Averbuch[3], M. Mikulska[4], P. Ljungman[5], R. de la Camara[6], J. Styczynski[7]

[1]Azienda Ospedaliera Universitaria Integrata, Verona, Italy, [2]EBMT Clinical Study Unit, Leiden, Netherlands, [3]Hadassah University Medical Center, Jerusalem, Israel, [4]Ospedale San Martino, University of Genova (DISSAL), Genua, Italy, [5]Karolinska University Hospital, Huddinge, Sweden, [6]Hospital de la Princesa, Madrid, Spain, [7]University Hospital, Collegium Medicum UMK, Bydgoszcz, Poland

Background: In the last decade, many studies have tried to introduce innovations in the diagnosis and treatment of cytomegalovirus (CMV) infection and disease after allogeneic stem cell transplantation (allo-SCT). The IDWP undertook in 2020 a survey to describe the approach to the management of CMV infection among EBMT centers.

Methods: A questionnaire was mailed to 579 EBMT centers performing allogeneic stem cell transplantation (SCT) in January 2020 with the deadline for the response by April 2020. A reply was returned by 180 centres (31%). The data relate to CMV infections occurred in 2019.

Results: Among responding centers, 58%, 24% and 18% were adult, pediatrics, and mixed adult/pediatric transplant centers, respectively.

CMV surveillance: CMV-DNAemia by PCR in blood plasma or serum was used in 175 (97%) of centers to diagnose CMV infection (missing data 1%); moreover, in 80 centers (46%) CMV-DNAemia was also tested at pre-transplant work-up. The patient CMV monitoring was performed in all types of allo-SCT in 97% of centers, mostly once (61%) or twice (30%) a week. The duration of CMV surveillance was limited to day + 100 in 27% of centers while in the remaining centers it continued for at least 6 months post-SCT or was modulated on duration of GVHD, immunosuppressive therapy and/or immune recovery.

CMV prophylaxis: in high-risk patients (R-or-D-CMV+), drug prophylaxis was used in 56% of centers with higher prevalence in adult/mixed than pediatric centers (62% and 61% vs. 37%), with the following drugs: letermovir, 61.4% (almost exclusively in adult patients), acyclovir/valacyclovir, 18.8%, gancyclovir/valgancyclovir, 7.9%, foscarnet 1%, CMV-CTLs, 1%, other (several combinations), 9.9%.

CMV infection and pre-emptive treatment: the median annual number of pre-emptive treatments for CMV infection was 12 per center, range 1-600. The drugs used as first-line treatment were: gancyclovir/valgancyclovir in 79%, foscarnet in 4 %, gancyclovir + foscarnet 13%, other or missing 4%; CMV-immunoglobulin were used together with drug prophylaxis in 3.3% of centers. The most frequent threshold to start pre-emptive therapy was: CMV-DNAemia of any positivity, $>10^2$, $>10^3$ and $>10^4$ copies/ml in 12.8%, 16.1% 56.7%, 8.4%, other 6% for unmanipulated allo-SCT, Pre-emptive treatment lasted until 2 consecutive CMV-DNAemia negative tests (76.7%), or CMV-DNAemia inferior to the threshold used to start treatment (14.4%), or other (9.9%).

CMV disease and treatment: 64.4% (116) of centers diagnosed ≥ 1 episode of CMV disease (median 2, range 1-50) for a total of 605 episodes, classified as proven, 217 (35.8%), probable, 183 (30.2%) and possible (33.8%). The first-line treatment used was gancyclovir/valgancyclovir, gancyclovir+foscarnet, foscarnet in 71.6%, 15.5%, 3.3% of centers, respectively (missing 9.6%). CMV-immunoglobulin were used in 7.2%. Fifty centers (28%) declared to use CMV-CTL in case of rescue treatment or in combination with antiviral drugs. CMV drug resistant infections were reported in 70 of 180 centers (median 2 episodes/center).

Conclusions: PCR-CMV-DNAemia monitoring and pre-emptive therapy remain the key interventions-More than half of centers treating adult patients have adopted the policy of letermovir prophylaxis. Further studies are needed to assess how prophylaxis impacts the burden of CMV infection in allo-SCT.

Disclosure: No conflict of interests to declare

P287

Safety and immunogenicity of a meningococcal recombinant vaccine in allogeneic hematopoietic cell transplantation: A prospective study with a 12 months follow-up

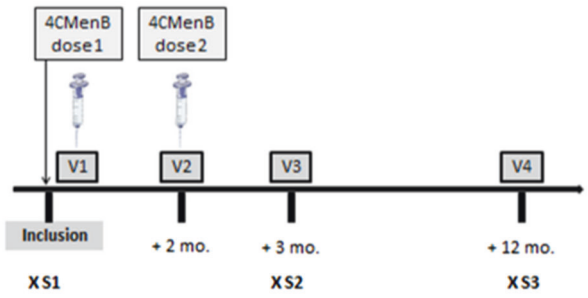
C. Robin[1], R. Redjoul[1], A. Terrade[2], A.-E. Deghmane[2], L. Cabanne[1], M.-K. Taha[2], C. Cordonnier[1]

[1]Henri Mondor Hospital, Creteil, France, [2]Pasteur Institute, Paris, France

Background: Meningococcal ACWY and B vaccinations are recommended after HCT. However, there is so far no data on MenB vaccination after HCT. We evaluated the safety and immunogenicity of the 4CMenB vaccine (Bexsero®) and the persistence of response 12 months later in allogeneic adult, HCT recipients (NCT03509051).

Methods: Patients were eligible from 6 months post-HCT, if they had no relapse of their underlying disease, and had not received antiCD20 antibodies since >6 months. They received 2 doses of 4CMenB at 2 months interval. Adverse events (AE) were prospectively collected. Blood samples were collected before the first vaccine dose (V1), 1 month after the second dose (V3), and 12 months after V1 (V4)(Fig. 1). Sera were immediately frozen at -80°C. The serum bactericidal activity (SBA) using human complement (hSBA) was assessed against fHbp, NadA, PorAP1.4 and NHBA antigens (Caron, LID 2011). The response was defined by ≥ one of these two criteria for ≥ one of the 4 vaccine antigens: (1) In patients with a hSBA titer <4 on V1: a titer ≥4 after vaccination; (2) In patients with a hSBA titer ≥ 4 on V1: at least a x4 increase from baseline. hSBA titers were described as % of responders. Geometric mean titers (GMT) [95%CI] were also calculated. Quantitative and qualitative variables described with median (ranges) and proportions respectively were compared with Kruskal Wallis test and chi-2 or Fisher test as appropriate. Univariate and multivariate analysis were performed using logistic regression.

Figure 1: Study design



V: visit. S: serum. X: Antibody assessment. The timing of the visits is expressed in months from inclusion which could be done from six months after transplant

Results: 40 patients were included a median of 2.14 years post-transplant. The median age at transplant was 52 y. Most patients had acute leukemia and were transplanted with an unrelated donor. Four patients had GvHD at inclusion, 8 were receiving immunosuppressive drugs. At V1, most patients had hSBA titers < 4 (93%, 100%, 95% and 90% for fHbp, NHBA, NadA and PorAP1.4, respectively) and 8/40 (20%) had titers ≥ 4 on ≥ 1 antigen.

The proportion of patients with a titer ≥ 4 was significantly increased between V1 and V3 (primary objective) for fHbp, NadA, and PorA but not for NHBA for which only 6/40 (15%) patients were responders. At V3, 36/40 (90%) patients were responders to ≥ 1 antigen, with 27 patients (67.5%) responding to 2 (25%), 3 (30%) and 4 (12.5%) antigens. At V4, 23/37 (62.2%) patients were still seroprotected although at lower titers and mainly against NadA (51.4%). Moreover, GMT did not differ significantly between V1 and V4 for fHbp, NHBA and PorA antigens suggesting rapid decline of hSBA titers. Age and CD4 counts were associated with a response at V3 in univariate analysis. AE were all minor, without any severe AE.

Conclusions: Considering a response rate of 90% for ≥ one vaccine antigen and the favorable safety data, our findings fully support the 4CMenB vaccination of HCT recipients from 6 months after transplant with 2 doses. However, a booster dose may be required. Meningococci B vaccination should be combined with ACWY vaccination for which data are already available.

Clinical Trial Registry: NCT03509051

Disclosure: none

P288

Impact of fluoroquinolone prophylaxis on bloodstream infection incidence in the first 30 days after allogeneic stem cell transplantation

C.M. Dellacasa[1], M. Cerrano[1], C. Secreto[2], S. Corcione[2], S. Butera[3], E. Santambrogio[4], L. Giaccone[2,1], I. Dogliotti[1], G. Gabrielli[2], J. Gill[2], S. Manetta[2], S. Zompi[1], A. Busca[1]

[1]AOU Città della Salute e della Scienza di Torino, Torino, Italy, [2]Università degli Studi di Torino, Torino, Italy, [3]Ospedale Maggiore di Chieri, Chieri, Italy, [4]AO Santa Croce e Carle, Cuneo, Italy

Background: The role of antibacterial prophylaxis in the pre-engraftment phase of allogeneic haemopoietic stem cell transplantation (HSCT) is still a matter of debate: prophylaxis may reduce bloodstream infection (BSI) incidence, but may also increase the rate of multidrug resistant (MDR) bacteria.

Based on these observations, fluoroquinolone (FQ) prophylaxis has been withheld in our Center from April 2016 onward.

The aim of this retrospective single center study was to evaluate the impact of the omission of FQ prophylaxis on the incidence of BSI in the first 30 days after HSCT.

Methods: Overall, 592 consecutive patients who received an allogeneic HSCT between January 2011 and August 2021 were included in the study. Patients who received an antibacterial prophylaxis other than FQ or were given broad spectrum antibiotic treatment at the time of transplant were excluded from the analysis.

Among the 444 evaluable patients, 195 received FQ prophylaxis (group A) while 249 did not (group B).

Baseline characteristics were superimposable in the two groups, except for bone marrow as stem cell source (23.1% in group A and 9.2% in group B, $p < 0.001$) and reduced intensity conditioning regimen (14.8% in group A and 21.7% in group B, $p = 0.043$). Median duration of neutropenia was 16 days in both group A (range 9-49) and group B (range 4-35).

Results: Overall, BSI was detected in 100 patients (22.5%), 32 (16.4%) in group A and 68 (27.3%) in group B ($p = 0.008$). Cumulative incidence of BSI at day 30 post transplant was 16.4% in group A and 27.5% in group B. In multivariate analysis, FQ prophylaxis was the only factor associated with the risk of BSI (SHR 0.59; 95% IC 0.39-0.91; $p = 0.016$).

Nine patients in group A (4.6%) and 41 patients in group B (16.5%) developed a gram-negative BSI ($p < 0.001$); 20 patients in group A (10.3%) vs 17 patients (6.83%) developed a gram-positive BSI ($p = 0.13$); a polymicrobic BSI occurred in 13 patients, 3 in group A (1.5%) and 10 in group B (4%) ($p = 0.1$).

Gram-negative bacteria accounted for 28.1% (n = 9) of BSI in group A and 60.3% (n = 41) in group B ($p = 0.005$). Overall, 8 patients in group A (25%) and 6 patients in group B (8.8%) developed MDR-gram negative BSI, unveiling a marginally significant trend towards the reduction of MDR gram-negative BSI after withholding FQ prophylaxis ($p = 0.06$).

Death attributable to BSI occurred in 4 of 100 patients (4%); 2 in group A and 2 in group B. Neither antibacterial prophylaxis ($p = 0.56$) nor the occurrence of BSI ($p = 0.9$) had a significative impact on overall survival (OS).

Conclusions: The results of our study show an increased rate of BSI, mostly caused by Gram-negative bacteria, in patients who did not receive FQ prophylaxis, with no impact on OS. By contrast, a lower incidence of MDR gram-negative BSI has been observed in patients not receiving FQ prophylaxis. Additional prospective studies are needed to confirm our data.

Disclosure: Nothing to declare

P289

Endothelial complications after allogeneic stem cell transplantation (HSCT) in patients with resolved covid 19 disease

C. Niederwieser[1], B. Weber[2], M. Reichard[1], N. Gagelmann[1], S. Ajib[2], V. Schlipfenbacher[2], Z. Zeng[2], F. Lang[2], D. Janson[1], C. Wolschke[1], F. Ayuk[1], G. Bug[2], N. Kröger[1]

[1]UKE Hamburg Eppendorf, Hamburg, Germany, [2]Goethe University Frankfurt/Main, Frankfurt am Main, Germany

Background: We recently reported favorable short-term outcome in patients with leukemia after HSCT and a history of COVID-19[1]. Considering the key role of endothelial-damage in HSCT causing transplant associated thrombocytopenic-microangiopathy (TA-TMA), veno-occlusive disease (VOD)/SOS and even more in COVID-19[2], we analyzed incidence and outcome of endothelial complications after HSCT following COVID-19 in 14 patients.

Methods: Patients with advanced leukemia and a history of COVID-19 were transplanted at the University-Medical-Center-Hamburg-Eppendorf UKE (n = 9) and University-Hospital-Frankfurt (n = 5). Patients experienced COVID before, during or after induction chemotherapy with persistent lung infiltrates in nine and required ICU admission in six patients. The time interval from diagnosis of COVID-19 to HSCT was median 143 (46-212) days and resolution of COVID-19 to HSCT 94 (35-136) days. Patients (median age 52.5 (33-69) years) had high risk AML (n = 8), in PR or higher CR (n = 2), high risk ALL (n = 3) or blast crisis of CML (n = 1). Donors were matched related (n = 3), haploidentical related (n = 4), matched unrelated (n = 4) or mismatched unrelated (n = 3). All patients received fludarabine in combination with total body irradiation (8 or 12 Gy, n = 7), thiotepa/busulfan (n = 3), melphalan (n = 3) or treosulfan (n = 1) + ATG (n = 10). TA-TMA was defined as previously described[3]. VOD was diagnosed according to Seattle-criteria.

Results: After a median follow-up of 221 (range 69-492) days, 11 (79%) of the 14 patients are alive. One patient died on day +146 from AML relapse, one from cardiac (d + 208) and one from liver complications (d + 179). Three female patients (out of 8 female and six male patients) had VOD, TA-TMA or both, all of them associated with polyserositis, a median of +67.5 (9-242) days after HSCT. All three are alive a median of +451 (range 221-492) days.

One patient(H1) with a history of severe pulmonary COVID-19 developed histologically confirmed TA-TMA eight months post-haplo HSCT. Cytomegalovirus (CMV) reactivation, bacterial uro-genital and clostridium difficile infection may have triggered TA-TMA. After successful treatment of infections, the patient was readmitted for CMV reactivation and polyserositis.The patient is alive 492 days after HSCT.

One patient(H4) recovered from COVID-19 after treatment with reconvalescent serum (7 d BID) and received a haplo-identical HSCT. On day +59 post-HSCT, CMV reactivation, BKV cystitis, polyserositis and ascites were detected. Pathological liver enzymes and liver histology confirmed VOD, which was treated successfully with defibrotide. The patient is alive 451 days post-HSCT.

One patient(F4) with AML had a HSCT from a mismatched (9/10) unrelated donor after COVID-19. The patient was diagnosed with VOD/SOS (day + 9) and treated successfully with defibrotide. On day +76, EBV reactivation, BKV cystitis and TA-TMA was diagnosed. The patient was treated with eculizumab, but remained on dialysis (+221 days).

Conclusions: After an uneventful early post-transplant period, three patients out of 14 were diagnosed with severe endothelial-damage and polyserositis. Interestingly, all patients were female, transplanted from non-matched donors and had viral/bacterial infections. The incidence of TA-TMA observed in this two-center study is 21% and in the range of complications observed after COVID and HSCT alone[2,4]. This observation should be confirmed in a larger cohort of patient receiving allogeneic HSCT after resolution of COVID-19.

Clinical Trial Registry:

References

1. Christopeit M, Reichard M, Niederwieser C, et al. Allogeneic stem cell transplantation in acute leukemia patients after COVID-19 infection. Bone Marrow Transplant. 2021;56:1478–81. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7871512/pdf/41409_2021_Article_1225.pdf).

2. Tiwari NR, Phatak S, Sharma VR, Agarwal SK. COVID-19 and thrombotic microangiopathies. Thromb Res 2021;202:191–8.

3. Dandoy CE, Rotz S, Alonso PB, et al. A pragmatic multi-institutional approach to understanding transplant-associated thrombotic microangiopathy after stem cell transplant. Blood Adv 2021;5:1–11.

4. Pagliuca S, Michonneau D, Sicre de Fontbrune F, et al. Allogeneic reactivity-mediated endothelial cell complications after HSCT: a plea for consensual definitions. Blood Adv 2019;3:2424–35.

Disclosure: No conflict of interest, G. Bug: Honoraria from Jazz Pharmaceuticals

P290

BK polyomavirus-loads reflect naked dna fragments affecting quantification and identification of variant immunodominant LTag and Vp1 epitopes in hct patients with bkpyv-associated hemorrhagic cystitis (bkpyv-hc)

K. Leuzinger[1,2], K.J Frank[1], F. Weissbach[1], B.S Oettli[2], M. Wilhelm[1], A. Kaur[1], H.H Hirsch[1,2]

[1]University of Basel, Basel, Switzerland, [2]University Hospital of Basel, Basel, Switzerland

Background: High-level BKPyV replication in patients after allogeneic hematopoietic cell transplantation (HCT) indicates failing immune control and increased risk of hemorrhagic cystitis. We investigated BKPyV-DNA genome loads in plasma and urine of HCT-patients, and sequenced large tumor-antigen (LTag) or capsid Vp1 epitopes predicted to mediate CD8 T-cell killing and antibody neutralization.

Methods: BKPyV-loads and human genome-loads were assessed with and without DNAse-I digestion prior to nucleic acid extraction in longitudinal urine (N = 61) and plasma samples (N = 64) from 17 HCT-patients with detectable BKPyV and hematuria (grade-1 N = 8; grade-2 N = 3; grade-3 N = 4; grade-4 N = 2). For BKPyV, three quantitative nucleic acid tests (QNAT) with different amplicon lengths (88bp, 133bp and 239bp) were used (*Leuzinger et al., 2019 J Clin Virol 121:104210 PMID:31759262*). Variation in BKPyV genome sequences was determined by next-generation-sequencing with different amplicon lengths (250bp, 1000bp and 5000bp).

Results: DNAse-digestion resulted in significant reductions of >90% of urine and plasma BKPyV-loads in HCT-patients with all three amplicon sizes ($p < 0.001$; **Figure 1**). Significantly higher BKPyV-loads were obtained with the 88bp compared to the 133bp and 239bp BKPyV QNAT in both urine and plasma samples ($p < 0.001$; **Figure 1**).

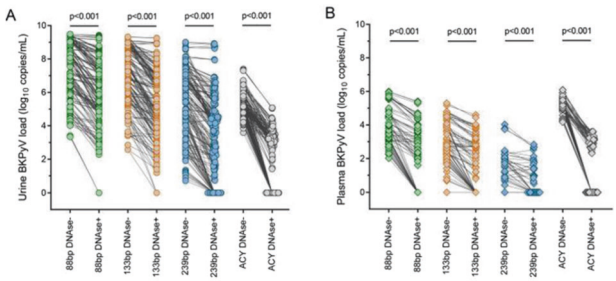


Figure 1. Assessment of BKPyV genome protection and fragment length.
DNAse-I sensitivity of urine (A) and plasma (B) BKPyV-loads using the indicated BKPyV-QNATs with different amplicon lengths (88bp, 133bp and 239bp), as well as of cell-free human genomic DNA using the aspartoacylase (ACY) QNAT (p-avlues by Mann-Whitney U-test).

Little sequence variation was determined by NGS in LTag and Vp1 when using large amplicons of 1000bp and 5000bp. In contrast, NGS of 250bp amplicons identified LTag and Vp1 minority variants with frequencies in up to 15%. This included non-synonymous aa-exchanges in immunodominant LTag-9mer T-cell epitopes reflecting different BKPyV-genotypes (I and IV) as well as genotype-independent variants. For example, genotype-IV dependent variation in the LTRDPYHTI LTag 9mer T-cell epitope altered HLA-A/HLA-B-binding scores, predicting reduced 9mer

epitope presentation and escape from T-cell activation (**Table 1**). Genotype-IV dependent H244Y/T245I exchange has been previously reported in 22.3% of LTag sequences in the NCBI protein database (*Leuzinger et al., 2020 Viruses 12:1476 PMID:33371492*). Moreover, we detected mutations at highly conserved positions in the BC-loop of Vp1 (A72, E73, E82), previously associated with escape from neutralizing antibodies.

Table 1. BKPyV genotype-I and -IV in 9mer T-cell epitopes and predicted HLA-A/HLA-B-binding scores.

BKPyV genotype-I 9mer aa sequence	HLA type	HLA-A /HLA-B binding score2	BKPyV genoytpe-IV 9mer aa sequence	HLA type	HLA-A / HLA-B binding score2
LTRDPYHTI1	HLA-B*51:01	0.416	**LTRDPYYII1**	HLA-B*51:01	0.234↓
	HLA-B*08:01	0.208		HLA-B*08:01	0.075↓
	HLA-B*07:02	0.128		HLA-B*07:02	0.038↓
	HLA-A*24:02	0.039		HLA-A*24:02	0.020

Amino acid, aa; human leukocyte antigen, HLA

1. Amino acid starting position 238 (BKPyV-WW numbering [acc. no. AB211371.1])
2. HLA binding was predicted with the Immune Epitope Database and Analysis Resource tool (http://tools.iedb.org/main/).

Conclusions: Urine and plasma BKPyV-loads in HCT-patients are mostly derived from DNAse-I sensitive, non-encapsidated BKPyV-DNA fragments of <100bp. This reduced diagnostic sensitivity by QNAT with larger amplicon-targets leading to under-quantification of BKPyV-loads. Moreover, BKPyV-diversity may be underestimated including immune escape in immunodominant LTag and Vp1 epitopes from CD8 T-cell killing (*Wilhelm et al., 2020 J Infect Dis 223:1410 PMID:32857163*) and antibody mediated naturalization. Importantly, the results change current models by indicating that BKPyV-loads in plasma are a direct marker of viral replication and cell/tissue damage releasing genomic-fragments and not virions, and hence being not susceptible to neutralizing antibodies. We discuss the implications in an updated model on BKPyV replication and disease for treatment approaches.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare

P291

The antibody response to bnt162b2 or mrna-1273 vaccines in allotransplant recipients depends on the existing response to endemic human coronaviruses and previous atg therapy

T.H.A. Tvedt[1], T. Gedde-Dahl[1,2], Ø. Bruserud[3], I.W. Abrahamsen[1], F. Lund-Johansen[4], A.E. Myhre[1]

[1]Oslo University Hospital Rikshospitalet, Oslo, Norway, [2]Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [3]University of Bergen, Bergen, Norway, [4]Oslo University Hospital, Oslo, Norway

Background: Endemic human coronaviruses (HCoV) are frequent causes of respiratory tract infections after allogeneic stem cell transplantation, and preexisting HCoV immunity possibly protects against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections because of cross-reactive antibodies binding to the spike protein. We therefore investigated whether pre- and postvaccination levels of antibodies directed against various community-acquired respiratory viruses correlates with antibody responses following SARS-CoV-2 vaccination.

Methods: Serum samples were collected from allotransplant recipient at Oslo University Hospital and analyzed for SARS-CoV-2 specific antibodies directed against the spike protein receptor binding domain (RBD), full-length spike protein and nucleocapsid. Antibody levels were also determined for four endemic human corona viruses (HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1) as well as four influenza A subtypes (H1N1, H3N2, H5N1, H9N2), Rhinovirus and Epstein-Barr-virus.

Results: The study included 16 females and 15 males (median age 58 years, range 21-73years) who had received at least two doses of mRNA-1273 (Moderna) or BNT162b2 (BioNTech/Pfizer). The median time from transplant to the second vaccine was 371 days (range 149-2443 days, IQR 715); 10 patients received systemic immunosuppression at the time of the first vaccination. One patient had pre-existing borderline protective levels of antibodies against RBD and spike protein without any history of coronavirus infection or increased levels of nucleocapsid antibodies. Twenty-five patients showed a detectable RBD response; which was classified as a strong response for 18 individuals. Preexisting levels of antibodies against endemic corona viruses varied considerably and were highest for HCoV-229E and HCoV-OC43. Prevaccination antibody levels against HCoV-229E showed a significant difference only with the full length spike protein vaccine response. The post-vaccination HCoV-229E antibody levels showed both a weak correlation with the post-vaccination RBD response (Kendall's τ 0.33/$p = 0.016$) and a moderate correlation with the full spike protein response (Kendall's τ 0.43/$p = 0.003$). No correlations with antibody levels for influenza A subtypes, EBV or Rhinovirus were observed. Both previous ATG exposure and short time from transplant to first vaccination were associated with weaker vaccine responses and lower levels of full-length antibody levels. Ongoing systemic immunosuppression at time of first vaccination and chronic GVHD were not associated with lower vaccine response.

Conclusions: 18 of 31 allotransplant recipients showed a strong antibody response to SARS-CoV-2 vaccination. The antibody response was associated with pre-vaccination antibody levels to HCoV-229E, previous ATG therapy and time from transplant to vaccination. Our study suggest that this vaccination regimen for allotransplant recipients should be individualized and possibly be guided by the RBD antibody responses.

Clinical Trial Registry: N/A

Disclosure: THAT: Advisory Board/ Honorary: Sanofi, Novartis, Sobi, Janssen

AEM: Advisory Board: Takeda

P292

Reconstitution of *bacteroides fragilis* and *faecalibacterium prausnitzii* associated with clinical response in acute intestinal GVHD

O. Goloshchapov[1], A. Chukhlovin[1,2], E. Bakin[1], O. Stanevich[1], M. Suvorova[3], V. Gostev[2], O. Glotov[2], M. Kucher[1], R. Klementeva[1], M. Goloshchapova[1], L. Zubarovskaya[1], I. Moiseev[1], A. Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, St. Petersburg, Russian Federation, [2]Pediatric Research and Clinical Center of Infectious Diseases, St. Petersburg, Russia, St.Petersburg, Russian Federation, [3]Explana Laboratory, St.Petersburg, Russian Federation

Background: Fecal microbiota transplantation (FMT) is now considered a potentially efficient option for microbiota reconstitution and recovery from different intestinal syndromes including

intestinal GVHD. Hence, the **aim** of present study was a search for informative bacterial markers associated with clinical response to FMT in severe gut GVHD.

Methods: The prospective, non-randomized study enrolled 27 children and adults (1 to 52 years) with intestinal form of GVHD (acute, chronic, or overlap syndrome) following allogeneic HSCT. FMT was used in the cases of severe refractory GVHD. In most cases, FMT was performed using ingestible gelatin capsules containing either third-party fecal biomaterial, or placebo in controls. On D + 3, D + 16, D + 30, D + 60, and D + 120 after FMT, 16 major bacterial groups were assayed in fecal DNA samples using real-time multiplex PCR (Colonoflor test system). Biodiversity of the bacterial microbiota was also studied by means of 16S rRNA sequencing (NGS platform). Clinical response was assessed by common scales for intestinal syndrome and GVHD evaluation.

Results: Complete response, according to Bristol intestinal scale, was registered in approx. 50% of cases following FMT, being less common in the placebo group (13%) . Multiplex PCR of fecal DNA has shown significant recolonization of fecal microbiota after FMT. Such positive shifts were demonstrable since D + 30 for total microbial mass ($p = 0.002$); *Escherichia coli* ($p = 0.001$); *Bacteroides fragilis group* ($p = 0.05$); *Faecalibacterium prausnitzii* ($p = 0.005$). In particular, the median copy numbers of *B.fragilis group and F.prausnitzii* showed sufficient increase along with evidence of clinical response after FMT. Meanwhile, a significantly lesser recolonization with these bacterial species was revealed in the patients with poor clinical response to FMT. Over 120 days of observation, the subgroups with complete response *versus* partial/no response showed significant increase for *B. fragilis group* ($p < 0.0001$), *F.prausnitzii* ($p < 0.0062$). To confirm this finding, we compared the results of multiplex PCR with the data on general Bacteroides class by means of 16SrRNA sequencing using NGS. The difference between FMT and placebo-treated patients was revealed on the days 16 and +30. By day +30, an increase over pre-FMT values was found for the *Bacteroidetes* phylum; *Bacteroidia* (Class); *Bacteroidales* (Order) which include *B.fragilis group*. Both *B.fragilis* and *F.prausnitzii* represent sufficient part of microbiota, promote immune tolerance. Therefore, they are considered potential probiotic microorganisms. Other groups of intestinal bacteria, e.g., *Lactobacillus spp*., and *Bacteroides thetaiotaomicron*, generally, were not changed over this time period. In the placebo group we did not find significant changes against initial levels over 120 d post-FMT.

Conclusions: 1. Quantitative PCR of major bacterial groups of, especially, *B. fragilis group, F. prausnitzii* could be used as useful tool for evaluation of gut microbiota shifts after HSCT followed by FMT. 2. Multiplex PCR of the common bacterial species allows routine semi-quantitative monitoring of intestinal dysbiosis and its recovery. 3. The genocopy counts of *B. fragilis group* correlate with clinical response in the patients with intestinal GVHD after HSCT, either with, or without FMT procedure. 4. Our results argue for potential usage of novel probiotics based on the non-toxic strains of *B. fragilis and/or F. prausnitzii*.

Disclosure: No conflicts of interest declared

P293

Anti-SARS-CoV-2 monoclonal antibody therapy is effective at preventing severe disease in stem cell transplant and cellular immunotherapy recipients diagnosed with sars-cov-2

E. Ajayi[1], A. Baluch[1], O. Klinkova[1], T. Nishihori[1], Y. Pasikhova[1], R. Quilitz[1], D. Marco[1], H. Elmariah[1], F. Locke[1], B. Mciver[1], A. Mishra[1], M. Jain[1], C. Anasetti[1], M. Nieder[1], N. Bejanyan[1], J. Pidala[1], M. Alsina[1], L. Perez[1], A. Lazaryan[1], H. Liu[1], L. Ochoa[1], F. Khimani[1], D. Hansen[1], O. Castanedapuglianini[1], C. Freeman[1], R. Faramand[1]

[1]H. Lee Moffitt Cancer Center, Tampa, United States

Background: Patients with hematologic malignancies are at high risk of severe illness and mortality from SARS-CoV-2 infection. Evolving data illustrates that patients with hematologic malignancies may have diminished responses to SARS-Cov-2 vaccinations further increasing their risk of severe infection. Several monoclonal antibody (MOAB) combinations have been approved under an emergency use authorization (EUA) as treatment of mild to moderate COVID-19 in non-hospitalized high-risk patients. The safety and efficacy of MOABs in recipients of hematopoietic cell transplantation (HCT) and cellular immunotherapy (CI) is undetermined. The aim of this study is to describe the safety and effectiveness of anti-SARS-CoV-2 MOAB in HCT/CI recipients at our institution.

Methods: We retrospectively reviewed the charts of HCT/CI recipients who were treated with MOAB for a diagnosis of SARS-CoV-2 between December 1, 2020-Sepetember 30, 2021. The primary end point was hospitalization and/or death related to severe SARS-CoV-2 infection.

Results: Fifty patients were identified and included in this analysis with a median of 360 days (12-4790) from time of HCT/CI to diagnosis of COVID19. The median age was 60 years (25-78 years) with 54% of patients being males. Twenty-eight patients (56%) were recipients of allogeneic HCT, 30% (15/50) autologous HCT and 14% (7/15) CAR-T cell therapy. Most patients in the allogeneic HCT group (89%, 25/28) were on immunosuppressive medications at time of diagnosis. Three of the 15 autologous HCT recipients had received rituximab within 90 days of diagnosis.

Twenty-four patients (48%) had previously completed 2 doses of SARS-CoV-2 vaccine. All treated patients met EUA criteria for the administration of MOAB for mild to moderate COVID19 infection. Casirivimab/imdevimab was the MOAB used in 76% (38/50) of patients, bamlanivimab in 18% (9/50) of patients and 6% (3/50) received bamlanivimab/etesevimab. Most patients (68%) received the MOAB infusion on the same day of diagnosis. There were no reported infusion reactions. With a median follow up of 81.5 days, the COVID-19 related hospitalization rate was 6% (3/50). Two of these 3 patients had received two COVID-19 vaccines. None of the hospitalized patients required intubation despite 67% (2/3) experiencing acute hypoxia requiring ≥2L of supplemental oxygen. The median duration of hospitalization was 5 days (4-23). There were no deaths related to SARS-CoV-2 infections.

Table 1: Baseline Demographics and Clinical Characteristics of Patients N = 50.

Median age (range)-yr. 60 (25-78)
Male sex no. (%) 27 (54)
Underlying malignancy-no. (%)
Leukemias 18(36)
Lymphoma 10 (20)
Myelodysplastic syndrome 5 (10)
Multiple myeloma 12 (24)
Other* 5 (10)
Cellular Therapy- no (%)
Allogeneic stem cell transplant 28 (56)
Autologous stem cell transplant 15 (30)
CAR T cell therapy 7 (14)

Median (range) WBC at COVID-19 diagnos 4.16 (0.93-14.28)
BMI – kg/m2. (range) 27.2 (13.6-43)
Median (range) platelet count COVID-19 diagn 134 (15-310)
Vaccination status – no. (%)
Fully vaccinated‡ 24 (48)
Partially vaccinated 2 (4)
No vaccination documented 24 (48)
Co-morbid conditions- no (%)
Chronic pulmonary disease 3 (6)
Chronic renal disease 2 (4)
Diabetes 5 (10)

* Myeloproliferative disorders and aplastic anemia
‡ After two doses of mRNA SARS-CoV-2 vaccine

Conclusions: Treatment with anti-SARS-CoV-2 MOAB in fifty HCT-CI patients at our institution demonstrates encouraging efficacy in a high-risk patient population. We show low rates of severe illness (6%) requiring hospitalization and no SARS-CoV-2 related deaths.

Disclosure: Nothing to declare.

P294

Antibody response after vaccination with bnt162b2 mrna vaccine against sars-cov-2 in patients with hematologic malignancies post hematopoietic stem-cell transplantation: A single-center prospective study

J.V. Asimakopoulos[1], E. Lalou[1], G. Seferlis[1], M. Malliarou[2], I. Vassilopoulos[1], I. Drandakis[1], A.N. Georgopoulou[1], P. Petsa[1], E. Konstantinou[1], D. Galopoulos[1], M.-P. Arapaki[1], A. Kopsaftopoulou[1], A. Machairas[1], A. Piperidou[1], A. Karapaschalidis[1], A. Alexandropoulos[1], M.-E. Lefaki[1], K. Keramaris[1], K. Benekou[1], F. Panitsas[1], P. Tsaftaridis[1], E. Plata[1], M.P. Siakantaris[1], A.G Papavassiliou[2], T.P. Vassilakopoulos[1], P. Panayiotidis[1], K. Konstantopoulos[1], A. Papapanagiotou[2], M.K. Angelopoulou[1]

[1]National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece, [2]Biochemistry Laboratory, Laikon General Hospital, Athens, Greece

Background: Patients with hematologic malignancies (HMs) are at higher risk for severe Covid-19 disease (CVD), reflected on twofold increased mortality than the affected general population. Vaccination against SARS-CoV-2 remains the most important measure for CVD prevention. However, HMs patients are characterized by lower antibody responses (AR), while they were excluded from the initial studies for *BNT162b2 mRNA* efficacy. Moreover, the immunological response and actual benefit of vaccination in hematopoietic stem-cell transplantation (HSCT) recipients has not yet been clarified. The aim of this study was to analyze the AR after vaccination against SARS-CoV-2 in HMs patients treated with HSCT.

Methods: HMs patients treated with HSCT beyond 6 months and within the last 5 years in our Department were included. Antibody-titers (AT) against SARS-CoV-2 prior to the first dose as well as 1 and 3 months after the second dose of *BNT162b2 mRNA* vaccine were assessed using *Elecsys® Anti-SARS-CoV-2 S immunoassay against spike protein RBD* [positivity limit ≥0.8IU/mL]. Median AT in healthy individuals 1 month after vaccination are reported ≥ 1000U/mL, measured by the same method.

Results: Patients' characteristics are depicted in *Table 1*. No patient had detectable antibodies prior to vaccination, while one month and three months after vaccination, 84.6% and 87.8% of them had detectable antibodies, respectively. A decline in AT between 1- and 3 months was observed: median AT at 1- and 3-months post-vaccination were 480.5(0.4-25000) and 293(0.4-7869)U/mL, respectively. Specifically, AT decreased in 75% of the patients, increased in 17%, while antibodies remained undetectable in 11%. The distribution of AT is shown in Table 1: AT ≥ 1000U/mL were detected in 38.5% and 30.6% of the patients at 1-month and at 3 months post-vaccination, respectively. Concerning potential influencing factors of AR, age, sex, underlying hematologic disease, type of HSCT and absolute lymphocyte/mononocyte counts did not prove significant. On the contrary, *hypogammaglobulinemia [IgG < 500mg/dL]*, time from HSCT ≤ 18 months and disease-related treatment at the time of vaccination proved significant unfavorable factors for AR ($p = 0.01$, $p = 0.03$, $p = 0.001$, respectively). Median AT for those with no treatment was 1488U/mL, while those treated with rituximab, lenalidomide or other regimens were 0.4, 210 and 18.5U/mL, respectively.

Table 1. Basic features of HM/HSCT patients included in this cohort.

CHARACTERISTICS	**N = 54, [%]**
AGE*(years)*, median, *(range)*	56(19-71)
TIME*(months)***FROM HSCT***(range)*	32,9(6,4-63,2)
SEX, MALE/FEMALE	30[55,6]/24[44,4]
HAEMATOLOGIC DISEASE, LYMPHOMA/MULTIPLE MYELOMA/ACUTE LEUKEMIA	30[55,6]/19[35,2]/5[9,3]
HSCT TYPE, AUTOLOGOUS	50 [92,6]
TREATMENT AT THE TIME OF VACCINATION, RITUXIMAB/LENALIDOMIDE/OTHER	24 [46] 5[10]/11[22]/8[14]

ANTIBODY TITERS POST-VACCINATION (U/mL)	<0.8	0.8-19.9	20-249.9	250-999.9	1000-1999.9	2000-4999.9	≥5000
1 MONTH AFTER, %	15.4	9.6	13.5	23.1	13.5	15.4	9.6
3 MONTHS AFTER, %	12.2	6.3	27.1	22.9	18.4	10.2	2

Conclusions: Over 80% of HM/HSCT patients developed positive AR after *BNT162b2 mRNA* vaccine. Consequently, the vaccination of these patients is highly recommended. However, the presence of a decreasing trend in AT 3 months post-vaccination suggests the need for a third dose in this group.

Disclosure: Nothing to declare

P295

Incidences of infections and viral reactivations more frequent with atg than with post-transplantion cyclophosphamide as GVHD prophylaxis in matched unrelated donor hematopoietic stem cell transplantations

M. Aydin[1], C.E. Rutten[1], D.C. de Leeuw[1], O.J. Visser[2], C. van Roessel[1], B.J. Biemond[1], J. Janssen[1], M.D. Hazenberg[1], E. Meijer[1], E. Nur[1,3]

[1]Amsterdam University Medical Centers, Amsterdam, Netherlands, [2]Isala Hospital, Zwolle, Netherlands, [3]Sanquin Research, Amsterdam, Netherlands

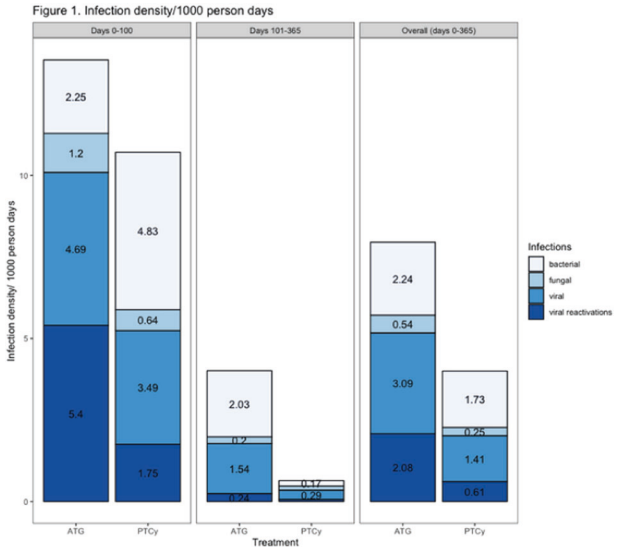
Background: In-vivo lymphocyte depletion methods such as anti-thymocyte globulin (ATG) and post-transplantation cyclophosphamide (PTCy) are used in unrelated donor (MUD) hematopoietic stem cell transplantations (HSCT). In this retrospective study, we compared the incidence of clinically relevant infections (necessitating intervention) and infections/reactivations related readmissions within one year following HSCTs with ATG or PTCy-based conditioning.

Methods: Patients undergoing MUD HSCT in two centers each using ATG-based (Center A) or PTCy-based (Center B) (nonmyeloablative) conditionings were compared with each other for incidence of infections/reactivations and readmissions. Incidence of bacterial/fungal infections was evaluated for the periods 0-30 vs. >30 days, as PTCy is associated with a significantly longer neutropenic phase in the first weeks post-HSCT. Viral infections/reactivations were evaluated for 0-100 vs. >100 days. Infection density per infection category, accounting for number of infections in a patient per 1000 person days, were compared over three periods (0-100 days, 101-365 days and overall, 0-365 days).

Results: We analyzed 118 patients with ATG and 79 with PTCy who were transplanted between 2009 and 2020. Cumulative incidence of bacterial infections was significantly higher in the PTCy group in the first 30 days (22% vs. 7%), but higher in the ATG group after >30 days (35% vs. 14%)(Table 1). The incidence of fungal infections was similar in both groups/phases. Patients receiving ATG had a higher incidence of CMV reactivations and disease as compared to PTCy (37% vs. 16% and 10% vs. 0%, respectively), which mostly occurred within 100 days post-HSCT. Other viral infections were comparable in the first 100 days but significantly higher in the ATG group after 100 days post-HSCT (22% vs. 6%, $p = 0.003$). Infection densities of bacterial, fungal and viral infections and reactivations are shown in Figure 1. Infection density analyses showed higher bacterial infection density (per 1000 person days) by day 100 for PTCy (4.83 vs. 2.25, $p < 0.01$) and it was higher in the ATG group after 100 days (2.03 vs. 0.17, $p < 0.01$). The overall density for bacterial infections was similar in the first year post-HSCT. The density of fungal infections was not significantly different for both treatment groups. Viral infections were significantly higher in ATG compared to PTCy patients from day 100 to 365 (1.54 vs. 0.29, $p < 0.01$) and in the overall density analysis in the first year post-HSCT (3.09 vs. 1.41, $p < 0.01$). Viral reactivations remained higher in the ATG group in all periods within 1 year. The incidence of readmission due to infections/reactivations after 30 days post-HSCT was 24% vs. 16%, for ATG and PTCy respectively.

Table 1. Cumulative incidence of infections.

	ATG (n = 118)	PTCy (n = 79)	P
Bacterial infections			
≤30 days	7%	22%	0.002
>30 days	35%	14%	0.002
Fungal infections			
≤30 days	8%	6%	0.58
>30 days	8%	3%	0.18
Viral infections			
≤100 days	31%	25%	0.45
>100 days	22%	6%	0.003



Conclusions: As both viral reactivations/infections and readmissions are more common in patients receiving ATG than in those receiving PTCy, replacing ATG with PTCy as GvHD prophylaxis might result in decreased disease burden and hospitalizations.

Disclosure: David de Leeuw: *Takeda:* Membership on an entity's Board of Directors or advisory committees.

Bart Biemond: *Celgene:* Honoraria; *Global Blood Therapeutics:* Honoraria, Research Funding, Speakers Bureau; *Novartis:* Honoraria, Research Funding, Speakers Bureau; *Novo Nordisk:* Honoraria; *CSL Behring:* Honoraria; *Sanquin:* Research Funding.

Jeroen Janssen: *Bristol-Myers Squibb:* Consultancy, Research Funding; *Novartis:*Consultancy, Research Funding; *Incyte Biosciences Benelux BV:* Research Funding, Speakers Bureau; *Pfizer:*-Consultancy; *Uppsala County Council:* Research Funding; *Glycomimetics:* Research Funding; *Avillion:* Research Funding; *Ellipses Pharma:* Research Funding; *Roche:* Speakers Bureau; *Celgene:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau.

Erfan Nur: *Novartis:* Research Funding, Speakers Bureau; *Roche:*Speakers Bureau; *Celgene:* Speakers Bureau.

P296

Clinical course and outcomes of covid-19 in pediatric patients after chemotherapy, immunosuppressive therapy and hematopoietic cell transplantation

T. Bykova[1], A. Gevorgian[1], O. Paina[1], A. Osipova[1], M. Averyanova[1], M. Popova[1], A. Kozlov[1], I. Kazantsev[1], E. Semenova[1], L. Zubarovskaya[1], A. Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, St.Petersburg, Russian Federation

Background: The incidence of coronavirus disease 2019 (COVID-19) is less in the pediatric than in the adult population. Although children with cancer, bone marrow transplantation recipients are considered a high-risk population for COVID-19 infection, published data specifically addressing the pediatric oncology are still limited.

Methods: We analyzed the clinical course and outcomes of

COVID-19 in a pediatric cohort of RM Gorbacheva Research Institute. The PCR test was performed at the admission to the hospital for all patients, weekly during hospitalization and in cases of developing symptoms of infection.

Results: A total of 54 (29 male and 25 female) pediatric patients (pts) had a laboratory-confirmed SARS-CoV-2 infection between April 2020 and August 2021. Median age was 7 years (4 months – 18 years). There were 3 diagnosis groups: hematological malignancies (33, 61%), solid tumors (13, 24%), non-malignant diseases (8, 15%). Twenty-seven (50%) pts received hematopoietic stem cell transplantation (auto HSCT – 2, 8%, MRD-HSCT – 2, 7%, MUD-HSCT – 2, 7%, haplo-HSCT – 21, 78%; median interval to COVID-19 infection: 94 days, range -2-2711). Chemo or IST were used in 24 (44%) pts with median interval to COVID-19 infection of 19 days (range, 4-39); 3 (6%) pts were without specific therapy (COVID-19 and cancer were diagnosed at the same time). The majority of pts (33, 61%) had asymptomatic forms, while 13 (24%) pts had mild (leukemia – 5 pts, SAA – 2, PNH – 1, solid tumors – 5); 3 (6%) - moderate (all pts with leukemia) and 5 (9%) – severe disease (leukemia – 3, SAA – 1, MPS 1 type - 1). Severity and clinical manifestation were the same in transplant and chemo/IST groups. The typical clinical manifestations were fever (90%), fatigue (50%), tachypnoea (30%) and cough (20%). Seventeen pts (31%) were hospitalized in infection units. Twelve (22%) pts received COVID-19-directed treatment (convalescent plasma – 8, ruxolitinib – 3, steroids – 2, tocilizumab – 1). Fifty (93%) pts recovered. Median time between symptom resolution and negative PCR was 25 days in symptomatic group, 14 days – in asymptomatic. Persistent SARS-CoV-2 PCR positivity (more than 21 day) observed in 16 pts (30%). Overall survival was 92%. Overall mortality was 8% and did not differ in HSCT and chemo/IST groups[MP1]. The only death was attributed to COVID-19, while ALL progression and complications after HSCT were causes of death in 1 and 2 patients, respectively.

Conclusions: In our cohort immunocompromised pediatric patients the incidence of severe COVID-19 does not exceed 10%, overall mortality was 8% and the only one death was attributed to COVID-19. There was no difference in the course of COVID-19 in subgroups analysis. Although this patient population is managed as high risk, according to our initial experience the clinical features of COVID-19 are milder and prognosis is relatively good. Nevertheless, further research should detail the therapeutic tactics for the underlying disease and HSCT complications in establishing the diagnosis of COVID-19.

Disclosure: Nothing to declare

P297

Efficacy and safety of mrna sars-cov-2 vaccination in hematopoietic stem cell transplant (HSCT) recipients: Single centre experience

M. Huguet[1], M. Morgades[1], B. Quirant[2,3], M. Boigues[2,3], E. Felip[4], T. Morán[4], M.J. Jiménez[1], D. Quintela[1], M. Sorigué[1], L. Abril[1], A. Torrent[1], J.M. Ribera[1], J.M. Sancho[1], C. Ferrà[1,5]

[1]Institut Català d'Oncologia de Badalona, Hospital Universitari Germans Trias i Pujol, Josep Carreras Research Institute, Badalona. Universitat Autonòma de Barcelona, Badalona, Spain, [2]Division of Immunology, LCMN, Germans Trias i Pujol University Hospital and Research Institute, Badalona, Spain, [3]Universitat Autonòma de Barcelona, Badalona, Spain, [4]Medical Oncology Institut Català d'Oncologia de Badalona, Hospital Universitari Germans Trias i Pujol, Badalona Applied Research Group in Oncology, Badalona, Spain, [5]Universitat de Vic – Universitat Central de Catalunya, Vic, Spain

Background: HCST recipients present high risk of severe COVID-19 infection and have been considered for priority vaccination. However, as they usually remain immunosuppressed for months after HSCT, vaccine efficacy might be compromised. Reports on serological response after vaccination in hematological patients confirm the lower antibody response rate, compared to the general population (>90%). The characterization of the response of transplanted patients could help to design more efficacious vaccination programs.

Methods: SARS-CoV-2 vaccination with mRNA1273 vaccine (Moderna) was prospectively evaluated in patients vaccinated from 6 months to 5 years after HSCT. Underlying disease, HSCT and vaccination characteristics were collected. The SARS-CoV-2 serological status and immunological conditions were determined before vaccination. Vaccines were administered as two doses 4 weeks apart and serological response was assessed 2-4 months after complete vaccination. In cases without serological response, we reassessed humoral and cellular response after a third dose vaccine.

Results: Eighty-seven patients (56 auto-HSCT and 31 allo-HSCT) received two doses between 23 March - 5 May 2021. No severe adverse effects were reported. Patients' characteristics are summarized in Table 1. At 2-4 months after vaccination, 75/87 (86%) patients presented seropositivity without differences between auto-HSCT and allo-HSCT. Considering patients with previous negative serological status, 65/77 (84%) patients presented seroconversion, without differences between both groups. The antibody response rate was higher in the allo-HSCT group, with a median of 2578 (40.8-42793.41) UI/mL, compared to 1675.5 (67.2-10686.09) UI/mL for auto-HSCT patients. Twelve patients showed a persistent negative serological status after vaccination. 6/12 patients had a NHL as HSCT indication and 8/12 were auto-HCST recipients. We found an association between negative serological response and B-lymphocyte count <113.5/mm^3 (29% *vs* 3% in the group with B-lymphocyte count ≥113.5/ mm^3, $p = 0.002$), IgG <700 mg/dL (31% *vs* 4% in the group with IgG ≥700 mg/dL, $p = 0.002$) and receiving anti-CD20 therapy in the last year before vaccination (100% *vs* 12% in patients without anti-CD20 therapy, $p = 0.003$). Eleven of twelve patients without seroconversion received a third dose of the vaccine. At 2-6 weeks, 5/11 patients achieved seroconversion and 6/11 presented cellular response (2 of them without seroconversion). At 6 months follow-up, no cases of COVID-19 infection have been reported.

Table 1.

	Whole series (n = 87)	Auto-HSCT (n = 56)	Allo-HSCT (n = 31)	p value
Age, median (range)	57 (17-72)	60 (39-69)	49 (17-72)	0.008
Diagnosis:				<0.001
LNH	13 (15%)	11 (20%)	2 (7%)	
MM	41 (47%)	41 (73%)	0	
AL	22 (26%)	0	22 (71%)	
Others	11 (12%)	4 (7%)	7 (22%)	
Time from HSCT to vaccination:				0.003
<12 months	23 (26%)	10 (18%)	13 (42%)	
≥12 months	64 (74%)	46 (82%)	18 (58%)	
Active GvHD	16/31 (52%)	-	16 (52%)	-
Last year anti-CD20 therapy	3 (3%)	3 (5%)	0	0.550
B-lymphocyte count, median (range)/mm3	113.5 (0-1287)	65 (0-728)	210 (0-1287)	0.043
IgG < 700 mg/dL	35 (41%)	21 (38%)	14 (45%)	0.527

Conclusions: SARS-CoV-2 vaccination seems to have clinical benefit in preventing COVID-19 infection in HSCT recipients, although seroconversion rate after mRNA SARS-CoV-2 vaccination is lower than in the general population. Receiving anti-CD20 therapy in the last year before vaccination, a low B-lymphocyte count and hypogammaglobulinemia are associated with no serological response after vaccination. Cellular and humoral response monitoring after SARS-CoV-2 vaccination could help to identify booster dose candidates.

Disclosure: Nothing to declare.

P298

The effect of HLA matching on early post-transplant infections in patients receiving triple ptcy-based GVHD prophylaxis

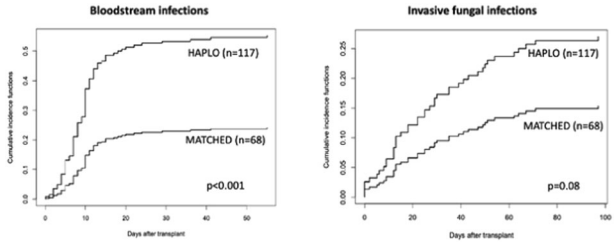
J. Marra[1], E. Galli[1], S. Giammarco[1], P. Chiusolo[1,2], E. Metafuni[1], F. Sora'[1,2], L. Laurenti[1,2], I. Innocenti[1], F. Autore[1], M.A. Limongiello[1], A. Bacigalupo[1,2], S. Sica[1,2]

[1]Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy, [2]Università Cattolica del Sacro Cuore, Roma, Italy

Background: Several studies have compared the outcome of patients undergoing a haploidentical transplant (HAPLO) or an HLA-matched transplant (MATCHED). In most cases, HAPLO grafts received triple post-transplant cyclophosphamide (PTCY)-based GvHD prophylaxis, whereas MATCHED grafts received a conventional cyclosporine, methotrexate prophylaxis with or without ATG. This has also been the case for studies comparing the risk of infections in these two different cohorts of patients.

Methods: The aim of the study was to assess the risk of infections in the first 100 days, in patients grafted from HAPLO or MATCHED donors, all of them receiving a homogenous GvHD prophylaxis: PTCY, mycophenolate, and cyclosporine. Eligible for this study were patients with hematological malignancies, with triple PTCy-based GvHD prophylaxis: This included 117 HAPLO and 68 MATCHED patients (29 from HLA identical siblings and 39 from 8/8 matched unrelated donors). HAPLO grafts were unmanipulated bone marrow transplants. The two groups were comparable for donor age ($p = 0.2$), intensity of the conditioning regimen ($p = 0.5$) and disease phase (Early, advanced) ($p = 0.4$). Data on post-transplant infections, including bloodstream infections (BSI), invasive fungal infections (IFI), and viral infections (CMV and EBV), were obtained retrospectively. For each infection type, a competing risk analysis was performed, with mortality from any cause as the competing risk. A confirmatory analysis with propensity matching was performed and included 68 HAPLO transplants and 68 MATCHED transplants. Criteria for propensity matching included donor and recipient age, disease phase, and intensity of the conditioning regimen (Myeloablative, reduced intensity). Kaplan Meier curves were used to compare actuarial survival.

Results: Patients who received a HAPLO transplant had an increased incidence of BSI (HR 2.9; 95% CI 1.7–5.1; $p < 0.001$); subanalysis revealed an increased incidence of gram-positive BSI (HR 2.8; 95% CI 1.4–5.6; $p = 0.003$) and a trend for increased incidence of gram-negative BSI (HR 1.9; 95% CI 0.9–3.8; $p = 0.08$). Among patients with BSI, the most frequently isolated gram-positive bacteria in the early post-transplant period (Days 0 to +20) were coagulase-negative *Staphylococcus*, and the most frequently isolated gram-negative bacteria were *E. coli*, both in HAPLO and MATCHED transplants; *Klebsiella* spp. were also frequently isolated in HAPLO patients. There was also a trend for increased incidence of IFI in HAPLO grafts (HR 1.9; 95% CI 0.9–3.9; $p = 0.08$), of CMV infections (HR 2.0; 95% CI 0.9–4.6; $p = 0.08$), and of EBV infections (HR 4.2; 95% CI 0.5–34; $p = 0.2$). In the propensity matched analysis, these results were confirmed. The actuarial 1-year survival was comparable: 74% for HAPLO and 78% for MATCHED grafts ($p = 0.2$).



Conclusions: In this single center study, patients with a HAPLO donor have an increased risk of early bloodstream infections and a trend for increased risk of invasive fungal and viral infections.

Disclosure: Nothing to declare

P299

Impact of levofloxacin prophylaxis withdrawal on pre-engraftment bloodstream infections after allogeneic stem cell transplant

D. Clerici[1], C. Oltolini[2], L. Galli[2], R. Greco[1], A.P. Lugli[3], F. Erbella[1,3], M. Ripa[2,3], C. Tassan Din[2], R. Nitti[1,3], F. Giglio[1], S. Mastaglio[1], F. Lorentino[1], E. Xue[1], F. Farina[1], C. Liberatore[1], A. Poli[2], S. Carletti[4], M.T. Lupo Stanghellini[1], A. Ruggeri[1], M. Bernardi[1], J. Peccatori[1], C. Corti[1], N. Mancini[4], P. Scarpellini[2], A. Castagna[2,3], F. Ciceri[1,3]

[1]Unit of Hematology and Bone Marrow Transplantation, IRCCS San Raffaele Scientific Institute, Milano, Italy, [2]Infectious Disease Unit, IRCCS San Raffaele Scientific Institute, Milano, Italy, [3]Vita-Salute San Raffaele University, San Raffaele Scientific Institute, Milano, Italy, [4]Laboratory of Clinical Microbiology and Virology, IRCCS San Raffaele Scientific Institute, Milano, Italy

Background: Fluoroquinolone prophylaxis (FQ-P) has been largely adopted worldwide in hematological patients undergoing allogeneic hematopoietic stem cells transplantation (allo-HSCT) with expected protracted neutropenia. However, sepsis sustained by Gram-negative bacteria (GNB), particularly if multidrug resistant (MDR), still affects mortality in neutropenic hematological patients. In recent decades, Italian epidemiological data has shown worrisome rates of fluoroquinolone (FQ) resistance. Moreover, alterations of the intestinal microbiome have been reported in patients receiving FQ-P, potentially affecting the occurrence of bloodstream infections (BSI) after allo-HSCT. In such a context, the benefit of FQ prophylaxis is controversial.

Methods: We prospectively analyzed a cohort of consecutive 223 adult allo-HSCT performed at our Bone Marrow Transplant Unit from January 2018 to December 2020. Since February 2019 FQ-P was withdrawal. During study period an active microbiological surveillance was performed weekly according to local practice and piperacillin/tazobactam was the first-line therapy of febrile neutropenia (FN). We collected data of FN according to FQ-P: 71 allo-HSCT receiving FQ-P (levofloxacin-group, January 2018-January 2019) and 152 allo-HSCT without FQ-P (withdrawal-group, February 2019-December 2020).

Study's outcomes were cumulative incidence function (CIF) of GNB pre-engraftment BSI (PE-BSI) and any changes in antimicrobial resistance, CIF of FN and infection-related mortality (IRM).

Results: Overall, 221 patients underwent 223 allo-HSCT. The levofloxacin-group and the withdrawal-group were superimposable for characteristics (age, sex, disease, disease status at

allo-HSCT, comorbidity-index score). The majority (73.5%) of patients was affected by myeloid disorders. The graft source was mainly (91%) unmanipulated peripheral blood, using a post-transplant cyclophosphamide strategy. Stem cell donors were matched unrelated volunteer (n = 105, 47.1%), family haploidentical (n = 61, 27.4%), HLA-identical sibling (n = 44, 19.7%), or cord blood (n = 13, 5.9%).

One FN episode occurred in 96.4% of transplants, with no differences among the two groups according to the usage of FQ-P [95.8% vs 96.7%; p = 0.72]. At least one PE-BSI occurred in 45.3% of allo-HSCT and a significant difference was observed in the 30-day CIF according to FQ-P [36.4% levofloxacin-group versus 51.9% withdrawal-group; p = 0.019]. At least one GNB PE-BSI occurred in 26.5% of allo-HSCT and a significant difference was observed in the 30-day CIF according to FQ-P [14.7% levofloxacin-group versus 34.4% withdrawal-group; p = 0.003].

Regarding GNB-PE-BSI etiology, among the levofloxacin-group 10 single-species GNB PE-BSI occurred in 10 patients; the most represented pathogens were *Escherichia coli* (n = 4), *Klebsiella pneumoniae* (n = 4) and *Pseudomonas aeruginosa* (n = 2).In the withdrawal-group 55 GNB PE-BSI occurred in 49 patients; the most represented GNB were *Escherichia coli* (n = 27), *Klebsiella pneumoniae* (n = 13) and *Pseudomonas aeruginosa* (n = 8). Comparing antimicrobial resistance among GNB, in the withdrawal-group a significantly higher proportion of pathogens was susceptible to piperacillin/tazobactam (71% versus 30%, p = 0.026) and FQ (49% versus 10%, p = 0.03), and a lower proportion was resistant to carbapenems (5% versus 50%, p = 0.001).

At 30-days CIF of IRM was 5%, superimposable in both groups [p = 0.62].

Conclusions: In allo-HSCT setting, the FQ-P reduced GNB PE-BSI, with no impact on IRM; its withdrawal concurred to decrease significantly antimicrobial resistance in GNB. These data confirm the safety of an approach based on FQ withdrawal in the in-patient setting where active surveillance is applied.

Disclosure: Nothing to declare

P300

Outcome of post-vaccination covid-19 in hematopoietic stem cell transplant and car t cell treatment recipients; results from an idwp prospective survey

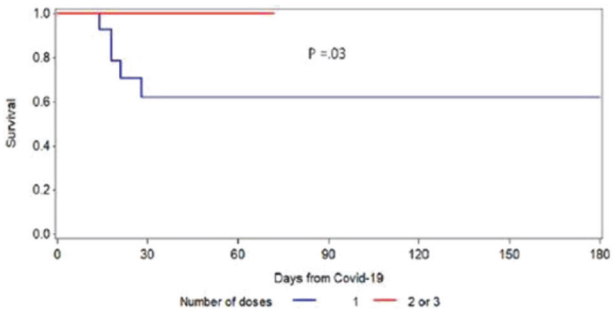
P. Ljungman[1], M. Mikulska[2], M. Collin[3], M. Gambella[4], S. Mielke[1], S. Sica[5], H. Sengeloev[6], M. Suárez-Lledó[7], Z. Arzu Yeğin[8], T. Valerius[9], K.M. Wilson[10], T. Zuckerman[11], I. Yonal-Hindilerden[12], H. Ghesquieres[13], N. Knelange[14], G. Tridello[15], D. Averbuch[16], C. Cordonnier[17], S. Cesaro[15], R. de la Camara[18]

[1]Karolinska University Hospital Huddinge, Karolinska Institutet, Stockholm, Sweden, [2]University of Genoa (DISSAL) and IRCCS Ospedale Policlinico San Martino, Genova, Italy, [3]Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom, [4]IRCCS Ospedale Policlinico San Martino, Genova, Italy, [5]Universita Cattolica S. Cuore, Rome, Italy, [6]Copenhagen University Hospital, Copenhagen, Denmark, [7]Hospital Clinic, Barcelona, Spain, [8]Gazi University Faculty of Medicine, Ankara, Turkey, [9]University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany, [10]Cardiff University School of Medicine, Cardiff, United Kingdom, [11]Rambam Medical Center, Haifa, Israel, [12]Ýstanbul Tip Fakultesi, Istanbul, Turkey, [13]Hospices Civils de Lyon, Lyon, France, [14]EBMT data office, Leiden, Netherlands, [15]Azienda Ospedaliera Universitaria Integrata, Verona, Italy, [16]Hebrew University of Jerusalem, Hadassah Medical Center, Jerusalem, Israel, [17]Henri Mondor hospital, Creteil, France, [18]Hospital de la Princesa, Madrid, Spain

Background: COVID-19 has resulted in high morbidity and mortality among hematopoietic stem cell transplant (HCT) recipients and CAR T cell treated patients. These population have therefore been regarded as high priority for vaccination. Little is known of the severity and outcome of COVID-19 contracted after vaccination. The IDWP has collected data on this topic through the continuing prospective data collection on patients with COVID-19. This abstract summarizes current results.

Methods: The EBMT registry has collected information on COVID-19 infection since end of February 2020. In February 2021 questions regarding COVID-19 vaccinations were added. To date, the registry has received reports on 28 patients contracting COVID-19 after the date of the first vaccine dose. 20 patients were after allo HCT, 6 after auto HCT, and 2 had received CAR T cells. The median age was 54.5 years (20-74). 11/20 allo HCT patients had active GVHD and 10 received immunosuppression at the time of COVID-19.

Results: The median time from the first vaccine dose to diagnosis of COVID-19 was 24 days (2 – 242 days). 10 patients required hospitalization while 16 were cared for as out-patients (data missing = 2). Four patients required ICU (data missing for 2 patients) and five patients died. For all 5 patients, the primary cause of death was COVID-19. Four patients were treated with monoclonal antibodies and one with hyperimmune plasma. Out of patients receiving one dose of vaccine, 7/14 (50%) were hospitalized, 4/14 (28.6%) required ICU, and 5/16 (31.2%) died including the patient, who had received one dose just before the HCT. Two patients having received one dose had not resolved COVID-19 at the time of reporting. Of patients receiving two doses of vaccine, 3/12 (25%) were hospitalized, none required ICU or died, and all COVID-19 infections had resolved. The overall survival probability was 79.1% at 6-weeks from the diagnosis of COVID-19. Excluding the patients vaccinated before HCT the survival probability at 6-weeks was 81.6%. The survival was superior in patients having received two doses (Fig. 1).



Conclusions: Two doses of any vaccine against COVID-19 resulted in lower risks for complications requiring ICU and death. Therefore, it is of uttermost importance to pursue vaccinations of HCT and CAR T cell treated patients.

Disclosure: Per Ljungman: Speaker for Pfizer

P301

Increased risk of bloodstream infections in adults undergoing allogeneneic hematopoietic cell transplantation combined with post-transplant cyclophosphamide

M.Q. Salas[1,2], P. Charry[1,2], P. Puerta-Alcalde[3,2], A. Pedraza[1,2], A. Doménech[1,2], M.T. Solano[1,2], J. Arcarons[1,2], N. de LLobet[1,2], N. Martínez-Cibrian[1,2], L. Rosiñol[1,2], G. Gutierrez-García[1,2], E. Carreras[1], J. Esteve[1,2], Á. Urbano-Ispizua[1,2], F. Fernández-Avilés[1,2], C. García-Vidal[3,2], C. Martinez[1,2], M. Rovira[1,2], M. Suarez-Lledo[1,2]

[1]Institute of Hematology and Oncology, Hospital Clínic de Barcelona, Barcelona, Spain, [2]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, [3]Hospital Clinic of Barcelona, Barcelona, Spain

Background: Bloodstream infections (BSIs) after alloHCT are prevalent secondary to the profound immunosuppression needed to preserve graft function and to prevent GVHD. The use of PTCY for GVHD prophylaxis is becoming more widespread in the transplant community, and further studies are needed to determine the incidence of BSIs among transplanted patients. This study investigates the incidence and risk factors for BSIs in adults undergoing alloHCT, and explores the effect of PTCY on the probability of presenting this complication.

Methods: Between January 2014 and March 2021, 334 adults with hematological malignancies underwent first alloHCT at our Institution, and 204 (61.1%) received PTCY-based GVHD prophylaxis. Antibiotic prophylaxis with levofloxacin was given to all patients during the aplastic phase. The diagnosis of at least 1 episode of BSI was considered the main dependent variable. And, among those patients that had more than 1 BSI, only the first episode was accounted. Data was updated in November 2021. The cumulative incidence of BSI was calculated considering death a competing event.

Results:

Baseline characteristics between patients receiving PTCY vs those that did not were balanced, except for the proportion of patients transplanted during 2018-2020 where the use of PTCY was more prevalent.

Overall, 165 (49.4%) patients had at least one episode of BSI. Of the 165 patients with BSI, the majority of them were diagnosed during the first 30 days after alloHCT (70%); and with an estimated cumulative incidence at day +30 of 34.7%. The median of days to the first BSI was 14 days (range: -5 – 1083). BSIs caused by Gram-positive bacteria were more prevalent that those cased by Gram-negative bacteria (50.9% vs 43.6%). With a median follow-up of 2 years, the estimated one-year OS and NRM of the entire cohort were 72.7% and 13.9%, respectively; and the 1-year incidence of first BSI mortality was 3%.

The cumulative incidence of BSI was higher for patients receiving PTCY compared with those receiving others GVHD prophylaxis (Day + 30 and +100 incidences of 46.6% vs 16.2% and 52.0% vs 20.8%, respectively; $P < 0.001$), and the median of days to the first BSI was shorter for patients treated with PTCY (13 vs 36 days, $P < 0.001$). The multivariate analysis confirmed that the use of PTCY-based GVHD prophylaxis can be considered a risk factor for being diagnosed with BSIs (HR 2.37, $P = 0.001$). Other risk factors were age at transplant (HR 1.02, $P = 0.01$), KPS ≤ 80% (HR 1.58, $P = 0.008$), and the use of MAC regimens (HR 1.47, $P = 0.05$).

Conclusions: The incidence of BSI at our institution was 49.4%, but the overall mortality rate attributed to this complication was 2%. The inclusion of PTCY for GVHD prevention was found to be an independent risk factor for being diagnosed with BSI; in fact, those patients were 2.37 times more likely to be diagnosed with BSI compared with patients that did not received PTCY. The use of PTCY for GVHD prevention is becoming prevalent, so further study will be required to refine antimicrobial prophylaxis and improve supportive care.

Clinical Trial Registry: No applicable

Disclosure: Conflicts of interest: PP-A has received honoraria for talks on behalf of Merck Sharp and Dohme, Gilead, Lilly, ViiV Healthcare and Gilead Science. CG-V has received honoraria for talks on behalf of Gilead Science, MSD, Novartis, Pfizer, Janssen, Lilly as well as a grant from Gilead Science and MSD.

The rest of the authors have nothing to declare.

P302

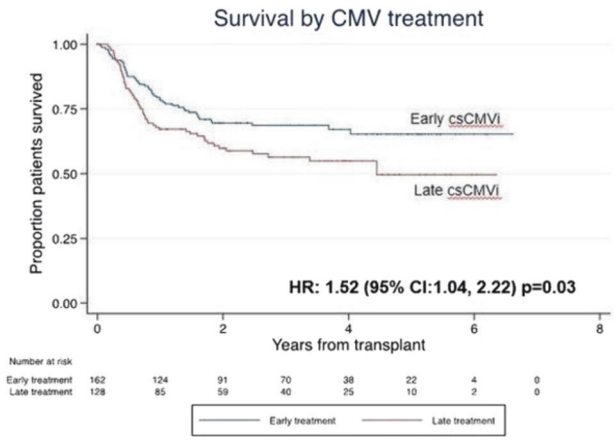
The timing of clinically significant cmv infection following allogeneic haematopoietic cell transplantation (allohct) is associated with poor survival; a national multi-centre cohort study

M. Yong[1,2,3,4], J. Lindsay[1,5,4], M. Greenwood[5], S.Y. Tio[1,4], J. Gallagher[1], S. Ho[1,4,3], M.J. Nasra[6], A. Rofe[6], J. Trubiano[6,4,3], A. Grigg[6,4], J. Othman[7], K. Crassini[7], S. Larsen[7], S. vanHal[7], S. Lam[8], P. Boan[8], D. Purtill[8], T. Spelman[1], A. Rivalland[2,1], J. Sasadeusz[2], L. Chee[2,1], M. Watson[8], D. Ritchie[2,1,3], M. Slavin[1,2,4,3]

[1]Peter MacCallum Cancer Centre, Melbourne, Australia, [2]Royal Melbourne Hospital, Parkville, Australia, [3]University of Melbourne, Melbourne, Australia, [4]National Centre for Infections in Cancer, Melbourne, Australia, [5]Royal North Shore Hospital, Sydney, Australia, [6]Austin Hospital, Melbourne, Australia, [7]Royal Prince Alfred Hospital, Sydney, Australia, [8]Fiona Stanley Hospital, Fremantle, Australia

Background: Clinically significant CMV infection (csCMVi) frequently complicates post-alloHCT care. We hypothesise that anti-CMV drugs may be better tolerated with improved neutrophil and immune recovery occurring after several weeks. The impact of csCMVi commencement for first CMV infections in the earliest period post-alloHCT compared to a later period post-alloHCT has not been thoroughly evaluated.

Methods: We conducted a national multi-centre retrospective cohort study across 6 adult HCT centres across Australia. Patients receiving an allo-HCT were included between the study period of 2015 to 2020. Patient and transplant demographics were collected as well as details of acute graft versus host disease, relapse and overall survival. csCMVi was defined as CMV DNAemia which was treated with specific anti-CMV treatment. HCT centres varied in the viral threshold with which to commence anti-CMV treatment depending on the type of transplant received. Early csCMVi was defined as <50 days from stem cell infusion based on the median time to csCMVi from previous studies.



Results: A total of 830 allo-HCT recipients were included with a median age of 53 years (IQR 42-60). The most common indications for transplantation were AML (38%), MDS (12%) and ALL (12%). Donor relationship included unrelated (54%), related matched sibling (38%) and haploidentical donors (8%). Reduced intensity conditioning was used in 42% and T-cell depletion used in 44% of the cohort. Peripheral blood stem cells were the most common source of cells (93%). Baseline CMV serostatus included R+/D+ (42%), R+/D- (25%), R-/D+ (11%) and R-/D- (22%). Pre-emptive CMV monitoring was the preventative strategy used in

99% of patients. Detectable CMV DNAemia occurred in 54% of patients at a median time of 20 days post-HCT (IQR 8-33). Two-hundred and ninety patients (35%) had csCMVi where the median time to anti-CMV treatment was 49 days (IQR 40-63). The first prescribed anti-CMV treatment was valganciclovir (57%), ganciclovir (29%), foscarnet (0.7%), others such as trial products and CMV-specific T cells (10%). The median neutrophil count at the start of CMV treatment was $2.8x10^9$/L (IQR 1.6-5). Grade 3-4 neutropenia occurred in 50% of patients during the course of treatment. AGVHD developed in 38% of the cohort of which 65% were Grade 2-4. Patients who received CMV treatment in the period 50+ days compared to the early period post-HCT had a significantly increased risk of all-cause mortality (HR 1.52 95% CI 1.04-2.22, $p = 0.03$) (Figure 1). In the R + /D- cohort, the risk of mortality was also increased (HR 2.2 95% CI 1.17-4.18, $p = 0.01$). In an adjusted model for AGHVD, late versus early CMV treatment remained an independent risk factor for all-cause mortality (adjusted HR 1.48 95% CI 1.01-2.17, $p = 0.04$).

Conclusions: There is a significant all-cause mortality burden on allogeneic HCT recipients who develop csCMVi in the period >50 days following transplantation. Severe neutropenia is common in patients using valganciclovir/ganciclovir as first line anti-CMV treatment.

Disclosure: MY, JL, AG, SvH, PB, JS, DR and MS have received consulting fees from MSD.

Financial declaration: This was an investigator initiated study sponsored by MSD

P303

Humoral response to anti-sars-cov2 vaccines in recipients of allogeneic hematopoietic stem cell transplants including cytometric analysis of peripheral blood lymphocytes

E. Karakulska-Prystupiuk[1], A. Tomaszewska[1], K. Pawlak[1], M. Feliksbrot-Bratosiewicz[1], M. Król[1], P. Kacprzyk[1], L. Chmielewska[1], P. Boguradzki[1], M. Grabowska[1], B. Blajer[1], A. Waszczuk-Gajda[1], W.W. Jędrzejczak[1], G.W. Basak[1]

[1]Medical University of Warsaw, Warszawa, Poland

Background: The efficacy of Covid-19 vaccine, and the optimal vaccination time in recipients of allogeneic hematopoietic stem cell transplants (allo-HSCT) are still unknown.

Methods: Our analysis involved adult outpatients after allo-HSCT, who have been receiving the mRNA-based SARS-CoV-2 vaccine. Vaccine-induced antibody responses against the SARS-CoV-2 were assessed in serum using the chemiluminescent immunoassay (CLIA) test, validated according to the WHO standard (the quantification range was 4.81- 2080 BAU/mL, and a cut-off for a positive result was 33.8 BAU/mL). Peripheral blood lymphocyte subpopulations CD3 + CD4 +, CD3 + CD8 +, CD19 +, and NK cells were analyzed using flow cytometry. Statistical analysis was performed using Spearman's Rho correlation coefficient to measure the strength and direction of correlation between antibody response and the lymphocyte subpopulations.

Results: Retrospective analysis involved a group of 57 patients (median age - 48 years), transplanted from HLA-identical siblings (35%), matched unrelated donors (57%) or haploidentical donors (8%) in the years 2006-2021 (31% of patients in the years 2020-2021). There were 53 patients (93%) transplanted for hematological malignancies of whom 30 (56%) received myeloablative conditioning, and 4 (7%) patients with aplastic anemia. Patients have been vaccinated against SARS-CoV-2 with two doses of vaccine. Ninety-five percent of patients were vaccinated with Comirnaty® (BNT162b2, Biontech/ Pfizer), and five percent of patients with mRNA-1273 (Moderna) vaccines according to the EBMT guidelines 2021 (v.4).

Five patients (8%) had previously mild or moderate COVID-19 according to the WHO guidelines. Immune responses were analyzed between 1-4 months after the second dose. Fifty one patients (89%) were receiving immunosuppressive treatment at the time of vaccination. Eleven patients (19%) were supplemented with immunoglobulins at least 4 weeks before the first dose of vaccine.

Altogether, vaccine-induced antibody responses were achieved in 42 patients (74%). Nineteen patients (33%) achieved high level of anti-SARS-CoV -2 titer above 2080 BAU/ml, 8 patients (14%) - antibody titer between 1000-2000, 12 patients (22%) between 100-1000, and the remaining 3 (5%) between 33-100 BAU/ml.

We did not detect anti-SARS-CoV-2 antibodies in 2/3 (66%) of patients vaccinated within 6 months after transplantation, in 6/13 (46%)- within 6-12 months, 7/41 (17%) – above one year after allo-HSCT. Most of them (14/15, 93%) suffered from Graft versus Host Disease.

No detectable SARS-CoV-2 antibodies were observed in 7/11 (64%) of patients with CD19 + deficiency, 11/33 (30%) patients with CD3 + CD4 + deficiency, and 5/11 (45%) – with NK cells deficiency.

In the multivariate analysis, a correlation was found between the number of CD3 + CD4 + lymphocytes, and the obtained anti-SARS-CoV-2 titer ($p = 0.012$).

Conclusions: These results indicate that the ability for humoral response after 2 doses of anti-SARS-CoV-2 vaccination develops during the 1st year after allo-HSCT provided the low intensity of graft versus host disease. CD3 + 4 + T-cells deficiency may play a role in the antibody response to SARS-COV2 vaccine.

However, none of our patients succumbed to COVID19. Apparently, both isolation procedures, and vaccinations provided sufficient protection even in this group composed of patients at particular risk of a severe course of COVID 19. The advisability of administering additional doses of the vaccine to non-responding patients requires further research.

Disclosure: Nothing to declare

P304

The value of baseline chest ct scan for the diagnosis of ipa in patients with AML treated with intensive chemotherapy: A retrospective single-centre cohort study

E. Janssens[1], S. Huygens[2], I. Moors[1], T. Kerre[1], A. Delie[1], L. Morbée[1], J. Boelens[1], A. Schauwvlieghe[1]

[1]Ghent University Hospital, Ghent, Belgium, [2]Erasmus MC, University Medical Center, Rotterdam, Netherlands

Background: Invasive pulmonary aspergillosis (IPA) is the most common invasive fungal disease in patients with AML and allogeneic stem cell transplant recipients. Without antimould prophylaxis, the incidence of IPA in these populations is 10-20%, with a fatality rate between 20-38% 6 to 12 weeks after diagnosis. Optimizing the management of IPA is key to reduce mortality and morbidity. At Ghent University Hospital, a diagnostic driven approach is followed for IPA. With this retrospective cohort study, we wished to evaluate the added value of baseline chest CT before start of classical induction 3 + 7 chemotherapy, a common practice in newly diagnosed AML patients in our centre since 2015.

Methods: All adult patients with newly diagnosed AML, MDS or myelofibrosis without intensive pretreatment, who were eligible for intensive chemotherapy and who had a baseline chest CT around start of chemotherapy (+/−7 days) were included. Data

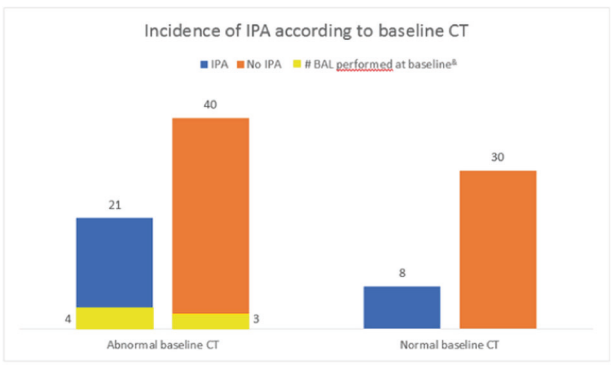
were collected retrospectively from the electronic health record (EHR) from patients admitted between January 2015 and October 2019. Diagnosis of IPA was classified using the EORTC/MSG-criteria. Statistical analysis was performed using SPSS statistic version 25.

Results: Ninety-nine patients were included (table 1). Baseline chest CT was abnormal in 61/99 patients (62%): 14/61 patients (23%) had radiological signs that met EORTC/MSG-criteria. Only 6/99 patients received mould-active antifungal prophylaxis. No patient was diagnosed with IPA at baseline. During treatment, 29/99 patients (30%) developed IPA (no proven, 29 probable). Of the patients with normal baseline CT, 8/38 (21%) developed IPA, versus 21/61 (34%) patients in the group with abnormal baseline CT. Mortality 12 weeks after start induction chemotherapy was 50% (7/14) in patients with IPA and 19% (5/27) without IPA. Seven patients with abnormal lesions at baseline received BAL, but no IPA was found (BAL GM and culture were negative, no PCR performed). However, 4 of these patients developed IPA during their first two cycles of chemotherapy (figure 1).

Table 1: baseline characteristics.

Characteristics	*All (N = 99)*	*No IPA (N = 70)*	*Probable/ proven@ IPA (N = 29)*	*P-value*
Age(yr)–median (IQR)	56 (44–66)	53 (35–63.25)	64 (54.5–67.5)	0.010
Age cat. (yr)–no.(%) 65 ≥	74 (74.8%)	56 (80.0%)	18 (62.1%)	0.062
65 <	25 (25.2%)	14 (20.0%)	11 (37.9%)	
Female – no. (%)	44 (44.4%)	31 (44.3%)	13 (44.8%)	0.961
No prophylaxis	1 (1.0%)	1 (1.4%)	0	0.101
Fluconazole	92 (92.6%)	63 (90.0%)	29 (100%)	
Posaconazole	6 (6.1%)	6 (8.6%)	0	
Neutropenia	32/96 (32.3%)	21/68 (30.0%)	11/28 (37.9%)	0.427

Figure 1: incidence of IPA vs baseline CT



Conclusions: Patients with abnormal baseline CT had a higher incidence of IPA during treatment. Baseline chest CT did not lead to any probable/proven IPA at admission however only few BAL were performed following abnormal baseline CT.

Disclosure: Nothing to declare

P305

Effective rapid diagnosis of bacterial bloodstream infections by t2 magnetic resonance technology in pediatric hematopoietic stem cell transplantation

F. Galaverna[1], M. Massa[2], P. Merli[1], B. Lucignano[1], M. Agosta[1], D. Pagliara[1], F. Del Bufalo[1], M. Algeri[1], M. Becilli[1], R. Carta[1], F. Quagliarella[1], E. Boccieri[1], P. Bernaschi[1], C.F. Perno[1,3], F. Locatelli[1,2]

[1]IRCCS Ospedale Pediatrico Bambino Gesu, Roma, Italy, [2]Universita' La Sapienza, Roma, Italy, [3]UniCamillus, Roma, Italy

Background: Children undergoing allogeneic hemaptopietic stem cell transplantation (HSCT) face a higher risk of severe and lethal blood stream infections (BSI). Rapid and sensitive diagnosis of acute infectious complication represents an unmet clinical need; the T2MR-technology is a direct, non-culture assay for rapid identification of 6 common BSI-pathogens (*P. aeruginosa, K.pneumoniae, E. coli, A. baumanii, S. aureus, E. faecium*).

Methods: We retrospectively analyzed 58 consecutive T2Bacteria performed in febrile patients undergoing HSCT from May 2018 to September 2020, with concurrent blood-culture (BC) requested as standard-of-care for suspected BSI. We wanted to test diagnostic real-life performance of T2Bacteria panels in the identification of proven, probable and possible BSI, and evaluation of possible benefits provided by T2MR-technology in children.

		T2Bacteria population, N = 58
Pediatric age groups, n (%)	Infant (1 month to 1 year)	4 (7)
	Toddler and preschool (2-5years)	10 (17)
	School age (6-12 years)	22 (38)
	Adolescent (13-18 years	21 (36)
	Young adult (19-21 years))	1 (2)
Disease, n (%)	Non-malignant	16 (28)
	Malignant	42 (72)
White blood cell count, n (%)	Within normal limits	8 (14)
	Leukocytosis	2 (3)
	Leukopenia	48 (83)
Body temperature **≥37.5°C, n(%)**		42 (72)
C-reactive protein (mg/dl), n(%)	≤0.5	6 (10)
	>0.5	52 (90)
Procalcitonin (ng/mL), n (%)	≤0.5	11 (30)
	>0.5	26 (70)
Central venous catheter, n (%)		56 (97)
Initial whole-blood volume sampled (mL), median(IQR) = 2.0-3.0	<2 mL	3 (5)
	2-3 mL	22 (38)
	≥ 3 mL	33 (57)
Initial whole-blood volume sampled **≥2 mL, n (%)**		55 (95)

Results: Clinical characteristics are listed in fig.1. T2Bacteria provided definitive microorganism identification in a mean time of 4.4 (SD: 0.7) hours, compared to 65.7 (SD: 24.5) hours for BC

($p < 0.001$). BC and T2Bacteria resulted positive in 7 and 11 cases, respectively, with 53/58 concordant results (91%). T2Bacteria identified *E.coli* in 3 cases, *P. aeruginosa* in 4 cases, *E. faecium* in 2, *K. pneumoniae* in 2. Four out of 7 proven BSI were concordant; one positive BC with T2MR negativity was considered blood contaminant, while probable- and possible-BSIs, defined by compatible cultural and/or laboratory characteristics, represented 2 and 5 additional T2MR-positive cases (7/11, 64%), respectively.

T2Bacteria had a sensitivity of 67% (95%CI: 1-0.28) and 86% (95%CI: 0.95-0.75) specificity in the identification of 4 BC-positive proven-BSI; relatively low sensitivity is probably due to the low number of BC-positive cases. Thus, when probable-, or probable/possible-BSI are classified as true-positives, sensitivity and specificity of T2Bacteria rose to 85% and 95%, respectively

Conclusions: T2Bacteria panel rapidly and accurately diagnosed pediatric BSIs caused by 6 common bacteria, with small blood volumes. These findings support its clinical use in the setting of pediatric HSCT, which is characterized by high risk of occurrence of serious and life-threatening infections.

Disclosure: Nothing to declare

P306

Development of a risk prediction model of subsequent bloodstream infection after carbapenem-resistant enterobacteriaceae isolated from perianal swabs samples in patients with hematological diseases

J. Liu[1], E. Jiang[1]

[1]Center for Blood Diseases, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China

Background: Patients with hematological diseases are at higher risk of developing carbapenem-resistant Enterobacteriaceae (CRE) bloodstream infection (BSI) and associated with high mortality. Prediction model for a subsequent CRE BSI in hematological patients with CRE isolated from previous perianal swab samples can provide timely and useful target treatment strategies.

Methods: The data were extracted from patients with CRE isolated from perianal swab samples at the Hematopoietic Stem Cell Transplantation Center of Blood Diseases Hospital, Chinese Academy of Medical Sciences between July 2017 to October 2020 January. Patients who developed subsequent CRE BSI were compared with those who did not develop BSI. Univariate logistic analysis, multivariate logistic analysis and stepwise regression analysis were carried on a variety of clinical factors.

Results: A total of 215 cases were included and 29 (13.4%) patients of them with CRE isolated from perianal swab samples developed CRE BSI subsequently. Of the 29 patients with CRE BSI, 9 (31%) died of CRE BSI within 30 days. The CRE strains isolated from perianal swab samples and blood cultures of these 29 patients were consistent, and the resistance to commonly used antibiotics was highly similar. Multivariate analysis showed that C-reactive protein(CRP)>30mg/l(OR 10.613, 95%CI 2.965~37.985, $P = 0.000$), perianal infection(OR 6.450, 95%CI 2.223~18.714, $P = 0.001$), concomitant gastrointestinal symptoms (OR 4.175, 95%CI 1.476~11.813, $P = 0.007$), age>4 years (OR 3.415, 95%CI 1.222~9.541, $P = 0.007$)and neutrophil count $<0.025\times10^9$/L (OR 4.583, 95%CI 0.939~22.369, $P = 0.060$) were risk factors for CRE BSI in patients with CRE isolated from perianal swab samples ($P < 0.01$). They were included in the Logistic regression model to predict BSI. According to receiver operating characteristic (ROC) curve analysis, the cut-off value of the model was 0.921 (0.851-0.968, $P < 0.001$).

Conclusions: Hematological patients with CRE isolated from perianal swab samples have a relatively low incidence of subsequent BSI but a relatively high risk of death. The risk prediction model based on CRP, perianal infection, concomitant gastrointestinal symptoms, age and neutrophil count can effectively predict subsequent CRE BSI in patients with isolated from perianal swab samples and provide timely and effective treatment reference for this kind of patients.

Disclosure: Nothing to declare

P307

Phase 3 trial of transplant recipients with refractory cytomegalovirus with/without resistance receiving maribavir or investigator-assigned therapies: Subgroup analyses of efficacy and safety by renal impairment

S. Dadwall[1], R. Duarte[2], A. Ho[3], N. Kamar[4], J. Gu[5], A. Sundberg[5]

[1]City of Hope National Medical Center, Duarte, United States, [2]Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain, [3]Singapore General Hospital, Singapore, Singapore, [4]Toulouse University Hospital, Toulouse, France, [5]Takeda Development Center Americas, Inc., Lexington, United States

Background: Cytomegalovirus (CMV) infection is a serious concern for transplant recipients; a Phase 3 trial (SOLSTICE) in transplant recipients with refractory CMV infection with/without resistance (R/R) demonstrated that maribavir treatment was superior to investigator-assigned therapy (IAT; ganciclovir, valganciclovir, foscarnet, cidofovir) in clearance of CMV viremia at Study Week 8, and in clearance at Week 8 with maintenance through Week 16. We report subgroup efficacy and safety data by baseline renal impairment.

Methods: Hematopoietic cell/solid organ transplant recipients (aged ≥ 12 years) with R/R CMV infection were randomized 2:1 to either maribavir (400 mg BID) or IAT for an 8-week treatment phase with 12 weeks of follow-up. The primary endpoint was confirmed CMV viremia clearance (2 consecutive post-baseline confirmed plasma viral loads of <137 IU/mL, ≥5 days apart) at Study Week 8. Baseline renal impairment was defined by creatinine clearance per Cockcroft–Gault equation: none (>80 mL/minute), mild (50 to 80 mL/minute), moderate (30 to <50 mL/minute), and severe (<30 mL/minute). Central clinical laboratory creatinine concentrations were assessed every two weeks.

Results: Overall, 352 patients were randomized: 235 to maribavir and 117 to IAT. Baseline renal impairment status was balanced between the maribavir and IAT arms (% patients maribavir and IAT, respectively): none (34.5% and 33.3%), mild (30.2% and 35.9%), moderate (25.5% and 18.8%), severe (3.4% and 2.6%), and missing data (6.4% and 9.4%). In all renal impairment categories, a greater proportion of patients in the maribavir arm than in the IAT arm achieved CMV viremia clearance at Study Week 8 (**Table**). There was no change in median serum creatinine level from baseline to last on-treatment visit in patients receiving maribavir in all renal impairment categories. In the IAT arm, an increase in serum creatinine (μmol/L) from baseline to last on-treatment visit was observed across all renal impairment categories (median change: none, 8.80; mild, 9.00; moderate/severe, 9.00); for foscarnet-treated patients, a greater increase in serum creatinine than in the overall IAT arm was observed across

all baseline renal impairment categories (median change: none, 9.00; mild, 18.00; moderate/severe, 35.50).

Baseline renal impairment	Maribavir % (n/N)	IAT % (n/N)	Adjusted difference in proportion of responders % (95% CI)
None	56.8 (46/81)	25.6 (10/39)	32.3 (14.47, 50.11)
Mild	47.9 (34/71)	26.2 (11/42)	21.6 (3.77, 39.39)
Moderate	68.3 (41/60)	18.2 (4/22)	49.7 (29.83, 69.51)
Severe	37.5 (3/8)	0.0 (0/3)	–
Missing	46.7 (7/15)	27.3 (3/11)	15.3 (−20.93, 51.48)

Conclusions: In these post-hoc analyses, a greater proportion of patients on maribavir achieved CMV viremia clearance at Week 8 than IAT in all renal impairment categories consistent with the primary endpoint analysis observed for the overall population. No changes in creatinine levels from baseline to last on-treatment visit were observed in the maribavir arm while an increase was seen in the IAT arm.

Funding: Takeda Development Center Americas, Inc.

Clinical Trial Registry: NCT02931539

Disclosure: Sanjeet Dadwal: consultant: Allovir, Cidara, Merck; research support (to institution): Allovir, Amplyx, Ansun Biopharma, Gilead, Karius, Merck; speakers bureau: Astellas, Merck; advisory board: Aseptiscope, Merck.

Rafael Duarte: research support (to institution): Janssen, Merck, Novartis, Omeros, Roche Diagnostics; speakers bureau: Bristol Myers Squibb, Gilead, Incyte, Jazz Pharmaceuticals, Merck, Omeros, Pfizer, Sanofi, Shire, a Takeda Company, Sobi; advisory board: Bristol Myers Squibb, Gilead, Incyte, Jazz Pharmaceuticals, Merck, Omeros, Pfizer, Sanofi, Shire, a Takeda Company, Sobi.

Alosiyus Ho: nothing to declare.

Nassim Kamar: consultant: AstraZeneca, Biotest, ExViR, Hansa, Merck Sharp & Dohme, GlaxoSmithKline, Novartis, Sandoz, Takeda; honoraria/travel expenses: Astellas, Biotest, Chiesi, Novartis, Sandoz, Takeda.

Joan Gu and Aimee Sundberg: employee and stockholder: Takeda.

P308

Persistence of the immune response after vaccination against sars-cov-2 in patients with oncohematological diseases who underwent autologous or allogenic stem cell transplantation

L. Pérez-Lamas[1], S. Rodríguez-Mora[2], G. Casado-Fernández[2], M. Corona[1], M. Torres[2], L. Vigón[2], M.A. Murciano-Antón[3], A. Luna[1], A. Chinea[1], P. Herrera[1], G. Moreno[1], J. López-Jimenez[1], M. Coiras[2], V. García-Gutiérrez[1]

[1]Hospital Universitario Ramón y Cajal. IRYCIS., Madrid, Spain, [2]National Center of Microbiology, Instituto de Salud Carlos III, Madrid, Spain, [3]Centro de Salud Doctor Pedro Laín Entralgo, Alcorcón, Spain

Background: Loss of vaccine immunity after hematopoietic stem cell transplantation (HSCT) is well established for some vaccines such as polio, varicella, rubella or tetanus. However, to date, there is no evidence assessing the loss or persistence of vaccine immunity against SARS-CoV2 after transplantation. The aim of the study is to evaluate SARS-CoV2 vaccine-induced immunity after HSCT.

Methods: Fourteen patients who received allogenic (n = 6) or autologous (n = 8) HSCT due to an oncohematological disease (3 acute leukemias, 3 myelodysplastic/myeloproliferative syndromes, 4 lymphomas, 4 multiple myelomas) after having received one or two-dose of the COVID-19 vaccine schedule (13/14; 92.8% mRNA-1273-Moderna) were recruited. In the case of allogeneic transplants, all donors were fully vaccinated. Sixteen healthy donors who had received the complete vaccination regimen were used as controls (87,5% BNT162b2 mRNA-Pfizer; 12,5% mRNA-1273). The immune response was analyzed pre-transplant and 2.5 months post-transplant. The mean time from vaccination to analysis was 64 days. In healthy subjects, the immune response was analyzed 1 month and 3 months after receiving the full vaccine regimen.

IgG titers against SARS-CoV-2 were quantified by Euroimmun-Anti-SARS-CoV-2 ELISA. Direct cellular cytotoxicity (DCC) was determined against Vero E6 cells infected with pseudotyped SARS-CoV-2, measuring caspase-3 activation after co-culture with peripheral blood mononuclear cell (PBMCs). Antibody-dependent cellular cytotoxicity (ADCC) analyses were performed using Annexin V on Raji cells as a target.

Results: Patients in the allogeneic HSCT group showed reduced levels of specific IgGs compared to healthy donors in the pre-transplant baseline sample (-2.6-fold; $p = 0.0011$) (Fig.1a). In the post-transplant sample, results were variable, with some patients showing a decrease in antibody levels after transplantation while others show an increase in comparison with the baseline sample. IgGs levels were also decreased (2.3 fold; $p = 0.0476$) in patients with autologous HSCT and did not change significantly after HSCT.

Unspecific ADCC response was decreased (-1.5-fold; $p = 0.0072$) before HSCT compared to healthy donors. However, previous response was maintained after HSCT (Fig.1b). DCC response against SARS-CoV-2-infected cells increased 2.1-fold in healthy donors 3 months after two-dose vaccine regimen (statistical significance was not reached); similar response was observed in individuals with autologous HSCT, but this response was reduced 2.7-fold after allogenic HSCT (Fig.1c). Consequently, PBMCs from individuals with allogenic HSCT showed a reduced capacity to eliminate SARS-CoV-2 infected cells (Fig.1d). DCC was reduced 7.9- and 6.2-fold ($p = 0.0043$) before and after HSCT, respectively, in comparison with healthy donors. In individuals who underwent autologous HSCT, this capacity was reduced 4.0- and 5.1-fold ($p = 0.0403$) before and after SCT, respectively.

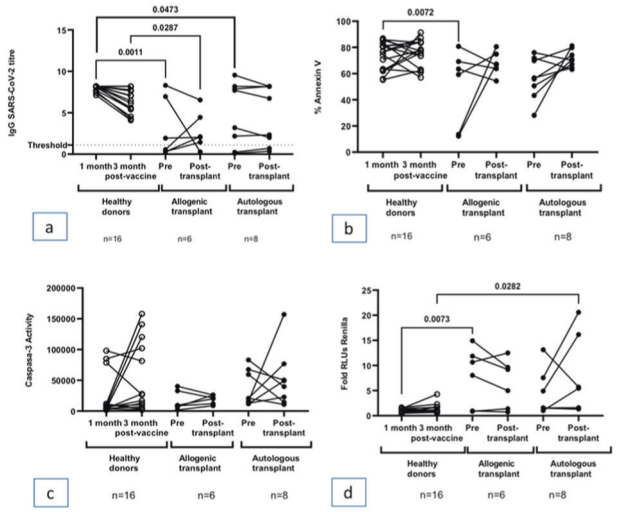


Fig1. Analysis of immunity against SARS-CoV2. a)Humoral response. b)ADCC. c)DCC. d)DCC- viral replication.

Conclusions:

- IgGs levels developed after receiving one- or two-dose vaccination schedule were maintained after autologous HSCT and increased in some patients with allogeneic HSCT, possibly due to donor vaccination.
- ADCC in PBMCs from oncohematological patients was slightly decreased in comparison with healthy donors before HSCT and it was recovered after HSCT in both groups with allogenic or autologous HSCT.
- DCC was mostly impaired in patients who received allogenic HSCT, but both groups showed a reduced capacity to eliminate SARS-CoV-2 infected cells before and after HSCT.

Disclosure: Nothing to declare

P309

Adenovirus infection in gi biopsies of immunocompromised patients who underwent allogeneic stem cell transplantation

H.Z. Pikkel-Geva[1], D. Wolf[2], M. Rivkin[2], E. Even-Or[2], I. Zaidman[2], E. Zimran[2], P. Stepensky[2], S. Grisaro[2], B. Avni[2]

[1]Hebrew University, Jerusalem, Israel, [2]Hadassah Medical Center, Jerusalem, Israel

Background: Human Adeno Virus (HAdV) infections are associated with significant morbidity and mortality in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT)(1)(2), Whereas the gastrointestinal (GI) tract is recognized as a major site of persistence and reactivation in pediatric HSCT recipients, the prevalence and consequences of HAdV GI infection in the adult setting are not well defined(3). Here we studied the prevalence, risk factors, and consequences of HAdV GI-tissue infection in HSCT recipients with GI symptoms undergoing GI biopsy.

Methods: Eighty-eight HSCT recipients (73 adults and 15 pediatric) who presented with GI symptoms leading to GI biopsy between 2012 and 2017, were retrospectively studied. The presence of HAdV DNA in the tissues was analyzed by Real-Time PCR. Patients' clinical data were retrieved from the patients' electronic files.

Results: HAdV GI tissue infection was detected in 23.9% of patients examined (33.3% and 23.9% of the pediatric and adult population respectively). No significant differences were found in patients' characteristics between the adults and pediatric population, except for a higher percentage of ATG used in the pediatric population. A higher prevalence of cGVHD was detected in the population presenting with GI positive HAdV-PCR before day +100. Twenty-one patients were found to have HAdV-PCR positivity in their GI biopsy, while twenty-seven patients were diagnosed with HAdV infection in other sites (14 of them were positive also in their GI biopsy). Arab ethnicity ($p = 0.001$), cGVHD ($p = 0.023$), the presence of bloody diarrhea ($p = 0.033$), and positive cytomegalovirus (CMV) PCR in the GI tissue ($p = 0.033$) were significantly correlated with HAdV detection in GI biopsies. Over a median follow-up of 9.3 (5.0-13.6) months. Detection of HAdV at any site was not associated with a lower survival rate.

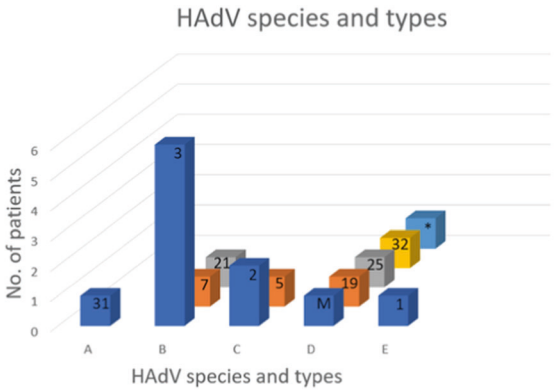


*Figure 1: HAdV species and subtypes among the research population. Legends: M- missing, *- types 60, 28 and 17 in the same sample.*

Conclusions: To our knowledge, this is the first study reporting on the prevalence of PCR positive HAdV infection in GI symptomatic HSCT recipients. Our data shows a trend towards a higher sensitivity of HAdV PCR in GI biopsies in detecting HAdV infections, compared to HAdV PCR in feces samples. These results might suggest that there is an under-diagnosis of GI HAdV infections in symptomatic patients following allogeneic stem cell transplantation. Real-time diagnosis might alter the treatment approach to GI symptomatic patients thus preventing further deterioration. Our results should be confirmed in larger prospective studies.

Disclosure: Nothing to declare

P310

Impact of colonization by multidrug-resistant gram-negative bacteria on bloodstream infections in early phase of hematopoietic stem cell transplantation

Y. Rogacheva[1], M. Popova[1], V. Markelov[1], O. Goloshchapov[1], A. Spiridonova[1], Y. Vlasova[1], S. Bondarenko[1], L. Zubarovskaya[1], A. Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, Saint Petersburg, Russian Federation

Background: Multidrug-resistant gram-negative bacteria (MDRGNB) are still one of the actual problems in oncology and hematology. The question remains whether colonization by MDRGNB leads to an increased risk of subsequent bloodstream infections (BSI) especially in patients after allogeneic hematopoietic stem cell transplantation (allo-HSCT)

Methods: The retrospective study included 288 patients received the first allo-HSCT between 2018 and 2019. The median age was 32 (18-66) years, male – 152 (53%). Majority of patients had acute leukemia (n = 178, 62%) and received transplant from

matched unrelated (n = 120, 42%) or haploidentical (n = 75, 26%) donor. We used a screening program with detecting bacteria by microbiological culture from non-sterile sites (stool, throat, urinary) twice a week during the HSCT.

Results: Colonization of non-sterile sites before allo-HSCT by at least one MDR bacteria was detected in 64 (28%). In most cases resistance is due to extended spectrum beta-lactamases (ESBL) – 55 (86%), while carbapenemases in combination with ESBL were detected in 9 (14%) of patients. Etiology of colonization was presented by *K. pneumoniae* -35 (55%), *E. coli* – 14 (21%), *Pseudomonas spp*. - 7 (11%), *Citrobacter spp*. – 2 (2.5%), *Enterobacter spp*. – 1 (1.5%), *Acinetobacter spp*. – 1 (1.5%) and 4 (7.5%) of patients were colonized with more than one bacteria including *K. pneumonia*.

After allo-HSCT the colonization was significantly higher than before transplantation (n = 161, 56%, p = 0.001), mainly due to carbapenem - and ESBL - producing bacteria – 118 (73%) (p = 0.001). The etiology of colonization after allo-HSCT was presented by *K. pneumoniae* – 99 (61.5%), *E. coli* - 12 (7.4%), *Pseudomonas spp*. - 23 (14%), *Enterobacter spp*. - 1 (0.6%), *Chryseobacterium indologenes* – 1 (0.6%), *Proteus spp*. - 3 (1.9%) *Acinetobacter spp*. – 6 (3.7%) and 16 (10.3%) of patients were colonized with more than one bacteria including *K. pneumonia*. BSI in the early period after transplantation developed in 76 (26%), and in 43 (56%) was caused by MDRGNB. The etiology of BSI included *K. pneumoniae* - 51%, *E. coli* - 26.5%, *Pseudomonas spp*. - 11.6%, *Acinetobacter spp*. - 4.6%, as well as *K. pneumonia* in combination with other bacteria - 6.3%. The etiology of BSI was the same bacteria that colonized non-sterile sites 2 weeks before the detection bacteria in bloodstream in 30 (69%) patients. Colonization by MDRGNB was associated with the development of BSI (p < 0.0001). The 100-day overall survival was significantly lower in patients with colonization of non-sterile sites compared with patients without colonization: 60.6% vs 88.2% (p = 0.001).

Conclusions: Colonization of MDRGNB after allo-HSCT reached 56%. *K. pneumonia* was predominant etiology in both colonization and bloodstream infections. Colonization by MDRGNB was significantly associated with the development of BSI in the early period after HSCT.

Disclosure: Nothing to declare

P311

Real-world experience with isavuconazole in allogeneic stem cell transplantation

G. Oarbeascoa[1,2], M. Torres[3], A. Perez Martinez[4], M. Suarez-Lledó[5], A. Chinea[6], M.J. Pascual Cascón[7], L. Vazquez[8], I. Espigado[9], I. Izquierdo[10], R. Parody[11], I. Garcia Cadenas[12], M. Calbacho[13], P. Gonzalez Sierra[14], I. Heras[15], L. Yañez[16], A. Torrent[17], G. Bautista[18], S. Gonzalez[19], E. Roldan[20,21], J.C. Vallejo[22], R. Bailen[1,2], A. Borrego[3], J. Lopez-Jimenez[6], M. Cuesta Casas[7], C. Solano[4], M. Kwon[1,2], . Spanish Group of Hematopoietic Stem Cell Transplantation and Cell Therapy (GETH-TC)[23]

[1]Hospital General Universitario Gregorio Marañon, Madrid, Spain, [2]Instituto de Investigación Sanitaria Gregorio Marañon, Madrid, Spain, [3]Hospital Universitario de Gran Canaria Dr. Negrin, Las Palmas de Gran Canaria, Spain, [4]Hospital Clínico Universitario de Valencia, Valencia, Spain, [5]Hospital Clinic Institute of Hematology & Oncology, Barcelona, Spain, [6]Hospital Universitario Ramon y Cajal, Madrid, Spain, [7]Hospital Regional de Málaga, Málaga, Spain, [8]Hospital Universitario de Salamanca, Salamanca, Spain, [9]University of Seville (Medicine dept.), HUV Macarena-HUV Rocío, IBiS/CSIC, Sevilla, Spain, [10]Hospital Universitario Miguel Servet, Zaragoza, Spain, [11]Institut Català Oncologia-Hospital Duran i Reynals, Barcelona, Spain, [12]Hospital de La Santa Creu I Sant Pau, Barcelona, Spain, [13]Hospital Universitario 12 de Octubre, Madrid, Spain, [14]Hospital Universitario Virgen de las Nieves, Granada, Spain, [15]Hospital Universitario Morales Meseguer, Murcia, Spain, [16]Hospital Universitario Marques de Valdecilla, Santander, Spain, [17]Institut Català d'oncologia, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain, [18]Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain, [19]Hospital Universitario Central de Asturias, Oviedo, Spain, [20]Hospital Universitario Vall d'Hebron, Barcelona, Spain, [21]Vall d'Hebron Instituto de Oncología (VHIO), Barcelona, Spain, [22]Hospital Universitario Donostia, Donostia, Spain, [23]GETH-TC, Madrid, Spain

Background: Invasive fungal infections (IFI) pose one of the most important infectious complications in hematopoietic stem cell transplantation (HSCT). Isavuconazole (ISV) is a new generation azole with a more favourable adverse and interaction profile approved for the treatment of invasive aspergillosis and mucormycosis.

Methods: To analyse the indications, effectiveness, adverse event profile and drug interaction management of ISV in the real-world setting in adults who received allogeneic-SCT within the Spanish Group of HSCT and Cell Therapy (GETH-TC).

Results: 166 adult patients treated from 2017 to 2021 were retrospectively analysed (Table 1). Median age was 48 years, 57% were male. The most common stem cell source was peripheral blood in 91%, the most frequent donor were haploidentical (39%) and matched siblings (35%). 57% used reduced intensity conditioning. GvHD prophylaxis consisted in post-transplant cyclophosphamide in 64%. In 81 patients ISV was used for treatment of IFI, and in 85 patients ISV was used as off-label prophylaxis (secondary in 25%). The median duration of ISV for the treatment of IFI was 86 days, 57 days as prophylaxis.Among patients who received ISV as treatment, it was empirically initiated in 5%. The most frequent indication was invasive aspergillosis (78%), followed by mucormycosis (6%), and in 5% a *Geotrichum spp* IFI or invasive *Candida* infection. In 52% ISV was used as second line (or more), usually as savage therapy (32%), due to adverse events of prior antifungals (26%) or as a directed de-escalation therapy (26%). 74% of the patients had received prior antifungal prophylaxis. The most frequent reason for ISV discontinuation was therapeutic success (45%). 58% of the patients showed at least one pharmacological interaction, mainly associated to immunosuppressive drugs (49% of the interactions). Only 9% of the patients reported ISV-related adverse events (AE), mainly related to liver enzyme alterations (71% of the AE). ISV was not discontinued due to these AE.

In the prophylaxis group, the most frequent reason for ISV withdrawal was the resolution of IFI risk in 62%. 6 breakthrough IFI were reported among the 81 patients (aspergillosis in 5 cases). 16% of the patients reported ISV-related AE: cholestasis (11%), hypertransaminasemia (9%) and hyperbilirubinemia (5%). 3% of the patients developed cytopenia (1 case of neutropenia and 1 case of thrombopenia). ISV was discontinued in 8% of the patients due to AE. 84% of the patients showed at least 1 interaction (multiple in 41%), mainly related to immunosuppressive drugs (53%), and in 10% of the cases, due to small molecules (mainly ruxolitinib and gilteritinib). With a median follow-up of 321 days since ISV initiation, the 1-year OS was 50% for the treatment group and 64% for the prophylaxis group (Figures 1 and 2).

Table 1. Patient characteristics (N=166)		
Age (median, range)	48 (18-73)	
Gender	Male 95 / Female 71	
SCT indication	AML	69 (42%)
	MDS	15 (9%)
	ALL	15 (9%)
	NHL	26 (17%)
	HL	10 (6%)
	Others	27 (16%)
Donor	Haploidentical	64 (39%)
	Matched sibling	58 (35%)
	Matched unrelated	27 (16%)
	Mismatched unrelated	14 (8%)
	Cord blood	3 (2%)
Conditioning	Myeloablative	71 (43%)
	Reduced intensity	95 (57%)
GvHD prophylaxis	PTCy based	106 (64%)
	MTX-CNI based	34 (20%)
	Tacro-Siro	15 (9%)
	Others	11 (7%)
Disease Risk Index	Low	14 (9%)
	Intermediate	74 (46%)
	High	57 (35%)
	Very high	17 (10%)
Prior lines (median, range)	2 (0-7)	
HCT-CI	0-2	97 (59%)
	≥3	69 (41%)
Comorbidities	84 patients (51%) presented at least 1	
	Mild liver disease	11 (7%)
	Mod-severe liver disease	3 (2%)
	Moderate lung disease	26 (16%)
	Severe lung disease	18 (11%)
	Obesity	9 (5%)
	Kidney failure	9 (5%)
Acute GvHD	Cumulative incidence of G2-4 on day +180	39%
Chronic GvHD	Cumulative incidence of moderate-severe on +2 years	32%

Figure 1. Survival since ISV initiation in the IFI treatment group

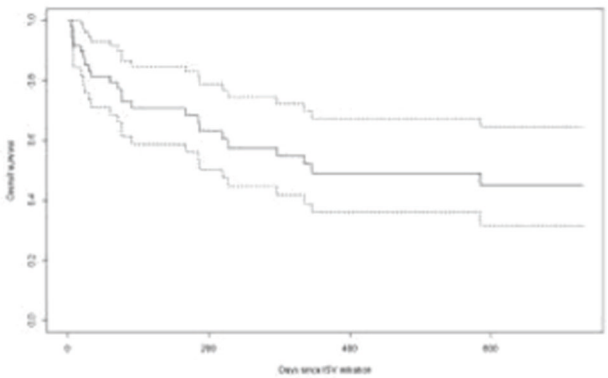
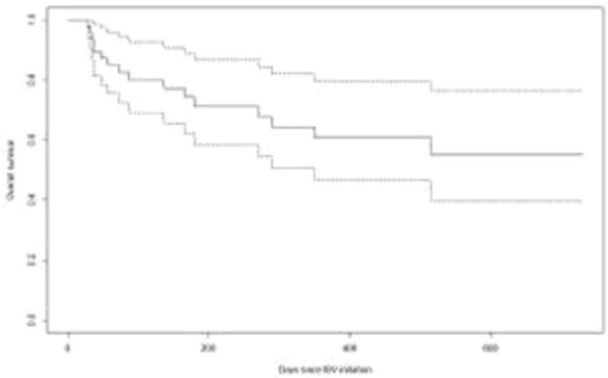


Figure 2. Survival since ISV initiation in the prophylaxis group



Conclusions: ISV is an effective option for IFI treatment and prophylaxis after allogeneic HSCT. The favourable interaction profile allowed a safe use of concomitant drugs, especially immunosuppressants. Of note, a significant proportion of its use in the real- world setting is in prophylaxis, and the incidence of breakthrough IFI is low. Adverse events were not common, and most of them resolved with ISV withdrawal.

Disclosure: Research funding: Pfizer.

P312

Impact of societal and healthcare infection control measures on incidence of non-sars-2-cov respiratory viral infections in HSCT in-patient admissions; a single uk centre experience

J. Murrell[1], T. Hill[2], A. State[1], S. Francis[1], L. Pickersgill[1], M. Raza[1], J.A Snowden[1]

[1]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom, [2]University of Sheffield Medical School, Sheffield, United Kingdom

Background: Seasonal and non-seasonal respiratory viral pathogens have potential to cause serious morbidity and mortality following HSCT, as well as health resource demands including in-patient hospital admissions and anti-viral treatment. In March 2020, outbreak of the COVID-19 pandemic in the UK led to several government-enforced measures aimed at reducing the spread of SARS-2-CoV, including shielding of the clinically vulnerable, social distancing, and face-masking in public, along with specific measures in healthcare and HSCT units (NICE Guidance NG164 and EBMT/BSBMTCT Guidelines). We considered that these measures may have impacted upon the incidence of non-SARS-2-CoV respiratory viral infections in HSCT patients, and associated morbidity, mortality and healthcare resource utilization.

Methods: We retrospectively evaluated in-patient admissions for positive non-SARS-2-CoV respiratory viral PCR tests in adult HSCT patients (16 and over) in Sheffield Teaching Hospitals in two 6-month autumn/winter cohorts 1) the 6-month period prior to COVID-19 measures (01/09/2019-29/02/2020) and 2) the same 6-month period one year later, when measures had been enforced

(01/09/2020-28/02/2021). PCR tests were performed on respiratory samples, including for Respiratory Syncytial Virus (RSV), Parainfluenza Virus (PIV) 1-4, Human Metapneumovirus (HMPV), Seasonal Coronavirus, Rhinovirus, Adenovirus, and Influenza A&B. In those testing positive, admission days, days on HDU/ITU, mortality, and costs of admission were compared between the two periods.

Results: During period 1 (01/09/2019-29/02/2020), there were 90 episodes of non-SARS-2-CoV respiratory viral infections in 263 admissions (34.2 per 100 admissions), due to RSV (n = 26), Rhinovirus (n = 22), PIV 1-4 (n = 14), Influenza A (n = 12), Seasonal Coronavirus (n = 9), Adenovirus (n = 4), and HMPV (n = 3). In period 2 (01/09/2020-28/02/2021), there were 13 episodes in 159 admissions (8.2 per 100 admissions) with Rhinovirus (n = 12) and Adenovirus (n = 1). Total number of in-patient bed days with non-SARS-2-CoV respiratory viral infections in period 1 was 555, including 19 HDU/ITU bed days. In period 2, there were 196 in-patient days, with HDU/ITU 5 bed days. There were 3 deaths within 28 days of non-SARS-2-CoV respiratory viral infection in period 1, compared to 1 death in period 2. Based on NHS costings, there was a major reduction in total cost of admissions relating to non-SARS-CoV respiratory viral infections (including HDU/ITU) in period 1 versus period 2.

Conclusions: Our data support a significant reduction in incidence of non-SARS-2-CoV respiratory viral infections consequent upon introduction of nationwide (societal and healthcare) infection control measures, with a reduction in ward admission days, HDU/ITU bed days, mortality, and associated costs. Whilst the COVID-19 pandemic also impacted on our HSCT activity (with 151 procedures in 2018, 140 in 2019, 97 in 2020, and 117 in 2021, with reduction in autografts, but allograft activity stable) and may explain some difference, it is likely that the impact of wide-ranging infection control measures resulted in significantly reduced infections, admission rates and healthcare resource utilization in HSCT centres. Analysis of a third cohort is ongoing, covering the current equivalent 6-month period (01/09/2021 – 28/02/2022), during which different UK COVID-19 measures are in place, with some national relaxations following SARS-2-CoV vaccination of majority of UK adults, whilst previous levels of HSCT activity within our programme is resumed.

Disclosure: Nothing to declare

P313

Infective complications following allogeneic stem cell transplantation for hematological malignancies: Results of an innovative program for surveillance, prophylaxis and treatment (batmo protocol)

M. Malagola[1], A. Turra[1], L. Signorini[2], N. Polverelli[1], L. Masina[1], G. Del Fabro[2], S. Lorenzotti[2], B. Fumarola[2], M. Farina[1], E. Morello[1], L. Gandolfi[1], E. Accorsi Buttini[1], T. Zollner[1], S. Bernardi[3], F. Castelli[2], D. Russo[1]

[1]University of Brescia, Bone Marrow Transplant Unit, ASST-Spedali Civili Brescia, Chair of Hematology, Brescia, Italy, [2]University of Brescia and ASST Spedali Civili Hospital, Brescia, Italy, [3]Centro di Ricerca Ematologico – AIL, ASST Spedali Civili di Brecia, Brescia, Italy

Background: Infective complications represent a relevant cause of morbidity and mortality in patients undergoing allogeneic haematopoietic stem cell transplantation (Allo-SCT). The BATMO (Best-Antimicrobial-Therapy-TMO) is an innovative program for infections prevention and management, adopted in our Center since 2019.

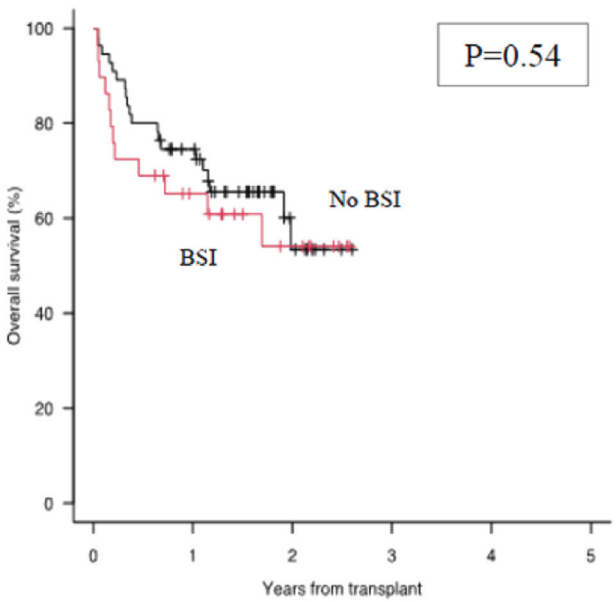
Table 1. Main characteristics of the BATMO program.

Prophylaxis	Therapy
1. STOP antibacterial prophylaxis with fluoroquinolone. 2. Fluconazole prophylaxis for patients at low risk of fungal infections (Stanzani et al 2019); posaconazole prophylaxis for high-risk patients. 3. Letermovir (day 0/+100) in CMV IgG+ patients.	1. Empirical therapy based on the patient's clinical history and its colonization by MDR microorganisms. 2. First-line therapy: piperacillin-tazobactam or ceftazidime or cefepime + glycopeptide in case of suspected infection with Gram + bacteria. 3. Second-line drugs, such as carbapenems, and new antibiotics, such as ceftazolan-tazobactam or ceftazidime-avibactam, should be used based on the antibiogram data, except in the patient colonized by *Klebsiella pneumoniae* KPC (first-line therapy)

Methods: Data on infective complications of 116 transplanted before BATMO protocol (cohort A; 2016 - 2018) were compared with those of 84 patients transplanted following BATMO protocol (cohort B; 2019 - 2021). The clinical and transplant characteristics of the 2 cohorts are well comparable, with the exception of a significantly higher proportion of myeloablative regimens and haploidentical donors in cohort B.

Results: No change in the incidence of infections with organ localization was observed between the two cohorts. A significant reduction in *Clostridioides difficile* infections by day +100 was observed in cohort B (47% vs 15%; p = 0.04). Neither the incidence of BSI and of the various etiological agents, nor the mortality from Gram negative bacteremia (Figure 1) and the incidence of invasive fungal infections was different in the two cohorts. The incidence of CMV reactivation by day +100 dropped drastically in patients of cohort B, following letermovir registration (51% vs 15%; p = 0.00001).

Figure 1. OS of the 84 patients undergoing allo-SCT from 2019 and 2021 (BATMO program), according to the development of Gram negative bacteremia by day + 100 (OS at 1 and 2 years – event vs no event: 65.1% vs 74.5% and 54% vs 53.4%, respectively; p = 0.54)



Conclusions: The results of this study suggest that the BATMO program is safe. In particular, the choice to avoid prophylaxis with fluoroquinolone was not associated with an increased Gram negative mortality and was associated with a significantly reduction of *Clostridiodes difficile* infections. Anti-CMV prophylaxis with letermovir confirmed its efficacy in significantly reducing CMV reactivation. Even though patients of cohort B were at higher risk of developing fungal infections (more haploidentical transplants with more myeloablative regimens), the extensive use of posaconazole for prophylaxis balanced this risk and no increase in incidence and mortality from fungi was observed.

Clinical Trial Registry: NA

Disclosure: All the Authors declare no conflict of interests

P314

Beyond the respiratory tract – the impact of a respiratory viral outbreak in a HSCT unit in india

R. Raj[1], R. Uppuluri[1], V. Swaminathan[1], S.K. Meena[1], H. Varla[1], I. Jayakumar[1], V. Venkatesan[1]

[1]Apollo Cancer Hospital, Chennai, India

Background: Introduction: Respiratory viral infections in children undergoing haematopoietic stem cell transplantation (HSCT) can result in mortality rates of 33%. We report a retrospective outcome analysis following an outbreak of respiratory viral infection in our transplant unit during a heavy monsoon season and its impact beyond the respiratory tract.

Methods: We collected retrospective data on the respiratory viral panel screening for influenza, parainfluenza, RSV, adenovirus, rhinovirus, coronavirus and enterovirus and its impact on respiratory, haematological, hepatic systems and mortality.

Results: A total of 42 HSCT patients developed respiratory viral infections between August 2021 and November 2021. All patients had upper respiratory tract symptoms. Amongst this cohort, we documented Parainfluenza-3 (PIV-3) in 23/42 (54.7%), Influenza in 2/42 (4.7%), RSV in 7/42 (16.6%), rhinovirus in 8/42 (19%) and enterovirus in 2/42 (4.7%). Adenovirus coinfection was seen 3 children with PIV-3. Sepsis with multi-organ failure and the presence of pulmonary co-pathogens caused mortality in 4 children and one child had refractory autoimmune haemolytic anaemia. All the 5 children who died had PIV-3 and although the overall mortality was 5/42 (11.9%), the PIV-3 associated mortality was higher at 5/23 (21.7%). In the second week of the infection all children had profound pancytopenia and altered liver enzymes was seen in 7/42 (16.6%) and significant autoimmune haemolytic anaemia in 6/42 (14.3%). Our series confirms that high mortality is associated with PIV-3 infection especially those with coinfection with other viruses. In HSCT recipients, significant hepatitis and autoimmune haemolytic anaemia were seen during this outbreak.

Conclusions: Despite strict enforcement of infection control policies, respiratory viral outbreaks do occur in HSCT units and children are the most vulnerable. We need to manage the respiratory effects with careful risk assessment, and effective broad-spectrum anti-microbials in those who are at risk of secondary infection. However, we also need to watch for hepatic dysfunction during the viraemia and provide supportive care with ursodeoxycholic acid, N acetyl cysteine and adequate nutrition. Life threatening autoimmune haemolytic anaemia needs urgent introduction of steroids and rituximab if refractory. The non respiratory complications result in morbidity and mortality in PIV-3 infection. There are no effective antivirals and aggressive healthcare interventions to contain and outbreak and isolation of actively infected patients to prevent spread is the only way forward.

Disclosure: NIL

P315

The humoral response to sars-cov2 vaccination is influenced by vaccination scheme, immunosuppression, lymphocyte counts and time after allohct

T. Meyer[1], R. Zeiser[1], R. Wäsch[1], H. Bertz[1], J. Finke[1], D. Huzly[2], C. Wehr[1]

[1]Medical Center, University of Freiburg, Germany, Freiburg, Germany, [2]Institute of Virology, University of Freiburg, Germany, Freiburg, Germany

Background: To determine factors influencing the vaccination response against SARS-CoV2 is of great importance in recipients of allogeneic hematopoietic cell transplantation (alloHCT) as they were reported to experience (1) an increased mortality after SARS-CoV2 infection, (2) an increased risk of extended viral persistence and (3) reduced vaccination response.

Methods: We retrospectively collected real-life data on humoral response after vaccination within Germany licensed vaccines (BNT™, Moderna™, AstraZeneca™, Johnson/Johnson™, heterologous scheme vector/mRNA) in recipients of alloHCT at our center. Anti-SARS-CoV-S1-IgG was determined by ELISA (SARS-CoV-2 IgG, Siemens™). Anti-S1-IgG titres of >100 BAU/ml were classified as sufficient response, values of 21.8-100 BAU/ml as low response and values <21.8 BAU/ml as no response. Lymphocyte subsets were quantified 0-3 months prior to the last documented vaccination with flow cytometry.

Results: Anti-SARS-CoV-S1-IgG titres were available in 192 adults vaccinated between January-September 2021. Median age at alloHCT was 54 years (range 19-79 years). More than 90% of patients were transplanted for malignant diseases. Half of patients received a graft from a MUD, one third from a MRD. Graft source was peripheral blood and conditioning intensity was MAC/reduced toxicity MAC in the majority of patients.

An mRNA based vaccination scheme was used in 58%, a vector based in 10% and 5% of patients were vaccinated with onetime vector and mRNA-based combination. Details on the vaccine were not available in ¼ of patients and 1% received a non-conventional combination. Median time between alloHCT and best vaccination response was 3.3 years (range 0.35-26.03 year). A sufficient humoral response was achieved in 131 (68%), a low response in 19 (10%) and no response was observed in 42 (21%) patients. All patients ($n = 10$, 100%) with onetime vector and mRNA combination responded sufficiently.

Immunosuppressive treatment was used in 74 patients. Of those, 56% responded sufficiently compared to 75% in the non-immunosuppression group ($p < 0.05$). Patients under ruxolitinib treatment ($n = 23$) had a sufficient humoral response rate in 61%, patients under glucocorticosteroids ($n = 14$) in 50%. Individuals receiving an ATG based GvHD prophylaxis showed a sufficient response in 63% compared to 78% without ATG ($p < 0.05$). Overall sufficient responders showed higher B-cell (median 183 vs 64 cells/ul, $p < 0.05$) and CD4 + T-cell counts (median 339 vs 240 cells/ul, $p < 0.05$) than non-suffcient responders 0-3 months before vaccination. Concurrent with these findings is that only 52% of individuals vaccinated in the first year after alloHCT responded sufficiently while 76% of patients vaccinated more than one year after alloHCT had a sufficient response ($n = 136$, $p < 0.05$).

Conclusions: Overall the sufficient humoral response rate of 68% in our single center retrospective cohort is comparable to published data of prospective studies after vaccination with mRNA vaccines. Humoral response was dependent on B- and CD4 + T-cell counts at vaccination, time after transplant, active immunosuppression and the use of ATG. Interestingly, the heterologous vaccination scheme (vector, mRNA) showed a 100% effectiveness in our cohort pointing towards possible strategies for vaccination in non-responders.

Disclosure: Robert Zeiser received honoraria from Novartis, Incyte and Mallinckrodt, all outside of the present work.

P316

Letermovir prophylaxis reduces peak cmv titres and need for additional antiviral treatment in allogeneic haematopoietic stem cell transplantation

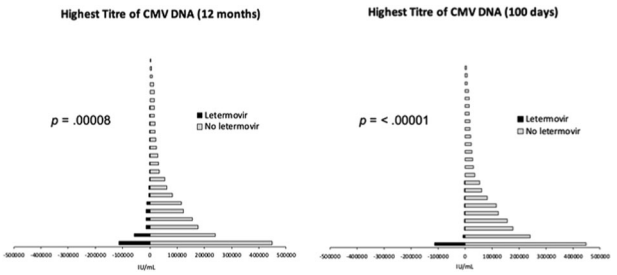
M. Buckton[1], S. Firbank[1], V. Bigley[1], M. Collin[1], E. Hurst[1], A. Publicover[1]

[1]The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom

Background: Prophylaxis with letermovir has become part of mainstream practice to prevent reactivation of human cytomegalovirus (CMV) in patients undergoing allogeneic haematopoietic stem cell transplantation (allo-HSCT). We reviewed the impact of letermovir prophylaxis in our institution by comparing two highly-matched cohorts of patients over a 100-day and 12-month period before and after its introduction.

Methods: We compared the incidence of CMV disease, DNA titres meeting the threshold for additional antiviral treatment and any detectable CMV DNA titres in a cohort who had received letermovir prophylaxis once daily for 100 days ($n = 29$) with a control cohort of patients treated before its introduction ($n = 29$). The cohorts were matched for conditioning regimen (stratified for T cell-deplete and T cell-replete regimens: $n = 22$ and 7, respectively), donor CMV IgG status (72% positive in letermovir cohort, 69% control), diagnosis and age. All patients were positive for CMV IgG prior to transplant and had DNA monitoring following transplant according to local protocols. We assume no other differences in clinical care between the cohorts.

Results: In the 100 days post-transplant, letermovir reduced the number of patients who met the threshold of > 3000 IU/mL to start antiviral treatment compared to the controls (6.9% and 82.8%, $p = <0.00001$). This was also seen over 12 months (27.6% and 82.8%, $p = 0.0051$). Furthermore, letermovir reduced the number of patients who developed any detectable CMV DNA in the first 100 days (31.0% and 82.8%, $p = 0.00015$), but results over 12 months were not significant ($p = 0.14$). In the cohort who received T cell-depletion conditioning, letermovir reduced the number of patients meeting the threshold over 100 days and 12 months (4.5% and 81.8%, $p = <0.00001$; 31.8% and 81.8%, $p = 0.0019$, respectively). Overall, peak viral titres recorded over both 100 days and 12 months was reduced in patients taking letermovir compared to the controls ($p = 0.00008$ and $p = <0.00001$, respectively). This was also seen in the T cell-deplete cohort ($p = 0.00058$ and $p = <0.00001$, respectively). The reduction in DNA titres did not translate into any significant difference in CMV disease, as only 1 patient (in the letermovir cohort) developed this. Results in the small ($n = 7$) T cell-replete regimen cohorts were also not significantly different. 17 patients died during 12 months (10 letermovir, 7 controls) - 7 during 100 days post-transplant (4 letermovir, 3 controls).



Conclusions: Letermovir significantly reduces peak and above-threshold CMV titres during the 100 days of treatment and 12 months following transplant in our cohort. This is also seen in the T cell-depletion subset, who are at greater risk of reactivation. Letermovir is well-tolerated and has low renal and myelotoxicity, in contrast to agents traditionally used for pre-emptive treatment. Our data shows that the benefits of letermovir persist beyond the 100-day window, reducing the risk of CMV reactivation and from antiviral treatment for 12 months.

Disclosure: Nothing to declare.

P317

Incidence and outcome of cmv reactivation in non-malignant pediatric HSCT recipients

Z. Szmit[1], J. Frączkiewicz[1], M. Salamonowicz-Bodzioch[1], A. Król[1], E. Gorczyńska[1], M. Mielcarek-Siedziuk[1], M. Ussowicz[1], T. Jarmoliński[1], I. Olejnik[1], A. Panasiuk[1], K. Kałwak[1]

[1]Wroclaw Medical University, Wrocław, Poland

Background: Hematopoietic stem cell transplantation is a curative approach for a constantly increasing number of non-malignant disorders. However, serious post-transplant complications remain a relevant obstacle for the broader and more common use of HSCT in the treatment of benign diseases. CMV reactivation/CMV disease is one of the most common infectious complications following HSCT, correlating with high morbidity and mortality. This issue is well investigated in transplant recipients with underlying malignancy; however, the data regarding the outcome of CMV viremia in pediatric non-malignant transplant recipients are sparse.

This single-center retrospective study aimed to evaluate the impact of CMV reactivation on the length of hospital stay and patients' general outcome.

Methods: The study incorporated all children and adolescents with a non-malignant disorder who underwent allogeneic HSCT in the Department of Pediatric Hematology, Oncology and Bone Marrow Transplantation during years 2015-2020. CMV reactivation was defined as CMV viremia at the level >1000 copies/ml (measured by qPCR) whereas patients with more than 10000 copies/ml were classified as individuals with high level CMV reactivation. Ganciclovir resistance was defined as an increase in CMV viremia followed by the need for second-line antiviral therapy.

Results: Among 94 patients (60 males/34 females; median age 3.8 years), 27 (29%) presented CMV reactivation, including 13 (14%) with high CMV viremia. Seventy HSCT recipients were CMV seropositive prior to transplant. Fifty-six received stem cells from a seropositive donor. Fourteen (15%) patients developed resistance for Ganciclovir. Nine (9.6%) presented with multiple CMV reactivations. Patients with CMV reactivation required longer hospitalization in comparison with those without CMV reactivation

(48 days vs 33 days, p = 0.007). We did not observe any correlation between CMV reactivation and the incidence of GvHD or invasive fungal infections. The survival analysis revealed significantly decreased overall survival (OS) and event-free survival (EFS) in those with high CMV viral load compared to patients with either low levels or no CMV reactivation (OS 0.7 vs 0.93, p = 0.016; EFS 0.6 vs 0.85, p = 0.007). Similarly, resistance for Gancyclovir correlated with worse survival (EFS 0.4 vs 0.87, p = 0.0004; OS 0.72 vs 0.93, p = 0.023) as well as multiple CMV reactivation (EFS 0.25 vs 0.84, p < 0.0001; OS 0.44 vs 0.94, p < 0.0001).

Conclusions: CMV reactivation is a common complication in non-malignant HSCT recipients. It correlates with a significantly longer hospital stay, affecting the patients' quality of life in early stage post-HSCT. Patients presenting with high CMV viremia, developing Ganciclovir resistance, or experiencing multiple reactivations had significantly lower chances for survival. Targeted anti-CMV prophylaxis should be strongly considered in non-malignant pediatric transplant settings, particularly for patients at risk of high CMV viral load reactivation.

Disclosure: Nothing to declare

P318

Low rate of documented infections as the cause of enterocolitis in allogeneic stem cell transplant recipients: Prospective study by the geth

S. Redondo[1,2,3,4], I. García-Cadenas[1,2,3,4], M. Cuesta[5], I. Sánchez-Ortega[6], F. Fernández-Avilés[7], E. Roldán[8], A. Torrent[9], M.C. Viguria[10], S. Villar[11], L. Bento[12], L. Yañez[13], R. Martino[1,2,3,4], J. Piñana[14,15]

[1]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [2]IIB-Sant Pau Research Institute, Barcelona, Spain, [3]José Carreras Leukemia Research Institute, Barcelona, Spain, [4]Universidad Autónoma de Barcelona, Barcelona, Spain, [5]Hospital Regional Universitario de Málaga, Malaga, Spain, [6]Institut Català d'Oncologia Hospitalet, Barcelona, Spain, [7]Hospital Clínic de Barcelona, Barcelona, Spain, [8]Hospital Vall D'Hebron, Barcelona, Spain, [9]Institut Català d'Oncologia Badalona, Barcelona, Spain, [10]Hospital Universitario de Navarra, Pamplona, Spain, [11]Clínica Universidad de Navarra, Pamplona, Spain, [12]Hospital Universitario Son Espases, Palma de Mallorca, Spain, [13]Hospital Universitario Marqués de Valdecilla, Santander, Spain, [14]Hospital Universitario Clinico de Valencia, Valencia, Spain, [15]GRUCINI Committe of the Grupo Español de Trasplante Hematopoyético y Terapia Celular (GETH), Madrid, Spain

Background: Diarrhea is a common and often debilitating complication of HSCT. Data regarding the longitudinal assessment of the infectious etiology of episodes of enterocolitis are limited.

Methods: Prospective, observational, and multi-center study. Between April 2017 and November 2018, all consecutive adult patients who underwent a reduced-intensity HSCT in 10 Spanish tertiary University Hospitals were included. Our objective was to determine the frequency and etiology of enterocolitis. Acute diarrhea episodes (grade ≥2 CTCAE) and the diagnostic yield of routinely performed microbiologic stool studies occurring in the first 6 months post-HSCT were collected.

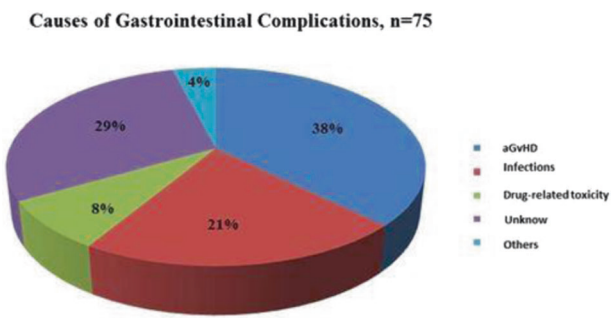
Results: One-hundred-forty-two patients were included, of whom 54 (38%) developed a total of 75 diarrhea episodes, (*Table 1)*. Thirty-seven out of 54 (69%) had a single episode, while 19 (35%) had two, and 2 had ≥3 (4%). The median time from HSCT to the first episode was 21 days (4-88). Sixty-seven % of the episodes occurred in hospitalized patients, while an additional 16 (43%) with an outpatient onset required admission for a median of 11 days (3-60).

Causative enteropathogens were identified in only 13/75 (17%), including: *C. difficile* (n = 10), Rotavirus (n = 2) and *Campylobacter jejuni* (n = 1). CMV-colitis was confirmed by biopsy in 1 (6%). Two patients had colitis during a severe influenza A and systemic HHV-6 infection. Recurrent *C. difficile*-related infection occurred in 2/10 (20%), without occurrence of gastrointestinal (GI) GvHD.

The most common cause of enterocolitis was acute GI-GVHD, in 28 (38%), followed by infections in 16 (21%), drug-related toxicity in 6 (8%) and others in 3 (4%). In 22 (29%) the cause of the diarrhea was not found (*Figure-1*). Of note, 80% of the patients had recent or active non-enteric infections.

At data cutoff—October 2020, the median follow-up for survivors was 32 months (5-41). The incidence of non-relapse mortality (NRM) at 100 days and 1 year was 11% (95% CI: 6-17%) and 20% (95% CI: 14-28%). Causes of NRM included non-enteric infections (n = 14), aGVHD (n = 5), cGVHD (n = 1), bleeding (n = 3), cardiac toxicity (n = 2), and other organ toxicity (n = 5). Grade 2-4 diarrhea was not associated with higher NRM ($p = 0.37$). The one-year overall survival and relapse free survival was 69% (95% CI: 61-77%) and 78% (95% CI: 70-86%).

Age, median (range)	60 (19-73)
Gender, male	83 (58%)
Baseline disease	AML 44 (31%)
	MDS 33 (23%)
	NHL/HL 27 (19%)/ 9 (6%)
	MM 5 (3.5%)
	Other 24 (17.5%)
Source, Peripheral blood	127 (89%)
Donor type	Unrelated identical 47 (33%)
	Related identical 42 (30%)
	Haploidentical 32 (22%)
	Unrelated mismatch 21 (15%)
CMV status −/−	8 (5.6%)
CD34/kg E6, median (range)	6 (1.3-8.9)
GvHD prophylaxis	PT-Cy 90 (63%)
	Sirolimus-Tacrolimus 19 (13.5%)
	Tacrolimus-based 19 (13.5%)
	Cyclosporine-based 14 (10%)
Prior GvHD	aGvHD II-IV 38 (27%) cGvHD moderate-severe 25 (17%)



Conclusions: This real-life multicenter study confirms that the diagnosis and management of acute diarrhea early after allo-HSCT is challenging. Previously reported infections, such as *C. difficile*, may be less common due to a more rational use of antibiotics and viral enteropathogens may be under recognized because of the lack of sensitivity of classical diagnostic methods.

Disclosure: There are no conflicts of interest to report.

P319

Open-label randomized controlled study of ciprofloxacin versus rifaximin as neutropenia prophylaxis in allogeneic hematopoietic cell transplantation: Survival benefit for ciprofloxacin

E. Gavriilaki[1], D. Mallouri[1], E. Laspa[2], A. Lazaridou[1], C. Varelas[1], E. Baldoumi[1], A. Giannakopoulou[1], C. Demosthenous[1], A. Vardi[1], Z. Bousiou[1], I. Batsis[1], E. Yannaki[1], G. Gkioula[2], A. Anagnostopoulos[1], I. Sakellari[1]

[1]G Papanicolaou Hospital, Thessaloniki, Greece, [2]Aristotle University of Thessaloniki, Thessaloniki, Greece

Background: Retrospective studies of allogeneic hematopoietic cell transplantation (alloHCT) recipients have suggested rifaximin as an antibiotic allowing higher microbiota diversity even in the presence of systemic broad-spectrum antibiotics. Although loss of diversity has been clearly associated with acute graft-versus-host-disease (GVHD) and poor outcomes in alloHCT, it remains unclear whether the use of rifaximin would improve outcomes. Therefore, we designed a prospective randomized study to compare our standard-of-care for neutropenia prophylaxis (ciprofloxacin) with rifaximin.

Methods: We prospectively enrolled consecutive adult patients that underwent alloHCT according to EBMT indications, at our JACIE-accredited Unit and provided written informed consent to participate in this study (2019-2020). Patients that received secondary prophylaxis due to pre-transplant infections with resistant bacteria were excluded. Patients were randomly assigned to receive standard doses of ciprofloxacin or rifaximin at day -1. Treatment of neutropenic fever was administered according to our Unit's protocol in both groups and included cessation of ciprofloxacin or rifaximin. The following variables were analyzed: pre-transplant (age, gender, disease risk index/DRI), transplant (donor, graft, conditioning) and post-transplant (infections, GVHD, treatment-related mortality/TRM, disease-free survival/DFS, overall survival/OS) characteristics.

Results: We studied 38 patients, the majority of whom were transplanted from matched unrelated (17/38) or alternative (5 haploidentical and 3 mis-matched unrelated) donors. After randomization, 20 received ciprofloxacin and 18 rifaximin. As expected, pre-transplant and transplant characteristics did not differ between groups. Cumulative incidence (CI) of acute graft-versus-host disease (GVHD) grade II-IV and moderate/severe chronic GVHD was similar in both groups (60% in ciprofloxacin versus 44.4% in rifaximin, $p = 0.516$; 58.3% versus 59.9%, $p = 0.84$, respectively). Bacterial, viral and fungal infections were similar between groups. With a median follow-up of 13.2 months (range 6.8-30.2) in surviving patients, 1-year CI of relapse was 20.8% in ciprofloxacin versus 17.8% in rifaximin ($p = 0.616$). Importantly, 1-year CI of TRM was significantly reduced in ciprofloxacin group (10.2% versus 27.8%, $p = 0.032$). This led to higher 1-year overall survival (OS 88.9% versus 74.6%, $p = 0.038$). In Cox-regression multivariate analysis, antibiotic prophylaxis remained the only predictor of OS (HR = 5.847, 95% Confidence Intervals 1.053-32.478, $p = 0.044$), independently of donor type, DRI and chronic GVHD.

Conclusions: We present the first open-label randomized controlled study to evaluate rifaximin as neutropenia prophylaxis. Our results suggest that standard-of-care with ciprofloxacin was superior leading to survival advantage. Further studies are needed to assess effects on microbiota diversity and confirm these outcomes.

Clinical Trial Registry: NA

Disclosure: Nothing relevant to disclose

P320

Changes in respiratory viral infections landscape among allogeneic stem cell transplant recipients during sars-cov 2 pandemia: Single centre real life experience

E. Metafuni[1], R. Santangelo[1], S. Giammarco[1], M.A. Limongiello[1], F. Frioni[1], S. Marchetti[1], P. Chiusolo[1], S. Sica[1]

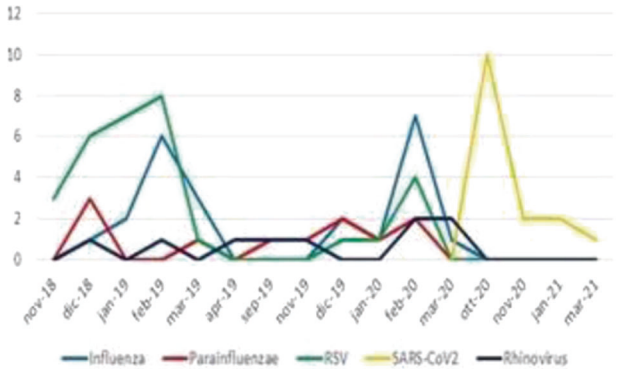
[1]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

Background: Respiratory viral infections represent an important cause of morbidity and mortality in immunocompromised patients, especially those recently submitted to allogeneic stem cell transplantation (HSCT) and receiving immunosuppressive drugs. The main common seasonal respiratory viruses (CSRV) who affected immunocompromised host are influenza, respiratory syncytial virus, parainfluenzae virus and, recently, severe acute respiratory syndrome coronavirus (SARS-CoV-2).

Methods: During flu season, hospitalized patients and outpatients coming at the clinic with respiratory symptoms or fever are routinely tested with nasal swab for respiratory viruses. Multiplex polymerase chain reaction (PCR) is usually performed on nasal swabs to detect the presence of respiratory viruses. The used panel includes: influenza A, influenza B, parainfluenzae 1-4, respiratory syncytial virus, coronaviruses NL63, OC43, 229E, HKU1, enterovirus/rhinovirus, adenovirus. Here we reported positive cases detected with nasal swab in the last three seasons among patients who had received a stem cell transplant in our unit.

Results: Between November 2018 and March 2021 a total number of 210 HSCTs were performed in our unit. Other 240 patients submitted to HSCT before January 2018 were followed during that period as outpatients in our clinic. A total of 90 positive swabs were detected. We identified three seasons, according to the local epidemiology: the first from November 2018 to April 2019, the second one from September 2019 to March 2020 and the third from October 2020 to march 2021. Positive swabs were distributed as follows: 44 cases in the first season, 31 cases in the second season and 15 cases in the third season. In the first season the identified viruses were Influenza A and B ($n = 11$), Parainfluenzae virus 1-3 ($n = 4$), RSV ($n = 25$), Coronavirus NL63 ($n = 1$), Coronavirus OC43 ($n = 1$), Rhinovirus/Enterovirus ($n = 2$). In the second season the viruses were Enterovirus/Rhinovirus ($n = 6$), Parainfluenzae virus 1-2 ($n = 5$), RSV ($n = 6$), Influenza A and B ($n = 10$), Coronavirus NL63 ($n = 1$), Coronavirus 229E ($n = 1$), Adenovirus ($n = 1$), Bocavirus ($n = 1$). In the third season, only SARS-CoV2 was identified.

Figure 1: Respiratory virus episodes of RSV, Parainfluenzae, Influenza A and SARS-CoV2. Prevalence of each common seasonal respiratory virus (CSRV) type by months.



Conclusions: Starting from the SARS-CoV2 pandemia onset, there has been a dramatically disappearance of the others common seasonal respiratory virus infections. In particularly, during the first lockdown period we have not even registered SARS-CoV2 cases, that come to the light starting from October 2020. This indicates that prevention measures adopted to prevent SARS-CoV2 spread, such as wearing masks, frequently washing of the hand, reducing inter-personal contact and maintaining social distances, resulted as weel effective in reducing others CSRV infections. However, at the beginning of the current season, we are observing a new rise of the CSRV infections, particularly due to Parainfluenzae virus, Rhinovirus and RSV.

Disclosure: Nothing to declare

P321

Fecal colonization in patients following hematopoietic stem-cell transplantation by multidrug-resistant bacteria: A single center study on microbial spectrum and resistance profile

D. Niyazi[1], I. Micheva[1], T. Stoeva[1]

[1]Medical University of Varna, Varna, Bulgaria

Background: Nowadays antimicrobial resistance is one of the most important medical and epidemiological problems. Patients after hematopoietic stem-cell transplantation (HSCT) are considered a high-risk group for infectious complications, caused by multidrug-resistant bacteria (MDR). The enteric microbial flora is considered a major source for these complications. The routine fecal screening for colonization by MDR bacteria helps the adequate choice of empirical antibacterial therapy, especially in the era of the COVID-19 pandemic and the increased consumption of antimicrobial agents. The aim of this study is to investigate the spectrum of the MDR gut colonizers and to detect the genes associated with resistance to beta-lactam and glycopeptide agents.

Methods: During a two-year period (November 2019 – November 2021), 74 patients were studied. A total of 44 non-duplicate MDR bacterial isolates were obtained from fecal samples of 28 patients after HSCT. All studied samples were inoculated on media containing cefotaxime (1 mg/L), CHROMagar^{TM} CPE (BD BBL^{TM}, USA) and blood agar (BD BBL^{TM}, USA) and were incubated at 37˚C for 24 hours. Species identification and antimicrobial susceptibility were determined by the Phoenix Automated System (BD, USA). PCR was used to identify the genes, encoding resistance to 3rd generation cephalosporins, carbapenems (*bla*$_{SHV}$, *bla*$_{CTX-M}$, *bla*$_{TEM}$, *bla*$_{KPC}$, *bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{IMP}$, *bla*$_{OXA-48}$) and glycopeptides (*vanA, vanB, vanC, vanD*). DNA was obtained by SaMag Bacterial DNA Extraction Kit (Sacace, Italy). Epidemiological typing by ERIC and RAPD PCR was performed to determine the genetic relationship between the isolates. The PCR products were resolved by gel electrophoresis.

Results: A total of 44 MDR fecal isolates were collected: *Enterococcus faecium*, n = 14; *E. coli*, n = 10; *Pseudomonas* spp., n = 8; *Enterobacter cloacae* complex, n = 7; *Klebsiella pneumoniae*, n = 4 and *Serratia marcescens*, n = 1. All *E. faecium* were vancomycin and teicoplanin - resistant and *vanA* positive. In the group of Gram negative bacteria, resistant to 3rd generation cephalosporins and/or carbapenems, the following genes were identified: *bla*$_{SHV}$ (n = 4, *K. pneumoniae*), *bla*$_{CTX-M}$ (*E. coli*, n = 9; *K. pneumoniae*, n = 3; *E. cloacae* complex, n = 7; *S. marcescens*, n = 1), *bla*$_{TEM}$ (*E. coli*, n = 5; *K. pneumoniae*, n = 2; *E. cloacae* complex, n = 6; *S. marcescens*, n = 1), *bla*$_{VIM}$ (*Pseudomonas* spp., n = 6; *E. cloacae* complex, n = 1). In 13 isolates (46.7%) more than one resistance gene were found: *bla*$_{CTX-M}$ + *bla*$_{TEM}$ (n = 13), *bla*$_{CTX-M}$ + *bla*$_{TEM}$ + *bla*$_{SHV}$ (n = 2) and *bla*$_{CTX-M}$ + *bla*$_{TEM}$ + *bla*$_{VIM}$ (n = 1). The epidemiological typing of *E. faecium*, *E. coli* and *Enterobacter cloacae* complex revealed both unique profiles and clusters of closely related strains, demonstrating identical profiles. All *K. pneumoniae* isolates exhibited unique ERIC profiles.

Conclusions: A high rate of fecal colonization by MDR bacteria was detected (38.3%). Resistance to 3rd generation cephalosporins was associated with *bla*$_{SHV}$, *bla*$_{CTX-M,}$ *bla*$_{TEM}$ genes and carbapenem resistance - with *bla*$_{VIM}$. Glycopeptide resistance was mediated by *vanA* gene. The identification of epidemiologically related isolates is an indication for possible intra-hospital dissemination of these MDR pathogens and a risk factor for nosocomial infections associated with these problematic bacteria.

Disclosure: Nothing to declare.

P322

Pre-engraftment bloodstream infections after first and second allogeneic hematopoietic cell transplantation: Incidence, etiology, risk factors and outcomes

M. Akhmedov[1], G. Klyasova[1], L. Kuzmina[1], V. Vasilieva[1], M. Drokov[1], V. Savchenko[1], E. Parovichnikova[1]

[1]National Research Center for Hematology, Moscow, Russian Federation

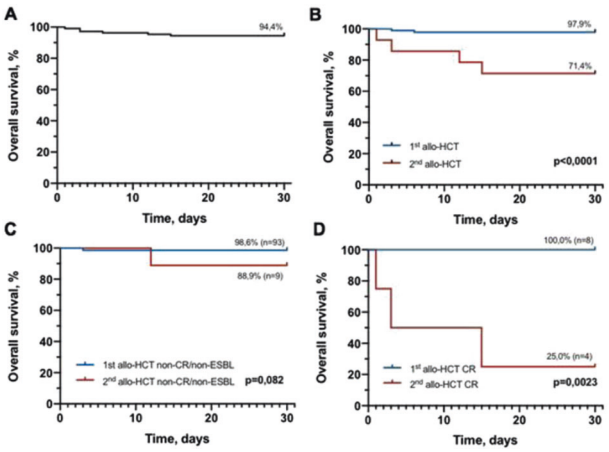
Background: Bloodstream infections (BSI) are common and serious complications after allogeneic hematopoietic cell transplantation (allo-HCT). This study aimed to analyze the incidence, etiology, risk factors, and outcomes of pre-engraftment BSI after the first and the second allo-HCT.

Methods: The retrospective study included 284 patients who underwent first allo-HCT and 37 patients who underwent second allo-HCT at the National Research Center for Hematology in Moscow, Russia, from January 2018 till September 2021. Patients in the second allo-HCT cohort had higher age adjusted hematopoietic cell transplantation-specific comorbidity index ($p < 0{,}0001$), were more likely to receive an allograft from haploidentical donor ($p = 0{,}006$) and reduced-intensity conditioning regimen ($p = 0{,}042$) as compared to the first allo-HCT cohort. Median graft cellularity ($p = 0{,}005$) and the rate of primary graft failure ($p = 0{,}002$) were also higher in the second allo-HCT group.

Results: Cumulative incidence of pre-engraftment BSI was 29.9% after the first allo-HCT and 35.1% after the second ($p = 0{,}805$). Median time to the first BSI was 9 days (range 0-61 days) after the first and 16 days (range 1-28 days) after the second allo-HCT ($p = 0.014$). A total of 111 pathogens were isolated during 94 BSI episodes after the first allo-HCT (gram-negative bacteria 51.3%; gram-positive bacteria 48.7%). Fourteen pathogens were isolated during 14 BSI episodes after the second allo-HCT (gram-negative bacteria 50.0%; gram-positive bacteria 50.0%). The rate of BSI caused by carbapenem-resistant gram-negative bacteria was higher after the second allo-HCT compared to the first (57.1% vs. 14.0%; $p = 0.048$). Mismatched unrelated donor transplantation was the only independent risk factor associated with a higher risk of pre-engraftment BSI after the first allo-HCT (HR = 2.93; 95% CI:1.55-5.51; $p = 0{,}008$). No risk factors associated with a higher risk of pre-engraftment BSI after the second allo-HCT could be identified. Overall 30-day survival after all BSI episodes was 94.4%. Survival was lower after the second allo-HCT compared to the first (71.4% vs. 97.9%; $p < 0{,}0001$), especially after BSI caused by carbapenem-resistant gram-negative bacteria (25.0% vs. 100.0%; $p < 0.0001$). Non-relapse mortality (NRM) rate at day +60 was 4.0%. The NRM risk was highly associated with primary graft failure (HR = 9.62; 95% CI: 1.33-71.43), second allo-HCT (HR = 6.80; 95% CI: 1.36-34.48), and pre-engraftment BSI caused

by carbapenem-resistant gram-negative bacteria (HR = 32.11; 95% CI: 4.91-210.15).

Figure 1. A – 30-day survival after all BSI episodes; B - 30-day survival after all BSI episodes according to allo-HCT number; C – 30-day survival after BSI caused by carbapenem-sensitive and non-ESBL producing bacteria according to transplant number; D – 30-day overall survival after BSI caused by carbapenem-resistant gram-negative bacteria according to transplant number. ESBL - extended spectrum beta-lactamase producing bacteria; CR – carbapenem-resistant gram-negative bacteria



Conclusions: Pre-engraftment BSI is still common after allo-HCT, particularly after mismatched unrelated donor transplantations. BSI incidence was higher after the second allo-HCT with significantly higher rate of carbapenem-resistant BSI. Although pre-engraftment BSI would generally follow benign clinical course, survival was dramatically lower during the second allo-HCT especially in case of carbapenem-resistant BSI.

Disclosure: none

P323

The patient's cmv serological status is an independent factor for cmv infection (CMVi) in the post-transplant cyclophosphamide (PTCy) as GVHD prophylaxis era

B. Herruzo[1], A. Esquirol[2], C. Martín[3], B. Gago[1], A.I. Gallardo[1], M. Cuesta[1], A. García[1], I. Sanchez[1], S. Martín[1], A. Doblas[1], D. Muñoz[1], M. Perez[1], A. Mena[1], M.J. Pascual[1]

[1]Hospital Regional Universitario de Málaga, Málaga, Spain, [2]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [3]Hospital Universitario Reina Sofía, Córdoba, Spain

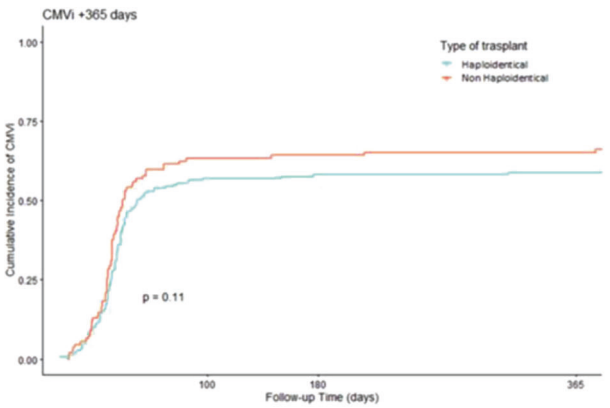
Background: With the use of PTCy, the high risk of CMVi in haploidentical HSCT has been widely described. Our aim was to analyse whether under the same GvHD conditioning and prophylaxis (PTCy) there are differences in CMVi, and its consequences between haplo and non-haplo-HSCT groups.

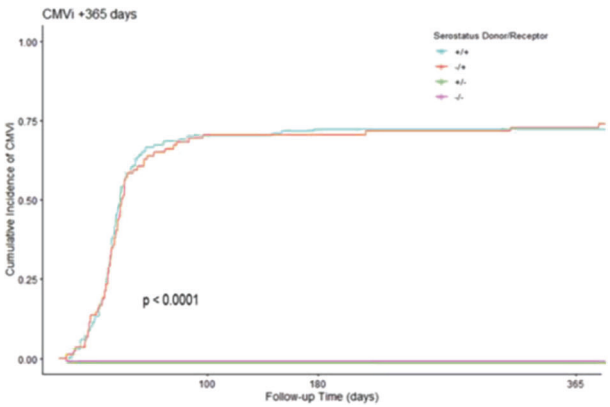
Methods: We conducted a multicentre, observational and retrospective study of three hundred patients (January 2013 – December 2018) from three Spanish hospitals.

Results: All patients received TBF ablative or reduced conditioning regimen and PTCy plus calcineurin inhibitors +/− Mycophenolate as GvHD prophylaxis. There were no statistically significant differences in age (53 vs 56 years), stem cell source (71% peripheral blood), ablative vs reduced TBF, diagnosis, HCT-CI, DR index or pre-transplant status between haplo (n = 191) and non-haplo-HSCT (n = 109) groups. One hundred and eighty-seven patients developed CMVi (113 – 59.2% – haplo-HSCT vs 74 – 67.9% – non-haplo-HSCT). There was no difference in day of onset or duration of CMVi episode between the two groups (+46/31 days haplo vs +50/32 days non-haplo-HSCT respectively). CMVi CI (cumulative incidence) requiring PET at day +365 was 50.3% (haplo-HSCT) and 61.5% (non-haplo-HSCT) with similar incidence also in recurrent CMVi for both groups (17.3% vs 20.2%).

The CMVi CI at 365 days was higher for CMV-seropositive recipients, a total of 74% (95% CI: 67%-78%) vs 3.9% (95% CI: 0%-9%) in CMV-seronegative recipients ($p < 0.0001$), regardless of donor CMV serostatus or HSCT type. The NRM CI at +365 day was 24.7%, with no differences in both groups. In the first year after HSCT, overall mortality (OM) was 32.7% (33.5% haplo-HSCT vs 32.2% non-haplo-HSCT). CMVi had no differential impact on OS, OM, NRM or relapse by study group. CI for II-IV aGvHD and severe moderate cGvHD was 30.3% vs 17.4% (p 0.05) and 16.8% vs 23.9% (p 0.007) at +100 and +365 days for haplo and non-haplo-HSCT respectively. However, the existence of aGVHD or cGVHD did not differentially impact CMVi.

We also did not find differences in hospitalisation days due to direct or indirect effects of CMVi. Among the infections most frequently associated with CMVi, the frequencies by haplo- and non-haplo-HSCT groups were: bacterial 16.2% vs 15.1%, viral 15.8% vs 10.4% and fungal infections 7.1% vs 2.8%. Eighteen patients developed CMV disease (14 haplo and 4 non-haplo-HSCT), 68% of whom developed gastrointestinal disease. Nine patients (3% of the total group of patients) died from direct or indirect effects of CMVi (5 in the haplo-HSCT group).





Conclusions: In our study, apart from the recipient's CMV seropositivity, no other risk factors were identified for the development of CMVi. The homogeneity of conditioning and GVHD prophylaxis could have contributed to this result. In the PTCy as GVHD prophylaxis era, this finding may help to better

define the target population at higher risk of CMVi in order to optimise the indication of CMVi prophylaxis with letermovir and thus reduce the morbimortality due to CMVi. Larger series are needed to confirm these results.

Clinical Trial Registry: FIM-CIC-2020-01

Disclosure: B. Herruzo: Nothing to declare
A. Esquirol: Nothing to declare
C. Martín: Nothing to declare
B. Gago: Nothing to declare
A. Gallardo: Nothing to declare
M Cuesta: Nothing to declare
A. García: Nothing to declare
I Sanchez: Nothing to declare
S Martín: Nothing to declare
A Doblas: Nothing to declare
D Muñoz: Nothing to declare
M Pérez: Nothing to declare
A Mena: Nothing to declare
MJ Pascual: Merck Sharp & Dohme SA

P324

Third-dose BNT162b2 vaccine is highly efficient at increasing anti-rbd sars-cov-2 igg titers in allo-hct recipients

L. Canti[1], S. Humblet-Baron[2], I. Desombere[3], P. Pannus[3], A. Henry[4], S. Servais[4], E. Willems[4], K.K. Arien[5], Y. Beguin[1], M.E. Goossens[3], A. Marchant[6], F. Baron[7,4]

[1]University of Liege, Liege, Belgium, [2]KU Leuven, Leuven, Belgium, [3]Sciensano, Uccle, Belgium, [4]CHU of Liège, Liege, Belgium, [5]Institute of Tropical Medicine, Antwerp, Belgium, [6]Université libre de Bruxelles, Gosselies, Belgium, [7]University of Liège, Liege, Belgium

Background: Allogeneic hematopoietic stem cell transplant (allo-HCT) recipients are particularly at risk of severe COVID-19 when infected by SARS-CoV-2. We previously reported that while >80% of allo-HCT recipients developed binding antibodies (Ab) to SARS-CoV-2 receptor binding domain (RBD) after 2 doses of BNT162b2 mRNA vaccine, only half of them developed neutralizing Ab against wild type SARS-CoV-2 (Canti et al., J Hematol Oncol 2021, 24: 174). Importantly, response rates correlated with counts of memory B cells and of naive CD4 + T cells.

Methods: Here we assessed the impact of a booster dose of the BNT162b2 vaccine on SARS-CoV-2 humoral immunity in a cohort of 41 allo-HCT included in a prospective vaccination study (EudractCT # 2021-000673-83).

Results: Data from 41 patients given the booster vaccine were analyzed. The booster dose was the third vaccine dose in 40 patients and the second vaccine dose in 1 patient (who was diagnosed with Covid-19 six days after the first dose). Median time from transplantation to first vaccine dose was 1037 days (range, 209-1903 days). Median time from first dose to booster dose was 153 days (range, 104-226 days). RBD binding Ab increased from a median of 141 (range: <5 – 2914) IU/mL the day of booster vaccination to a median of 3082 (range: <5 – 47131) IU/mL three weeks later ($P < 0.0001$). Five patients had undetectable RBD Ab after two vaccine doses and 4 of them seroconverted after the third dose. The non-seroconverter had received rituximab 298 days before third vaccine dose.

Conclusions: The administration of a third dose of the BNT162b2 vaccine was highly efficient at increasing anti-RBD IgG titers in allo-HCT recipients. The impact of the booster dose on neutralizing Ab response as well as correlations between baseline immune parameters and Ab response will be presented.

Clinical Trial Registry: EudractCT # 2021-000673-83

Disclosure: The authors have no COI to disclose in regards to this abstract

P325

Posoleucel for the prevention of clinically significant infections in high-risk allogeneic hematopoietic cell transplant recipients: Design of a phase 2/3, randomized, double-blind, placebo-controlled trial

S. Sica[1], C. Besley[2], K. Boundy[3], M. Matzko[3], N. Tripkovic[3], G. Socie[4]

[1]IRCCS Fondazione Policlinico Universitario A. Gemelli, Rome, Italy, [2]Bristol Haematology and Oncology Centre, Bristol, United Kingdom, [3]AlloVir, Cambridge, United States, [4]Hôpital St Louis, Paris, France

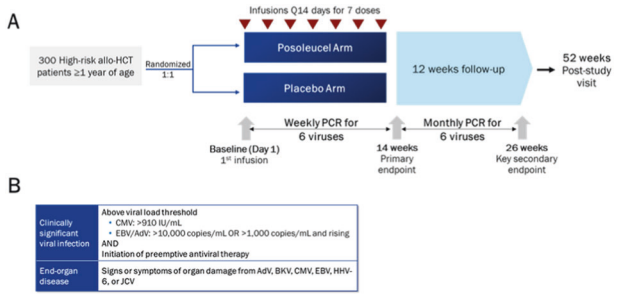
Background: The use of immunosuppressive conditioning regimens in allogeneic hematopoietic cell transplantation (allo-HCT) leaves recipients with prolonged T cell-specific immunodeficiency in the post-transplant period, rendering them susceptible to severe viral infections and death. The most common viral infections following allo-HCT include adenovirus (AdV), BK virus (BKV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV 6), and JC virus (JCV). Up to 70% of patients experience a clinically significant infection post allo-HCT, highlighting the serious unmet need for improved preventive antiviral therapies in high-risk allo-HCT recipients.

Methods: We are conducting a two-part, phase 2/3, multicenter, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of posoleucel compared to placebo for the prevention of clinically significant AdV, BKV, CMV, EBV, HHV-6, and JCV infection in high-risk pediatric and adult allo-HCT recipients. Posoleucel is an ex-vivo expanded, partially HLA-matched, off-the-shelf, multivirus-specific T cell investigational product targeting CMV, EBV, HHV-6, AdV, BKV, and JCV.

The open-label cohort of the trial is fully enrolled for DSMB review of the Phase 2 data to commence the randomized Phase 3 cohort. To date the seven doses of posoleucel administered in the Phase 2 study have generally been well tolerated with a low incidence of breakthrough infections through 14 and 26 weeks.

In the Phase 3 cohort approximately 300 patients will be randomized 1:1 to receive posoleucel or placebo to achieve statistical power of 90%. Patients must be >1 year of age and have undergone high risk allo-HCT from 15-42 days before randomization and have demonstrated clinical engraftment. High risk allo-HCT is defined as receiving a transplant from a mismatched related donor, haploidentical donor, unrelated donor, cord blood donor, or undergoing T cell depletion from ATG, alemtuzumab, or ex-vivo graft manipulation. Patients with Grade ≥3 acute GVHD and those receiving ongoing high-dose corticosteroids, or ongoing clinically significant AdV, BKV, CMV, EBV, HHV-6, or JCV infections are excluded. The Primary Study Period is 14 weeks for evaluation of efficacy, the primary endpoint is a composite of the number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV through Week 14, with the key secondary endpoint consisting of the same criteria through week 26. An independent, blinded CAC will adjudicate all potential cases of clinically significant infection or end-organ disease for the primary and key secondary endpoints.

Figure. A) Study schematic. B) Definitions of clinically significant infection and end-organ disease for primary endpoint



Results: Planned enrollment is approximately 300 patients at approximately 70 international sites. The Phase 3 cohort of the study is due to commence enrollment first half of 2022 and to be completed in 2024.

Conclusions: This phase 3 trial cohort will provide pivotal data on the efficacy and safety of posoleucel compared with placebo for the prevention of clinically significant infection and disease from CMV, EBV, HHV-6, AdV, BKV, and JCV in high risk allo-HCT recipients.

Clinical Trial Registry: Clinicaltrials.gov: NCT04693637

Disclosure: Simona Sica has received honoraria from Jazz, Alexion, Novartis, Gilead, and Incyte, and has served on advisory boards for Jazz, Novartis, Astellas, and Alexion.

Caroline Besley has received honoraria from Novartis and Kite (Gilead), and has served on advisory boards for Novartis and Kite.

Gerard Socie has received honoraria from Novartis, Elsalys, and Incyte, and has served on advisory boards for Novartis, Elsalys, and Incyte, and has received research support from Alexion. Keith Boundy, Michelle Matzko, and Nikola Tripkovic are employees of and hold stock in AlloVir.

P326

Bloodstream infections in hematopoietic stem cell transplant recipients colonized by multidrug-resistant bacteria

A.P. Gonzalez-Rodriguez[1,2,3], P. Palomo-Moraleda[1], J. Suarez-Pañeda[4], J. Zanabili[1], S. Gonzalez-Muñiz[1], L.R. Morais Bras[1], S. Lorenzo Herrero[5,2,3], C. Sordo-Bahamonde[5,2,3], A. Martinez-Perez[5,2,3], A.J. Gonzalez-Huerta[1]

[1]Hospital Universitario Central de Asturias, Oviedo, Spain, [2]Instituto Universitario de Oncologia del Principado de Asturias, Oviedo, Spain, [3]Instituto de Investigación sanitaria del Principado de Asturias, Oviedo, Spain, [4]Universidad de Oviedo, Oviedo, Spain, [5]Universidad de Oviedo, Oviedo, Spain

Background: Antibiotic resistant bacteria have spread worldwide and, therefore, increased rates of mortality and treatments cost are seen. Patients who undergo Hematopoietic Stem Cell Transplantation (HSCT) are specially exposed due to immunosuppression and long hospitalizations. However, data of the incidence of multidrug-resistant (MDR) colonization and related bloodstream infections (BSIs) are scarce and there is a wide distribution in resistance rates between countries.

Methods: This prospective observational study aimed to describe risk factors and incidence of colonization, relationship with GNR bacteriemia and impact on survival in 113 patients who underwent HSCT (88 Auto-HSCT and 25 Allo-HSCT) at Hospital Universitario Central de Asturias from April 2019 to September 2020. Median lenght of hospitalization was 24 days and all of them had routine weekly surveillance rectal cultures beginning at admission.

Results: 44 patients (38,9%) presented MDR rectal colonization, particularly Gram-negative strains and median lenght of colonization was 28,9 days. Thirty patients were colonized by extended spectrum beta-lactamase (ESBL) and 13 by carbapenem resistant (CR) enterobacteriae. The most common isolated bacteria were: *Klebsiella* (24), *Escherichia* (25), *Enterobacter* (19) y *Citrobacter* (7). Colonization was observed at admission in 25% with significant higher incidence in patients with previous betalactamic antibiotic exposure and mucositis.

There was no seen a significant higher incidence of fever between colonized patients. Table 1 shows risk factors of colonization.

Overall, 100 patients developed fever during admission and 38 patients developed at least one episode of gram-negative BSI. Ten of them developed BSI due to MDR bacteria (35,7% of all isolated pathogens); 6 due to the MDR-colonizing pathogen. In colonized patients, length of antibiotic therapy was higher (11 vs 8,5 days), need to change antibiotic therapy was more frequent and as well as use of meropenem, vancomycin and amikacin. Only one patient died before day 100 due to MDR BSI (CR Klebsiella), that there was not been detected in surveillance cultures previously.

We did not find significant differences in overall survival between colonized vs not nor between CR vs ESBL.

			p
Transplantation type	Autologous-HSCT 28 (31,8%)	Allogeneic-HSCT 16 (64%)	0,004
Number of admissions in previous year	2 or less 34 (34,7%)	3 or more 10 (66,7%)	0,020
Previous hospital admissions (one year before)	HUCA-Tertiary hospital 26 (53,1%)	Other hospitals: 4 (17,4%)	0,004
Previous antibiotic prophylaxis (3 months before)	Yes 8 (34,8%)	No 36(40%)	ns
Previous antibiotic therapy (4 weeks before)	Yes 10 (71,4%)	No 34(34,3%)	0,008
Lenght of hospitalization (median days)	Colonized: 26	Non-colonized 20,5	0,003
Lenght of antibiotic therapy (median days)	Colonized: 13	Non-colonized :10	0,003
Change of antibiotic therapy during admission	Yes: 30 (50,8%)	No: 10 (25%)	0,008

Table 1: Risk factor for colonization

Conclusions: We found higher resistance rates in our media compared with Northern countries and similar to reported in other South Europe countries.

We did not demonstrate higher mortality rates caused by MDR bacteria. Knowledge of colonization and pathogen resistant patterns can help to direct appropriate antibiotic therapy. In high risk hospitalized patients (previously treated with betalactamic antibiotic or mucositis) is mandatory the development of a screening programme for MDR strains and guidelines of contact isolation and antibacterial use.

Disclosure: Nothing to declare

P327

Covid-19 in allogeneic stem cell transplant patients: A longitudinal study trough eighteen months of pandemic

M. Cabrero[1], E. Perez-Lopez[1], A.A. Martin[1], S. Marcos[1], M. Baile[1], A. Avendaño[1], A. Cabero[1], E. Puche[1], J. Garcia[1], M. Cortes[1], L. Lopez-Corral[1], F. Sanchez-Guijo[1], L. Vazquez[1], D. Caballero[1]

[1]*Hospital Universitario de Salamanca-IBSAL, Salamanca, Spain*

Background: Allogeneic stem cell transplant recipients have been considered as high-risk patients for Covid-19 due to their immunosuppression (IS) status. However, most of published studies are referred to the first wave of the pandemic when diagnosis capability was limited, so a better understanding of Covid-19 in AlloSCT is needed now that we have a higher diagnosis power and almost 100% of AlloSCT recipients have received complete vaccination.

Methods: All AlloSCT recipients from our center who tested positive for Covid-19 by PCR or serological test between March 1st2020 and December 15th 2021 were included. We included patients diagnosed after presenting symptoms, history of close contact or routine screening before any procedure or visit to the hospital. We collected data related to AlloSCT, immune status and Covid-19 severity (mild: symptoms without pneumonia; moderate: pneumonia without or with low oxygen requirements; severe: pneumonia with high oxygen requirements or mechanic ventilation).

Results: Thirty-six AlloSCT patients had a confirmed diagnosis of Covid-19, 32 by PCR and 4 by serological antibodies test. Nine cases were diagnosed during the 1st wave (March-June 2020), 5 during 2nd (August-Nov 2020), 12 during 3rd (Dec-Feb 2021), 2 during 4th (Apr-June 2021), 3 during 5th (July-Sept 2021) and 4 during the 6th wave (From Nov2021). Five (14%) had received SARS-CoV-2 vaccine with 1 (n = 1), 2 (n = 1) or 3 (n = 3) doses.

Diagnosis were MDS/AML (n = 18), NHL (n = 8), MPD (n = 4), Hodgkin lymphoma (n = 3), MM (n = 1) and ALL (n = 2). Median time from AlloSCT to Covid-19 was 43 months (2-204), and only 6 patients were diagnosed in the first 12 months after AlloSCT, suggesting higher standards in prophylactic measures taken by patients at early post-AlloSCT period. Thirty-two patients (89%) were in complete remission and 17 of them (47%) had finished IS more than 6 months before contagious. Five (14%) and 13 (36%) patients respectively had active acute or chronic GVHD under treatment at the moment of Covid-19 diagnosis. Median CD4/uL was 321 (50-762), median IgG was 1170 (300-1470) and median lymphocytes count was 3100 (400-4100), and there were not significant differences in Covid-19 severity based on these parameters.

Seven patients (19%) were asymptomatic and PCR was performed as screening before some medical procedure (n = 4) or after a close contact (n = 3). Covid-19 was mild in 20 (56%), moderate in 4 (11%) or severe in 5 (14%). Thirteen patients were admitted to the hospital, 10 due to Covid-19 and 4 because causes different from Covid-19 (GVDH, colon surgery, bacterial coinfection and hemorrhagic cystitis). None of these patients required mechanical ventilation Only 3 patients who were not candidates for mechanical ventilation due to severe comorbidities (2 post-AlloSCT relapses and 1 secondary lung neoplasm), died from Covid-19. Fatality rate was 8% among diagnosed patients.

Conclusions: Our data suggests that AlloSCT patients in complete remision and without significant comorbidities have a similar outcome than general population, independently of their immunosuppression status.

Considering percentage of asymptomatic cases, probably Covid-19 incidence in underestimated in AlloSCT patients.

Contagious is possible, even after a SARS-CoV-2 booster, but most of cases are asymptomatic or mild.

Disclosure: Nothing to declare

P328

Analysis of the expression of cytomegalovirus drug resistance gene mutations in patients having cytomegalovirus infection with poor efficacy after transplantation

J. Wen[1,2], Y. Zhang[1], Y. Zheng[1], G. Li[1], S. Chen[1], A. Pang[1], Y. He[1], J. Wei[1], Q. Ma[1], W. Zhai[1], R. Zhang[1], X. Chen[1], D. Yang[1], S. Feng[1], M. Han[1], E. Jiang[1]

[1]*State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China,* [2]*Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Mianyang, China*

Background: Cytomegalovirus (CMV) infection is the most important complication after allogeneic hematopoietic stem cell transplantation (Allo-HSCT) and threatens the prognosis of patients seriously. There are limited data on CMV drug-resistant gene mutations in CMV infection after transplantation in China currently. In order to further understand the expression of CMV drug-resistant gene mutations in patients with poor efficacy of CMV infection, this study was conducted.

Methods: Clinical data of 41 patients with CMV infection after allo-HSCT were retrospectively analyzed from January 2019 to July 2021 in transplantation Center of Hematology Hospital, Chinese Academy of Medical Sciences, due to poor clinical efficacy or the possibility of clinical drug resistance, who were tested for CMV resistance gene mutation.

Results: ①Of 41 patients included, 1 patient (2.4%) had UL97 mutation, 19 patients (46.3%) had UL54 mutation, no patients occur simultaneously with UL54 and UL97 mutation. The overall mutation frequency was 48.8% (20/41), and all mutation types were missense mutation.② UL54 gene were detected 8 cases of T691S mutation (8/41, 19.5%), 3 cases of M827I mutation (3/41, 7.3%) and 1 case of A786V mutation (1/41, 2.4%). All above these 3 mutation sites had been reported, but the drug resistance significance was unknown. There were 1 site (A543S) of UL97 gene and 19 sites of UL54 gene that had not been reported. In all the 41 patients, only one patient exhibited a mutation with definite anti-CMVdrug resistance significance: Q578H mutation of UL54 gene. The patient was diagnosed CMV DNAemia on Day 31 after transplantation, T691S mutation was found in the first sequencing on +43d. The patient still in CMV DNAemia on +98d and Q578H drug-resistant mutation was found in the second sequencing with T691S mutation,who was successfully treated with cytomegalovirus specific T cells.③Compared with patients without UL54 mutation, patientswith UL54 mutation strains had a higher proportion of CMV-DNA repositive rate in 10 days after remission of CMV DNAemia (42.1% vs.9.5%, $\chi 2 = 5.647$, $P = 0.028$),and had a significantly longer complete clearance time of CMV DNAemia (40 days vs. 24 days, $Z = 2.198$, $P = 0.027$).④ Compared with those patients without CMV gene mutation, the patients with T691S mutation had a higher incidence in terms of CMV-DNA turned repositive in 10 days and 14 days after remission of CMV DNAemia (71.4% vs. 19.0%, $P = 0.008$; 71.4% vs. 9.5%, $P = 0.001$; 71.4% vs. 9.5%, $P = 0.001$, respectively). The median time of CMV-DNA reaching the peak was significantly later (14 days vs. 10 days, $P = 0.016$). The median clearance time of CMV DNAemia was significantly longer (56 days vs. 24 days,

P = 0.002). Compared with the non-T691s UL54 mutation, the patients with T691S mutation also had similar results.

Conclusions: Most of CMV gene missense mutations occurred in UL54 gene and T691S mutation is a common site. The incidence of missense mutations with clear drug resistance was low and might be induced by antiviral therapy. The median clearance time of CMV DNAemia in UL54 mutated patients was significantly longer, and the proportion of CMV-DNA turned repositive was increased which might be caused by T691S mutation in UL54 gene.

Disclosure: Nothing to declare.

P329

Allogeneic hematopoietic stem cell transplantation in patients with prior infection caused by the sars-cov-2 (covid-19)

A. Siniaev[1], V. Yanbukhtina[1], E. Kulagin[1], M. Popova[1], Y. Rogacheva[1], M. Vladovskaya[1], S. Bondarenko[1], I. Moiseev[1], A. Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, Saint-Petersburg, Russian Federation

Background: There are limited data on outcomes of allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients with prior COVID-19.

Methods: This single-center retrospective study included 54 adult patients who received allo-HSCT from July 2020 to September 2021 after the previous COVID-19. The median age was 33 years (18–76), there were 30 (56%) females and 24 (44%) males. The underlying disease were AML (n = 22, 40.8%), ALL (n = 17, 31.5%), MDS (n = 6, 11.1%), AA (n = 4, 7.4%), CML (n = 3, 5.5%) and HL (n = 2, 3.7%). The median follow-up was 138 days (11 - 391). The control group included 122 patients without a history of COVID-19 who underwent allo-HSCT during the same period. The median age was 35 years (18 – 69) and the median follow-up time - 223 days (13 – 502). We assessed the transplant-related mortality (TRM), overall survival (OS) and GVHD, and relapse-free survival (GRFS).

Results: The median time from COVID-19 onset to the diagnosis of underlying disease was 129.5 days (-183 - 5135). To the date of COVID-19 manifestation 23 (42.6%) patients were in remission of the underlying disease, 18 (33.3%) in relapse/progression and remaining 13 (24.1%) had a simultaneous manifestation. The median time of COVID-19 onset since the last chemotherapy was 11 days (0 - 616). The severity of COVID-19 is known in 36 patients: mild in 11 (30.5%), moderate in 24 (66.7%) and severe in 1 (2.8%). The median time from COVID-19 to allo-HSCT was 211 days (31 - 447). The comorbidity index of HSCT was 0 points in 55.5% (n = 31), 1 point - 33.3% (n = 18), 2 points - 5.5% (n = 3), 3 points - 5.5% (n = 3). Donors were haploidentical – 16 (29.6%), MUD – 16 (29.6%), MMUD – 11 (20.4%) and MRD – 11 (20.4%). The source of HSC: PBSC – 41 (75.9%) and BM – 13 (24.1%). RIC and MAC were used in 41 (75.9%) and 13 (24.1%) recipients, respectively. Majority of patients (n = 48, 88.9%) received posttransplantation cyclophosphamide-based GVHD prophylaxis. The median time to the engraftment was 20 days (13 - 28). Acute GVHD developed in 16 (29.6%) patients, including grade 3-4 in 10 cases, chronic GVHD - in 4 (7.4%) patients. The main complications of post-transplant period included venous thrombosis (n = 4, 7.4%), TMA (n = 1, 1.85%), VOD (n = 1, 1.85%), bloodstream infections (n = 28, 51.8%), pneumonia (n = 8, 14.8%), soft tissue infections (n = 8, 14.8%), viral infections (n = 26, 48.1%), invasive mycoses (n = 5, 9.2%). The 100-day OS, GRFS and TRM were 88.9%, 74.1% and 9.3% respectively. The control group demonstrated the same short-term outcomes of allo-HSCT: 100-day OS – 89,3%, GRFS – 80,3% and TRM – 8,2%.

Conclusions: Allo-HSCT is feasible in patients with a history of COVID-19 and characterized by common post-transplant complications. The history of COVID-19 did not affect the short-term results of allo-HSCT. Nevertheless, further studies are required in subgroups of patients with different consequences of COVID-19.

Disclosure: Nothing to declare.

P330

Rituximab therapy after pediatric hematopoetic stem cell transplantation can cause prolonged b cell damage and increases the risk for infections

M. Launspach[1], D. Temel[1], E. Ohlendorf[1], A. Pruß[1], H. von Bernuth[1], L. Oevermann[1], A. Künkele-Langer[1], A. von Stackelberg[1], A. Eggert[1], P. Lang[2], J. Schulte[1]

[1]Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]University Hospital of Tuebingen, Tuebingen, Germany

Background: In the context of hematopoetic stem cell transplantation (HSCT) the CD20-specific monoclonal antibody Rituximab is used as a highly effective treatment for EBV infection and EBV-associated post-transplant lymphoproliferative disease. To a lesser extent, it is also used in other situations (I.e. autoimmune hematologic diseases or included in the treatment regimen for CD20 + lymphoma). However, knowledge of immunological consequences and impact on immune reconstitution after pediatric HSCT are insufficient.

Methods: To produce further insight we performed a retrospective analysis of a cohort of pediatric patients treated with rituximab within 365 days after HSCT. We included 44 (17,8%) out of the 248 patients that received HSCT in our clinic in the period from 01/01/2015 to 12/31/2019. Patients with a drop out event (I.e. relapse or death) before d30 were not included. We compared this group to a second cohort of 44 matched control cases from the same population. To eliminate immortal time bias, potential control patients were only considered if no drop out event occurred before the first dose of rituximab was administered to the corresponding rituximab patient. Data was collected and analyzed for an observation period of up to 3 years after HSCT.

Results: Evaluating general outcomes, we did not find differences regarding overall survival. We could confirm, however, that rituximab therapy led to an increased time to recover normal CD19 + B-lymphocyte levels in the blood (Median B cell recovery: d282 vs d120) and impaired lymphocyte function making prolonged intravenous immunoglobulin (IVIG) substitution necessary (Median last day of IVIG: d254 vs d109). Analyzing the occurrence of other complications, we observed higher rates of other viral infections (75% vs 43%) and signs of increased rates of bacterial infections, longer re-hospitalization durations and higher necessity for transfusions. We did not find differences regarding the development of GvHD. Furthermore, we were able to identify a subgroup of 9 patients (21%) in the rituximab group compared to 0 in the control group, that received IVIG substitution during the entire observation period. Patients in this subgroup showed especially high rates of occurrence of the aforementioned complications.

Conclusions: To our knowledge, this is the first systematic analysis of implications of rituximab therapy after pediatric HSCT in a larger cohort. In line with reports from rituximab

applications in non-HSCT related settings, our findings provide strong evidence that rituximab harbors a risk for prolonged B cell damage when administered shortly after HSCT. Our study moreover shows that regular IVIG substitutions cannot prevent completely the occurrence of secondary complications. The similar overall survival of the compared groups, however, suggests that the occurring complications can be managed via specific treatments. As the observed complications or subgroup allocation did neither correlate with maximal EBV copy numbers in the serum nor with the number of rituximab doses that a patient received, we propose that the initial indication for rituximab treatment should be considered carefully. A repeated dosing over up to 4 weeks on the other hand, does not seem to increase the risk of rituximab-related impairment of immune reconstitution compared to a single dose.

Disclosure: Nothing to declare

P331

Cidofovir treatment for bk-associated hemorrhagic cystitis after allogenic steam cell transplantation with post-transplant cyclophosphamide: A retrospective analysis at a single institution

M.A. Sanchez-Salinas[1], A. Perez-Martinez[1], A. Benzaquen-Vallejos[1], R. Hernani-Morales[1], J.C. Hernandez-Boluda[1], E. Gimenez[1,2], D. Navarro[1,2], C. Solano-Vercet[1,3,4], J.L. Piñana[1]

[1]Hospital Clínico Universitario de Valencia, Valencia, Spain, [2]University of Valencia, Valencia, Spain, [3]University of Valencia, Valencia, Spain, [4]INCLIVA Instituto de Investigación Sanitaria, Valencia, Spain

Background: Post transplant cyclophosphamide (PTCy) is increasingly used as Graft-versus-Host Disease (GVHD) prophylaxis. Hemorrhagic cystitis (HC) is a common complication following PTCy usually linked to BK virus reactivation. Although intravenous cidofovir has been reported to improve and/or reduce BK viraemia or viruria, current data do not support its regular use.

Methods: We retrospectively analyzed HC management and outcome data from a consecutive cohort of adult recipients who underwent an allogenic stem cell transplant (allo-SCT) at our institution between October 2012 and October 2021. The inclusion criterion was the use of PTCy-based GVHD prophylaxis. Cidofovir therapy was considered in case of grade III-IV HC with BK viremia without any symptomatic improvement after at least 7 days after adequate supportive measures. The primary endpoint was to assess cidofovir efficacy and safety. Secondary endpoints included comparison of grade III-IV HC duration between the cidofovir cohort and a non-treated cohort.

Figure 1: OS hemorrhagic cystitis vs No hemorrhagic cystitis

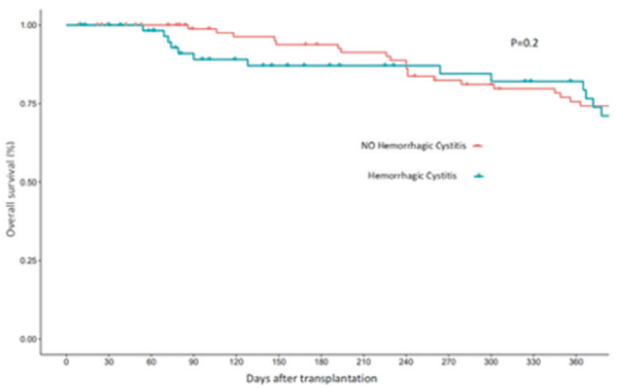


Table 1. Patient characteristics.

Characteristic	Global n= 158	No HC n=96	HC n= 62	p
Age, median (IQR)	55 (43-62)	56 (42-62)	55 (46-62)	0,62
Male gender, no. (%)	95 (60)	59 (61)	36 (58)	0,67
Diagnosis, no. (%)				0,85
AML	46 (29)	26 (27)	20 (32)	
MDS	12 (8)	8 (8)	4 (7)	
ALL	6 (4)	2 (2)	4 (7)	
NHL	35 (22)	22 (23)	13 (20)	
HL	30 (19)	20 (21)	10 (16)	
MPD	9 (6)	5 (5)	4 (7)	
MPD-MDS	7 (4)	5 (5)	2 (3)	
Others	13 (8)	8 (9)	5 (8)	
Disease risk index, no. (%)				0,72
Low risk	35 (22)	23 (24)	12 (19)	
Intermediate risk	83 (53)	51 (53)	32 (52)	
High risk	34 (21)	18 (19)	16 (26)	
Very high risk	6 (4)	4 (4)	2 (3)	
Donor type, no. (%)				0,14
HLA-matched related	34 (22)	25 (26)	9 (15)	
Haploidentical	81 (51)	49 (51)	32 (52)	
Unrelated	43 (27)	22 (23)	21 (33)	
Conditioning regimen, no. (%)				0,19
Myeloablative	21 (13)	10 (10)	11 (18)	
Reduced-intensity	137 (87)	86 (90)	51 (82)	
Disease status at HCT, no (%)				0,25
Complete remission	101 (64)	59 (61)	42 (68)	
Not in complete remission	57 (36)	37 (39)	20 (32)	
PTCy associated immunosuppressive agent				0,62
Cyclosporine	38 (24)	28 (29)	10 (16)	
Sirolimus	120 (76)	68 (71)	52 (84)	

Results: We included 158 allo-SCT recipients. The main clinical and transplant characteristics are shown in table 1. Most recipients received an allo-SCT from alternative donors (78%). Most of recipients (76%) received mycophenolate mophetil (MMF) plus sirolimus whereas the remaining (24%) received MMF plus cyclosporine A as GvHD prophylaxis. The median follow-up was 13 months (IQR, 5 to 35 months). HC grade II to IV was diagnosed in 62 patients (39%) at a median of 26 days (IQR, 13,5 to 48,2) after stem cell infusion. Of them, 30 patients (19%) developed grade III-IV HC. The cumulative incidence of grade II-IV HC was 37% (29-44%). BK viremia was detected in 47 (76%) recipients at the HC onset. The median BK viremia before cidofovir onset was 2749 copies/mL (IQR, 1142-8421), whereas it was 3095 copies/mL (IQR, 820-4931) at the time of HC diagnosis in the non-treated. Intravenously cidofovir was given in 12 (40%) out of 30 recipients with grade III-IV HC, at a median of 13 days (IQR 11-26) after HC onset. Median cidofovir dose was 3mg/kg/week and the median number of doses was 2 (range 1-4). One treated recipient died from sinusoidal obstruction syndrome 10 days after first cidofovir dose. Then, only 11 recipients were evaluable for response and 10 (91%) achieved a complete remission. To evaluate the effect of cidofovir therapy, we compared the symptoms duration from the day of cidofovir in the treated cohort and from HC onset in the non-treated cohort with grade III-IV HC having BK viremia ($n = 13$). Median time of resolution in the treated cohort was 11 days (range 8-24) and 31 days (range 24-37) in the non-treated ($p = 0.09$). Two (15%) patients develop cidofovir related nephrotoxicity grade 2 and two (15%) patients develop myelotoxicity (neutropenia grade 2 and 3).

Conclusions: Despite the inherent limitations of this study and the reduced number of patients, cidofovir was able to resolve severe forms of HC in most of recipients with uncontrolled HC symptoms despite intensive supportive measures. The safety profile was favourable. Prospective randomized trials are required in this setting.

Disclosure: Nothing to declare

P332

Bloodstream infections due to carbapenem-resistant enterobacteriaceae in hematological patients: A retrospective single-center study

L. Zhang[1], Q. Lin[1], E. Jiang[1], M. Han[1], J. Wang[1], S. Feng[1]

[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China

Background: The emergence and global spread of Carbapenem-resistant Enterobacteriaceae (CRE) has represented a major threat to public health. Patients with hematologic malignancies, who frequently experience prolonged neutropenia, immunosuppression, chemotherapy-induced mucositis and invasive procedures, are more vulnerable to CRE infection. Although many studies on CRE infection have been reported in the literature, there are only a few on patients with hematologic malignancies. Therefore, we conducted a retrospective study to describe the clinical outcomes in hematological patients with bloodstream infection (BSI) due to CRE.

Methods: Our retrospective study included patients with monomicrobial CRE BSI between January 2012 and April 2021. The primary outcome was all-cause mortality 30 days after BSI onset. Risk factors were evaluated by comparing the variables of survivors with those of non-survivors.

Results: A total of 94 patients with CRE BSI were documented in the study period. Escherichia coli was the most common Enterobacteriaceae, followed by K. pneumoniae. 66 CRE strains were tested for carbapenemase genes, and 81.8% (54/66) were positive, including NDM (68.5%, 37/54), KPC (29.6%, 16/54), IMP (1.9%, 1/54). Besides, one Escherichia coli isolate was found to express both NDM and OXA-48-like genes. Overall, 28 patients received an antimicrobial treatment containing CAZ-AVI, the remaining 66 patients were treated with other active antibiotics (OAAs). The 30-day mortality rate was 28.7% (27/94). Univariate analysis revealed that patients with high-risk hematological diseases, prolonged neutropenia (≥14 days), pulmonary infection, septic shock and the Pitt bacteremia score≥2 were risk factors for increased mortality. The administration of appropriate empirical therapy within 24 hours of BSI onset was protective factors. For patients treated with CAZ-AVI, the 30-day mortality rate was only 7.1% (2/28), which was significantly lower than those treated with OAAs (37.9%, 25/66, $p = 0.003$). In multivariate analysis, the presence of septic shock at BSI onset (OR, 10.53, 95% CI, 1.38 to 76.92) and pulmonary infection (OR, 6.29, 95% CI, 1.35 to 29.41) were independently risk factors for 30-day mortality. Comparing different antimicrobial regimens, CAZ-AVI showed a significant survive benefit than OAAs (OR, 14.64, 95% CI, 1.54 to 139.55).

Conclusions: Timely appropriate empirical therapy is essential and CAZ-AVI-containing regimen is superior to OAAs for CRE BSI.

Disclosure: This work was supported by the Natural Science Foundation of Tianjin City (18JCZDJC34400); the nonprofit Central Research Institute Fund of Chinese Academy of Medical Sciences (2018PT32034); CAMS Innovation Fund for Medical Sciences (CIFMS)

P333

Antibody responses to sars-cov-2 vaccination/infection in hematological malignances and allogeneic hematopoietic stem cell transplantation patients – a single-center experience

E. Jaskuła[1,2], M. Mordak-Domagała[1], I. Dereń-Wagemann[1], K. Suchnicki[1], M. Sędzimirska[1], J. Lange[1], E. Koćwin[1], I. Wodzińska-Maszko[1], J. Bocheńska[1], J. Dybko[1]

[1]Silesian Canter of Oncology, Wroclaw, Poland, [2]Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Wroclaw, Poland

Background: Vaccines or SARS-CoV-2 infection are highly effective in inducing immunological responses in healthy individuals, however, they are able to induce protective immunity in hematological malignances and allogeneic HSCT recipients is still unknown.

Methods: For this aim, 83 patients of the Department of the Hematology and Transplant Center of the Lower Silesian Oncology Center in Wroclaw (M/F:35/48, age: range: 20-86, mean: 52 years old, diagnosis: ALL = 13, AML = 21, MDS = 6, NHL = 20, CLL/SLL = 12, HL = 1, MM = 7, SAA = 3, including 18 SIB-, 21 MUD-, 1 haploidentical-, and 14 auto-transplantations) were evaluated for the presence of anti-SARS-COV-2 antibodies (anti S1 antibodies in IgG class) in serum between December 2020 and September 2021.

Results: In this group:

- 21 (25%) patients had documented SARS-CoV-2 infection by PCR and/or antigenic test
- 59 (70%) patients were vaccinated with one of the available SARS-CoV2 vaccines
- 39 patients had SARS-CoV-2 antibodies after infection or/and vaccination (from 9 to 161 post-vaccination or infection)
- 17 (20%) patients had had SARS-CoV-2 antibodies without previous SARS-CoV-2 history or vaccination
- 11 patients did not have anti-SARS-CoV-2 antibodies despite vaccination and/or a history of confirmed infection (from days 29 to 201 post-vaccination or/and infection) which constitutes 28% of vaccinated and/or previous COVID-19 history patients (4 patients were excluded from antibody analysis due to short time post-vaccination (6-10 days)).

It was found:

- Patients diagnosed with NHL (excluding alloHSCT) lacked more frequently anti-SARS-CoV-2 IgG antibodies after vaccination and/or SARS-CoV-2 infection compared to patients with other diagnoses who were vaccinated and or had SARS-CoV-2 infection (6/14 vs 3/39 $p < 0.001$). Six of 8 NHL patients who were negative for antibodies to SARs-CoV-2 had reduced IgG antibody levels (225-639 mg/dL, median: 507 mg/dL with a reference value of 700-1600 mg/dL).
- The absence of anti-IgG SARS-CoV-2 antibodies after vaccination or infection was associated with lower IgG antibody levels. Five out of 11 patients with lower IgG levels had no anti-SARS-CoV-2 antibodies after vaccination or infection (5/11 vs 14/68, $p = 0.001$). The majority of patients in the entire group had reduced IgM levels at the time of the study - 52/79 patients had levels of IgM antibodies below reference and no association was observed between low IgM levels and lack of anti-IgG SARS-CoV-2 antibodies after vaccination or infection.
- Group of patients who had SARS-CoV-2 antibodies despite no evidence of a past history of SARS-CoV-2 and were not vaccinated was most commonly comprised of post-HSCT patients (13/40 vs 4/44, $p = 0.013$).
- Patients who lacked anti-SARS-CoV-2 antibodies after vaccination and/or infection were not statistically different in WBC and lymphocyte levels compared to patients who had anti-SARS-CoV-2 antibodies after vaccination or infection.
- 2 patients in this group died due to COVID-19, both patients have lowered IgG levels.

Conclusions: Conclusions:

- NHL patients should be given special SARS-CoV-2 surveillance, in those who do not have anti-SARS-CoV-2 antibodies, the cellular response after vaccination or infection should be examined, and advised to take 3 doses of vaccine.
- HSCT patients more frequently undergo asymptomatic SARS-CoV-2 infection.

- Including asymptomatic patients, 45% of subjects underwent SARS-CoV-2 infection.

Disclosure: Nothing to declare

P334

Epidemiology of invasive aspergillosis caused by *aspergillus non-fumigatus* vs *aspergillus fumigatus* in adults after allogeneic hematopoietic stem cell transplantation

M. Popova[1], V. Markelov[1], Y. Rogacheva[1], A. Volkova[1], I. Nikolaev[1], O. Pinegina[1], S. Ignatieva[2], T. Bogomolova[2], O. Goloshchapov[1], Y. Vlasova[1], M. Vladovskaya[1], N. Klimko[2], A. Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, Saint Petersburg, Russian Federation, [2]Mechnikov North-Western State Medical University, Ministry of Health of Russia, Saint Petersburg, Russian Federation

Background: *Aspergillus fumigatus* is the most common etiologic agent of IA reported in severely immunocompromised patients. However, IA caused by *A*. non-*fumigatus* species are becoming increasingly important and poorly studied.

Methods: We designed the retrospective study in order to investigate the epidemiology of A. non-*fumigatus* IA vs *A. fumigatus* in adult patients (≥18 years) underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT), who subsequently developed culture-positive IA from 2016 to 2021. During the observation period 33 patients with IA caused by *Aspergillus* non-*fumigatus* (n = 20) and *A. fumigatus* (n = 13) were identified.

Results: The most common underlying diseases in patients with *A*. non-*fumigatus* were acute leukemia – n = 6 (30%) and non-Hodgkin's lymphoma – n = 5 (25%), in *A. fumigatus* group – acute leukemia – n = 7 (54%). Transplantation from matched related donor was performed in n = 7 (35%) and n = 3 (23%), from matched unrelated – m = 3 (15%) and n = 3 (23%), from haploidentical – n = 8 (40%) and n = 4 (31%), from mismatched unrelated – n = 2 (10%) and n = 3 (23%) in patients with *A*. non-*fumigatus* and *A. fumigatus*, respectively. Myeloablative conditioning regimen was used in n = 4 (31%) patients from *A. fumigatus* group, in n = 7 (35%) - *A*. non-*fumigatus* group.

Both groups received primary antifungal prophylaxis in post-transplant period (tabl.1). Etiology agents in *A*. non-*fumigatus* group were *A. niger* – n = 11 (55%), *A. flavus* – n = 2 (10%), *A. terreus* – n = 2 (10%), *A. versicolor* – n = 1 (5%), *A. spp*. – n = 1 (5%), combination *A. fumigatus*, *A. flavus* and *A. niger* – n = 1 (5%), combination *A. fumigatus*, *A. niger* and *A. nidulans* – n = 1 (5%). The median day of diagnosis IA caused by *A*. non-*fumigatus* was day +110 (17 – 2093), for *A. fumigatus* – day +46 (2 – 866). The main site of infection were lungs – n = 13 (100%) in patients with *A. fumigatus*, n = 18 (90%) in patients with *A*. non-*fumigatus*. Overall survival at 12 weeks was 55% and 59,2% in *A*. non-*fumigatus* and *A. fumigatus* groups, respectively ($p = 0.617$).

Frontline therapy in *A*. non-*fumigatus* group was voriconazole in n = 16 (80%) patients, voriconazole in combination with echinocandin – n = 2 (10%), liposomal amphotericin B in monotherapy – n = 1 (5%) or in combination with posaconazole -n = 1 (5%); in *A. fumigatus* group voriconazole was used in n = 10 (77%) patients, voriconazole in combination with echinocandin – n = 1 (8%) or liposomal amphotericin B – n = 1 (8)%, isavuconazole – n = 1 (8%). Second line therapy received two patients with IA caused by *A*. non-*fumigatus*: liposomal amphotericin B in combination with echinocandin or with echinocandin and posaconazole, and two patients with IA caused by *A. fumigatus*: liposomal amphotericin B and voriconazole in combination with echinocandin. Comparative analysis showed that none of the assessed characteristics (sex, age, diagnosis, disease status, source of HSC, conditioning regimen, donor type, allo-HSCT number, type antifungal prophylaxis, CMV-reactivation, severe acute and chronic graft versus host disease) in patients from the two groups were not significantly differed.

Conclusions: *A. niger* was dominant agent among *A*. non-*fumigatus*. IA etiology (*A*. non-*fumigatus* vs *A. fumigatus)* was not associated with specific patient characteristics and did not impact on treatment and outcomes in adults after allo-HSCT.

Disclosure: Nothing to declare

P335

Prevention of CPE bloodstream infection and death in a paediatric allogenic HSCT population: The manchester story

A. Shears[1], Z. Aiken[2], R. Hanasoge-Nataraj[1], H. Webster[1], D. Bonney[1], P. Ashcroft[2], K. Dodgson[2], R. Wynn[1]

[1]Royal Manchester Childrens Hospital, Manchester, United Kingdom, [2]Manchester Foundation Trust, Manchester, United Kingdom

Background: Carbapenemase-producing Enterobacteriales (CPE) are a significant risk to stem cell transplant recipients, with mortality rates from CPE blood stream infection (BSI) during transplant of up to 70%. This study assesses the impact of a series of measures introduced by Royal Manchester Children's Hospital, with the aim to use screening and surveillance to reduce CPE BSI and death, in a paediatric allogenic HSCT population.

Methods: This was a retrospective review of the Manchester bone marrow transplant database and microbiology laboratory information management system. Eligibility criteria were age < 18 years and allogenic stem cell transplant performed between July 2009 and October 2021 at Royal Manchester Children's Hospital. The study endpoints were incidence of CPE BSI within 1 year of transplant and incidence of death from CPE BSI within 1 year of transplant.

Results: A total of 585 patients were included. Sixty-two (10.6%) patients were colonised with CPE and 9 (1.5%) patients had CPE BSI within 1 year of transplant; *Klebsiella pneumoniae* carbapenemase (KPC) was the predominant CPE enzyme, and was detected in 7 patients, a carbapenemase enzyme was not identified in the remaining 2 patients. Five of the patients with CPE BSI died, in 3 patients CPE BSI was thought contributory although all had significant underlying issues. Incidence of CPE BSI within 1 year of transplant for all patients was 0.015. Incidence of death from CPE BSI within 1 year of transplant was 0.005. CPE-infection related mortality rate in those with CPE BSI within 1 year of transplant was 33%. All-cause mortality rate in patients with CPE bacteraemia within 1 year of transplant was 55%.

Conclusions: Transplant recipients are at risk of CPE colonisation and infection due to immunosuppression, prolonged hospital stays, central venous access and exposure to broad-spectrum antibiotics. The Royal Manchester Children's Hospital is within a Trust where transmission of plasmid-mediated bla_{KPC} had become endemic, and a number of measures were introduced to reduce CPE colonisation and subsequent infection. These measures included screening all patients admitted for HSCT on admission and throughout for CPE, isolating patients colonised with CPE and ensuring empiric antibiotic for these patients include appropriate CPE cover. Our study demonstrates the success of this approach as incidence of CPE bacteraemia and death in our cohort was low, despite a relatively high baseline colonisation rate.

Disclosure: Nothing to declare.

P337

Cytomegalovirus reactivation under pre-emptive therapy during allogeneic hematopoietic stem cell transplant: The pattern, survival, and risk factors in South Korea

K.-W. Kang[1], B.-H. Lee[1], M.J. Jeon[1], E.S. Yu[1], D.S. Kim[1], S.R. Lee[1], H.J. Sung[1], C.W. Choi[1], Y. Park[1], B.S. Kim[1]

[1]Korea University College of Medicine, Seoul, Korea, Republic of

Background: South Korea is an endemic area of cytomegalovirus (CMV), and the CMV seropositivity of Koreans is estimated to be over 90%. Recently, letermovir has been considered as primary prophylaxis for CMV in CMV-seropositive recipients of allogeneic hematopoietic stem cell transplant (HSCT). Consequently, most HSCT recipients in South Korea are indicated for the use of letermovir. However, its high costs make this strategy non-feasible. In this study, we analyzed the pattern and survival of CMV reactivation in patients undergoing pre-emptive therapy for CMV infection during HSCT, and assessed high-risk patients who can benefit from CMV prophylaxis.

Methods: We retrospectively analyzed the patients undergoing pre-emptive therapy for CMV infection during HSCT in the Korea University Transplant Registry from November 2003 to July 2020. CMV monitoring was performed in all enrolled patients using CMV antigen (from 2003 to 2013) or CMV polymerase chain reaction (PCR) (from 2013 to 2020), and pre-emptive therapy for CMV was done using ganciclovir (5 mg/kg, intravenous injection every 12 hours) in the patients who presented CMV antigenemia or PCR titer more than 1,000 copies/ml.

Results: A total of 295 patients with HSCT were analyzed. The median age was 47 years (range: 16–68), and the reasons for HSCT were aplastic anemia (26 patients, 8.8%), acute myeloid leukemia/myelodysplastic syndrome (182 patients, 61.7%), acute lymphoblastic leukemia (64 patients, 21.7%), multiple myeloma (11 patients, 3.7%), and lymphoma (12 patients, 4.1%). CMV-seropositivity was confirmed in 87.2% (donor + or recipient +). Antithymocyte globulin (ATG) was used in 68.8% of patients.

Pre-emptive therapy for CMV was performed in 142 patients (48.1%), and the median time from day 0 of HSCT to the start of therapy was 33 days (range: 3–192). The overall survival of the patients who were treated with pre-emptive therapy for CMV was not different compared to those who were not treated. Of these 142 patients, 75 patients (52.8%) underwent more than two pre-emptive therapies for CMV during HSCT. The median duration of pre-emptive therapy for CMV was 14 days (range: 1–74). In the multivariate analysis, the risk of the use of pre-emptive therapy for CMV was high in patients with multiple myeloma (OR: 14.979, 95% CI: 1.436–156.282, $p = 0.024$), acute graft-versus-host disease of grade more than 3 (OR: 2.262, 95% CI: 1.175–4.356, $p = 0.015$), and ATG. In case of patients with ATG use, the risk escalated with an increase in the total dose of ATG (< 5 mg/kg, OR: 2.601, 95% CI: 1.227–5.515, $p = 0.013$; ≥5 mg/kg and <9 mg/kg, OR: 4.846, 95% CI: 2.235–10.507, $p < 0.001$; and ≥9 mg/kg, OR: 17.905, 95% CI: 5.255–61.012, $p < 0.001$) compared to that in those with no use.

Conclusions: In this study, half of the patients with HSCT were treated with pre-emptive therapy for CMV, without any effect on their survival, reflecting that pre-emptive therapy has enough advantage even in CMV endemic area. However, 50% of the patients experienced CMV reactivation repeatedly with a median duration of 14 days more than twice; therefore, it is necessary to re-evaluate the cost-effectiveness of CMV prophylaxis in high-risk patients.

Disclosure: The authors declare that they have no competing interests.

P338

Cmv reactivation after allohct in two groups of recipients: From haploidentical and mismatched unrelated donor – a preliminary analysis on behalf of polish adult leukemia group

J. Dybko[1], M. Sobczyk-Kruszelnicka[2], A. Piekarska[3], P. Mensah-Glanowska[4], S. Giebel[2], L. Gil[5]

[1]Lower Silesian Canter of Oncology, Wroclaw, Poland, [2]National Oncology Institute, Gliwice, Poland, [3]Gdańsk Medical University, Gdańsk, Poland, [4]Jagiellonian University Medical Collage, Kraków, Poland, [5]Poznań University of Medical Sciences, Poznań, Poland

Background: CMV reactivation remains one of the most common and serious infectious complications after allogeneic HCT. Patients transplanted from unrelated or mismatched donors are at high risk of CMV reactivation.

We found interesting to compare reactivation rate in this two groups due to different immunosuppressive approach.

Methods: All patients were transplanted before letermovir prophylaxis was widely available and none of them received it. 94 patients with hematological malignancies were included in the study – 55 transplanted from haploidentical donor (haplo group) and 39 transplanted from mismatched unrelated donor (mmud group). Conditioning was based on post-transplant cyclophosphamide (with tacrolimus and MMF) in 100% of patients in a haplo group and in 18% (7/39) in a mmud group. 32/39 patients of a mmud group received classical immunosuppression based on ATG/CsA/Mtx. Median age was 38 in a haplo and 41 in a mmud group, F/M ratio – 29/26 and 20/19, respectively. In a mmud group – there were single HLA mismatches in locus A, B, C and DQ in 15, 4, 14 and 6 cases.

Results: We did not find any differences between groups in patients' and donors' age, conditioning intensity, diagnosis and CMV preemptive treatment. The median number of CD34 cells transplanted was significantly higher in a haplo group (9.84 vs 7.51 x 10^6/kg b.w., $p = 0.007$) Overall, CMV reactivation rate was as follows: 23/55 (41,8%) in a haplo group and 23/39 (58,9%) in a mmud group ($p = 0.08$) and CMV positive donors (D +) rate was 44/55 and 24/39, respectively ($p = 0.04$). Acute GvHD was more frequent in a mmud group (20/39 (51,3%) vs 17/55 (31,0%), $p = 0.04$, including grades 3/4 (6/39 (15,4% vs 1/55 (1,8%), $p = 0.04$). In opposite, chronic GvHD was more frequent in a haplo group (11/55 (20,0%) vs 2/39 (5,1%), $p = 0.03$). On the other hand, in a mmud group, HLA-C mismatch was correlated with the highest rate of reactivation (HLA-A - 8/23 (34,8%), HLA-B - 0/23, HLA-C 11/23 (47,8%) and HLA-DQ - 4/23 (17,4%), $p = 0.03$).

Conclusions: We are aware the results are preliminary; the study is still ongoing, we are collecting new data. The results, if confirmed in a larger group, may support a wider use of posttransplant cyclophosphamide instead of ATG in a mmud groups both due to CMV reactivation and acute GvHD rate. On the other hand, the results may be helpful to better define recipient groups for strict CMV prophylaxis.

Disclosure: Nothing to declare

P339

Antibody responses and safety of the commercially available vaccines against sars-cov-2 virus in allografted patients: Real world data from a single center

P. Kaloyannidis[1], B. Blowi[2], R. Yahya[3], H. Al Khaldi[3], R. Attas[4], A. Dayel[5], S. Kanfar[6]

288

[1]King Fahad Specialist Hospital, Dammam, Saudi Arabia, [2]King Fahad Specialist Hospital, Dammam, Saudi Arabia, [3]King Fahad Specialist Hospital, Dammam, Saudi Arabia, [4]King Fahad Specialist Hospital, Dammam, Saudi Arabia, [5]King Fahad Specialist HospitalKing Fahad Specialist Hospital, Dammam, Saudi Arabia, [6]King Fahad Specialist Hospital, Dammam, Saudi Arabia

Background: Allografted patients are at high-risk for life-threating complications post SARS-CoV-2 infection, as the mortality rates in this group of patients has been reported of approximately 30-35%. The currently available vaccines proved their safety and efficacy by reducing the severity of the COVID-19 infection in the general population however, scant data exist in allografted patients.

Methods: We evaluated the safety and efficacy of the commercially available vaccines in 20 allografted patients aged of 29,8 (21-50) years, vaccinated from March to November 2021 according to Saudi Arabia national vaccination program, after a median of 2,7 (0,3-6,7) years post-transplant. At the time of vaccination all patients were in complete remission however, one allografted patient for severe aplastic anemia had delayed engraftment. Fifteen were off immunosuppression without evidence of active GvHD, one was only on Cyclosporine while 5 were on steroids plus Cyclosporine or Mycophenolate Mofetil or Ibrutinib as treatment for chronic GvHD. Eight had additional co-morbidities: hyperglycemia (n = 4), post-transplant metabolic syndrome (n = 2), thyroid dysfunction (n = 2), all on specific treatment. One had received 5 months before vaccination Rituximab because of EBV-reactivation. The side effects post vaccination were estimated according to WHO grading system, while the antibody response was evaluated using automated commercial chemiluminescence immunoassay (CLIA) against spike (S1/S2) protein); antibody detection of >15.0 arbitrary units/ml (AU/ml) was considered as positive, between 12-15.0 as equivocal and less than 12.0 AU/ml as negative. Additionally, blood counts, lymphocytes sub-populations, immunoglobulins and D-Dimers were evaluated before and after each vaccination to evaluate any vaccine-related effect on the above parameters. Despite none patient had prior documented COVID-19 infection, three (15%) found to have detectable anti-SARS-CoV-2 antibodies before vaccination. Within a median of 42 (19-156) days, 2 doses were administered either of Pfizer (n = 17) or combinations of Pfizer/Moderna (n = 2) or AstraZeneca/Pfizer (n = 1) products.

Results: After a median follow-up of 5,3 (2,6-7,7) months post 1st vaccination, no side effects grade ≥3 (WHO) reported. No allergy, thrombosis or heart dysfunction were noticed. The commonest complains were generalized fatigue (n = 4, 20%), bony pain (n = 2, 10%) while 2 (10%) patients reported fever <38.5°C (one over 24 hours and one for 5 days). No laboratory abnormalities were found post vaccination on the aforementioned evaluated parameters. Eventually 18/20 patients were available for humoral responses after 1st and 19/20 after the 2nd dose. Twelve (66%) and 18 (95%) achieved antibody responses after the 1st and 2nd dose respectively. One patient (with delayed marrow recovery post-transplant) failed to produce antibodies after completion of 2 vaccinations. Importantly, patients with active cGvHD and intensive immunosuppression, were capable for adequate humoral responses. None of the vaccinated patients developed COVID infection of any severity.

Conclusions: Our retrospective study although with small number of patients and with short term follow-up, in agreement with others, confirms that the current commercially available vaccines against SARS-CoV-2 are safe and highly effective in producing detectable humoral responses in allografted patients. Prospective studies with longer follow-up are needed to elucidate the proper timing and the number of necessary doses for a safe and effective approach in preventing severe COVID infection.

Disclosure: Nothing to declare

P340

Letermovir is effective as primary prophylaxis against cytomegalovirus in hematopoietic stem cell transplant recipients, but late infections occur following discontinuation when cellular immunity is impaired

I. Tzannou[1], M. Dellatola[1], T. Tzenou[1], I. Tsonis[1], E.-K. Dimitraki[1], V. Babali[1], M.-E. Karatza[1], Z. Poulopoulou[1], S. Tryfonidou[1], M. Papageorgiou[1], M. Katsareli[1], S. Gigantes[1], D. Karakasis[1], I. Baltadakis[1]

[1]Evaggelismos General Hospital, Athens, Greece

Background: Cytomegalovirus (CMV) reactivation or disease is the most common infectious complication following allogeneic stem cell transplantation (allo-HSCT). All CMV seropositive recipients are in risk for CMV reactivation, especially those who receive a mismatched, T-cell depleted or umbilical cord blood graft, and those who develop GvHD requiring corticosteroid treatment. Prophylactic therapy with letermovir became available quite recently, and is approved for administration in CMV seropositive patients during the first 100 days post HSCT. The aim of our study was to evaluate the efficacy of primary CMV prophylaxis with letermovir and the frequency of late CMV reactivation and disease.

Methods: In this retrospective study, we evaluated 29 transplant recipients who received letermovir prophylaxis between August 2018 and February 2021. Letermovir was administered from day +7 through day +100. CMV viral load was monitored by quantitative PCR 1-2 times weekly, for a minimum of 6 months following transplant. We studied the frequency of CMV reactivation during administration of letermovir and after cessation of therapy.

Results: Twenty-nine patients with a median age of 55.4 (range, 21-71) years were evaluated. The indication for HSCT was AML/MDS (n = 23), NHL/CLL, (n = 3), MPN (n = 2) or ALL (n = 2). Twenty patients received myeloablative and 9 patients reduced-intensity conditioning. Eighteen of 29 patients were high-risk for CMV reactivation, based on mismatched unrelated (n = 3) or haploidentical (n = 1) transplant, acute GvHD grade ³II (n = 15) and/or high-dose corticosteroid treatment (n = 13). During the first 100-day follow-up period, 11 cases of CMV DNA detection were noted in 10 patients (5 of whom were high-risk) at a median time of 25 (8-96) days from transplant. 10/11 events involved low viral load that subsequently resolved without antiviral treatment. Only one case of clinically significant CMV reactivation was observed, which responded to pre-emptive therapy with foscarnet without evidence of CMV disease. Following letermovir discontinuation, 14 patients experienced CMV reactivation at a median of 160.5 (116-195) days post transplant. 8/14 received antiviral therapy with valgancyclovir (n = 7) or foscarnet (n = 1). Two patients required second-line antiviral treatment. No case of CMV disease was documented. The absolute CD3 + cell count was significantly lower in patients with versus without CMV reactivation after completion of letermovir prophylaxis (median, 438/μL vs 701/μL, respectively, p = 0.02).

Conclusions: Letermovir is effective as primary prophylaxis, albeit with a considerable risk of CMV reactivation following discontinuation. Patients with better T cell reconstitution had a lower risk of late CMV infection, presumably due to the presence of CMV-specific T cells. T cell immunity could therefore serve as a marker for the optimal duration of letermovir prophylaxis.

Disclosure: Nothing to declare

P341

SARS CoV-2 infection and covid-19 in health care workers from a hematopoietic stem cell transplant (HSCT) unit before and after vaccination: A prospective cohort study

A.C. Ferrari dos Santos[1], J. Do Prado Moreno[1], L. Perilio Zanetti[1], L.C. de Oliveira[1], L.H. de Almeida Testa[1], A.J. Simione[1], M.P. de Souza[1], V.A. Rensi Colturato[1], C. Machado[2,1]

[1]Fundação Hospital Amaral Carvalho, Jaú, Brazil, [2]Institute of Tropical Medicine, University of São Paulo Medical School, São Paulo, Brazil

Background: HSCT recipients are profoundly immunosuppressed and health care workers (HCW) of transplant units need to be tested periodically by SARS CoV-2 PCR to avoid patient transmission during hospitalization.

Methods: We conducted a prospective cohort study with periodic serology and nasal wash (NW) sampling to estimate the cumulative incidence of COVID-19 in health professionals from HSCT unit before (May 2020 to January 2021) and after COVID-19 vaccination (January to October 2021) and to evaluate the occurrence of hospital acquired COVID-19 in HSCT recipients. In addition to periodic sampling, from inclusion (dzero) onwards, HCWs were daily surveyed for the presence of symptoms. NW was taken if symptoms and/or exposure to a confirmed or suspected case of COVID-19. If tested positive by PCR, they were away for 14 days and returned to work with at least 1 negative PCR test. Detection of SARSCoV-2 was performed by PCR (RealStarÒ SARSCoV-2, Altona Diagnostics/ Germany) and monthly serology by ELISA (Anti-SARSCoV-2 ELISA, Euroimmun/ Brazil). The incidence of SARSCoV-2/COVID-19 was estimated by cumulative incidence. Study participants received the 1st dose of COVID-19 vaccines (Sinovac/Butantan or Oxford/AstraZeneca/Covishield) between January and March 2021, and the 2nd dose between February and June 2021. Vaccine Effectiveness (VE) was identified by the formula VE = (r0-r1)/r0 (r0 = rate in unvaccinated individuals; r1 = rate in vaccinated).

Results: Between May 13, 2020 and March 22, 2021, 109 HCWs were included. The median follow-up was 259 (79-309) days. Before vaccination, 29 cases of SARS CoV-2/COVID-19 were diagnosed at a median of 53 days, for a cumulative incidence of 30 %. Thirteen cases (11.9%) were detected at inclusion and 16 during follow-up. Of the 13 cases detected at inclusion, 8 (30.8%) were diagnosed by serology, showing previous infection. During follow-up, 7 individuals dropped out of the study and one was not vaccinated. Thus, 101 HCWs were included in the post-vaccine analysis. Eight PAS (8%) received chAdOx1 (Oxford/Astrazeneca/Covishield) and 93 (92%) Sinovac (Butantan). After vaccination, 76 of the 78 susceptible HCWs tested positive (97.4%), 1(1.3%) had an indeterminate result, and 1(1.3%) had a negative result after the 2nd dose. Within a median post-vaccine follow-up of 153 (91-165) days, 9 HCWs acquired COVID-19 (6 between the first and second dose) for a cumulative incidence of 9.7%. Three (33.35) acquired COVID-19 despite the presence of specific SARS CoV-2 antibodies. Considering only the susceptible subjects at vaccination (n = 78), the rate of COVID-19 in unvaccinated (n = 29) or partially vaccinated (n = 6) was 44.8% (35 of 78) and the rate in those fully vaccinated was 3.8% (3 of 78), for a VE of 91.5%. Due to this intense surveillance of COVID-19 in the HSCT unit, no hospital-acquired COVID-19 was observed in HSCT recipients during the study period.

Conclusions: In conclusion, a good serological response was observed after vaccination (97,4%), resulting in a decrease in the incidence of COVID-19 from 30% to 9,7%. The current pandemic scenario continues to represent a great challenge in HSCT units. COVID-19 control policies in HSCT health professionals successfully avoided hospital transmission of SARS CoV-2 to HSCT recipients.

Disclosure: C Machado - speaker fee from MSD, Altona and Takeda.

Source funding - Virology lab, Institute of Tropical Medicine, University of São Paulo Medical School.

P342

Off-label use of letermovir in a pediatric cohort of patients undergoing allogeneic hematopoietic stem cell transplantation

F. Quagliarella[1], F. Galaverna[1], F. Del Bufalo[1], E. Boccieri[1], D. Pagliara[1], M. Algeri[1], M. Catanoso[1], R. Carta[1], M. Becilli[1], C. Rosignoli[1], C. Canino[1], M. Massa[1], P. Bernaschi[2], C.F. Perno[3], T. Corsetti[4], P. Merli[1], F. Locatelli[1,5]

[1]Bambino Gesù Children's Hospital, Roma, Italy, [2]Microbiology Unit, Bambino Gesù Children's Hospital, Roma, Italy, [3]Microbiology and Immunology Diagnostics Unit, Bambino Gesù Children's Hospital, Roma, Italy, [4]Pharmacy Unit, Bambino Gesù Children's Hospital, Roma, Italy, [5]La Sapienza University, Roma, Italy

Background: Letermovir (LMV) is the first drug approved for prophylaxis of Cytomegalovirus (CMV) infection in adult CMV-seropositive patients undergoing hematopoietic stem cell transplantation (HSCT). It acts by inhibiting the viral DNA terminase complex, interfering with virion maturation.

Clinical efficacy and particularly favorable toxicity profile make the drug attractive in pediatric settings, both for the prophylaxis of CMV infection and for the treatment of resistant cases.

Methods: Between July 2020 and November 2021, Letermovir was administered to 20 pediatric patients at the Bambino Gesù Children's Hospital. The off-label clinical indications for LMV were: primary prophylaxis (n = 9), secondary prophylaxis (n = 2), pre-emptive treatment (n = 7) and CMV-disease treatment (n = 2).

Letemovir was administered at median dose of 240 mg/die (range 50-480 mg/die); notably, patients taking cyclosporine (n = 14, 70%) as prophylaxis/therapy of Graft-versus-Host Disease (GVHD), received half of the planned dose.

Primary prophylaxis (CMV positive recipient with negative donor) with LMV was administered at least until day 100 post HSCT.

Five patients were already taking antiviral therapy (Ganciclovir and/or Foscarnet) for CMV-DNA positivity on blood; two of them had CMV disease (pneumonia and encephalitis).

Results: All patients were able to assume Letermovir with only mild nausea and vomiting in 2 patients (14%), and none of them discontinued the treatment. Eight out of 9 patients who assumed LMV as primary prophylaxis did not reactivate CMV viremia up to day 100 after transplant.

All 7 patients who started LMV with positive CMV-DNA on blood (median 4400 copies/ml) achieved negative CMV-viremia at a median time of 27 days; 5 of them (71%) received a T-depleted HSCT.

Two patients on secondary prophylaxis therapy did not exhibit CMV reactivation until drug discontinuation.

One patient with CMV pneumonia treated with Letermovir in combination with Ganciclovir and Foscarnet presented a rapid decrease of CMV-DNAemia, despite subsequent death due to interstitial pneumonia (CMV-), while one patient with CMV encephalitis, already treated with dual antiviral therapy, had CMV-DNA negativity on blood and CSF after initiation of therapy with LMV.

Overall, probability of negative CMV-DNAemia at 60 days after start of Letermovir was 90%.

Conclusions: With the limit of sample size, Letermovir seems safe and effective in all indications tested in our pediatric cohort.

More studies are needed to address precisely the duration of primary and secondary prophylaxis, considering type of transplantation (e.g. T-depleted), immune reconstitution and any

concomitant immunosuppression (GVHD prophylaxis and therapy). Preliminary results with Letermovir as third-line therapy for treatment-refractory CMV-reactivation show clinical efficacy which could be assessed in larger trials.

Disclosure: Nothing to declare

P343

Monitoring and management of cytomegalovirus reactivation in autologous stem cell transplant recipients: Results of more than a decade of experience

İ.E. Pınar[1], V. Özkocaman[1], F. Özkalemkaş[1], Z.H. Erdoğan[1], T. Ersal[1]

[1]Bursa Uludag University, Bursa, Turkey

Background: Follow-up of cytomegalovirus (CMV) reactivation in autologous peripheral stem cell transplantation (ASCT) is not recommended because of the low risk of reactivation. This study created a model for the high risk of CMV reactivation in patients undergoing ASCT, and the results were examined.

Methods: The study was conducted with 360 patients who underwent ASCT between August 2009 and August 2021. For the transplant conditioning regimen, melphalan 200 mg/m^2 was administered to all multiple myeloma patients and BEAM to lymphoma patients. CMV DNA follow-up after ASCT was checked weekly only in patients with prolonged fever, diarrhea, and pneumonia in the absence of bacterial or fungal infection, unexplained elevations of liver enzymes greater than 1.5-fold, or delay or loss of engraftment neutrophils and platelets. Engraftment delay was defined as an unsupported absolute neutrophil count (ANC) of 500/mm^3 and a platelet count of no more than 20000/mm^3 at 14 and 21 days after ASCT. In addition, ANC and platelet counts <1000/mm^3 and <100000/mm^3 after recovery, respectively, were considered as engraftment loss.

Results: CMV reactivation was detected in 43 patients, 29 male and 14 female, and the cumulative incidence was 11.9%. The patients' ages ranged from 25 to 73, with a median of 56. The median time to CMV reactivation was 39 days (8-1825 days).

Three patients died within three days of CMV reactivation. All other patients, including six patients with end-organ disease, recovered with anti-CMV therapy.

Twenty-one (48.8%) patients with CMV reactivation were treated 12 ganciclovir and 9 valganciclovir. For CMV reactivation, induction and consolidation treatments were each administered for a median of 14 days. Cytopenia in 4 patients and electrolyte disturbances in 6 patients were detected as treatment-related toxicity.

In our study cohort with CMV reactivation with a median follow-up of 47.7 (10.2-277) months, the 100-day mortality was 6.9%, and the overall mortality was 46.5%. More detailed information of patients with CMV reactivation after ASCT is shown in table 1.

Table 1: Clinical features and distribution of patients with CMV reactivation

Parameters (n = 43)		Number (%) or median (min-max)	
Age (year)		56	(25-73)
Gender (Female/Male)		14/29	
Disease	Multiple Myeloma	26	(60,4)
	Hodgkin Lymphoma	4	(9,4)
	Non-Hodgkin Lymphoma	13	(30,2)
Pre-transplant chemotherapy line	≤3	37	(86)
	>3	6	(14)
Pre-transplant response to therapy	Complete remission	35	(81,3)
	Partial remission	7	(16,2)
	Stabil disease	1	(2,5)
CMV status pre-transplant	CMV IgG positive	43	(100)
	CMV IgM positive	0	(0)
Engraftment time (day)	Neutrophil count	12	(9-51)
	>500/mm^3	14	(8-51)
CMV reactivation in the study cohort	Platelet count > 20000/mm^3	43	(11,9)
	Yes	317	(88,1)
	No		
Reason for checking CMV level	Prolonged fever	14	(32,5)
	Diarrhea	5	(11,6)
	Pneumonia	9	(20,9)
	Liver enzyme elevation	6	(14,1)
	Cytopenia	9	(20,9)
Time to reactivation (day)		39	(8-1825)
CMV antigenemia (IU/mL)	Moment of diagnosis	467	(27-36385)
	Peak level	482	(27-78987)
Anti-CMV therapy	Ganciclovir	12	(57,1)
	Valganciclovir	9	(42,9)
Treatment-related toxicity	Neutropenia	2	(20)
	Pancytopenia	2	(20)
	Hypomagnesemia	3	(30)
	Hypocalcemia	2	(20)
	Acute kidney failure	1	(10)
Anti-CMV therapy (day)	Induction therapy	14	(7-28)
	Maintenance therapy	14	(7-32)
Development of CMV disease	Yes	6	(13,9)
	No	37	(86,1)
Mortality (%)	100-day	6,9	
	Overall	46,5	

Conclusions: Our data suggest that high-dose chemotherapy regimens administered with ASCT may also be a reason for the risk of CMV reactivation. Both ganciclovir and valganciclovir are effective in treating CMV reactivation after ASCT. More frequent evaluation of CMV infection may be recommended in high-risk ASCT patients included in the criteria of our study. Thus, with rapid diagnosis, treatment can arise without significant toxicity.

Disclosure: Nothing to declare.

P344

COVID-19 in hematopoietic stem-cell transplantation recipients: Single center experience

Z.T. Guven[1], S. Çelik[1], M. Keklik[1], A. Ünal[1]

[1]Erciyes University Medicine Faculty, Kayseri, Turkey

Background: COVID-19 infection has been associated with adverse outcomes in hematopoietic stem cell transplantation (HSCT) recipients. In this study, we aimed to evaluate the clinical features and outcomes of COVID-19 in HSCT recipients followed in our center.

Methods: Patients who were followed up in our Blood and Marrow Transplantation Center and had post-transplant COVID 19 infection were retrospectively screened. Features such as age, diagnosis, donor type, graft source, conditioning regimens and COVID 19 disease severity were included in the analysis. The main outcome was overall survival 30 days after diagnosis of COVID-19. Survival analysis was calculated using the Kaplan-Meier method. Factors associated with death after diagnosis of COVID-19 were examined using Cox proportional hazards models

Results: 76 HSCT recipients diagnosed with COVID-19 were included in the study. The median age of the patients included in the study was 55 (range, 20 - 73) and 41 (54%) were male. The median time from HSCT to diagnosis of COVID-19 was 26 months (range, 3-146) for HSCT recipients. While 43 (57%) of the patients were autologous HSCT receivers, 33 (43%) were allogeneic HSCT receivers. Of the 33 allogeneic HSCT recipients, 5 (15%) were receiving immunosuppression within 6 months of COVID-19 diagnosis. The majority of patients (88%) were in remission for hematological disease. Of 76 patients, 14 (18%) had mild disease severity and 10 (13%) had severe disease requiring mechanical ventilation. While 52 patients used favipravir as treatment, 21 patients used a combination of steroid and favirpravir. Convalescent plasma was given to 3 (4%) patients. Ten (13%) patients died due to covid. Five of these patients were autologous HSCT receivers and 5 were allogeneic HSCT receivers. At 30 days after diagnosis of COVID-19, overall survival for HSCT recipients was 90%. Disease status was associated with a higher risk of death among all HSCT recipients ($p = 0.018$) When 10 patients who died were evaluated, 4 of them had active hematological cancer when they were diagnosed with COVID-19

Conclusions: COVID-19 infection is a feared situation in hematopoietic stem cell recipients. HSCT recipients should avoid contact with COVID-19 patients as much as possible and carefully maintain routine hygiene practices. Patients with active disease are in higher risk group in terms of mortality.

Disclosure: nothing to declare

P345

Infectious complications after hematopoietic allogeneic transplantation in the era of flt3 inhibitors

I. Cutini[1], R. Boncompagni[1], A. Fani[1], A. Gozzini[1], C. Innocenti[1], S. Mariotti[1], C. Nozzoli[1], G. Raugei[1], R. Saccardi[1]

[1]*Careggi Univeristy Hospital, Florence, Italy*

Background: Midostaurin in combination with chemotherapy become the standard of care of FLT3 positive AML. Although its favorable role is well known in terms of OS and EFS, there is lack of data regarding its impact on infectious complications after HSCT.

Methods: We retrospectively evaluated 48 consecutive patients underwent HSCT for FLT3 ITD positive AML over the last 10 years (from 2012 to 2021). All patients from 2018 received Midostaurin as a part of induction and consolidation treatment and we compared them to an historical cohort which did not receive any FLT3 inhibitors. Monitoring of mucositis during aplasia phase, incidence of infectious events (sepsis, septic shock and GI infection), acute or chronic GVHD, relapses and 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 time to event analysis.

Results: Midostaurin was administered to 29 patients as a part of AML treatment during induction and consolidation before allogeneic transplant. No difference was observed between the two cohorts in age at HSCT, gender, status of disease at time of HSCT, ATG as GVHD prophylaxis, intensity of conditioning regimen, type of donor, graft source, CMV reactivation and incidence of relapse. Midostaurin group reported a higher number of both pre-existent colonization ($p = 0{,}011$) and incidence of septic shock ($p = 0{,}019$). The incidence of aGHVD was lower in Midostaurin group ($p = 0{,}021$). No difference was observed for 1-year OS and 1year PFS between the two groups (49% vs 51,7%, p=ns; 40% vs 44,7%, p=ns).

	Midostaurin n(%)	No Midostaurin n(%)	p
AML	19 (39,6)	29 (60,4)	ns
NPM1 mut/ FLT3 ITD	13 (50)	13 (50)	
NPM1 wt/ FLT3 ITD	6 (27,3)	16 (72,7)	
Gender: M/F	9 (47,4) /10 (52,6)	15 (51,7) /14 (48,3)	ns
Status at transplant			
RC MRD neg	8 (42,1)	13 (44,8)	ns
RC MRD pos/ No RC	11 (57,9)	16 (55,2)	
Pre-existent colonization	13 (68,4)	9 (31)	
- bacteria	4 (30,8)	6 (66,7)	0,011
- yeast	3 (23,1)	1 (11,1)	ns
- MDRO	6 (46,2)	2 (22,2)	
Type of conditioning regimen:			
RIC	2 (10,5)	5 (17,2)	ns
MAC	17 (89,5)	24 (82,8)	ns
ATG	10 (52,6)	14 (48,3)	
Mucositis gtrade 3-4	9 (47,4)	17 (58,6)	ns
Infectious events			
• Sepsis	8 (42,1)	20 (69)	ns
• Septic shock	5 (26,3)	1 (3,4)	0,019
• GI infections	2 (10,5)	1 (3,4)	ns
aGVHD	6 (31,6)	19 (65,5)	0,021
cGVHD	5 (33,3)	8 (27,6)	ns
Relapse	5 (33,3)	10 (40)	ns

Conclusions: Patients previously exposed to Midostaurin who underwent HSCT reported a higher incidence of pre-existent colonization and thereafter to life threatening infections, such as septic shock. It seems to have a protective role against aGVHD. This result may be explained by the gastrointestinal toxicity related to Midostaurin. However, the small sample size of Midostaurin group might prevent to assess other differences among the two groups.

Disclosure: nothing to disclose

P347

Antibody responses to SARS-CoV-2 vaccination in allogeneic hematopoietic stem cell transplant recipients

M. Liga[1], D. Tsokanas[1], A. Gkikas[1], E. Sagiadinou[1], S. Vamvakopoulou[1], F. Paliogianni[1], A. Spyridonidis[1]

[1]University Hospital of Patras, Rio, Patras, Greece

Background: Allogeneic hematopoietic cell transplantation (allo-HCT) is the only curative treatment for many malignant and non malignant haematological diseases. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the coronavirus that causes COVID-19 (coronavirus disease 2019), the respiratory illness responsible for the ongoing COVID-19 pandemic. The COVID-19 pandemic led to the fast invention and wide use of mRNA and viral vector based vaccines. While the protection of the general population against SARS-COVID-19 after vaccination is undoubtedly, the question about protection in immunocompromised people remains unknown. The goal of this study is to examine the extent in which a subpopulation of immunocompromised patients, those who have underwent allogenic stem cell transplantation are able to produce immune response against SARS-COVID-19 after vaccination.

Methods: Vaccination against SARS-CoV-2 was recommended to all allo-HCT patients after interruption of the immunosuppression. Low dose Campath (10 mg – 20 mg) was used as GvHD prophylaxis along with cyclosporine. Levels of serum IgG antibodies against spike protein S of SARS-CoV-2 were measured at least 2 weeks after the 2nd vaccine dose. The quantitative anti-spike RBD IgG antibody responses were measured using the Abbott SARS-CoV-2 IgGIIQuant assay (cut off ≥50 AU/mL).

Results: Totally 35 patients who underwent allo-HCT had serum IgG antibodies levels measured against SARS-CoV-2. Patients characteristics are listed in Table 1. Thirty two (91%) patients were vaccinated with mRNA vaccines (Comirnaty, Pfizer-BioNTech) and 3 (9%) with viral vector based vaccines (Vaxzervia, AstraZeneca). The median day after transplantation that patients were vaccinated was 913.5 (range: 137-4086). Thirty patients (86%) had immune response against SARS-CoV-2 and 5 (14%) hadn't. The median day of IgG antibodies measurement was 913.5 (range: 137-4086). It is worth of notice that 5 patients had serum IgG against SARS-CoV-2 measured after the 3rd vaccine dose. One didn't respond to the third dose, one that was negative after the 2nd dose became IgG positive after the 3rd dose and the remaining three continued to be positive. One patient presented a serious adverse event after the first dose of mRNA based vaccine, that was thrombocytopenia that required hospitalization and treatment with immunoglobulins and corticosteroids with complete resolution of the thrombocytopenia. All patients that were vaccinated against SARS-CoV-2 haven't presented COVID-19 disease and are alive.

Table 1. Characteristics of patients who underwent allo-HCT and where vaccinated against SARS-CoV-2.

Patients Characteristics	**n = 35**
Age (range)	48 (21-76)
Sex (M/F)	19/16
Disease	
AML	18
ALL	8
CML	3
Myelofibrosis	1
Hodgkin Lymphoma	3
Non Hodgkin Lymphoma	3
Δότης	
Sibling	6
WMUD	16
MMUD	8
Haplo	5
Type of vaccine, mRNA/viral vector based	32 (91%)/3 (9%)
Median d + of vaccination after allo-HCT (range)	913.5 (137-4086)
SARS-Cov-2-IgG, positive/negative	30 (86%)/ 5 (14%)
Measurement IgG levels after vaccination (range)	171 (14-257)
Immunereconstitution at vaccination (range)	
CD20	172 (0-2168)
CD4	338 (72-1316)
CD8	637 (196-2168)

Conclusions: Our experience demonstrates the efficacy of vaccination against SARS-CoV-2. Although further prospective studies with longer follow up are required.

Disclosure: Nothing to declare

P350

Efficacy of cytomegalovirus specific immunoglobulins (cmv-ig) in reducing cmv reactivation in paediatric haematopoietic stem cell transplant

C. Geurten[1], R. Ghinai[2], H. Munford[3], N. Cole[2], A. Norton[2], S. Lawson[2]

[1]University Hospitaly in Liege, Liège, Belgium, [2]Birmingham Women and Children's NHS Foundation Trust, Birmingham, United Kingdom, [3]Biotest UK Ldt, Birmingham, United Kingdom

Background: Cytomegalovirus (CMV) infection is a serious, potentially lethal complication of paediatric hematopoietic stem cell transplant (HSCT). To date, antiviral therapy has been the mainstay of prophylaxis and encouraging results with Letermovir are limited in paediatric transplant by its restricted use to children aged 12 and over. Development of alternative CMV prophylaxis agents such as CMV-specific immunoglobulins could meet a clinical need in younger recipients. So far, however, studies focusing on CMV-specific immunoglobulins (CMV-Ig) prophylaxis have met with conflicting results.

Methods: After introducing prophylactic CMV-Ig for HSCT recipients at risk (seropositive recipient and/or donor), we conducted a single center retrospective study comparing incidence and severity (symptomatic infection, peak CMV titres, duration, requirement for treatment, and outcome) of CMV infection between patients who were at risk of CMV reactivation and did or did not receive CMV-Ig (historical controls).

Patients in the CMV-Ig group received CMV-Ig at 0.5 g/kg fortnightly for six doses, starting along with the initiation of conditioning.

We identified 49 'at risk' recipients from 76 consecutive HSCTs over 3.5 years: 39 did not receive CMV-Ig and 10 did. There was no significant difference in donor type, cell source, intensity of conditioning or CMV status between the groups.

Results: We observed a non-significant reduction ($p = 0.620$) in incidence of CMV reactivation with CMV-Ig ($n = 3$, 30%) versus without ($n = 15$, 38.4%). No patient who received CMV-Ig developed symptomatic or lethal infection, all serious infections occurring in the non CMV-Ig group.

Formal analyses on infection severity are limited by the small number of CMV infections in the group who received prophylaxis with CMV-Ig, however, duration of infection appeared shorter (21 (+/−7) vs 51.4 (+/− 55) days) and peak titers lower (4578 (+/− 4788) vs 24 131 (+/− 49 257)) with CMV-Ig. CMV infection tended to occur earlier following transplant in patients receiving CMV-Ig (25.6 (+/− 5.5) days following HSCT vs 47 (+/−86.1) days for patients who did not ($p = 0.681$). Active CMV treatment was started for all patients who developed CMV infection after receiving CMV-Ig, and for 70% of patients in historical control group ($p = 0.290$), which is more likely to reflect a change in practice rather than severity of infection. No adverse events during CMV-Ig infusions were noted.

Conclusions: CMV-Ig administered fortnightly for a total of six doses starting with the initiation of the conditioning regimen appears to be a safe CMV-directed prophylactic measure, and is worth consideration for HSCT recipients at risk of CMV reactivation younger than 12. CMV-Ig potentially reduces CMV incidence, but more convincingly may reduce severity of infection and duration of treatment with myelosuppressive antivirals, sparing transplant-related morbidity, thus potentially improving transplant outcomes.

Disclosure: Haydn Munford, PhD is a medical science liaison at Biotest UK, Ldt and has offered support with data analysis suggestions and graphic illustrations.

P351

Outcomes of covid-19 in patients after hematopoietic stem cell transplantation or cellular therapy: A single center experience

F. Kovácsová[1], T. Kabut[1], B. Weinbergerová[1], M. Krejčí[1], F. Folber[1], J. Mayer[1]

[1]Masaryk University Hospital Brno, Brno, Czech Republic

Background: The SARS-CoV-2 pandemics has been spreading in Czechia since March 2020. The course and mortality of this infection are substantially more serious in immunocompromised patients compared to normal population. The aim of this study was to monitor the course of COVID-19 disease in patients undergoing allogeneic or autologous hematopoietic stem cell transplantation (HSCT) or chimeric antigen receptor T-cell (CAR-T) therapy at our department.

Methods: All patients with SARS-CoV-2 positivity detected between October 2020 and April 2021 who previously underwent allogeneic or autologous HSCT or CAR-T therapy were included into this retrospective study. We describe the time interval between infection and transplantation or CAR-T therapy, need and length of in-patient stay, use of mechanical ventilation, antiviral therapy and infection outcomes.

Results: A total number of 34 patients (average age 55 years) were included into this analysis, 10 after allogeneic HSCT, 21 after autologous HSCT, and 3 after CAR-T therapy. The average number of days since HSCT or CAR-T therapy to the first positivity was 1324, with a maximum of 7799 and a minimum of -2 days (infection started during the conditioning regimen). Twenty-five (73%) patients were hospitalized, 10 of them were admitted to the intensive care unit (ICU), and three required mechanical ventilation. Average length of in-patient stay was 17 days (range 3 to 44), and 16 days at the ICU (range 7 to 38). Sixty percent of hospitalized patients received convalescent plasma transfusion, 52% antiviral treatment with remdesivir (3 patients were reinfused for prolonged viral shedding), and one patient received monoclonal antibody (bamlanivimab). Twenty-four patients recovered from the infection, and 10 died (29%), all of them during their hospitalization.

Conclusions: Although the general COVID-19 mortality (case fatality rate) is about 2%, in patients who underwent hematopoietic stem cell transplantation or cellular therapy it reaches up to 20 to 30%, which corresponds to our cohort. Thorough standard precautions, vaccination of family members, and monoclonal antibodies and antivirals early after contact or at the very beginning of the infection are the inevitable essentials to protect these fragile patients from severe COVID-19 disease associated with high risk of fatal outcome.

Disclosure: Nothing to declare.

P352

Posoleucel for adenovirus infection in pediatric and adult allogeneic hematopoietic cell transplant recipients: Design of a phase 3, randomized, double-blind, placebo-controlled trial

K. Rao[1], G.D. Myers[2], I. Fraser[3], E. Stoner[3], P. Ljungman[4]

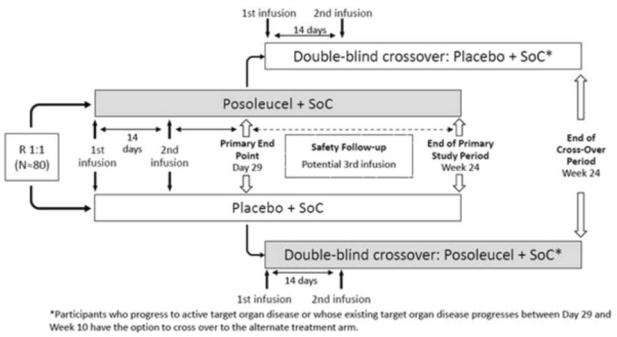
[1]Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [2]Children's Mercy Hospital and University of Missouri, Kansas City, United States, [3]AlloVir, Cambridge, United States, [4]Karolinska University Hospital Huddinge, Karolinska Institutet, Stockholm, Sweden

Background: Adenovirus infections are an important cause of morbidity and mortality after allogeneic hematopoietic cell transplantation (allo-HCT) especially in children. There are no approved antivirals for adenovirus infection. Posoleucel is an allogeneic, off-the-shelf investigational T cell therapy designed to target adenovirus as well as five other common opportunistic viruses: BK virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, and JC virus. In a phase 2 trial of posoleucel in hematopoietic cell transplant recipients, 83% (10/12) of those with adenovirus disease had a clinical response.

Methods: We are conducting a phase 3, multicenter, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of posoleucel for the preemptive treatment of adenovirus infection in pediatric and adult allo-HCT recipients. The table shows eligibility criteria, endpoints, and definitions. Patients will be randomized 1:1 to receive posoleucel or placebo in two infusions separated by 14 ± 3 days stratified by level of adenovirus viremia (≥10,000 or <10,000 copies/mL DNA) and age (≥12 or <12 years) (Figure). Posoleucel will be infused at dosages of 2×10^7 cells for patients <40 kg or 4×10^7cells for those ≥40 kg. Patients who progress to active target organ disease or whose existing target organ disease progresses will have the option to cross over to the alternate treatment arm between Day 29 and Week 10, but study treatment will remain blinded. To be eligible for cross-over, patients must not have evidence of GVHD > 2, must not be receiving >0.5 mg/kg/day prednisone or equivalent, and must not have experienced an infusion-related reaction with prior

doses of posoleucel or placebo.

Eligibility Criteria	
Inclusion	• >1 year of age • Allo-HCT (including umbilical cord) ≥21 days before randomization • Demonstrated engraftment with an absolute neutrophil count >500/mm^3 • AdV viremia DNA ≥ 10,000 copies/mL or 2 consecutive and rising viremia of ≥1,000 copies/mL AND an ALC < 180/mm^3 or have received T cell depleted graft • Availability of at least one appropriately HLA-matched posoleucel VST line
Exclusion	• Grade >2 acute GVHD • Ongoing high-dose corticosteroids
Endpoints	
Primary	Proportion of patients with resolution of adenovirus viremia at Day 29
Secondary	Proportion with disease progression or non-relapse mortality by Day 29
Definitions	
Progression	Progression to target organ disease (for patients without target organ disease at screening), or progression of target organ disease (for those with target organ disease at screening)
Target-organ disease	AdV-associated pneumonia, hepatitis, enterocolitis, pancreatitis, hemorrhagic cystitis, nephritis, encephalitis/ myelitis, or retinitis



Results: Planned enrollment is approximately 80 patients at approximately 40 sites in the United States and Europe. The study is currently ready to initiate.

Conclusions: This phase 3 trial will provide data on the efficacy and safety of posoleucel compared with placebo for the treatment of adenovirus infection and disease in allogeneic HCT recipients.

Clinical Trial Registry: Pending

Disclosure: Kanchan Rao is the National Coordinating Investigator for the study in the UK, and is an advisor to AlloVir.

G. Doug Myers is an advisor to AlloVir.

Iain Fraser is employed by and holds stock in AlloVir.

Elizabeth Stoner is a Senior Clinical Advisor to AlloVir.

P. Ljungman is the National Coordinating Investigator for the study in Sweden.

P353

Overview of cytomegalovirus viremia in allogeneic hematopoietic stem cell transplant recipients: Experience of a population with high seroprevalence

C. Bourlon de los Rios[1], C.O. Vargas Serafin[1], A.K. Toledo Riquelme[1]

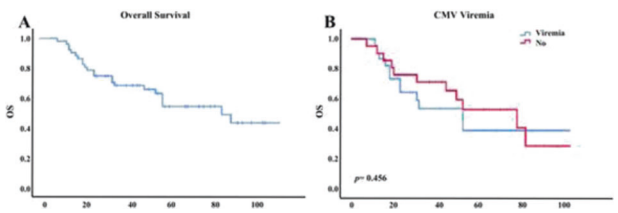
[1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de México, Mexico

Background: Cytomegalovirus (CMV) infection after allogeneic hematopoietic stem cell transplant (allo-HSCT) is a catastrophic complication, as it can result in graft failure and increased mortality. Higher CMV seroprevalence has been reported in low- and middle-income countries (LMIC). Our aim was to describe risk factors, monitoring and treatment strategies, and outcomes of allo-HSCT patients with CMV infection.

Methods: Retrospective, single-center, observational study that included patients >18years who underwent allo-HSCT between January 2016 and March 2020.

Results: A total of 52 patients were included. Median age was 32.9 years (range 20-60). Most common baseline diagnosis was lymphoblastic leukemia in 57.7% (n = 30), followed by myeloblastic leukemia in 19.2% (n = 10). Disease status was complete remission in 44.2% (n = 23). Regarding transplant procedures a median of 2.3x106CD34+cells/kg (0.9-5.9) were infused, bone marrow source was used in 79.6% (n = 41), donors were matched related in 74.1% (n = 44), and 88.5% received a myeloablative conditioning regimen. Patients developed mucositis in 90.4% (n = 40), acute graft versus host disease (aGVHD) in 30.7% (n = 16), and chronic GVHD (cGVHD) in 28.8% (n = 15).

CMV risk was categorized as low in 10.2% (n = 5), intermediate in 18.4% (n = 9), and high in 71.4% (n = 35). A 98% (n = 51) of our cohort proceeded with preemptive strategy. With a median of 4 (1-5) tests per month, a total of 27 patients (51.9%) developed CMV viremia and 21 (77.8%) received antiviral therapy. The median time from HSCT to a positive test was 46 days (20-153) with a median viral load of 1724.22 IU/ml (69-12986). T-cell depletion with post-HSCT cyclophosphamide (p = 0.049) conferred an increased risk for CMV viremia. Median time to resolution of viremia (TV) was 107 days (7-1804), being cGVHD (p = 0.032) related to a longer TV. Median overall survival (OS) was 52 months (8-169). On univariate analysis, CMV viremia was not a factor associated with a decreased OS.



Patients' cytomegalovirus characteristics	Total ***N* = 52**
CMV Risk, *n* = 49 (%)	
Low risk	5 (10.2)
Intermediate risk	9 (18.4)
High risk	35 (71.4)
Predefined risk strategy, *n* (%)	
Preemptive therapy	51 (98)
Prophylaxis	1 (2)
CMV viremia Post-HSCT, *n* (%)	
Yes	27 (51.9)
No	25 (48.1)

Patients' cytomegalovirus characteristics	Total N = 52
Treatment, n = 27 (%)	
Yes	21 (77.8)
No	6 (22.2)
Antiviral, n = 21 (%)	
Ganciclovir	9 (42.9)
Valganciclovir	9 (42.9)
Both	3 (14.3)
Viral load (UI/ml), *median* (range)	1724.22 (69-12986)
Treated	2064.54 (227-12986)
Untreated	226 (69-319)
Number of PCR per month, *median* (range)	4 (1-5)
Time to resolution of viremia, *median* (range)	107 (7-1804)
Post-HSCT cyclophosphamide, n = 15 (%)	
Yes	11 (73.3)
No	4 (26.7)

Conclusions: There is limited information regarding incidence and outcomes of CMV infection after allo-HSCT in LMIC, in which limited access to diagnostic tests, as well as a high seroprevalence can negatively impact. Interestingly, despite having characterized as high risk >70% of our population, incidence of CMV was similar to the previously reported. Concordant to information of other study groups, increased immunosuppression was the sole factor related to increased risk of CMV incidence and duration. We report good monitoring and no impact of CMV on mortality, with no cases of disease. Further multicentric studies are required to define the most adequate monitoring and treatment strategies in vulnerable populations.

Disclosure: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

P354

Cytomegalovirus viremia rate and healthcare burden of disease in adult allogenic hematopoietic stem cell transplantation patients

J. Ranti[1], K. Perkonoja[1,2], T. Kauko[1,2], R. Korhonen[3]

[1]Turku University Hospital, Turku, Finland, [2]Auria Clinical Informatics, Turku, Finland, [3]MSD Finland Oy, Espoo, Finland

Background: This study investigated the association of CMV viremia and healthcare resource utilization (HCRU) in adult allogenic HSCT patients.

Methods: This was a single-center retrospective observational cohort study from the Turku University Hospital Stem Cell Transplantation center. The study included patients with their first allogenic HSCT between January 1, 2013 and December 31, 2018. CMV viremia was defined as detection of CMV DNAemia ≥ 1000 copies/mL or start of preemptive therapy due to CMV DNAemia. Co-variates studied included: age, gender, D/R status, underlying malignancy (grouped as acute leukemias, lymphoproliferative diseases, and myeloproliferative diseases including aplastic anemia), preconditioning, donor type and HLA matching, graft source, and GVHD. Data for CMV viremia, hospital readmissions, hospital days, intensive care admissions, outpatient visits and anti-CMV medication were collected by 1 year. Data analyses included descriptive statistics, Mann-Whitney U-, Pearson's chi-squared and two-proportions z-test, multiple Cox's regression model including all co-variates and simple negative binomial regression model.

Results: The study included 251 patients. CMV seroprevalence was 69.7%. One hundred thirty-five (77.1%) R + patients and 16 (21.1%) R- patients had CMV viremia, and 76.8% of patients had ≥2 viremias. The median time to CMV viremia was 40 (IQR 33, 53) days. In multiple Cox regression, co-variates associated with higher CMV viremia risk included R + (HR 7.31, 95% CI 3.77-14.19, $p < 0.001$), lymphoproliferative diseases (HR 1.69, 95% CI 1.09-2.60, $0 = 0.018$), and grade 3-4 acute GVHD (HR 1.74, 95% CI 1.11-2.71, $p = 0.015$). HLA identical donor was associated with lower CMV viremia risk (HR 0.53, 95% CI 0.32-0.89, $p = 0.017$).

Patients with CMV viremia had more hospital readmissions (IRR 1.56, 95% CI 1.24-1.95, $p < 0.001$) and longer hospital length of stay (IRR 1.77, 95% CI 1.35-2.13, $p < 0.001$) compared to patients without CMV viremia (Table 1). We did not see differences in ICU admissions or out-patient visits.

149 patients received anti-CMV medication. Valganciclovir (70.5%) and foscarnet (60.9%) were the most used anti-CMV drugs, and valganciclovir was used more often in patients with ≥2 viremias compared to patients with 1 viremia (82.8% vs 36.4%, $p < 0.001$). Foscarnet was more often used in patients with grade 3-4 acute GVHD compared to patients with grade ≤2 acute GVHD (50.0% vs 33.2%, $p = 0.037$). Ganciclovir was used in 36.8%, and there was no difference in patients with 1 viremia or ≥2 viremias (30.3% vs 37.9%, $p = 0.550$).

Table 1. Healthcare resource utilization in 1 year post allogenic HSCT.

	no CMV viremia (n = 100)	CMV viremia (n = 151)	p value
Number of patients with readmission[#] (n, %)	73 (73.0%)	135 (89.4%)	<0.001
Number of hospital readmissions, median (IQR)	2.0 (1.0, 3.0)	3.00 (2.0, 5.0)	<0.001
Readmission length of stay (days) median (IQR)	13.0 (4.0, 3.0)	32.0 (17.0, 61.0)	<0.001

Differences were tested using Mann-Whitney U-test. # Differences was tested with chi-square test.

Conclusions: CMV seroprevalence is relatively high among allogenic HSCT patients. CMV viremia occurs commonly and is often repeated. CMV viremia was associated with higher hospital readmission rate and longer additional hospital length of stay. Prevention of CMV viremia may reduce additional HCRU associated with CMV viremia post allogenic HSCT.

Disclosure: Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. JR received Principal Investigator fee, and Turku University Hospital received institutional research funding. RK is

an employee of MSD Finland Oy, and owns stocks of Merck & Co, Inc., Kenilworth, NJ, USA.

P355

Allogeneic hematopoietic stem cell transplantation for human t-lymphotropic virus type 1 (htlv-1) leukemia-lymphoma: Two cases report

S. Diaz-Lopez[1], C. Mayor Bastida[1], A. Puchol Crespo[1], A. Figuera Alvarez[1], A. Alegre Amor[1], B. Aguado Bueno[1]

[1]*Hospital Universitario de la Princesa, Madrid, Spain*

Background: Human T-lymphotropic virus type I is a retrovirus that infects 10 to 20 million people worldwide. However, is associated with disease only in 5% of infected individuals. Two diseases associated: Adult T cell leukemia-lymphoma and HTLV-I-associated myelopathy. Impact of infection is unclear among patients who undergo allogeneic hematopoietic stem cell transplantation (HSCT) due to limited clinical reports.

Methods: We report two HTLV-I leukemia/lymphoma allotransplanted patients.

Results: CASE 1:

41-year-old male from Chile, presented with decrease state of consciousness, requiring admission at ICU. Diagnosis of Adult T cell leukemia was done. Laboratory tests showed leukocytosis (11.400/mm3), lymphocytosis with immunohistochemical profile of ATLL. Serological tests showed HTLV-1 antibodies. Bone marrow: 61% blasts; cerebrospinal fluid: normal. Initially treated in ICU with CHOP, subsequently 6 cycles of VCAP-AMP-VECP and zidovudine 200 mg BID. The patient was referred to our center in first CR for HSCT from mismatched unrelated donor, conditioning with TBF and post-cyclophosphamide. On admission, HTLV1 viral load was 32. 000/106 copies. Switch to lamivudine was decided for hepatitis B reactivation prophylaxis and to avoid zidovudine myelotoxicity. HTLV1 viral load monitoring was performed on day +17 with a load of 2.000/106copies. Lamivudine was continued on discharge and zidovudine restarted. Serial viral load monitoring was performed during follow-up at outpatient clinic: negative since day +46. Currently with both antivirals and in CR with full donor chimerism 6 months posttransplant.

CASE 2:

54-years-old woman from Dominican Republic, diagnosed with Adult T cell lymphoma/leukemia IV-B in 2018. She presented hypercalcemia, hepatomegaly, lymphadenopathy, and bone marrow infiltration of 25% lymphoid blasts with a ATLL phenotype. No CNS infiltration. Serological tests: HTLV-1-IgG antibodies. She received treatment with Hyper-CVAD scheme.

In first CR, she received haploidentical transplantation, TBF conditioning. HTLV-1-load was 47.665/106 copies. Treatment with tenofovir 245 mg/24h and raltegravir 300 mg/12h was started and continued at discharge (day + 23) with undetectable HTLV-1-load. As post-transplant complications: grade II gastrointestinal GVHD treated with steroids, CMV reactivation treated with gancyclovir and grade 2 hemorrhagic cystitis.

HTLV-1-load monitoring was performed during follow-up, ending antiviral treatment on day +42. On day +145 the patient required admission for abdominal pain and confirmed relapse, with a HTLV-1-load of 4.935/106 copies. She received GEMOX scheme and restart of raltegravir + tenofovir. Patient returned to her country. No additional follow-up was possible.

Conclusions: While most HTLV-I-infected individuals remain asymptomatic, 1–5% will develop ATLL. The experience in european countries is limited and the role of HTLV-1 during treatment and HSCT is not clear. Further studies are needed to assess the role of antiviral treatment, its complications, and their impact on maintaining remission of hematological neoplasia.

Disclosure: Nothing to declare.

P356

High dose cidofovir, cipro, and ivig combination treatment for bk virus hemorrhagic cystitis

S. Brake[1]

[1]*spectrum health, Grand Rapid, United States*

Background: BK polyomavirus (BKPyV) is a common cause of hemorrhagic cystitis during the early post engraftment phase. It occurs most commonly at 21 to 42 days following HCT. The clinical manifestations of BKPyV-associated hemorrhagic cystitis after HCT may include cystitis, hematuria, renal failure, and rarely, life-threatening bleeding.

Methods: We report in this case series the treatment approach in five of our patients who developed symptomatic infection as listed below

Our treatment approach was to initiate aggressive hydration, decrease immunosuppression, and start cidofovir, Cipro and IVIG. Cidofovir has a modest in vitro antiviral activity against BKPyV, and has been widely used to treat patients with BKPyV hemorrhagic cystitis. On the other hand, immunoglobulin preparations contain BKPyV neutralizing antibodies against all major genotypes of BKPyV. Our patients had low immunoglobulin level, and for that reason adding IVIG to their treatment regimen was considered. All five patients received the first treatment with cidofovir (5 mg/kg/dose), Our treatment approach was to initiate aggressive hydration, decrease immunosuppressive medications, and start treatment with combination high dose cidofovir, and IVIG. Cidofovir has a modest in vitro antiviral activity against BKPyV, and has been widely used to treat patients with BKPyV hemorrhagic cystitis, even though it is not FDA approved for that indication. On the other hand, immunoglobulin preparations

Patient	Malignancy	Conditioning regimen	Donor	Symptomatic infection	BK virus level (copies/mL) initial	Week 1	Week 2	Week 3
1	Pre B-ALL	MA CY/TBI + r ATG	MUD	D 38	4.00E + 08	2.70E + 08	1.20E + 08	0
2	T-Cell lymphoma	RI BU/FLU	MRD	D 35	9.60E + 07	1.40E + 07	1,700,000	35,800
3	Mixed phenotype AML	RI BU/FLU	MRD	D 31	3.50E + 08	210,000	0	N/A
4	AML	MA BU/FLU	MUD	D 40	6.50E + 08	2.0E + 08	1,500,000	10,000
5	T-ALL	MA CY/TBI	MRD	D 32	4.90E + 08	180,000	20.000	0

contain BKPyV neutralizing antibodies against all major genotypes of BKPyV. All five patients received the first treatment with cidofovir (5 mg/kg/dose), cipro and IVIG, immediately after their symptoms started, and the diagnosis was confirmed.

Results: All five patients noticed significant improvement in their symptoms after the first treatment. Patients 1, 2 and 4, received three treatments with weekly cidofovir, over three weeks, while patient 3 and 5 received 2 treatments only, and the third treatment was held due to complete resolution of the symptoms. As shown in the table above, we can see how the BKPyV level was trending down as the patients were receiving their treatment; this also coincided with the improvement in their macroscopic hematuria, the amount of blood clots in the urine, urinary frequency and bladder spasms that they presented with.

Conclusions: BKPyV hemorrhagic cystitis is a significant cause of morbidity, occurring in up to 20 % of stem cell transplant recipients. At the present time treating these patients centers around hydration, reduce immune suppression, and sometimes using cidofovir, which is still not FDA approved for this indication. In this case series we demonstrated that starting our five patients on combination treatment with cidofovir, Cipro, and IVIG, helped improve their symptoms and reduce their BKPyV level, just after the first treatment, with complete resolution of their symptoms in 2-3 weeks.

Disclosure: nothing to declare

P357

Active SARS-CoV-2 infection on the day before autologous stem cell transplant in a patient with multiple myeloma

M. Henriques[1], P. Baptista[1], P. Medeiros[1], C. Marini[1], J. Bastos[1], A.L. Pinto[1], R. Bergantim[1], F. Trigo[1]

[1]Centro Hospitalar Universitário de São João, Porto, Portugal

Background: The different clinical presentations of SARS-CoV-2 infection reflects the diversity of immune responses, especially in immunocompromised patients. Immunosuppression in Multiple Myeloma (MM) raises the question of whether these patients are at a higher risk of developing severe COVID-19, in whom uncontrolled MM was associated with an increased risk of death. We report a case of a MM patient diagnosed with SARS-CoV-2 infection a day before autologous stem cell transplant (ASCT) infusion.

Methods: Conditioning regimen used was Melphalan 200mg/m2, in an isolation room with HEPA filters and positive airflow. All patients performed a SARS-CoV-2 PCR screening, with a negative test required for admission, which was repeated at 48h and after, every five days.

Results: The patient was a 57-year-old woman with a personal history of obesity and chronic obstructive pulmonary disease. She was diagnosed with light chain MM, International Staging System (ISS) stage I and amplification 1q, with a complete remission after induction with four cycles of Bortezomib, Thalidomide and Dexamethasone. At admission, her SARS-CoV-2 PCR screening test was negative but, on day -1, the screening result was positive. As expected, the patient proceeded with the transplant with a known COVID-19 infection. She did not develop symptoms suggestive of SARS-CoV-2 infection. On day +6 she was started on Meropenem and Vancomycin for a febrile neutropenia with hypotension, of which she completed a course of 7 and 5 days, respectively. At this time, pulmonary tomography scan showed no evidence of respiratory infection. Grafting was recorded at day +15. On day 21 of COVID-19 infection (day + 20), an antigen test for SARSCoV-2 was performed with a negative result and the patient was discharged, maintaining a complete remission at day +100.

Conclusions: SARS-CoV-2 infection progressing to acute respiratory stress syndrome in patients with MM has a mortality rate of about 55%. Previous studies have identified age, stage III-ISS, high risk cytogenetic disease, kidney disease, and active or progressive MM as risk factors for higher death rates. Immunosuppressive treatment was not associated with an increased risk of death. Patients with MM undergoing ASCT have severe acute immunosuppression and long-term reconstitution of the immune system. Studies in this matter recognize that in patients who did ASCT and COVID-19 infection within 12 months, the expected and combined adverse outcome of these factors was not significantly high. Although is not consensual, there are no data to support prevention and expectant attitude in any specific treatment for MM, whether steroids or high-dose chemotherapy, as in cases like the reported. In patients with high-risk MM features, even taking account for the immunosuppression, treatment should be continued. This case report exposes the need and difficult management of the MM in the COVID-19 era, as well as reinforces the importance of SARS-CoV-2 monitoring in inpatient care. MM requires careful consideration relatively to the disease and the therapy to be discussed, in order to reduce patient risk of having COVID-19, without compromising disease outcome. Controlled MM is associated with a better outcome, even with SARS-CoV-2 infection.

Disclosure: Nothing to declare

P358

COVID-19 in patients with hematological diseases after sct: Single center observation from bulgaria, sofia, 859 bmt unit

P. Ganeva[1], K. Milcheva[1], K. Venkov[1], G. Arnaudov[1]

[1]SHATHD, Sofia, Bulgaria

Background: Coronavirus disease 2019 (COVID-19) is a serious viral infection associated with high mortality in patients with hematological diseases. Patients after haematopoietic stem cell transplantation are at higher risk of Covid-19 disease due to their immunocompromised status. There is still insufficient information concerning this cohort of patients. Our study presents first single data from Bulgarian BMT unit (859) in patients in whom COVID-19 was confirmed.

Methods: This study is the first analysis of patients with haematological malignancies after SCT, with COVID-19 infection in the period of 03.2020 till 11.2021 at BMT Unit 859 in Sofia Bulgaria (SHATHD).

Results: The study included 45 patients; aged 23 -69 years (median, 47.6 years); men/women 26 /19 ; who had SCT (autoSCT - n = 28 ; AlloSCT - n = 17), with diagnosis as follows: MM- 21; MX-2; NHL-6; AA – 2; AML-8; ALL- 4; MDS-2. At the time of COVID-19 infection 36 (80%) of patients were in CR/VGPR, 9 (20 %) in progression/relapse, 6 (13.3%) patients were on immusupression therapy. In most patients, the infection was relatively mild, in outpatient settings; 9 (20%) had severe course of infection with bronchopneumonia, and 3 (6.6%) patients required intubation. Over the study period a total of 6 (13.3 %) patients died. The average age of this patients is 56y.old (median 51-67), 3 of them were diagnosed with Covid 19 shortly after the ASCT (2 at +1 months; +3 months respectively).

Conclusions: Despite the small group of observed patients, these results confirm the prognostic significance of age for severity and mortality of COVID-19 in hematological patients. The infection is more severe, with higher mortality rates in elderly patients, especially soon after ASCT.

Disclosure: Nothing to declare.

P359

Mycobacterium abscessus catheter related infection bloodstream in autologous hematopoeitic stem cell transplantation

M. López[1], L. Solan[1], M. Morante[1], J. Cornago[1], A. Lopez[1], J.L. López[1], P. Llamas Sillero[1]

[1]University Hospital Fundación Jiménez Díaz, Madrid, Spain

Background: Autologous hematopoeitic stem cell transplantation (Auto-HSCT) is part of the first-line treatment of fit patients with Multiple Myeloma (MM). Bloodstream infections (BSI) occur in 5–10% of auto-HSCT. The incidence rates of Non-tuberculous mycobacteria (NTM) as *Mycobacterium abscessus* among recipients of HSCT ranging between 0.4 and 10%, being reported more frequently in recipients of allografts than in autograft.

Methods: We report a case of a 42 years-old male with an Auto-HSCT by Bences-Jones Kappa MM in complete response who developed a catheter-related bloodstream infection (CRBSI) by *Mycobacterium abscessus*.

Results: At day +47 after Auto-HSCT, our patient was accepted at the emergency department whit fever, headache and myalgias. Physical examination was anodyne, the blood test and radiology thorax image showed no findings and he was discharged home with empiric antibiotic treatment with levofloxacin. Five days later, peripheral blood and catheter blood cultures were positive for fast-growing mycobacteria (FGM), so the patient was admitted to the hematology unit for clinical evaluation and directed treatment.

Upon reassessment, he had blood pressure 129/79 mmHg, 101 beats per minute, 97% saturation breathing ambient air. The patient reported having been asymptomatic at home, but at the time of the assessment he had a febrile episode with associated shivering, so blood cultures were extracted again. Empiric antibiotic treatment with clarithromycin, ciprofloxacin and amikacin was started. *Mycobacterium abscessus* was identified, and central venous catheter was removed and cultivated, subsequently confirming colonized by the same microorganism.

Clarithromycin was suspended because of a severe hepatitis consisting of cholestasis and hypertransaminasemia.

Finally, after 18 days of admission, our patient became afebrile, with an improvement of the liver profile and negative blood cultures, so he was able to continue his triple antibiotic therapy at home until completing a total of 4 weeks.

Conclusions: Fast growing NTM species such as *M. abscesuss* are a rare cause of CRBSI in patients with Auto- HSCT and usually affect lungs and skin.

In our patient, despite suffering from MM and being recently transplanted, *M. Abscessus* infection only represented a febrile syndrome without other complications, which allowed continuing treatment on an outpatient basis with an excellent impact on his quality of life.

Disclosure: Nothing to declare

P360

Hemophagocytic lymphohistiocytosis after allogeneic hematopoietic stem cell transplantation: Easy diagnosis and management? a case report

A. Harmouche[1], R. Moghnieh[1], T. Jisr[1], A. Ibrahim[1]

[1]Makassed Hospital, Beirut Arab Univeristy, Beirut, Lebanon

Background: Hemophagocytic Lymphohistiocytosis (HLH) occurring after allogeneic hematopoietic stem cell transplantation (HSCT) is a rare and serious disease. Differential diagnosis may be other complications post-HSCT such as acute graft-vs-host disease (GVHD), thrombotic microangiopathy, engraftment syndrome, graft failure and particularly infection, which induced symptoms and parameters overlapping with the diagnosis criteria for HLH. In the absence of clear guidelines, the management of HLH post-HSCT is challenging (Sandler R. D. et al, *Bone Marrow Transplantation 2020;* 55: 307-316) We present a case of HLH post-allogeneic HSCT illustrating this critical issue.

Methods: Case Report.

Results: A 50-year-old female underwent an allogeneic HSCT from her HLA identical brother for a chronic myelomonocytic leukemia. Conditioning consisted in Flu-Bu-ATG and GVHD prophylaxis in cyclosporin. The patient (pt) had persistent pancytopenia after 3 weeks of allogeneic HSCT without symptoms of infection while being on large spectrum antibiotics, anti-fungal and prophylaxis with valacyclovir. On day 23 of allogeneic HSCT, she manifested high grade fever followed by abdominal pain and transfusion resistance for severe anemia and thrombocytopenia. Bone marrow aspirate showed on cytology an increase of activated macrophages with hemophagocytosis. The level of ferritin in serum was high at 2529 ng/mL (reference range: 13-150) as well as LDH at 591U/L (reference range: 135-225). Fibrinogen level was low at 151 mg/dL (normal range: 200-400). CT scanner of the abdomen showed hepatomegaly (23cm) and splenomegaly (20cm). Neither veno-occlusive disease nor thrombotic microangiopathy was documented. The diagnosis of HLH was made and the patient was treated with methylprednisolone pulse followed by one dose of etoposide (100mg/m^2) administered on day 25 of allogeneic HSCT. Starting day 28, the pt recieved treatment with ganciclovir after PCR for cytomegalovirus (CMV) came positive (3270 copies/mL). Epstein-Bar virus, human herpes virus-6, parvovirus B19 and adenovirus B11 were not detected. Then, the pt started gradual improvement with progressive normalization of the abnormal parameters simultaneously to hematological recovery and non-detection of CMV in blood by PCR. She was discharged on day 82 of allogeneic HSCT.

Conclusions: Our case, with the diagnosis made of HLH post-allogeneic HSCT possibly due to CMV, illustrates the importance of being aware of the clinical manifestations of HLH post-allogeneic HSCT, which is often under-recognized. Our case highlights that the cause of HLH is not always easy to establish. It is also important to treat HLH post-allogeneic HSCT early with an individualized approach for the most optimal outcomes.

Disclosure: Nothing to declare

LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA

P361

Allogenic stem cell transplantation for secondary central nervous system lymphoma (SCNSL)

K. Alzahrani[1], J. Ramdial[1], I. Khouri[1], C. Hosing[1], S. Saengboon[1], U.R. Popat[1], S. Ahmed[1], F. Maadani[1], P. Kebriaei[1], E. Shpall[1], R.E. Champlin[1], Y. Nieto[1], S.A. Srour[1]

[1]University of Texas, MD Anderson Cancer Center, Houston, United States

Background: Patients with relapsed/refractory SCNSL have generally poor prognosis with limited treatment options. Autologous stem cell transplant (SCT) is associated with improved survival in patients who achieve remission prior to transplant and/or those who received ≤2 lines of therapy. Refractory and heavily pretreated patients have dismal prognosis. Limited data exist for the role of allogeneic SCT (allo-SCT) in these high-risk patients. We sought from this report to assess the outcomes of SCNSL patients who underwent allo-SCT at our center and identify predictor factors for prognosis.

Methods: We included all consecutive adult patients with SCNSL who underwent allo-SCT between July 1993 and November 2018. Excluded patients who received mismatched or cord blood grafts. The primary objectives were to assess progression-free survival (PFS) and overall survival (OS). Secondary objectives included assessment of cumulative incidence of relapse (CIR), non-relapse mortality (NRM), and graft-versus-host disease (GVHD).

Results: Sixty-one patients with a median age of 49 (range, 18-69) years, with male predominance (62%), were identified. Overall, patients were heavily pretreated with a median of 3 prior lines of therapy (range, 1-13), 11 (18%) had prior autologous SCT, and 31 (52%) had active disease at time of transplant. Twenty-seven patients had large B-cell lymphoma, 23 had indolent B-cell lymphoma, and 11 had T-cell lymphomas. Thirty (49%) patients had matched related donor (MRD) and 36 (59%) received myeloablative conditioning (MAC). Forty-two percent had HCT-CI > 3. Eighteen (30%) patients transplanted in time period 1993-220, 24 (39%) period 2001-2010, and 19 (31%) in the 2011-2019 period. With a median follow up of 7.09 (range, 0.84-16.72) years, the 2 and 5-year PFS/OS rates were 21%/30% and 19%/23%, respectively. The 2 and 5-year NRM/relapse rates were 31%/48% and 33%/48%, respectively. In MVA for PFS, MAC was the only factor associated with inferior outcome (HR 2.059, 95%CI 1.055-4.016; $p = 0.0342$). In MVA for OS, age ≥50 years (HR 2.071, 95%CI 1.028-4.176; $p = 0.0418$), MAC (HR 3.609, 95%CI 1.659-7.852; $p = 0.0012$), and receiving MUD graft (HR 4.566, 95%CI 1.78-11.712; $p = 0.0016$) were associated with inferior outcome. OS improved over time (reference, transplant year 1993-2000) with HR of 0.302 (95% CI: 0.128-0.712; $p = 0.0062$) and 0.413 (95% CI: 0.153-1.112; $p = 0.0802$) in transplant years 2001-2010 and 2011-2019, respectively. In subgroup analyses to explore predictive factors for prognosis, patients <50 year who received reduced intensity conditioning (RIC) had better OS (67% at 5 years). Likewise, recipients of MRD with RIC conditioning had 2 and 5-year OS of 50% and 38%, respectively, compared to 7% and 0% survival for MUD recipients with MAC ($p = 0.0053$). The CI of grades 3-4 aGVHD was 14 % at 3 months. CI rates of cGVHD at 1 and 3 years were 15 and 21%, respectively.

Conclusions: In this heavily pretreated patient population of SCNSL, allogeneic SCT was associated with durable remissions and potential cure, particularly for younger patients, recipients of matched related donors, and those who received reduced intensity conditioning.

Disclosure: Nothing to declare.

P363

Allogeneic stem cell transplantation for cutaneous t-cell lymphoma - a national analysis

D. Angelov[1], J. Dillon[1], L. Mellerick[1], E. Pender[1], L. Bacon[1], G. Lee[1], L. Higgins[1], H. McCarty[2], C. Gillham[1], J. Quinn[3], S. O'Gorman[1], N. Leonard[1], M. McMenamin[1], E. Vandenberghe[1]

[1]St. James's Hospital, Dublin, Ireland, [2]Belfast Cancer Centre, Belfast, United Kingdom, [3]Beaumont Hospital, Dublin, Ireland

Background: Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common subtypes of cutaneous T-cell lymphoma (CTCL) and those with progressive/transformed MF or SS have a median survival of <5 years with conventional treatment. Allogeneic stem cell transplantation (allo-SCT) can prolong overall survival and cure a subset of patients with CTCL but optimal timing, pre-SCT therapy and conditioning therapy remain unclear.

Methods: Consecutive patients undergoing allo-SCT for CTCL from January 2010 to December 2020 at a national transplant centre were included in this retrospective analysis. Pre-transplant demographics, pre-SCT therapy, standard SCT data and post-SCT survival, relapse, toxicity and chimerism was collected. Pathology review including CD30 expression and T-cell receptor gene clonality was performed. Statistical analyses were carried out using GraphPad Prism version 9.0.1.

Results: Fifteen patients (10 male, 5 female) with a median age at transplant of 49 years were included. Eight patients had SS, while 7 patients had MF, including 4 with transformed MF (tMF) who expressed CD30. The median number of pre-transplant therapies, excluding skin directed treatments and bexarotene, was 2.5. All 8 SS patients achieved a partial response (PR) pre-transplant, while MF patients were in either PR ($n = 1$), stable disease ($n = 3$), or progressive disease ($n = 3$). Median time from CTCL diagnosis to transplant was 12 months. Conditioning used included Cy-TBI ($n = 5$), Total skin electron beam therapy (TSEBT) based reduced intensity conditioning (RIC) ($n = 4$) and Flu/ATG/Mel RIC ($n = 6$). Acute GVHD grade ≥2 (with skin involvement) occurred in 13 patients. Five patients (2 SS, 3 MF) developed chronic skin GVHD (3 extensive, 2 limited stage). There were two early treatment related mortalities (<100 days), and one late (>100 days) treatment related mortality due to infection. Five patients relapsed at a median of 5 months which were managed by combining debulking strategies such as radiotherapy, gemcitabine, brentuximab vedotin with immune modulation. Donor lymphocyte infusion was used in 5 patients (Table 1). One relapsed MF patient died 5 months post allo-SCT from progressive disease, but 4 patients remain alive at a median follow up of 40 months. With a median follow-up of 32 months, overall survival (OS) and progresson-free survival (PFS) at 5 years were 72.7% and 41.0% respectively.

Conclusions: We report an improved OS and PFS at 5 years of 72.7% and 41.0% respectively compared to registry data. This may reflect a shorter time from CTCL diagnosis to allo-SCT; use of

Table 1: DLI indications/outcomes.

	DLI indication	DLI timing post HSCT (months)	Number of DLI treatments	Chimerism day 100	Chimerism 6 mo	cGVHD	Response
Patient 1	MRD positive relapse	11	1	Total MNC 100%, CD3 100%	Total MNC 100%, CD3 100%	No	CR
Patient 2	Mixed chimerism	6	2	Total MNC 68%, CD3 NA	Total MNC 78%, CD3 3%	No	Total 88%, CD3 83%
Patient 3	Relapse CTCL	5	2	Total MNC 100%, CD3 NA	Total MNC 99%, CD3 NA	No	CR
Patient 4	Relapse CTCL	53	1	Total MNC 100%, CD3 NA	Total MNC 100%, CD3 NA	No	CR
Patient 5	Relapse CTCL	7	1	Total MNC 93%, CD3 99%	Total MNC 94%, CD3 100%	Yes	CR

TSEBT-based conditioning; and higher rates of acute GVHD skin possibly associated with a lower relapse rate. Our data supports early referral to a transplant unit of CTCL patients <70 years old who are failing skin directed therapy.

Disclosure: Nothing to declare

P364

Outcome of patients with newly diagnosed primary central nervous system lymphoma after sequential high-dose methotrexate, cytarabine, thiotepa based chemoimmunotherapy followed by autologous stem cell transplantation

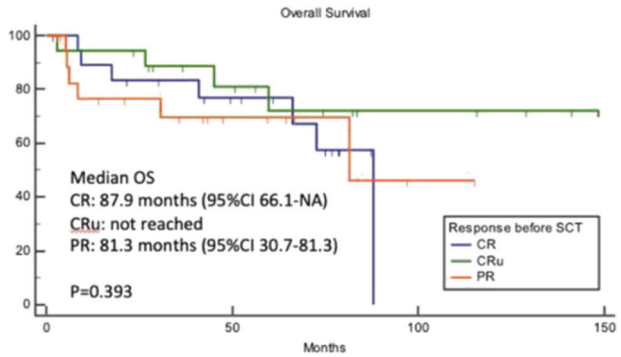
S. Cernauskiene[1], U. Ringeleviciute[1,2], A. Zucenka[1,2], V. Peceliunas[1,2], L. Griskevicius[1,2]

[1]Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania, [2]Vilnius University, Institute of Clinical Medicine, Vilnius, Lithuania

Background: The curative treatment for primary central nervous system lymphoma (PCNSL) includes induction consisting of high-dose methotrexate (HD-MTX), rituximab (Rtx), cytarabine (AraC) and thiotepa (TT) followed by consolidation by autologous stem cell transplant (ASCT). Here we report our 12-year experience of patients who have been treated with HD-MTX, AraC, TT, Rtx containing induction protocol and consolidation with ASCT.

Methods: We retrospectively reviewed the medical records of all newly diagnosed PCNSL patients who underwent ASCT as consolidation in Vilnius University Hospital Santaros Klinikos over the period of 2009-2021. These patients received a sequential induction therapy consisting of 4 cycles of Rtx (375 mg/m^2) and HD-MTX (3,5 - 8 g/m2) every 10 days followed by 2 cycles of high-dose AraC (2-3 g/m^2 BID), TT (40 mg/m^2) and Rtx (375 mg/m^2) every 21 days. MRI was performed after 4 R-HD-MTX cycles and then after 2 R-HD-AraC-TT cycles. Stem cell mobilization and collection were done after first R-HD-AraC-TT cycle. Patients who reached complete remission (CR), unconfirmed complete remission (CRu) or partial response (PR) (based on International PCNSL Collaborative Consensus Guidelines for the Assessment of Response in PCNSL) proceeded to ASCT. The ASCT conditioning regimen consisted of Rtx on day -7, carmustine 400 mg/m^2 on day -6 and TT 5 mg/kg on days -5 and -4. Endpoints included progression-free and overall survival (PFS, OS) and grade 3-5 non-hematological toxicity (CTCAE v. 5.0).

Results: 57 patients were enrolled. The median age at diagnosis was 55 years (range 36 - 75). 35 % of the patients were older than 60 years. DLBCL was the most common histologic type comprising 96%. 42% of patients had poor performance status (ECOG ≥ 2) and 59% were classified into intermediate or high-risk groups by IELSSG score. The median time to transplantation was 4 months from diagnosis. The median number of hematopoietic stem cells reinfused was 5.5 x 10^6/kg . All patients achieved prompt hematopoietic recovery with a median duration of hospitalization of 26 days. The most common complications were infectious (26 patients with febrile neutropenia, 9 patients developing bacteremia, 3 – pneumonia, 2 – urinary tract infection). 24 patients had grade 3-4 mucositis and 2 patients had pseudomembranous colitis. There was one treatment-related death caused by sepsis and fungal pneumonia. 65 % (37/57) patients achieved CR or Cru prior to transplant and 35% (20/57) achieved PR. At day +100 post-transplant, the CR rate increased to 93%. After a median follow-up of 64.5 months, 40 of 57 (70%) patients are still alive. The median OS and PFS was not reached at the last follow-up. The 2-year and 5-year PFS were 85% and 71% and the 2- and 5-year OS were 85% and 72%, respectively. Responding patients had similar outcome (Figure 1).



Conclusions: Our results with a long follow-up period show that sequential HD-MTX, AraC, TT and Rtx containing induction chemotherapy followed by consolidation with ASCT is safe and leads to high survival rates in transplant eligible patients with newly diagnosed PCNSL.

Disclosure: Cernauskiene: Registration fees: *Abbvie, Takeda*.

Ringeleviciute: Registration fees: *Abbvie, Roche*; Travel expenses: *Abbvie*.

Zucenka: *Jannsen:* Honoraria, travel-expenses; *Takeda:* Travel Expenses; *Novartis:* Honoraria, travel Expenses; *Pfizer:* Honoraria, Travel Expenses; *Astellas:* Honoraria; *Abbvie:* Honoraria, travel Expenses.

Peceliunas: nothing to declare.

Griskevicius: nothing to declare.

P365

High-dose therapy and autologous stem cell transplantation following platinum-free high-dose cytarabine induction results in excellent long term survival in younger patients with mantle cell lymphoma

B.-N. Baermann[1], P. Jäger[1], J.H. Chae[1], T. Ulrych[1], K. Nachtkamp[1], R. Fenk[1], U. Germing[1], G. Kobbe[1]

[1]University Hospital Düsseldorf, Duesseldorf, Germany

Background: High-dose therapy followed by autologous hematopoietic stem cell transplantation (HSCT) has been implemented as standard first line treatment in younger/fit patients with mantle cell lymphoma (MCL). In recent years R-CHOP has been the preferred regimen for induction therapy and some studies suggest a positive effect of high dose Cytarabine (HDAC) as part of induction therapy as well as Rituximab (R) maintenance. The introduction of Bruton-Tyrosine-Kinase inhibitors currently challenges the high-dose concept in MCL.

Methods: We retrospectively analyzed clinical outcome of 47 patients (38 male, 9 female, median age 57 years, range 34-75) with MCL receiving autologous HSCT (autoHSCT) at the UKD, Heinrich Heine University of Düsseldorf between 1993 and 2019.

Forty-six of 47 patients presented with advanced stage (III/IV) at diagnosis. Thirty-five patients (74%) received HSCT as first line therapy, 30 (86%) of these following induction with sequential R-CHOP and HDAC (28 Cytarabine alone or with Mitoxantrone but without Platinum, 2 with Platinum). Twelve patients (26%) received HSCT as salvage therapy. In these median time to first relapse/progression from diagnosis was 13 months (5-77). BEAM/TEAM + -R was used for conditioning in 39 patients (83%) and 22 (47%) received R maintenance therapy.

Results: Median follow up after HSCT was 4 years for surviving patients. Thirty-one patients (66%) were alive at last follow up. Median event free survival (EFS) was 55 months and overall

survival (OS) was 132 months. Twenty-three patients (51%) relapsed at a median of 67 months (2-113).

After relapse eight patients received allogeneic transplantation, 10 patients chemoimmunetherapy and four patients were treated with Ibrutinib. Median OS after relapse was 44 months. (0-85). Nine patients died of lymphoma, three died of secondary neoplasms and three died of therapy associated complications after allogeneic transplantation.

In univariate analysis EFS and OS were superior when autoHSCT was performed as first line versus salvage therapy (median EFS 88 vs. 7 months, $p < 0,01$, median OS 132 vs. 29 months, $p < 0.01$). In the salvage group EFS was significantly longer when pre-transplant relapse occurred later than 24 months after diagnosis (POD24, median 37 vs. 4 months, $p < 0.03$).

Thirteen patients (37%), who received first line autologous HSCT relapsed at a median of 88 months (2-113)) after HSCT and median OS after relapse was 54 months (0-85).

Median EFS for Patients receiving R-CHOP and HDAC without use of Platinum was not reached at the end of follow up with 5 year EFS of 59%. EFS after autoHSCT was shorter in patients not receiving Rituximab maintenance (median 18 vs. 89 months, $p < 0.04$).

Conclusions: In younger patients with MCL, response to R-CHOP and R-HDAC without Platinum allows long term EFS and OS after autoHSCT sparing the toxic side effects of Platinum therapy. In addition data suggests a positive effect of Rituximab maintenance therapy on EFS after autoHSCT.

Following relapse after first line autoHSCT long term survival may be achieved in individual patients following treatment with Ibrutinib and allogeneic HSCT.

Disclosure: Ben-Niklas Baermann: Nothing to declare
Paul Jäger: Nothing to declare
Ju Hee Chae: Nothing to declare
Thomas Ulrych: Nothing to declare
Kathrin Nachtkamp: Nothing to declare
Roland Fenk: Nothing to declare
Ulrich Germing: Institutional Research Support Celgene, Novartis, Speaker honorarium Celgene, Novartis, Jazz, Advice: Celgene
Guido Kobbe: received honoraria for an advisory role from Abbvie and Gilead

P366

Treatment patterns and clinical outcomes in patients with relapsed/refractory hodgkin lymphoma receiving stem cell transplantation outside europe and north america: Results from the b-holistic study

M. Al-mansour[1,2], B. Ferhanoglu[3], M. Zerga[4], D. Brittain[5], S.-P. Yeh[6], G. Tumyan[7], Y. Song[8], A. Karduss[9], S. Rivas-Vera[10], M. Hertzberg[11,12], L.S. Tye[13], Y.L. Kwong[14,15], Z. Huang[16], K.-W. Wu[17], T.M. Kim[18]

[1]Princess Noorah Oncology Centre, Jeddah, Saudi Arabia, [2]King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia, [3]Koc University School of Medicine, Istanbul, Turkey, [4]Angel Roffo Institute, Buenos Aires, Argentina, [5]Albert Alberts Stem Cell Transplant Centre, Pretoria East Hospital, Pretoria, South Africa, [6]China Medical University Hospital, Taichung, Taiwan, Province of China, [7]Blokhin Russian Cancer Research Centre, Moscow, Russian Federation, [8]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital, Beijing, China, [9]Instituto de Cancerologia, Clínica las Américas, Medellin, Colombia, [10]Instituto Nacional de Cancerologia Mexico, Mexico City, Mexico, [11]Prince of Wales Hospital, Sydney, Australia, [12]University of New South Wales, Sydeny, Australia, [13]National Cancer Centre Singapore, Singapore, Singapore, [14]Queen Mary Hospital, Hong Kong, Hong Kong, SAR of China, [15]University of Hong Kong, Hong Kong, Hong Kong, SAR of China, [16]Takeda Development Center Americas, Inc, Lexington, Massachusetts, United States, [17]Takeda Pharmaceuticals International AG –Singapore Branch, Singapore, Singapore, [18]Seoul National University Hospital, Seoul National University Cancer Research Institute, Seoul, Korea, Republic of

Background: The B-CD30 + **HO**dgkin **L**ymphoma **I**nternational Multi-Center Retrospective **S**tudy of **T**reatment Pract**I**ces and Out**C**omes (B-HOLISTIC) assessed real-world treatment patterns and outcomes in patients with Hodgkin lymphoma (HL) from Latin America, East Asia, Africa and the Middle East, Russia, and Australia. A subgroup analysis of patients with relapsed/refractory HL (RRHL) receiving stem cell transplantation (SCT) is presented here.

Methods: The primary B-HOLISTIC study involved a retrospective chart review of newly diagnosed adult patients with previously untreated Stage IIB–IV classical HL (cHL) or RRHL from January 2010–December 2013. This subgroup analysis assessed treatment patterns and clinical outcomes in patients with RRHL who received SCT.

Results: Of the 426 patients with RRHL, 302 were SCT-eligible and 222 (73.5%) underwent SCT (52.1% in overall RRHL group). The main reasons for not undergoing SCT were patient refusal (26.3%) and pre-SCT lymphoma progression (16.3%). Autologous SCT (ASCT) was performed in 188 (84.7%) patients, allogeneic SCT (allo-SCT) in 10 (4.5%) patients, and 24 (10.8%) patients received both ASCT and allo-SCT. The median (range) age at RRHL diagnosis was 29.0 (18.0–67.0), 28.5 (19.0–46.0), and 27.5 (19.0–45.0) years in patients receiving ASCT, allo-SCT, and both, respectively. Most patients who underwent SCT had Stage IVB disease (19.0%), and only 49.4% and 39.1% of patients achieved a complete and partial response, respectively, with chemotherapy prior to SCT.

Prior to SCT, the regimen consisting of etoposide/methylprednisolone/cytarabine/cisplatin (ESHAP) was the most common salvage chemotherapy (26.3%) in patients with RRHL. The combination of carmustine/etoposide/cytarabine/melphalan (BEAM) was received as pre-SCT conditioning regimen in 61.1% patients undergoing ASCT. Only 4 transplanted patients received consolidation therapy with brentuximab vedotin (BV). A total of 63 (28.4%) patients relapsed post-SCT, and the most frequent salvage regimen in these patients was again ESHAP (45.9%). The most common third-line regimens post-SCT relapse were BV monotherapy (16.4%) and the combination of ifosfamide/gemcitabine/vinorelbine/prednisone (IGEV) (16.4%), and 24 (38.1%) patients received a subsequent SCT.

The median PFS was 20.6 (95% CI: 13.2–31.1) months, and the 1-, 3-, and 5-year PFS rates post-SCT from initiation of first treatment for RRHL were 58.4%, 42.4%, and 38.2%, respectively. The 1-, 3-, and 5-year overall survival rates from cHL diagnosis were 100.0%, 88.1%, and 80.4%, respectively.

Conclusions: The SCT rate and clinical outcomes with SCT reported in this study were similar to previous reports from Europe and North America. The treatment patterns pre- and post-SCT, and post-SCT relapse, align with standard clinical practice and guideline recommendations at the time of the study. However, the clinical outcomes remained suboptimal. The most important parameter predicting SCT outcomes is the pre-SCT complete metabolic response rate, based on positron emission tomography/computed tomography imaging, which was achieved in only 49% patients with RRHL in this study. Novel agents were mostly used in the post-SCT and third-line settings when patients had poor prognosis or significantly inferior outcomes with SCT or conventional treatments. Introducing novel targeted therapies (alone or in combination) earlier in the treatment continuum, may increase responses pre-SCT, which, in turn, can lead to better long-term outcomes in patients with RRHL.

Clinical Trial Registry: NCT03327571

Disclosure: This study was funded by Takeda Pharmaceuticals International AG – Singapore Branch.

Mubarak Al-mansour serves as member of a board of directors or advisory committee for Takeda. Burhan Ferhanoglu serves as a member of a board of directors or advisory committee of Takeda, Roche, AbbVie, and Janssen. Marta Zerga has received conference fees from Bristol Myers Squibb, Janssen, Roche, and Takeda, has received support for attending meetings from Sandoz, Amgen, AbbVie, Teva, and Pint Pharma, has received honoraria from Takeda, AbbVie, Astra Zeneca, Teva, and Sandoz, and has participated on the advisory board for Takeda, Janssen, and Merck. David Brittain has received honoraria from Takeda, Roche, AbbVie, and Janssen, and serves as members of a board of directors or advisory committee for Takeda. Su-Peng Yeh has received honoraria from AbbVie, Amgen, Janssen, Astellas, Astra Zeneca, Novartis, Sanofi, Roche, Bristol Myers Squibb, and Takeda, and has served in an advisory role for AbbVie, Amgen, Janssen, Astellas, Astex, Novartis, Sanofi, and Takeda. Gayane Tumyan serves as member of a board of directors or advisory committee for Takeda. Yuqin Song has received conference fees from Takeda and has participated on the advisory boards for Roche, Takeda, and Janssen. Amado Karduss has received honoraria from Takeda, Amgen, and Janssen, and serves as a member of a board of directors or advisory committee of Novartis. Silvia Rivas-Vera has received honoraria from Roche and serves on the advisory board for Takeda. Mark Hertzberg has received honoraria, consulting fees, and serves as a member of a board of directors or advisory committee of Takeda, Roche, BMS, Gilead, and MSD. Lim Soon Thye's institution has received honoraria from Takeda. Yok Lam Kwong serves as a consultant and has received honoraria or research funding from Amgen, Astellas, Bayer, BeiGene, Bristol Myers Squibb, Celgene, Gilead, Janssen, Merck, Novartis, Roche, and Takeda. Zhongwen Huang and Kwang-Wei Wu are employees of Takeda Pharmaceuticals and hold shares in the company. Tae Min Kim has consulting and advisory roles for AstraZeneca, Boryung, Hanmi, Janssen, Novartis, Takeda, Sanofi, and Roche/Genentech, and receives a grant from AstraZeneca-KHIDI and has received consulting fees from AstraZeneca, Hanmi, Janssen, Novartis, and Takeda outside this work.

P368

Allogeneic hematopoietic stem cells transplantation (allo-hsct) for hodgkin lymphoma in switzerland: 20 years of experience 2001-2020. For sbst working group

H. Simeunovic[1], M. Nabergoj[2], M. Dickenmann[3], H. Baldomero[4], S. Masouridi-Levrat[5], C. Dantin[5], A. Rovo[1], G. Nair[6], U. Schanz[6], J. Passweg[7], Y. Chalandon[5], E. Rebmann Chigrinova[1,8]

[1]University Hospital of Bern, Bern, Switzerland, [2]Hopital Du Valais, Sion, Switzerland, [3]Aarau Hospital, Aarau, Switzerland, [4]Swiss National Stem Cell Transplant Registry/SBST, Basel, Switzerland, [5]Geneva University Hospital, Geneva, Switzerland, [6]University Hospital of Zurich, Zürich, Switzerland, [7]Univeristy Hospital of Basel, Basel, Switzerland, [8]Hospital of Neuchatel, Neuchatel, Switzerland

Background: Despite the high cure rate with initial therapy, approximately 10% of HL patients are refractory to initial treatment, and up to 30% of patients will relapse after achieving the initial complete remission (CR). Monoclonal antibodies, targeting the programmed cell death 1 (PD-1) receptor showed promising results with high response rates in relapsed/refractory HL (rrHL). Most responders, however, would eventually progress. For those patients, allogeneic hematopoietic stem cell transplantation (alloHSCT) remains so far the last potentially curative option. Its use in rrHL patients has been argued due to the high rates of NRM although the introduction of reduced intensity conditioning regimens has undoubtedly contributed to the better outcomes. Here we report the Swiss experience in alloHSCT for HL from 2001 to 2020.

Methods: This retrospective analysis included 62 adult patients with HL, who received the allo-HSCT in one of three University Hospitals of Switzerland (Zurich, Basel and Geneva) between May 2001 and January 2020. The primary endpoint was OS (overall survival). Secondary endpoints were relapse free survival (RFS), non-relapse mortality (NRM), relapse incidence (RI), acute (aGVHD) and chronic (cGVHD) rates, which were assessed in univariate analysis.

Results: Median follow-up was 61 months (IQR 59-139). The median age of patients at the time of allo-HSCT was 28 years (24-33), there were more male patients (74%). Prior autologous HSCT was performed in 50 (82%) and 9 (15%) patients have previously undergone an allo-HSCT. Performance status with Karnofsky index ≥80 was reported in 42 (98%) patients. Only 19 (31%) of 62 patients presented CR at the time of allo-HSCT.

Regarding conditioning regimen, 48 (77%) patients were treated with a reduced-intensity conditioning regimen (RIC) and 13 (21%) received total body irradiation (TBI). Stem cell source was peripheral blood for 54 (87%) of patients and 8 (13%) patients received bone marrow. Donor was an HLA-identical sibling or an HLA-matched unrelated donor for 29 (47%) and 22 (35%) patients, respectively, 3 (5%) patients had a mismatched unrelated donor and 8 (13%) had a partially matched related donor. Successful neutrophil engraftment occurred in 60 (98%) patients in a median of 15 days (13-17).

2- and 5-year OS was 54% (SE ± 12) and 50.2% (SE ± 13.3), respectively, and 2- and 5-years RFS was 40.7% (±16.3) and 34.4% (SE ± 19.0). NRM was 23.1 % (SE ± 2.2) and 27.4% (SE ± 2.5) at 2 and 5 years respectively. The cumulative incidence of relapse was 36.1% (SE ± 5.6) at 2 years and 38.2 % (SE ± 6.6) at 5 years.

Conclusions: Our analysis of allo-HST outcome in the context of rrHL shows encouraging OS and RFS rates with mortality rate reaching plateau at 50% at 2 years after the allo-HSCT. This confirms that allo-HSCT still remains a potentially curative option for half of patients with rrHL. Relatively high NRM rates in this young population could be explained by the accumulated toxicities due to the multiple previous treatments. The better timing with earlier allo-HSCT application in the rrHL setting should perhaps be considered.

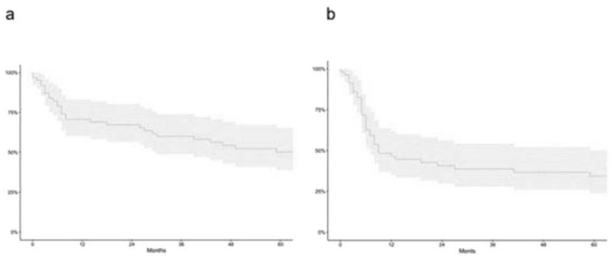


Figure 1: Overall survival (a) and relapse free survival (b)

Disclosure: Nothing to declare.

P369

Hematopoietic stem cell transplant outcomes in north american adult t-cell leukemia/lymphoma

D. Reef[1], A. DeCastro[1], J. Mustafa[1], F. Khatun[1], A. Lombardo[1], L. Townsend-Nugent[1], Y. Wang[1], Y. Shi[1], K. Gritsman[1], M. Goldfinger[1], N. Shah[1], N. Kornblum[1], A. Shastri[1], I. Mantzaris[1], L. Bachier-Rodriguez[1], A. Verma[1], I. Braunschweig[1], R.A. Sica[1]

[1]Montefiore Medical Center, Bronx, United States

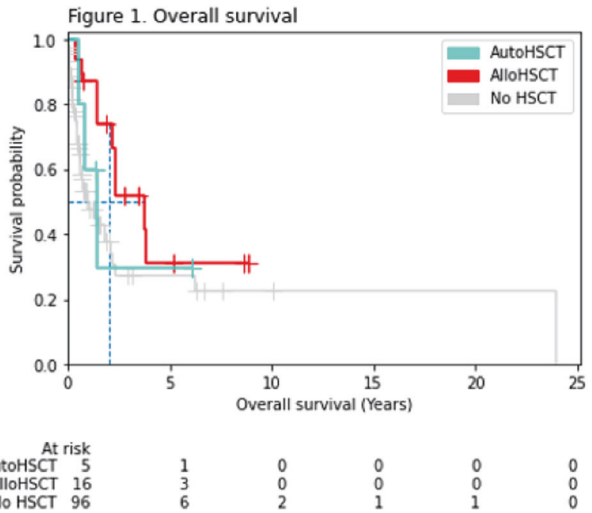
TABLE 1	n (%)	Median OS (years)	Log-rank p (v. no HSCT)	Log-rank p (v. autoHSCT)	2-y OS (95% CI)	χ2 p (v. no HSCT)	χ2 p (v. autoHSCT)	HR (95% CI)	Likelihood ratio test p (v. no HSCT)
No HSCT	96 (82.05%)	0.95	-	-	0.38 (0.25-0.50)	-	-	1.00 (ref)	-
AutoHSCT	5 (4.27%)	1.41	0.645	-	0.30 (0.01-0.72)	0.7593	-	0.87 (0.27-2.78)	0.8093
AlloHSCT	16 (13.68%)	3.75	0.0518	0.3683	0.74 (0.45-0.89)	0.0277	0.0949	0.50 (0.24-1.03)	0.043

Background: Adult T-cell Leukemia/Lymphoma (ATLL) is a rare subtype of mature T-cell lymphoma with generally poor outcomes. Hematopoietic stem cell transplant is undertaken to ameliorate disease, but additional data are needed to support its optimal use. Much of the published literature on ATLL comes from Japan where HTLV-1, the retrovirus that causes ATLL, is endemic. Caribbean populations carry a significant portion of the global burden of ATLL and there may also be an underappreciated burden of ATLL in Latin America, Africa, and the Middle East as well. Our center in Bronx, New York provides care to a large population of Caribbean immigrants and we care for a significant proportion of patients with ATLL in the United States. Here, we describe hematopoietic stem cell transplant outcomes in North American ATLL.

Methods: Patients were identified from an institutional database of patients with mature T-cell lymphomas. Data were collected by chart review. Subjects were excluded for receipt of investigational cellular therapies or if pathological diagnosis only became available after follow-up ended. Individuals who underwent autoHSCT with subsequent alloHSCT were analyzed with the alloHSCT group. Survival outcomes were assessed using the Kaplan-Meier method and Cox regression. Follow-up began at diagnosis and ended at death or censoring. Subjects were censored at date of last contact or the study end date 6/8/2021. Data were analyzed using Python and lifelines.

Results: 117 individuals with ATLL were identified with median follow-up 7.3 months (2 days-23.9 years). Subjects were diagnosed with ATLL 6/30/1995-4/16/2021. Median age at diagnosis is 59.1 years (25.2-87.6). The cohort is 59% female, 66.1% African American, 3.5% Caucasian, and 0.9% Asian. 30.8% are Hispanic.

16/117 underwent alloHSCT, 5/117 underwent autoHSCT, and 96/117 did not have any HSCT (Table 1). Data on alloHSCT suggest superiority over no HSCT, though statistical measures were inconsistent (median OS 3.75 vs. 1.41 years, log rank p 0.0518, 2-year OS 74% [95% CI 45-89] vs. 30% [95% CI 1-72], $\chi^2 p = 0.0277$, HR 0.50 [95% CI 0.24-1.03, likelihood ratio test $p = 0.0430$]). Outcomes with autoHSCT were similar to those with no HSCT. AlloHSCT outcomes were not statistically different from those of autoHSCT.



Conclusions: Our data lend support to the use of alloHSCT to improve outcomes in ATLL. We hope that as we further characterize the cohort we will be able to optimize selection of ATLL patients for alloHSCT.

Disclosure: Gritsman, Kira: iOnctura: Research Funding.

•Shastri, Aditi: Onclive: Honoraria; GLC: Consultancy; Kymera Therapeutics: Research Funding; Guidepoint: Consultancy.

•Verma, Amit: Acceleron: Consultancy; Novartis: Consultancy; Stelexis: Consultancy, Current equity holder in publicly-traded company; Eli Lilly: Research Funding; Curis: Research Funding; Medpacto: Research Funding; Incyte: Research Funding; GSK: Research Funding; BMS: Research Funding; Celgene: Consultancy; Stelexis: Current equity holder in publicly-traded company; Throws Exception: Current equity holder in publicly-traded company.

P370

Does high dose therapy with autologous stem cell transplantation affect bone mineral density in patients with lymphoma?

R. Fredriksson[1], C. Lewerin[1], P. Johansson[1], D. Mellström[1], H. Lind Kristjansdottir[1]

[1]University of Gothenburg, Gothenburg, Sweden

Background: Osteoporotic fracture has been shown to be more common in lymphoma patients compared with the general population. Studies have shown that bone mineral density (BMD) decreases after hematopoietic stem cell transplantation, however, few have focused on change in BMD in lymphoma patients after autologous stem cell transplantation (ASCT). We intended to fill this knowledge-gap.

Methods: Lymphoma patients in the Västra Götaland region in Sweden aged at least 18 years old, with a planned ASCT in 2015 – 2019 were eligible to participate. Participants did dual-energy X-ray absorptiometry (DXA) one month before, and six, 12 and 24 months after ASCT. DXA-measures were performed in the hip, femoral neck and lumbar spine, and differences in BMD, Z- and T-score were analyzed using paired T-tests.

Results: 42 lymphoma patients were included, of whom 24 completed all four DXA-scans. The median age at ASCT was 55.5 years and 42% were women. The greatest change in BMD and Z-score was seen in the first six months and was more pronounced in the total hip and femoral neck compared to the lumbar spine. BMD in the lumbar spine recovered to baseline within the study period, while BMD in the total hip and femoral neck remained decreased.

Conclusions: BMD, Z- and T-scores decreased in the first six months, after which they increased, after ASCT in patients with lymphoma. The restoration of BMD was faster in the spine compared with total hip and femoral neck. The spine recovered to baseline levels within the 24-month period while the total hip did not. Further research is needed, particularly to identify which patients might benefit from prophylactic osteoporosis treatment.

Disclosure: Nothing to declare.

P371

Hematopoietic cell transplantation in mantle cell lymphoma: A long-term single center experience

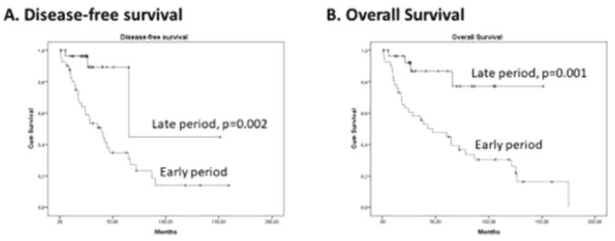
M. Iskas[1], E. Gavriilaki[1], P. Dolgyras[1], Z. Bousiou[1], I. Batsis[1], D. Mallouri[1], A. Kourouklidou[1], M. Masmanidou[1], C. Lalayanni[1], C. Vadikoliou[1], N. Stavroyanni[1], S. Papaemmanouil[1], T. Geroukis[1], D. Sotiropoulos[1], G. Arsos[2], A. Anagnostopoulos[1], I. Sakellari[1]

[1]G Papanicolaou Hospital, Thessaloniki, Greece, [2]Aristotle University of Thessaloniki, Thessaloniki, Greece

Background: In the era of novel biologic agents, the role of hematopoietic cell transplantation (HCT) in mantle cell lymphoma (MCL) remains under investigation. Therefore, we aimed to compare strategies and outcomes of MCL patients in the current period of biologic agents versus the early period.

Methods: We retrospectively enrolled consecutive adult patients treated with MCL at our center over the last two decades (2000-2020). Patients were divided into two treatment periods: early (2000-2011) and late (2012-2020). According to each period's department protocol, RCHOP/RCHEPOM was used as first-line treatment in the early period. Although we planned for autologous HCT as consolidation treatment in the early period, this was not feasible due to patient eligibility and poor mobilization. Therefore, intensified treatment with alternating cycles of RCHOP/RDHAP in fit-transplant eligible was given in the late period with autologous HCT as consolidation treatment. Unfit patients received R-Bendamustine, R-VCAP in first line along with ibrutinib in relapse, in the late period. In both periods rituximab consolidation was planned for 2 years. The following variables were analyzed: pre-transplant (age, gender, MIPI, performance status, blastoid variant, cytogenetics, stage, different lines of treatment), transplant (donor, graft, conditioning) and post-transplant (disease-free survival/DFS, overall survival/OS) characteristics.

Results: We studied 81 MCL patients, 68 male:13 female, with a median age of 59.4 years (range 18-82). Median MIPI score at diagnosis was 6 (1-12), and performance status 1 (0-4). Patient and disease factors were similar in both treatment periods. Autologous HCT was performed more frequently in the late treatment period compared to the early (44% versus 12%, $p = 0.008$) due to patient eligibility and stem cell mobilization. Allogeneic HCT was performed at a similar rate in the two periods (7% versus 13%, $p = 0.125$). With a median follow-up of 40.7 months (4.3-269.3) in surviving patients, disease-free and overall survival (DFS and OS) were significantly higher in the late treatment period ($p = 0.002$ and $p = 0.001$, Figure 1). Among studied factors, age and performance status were also univariately associated with DFS and OS. It should be noted that autologous or allogeneic HCT per se was not significantly associated with improved survival. In the multivariate analysis, treatment period remained an independent predictive factor of both DFS and OS ($p = 0.034$ and $p = 0.032$), independently of age and performance status.



Conclusions: Our study suggests that the integration of autologous HCT as consolidation treatment along with novel agents in the late treatment period was associated with improved survival. Thus, it highlights the need of further refinement of MCL treatment in the era of personalized medicine.

Clinical Trial Registry: NA

Disclosure: Nothing to declare

P372

Autologous hematopoietic cell transplantation for primary central nervous lymphoma. A single institution experience

B. Ostrowska[1], J. Romejko-Jarosinska[1], K. Domanska-Czyz[1], M. Osowiecki[1], L. Poplawska[1], L. Targonski[1], R. Konecki[1], A. Borawska[1], A. Dabrowska-Iwanicka[1], A. Druzd-Sitek[1], M. Kotarska[1], E. Mroz-Zycinska[1], W. Osiadacz[1], E. Paszkiewicz-Kozik[1], M. Swierkowska[1], P. Szafran[1], M. Szymanski[1], J. Tajer[1], E. Wojciechowska-Lampka[1], G. Lapinska[1], G. Rymkiewicz[1], J. Walewski[1]

[1]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Background: Primary CNS lymphoma (PCNSL) induction therapy is based on systemic high dose methotrexate (HD-MTX) followed by consolidative therapy. Consolidation with high-dose chemotherapy and autologous stem cell transplant (HDC-ASCT) is used for younger patients. In this study we evaluate efficacy and tolerability of rituximab, methotrexate, ifosfamide, vincristine (R-MIV) followed by a course of cytarabine with thiotepa and HDC-ASCT.

Methods: We evaluated the outcome of 60 immunocompetent adult patients with PCNSL treated at the Maria Sklodowska-Curie National Research Institute of Oncology between February 2015 and March 2021. Six cycles of induction chemotherapy with rituximab, methotrexate (3.5 g/m^2), ifosfamide and vincristine (R-MIV/every two weeks) and one additional cycle of cytarabine with thiotepa were given. Patients with a complete or partial response (CR/PR) proceeded to consolidation with thiotepa 5 mg/kg/bid on day -5,-4; carmustine (BCNU) 400 mg/m2 on day -5; and etoposide 150 mg/m2 on day -5,-4,-3, followed by ASCT. Alternatively, whole brain radiotherapy (24-36 Gy) was given to patients not eligible for HDC-ASCT.

Results: 39 (65%) patients were eligible for HDC-ASCT of whom 30 patients actually received HDC-ASCT. Two patients with CR are currently awaiting HDC-ASCT. Seven patients did not undergo HDC-ASCT due to progression ($n = 2$), patient's refusal ($n = 2$) and toxicity related to induction treatment ($n = 3$; one patient died in PR due to SARS-CoV-2 infection).

Median age (range) of 30 transplanted patients was 56 years (19-66). 17/7 patients were in CR/CRu following induction therapy and six in PR, based on CT/MRI assessment. For all 21 patients with PET-CT done before ASCT, metabolic-CR was confirmed (initially active changes were seen in 14 of 21 tested patients). Peripheral blood stem cell collection was performed after one of R-MIV cycles. Mean (range) number of 483.4 (187-1040.7) x 10^6 CD34 + cells were collected corresponding to 5.73 x 10^6 cells/kg (2.55-11.64x10^6 cells/kg). Mean hospitalization time from the day of stem cell reinfusion was 14 days. Mean time to hematologic recovery with PLT > 25 G/L and NEU > 0.5 G/L was 9 and 8 days, respectively. Neutropenia and thrombocytopenia grade 3-4 (CTCAE v5.0) were observed in all patients (mean 6 and 7 days, respectively), anemia grade ≥ 3 was observed in 7 patients (mean 1 day), elevated transaminases grade 3 (1 patients for 2 days). No renal toxcicity was observed. The most common grade 3-4 toxicities observed were: diarrhea (10 patients, mean 4 days),

mucositis (17 patients, mean 5 days). Febrile neutropenia occured in 17 patients (mean 2.5 days). Blood cultures did not reveal any relevant pathogens except one patient with blood culture with confirmed *Enterobacter cloacae*-ESBL and *Klebsiella oxytoca*. Two patients (6.6%) died of transplant-related complications: septic shock and neurotoxicity.

At a median (range) follow-up of 22 (2-69 months), 23 transplanted patients are alive in CR, 2-year progression free survival (PFS) and overall survival (OS) post-ASCT was 79% (95% CI: 66-92) and 79% (95%CI: 66-92). Relapse occurred in 4 patients - 2,5,6 and 42 months after ASCT.

Conclusions: R-MIV induction therapy followed by HDC-ASCT is a relatively safe and highly effective treatment for PCNSL patients.

Disclosure: NO DISCLOSURE

P373

Gemcitabine, cisplatin and dexamethasone as a salvage and mobilization chemotheraphy before autologous stem-cell transplantation is effective and safe outpatient regimen in relapsed/refractory hodgkin lymphoma patients

A. Gokmen[1], U. Sahin[1], E. Soydan[2], M. Kurdal[1], U. Ozan[3], O. İlhan[4], O. Arslan[4], M. Ozcan[4]

[1]Medicana International Ankara Hospital, Ankara, Turkey, [2]Guven Hospital Ankara, Ankara, Turkey, [3]Medicana Bursa Hospital, Bursa, Turkey, [4]Ankara University, Faculty of Medicine, Ankara, Turkey

Background: Second-line salvage chemotherapy followed by high-dose chemotherapy (HDT) and autologous stem-cell transplantation (ASCT) is the current standard treatment for eligible patients with relapsed/refractory (R/R) Hodgkin lymphoma (HL). Several multiagent salvage chemotherapy regimens have been used to to provide cytoreduction and stem cell mobilization before HDCT. However the optimal salvage regimen is unclear. We report outcome of patients with R/R HL treated with salvage gemcitabine, cisplatin and dexamethasone (GDP) regimen before ASCT in this study aiming at evaluating efficacy, stem cell mobilization activity and safety of GDP.

Methods: Fourty-five patients with R/R HL who were treated with GDP as salvage and mobilization regimen before ASCT in Medicana International Ankara Hospital between february 2013 and february 2021 were analysed retrospectively. GDP regimen was administered in an outpatient setting. Chemotherapy consisted of gemcitabine at a dose of 1000 mg/m2 intravenously (i.v.)on days 1 and 8, cisplatin at a dose of 75 mg/m2 i.v. and dexamethasone at a dose of 40 mg orally on days 1 to 4, of each 3-week course. PBSC were collected after first or second course of GDP. All patients underwent autologous stem cell transplantation after salvage GDP treatment and stem cell mobilization .

Results: Median age of patients at study entry was 32 years (15-65 years). Thirty patients (66.7%) had relapse (7 early relapse, 23 late relapse) and 15 (33.3 %) had refractory disease. Fourteen patients (31.1 %) had advanced stage disease (stage III-IV) before salvage therapy. Thirty-six (80%) patients achieved overall response including 24 (53.3 %) CR and 12 (26.7 %) PR. Nine (20%) patients had no response. There was no association between risk factors at study entry and achievement of CR significantly (P:0.353). Peripheral stem cells were collected after the first or second cyle of GDP in 42 of 45 (93.3 %) patients. Peripheral blood stem cell collection were adequate in all patients with a median number of $11.18x10^6$/kg CD34 + cells (range 2.6 to 36.6). No treatment-related deaths have been documented during therapy. The most common grade 3 or 4 hematological adverse event was thrombocytopenia (42.2%), followed by neutropenia (22.2%). Platelet and red blood celltransfusion supports were required in 11% and 11% of patients. There were no febrile neutropenic episodes that required hospitalization or treatment delay. Grade 3 or 4 renal, neurological, hepatic, or cardiac toxicity was not observed. With a median follow up time of 43 months (range 5–94 months), the 3 year PFS and OS for patients receiving 2cyles of GDP followed by ASCT were 72% and 92% respectively

Conclusions: Our results suggest that GDP is a viable therapeutic option before ASCT with high response rate, favorable toxicity profile and excellent mobilization potential and may serve as a bridge for ASCT. Applicability of GDP on an outpatient setting also provides advantage over other effective salvage regimen.

Disclosure: no disclosure

P374

Efficacy of PD1-blockade immediately followed by autologous stem cell transplantation in relapsed/refractory hodgkin's lymphoma, but investigations needed to elucidate the impact on autologous transplantation

A. Ibrahim[1], A. Khalil[1], A. Abyad[1], A. Harmouche[1], J. Ibrahim[2], K. Al Zahran[1], A. Mogharbel[1], R. Jalloul[1], A. Youssef[1], T. Jisr[1]

[1]Makassed Hospital and Middle East Institute of Health, Lebanese University, Beirut, Lebanon, [2]American University of Beirut, Beirut, Lebanon

Background: Autologous peripheral blood stem transplantation (APBSCT) after PD-1 blockade results in favorable outcome among patients (pts) with multiply relapsed/refractory R/R Hodgkin's lymphoma (HL). Anti-PD-1 monoclonal antibodies (mAbs) can sensitive pts to high dose chemotherapy (HDCT) followed by APBSCT. Response to PD-1 blockade, and not prior chemo-sensitivity, best predicted post – APBSCT outcome (Merryman R.W. et al, Blood adv (2021) 5 (6): 1648-59). Few studies were reported on the impact of anti-PD-1 mAbs immediately followed by APBSCT in multiply R/R HL.

Methods: Between October 2017 and June 2021, 8 pts with multiply R/R HL received anti-PD-1 mAbs alone immediately followed by APBSCT. Anti-PD-1 mAbs consisting in Pembrolizumab in 5 pts and Nivolumab in 3 pts. All the pts were in complete remission (CR) before HDCT. HDCT was TEAM regimen (Thiotepa, Etoposide, Aracytine, Melphalan). All the pts were re-evaluated by PET-Scan done every 3 months after APBSCT.

Results: The median age was 33 yo (24-38). There were 5 females and 3 males. The pts received a median of 4 systematic therapies (3-5) before APBSCT. Anti-PD-1 mAbs were administered as third line therapy in 2 pts, as fourth line in 4 pts, and as fifth line in 2 pts. The median number of CD34 + cells transfused was 3.95 10^6/kg (3-4.6). The median time to neutrophil recovery was 14 days (d) (10-24), and for platelets recovery 17d (8-32). All the pts developed febrile neutropenia. On neutrophil recovery, while being apyretic, 5 pts developed maculopapular skin rash of grade 1 in 1 patient (pt), grade 2 in 3 pts and grade 3 in 1 pt. Two pts (with grades 2 and 3 skin rash) developed concomitantly lung infiltrates. The pt with grade 1 skin rash recovered without specific therapy after 5 days; however, the other 4 pts received corticosteroids IV at the dose of 2 mg/kg/d which induced a total resolution of skin lesions and lung infiltrates within 5 to 8 days. Biopsy of skin lesions performed in 2 of these 4 pts showed pathological findings similar to those of acute cutaneous graft - vs - host disease. All these 5 pts are alive in CR at a median of 38 months (m) (18-50) after APBSCT. The 2 remaining pts relapsed

at 13 and 17 m after APBSCT; one pt died of HL after 2m of relapse, and the other underwent haploidentical allogeneic bone marrow transplantation (BMT) and is still alive in CR at 5 m after allogeneic BMT, (at 22 m of APBSCT).

Conclusions: Anti-PD1- mAbs immediately followed by APBSCT are efficient in multiply R/R HL pts, but further investigations are needed to better elucidate their immunological impact on APBSCT.

Disclosure: Nothing to declare

P375

Allogenic hematopoietic cell transplantation in relapsed follicular lymphoma: Unicentric analysis with 20 years of follow-up

R. Pinho Peixeiro[1], C Pinho Vaz[1], M. Quintela[1], P Coelho[1], L Leite[1], R Branca[1], S Roncon[2], A Campos[1]

[1]Bone Marrow Transplantation Service, Instituto Português de Oncologia do Porto Francisco Gentil, Porto, Portugal, [2]Celular Therapy Service, Instituto Portugês de Oncologia do Porto Francisco Gentil, Porto, Portugal

Background: Despite having curative potential in relapsed Follicular Lymphoma (FL), allogenic hematopoietic cell transplantation (AlloHCT) remains underused and the ideal timing for its performance is still to be defined. Although transplant-related mortality (TRM) is not negligible, good overall survival (OS) and progression free survival (PFS) rates have been described.

Methods: Characterization of patients (Pts) with FL who underwent HLA-matched AlloHCT at our institution between 2000 and 2020, response assessment and analysis of OS, PFS and TRM.

Results: 43 Pts with relapsed FL were included, with male predominance (n = 24; 56%) and median age at diagnosis of 44 years old (yo) (range 28-58). 36 Pts (84%) had advanced stage disease, 20 Pts (47%) with bone marrow involvement and 7 (16,3%) with extra-nodal disease. The median time of follow-up was 134 months (range 2-229).

First line treatment with chemotherapy alone or chemotherapy plus rituximab were used in 28 (65,1%) and 15 (34,9%) Pts, respectively. 27 Pts (62.8%) achieved complete responses (CR), 12 (27.9%) partial responses (PR), 1 (2.3%) stable disease (SD) and 3 (7%) progressive disease (PD). 4 Pts performed AutoHCT, with a median event-free survival (EFS) of 10 months (min 3, max 120). A median of 3 lines of treatments (range 1-6) were used before AlloHCT.

The median time to AlloHCT was 34 months (range 11-177). At the time of AlloHCT, the median age of Pts was 49 yo (range 30-62), all with ECOG < 2. Forty grafts were obtained from HLA-matched related donor (FluBu conditioning) and three from HLA-matched unrelated donor (FluBuATG conditioning). Graf versus host disease prophylaxis were: Cyclosporine+ mycophenolate mofetil (related donor) and Tacrolimus+ mycophenolate mofetil (unrelated donor). The source of hematopoietic progenitors was peripheral blood in 42 Pts and bone marrow in 1 Pts. No graft failures were reported, with a median recovery of 15 days (range 6-72).

Twenty Pts developed acute graft-versus-host disease (GvHDa), with isolated cutaneous involvement being the most frequent. 4 Pts had grade 3 GvHDa. 25 (58%) Pts had chronic GvHD.

After AlloHCT, 37 Pts (86%) achieved CR, 2 (4.7%) PR, 1 (2.3%) SD and 1 (2.3%) PD. The response was not evaluated in 2 Pts.

During follow-up 3 relapses and 11 deaths were reported. The median of PFS and OS at 5 and 10 years were not reached. The TRM was 4.7%. Estimated OS at 5 and 10 years was 90%.

A trend towards reduction of OS was verified on comparative analysis in Pts submitted to more than 2 previous lines of treatment, without statistical significance (p = 0,143).

Conclusions: Our study demonstrates the safety and efficacy of AlloHCT in young multi-treated Pts with relapsed FL, as the only curative option. Prospective and comparative studies are still needed to validate this strategy in the era of immunochemotherapy and targeted therapies.

Disclosure: No conflicts of interest to declare

P376

Secondary hypogammaglobulinemia in cll

A. Ünal[1], K. Fidan[1], M. Keklik[1], S. Çelik[1], M. Baydar[1], N. Mandacı Şanlı[2], Z.T. Güven[1], E. Yıldızhan[2], N. Taşer Kanat[1], S.S. Durusoy[3]

[1]Erciyes University, Kayseri, Turkey, [2]Kayseri City Hospital, Kayseri, Turkey, [3]Sanko University, Gaziantep, Turkey

Background: Secondary hypogammaglobulinemia (SHG) in CLL is associated with both leukemia-related immunodeficiency and immunosuppression from CLL-specific therapy.

Methods: Patients followed with CLL in Erciyes University Faculty of Medicine, Hematology Department between 2010-2021 (73 received treatment and 35 untreated) were divided into two groups. According to BCSH 2012 and ESMO 2015 criteria, patients with IgG<500 g/L and recurrent infections were given IVIG and named SHG. This group was compared with non-SHG. IgG at the time of diagnosis and last follow-up were noted in all patients. The relationship between IgG levels and SHG was examined. In addition, infections that developed in the patients during the follow-up period were reported and its relations with immunoglobulin replacement therapy (IgRT) were examined.

Results: The number of infections in those who received IgRT treatment (n = 12) was statistically less than those who did not receive IgRT (n = 25) (p = 0.003) **(table 1)**.In patients with SHG, the IgG level at the time of diagnosis (mean: 909) was lower than the group without SHG (mean: 1125) (p = 0.031). The pre-treatment IgG level was lower in SHG (median 750 versus 1000) (p = 0.001). Post-treatment IgG level (median: 452.5) in patients with SHG was lower than the group without SHG (median: 896) (p < 0.001). While 17 patients (94.4%) of 18 patients who developed SHG were receiving any chemo-chemoimmunotherapy, 56 (62%) of 90 patients who did not develop SHG were receiving treatment. This difference was found to be statistically significant (p = 0.006). SHG development was statistically higher in those treated with Chlorambucil plus Prednisolone, Fludarabine plus Cyclophosphamide plus Rituximab(FCR), Venetoclax and Ibrutinib (p < 0.05). Ibrutinib treatment was observed as a single independent variable in predicting the development of SHG in the multivariate logistic regression analysis (p = 0.002).

Table-1. General features of the study population.

	CLL patients with SHG (n = 18)	CLL patients without SHG (n = 90)	p
Infection numbers	12	25	0.003
IgG at diagnosis	909 ± 464	1125 ± 359	0.031
IgG before treatment	750 (330- 1360)	1000 (355 – 2390)	0.001
IgG at last status	452.5(120-1220)	896 (285 – 1892)	<0.001

	CLL patients with SHG (n = 18)	CLL patients without SHG (n = 90)	p
Receiving treatment	17, 94.4%	56, 62%	0.006
Chlorambucil-prednisolone	8,44.4%	16,17.7%	0.003
FCR	6, 33.3%	9, 10%	0.02
Venetoclax	3,16.6%	1,1.1%	0.014
Ibrutinib	13,72.2%	24,26.6%	0.001

Conclusions: One of the immunological defects in CLL disease is hypogammaglobulinemia (HG). Studies have reported that 10-44% of CLL develops HG at the time of diagnosis and 25-85% during treatment. Chemotherapy agents such as Anti-CD20 antibodies, BTK inhibitors, Phosphoinositide-3 kinase inhibitors, bcl-2 inhibitors, alkylating agents and purine analogs used in the treatment of CLL have been reported to cause SHG. In the study of Çelik S. et al.in CLL patients using ibrutinib, it was determined that IgG levels decreased during and after ibrutinib treatment. In our study, SHG development was statistically higher in those who received treatment. We also observed that ibrutinib was the only independent risk factor in predicting the development of SHG.

Disclosure: Nothing to declare

P377

Post-market clinical follow-up of the amicus blue™ online ecp system for treatment of cutaneous t-cell lymphoma (CTCL)

T. Kanouni[1], N. Garcia[2], S. Ortega[2], A. Ruf[3], B. Barta[3]

[1]CHU Montpellier, Montpellier, France, [2]L'Hospital Universitari, Bellvitge, Spain, [3]Städtisches Klinikum, Karlsruhe, Germany

Background: The Amicus Blue™ ECP System (Fresenius Kabi, Germany) was CE marked and commercially available in Europe since 2019. The system incorporates the Amicus Separator®, the Phelix photoactivation device, a functionally closed disposable kit, and 8-MOP to perform ECP therapy in an online, closed system. A post market clinical follow up study was performed at 3 sites in the EU to obtain data from at least 38 procedures over approximately 24 months. The primary objective of this study was to assess the safety of the Amicus ECP System during routine clinical ECP procedures in CTCL patients by analyzing adverse device effects (ADEs) that are unanticipated. The secondary objective was to assess system performance of the system in CTCL patients.

Methods: A minimal sample size of 38 procedures was statistically established to demonstrate a 10% incidence rate of unforeseen ADEs with a confidence level of 90%. Patients were screened for entry into the study according to stated inclusion/exclusion criteria. Subjects received ECP treatment with Amicus Blue as defined by their individual treatment regimen for up to 24 months or according to physician discretion. Each patient could complete more than one procedure. Amicus v6.0, Phelix v2.0 and double-needle disposable kits were used. Procedure parameters were not defined in the study protocol as the intent was to assess system safety in routine use, however that is defined by each site. Most procedures targeted 2000ml WB processed (n = 36), while ca. 4000ml (n = 21) was targeted by 1 site.

Sites documented all adverse events, and primary analysis was conducted on ADEs that are unanticipated. Procedure results such as whole blood processed, procedure time, photoactivation time, and percent photoactivation complete were recorded. All data collected were entered directly into the Electronic Data Capture system by authorized and trained personnel from the study sites.

Results: Between September 2020 and May 2021, 17 adult patients (12 male, 5 female) enrolled in the study at 3 different sites in 3 different countries. Each site performed a minimum of 12 procedures. No patients were withdrawn from the study. 16 patients were under treatment for Sézary syndrome, and 1 patient for mycosis fungoides. Mean (SD) age of subjects was 71.6 (7.77) years. 57 procedures were completed, and 6 patients received >3 treatments on Amicus Blue. All procedures had photoactivation completed to 100%. One adverse event was recorded (itching) but was determined not to be device related. Zero ADEs were reported. Procedure data is presented in the table, median (range).

	2000 mL n = 36	4000 mL n = 21	Combined n = 57
WB Processed (ml)	2002 (1939 – 2324)	4009 (3636 – 4020)	2011 (1939 – 4020)
Photoactivation Time (min)	21 (15 – 24)	20 (18 – 23)	20 (15 – 24)
Total Procedure Time (min)	92 (77 – 117)	134 (105 – 205)	97 (77 – 205)

Conclusions: All 57 ECP procedures were safely completed, and the primary objective of the study was satisfied. Only one non-device related adverse event was recorded. The Amicus Blue ECP System performed as expected in CTCL patients with evaluation of safety and performance.

Disclosure: Tarik Kanouni: hospitality fees from Fresenius Kabi

P378

The expression of cd268 helps to distinguish chronic lymphocytic leukemia from other mature b-cell lymphomas

A. Wang[1], X. Wu[1], M. Gong[1], J. Zhen[1], M. Chen[1], H. Wang[1]

[1]Hebei Yanda Lu Daopei Hospital, Langfang, China

Background: Mature B-cell lymphoma is a group of heterogeneous diseases, and multiparameter flow cytometry (MFC) plays an irreplaceable role in its diagnosis, especially in the identification of chronic lymphocytic leukemia (CLL) and other B cell lymphomas. However, immunophenotypic overlap is still encountered in clinical work. Besides, with the widespread application of chimeric antigen receptor-modified T cells (CAR-T) therapy, more markers with high coverage and expression level need to be found as promising targets for CD19 and CD20 may loss after target therapy. Therefore, we used MFC to simultaneously detect the classic markers CD5, CD23, CD200, CD79b, CD19, and CD20, and the new marker CD268, in an attempt to evaluate the role of these markers in distinguishing CLL from non-CLL small B lymphoma.

Methods: From December 2018 to December 2020, 158 mature B-cell lymphoma patients, including 75 CLL patients and 83 non-CLL B lymphoma patients, were admitted to Hebei Yanda Lu Daopei Hospital. The expression of CD5, CD23, CD200, CD268, CD79b, CD19 and CD20 on malignant B cells was detected by 10-color flow cytometry.

Results: CD5, CD23, and CD200 were higher in CLL patients (P = 0.000) and CD79b was lower in CLL patients (P = 0.000)

compared with non-CLL B-cell lymphomas. CD268 was expressed in both CLL and most non-CLL B-cell lymphomas, but that in CLL was significantly higher ($P = 0.001$). The expression of CD19 and CD20 showed not significantly differences between the two groups. In addition to the classic differential diagnostic markers CD5, CD23, CD200, and CD79b, CD268 may be one of the new immune markers to differentiate CLL from non-CLL small B lymphoma. CD19 and CD20 lack specificity and cannot be used as immune markers specific to CLL. To further simplify the score, we tried to group patients with CD5 + /CD23 + /CD200 + expression over 80%, and found that the sensitivity, specificity, positive predictive value and negative predictive value of CLL were 80.0%, 98.8%, 98.36% and 84.54% respectively. The sensitivity, specificity, positive predictive value and negative predictive value of CLL were 73.3%, 100%, 100% and 0%, respectively, when CD79b expression was added (≤90%). The sensitivity, specificity, positive predictive value, and negative predictive value of CLL were 70.7%, 100%, 100%, and 0%, respectively, when the expression of CD268 was added (≥90% as the cut-off). Thus, these antibody combinations can be used as one of the combinations to distinguish CLL from non-CLL specific immune markers.

Conclusions: The combination of immune markers CD5, CD23, CD200 and CD79b detected by multi-parameter flow cytometry can effectively distinguish CLL lymphoma from non-CLL lymphoma, and the new marker CD268 provides a new diagnostic basis for differential diagnosis. Moreover, it is highly expressed in most mature B-cell lymphomas and is expected to be an effective therapeutic target.

Disclosure: Nothing to declare

MINIMAL RESIDUAL DISEASE, TOLERANCE, CHIMERISM AND IMMUNE RECONSTITUTION

P379

Focusing atg towards host t-cell depletion eliminates grade iii-iv acute GVHD and is associated with early graft versus leukemia (GVL) immune responses

Z. Al-Kadhimi[1], S. Pirruccello[1], Z. Gul[2], L. Maness-Harris[1], V. Bhatt[1], K. Gundabolu[1], M. Lunning[1], G. Bociek[1], C. D'Angelo[1], K. Abdullah[1], A. Hunter[1], S. Mccaslin[1], E. Lyden[1], L. Smith[1], M. Callahan[1], K.E Cole[1], J. Armitage[1], S. Hinrichs[1], J. Talmadge[1], J. Vose[1]

[1]University of Nebraska Medical Center, Omaha, United States, [2]Aurora Health Care, Milwaukee, United States

Background: The primary limitations to successful allogeneic hematopoietic stem cell transplantation (AHSCT) are relapse and non-relapse mortality (NRM). The later is primarily driven by graft versus host disease (GVHD). Despite multiple phase III trials documenting the efficacy of rabbit anti-thymocyte globulin (ATG) in preventing both acute and chronic GVHD, there is no clear survival benefit. It is believed that ATG given over 3-4 days before transplant may result in excessive graft T-cell depletion, delayed immune reconstitution, resulting in a higher risk of infection and relapse. Recent data has shown that residual host T-cells play an important role in acute GVHD pathology. We adopted a new dosing strategy, which focused most of ATG bioactivity towards host immune cell depletion.

Methods: This is a retrospective analysis of clinical and immunologic outcomes for 55 consecutive AHSCT patients (Pts) who received Thymoglobulin (ATG) between January 2020 and March 2021. 80% of the ATG dose (total of 5.5 mg/kg) was given early in the preparative regimen on days -6, -5, -4, and 20% on day -1. Pts received tacrolimus (0.03 mg/kg) and mini methotrexate 5mg/m^2 on days +1, +3, +6, +11 post-transplant for GVHD prevention. The graft was HLA matched peripheral blood stem cells from related or unrelated donors. Preparative regimen was reduced intensity Fludarabine(Flu)/ Busulfan(Bu)/ TBI (total body irradiation 200 rad) in 70% of Pts, and myeloablative Bu/Flu or Cyclophosphamide/TBI (1200 rad) in 30%. We analyzed day 30 and 100 post-transplant immune reconstitution phenotypes for 49 Pts.

Results: Disease diagnoses included AML, MPN, MDS, and ALL.98% of Pts had high or intermediate risk for relapse based on disease risk index, and 64% had a high transplant comorbidity index (≥3). The median age was 61(32-75) years, with 40% of the pts ≥65 years old. The cumulative incidence(CI) of all clinical outcomes is at 1 year post transplant. CI of grades III/IV aGVHD was 0. CI of grade II aGVHD was 94%(95% confidence interval 87-100%), 83% of which was upper gastrointestinal (GI) +/− skin(<50% body surface area). CI of lower GI aGVHD was 18% (10-34%). The CI of cGVHD was 2%(0.3-12%; NIH 2015 consensus criteria). The median follow-up for surviving Pts is 10 months (6-20 months). The CI of NRM was 11%(5-22%) for all the pts, and 2% for pts <70 years of age. CI of CMV viremia was 29%(18-47%), EBV 7%(2-17). The CI of relapse was 20%(12-35%). One year overall survival, relapse free survival, and cGVHD/relapse free survival (GRFS) was 75%(60-85%), 69%(54- 80%) and 67%(52-78%) respectively. We observed a favorable reconstitution of CD4, CD8, total NK cell numbers, and mature NK proportions compared to published literature. In addition, we report for the first time a correlation between increased frequency of day 30 CD8 + CD57 + and CD8 + CD16 + T-cells with no relapse at one-year post-transplant in a univariate and multivariate analysis. Pts with CD8 + CD57 + and CD8 + CD16 + T-cells above 57% & 32% (of total CD8) respectively, did not relapse.

Conclusions: This simple and novel GVHD prevention platform shows encouraging clinical outcomes with exciting surrogate immunologic markers supporting of early GVL.

Disclosure: No disclosures.

P380

Combination of ruxolitinib and interferon α-2b is effective for treatment of relapse or minimal residual disease after ALLO-SCT: Phase i/ii study of nct02185261 and nct02568241

M. Lv[1], X.-D. Mo[1], Y.-Y. Zhang[1], T.-T. Han[1], Y.-J. Chang[1], Y.-Q. Sun[1], Y. Wang[1], X.-H. Zhang[1], L.-P. Xu[1], K.-Y. Liu[1], X.-J. Huang[1]

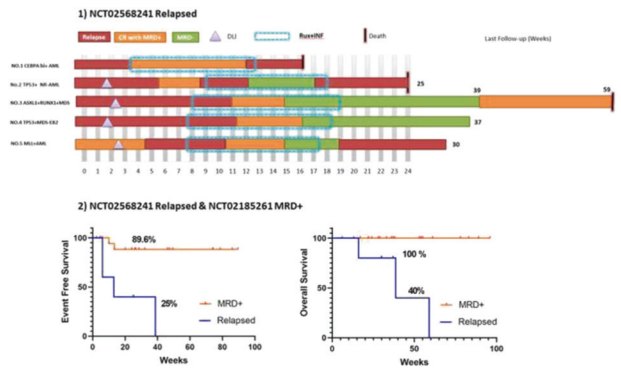
[1]Peking University People's Hospital, Beijing, China

Background: Interferon α-2b is effective for preventing relapse of acute leukemia. We investigated the safety and efficacy of new combination with ruxolitinib and interferon α-2b for relapse or minimal or measurable residual disease (MRD) after allogeneic stem cell transplantation.

Methods: Patients with relapse status (NCT02568241) or positive MRD (NCT02185261) are enrolled to receive intervention after day 60 post all-SCT: 1) Interferon α-2b (subcutaneously at dosages of 3 million units 2-3 times per week) for 8 weeks in the absence of disease progression or unacceptable toxicity/GVHD; 2) ruxolitinib (Jakafi) taken orally 5mg Bid. MRD is defined as reemerged fusion gene (≥0.1% for core binding factor) or LAIPs by flow cytometry. Overall response rate (ORR) is defined as patients who get complete remission, or with lower MRD (negative or at least 10-fold-reduction of fusion genes). MAGIC or NIH criteria was applied to evaluate acute or chronic GVHD. Event free survival(EFS) is defined as survival without relapse, mortality, or progression of MRD.

Results: In the present phase I/II study between Feb 2020 to Oct 2021, consecutive patients after allo-SCT (n = 26, 5 Rel and 21 MRD +), including AML (n = 21, Rel 3 and 18 MRD +), Ph-ALL (MRD + , n = 3) and MDS (Rel, n = 2) were enrolled. 23 and 3 patients received SCT from haplo and MSD, respectively. The median follow-up was 9 months. The median time of intervention was 10 weeks (range: 1-20). The incidence of grade-II aGVHD is 11.5% (n = 3) which resulted in discontinued Interferon, while III-IV aGVHD was absent. NIH mild, moderate, severe cGVHD occurred in 15.3%, 7.7% and 11.5% of enrolled patients. The GVHD related mortality was absent. All the relapsed patients (n = 5, 4 MRD- and 1 CR with MRD +) and 95.2% MRD + patients (n = 20, 18 MRD- and 2 ten-fold-reduction) responded to the intervention respectively. However, 4 relapsed patients experienced progression at 6, 6, 13 and 39 weeks after response (HLA loss n = 3), while the fusion gene of one MRD + patient increased over ten-fold at 10 weeks after response. The sustained response rate was 20% for relapsed or 90.5% for MRD + patients, respectively.

Trial		NCT02568241	NCT02185261
Enrolled time post allo-SCT: months median(range)		13.4(3.6-73.5)	4.1(2.9-26.3)
DLI within 2 months % (n)		100% (n = 5)	23.8% (n = 5)
Intervention weeks		10(9-16)	10(1-22)
ORR % (n)		100%(n = 5)	95.2%(n = 18)
ORR weeks median(range)		3(2-4)	3(2-7)
Best Response	MRD-	80%(n = 4)	85.7% (n = 18)
Best Response	CR with MRD reduction	20%(n = 1)	9.5% (n = 2)
Best Response weeks median(range)		6(3-9)	5(2-18)
Maintaining Response weeks median(range)		13 (6-38.7)	28 (3-90)



Conclusions: Our results suggested that combination of ruxolitinib and interferon α-2b can be effective for relapse or MRD after allo-SCT without increasing risk of GVHD compared to interferon α-2b alone. Considering HLA loss frequently lead to treatment failure for relapsed leukemia, patients might be bridged to 2nd SCT after intervention.

Clinical Trial Registry: NCT02185261; NCT02568241

Disclosure: Nothing to declare

P381

Assessment of SARS-CoV-2 specific t-cell response in immunocompromised patients failing to seroconvert in response to sars-cov-2 vaccine

E. Wiercinska[1], A. Jarisch[2], S. Daqiq-Mirdad[1], H. Hellstern[1], S. Ajib[3], A. Cremer[3], N.T.T. Nguyen[3], A. Dukat[4], E. Ullrich[5,6,7], S. Ciesek[8], K.-U. Chow[4], H. Serve[3,6,7], E. Seifried[1], P. Bader[2], H. Boenig[1,9], G. Bug[3,6,7]

[1]Institute for Transfusion Medicine and Immunohematology of Goethe University and German Red Cross Blood Service, Frankfurt am Main, Germany, [2]Goethe University Frankfurt, Frankfurt am Main, Germany, [4]Outpatient Cancer Clinic AKS Schaubstraße, Frankfurt am Main, Germany, [5]Goethe University Frankfurt, Frankfurt, Germany, [6]Frankfurt Cancer Institute (FCI), Goethe University, Frankfurt am Main, Germany, [7]German Cancer Consortium (DKTK), partner site Frankfurt/Mainz, and German Cancer Research Center (DKFZ), Frankfurt am Main, Germany, [8]Goethe University Frankfurt, Institute for Medical Virology, Frankfurt am Main, Germany, [9]University of Washington, Seattle, United States

Background: Immunocompromised patients, including patients after allogeneic hematopoietic stem cell transplantation (HSCT), are at excessive risk for severe SARS-CoV-2 infection and were therefore assigned priority for SARS-CoV-2 vaccination. As not all patients developed specific vaccination antibodies, we aimed to assess induction of S1 domain of spike protein-specific (S1-specific) T-cell responses in order to distinguish whether seronegative patients had an isolated B-cell or a more global adaptive immune incompetence.

Methods: In our study, we included 17 patients after allogeneic HSCT remaining anti-spike protein antibody-negative after double-vaccination with the BioNTech/Pfizer mRNA vaccine Comirnaty (n = 13) or AstraZeneca vector vaccine Vaxzevria (n = 4). Enumeration of SARS-CoV-2 specific T-cells was performed using SARS-CoV-2 T-cell Analysis Kit (Whole Blood, Miltenyi Biotech). T-cell responses to a TCR-MHC-cross-linking reagent (positive stimulation control) and an S1 peptide library were measured at a median of 55 days (range, 21-127) after the second vaccination and compared to similarly vaccinated patients with malignant B-cell lymphomas and iatrogenic B-cell aplasia (n = 5) or healthy controls (n = 22).

	HSCT cohort	NHL cohort
Age (median, range) years	58(19-73)	57(29-72)
Sex (male/female) (n, %)	10(59)/7(41)	3(60)/2(40)
Diagnosis (n)	AML/ ALL(14), MDS/MPN(3)	NHL(4), monoclonal gammopathy(1)
Prior CAR T-cell therapy (n, %)	2(12)	0
Anti-CD20/22 mAb therapy within 6 months prior to vaccination (n, %)	3(18)	5(100)
GVHD status at vaccination (n, %)		
- no active GVHD	5(29)	
- late onset acute GVHD (grade 2)	2(12)	
- chronic GVHD (moderate/ severe)	10(1/9), (59)	

Results: At the time of vaccination, 16/17 patients were more than six months out from their HSCT (median 47, range 5-1409 months) from a matched sibling (n = 6) or at least 9/10 HLA matched unrelated donor (n = 11) using T-cell depletion in 11 (65%) patients. B-cells were detected in 14/17 and numerically normal in 10/17 patients. CD8 + T-cell counts were at least normal in 16/17 patients, but absolute CD4 + helper cell lymphopenia was prevalent (14/17) and even in the three patients where CD4 + cell counts were low-normal, CD4:CD8 ratios were skewed in favor of cytotoxic T-cells. Seven/17 seronegative transplanted patients had mounted a CD4 (n = 2), a CD8 (n = 4) or both a CD4 and CD8 response (n = 1) to S1 peptide pool. Of note, all three patients with B-cell aplasia due to previous anti-CD19 CAR T-cell therapy (n = 2) or B-cell depleting post-transplant therapy for EBV reactivation (n = 1) were among the seven T-cell responders. We further distinguished patients receiving systemic immunosuppressive therapy („IS") or not („no IS") concurrent to the vaccination. Four/12 IS and 3/5 no IS patients generated spike-protein specific T-cells at least in one of the T-cell subtypes with no difference between groups. For comparison, 5/5 lymphoma patients had T-cell responses, 4/5 in both CD4 and CD8, 1/5 only in CD4 subsets. Similarly, 20/22 healthy volunteers harbored CD4, 16/22 CD8 cells responding to S1 peptide.

Conclusions: We conclude that isolated T-cell responses after SARS-CoV-2 mRNA or vector vaccine occur, albeit relatively less frequently after HSCT than in patients receiving specifically B-cell-targeted therapies.

Disclosure: Nothing to declare

P382

Immune reconstitution following basiliximab treatment for steroid-refractory acute graft-versus-host disease after haploidentical hematopoietic stem cell transplantation

D.-X. Deng[1], S. Fan[1], M.-Z. Shen[1], X.-H. Zhang[1], L.-P. Xu[1], Y. Wang[1], C.-H. Yan[1], H. Chen[1], Y.-H. Chen[1], W. Han[1], F.-R. Wang[1], J.-Z. Wang[1], K.-Y. Liu[1], X.-J. Huang[1], X.-D. Mo[1]

[1]Peking University People's Hospital, Beijing, China

Background: Immune reconstitution (IR) is important for long term survivors after allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, the characteristics and evolution of IR in steroid-refractory acute graft-versus-host disease (SR-aGVHD) human leukocyte antigen haploidentical donor (HID) patients were unknown. Thus, we aimed to identify the characteristics and evolution of IR in SR-aGVHD patients receiving basiliximab treatment after HID HSCT.

Methods: Consecutive HID HSCT recipients achieving overall response (ORR) after basiliximab treatment for SR-aGVHD at the Peking University Institute of Hematology from January 2016 to December 2018 were enrolled in this study. Immune cell subsets were identified and measured by multiparameter flow cytometry at 3, 6, 9, and 12 months following allo-HSCT. This work was supported by the Foundation for Innovative Research Groups of the National Natural Science Foundation of China (grant number 81621001), CAMS Innovation Fund for Medical Sciences (CIFMS) (grant number 2019-I2M-5-034), the Program of the National Natural Science Foundation of China (grant number 82170208), the Key Program of the National Natural Science Foundation of China (grant number 81930004), and the Fundamental Research Funds for the Central Universities.

Results:

A total of 179, 124, 80 and 92 patients were included in the analysis for IR at 3, 6, 9, 12 months, respectively, after HID HSCT. A total of 399 and 76 patients received < 5 doses and ≥ 5 doses of basiliximab, respectively. We observed that (1) IR was fast for monocytes and CD8 + T cells, intermediate for lymphocytes, CD3 + T cells, and CD19 + B cells, and very slow for CD4 + T cells in the whole cohort; (2) almost all immune cell subsets recovered comparably between patients receiving < 5 doses and ≥ 5 doses of basiliximab; (3) most immune cell subsets recovered comparably between SR-aGVHD patients receiving basiliximab treatment and those without aGVHD; (4) all immune cell subsets except CD4 + T cells achieved comparable level with healthy donor within 1 year after HID HSCT. Kinetics of immune reconstitution in SR-aGVHD HID patients receiving basiliximab treatment. Data are showed as median absolute counts with error bars indicating 25th–75th percentiles. The horizontal dotted lines represent the median value of healthy cohorts, and the gray areas represent the 25th–75th percentiles for the healthy cohorts. *P < 0.05, **P < 0.01, basiliximab low dose (< 5 doses) vs. basiliximab high dose (≥5 doses)

Conclusions: In conclusion, most immune cells recovered rapidly in SR-aGVHD HID patients achieving ORR after basiliximab treatment, which was comparable with those without aGVHD after HID HSCT. Thus, basiliximab treatment may not seriously impact the IR of SR-aGVHD patients.

Disclosure: Nothing to declare

P383

Highly-sensitive chimerism analysis in blood after allogeneic hematopoietic cell transplantation in childhood leukemia: Results from the nordic microchimerism study

A.K. Haugaard[1], H.O. Madsen[1], T.N. Masmas[1], K. Vettenranta[2], J. Buechner[3], K. Mellgren[4], D. Turkiewicz[5], S. Rosthøj[6], H.V. Marquart[1], C. Heilmann[1], K.G. Müller[1], M. Ifversen[1]

[1]Copenhagen University Hospital Rigshospitalet, Copenhagen Ø, Denmark, [2]Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland, [3]Oslo University Hospital, Oslo, Norway, [4]Sahlgrenska University Hospital, Gothenburg University, Gothenburg, Sweden, [5]Skåne University Hospital Lund, Skåne, Sweden, [6]University of Copenhagen, Copenhagen, Denmark

Background: Relapse remains the primary treatment failure after HCT for acute childhood leukaemia. Analysis of chimerism in blood post-HCT using STR-PCR is routinely applied in parallel with quantification of MRD to monitor for relapse. Real time quantitative PCR (RQ-PCR) chimerism is 10- to 100-fold more sensitive than STR-PCR, but clinical studies in children are sparse. We aimed to analyse the clinical applicability of the method by two different cut-offs.

Methods: This prospective multicenter study was performed in 64 children consecutively transplanted for leukemia between December 2014 and March 2018 at the paediatric transplant centres in Copenhagen, Denmark, Helsinki, Oslo, Gothenburg, and Lund. RQ-PCR chimerism was performed using a commercial kit (KMRtype/track, GenDx, Utrecht, Netherlands). Increasing mixed chimerism (IMC) was defined based on results in a seperate study as a minimum increase of either 0.1% or 0.05% recipient DNA between two samples or a ≥ 10-fold increase. Samples closer than 30 days to diagnosis of relapse were omitted. Endpoints were overt and molecular relapse.

Results: In total, 986 samples of whole blood DNA were analyzed, with a median of 15 (1-23) samples per child. Sixty samples from 27 children had IMC ≥ 0.1%, and 107 samples from 40 children had an IMC ≥ 0.05% recipient DNA. The risk of relapse was higher in children with IMC of both 0.1% and 0.05% compared to children without IMC (27.8 (95% CI 4.4-175.8; P < .001), and 18.4 (95% CI 2.8-120.5; P = 0.002), respectively). From the date of IMC, the 3-year CI of relapse or MRD-positivity

was 26.7% (CI 9.4-47.0) and 18.5% (6.4-35.3) for IMC ≥ 0.1% (n = 27) and ≥ 0.05% (n = 40), respectively. In the subset of children without an IMC ≥ 0.1% and ≥ 0.05%, CI of relapse or molecular relapse were 10.8% (3.4 -23.3) and 16.7% (5.0 -34.1), respectively. In all cases with a relapse undetectable by IMC, standard chimerism and MRD both remained negative prior to relapse. In a landmark analysis, neither an IMC ≥ 0.1% nor ≥ 0.05% prior to 90 days post-HCT was significantly associated with relapse Of six children with detectable MRD during follow-up, one progressed to overt relapse, two received donor lymphocyte infusions and are in complete remission and three had only a transient MRD below 10^{-3} and are in complete remission.

Conclusions: We confirm that by RQ-PCR chimerism analysis, one IMC is associated with a higher risk of relapse and two IMCs imply a poor outcome. These results indicate that serial monitoring of RQ-PCR chimerism in peripheral blood post-HCT may be a useful analysis rather than STR-PCR chimerism and might allow for fewer bone marrow analyses. Using an IMC ≥ 0.05% provided no benefits compared to ≥ 0.1% but entailed more false positive results.

Disclosure: Anna Karen Haugaard: reagents for this study were available at a discounted rate from GenDx, Utrecht, The Netherlands. All other authors: Nothing to declare.

P384

NGS-based verification of low mrd positivity is highly specific in prediction of relapse in post-transplant all patients

M. Svaton[1,2], K. Seferna[1,2], A. Rennerova[1,2], A. Skotnicova[1,2], L. Reznickova[1,2], P. Sedlacek[1,2], P. Riha[1,2], R. Formankova[1,2], P. Keslova[1,2], V. Valkova[3,4], L. Sramkova[1,2], J. Stary[1,2], J. Zuna[1,2], J. Horakova[5,6], A. Kolenova[5,6], C. Salek[3,4], J. Trka[1,2], E. Fronkova[1,2]

[1]CLIP – Childhood Leukaemia Investigation Prague, Charles University and University Hospital Motol, Prague, Czech Republic, [2]Charles University and University Hospital Motol, Prague, Czech Republic, [3]Institute of Haematology and Blood Transfusion, Prague, Czech Republic, [4]Institute of Clinical and Experimental Haematology, First Faculty of Medicine, Charles University, Prague, Czech Republic, [5]Comenius University Medical School, Bratislava, Slovakia, [6]University Children's Hospital, Bratislava, Slovakia

Background: In patients transplanted for acute lymphoblastic leukemia (ALL), decisions about early therapy intensification are based on minimal residual disease (MRD) levels. MRD testing via quantitative PCR (qPCR) using clone-specific immunoglobulin (Ig) and T-cell (TR) receptor gene rearrangements is a standard for MRD detection in ALL and is the most widespread method for post-transplant MRD monitoring. We have previously shown that MRD detection using Ig/TR monitoring via next-generation sequencing (NGS) is more specific than qPCR (Kotrová, BMT 2017). Since then, NGS-MRD detection has been standardized within the EuroClonality-NGS consortium. In the current study, we investigated the clinical outcome of prospectively verifying positive non-quantifiable (PnQ) qPCR results via NGS-MRD.

Methods: Sequential post-transplant MRD monitoring in pediatric and young adult ALL patients after hematopoietic stem cell transplantation (HSCT) was performed in our facility for patients from 4 transplant centers in the Czech Republic and Slovakia. For qPCR-MRD monitoring, we used the standardized EuroMRD approach. For NGS-MRD we used the EuroClonality-NGS protocols for library preparation (Brüggemann, Kotrova, Leukemia 2019). The qPCR products with PnQ result were first retested for length using Agilent-on-a-chip analysis (Fronkova, BMT 2008) and if the length did not match the diagnostic sample, the qPCR results were concluded as negative. In cases with irresolvable or unavailable PCR products size comparison, the results were reported as positive according to the EuroMRD criteria and further retesting via NGS was performed.

Results: In total, we reevaluated MRD via NGS in 26 patients. In 8 patients (31%), the results were confirmed as positive using NGS and reported to clinicians. Out of these 8 patients, 5 relapsed despite therapeutic efforts to avert relapse (median time to relapse: 2 months). All 3 patients positive by NGS who did not progress to relapse had immunosuppressive treatment (IST) reduced and one received 4 doses of donor lymphocyte infusions (DLI) in reaction to the qPCR-detected positivity. One patient died of GvHD reactivation after IST withdrawal. Among the 17 patients identified as negative by NGS, only one relapse occurred (5 months after testing), despite the fact that only in 5 NGS-negative patients therapy was intensified (IST reduction) on the basis of the qPCR result (including the patient who progressed to relapse, who also received 2 doses of DLI). In one patient (who did not relapse), NGS testing was evaluated as inconclusive due to low sensitivity.

Conclusions: Ig/TR monitoring via qPCR still represents the most cost-effective and time-efficient method for post-transplant MRD monitoring. Although the NGS method has comparable cost-efficiency to qPCR, its main challenge remains the longer turnaround time, depending on the laboratory throughput. In our study, we confirmed that the NGS method is more specific for discerning low positive MRD from background in physiological lymphocytes and thus more reliable for clinical decisions. The combination of qPCR measurements and subsequent verification of low positive results via NGS appears to be the safest method for post-transplant MRD-guided clinical decision-making.

Supported by NU20-03-00284 and GA UK 318321.

Disclosure: Nothing to declare

P385

Post-transplant day +100 mrd detection rather than mixed chimerism predicts relapses after ALLO-SCT for intermediate risk AML patients transplanted in cr

E. Klyuchnikov[1], A. Badbaran[1], R. Massoud[1], P. Freiberger[1], F. Ayuk[1], C. Wolschke[1], U. Bacher[2], N. Kröger[1]

[1]University Cancer Center Hamburg-Eppendorf, Hamburg, Germany, [2]University of Bern, Bern, Switzerland

Background: Chimerism and minimal residual disease (MRD) were suggested to be predictive for relapses after allograft in AML patients (pts). Nevertheless, the predictive values of both approaches remain underinvestigated. Though several studies showed a significant correlation between mixed chimerism and relapses, some pts may require very frequent monitoring that may not be reliable in real-world practice. We suggest the post-transplant MRD may have a higher predictive value for relapses as chimerism and may lead to improved early relapse recognition in intermediate risk AML pts early after allograft.

Methods: 79 pts with intermediate risk AML (40 males, median age 57 years (19-77)) transplanted in CR during 2015-2020 at the University Cancer Center Hamburg-Eppendorf with available chimerism measurements during the first 100 days and post-transplant (day + 100) MRD data were included. Majority of the pts received allografts after MAC (75%) from MUD (50%). Post-transplant MRD detection on day +100 was performed in bone marrow according to ELN guidelines (flow, n = 79; qPCR, n = 25). Sensitivities were $10^{-4}/10^{-5}$ (flow) and 10^{-6} (qPCR). Chimerism analysis was performed in peripheral blood samples at least once per week based on deletion/insertion polymorphisms for duplex analysis combined with a reference gene or Y-chromosome specific PCR (sensitivity 10^{-4}). Full donor chimerism (FDC) was

defined as persistence of ≥99.9% of donor alleles; mixed chimerism (MC) was defined as persistence of <99.9% of donor alleles during the first 100 days post-transplant.

Results: Day +100 flow-MRD status correlated both with qPCR-MRD status (neg/neg: 89% vs pos/pos: 57%, p = 0.032) and with chimerism dynamics (neg/FDC: 70% vs pos/MC: 65%, p = 0.005). The concordances between flow-MRD/qPCR-MRD; qPCR-MRD/chimerism dynamics; and flow-MRD/chimerism dynamics were 80% (20/25), 56% (14/25), and 39% (54/79), respectively. The relapses at 3 years was 21% (13-32%) with a median of 216 days (98-722). MC (n = 32) had unfavourable impact on relapses (HR 3.2, 1.1-9.5, 0.038) and LFS (HR 2.8, 1.1-6.8, p = 0.027) compared to FDC (n = 47). Day +100 flow- and qPCR-MRD negativity had favorable impact on relapses (HR 0.1, 0.02-0.3, p < 0.001 and HR 0.02, 0.01-0.3, p = 0.0023, respectively) and OS (HR 0.1, 0.04-0.4, p = 0.001 and HR 0.1, 0.01-0.4, p = 0.004, respectively).

qPCR-MRD showed the highest sensitivity and specificity for relapses (86% and 100%) followed by flow-MRD (70% and 85%), and MC (60% and 34%). Also, positive-predictive and negative-predictive values were highest for qPCR-MRD (100% and 95%), followed by flow-MRD (83% and 79%) and MC (38% and 83%). The area under the ROC curve was highest for qPCR-MRD (0.93, 77-100%, p = 0.001) followed by flow-MRD (0.70, 46-95%, p = 0.13) and MC (0.55, 29-81%, p = 0.72). Day +100 flow-MRD negative pts with MC (n = 17) experienced significantly lower relapse rate at 1 year (6% vs 67%, p = 0.003) and higher 1-y LFS (81% vs 48%, p = 0.017) comparing to positive ones (n = 15).

Conclusions: Molecular and flow MRD measurements at day +100 have a stronger predictivity for post-transplant relapses compared to early chimerism dynamics in intermediate risk AML. Intensified MRD monitoring early post-transplant together with chimerism studies may improve the identification of AML pts with increased relapse risk who may be candidates for early post-transplant interventions.

Disclosure: Nothing to declare

P386

Clinical characteristics and outcome analysis for HLA loss patients between myeloid and lymphoid malignancies by next-generation sequencing

A. Wang[1], W. Li[2], F. Zhao[3], Q. He[4], T. Yang[5], S. Wang[6], J. Yan[7], J. Lan[8], S. Fan[9], M. Zhao[10], J. Shen[11], X. Li[12], T. Yang[13], Q. Lu[14], Y. Lu[15], H. Bai[16], H. Zhang[17], D. Cai[18], L. Wang[19], Z. Yuan[4], E. Jiang[3], F. Zhou[2], X. Song[1,20]

[1]Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [2]No. 960 Hospital of People's Liberation Army, Jinan, China, [3]Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China, [4]Tissuebank Biotechnology Co., Ltd, Shanghai, China, [5]Fujian Medical University Union Hospital, Fuzhou, China, [6]920th Hospital of Joint Logistics Support Force, Kunming, China, [7]Liaoning Medical Center for Hematopoietic Stem Cell Transplantation, Second Hospital of Dalian Medical University, Dalian, China, [8]Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou, China, [9]The first affiliated hospital of Harbin Medical University, Harbin, China, [10]Tianjin First Central Hospital, Tianjin, China, [11]Zhejiang Provincial Hospital of Chinese Medicine, Hangzhou, China, [12]The Third Xiangya Hospital of Central South University, Changsha, China, [13]First People's Hospital of Yunnan Province, Kunming University of Science and Technology Affiliated Kun Hua Hospital, Kunming, China, [14]Zhongshan Hospital of Xiamen University, Xiamen, China, [15]the Affiliated People's Hospital of Ningbo University, Ningbo, China, [16]The 940th Hospital of the Joint Logistic Support Force of PLA, Lanzhou, China, [17]Linyi People's Hospital, Linyi, China, [18]The First Hospital of China Medical University, Shenyang, China, [19]Affiliated Qingdao Central Hospital, Qingdao University, Qingdao, China, [20]Engineering Technology Research Center of Cell Therapy and Clinical Translation, Shanghai Science and Technology Committee (STCSM), Shanghai, China

Background: Genomic loss of mismatched HLA (HLA loss) is a vital immune escape mechanism of leukemic cells after hematopoietic stem cell transplantation (HSCT). However, limited literature has been published, especially in lymphoid malignancies. The methods currently used for HLA loss detection have some limitations.

Methods: 162 post-transplant patients from 18 centers in China were selected out for this study. HLA loss analysis was performed with HLA-KMR and next-generation sequencing (NGS)-based methods. Variables of the prognostic risk factors for HLA loss or HLA loss relapse were examined in the proportional hazards model or competing risk regression model.

Results: An HLA loss detection system, HLA-CLN (HLA chimerism for loss of heterozygosity [LOH] analysis by NGS), was successfully developed. To our knowledge, the largest scale of 40 (24.7%) patients with HLA loss was reported including 27 with myeloid and 13 with lymphoid malignancies, whereas 6/40 (15.0%) did not relapse. The 2-year cumulative incidences of HLA loss (22.7% *vs* 22.0%, $P = 0.731$) and HLA loss relapse (18.4% *vs* 22.0%, $P = 0.571$) were similar between patients with myeloid and lymphoid malignancies in partially mismatched related donor (MMRD) transplantation. The genomic loss of both HLA I and II loci occurred in 82.5% of patients (33/40). The number of HLA mismatches (5/10 *vs* < 5/10) was significantly associated with HLA loss in the whole cohort (HR: 3.15, $P = 0.021$) and myeloid malignancies (HR: 3.94, $P = 0.021$). A higher refined-disease risk index (HR: 6.91, $P = 0.033$) and donor-recipient ABO incompatibility (HR: 4.58, $P = 0.057$) contributed to HLA loss in lymphoid malignancies.

Conclusions: HLA-CLN system for HLA loss detection could cover a higher percentage of patients and have a broader range of clinical applications with a higher accuracy. With the new system, the largest scale of 40 HLA loss patients was reported. The cumulative incidence of HLA loss and other clinical characteristics were similar between patients with lymphoid and myeloid malignancies. The results suggested that a patient with HLA loss was not necessary to relapse.

Disclosure: Nothing to declare.

P387

Sequential conditioning in npm1 positive AML with measurable residual disease pre-transplant might overcome negative impact of residual leukemia

A. Fraccaroli[1], E. Stauffer[1], H. Drolle[1], M. von Bergwelt[1], K. Spiekermann[1], T. Herold[1], J. Tischer[1]

[1]University Hospital Munich, Munich, Germany

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) offers the best chance for relapse-free long-term survival for most patients with acute myeloid leukemia (AML). Thereby, sequential conditioning regimens are successfully used for high-risk disease. Presence of measurable residual disease (MRD) at time of allo-HSCT has recently been shown to be associated with an increased risk of relapse post-transplant. Yet, the reported effect might vary according to genetic and immunophenotypic diversity of the disease, as well as transplant-setting and MRD method. The negative impact might be overcome with sequential therapy in MRD positive patients.

Here, we aim to determine the impact of *NPM1*-MRD assessed by qPCR on outcome in a homogeneous patient cohort undergoing sequential conditioning.

Methods: We retrospectively analyzed sixty adult AML patients harboring *NPM1* mutations, who underwent a first allo-HSCT from a matched sibling (n = 17), unrelated donor (n = 26), or HLA-haploidentical family donor (n = 17). All patients were transplanted between January 2015 and November 2021 at our institution. Sequential conditioning using FLAMSA-RIC was the treatment of choice for patients transplanted with either active disease, evidence of molecular marker or high-risk cytogenetics. Nine patients deemed ineligible for sequential treatment due to age or comorbidity. *NPM1*mutation status was assessed at diagnosis and monitored by qPCR throughout the treatment course. MRD status pre-transplant was correlated with outcome.

Results: Sixty patients had an initial diagnosis of *NPM1*-positive AML (secondary AML n = 15) of whom forty-two were in complete remission (CR)1 or CR2 and eighteen had active disease (primary refractory or relapsed AML) at time of allo-HSCT. Whereas forty-six patients had cytogenetically normal AML, three had a complex karyotype. At diagnosis twenty-one patients were classified as favorable according to ELN risk stratification, thirty-three as intermediate and six as adverse. Median age of the entire cohort was 56 years (21-75). No graft rejection occurred. At a median follow up of 27 months (range 0,6 – 79) the estimated probability of overall survival (OS) and leukemia-free survival (LFS) at 1- and 2-years was 88% and 67% and 70% and 63%, respectively. If stratified in patients transplanted in any remission vs non-remission, there was a trend towards better OS and LFS at one year for patients in CR and molecular CR (molCR) in comparison to non-remission patients (OS 82% and 83% vs 64%; p = 0.07; LFS 74% and 75% vs. 61%; p = 0.21). Yet, if considering only patients in remission (n = 42) no difference could be detected depending on *NPM1*-MRD status at transplantation (OS p = 0.46 and LFS p = 0.6). Cumulative incidence (CI) of non-relapse mortality (NRM) at 1-year was 11%, 0% and 0% for CR, molCR and nonCR patients, respectively (p = 0.97), whereas CI of relapse was 15%, 25% and 36% within the first year (p = 0.18).

Conclusions: Sequential conditioning improved disease control and survival in patients transplanted with *NPM1*-positive AML, regardless of pretransplant MRD status assessed with qPCR, in this single-center study.

Disclosure: Nothing to declare.

P388

The pattern of immune reconstitution determines the survival at three months and the development of chronic graft-versus host disease in allo-hsct

V. Gómez García de Soria[1], P. Díaz Fernández[1], I. García-Calvillo Zapatero[1], Y. Pérez García[1], I. Portero Sainz[1], S. Feijóo Monroy[1], C. Muñoz Calleja[1]

[1]Instituto de Investigación H.U. La Princesa. Universidad Autónoma de Madrid, Madrid, Spain

Background: The pattern and quality of the immune reconstitution (IR) from the long-lasting immunodeficiency after transplantation may affect the outcome of hematopoietic allogeneic stem cell transplantation (allo-HSCT). However, there are limited data on the association of the quality of the IR on either the development of graft vs host disease (GvHD) or survival.

We therefore aimed to explore the factors conditioning the IR and its impact on survival, and on the development of GvHD.

Methods: To this end, 163 patients who received a non T-cell depleted allo-HSCT in our center from 2011 to 2019 were prospectively studied. Acute and chronic GVHD were diagnosed according to published criteria. Lymphocyte immunophenotyping was performed on fresh whole blood by flow cytometry to quantify total CD4 + and CD8 + T cells and their subsets: naïve, stem cell-like, memory central, effector memory and CD45RA + effector memory cells. Data were collected at days +30, +60, +90, +180 and +365 after allo-HSCT.

The association between pretransplant factors and the IR was studied with ANOVA followed by a Bonferroni test. The association between IR and either the survival or the development of GvHD was studied through generalized estimating equation (GEE) models which included the confounding variables with $p < 0.10$ in the multivariate GEE models.

Results: The absolute counts of CD3 + T lymphocytes reached normal levels within six months. CD8 + T lymphocytes recovered much faster than CD4 + T cells and, after one month, the median CD8 + T cells count was within the normal range. Conversely, it took nearly one year for the CD4 + T cells to reach normal values. Recovery of the different subsets of CD4 + and CD8 + T cells followed the same pattern of their parent populations with the exception of naïve CD8 + T lymphocytes, which hardly recovered normal counts after one year.

Naïve and stem cell like CD4 + T cells were identified among the different lymphoid subsets whose reconstitution was strongly affected by the characteristics of the transplant. Their IR was particularly poor in non-identical HLA transplants, with the worst results for haploidentical transplants. Similarly, patients with myelodysplastic syndromes, acute myeloid leukemia and acute lymphoblast leukemia had a worse IR, probably because of a connection with myeloablative conditioning regimens.

Regarding the influence of IR in either survival or GvHD, multivariate GEE models showed that the recovery of the absolute number of total lymphocytes and CD3 + T lymphocytes determined the survival at 3 months. In the univariate models we found that higher numbers of CD8 + T cells and naïve CD8 + T cells were associated with survival at 3 months. Similarly, the recovery of CD4 + T cells was associated with a greater survival at 3, 6 and 12 months. Finally, a faster restoration of TEM CD4 + T cells was associated with the development of chronic GVHD in the multivariate analysis.

Conclusions: In conclusion, we identified IR variables that could be used as biomarkers for both the survival in the first 3 months and the development of chronic GvHD. Also this study can be the basis for therapeutic strategies to recover immune function.

Disclosure: Nothing to declare

P389

GVHD is associated with compromised reconstitution of b-cell precursors in the bone marrow following allogeneic HSCT

E.C. Peen[1], H.V. Marquart[1], C.H. Nielsen[1], K. Müller[1], K. Kielsen[1]

[1]Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

Background: The outcomes after allogeneic HSCT has improved significantly but is still challenged by the risk of GvHD and related infections that contributes substantially to morbidity and mortality. aGvHD has been shown to negatively impact B-cell reconstitution by targeting the bone marrow and disrupting the normal B cell ontogeny and/or through the immunosuppressant treatment given to control the disease. A delayed B-cell recovery and impaired B-cell immunity in peripheral blood have previously been described in patients with cGvHD, but the mechanisms are unclear and few studies have looked into the B-cell development in the bone marrow compartment.

In this study, we expand current insights by investigating the B-cell reconstitution in the bone marrow after pediatric HSCT and how this relates to alloreactivity.

Methods: We included 30 children undergoing HSCT for ALL (n = 19) or AML (n = 11) from 2015-2020 with a median age of 9.3 years (range: 3.1-16.6). All patients received myeloablative conditioning based on TBI (n = 12) or chemotherapy alone (n = 18). Patients received a bone marrow (n = 29) or peripheral blood stem cell (n = 1) graft from MSD (n = 8) or MUD donors (n = 22). GvHD prophylaxis consisted of cyclosporine A alone (n = 8) or in combination with methotrexate and ATG (n = 22). Fresh bone marrow samples were analyzed for specific B-cell subsets using flow cytometry at month +1, +2, +3, +6, +9, +12, +15 and +18 post-HSCT.

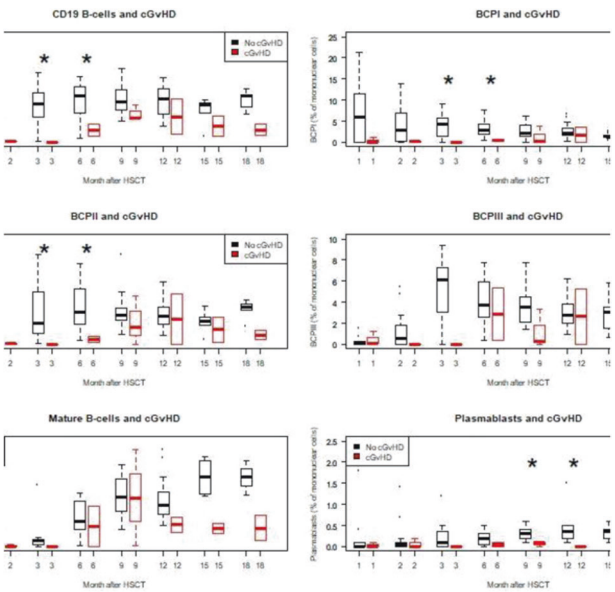
Results: The B-cell compartment mainly comprised naïve B-cell precursors stage I (BCPI) and BCPII cells during the first months post-transplant and was gradually replaced by more mature subsets, such as BCPIII, mature B-cells, and plasmablasts. The percentage of CD19 B-cells in the bone marrow correlated positively with the same-day CD19 B-cell concentration in peripheral blood from month +2 to +12 (r = 0.5-0.8, all $p < 0.05$).

TBI-based conditioning was associated with undetectable levels of plasmablasts in the bone marrow during the first three months following HSCT (p = 0.03-0.06), while a higher nucleated cell dose correlated positively with the percentage of CD19 B-cells including naïve and mature subsets (all $p < 0.05$). In patients with aGvHD grade II-IV (n = 15), development of the B-cell lineage appeared generally compromised in bone marrow samples, with reduced CD19 B-cells and BCPII cells at month +3 (both p = 0.03), and fewer plasmablasts from month +6 to +12 ($p \leq 0.05$).

In children developing extensive cGvHD (n = 3), B-cell reconstitution appeared considerably delayed with less CD19 B-cells and naïve B-cell subsets from month +2 to +6 and fewer plasmablasts from month +9 to +15 (Figure).

Patients treated with immunoglobulin-substitution (57.1%) (day 6-786) due to reduced immunoglobulin production post-transplant had significantly less CD19 B-cells at month +2 and +3 ($p < 0.05$), but not significantly reduced percentages of the other B-cell subsets.

Conclusions: Our findings suggest that alloreactivity following HSCT is associated with a delayed B-cell reconstitution in the bone marrow rather than a more targeted loss of specific B-cell precursors. Risk factors for impaired B-cell recovery include TBI-based conditioning and low numbers of transplanted donor cells. Further studies are warranted to further explore deficiencies in B-cell maturation and the potential for prediction of chronic GvHD based on B-cell monitoring.



Disclosure: None to declare.

P390

Identification of relationship between quantitative chimerism and npm1 positivity cut off, as predictive for haematological relapse in AML-npm1+ adult patients after allogeneic stem cell transplant

S.M. Muggianu[1], M. Celentano[1], S. Marotta[1], I. Migliaccio[1], M. Pedata[1], C. Riccardi[1], M. Caputo[1], R. Peluso[1], C. Falco[2], A. Viola[3], F. Ferrara[3], A. Picardi[1,4]

[1]Stem Cell Transplant Program, AORN A. Cardarelli, Napoli, Italy, [2]Collection Facility of Transplant Program, AORN A. Cardarelli, Napoli, Italy, [3]Hematology, AORN A. Cardarelli, Napoli, Italy, [4]Dep. of Biomedicine and prevention, Tor Vergata University, Rome, Italy

Background: Currently, the relapse after allogeneic stem cell transplantation (SCT) remains the main risk factor in term of transplant outcome of adult patients affected by Acute Myelogenous Leukemia (AML). However, although the detection of minimal residual disease (MRD) in AML patients after allogeneic SCT plays an important role, the cut off of NPM1 positivity related to haematological relapse is still unclear. The aim of this study was to analyze, prospectively, the correlation between NPM1 and recipient chimerism values, after allogeneic SCT in AML-NPM1 + adult patients, in order to identify a predictive cut off for haematological relapse

Methods: From June 2019 and December 2021, 57 allogeneic SCT were performed at AORN Cardarelli Single Transplant Program in Naples. Indication to allogeneic SCT was AML in 29 cases, of whom 14 NPM1 +, associated with FLT3-ITD + (N = 10) or TKD + (N = 2) in 12 cases. In this subset of patients, 7/14 were males, the median age was 42,5 (range 22-64), reduced conditioning regimen (RIC) was used in 6/14 allogeneic SCT procedures, the donor was an HLA identical sibling, haplo-identical or unrelated in 7,4 and 3 cases, respectively. Disease status at transplant was: 1st CR, 2nd CR or active disease in 10, 3 and 1 cases, respectively. RIC or myeloablative TBF conditioning regimen was used in all patients whereas GVHD prophylaxis depended on the donor's type. Overall, 258 bone marrow samples were analysed using quantitative RT-PCR to detect chimerism (N = 128), by insertion/deletion genomic biallelic polymorphisms, and type A NPM1 mutation (N = 130). In this study, the time points for monitoring quantitative chimerism and NPM1 mutation were: before allogenic SCT, as baseline values, every month along 24 months and, then, every 3 months until 5 years after allogeneic SCT

Results: Overall, 13 patients are alive and in complete remission after a median follow up of 18 months (range 1-30) while 1 died for relapse. Concerning the relationship between quantitative chimerism and NPM1 mutation, the analysis has shown that day +30 after allogeneic SCT is a too early time point not reliable for prognostic purpose. Conversely, time points included between day +60 and +180 show linear correlation between NPM1 and recipient chimerism with r-value very close to 1. Long term median follow up is necessary to evaluate recipient chimerism and NPM1 mutation relationship after day 180. Moreover, recipient chimerism>1% associated with NPM1 > 100 copies led to haematological relapse whereas the quantitative recipient chimerism value ≥1% with the NPM1 copies value included between 1 and 99 did not

Conclusions: The strict and contemporary monitoring and quantification of recipient chimerism and NPM1 mutation positivity, after allogeneic SCT, could led to a better selection of patients who can benefit from immunomodulation and relapse pre-emptive therapy. From these preliminary data, the association

between recipient chimerism>1% with NPM1 > 100 copies, may be identified as a risk factor for haematological relapse

Disclosure: Nothing to declare

P391

Immune-monitoring for virus-specific t-cell responses in allogeneic HSCT recipients: A survey from the ebmt cellular therapy & immunobiology working party

R. Greco[1], J. Hoogenboom[2], E. Bonneville[3], A. Anagnostopoulos[4], A. Cuoghi[5], J.-H. Dalle[6], A. Ganser[7], P. Lang[8], F. Locatelli[9], M. Martino[10], A. Maschan[11], C. Mauz-Körholz[12], M. Noviello[13], J. Passweg[14], J. Peccatori[1], M. Rovira[15], C. Solano[16], J.H. Veelken[17], A. Velardi[18], E.M. Wagner-Drouet[19], X. Zhang[20], F. Ciceri[21], C. Bonini[13], L. Vago[22], A. Ruggeri[1], C. Chabannon[23]

[1]Unit of Hematology and Bone Marrow Transplantation, IRCCS San Raffaele Hospital, Milano, Italy, [2]EBMT Leiden Study Unit, Leiden, Netherlands, [3]Leiden University Medical Center, Leiden, Netherlands, [4]George Papanicolaou General Hospital, Thessaloniki, Greece, [5]Azienda Ospedaliero Universitaria di Modena Policlinico, Modena, Italy, [6]Hôpital Robert Debre, Paris, France, [7]Hannover Medical School, Hannover, Germany, [8]University Hospital, Tuebingen, Germany, [9]IRRCS Ospedale Pediatrico Bambino Gesù, Rome, Sapienza, University of Rome, Rome, Italy, [10]Grande Ospedale Metropolitano Bianchi Melacrino Morelli - Centro Unico Trapianti A. Neri, Reggio Calabria, Italy, [11]Federal Research Center for Pediatric Hematology, Moscow, Russian Federation, [12]Justus-Liebig-University Giessen, Giessen, Germany, [13]Experimental Hematology Unit, Division of Immunology, Transplantation and Infectious Disease, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milano, Italy, [14]University Hospital, Basel, Switzerland, [15]ICMHO, IDIBAPS Hospital Clinic, Josep Carreras Institute, Barcelona, Spain, [16]Hospital Clínico de Valencia, Valencia, Spain, [17]Leiden University Hospital, Leiden, Netherlands, [18]Sezione di Ematologia, Perugia, Italy, [19]University Medical Center Mainz, Mainz, Germany, [20]Xinqiao Hospital of Army Medical University, Chongqing, China, [21]Unit of Hematology and Bone Marrow Transplantation, IRCCS San Raffaele Hospital; Vita-Salute San Raffaele University, Milano, Italy, [22]Unit of Immunogenetics, Leukemia Genomics and Immunobiology, Vita-Salute San Raffaele University, San Raffaele Scientific Institute, Milano, Italy, [23]Institut Paoli Calmettes, Marseille, France

Background: Post-transplant immune reconstitution plays a major role in determining the outcome of allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients. Immune cell counts provide only a general indication of the competence of the patient immune system, whereas the quantitative and functional assessment of virus-specific T-cell responses may be more relevant to patient's risk stratification and clinical decision-making. However, information is lacking about the current practice across centers.

Methods: In September 2021, the CTIWP conducted a survey across EBMT centers to identify current policies to monitor virus-specific immune reconstitution in patients undergoing allo-HSCT.

Results: Policies for post-transplant virus-specific immune monitoring have been reported by 152 (30%) EBMT centers, active in 37 countries. Centers perform allo-HSCT in adults only (43%), children only (26%) or both (31%), and use various donor sources (100% HLA-identical related, 94% matched unrelated, 99% mismatched related, 56% cord blood).

Although cytomegalovirus (CMV) viremia is monitored after allo-HSCT in all centers, 17 (11%) centers are currently testing CMV-specific T-cell responses, either within clinical (35%) and/or experimental practice. Flow-cytometry based tests (e.g. intracellular cytokines, MHC multimer binding), mainly set up in house, are used in 9/152 centers (6%) to assess CMV-specific T-cells. IFN-γ ELISpot is adopted in 15 (9.9%) centers, either with home-made or commercial assays. CMV Quantiferon is used in only 4 (2.6%) centers and mainly through commercial assays. Additionally, other home-made tests (e.g. proliferation assays or CMV specificities within different T-cell subsets) are rarely applied. Thresholds are not harmonized among centers.

Longitudinal monitoring for human herpesvirus 6 (HHV6) viremia in allo-HSCT recipients is performed in 45% of the centers, while 22% search for the virus only in case of clinical suspicion. Tests for HHV6-specific T-cell responses are reported by two centers, adopting home-made IFN-γ ELISpot or limiting dilution analysis for antigen-specific T-cells.

In 51% of the centers, adenovirus viremia was monitored in allo-HSCT recipients, whereas 32 (21%) centers only monitored in case of symptoms. Moreover, 8 centers check for adenovirus-specific T-cell responses, using different home-made or commercial assays (e.g. MHC multimer binding, intracellular cytokines, IFN-γ ELISpot, limiting dilution analysis), both as experimental and clinical practice. Frequencies of T cells specific for other viruses, mainly Epstein-Barr virus, are currently tested in 15 (9.9%) centers.

Overall, 21 (13.8%) centers are performing at least one type of virus-specific immune monitoring. Furthermore, 47 (31%) centers are planning to start monitoring for virus-specific immune responses in the future.

Conclusions: Immune monitoring for virus-specific T-cell responses is currently performed in a limited number of centers and is highly variable in terms of targets, technologies and interpretation. These results underline the need to harmonize and standardize methods, both for routine and investigational purposes, and to stimulate clinical curiosity questing for information. Monitoring of CMV-specific responses should probably be more widely adopted for its clinical value in the new era of letermovir prophylaxis. Overall, improved reporting and communication between centers adopting these technologies is needed to foster collaborative and comparative research studies in the future, which may translate into new immune monitoring guidelines.

Clinical Trial Registry: CTIWP survey EBMT study number 8420021

Disclosure: Nothing to declare.

P392

High-sensitive indel-qpcr chimerism to individualized post-HSCT follow-up in myeloid neoplasms

C. Ceballos[1,2], I. Múgica[1,2], J. Illarramendi[1,2], G. Gabaldón[1,2], A. Casamayor[1,2], R.J. Breeze[1,2], A. Jauregui[1], P. Arnedo[1], A.M. Redondo[1,2], M.T. Zudaire[1,2], M.C. Viguria[1,2], E. Bandrés[1,2]

[1]Hospital Universitario de Navarra, Pamplona, Spain, [2]Navarra Institute for Health Research (IdiSNA), Pamplona, Spain

Background: The relapse of malignant disease is one of the main complications of hematopoietic stem cell transplantation (HSCT) in myeloid neoplasms. Mixed chimerism (MC) is considered an important factor to predict relapse. Therefore, reliable detection is crucial for early diagnosis of relapse. The aim of this study is the evaluation of indel-qPCR non-classical chimerism analysis in peripheral blood to predict the outcome of patients with myeloid pathologies post-HSCT by individualized follow-up.

Methods: We monitored chimerism of 44 patients diagnosed of AML and MDS considering risk factors and clinical grounds. The analysis was performed by KMR Track kit (GeneDx) and

results was represented as host-DNA percentages. We defined complete chimerism (CC) as host-DNA percentage inferior to 0.05% and mixed chimerism as host-DNA percentage above this threshold.

Results: Our results show that the kinetic profile of chimerism is heterogeneous and could be influenced by different factors, such as the pre-transplant conditioning regimen. In our series, a statistical difference is only detected between RIC (reduced-intensity conditioning) and cyclophosphamide treatment after transplantation (PTCy) at day 30 post-HSCT. In patients without relapse or progression, CC is detected over a wide range of time, 30-240 days (median 144 days). In a group of 8 patients CC is detected at day +30 and of those, 75% (6/8) had been treated with PTCy.

Despite point values of chimerism not correlating with outcome, we observed an association between the evolution of the disease and three different kinetic profiles.

The first profile consists of 21 patients with CC (N = 2) or decreasing mixed chimerism (DMC) (N = 19) who achieved CC. Of this group, 71% (15/21) of patients have not relapsed after one year of follow-up and only one patient showed early MRD + despite detecting CC. Late relapse was observed in 23% of patients (5/21) with a median of 846 days post-HSCT. In 4/5 patients, continuous monitoring of chimerism allows to predict relapse by increasing of mixed chimerism (IMC).

The second profile consists of 3 patients with stable mixed chimerism (SC-MC) after HSCT. In 2/3 patients a late relapse is observed (400 and 800 days post-HSCT) and 1/3 no relapse is observed.

The last profile consists of 20 patients with IMC over time. Early relapse/progression is observed in 19/20 patients (median = 110 days post-HSCT).

Moreover, we observed that out of 25 relapsed patients, 52% had continuous IMC and died. Eventually, 24% achieved CC and 24% are still alive with MC.

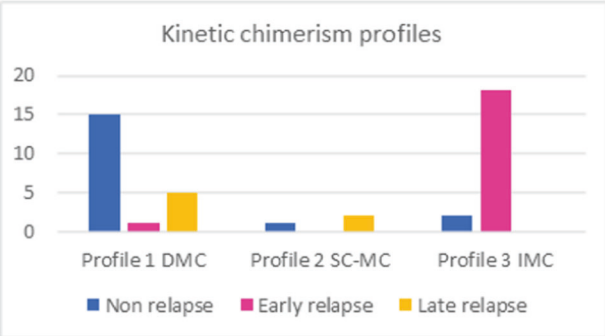


Figure 1. Association of early-relapse, late-relapse or non-relapse with chimerism kinetic profiles.

Conclusions: - Post-HSCT follow-up by means of chimerism must be carried out on an individualized basis according to the patient's evolution, just as it occurs in the transplant procedure.

- Our results show that despite the heterogeneity of chimerism, three different kinetic profiles correlate with disease progression.

- The short experimental time, relatively cost-effective and minimally invasive nature of the peripheral blood, could make the close monitoring of chimerism by qPCR technique a very useful tool for predicting outcome in AML/MDS allografted patients, especially in the absence of a molecular marker.

Disclosure: Nothing to declare.

P393

Oxidative burst flow cytometry assay for chimerism in patients with chronic granulomatous disease after hematopoietic stem cell transplantation

D. Pershin[1], V. Brilliantova[1], V. Vedmedskia[1], M. Fadeeva[1], E. Kulakovskaya[1], E. Malahova[1], T. Sozonova[1], J. Rodina[1], G. Novichkova[1], D. Balashov[1], A. Shcherbina[1], M. Maschan[1]

[1]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation

Background: Chronic granulomatous disease (CGD) is a primary immunodeficiency caused by the inability of phagocytic cells to produce reactive oxygen metabolites required for microbial killing. The dramatic reduction in oxidative burst intensity characteristic of patients with CGD can be demonstrated by flow cytometry (FC) used routinely to analyze expression of various cell surface and intracellular markers. Hematopoietic stem cell transplantation (HSCT) is curative for CGD - the success is based on the engraftment of myeloid lineage and production of functionally competent granulocytes. Chimerism tests allow evaluation of the donor/recipient origin of the post-HSCT hematopoietic system. The purpose of our study was to compare the utility of two methods, quantitative real-time polymerase chain reaction (qPCR) and FC, for chimerism tests.

Methods: Clinical samples of peripheral blood (a total of 35) were collected from 15 patients aged 3–13 years (median age 6 years) at different time points after stem cell transplantation, within a period from 2018-09 to 2021-11. The cohort included 14 boys with X-linked CGD (*CYBB*-mutated) and one girl with autosomal-recessive CGD (*CYBA*-mutated). All patients received either TCRαβ/CD19-depleted allogeneic HSCT (n = 12) or bone marrow transplantation (n = 3). Chimerism was determined in total leukocytes (35 samples) or CD15 + myeloid cells obtained by immunomagnetic separation (25 samples). Quantitative PCR assays were carried out with test systems for insertion/deletion polymorphisms developed and provided by Research Center for Medical Genetics, Moscow. Functional activity of neutrophils was assessed by FC using FagoFlowEx Kit (EXBIO Praha, a.s.) to measure the oxidative (respiratory) burst after stimulation by detection of fluorescence of rhodamine 123. Pearson correlation coefficients were calculated to estimate relationships.

Results: There was a complete concordance between the molecular PCR-based and flow-based assessment of chimerism among samples with complete donor chimerism both in whole blood and selected CD15 + fraction. With the absolute predominance of myeloid donor cells in all tested CD15 + populations (>99% as measured by qPCR), 24 (96%, all but one) of them exhibited unimodal oxidative burst patterns.

Among cases with mixed chimerism in the whole blood, as determined by PCR -based method, there was a highly significant positive correlation between the two methods (Pearson r = 0.651, p > 0.0001). The discordance of quantitative assessment by two methods is presumed to be due to different potential sources (CD3 + T cells vs CD15 + granulocytes) of the recipient signal.

Conclusions: Direct oxidative burst measurements by FC provide a rapid and sensitive test to assess the proportion of functionally competent granulocytes in peripheral blood. Mixed granulocyte populations produce bimodal negative-positive distributions. Comparison of qPCR results with FC data reveals a strong positive correlation for CD15 + lineage chimerism, albeit a

moderate positive correlation for mixed chimerism in total blood leukocytes. Overall, FC provides robust and reliable means for evaluation of HSCT efficacy in patients with CGD.

Disclosure: Nothing to declare

P394

The application of digital polymerase chain reaction for chimaerism engraftment monitoring in selected haematological malignancies: A single centre experience

K. Robinson[1], H. Lee[2], A. Barker[2], K. Poulton[2], R. Wynn[2], E. Tholouli[2]

[1]University of Manchester, Manchester, United Kingdom, [2]Manchester University NHS Foundation Trust, Manchester, United Kingdom

Background: Chimaerism monitoring post-HPCT is a powerful tool used to assess engraftment and relapse. An emerging technology for chimaerism analysis is digital PCR (dPCR), reported to have greater sensitivity for target DNA detection. This method has not yet been clinically implemented over the predominant use of STR-PCR based monitoring.

Methods: The sensitivity of chimaerism results obtained using dPCR and STR-PCR were compared. As part of the study, an evaluation of the technical applicability of dPCR in a clinical Histocompatibility & Immunogenetics laboratory was carried out.

Chimaerism analysis was carried out for a cohort of 50 HPCT recipients aged between 9 months and 65 years and transplanted between 2015 and 2020 as treatment for haematological malignancy (n = 19 multiple myeloma, n = 7 juvenile myelomonocytic leukaemia, n = 24 high relapse risk paediatric AML, HR-AML). A total of 117 samples were selected according to: (1) recipient consistently displaying 100% donor chimaerism (DC) by STR-PCR, two most recent samples, (2) deceased recipient, final two samples available, (3) recipient displaying mixed chimaerism with samples considered 'borderline' between 95%-100% DC.

Artificial chimaerism mixtures (100, 99.5, 99, 98 %DC) were also generated and evaluated on both technologies.

Patient-donor chimaerism was evaluated using the QuantStudio™ 3D Digital PCR System (Applied Biosystems™) with Imegen-Quimera dPCR informative marker kits (Imegen) and compared to STR-PCR results *(Geneprint®* 24 System, Promega) processed using the ABI 3500XL Genetic analyser (Applied Biosystems™) in accordance with manufacturers' instructions.

Results: dPCR demonstrated higher sensitivity for the detection of very low levels of the artificial 'HPCT recipient' DNA when DC is ≥99%. Conversely STR-PCR is more accurate than dPCR when a greater level of artificial recipient DNA is present, ≤98% DC. Above 99.5% DC, the lower values given by dPCR, compared with the values from the STR technique, may identify recipient DNA that would be missed by STR-PCR as the sensitivity limits of STR-PCR are known to be approximately 1-2% of minor component.

Direct comparison of technologies showed dPCR quantification situates tightly around 99-100% DC, whereas STR-PCR shows a greater spread of values (92-100% DC; image panel A). In contrast, the results indicate STR-PCR has better performance at increasingly mixed recipient chimaerism, where DC is ≤98% (artificial mixture analysis).

The technical evaluation of dPCR and STR-PCR platforms presented several differences which impact performance and the technical considerations for clinical implementation. Aspects include DNA concentration, labour/ technical demands, financial cost, ad hoc versus batch testing suitability and turnaround time.

Conclusions: In this single centre study, dPCR was found to supersede STR-PCR for detection and quantification of extremely low-level recipient chimaerism (99-100% DC), whereas STR-PCR was more accurate for increasingly mixed recipient chimaerism (<99% DC). A technical evaluation found dPCR can provide a faster turnaround for small sample numbers. Conversely, STR-PCR is suitable for batch testing. Overall, it is suggested that dPCR is advantageous for rapid chimaerism analysis monitoring in urgent scenarios in early engraftment, early suspected relapse or high-risk leukaemia patients. In contrast, STR-PCR should remain the technique of choice for patients with overtly mixed chimaerism.

Disclosure: Nothing to declare

P395

Circulating micro-RNA profiling in patients relapsing after allogeneic hematopoietic transplantation

M. Waterhouse[1], S. Pennisi[1], D. Pfeifer[1], R. Zeiser[1], J. Duyster[1], H. Bertz[1], J. Finke[1], J. Duque-Afonso[1]

[1]University of Freiburg/Klinik für Innere Medizin I, Freiburg, Germany

Background: MicroRNAs (miRNAs) has been used to predict outcome after allo-HSCT, most of them related with the development of aGvHD. However, few reports connect miRNA expression to other outcome variables such as relapse. We performed a high throughput profilling in circulating miRNAs. Overexpressed miRNAs were used to identify potential target genes.

Methods: We performed in a discovery cohort miRNA profilling using a miRNA array containing 175 miRNAs. We validated individual overexpressed miRNAs using droplet digital PCR (ddPCR) in a validation cohort including patients relapsing after allogeneic hematopoietic transplantation (allo-HSCT). By bioinformatics anaylisis, we identified candidate target genes and analysed the target gene expression in peripheral blood mononuclear cells (PBMCs) in patients at relapse after allo-HSCT.

Results: Four miRNAs (hsa mir 363, hsa mir 505, hsa mir 200c and has mir 320c) were identified in the miRNAs profiling of circulating nucleic acids to be overexpressed (>1.5 fold) in patients relapsing after allo-HSCT. In silico analysis, identified *DNAJB9* and *TUBB* as the target genes for the combination of the four overexpressed miRNAs. We further analysed *DNAJB9* expression in PBMCs in three groups of patients: complete remission (n = 13), pre-transplant with active disease (n = 5) and relapse after HSCT (n = 11). Mean Log dd Ct *DNAJB9* expression was: -0.01, -0.39 and -0.23 for those patients in complete remisssion, pre-transplant with active disease and relapse after allo-HSCT, respectively. A significant *DNAJB9* expression difference between patients in complete remission and those patients with either active disease before transplant or relapse after allo-HSCT was observed (p = 0.0056 and p = 0.036). We assessed the assay perfomance of the *DNAJB9* expression between the different analyzed groups, using the area under the curve (AUC) of a ROC curve. The AUC was 0.923 and the optimal *DNAJB9* expression threshold to discriminate relapse from complete remission was Log dd Ct *DNAJB9* -0.17. Within the group of patients relapsing after allo-HSCT, two groups were observed: high (mean Log dd Ct *DNAJB9* -0.049, n = 7) and low (mean Log dd Ct *DNAJB9* -0.55, n = 4) *DNAJB9* expression. The mean time to relapse in patients with a high *DNAJB9* expression was 26 months whereas in those with low *DNAJB9* expression was 9.6 months. This time difference reached statistical significance (p = 0.011).

Conclusions: miRNAs profiling of circulating nucleic acids identified *DNAJB9* gene, which is associated with disease progression after allo-HSCT.

Disclosure: This work was supported by a grant of the Else Kröner-Fresenius-Stiftung (Nr. 2018-A56).

P396

Late recovery of donor stem cell chimerism after apparent graft failure with autologous reconstitution: Implications for planning second transplants

D. Stonehewer[1], K. Poulton[1], H. Lee[1], H. Church[1], D. Bonney[1], H. Campbell[1], R. Hanasoge-Nataraj[1], R. Wynn[1]

[1]Manchester University NHS Foundation Trust, Manchester, United Kingdom

Background: Late graft failure with mixed chimerism and autologous reconstitution is not uncommon after haematopoietic stem cell transplant (HSCT) for non-malignant disease, and is considered an indication for second transplant. Such second transplant is associated with significant morbidity and mortality and should therefore only be undertaken if necessary. We discuss 3 cases where late recovery of donor chimerism was described, after apparent graft failure with loss of donor chimerism, and without any medical intervention. This observation has implications for the planning of second transplants.

Methods: The chimerism data of patients over the last 20 years receiving transplant in Royal Manchester Children's Hospital was reviewed. The clinical data, including enzyme and substrate levels, were included in the analysis.

Results: We examined and highlight the graft experience of 3 patients, who experienced apparent graft loss, with significantly falling donor chimerism, and who experienced later recovery of donor chimerism despite no medical intervention.

Patient A HSCT indication ELA2 constitutional neutropenia with GCSF resistance, long –term donor chimerism to less than 10% after BuCyCampath MAC allograft. The donor cells retained sensitivity to post-transplant GCSF and so second transplant not performed, and eventually donor engraftment improved, and GCSF could be discontinued (perhaps as marrow failure associated with ELA2, and donor cells occupying hypoplastic recipient marrow).

Patients B + C HSCT indication MPS1H. Patient B initially 95% chimerism, reduced to 15% at 20 months then recovered to 80% donor chimerism at 50 months with graft producing iurondiase enzyme level sufficient to allow substrate reduction and clinical correction. C has experienced a primary graft failure with autologous reconstitution and received a second transplant. He experienced second graft loss, to less than 50% door chimerism but recovered to 90% donor chimerism without intervention. Enzyme and substrate levels mirrored chimerism.

Conclusions: Transplant in non-malignant disease is to correct disease, and the level of chimerism required is that to correct the disease. This report emphasises this statement, especially since it demonstrates that donor chimerism can recover without medical intervention. Repeat HCT may be indicated for mixed chimerism after transplant, but not always so, avoiding its associated morbidity and mortality.

Disclosure: Nothing to declare.

P397

Day +21 absolute lymphocyte count could be an independent predictor for the outcome of alogeneic transplation of hemopoetic stem cells in patients with acute leukaemia

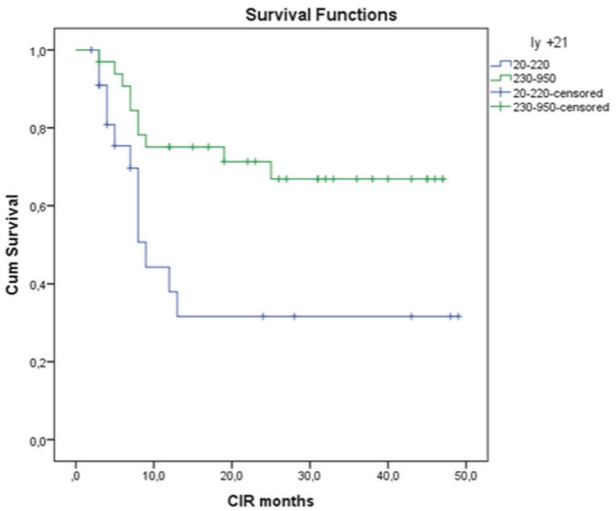
K. Milcheva[1], V. Krasen[1], I. Tonev[1], E. Naseva[2], P. Ganeva[1], G. Arnaudov[1]

[1]Specialized Hospital for Active Treatment of Hematological Diseases, Sofia, Bulgaria, [2]Medical University of Sofia, Sofia, Bulgaria

Background: A retrospective analysis of patients with AML, ALL or MDS, who received allogeneic hematopoietic stem cell transplantation for the period 2017-2019 in TU at SBALHZ was performed. The aim of the study is to identify the cut off value and time point of early lymphocyte recovery, presented as an absolute lymphocyte count (ALC), that would have prognostic significance for the outcome of AloHSCT and whether it can serve as a surrogate marker for NK cell recovery.

Methods: The electronic files of 56 patients, followed until 20.01.2021, were analyzed. The demographic, clinical and laboratory data were obtained from HIS. Peritransplantation factors were evaluated. Spearman's correlation coefficient, chi-square analysis, Mann-Whitney test, Cox regression analysis, log-rank test, ROC-curves were applied in the statistical analysis. Values of $p < 0.05$ were considered significant.

Results: The significance of the factors ALC - D + 21 and D + 30 for overall survival was checked with Cox regression analyze. D21 proved to be significant ($p = 0.016$, HR = 0.998, 95% CI 0.995-0.999). The limit value of the function was set at 0.5376, which corresponds to ALC 230/μl of D + 21. The risk factor shows that the survival of patients in the group with ALC D + 21 > 230 /μl is 3.78 higher and 2.87-fold higher risk of disease relapse in patients with ALC D + 21 < 230 /μl (fig. 1). We have also investigated the NK cell recovery by FCM at D + 30 ± 7 days, the mediana count is 148/μl. No association of NK D + 30 with OS, PFS, CIR, NRM and ALC D + 21 has been demonstrated. We found a correlation between NK cell recovery and aGVHD.



Conclusions: ALC D + 21 ≥ 230/μl in the study group of patients was associated with improved overall survival and reduced risk of recurrence, but a higher incidence of cGVHD. ALC D + 21 ≥ 230/μl may be a surrogate for engraftment. ALC D + 21 is a biologically significant predictor of the outcome of transplantation - universal, affordable, easily measurable and inexpensive. we couldn't prove that ALC D + 21 can serve as a surrogate marker for NK cell recovery, probably due to small number of patients included in the analysis.

Clinical Trial Registry: N/A

Disclosure: We have no conflict of interest to declare

P398

Next generation sequencing (NGS) for chimerism monitoring following haematopoeitic stem cell transplant (HSCT): A service development proposal

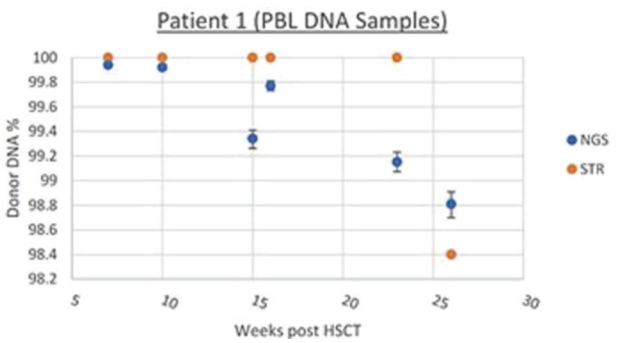
L. Kusyk[1], S. Mathers[1], A. Logan[1], A. Barker[1], H. Lee[1], N. Diaz Burlinson[1], K. Poulton[1], R. Wynn[1]

[1]Manchester University NHS Foundation Trust, Manchester, United Kingdom

Background: Chimerism monitoring is routinely used following haematopoietic stem cell transplant (HSCT) to analyse donor engraftment through detection of donor and recipient cells, and subsequently detect graft failure or relapse of malignant disease. Higher quality monitoring can impact patient care by allowing earlier intervention in the event of disease relapse or graft failure post-HSCT. Short tandem repeat (STR) polymerase chain reaction (PCR) is the current gold standard for chimerism analysis in clinical practice, but its utility is limited by low sensitivity, high variability, and limited throughput. There is a need for chimerism monitoring that incorporates the highest sensitivity testing possible, can be standardised across clinical practice and has the potential to monitor both donor/recipient cells and disease present. Several other innovative methods with higher sensitivity and accuracy are being explored. Next generation sequencing (NGS) has extended applications in genomics, forensic science, and clinical diagnostics and has shown promise as the future of chimerism analysis in both solid and haematological transplantation. Higher sensitivity and precision, combined with the possibility to monitor disease levels in haematological malignancy, present NGS as a viable candidate to explore for routine clinical chimerism analysis within the NHS. This has the potential for better patient outcomes through earlier detection of relapse of disease or loss of donor graft. NGS technology also has the potential to revolutionise monitoring following gene therapy HSCT (HSCGT).

Methods: Post-transplant engraftment monitoring by STR-PCR was carried out using GenePrint® (Promega) on an ABI3500xl platform in 4 patients who had previously undergone HSCT for malignant or non-malignant disease. DNA from each peripheral blood sample was also tested using AlloSeq^{TM} HCT (CareDx®) on a MiSeq (Illumina) instrument, a technique which uses NGS to facilitate more accurate quantification of donor and recipient templates present in the sample. Analysis was carried out using AlloSeq HCT Software.

Results: The preliminary work undertaken in the Transplantation Laboratory at Manchester University NHS Foundation Trust demonstrated the earlier detection than STR of mixed chimerism in patients. Micro chimerism was detected from week 7 post-transplant in peripheral blood DNA samples using NGS, compared with first detection of mixed chimerism at week 26 post-transplant with STR-PCR. Earlier detection of recipient micro chimerism in CD15^{+} DNA was observed at week 8 post-transplant, compared with 100% donor DNA detection at 22 weeks using STR-PCR.



Conclusions: Further research is required on larger patient sample numbers to further validate this method and demonstrate reproducibility of results on a large scale. This research will support the validation required to meet ISO accreditation standards for clinical laboratory use, and work towards commissioning through the NHS England service development process.

Disclosure: Nothing to declare.

P399

Quantiferon-monitor - a predictive tool of infectious complications in patients after allogeneic hematopoietic stem cell transplantation

K. Žibřidová[1,2], O. Souček[1,2,2], F. Vrbacký[1,2], I. Sejkorová[1,2], M. Lánská[1,2], B. Víšek[1,2], J. Radocha[1,2], P. Žák[1,2]

[1]University Hospital Hradec Králové, Hradec Králové, Czech Republic, [2]Charles University, Hradec Králové, Czech Republic

Background: Hematopoietic stem cell transplantation (HSCT) is one of the treatment approaches in variety of hematologic malignancies. Its risks include mainly severe infectious episodes. QuantiFERON-monitor (QFM) is a method assessing an unspecific cellular immune function. The method is based on detection of a value of interferon gamma (IFNγ) in plasma after previous stimulation of both innate and adaptive immune system response.

Methods: In our work we focused on analysis of the relationship between the dynamics of a QFM value in patients treated with HSCT for a hematooncologic disease and the incidence of severe infectious complications in early post-transplant period. Our hypothesis was increased or stationary QFM in patients without severe infection history. Consecutive patients who underwent HSCT from 2017 to 2020 were included in the study. We performed an analysis of specimens of whole blood from our subjects by QuantiFERON-Monitor testing kit (QIAGEN, Hilden, Germany). Each specimen was processed according to the manufacturer's manual. The production of IFNγ in plasma was measured after 24 hours of incubation with a specific stimulus by ELISA (normal range 15–1000 IU/ml).

Results: Our patients were divided into two groups. In the first group, blood specimens were obtained from 13 subjects for QFM analysis 2 weeks before the conditioning regimen (median value 63.2 IU/ml) and 3 months after the allograft infusion (median value 65 IU/ml). The second group consisted of 26 patients; assessment of a QFM was performed 2 weeks before the conditioning regimen (median value 122.8 IU/ml) and 6 to 9 months after HSCT (median value 57.0 IU/ml). We evaluated the change of IFNγ levels in the samples before and after HSCT. In the patients in the first group with non-decreased QFM, infection was present in 3 cases and absent in only 1 case. Decrease of the QFM value was associated with the infection in 6 cases and was not present in 3 cases (p-value = 0.8238). Corresponding blood samples were compared in the second group. In patients with increased/stationary QFM, the infection was observed in 4 and was absent in 9 out of 26 subjects. Decreased QFM result was not associated with infection in 8, more precisely 5 subjects (p-value = 0.5).

Conclusions: We did not confirm an association between the elevation of QFM and the decreased risk of infection in the 3-month follow-up neither at 6 to 9 months. No predictive value of QFM in association with the presence of an infection was seen in our cohort of patients after HSCT. QFM results need to be interpreted with caution mainly because of a wide normal value range.

Disclosure: Nothing to declare.

P400

Persistence of first donor natural killer cells after a second transplant for infant acute lymphoblastic leukemia

320

D. Madalese[1], L. Auriemma[1], M. Toriello[1], S. Nappo[1], G. Maisto[1], R. Penta de Vera d'Aragona[1], W.G. Wierda[2], K.M. Mahadeo[2], F.P. Tambaro[1]

[1]AORN Santobono - Pausilipon, Napoli, Italy, [2]The University of Texas- MD Anderson Cancer Center, Houston, United States

Background: An 18-month-old child affected by KTM2A infant acute lymphoblastic leukemia (ALL) underwent allogenic transplant from Match Unrelated Donor (MUD) and achieved measurable residual disease (MRD)-negative complete remission (CR) with 100% full donor chimerism. Six months post-transplant the patient relapsed, with loss of full donor chimerism (45% donor chimerism), and underwent treatment with azacytidine, again reaching MRD-negative CR2 full donor chimerism. A second allo-SCT from a haploidentical donor (mother) was performed. We correlated CD56-NK chimerism with MRD status after second transplant.

Methods: Polymerase chain reaction (PCR)-based short tandem repeat (STR) assays were performed on peripheral blood at +15 days and +19 days after second transplant. For each sample, a MACS (Magnetic-activated cell sorting) for CD56 + isolation (StemCell Technologies™ - EasySep™ Human CD56 Positive Selection Kit) was performed and purity of separated cells was evaluated by flow cytometry (BD FACSCanto II) as recommended by manufacturer. DNA was extracted with Maxwell® 16 instrument (Promega) and Maxwell® RSC Whole Blood DNA Kit (Promega) and a AB 3500 (Applied Biosystem) and ChimerMarker™ (SoftGenetics®) analysis software were used for STR analysis.

Results: Chimerism analysis performed on peripheral blood on day+15 day after second transplant revealed 99.5% Total Donor 2 Chimerism (Haplo). Interestingly CD56 + NK cells, isolated from the same sample revealed 98.2% from Donor 2 (Haplo) and 0.24% from Donor 1 (MUD). Same results were also observed at day +19 and day +32, although with a decrease of the CD56 + spike observed on day +15 (110/µl. vs 370/ µl). The patient remains in MRD-negative CR at day +45

Day after second HSCT	Total Donor Chimerism, %	CD56 + Donor 2 chimerism, %	CD56 + Donor 1 chimerism, %	Total CD56 + isolated, x 10^3/µl
+15	99.5	98.2	0.24	0.37
+19	99.6	99.3	0.10	0.11
+32	99.3	98.9	0.23	0.15

Conclusions: NK cells have anti-leukemic activity (GvL) in both adult AML and pediatric ALL. We hypothesize that the persistence of donor NK chimerism can improve transplant outcome through elimination of leukemic cells without GVHD. The rapid reconstitution of NK cells after haplo-HSCT is based on expansion of the cytokine-producing $CD56^{bright}$ NK cell subsets. We hypothesize that this patient with KMT2A + leukemia, which has dismal prognosis, had a quick response to treatment (single-agent hypomethylating treatment), due to the persistence of 1st donor NK cells, which persisted after 2nd transplant. The two populations of cells co-exist with no toxicities for the patient and both participated in achieving the MRD-negative CR response. The two populations of NK cells represent a reciprocal tolerance, and a possible synergistic effect. A clear knowledge and understanding of the number and chimerism of NK cells could drive donor NK cell treatment (NK-add back). The tolerance between the 2 NK populations potentially supports a rationale for third party/off shelf NK cell treatment.

Disclosure: Nothing to declare.

MULTIPLE MYELOMA

P401

Best treatment strategy before autologous peripheral blood stem cell transplantation in poems patients

F. Autore[1], S. Bramanti[2], F. Lessi[3], I. Innocenti[1], A. Piciocchi[4], E. Galli[1], S. Rocchi[5], R. Ribolla[6], D. Derudas[7], S. Oliva[8], P. Stefanoni[9], M. Marcatti[10], A. Schenone[11], G. La Nasa[7], C. Crippa[6], E. Zamagni[5], M. Riva[3], R. Mazza[2], D. Mannina[2], S. Sica[1], A. Bacigalupo[1], L. Laurenti[1]

[1]Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy, [2]Istituto Clinico Humanitas IRCCS, Rozzano, Italy, [3]Azienda Ospedale Università Padova, Padova, Italy, [4]GIMEMA, Data Centre, Roma, Italy, [5]IRCCS Azienda Ospedaliero-Universitaria S. Orsola-Malpighi, Bologna, Italy, [6]Spedali Civili, Brescia, Italy, [7]A. Businco, Cagliari, Italy, [8]S. Giovanni Battista, Torino, Italy, [9]ASST Papa Giovanni XXIII, Bergamo, Italy, [10]S. Raffaele, Milano, Italy, [11]San Martino, Genova, Italy

Background: POEMS syndrome is a rare paraneoplastic condition associated to an underlying plasma cell dyscrasia. The role of autologous peripheral blood stem cell transplantation (aPBSCT) with the use of alkylating agents as conditioning regimen seems to provide optimal outcomes. At present aPBSCT should be considered the first line therapy in young patients with POEMS, eligible for high-dose Melphalan (HD-Mel), in the absence of organ dysfunction. The best treatment before aPBSCT remains to be defined, because of the disease rarity and the heterogeneity of published case series.

We therefore decided to collect the patients from major Italian institutions, to describe and compare results and outcomes of patients with POEMS, eligible for aPBSCT.

Methods: We collected clinical and laboratory data of patients with POEMS syndrome from 10 Italian centres. We included all the consecutive patients with diagnosis of POEMS undergoing to aPBSCT from 1998 to 2020.

Results: Our data set consisted of 44 patients who underwent aPBSCT with a median follow-up of 77 months (37-169 months). Progression free survival (PFS) and overall survival (OS) rates at 6 years for transplanted patients was 65% (49-85) and 92% (84-100), respectively. The cumulative incidence of transplant related mortality and relapse was respectively 4% and 36%.

We then divided patients in three subgroups: front-line patients who did not receive any treatment before transplant (15 patients, Group 0), patients treated pre transplant with cyclophosphamide (14 patients, Group 1) and patients treated with other agents such as lenalidomide, chemioterapics or radiotherapy (15 patients, Group 2). The three groups did not show differences in terms of demographic and clinical characteristics. All patients underwent aPBSCT after Mel conditioning regimen (HD-Mel, 200 mg/m^2, in 86% of patients) and achieved a successful engraftment. The response rates after transplantation were complete response (CR) in 46%, very good partial response (VGPR) in 23%, partial response (PR) in 18%, stable disease (SD) in 8% and progressive disease (PD) in 5%. The responses (CR vs PR/VGPR vs SD/PD) showed a significant impact in terms of progression free survival (PFS). When comparing the response rate (CR vs PR/VGPR vs SD/PD) between the 3 groups any differences was found (p 0.25).

When analysing PFS and OS, the 3 groups did not show significant differences; there was a tendency to unfavourable PFS for patients of Group 1 but no variable was found to negatively affect PFS, neither the treatment chosen before transplantation. In 10 cases it was necessary a re-admission in hospital: in 5 cases for relapse and in 5 for infectious complications. We then considered VEGF levels after aPBSCT and we found out that patients with VEGF levels higher than

758 pg/mL were at higher risk of relapse (AUC 0.86, sensibility 78% specificity 86%), with very high potency in Group 1.

Conclusions: This is a relatively large series of patients with POEMS treated with autologous PBSCT. We show durable and impressive PFS and OS, without significant differences between groups of pre-treated patients and patients who underwent front-line aPBSCT.

Disclosure: Nothing to declare.

P402

Impact of double-hit genetics on real-world outcomes of multiple myeloma patients undergoing autologous stem cell tranplantation (ASCT) – a uk asct centre experience

A. Panopoulou[1,2], S. Easdale[2], M. Ethell[2], E. Nicholson[2], M. Potter[2], A. Giotas[2,3], H. Woods[2], T. Thornton[2], C. Pawlyn[1,2], K. Boyd[1,2], M. Kaiser[1,2]

[1]Institute of Cancer Research, London, United Kingdom, [2]Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom, [3]Mater Dei Hospital, Msida, Malta

Background: Despite the considerable improvements in newly diagnosed (ND) Multiple Myeloma (MM) outcomes in recent decades, remission times, in particular after ASCT, remain variable. Better outcome prediction post-ASCT could highlight populations in particular need for individualised post-ASCT management and potentially inform optimal allocation of resources. Genetic biomarkers including chromosomal aberrations t(4;14), t(14;16), and t(14;20) translocations, gain of 1q and deletion of 17p, have been associated with adverse outcome, and co-occurrence of ≥2 such aberrations (a Double-Hit) is predictive of especially aggressive disease. We investigated the prognostic impact of genetics in a real-world setting.

Methods: Electronic records of all patients who received an ASCT at the Royal Marsden Hospital between Jan 2014 – Oct 2019, were retrospectively reviewed. Cut-off for record review was May 2021. Only patients with sufficiently long follow-up post stem cell re-infusion were considered (>18 months). Cytogenetics and Fluorescent in situ Hybridisation (FISH) data from diagnostic samples were obtained through our reference laboratory's database and clinical data were obtained by review of electronic records.

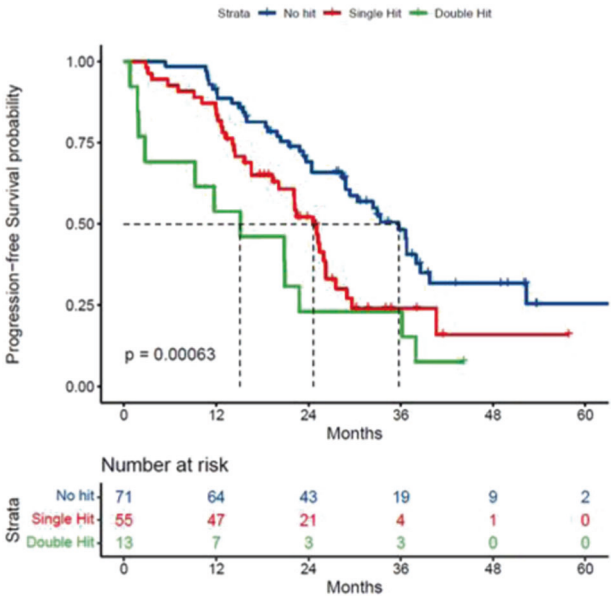
Only patients with a full complement of cytogenetic risk reported were included (defined as fully reported probes for lesions t(4;14), t(14;16), t(14;20), gain(1q) and del(17p)). Co-occurrence of ≥2 lesions was classified as Double-Hit, and a single lesion as Single-Hit. Presence of amyloidosis/POEMS, participation in interventional clinical trial and transplant-related death or treatment-associated malignancy were pre-specified as exclusion criteria.

Progression-free Survival (PFS) and Overall Survival (OS) were calculated from time of stem cell re-infusion. Groups were compared using the log-rank test. The study was approved by the hospital's internal review board as a service evaluation.

Results: We identified 139 patients eligible for evaluation as per above criteria. Clinical and genetic characteristics were representative of a transplant-eligible cohort with regards to age (median 64 years; range 32-76), sex (62% male), ISS (Stage I 22.3%, Stage II 33.8%, Stage III 17.2%, unknown 26.7%) and number of genetic lesions (No-Hit 51%, Single-Hit 39.6%, Double-Hit 9.4%).

Double-Hit patients had significantly shorter median PFS (15.1 months, 95% CI: 2.73-NA) compared with Single-Hit (24.6 months, 95% CI: 20.12-27.6) and No-Hit (35.7 months, 95% CI: 28.8-39.7), ($p = 0.00063$). Median OS for Double-Hit was 49.2 months (95% CI 40.7-NA), whereas it was not reached for the remaining groups ($p = 0.034$). In only 1.4% of the No-Hit cohort did the myeloma relapse in the first 6 months post-ASCT, whereas relapses in the same timeframe were observed in 7.3% of Single-Hit and 30.8% of Double-Hit cohorts.

On univariate analysis, advanced ISS and high-risk cytogenetic lesions ("hits"), were associated with a shortened progression free survival, and significance was maintained for both on multivariate analysis. Age was not associated with PFS in either univariate or multivariate analysis, although in the UK there is no numerical age-driven cut-off for ASCT consideration.



Conclusions: We demonstrate here that detailed genetic profiling, specifically the combined assessment of adverse genetics, can help stratify NDMM patients undergoing ASCT in a standard of care setting. This approach can support identifying patients with particular need for intensified monitoring and post-ASCT therapy in a standard clinical setting already at diagnosis.

Disclosure: Aikaterini Panopoulou- nothing to declare.
Sandra Easdale- nothing to declare.
Mark Ethell- nothing to declare.
Emma Nicholson- nothing to declare.
Mike Potter- nothing to declare.
Asterios Giotas- nothing to declare.
Helena Woods- nothing to declare.
Tracy Thornton- nothing to declare.
Charlotte Pawlyn reports personal fees and non-financial support from Sanofi, personal fees and non-financial support from Janssen, personal fees and non-financial support from Celgene, personal fees and non-financial support from Amgen, non-financial support from Oncopeptides, outside the submitted work.
Kevin Boyd reports personal fees from Janssen, personal fees from Celgene, personal fees from Takeda, personal fees from GSK, outside the submitted work.
Martin Kaiser reports personal fees from AbbVie, grants and personal fees from BMS/Celgene, personal fees and other from Amgen, personal fees and other from Janssen, personal fees from Karyopharm, personal fees from Seattle Genetics, personal fees and other from Takeda, personal fees from GSK, outside the submitted work.

P404

Cumulative effect of cytogenetic hits on multiple myeloma relapse after front-line autologous stem cell transplant

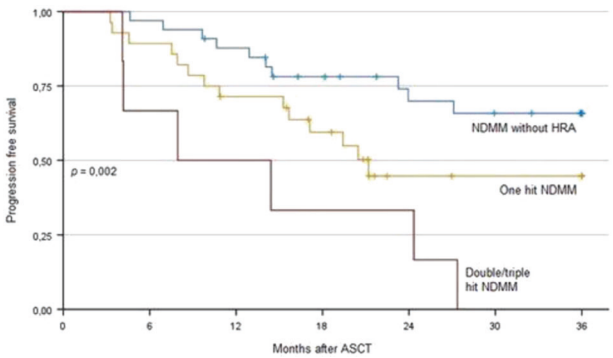
P. Baptista[1], M. Henriques[1], A.A. Pardal[1], P. Monteiro[1], P. Chorão[1], M.J. Soares[1], A. Barbosa[1], P. Gomes[1], R. Bergantim[1], E. Aguiar[1], J.C. Pires[1], F. Trigo[1]

[1]Centro Hospitalar Universitário de São João, Porto, Portugal

Background: Risk stratification at the initial approach of newly diagnosed multiple myeloma (NDMM) is essential to predict overall survival and response to therapy, especially in patients in whom front-line treatment with autologous stem cell transplantation (ASCT) is being considered. Fluorescence in situ hybridization (FISH) is the basis for cytogenetic risk assessment in various prognostic scores, and the presence of high-risk abnormalities (HRA), or "hits", can be used to define a high risk disease. The aim of this study was to evaluate the impact of the cumulative effect of HRA on relapse after front-line ASCT.

Methods: We retrospectively studied NDMM patients submitted to ASCT with melphalan conditioning, between 2012 and 2020, after induction with proteasome inhibitor (PI) and/or immunomodulatory drugs (IMiD). Only patients with available data on R-ISS staging and FISH analysis for del(17p), t(4;14), t(14;16) and 1q+ were included. We evaluated the progression free survival (PFS) and calculated hazard ratios (HR) for the groups with *one hit* NDMM (1 HRA) and *double* or *triple hit* NDMM (2 or 3 HRA), including multivariate analysis with other factors with impact on PFS.

Results: Within a total of 67 patients, 28 had *one hit*, 5 *double hit* and 1 *triple hit* NDMM. Median age at transplant was 60 years (interval 38-71) and 51% of the patients were male. Most patients (70%) were treated with PI and IMiD during induction while 30% received PI with cyclophosphamide and corticosteroids, achieving complete remission (CR) rate of 48%. Stem cell mobilization was performed with cyclophosphamide and G-CSF in 61%, while the remaining received G-CSF alone. CR after transplant was 66% and maintenance treatment was initiated on 55% of the patients. PFS 3 years after ASCT was not achieved in the group of patients without HRA, while the *one hit* NDMM and the *double/triple hit* NDMM groups showed a PFS of 21 ± 2 months and 7 ± 6 months, respectively (p = 0.002). On multivariate analysis, 3-year PFS was negatively impacted by the presence of 1 HRA (HR 5.25, confidence interval [CI] 95% 2.04-13.50), more than 1 HRA (HR 4.52, CI 95% 1.63-12.55) and the absence of maintenance treatment after ASCT (HR 7.15, CI 95% 2,83-18,09). There was no statistically significant impact on PFS for age, R-ISS staging, induction treatment and response, mobilization therapy and response after ASCT.



Conclusions: Our study suggests that cytogenetic risk stratification through the cumulative effect of HRA independently influences PFS in NDMM patients that underwent frontline ASCT. This strategy could define biological subtypes of NDMM better than the R-ISS and, thus, individualize therapeutic options for these patients.

Disclosure: Nothing to declare.

P405

Loss of 13p as an independent prognostic factor for early relapse after first line autologous stem cell transplant in multiple myeloma

M. Henriques[1], P. Chorão[1], P. Baptista[1], A. Pardal[1], P. Monteiro[1], E. Aguiar[1], J. Cancela Pires[1], A. Barbosa[1], M.J. Soares[1], P. Gomes[1], R. Bergantim[1], F. Trigo[1]

[1]Centro Hospitalar Universitário de São João, Porto, Portugal

Background: Deletions involving chromosome 13 identified by chromosome studies were one of the first recognized adverse prognostic factors in patients with newly diagnosed multiple myeloma (NDMM). However, recent evidence has challenged its prognostic value due to cooccurrence with other high-risk abnormalities (HRA). Our aim was to analyse the impact of 13p deletions in early relapsed in NDMM after first line autologous stem cell transplant (ASCT).

Methods: Single-centre retrospective study of patients with NDMM submitted to frontline ASCT with melphalan conditioning, between January 2008 and August 2020, with at least one year of follow-up. Genetic abnormalities ((17p and 13p deletion, t(4;14), t(11;14), t(14;16)) were identified by fluorescence in situ hybridization (FISH) at the time of diagnosis. Logistic regression was used to identify the variables of prognostic interest that correlate with early relapse, defined as relapse less than 12 months after ASCT.

Results: Out of 298 transplanted patients, 171 had complete FISH data at diagnosis. Median age at ASCT was 60 years (range 37-71) and 55% were male. 21% had hypercalcemia, 21% presented with renal failure, 55% anaemia, 18% extramedullary disease and, considering HRA by WHO, 27% were defined as high risk. Patients were treated with combinations of Immunomodulator and Proteosome Inhibitor (PI) 50% and only with PI 46%. Cyclophosphamide was used for stem cell mobilization in 74%, 13% performed tandem ASCT and 40% did maintenance therapy. Multivariate analysis-showed that patients who had higher odds of early relapse were the ones with paraprotein non-IgG/non-light chain NDMM (odds ratio [OR] 3.23, 95% confidence interval [CI] 1.14-9.15), not achieving complete remission (CR) at day +100 of ASCT (OR 2.79, 95%CI 1.14-6.84), no use of maintenance therapy (OR 3.07, 95%CI 1.10-8.60), presence of HRA (OR 2.41, 95% CI 0.98-5.94) and the 13p delection (OR 2.53, 95% CI 1.05-6.19). Amp(1)q was not included by missing data. Age of diagnosis, presence of anaemia, hypercalcemia, renal failure, bone lesions, extramedullary disease at diagnosis, induction chemotherapy regimen and its response, tandem ASCT and year of transplant were not statistically significant.

Conclusions: Our study suggests that 13p deletion is an independent prognostic factor for early relapse, regardless of the presence of other HRA, response at day +100, use of maintenance therapy and NDMM immunological subtype. Our findings support the importance of the loss of 13p as a marker of poor prognostic in patients with NDMM. Whether this alteration is a surrogate of other high-risk genetic alterations or carries true biological poor risk needs to be addressed in future studies.

Disclosure: Nothing to declare

P406

Impact of timing of stem cell return following high-dose melphalan in myeloma patients with renal impairment

G. Nesr[1], N. Rabin[1], C. Kyriakou[1], J. Sive[1], R. Popat[1], K. Yong[1], B. Wisniowski[1], K. Xu[1], A. Wechalekar[1], L. Lee[1], S. Ings[1], X. Papanikolaou[1], S. Mahmood[1], A. Mcmillan[1], J. Horder[1], F. Newrick[1], J. Marfil[1], L. Ainley[1], S. Asher[1], S. Cheesman[1], R. Shah[1]

[1]*University College London Hospitals NHS Foundation Trust, London, United Kingdom*

Background: Consolidative autologous stem cell transplantation (ASCT), incorporating high dose melphalan (HDM) for conditioning, is the UK standard of care for transplant-eligible multiple myeloma (MM) patients. Melphalan undergoes rapid hydrolysis in plasma with a short half-life (60-90 minutes). The duration between HDM and haematopoietic stem cell return (HSCR) varies between institutions, with limited data on optimal timing for patients with renal impairment (RI). In March 2020 we reduced the time between HDM and HSCR from 48 to 24 hours (h) in patients with a glomerular filtration rate (GFR) of <60 ml/min to improve resource utilisation. We retrospectively compared the impact of 24 versus 48 h HSCR on time to neutrophil engraftment (TTNE), hospital stay (HS), need for renal replacement therapy (RRT), intensive care unit (ICU) admission and death.

Methods: We identified MM patients with a GFR < 60 ml/min, assessed by ^{51}Cr-EDTA, who underwent ASCT between June-December 2019 and July 2020-July 2021 in our institution, and compared those with 24 or 48 h HSCR after HDM. HS was calculated from the date of HDM administration to discharge. Neutrophil engraftment date was defined as the first of 2 consecutive days with a neutrophil count > 0.5 x 10^9/L. High risk cytogenetics were defined as per the International Myeloma Working Group definition.

Results: Of the 239 MM patients who underwent ASCT, 37 (15%) had a GFR < 60 ml/min (Table 1). Males represented 53% and 55% of the 24 and 48 h groups, respectively. Age, prior therapy lines and stem cell dose were similar between both groups. Median HS for both groups was 17 days (24 h group range: 15-42; 48 h group range: 14-28). Median TTNE was 12 days in the 24 h group (range: 10-13) and 11 days in the 48 h group (range: 10-13; $p = 0.143$). No patients required ITU admission or RRT. Three deaths occurred in the 48 h group (2 received HDM at 200 mg/m^2; causes included COVID and MM relapse).

Table 1: Patients' characteristics.

	24 h group (n = 15)	48 h group (n = 22)
Age, years; median (range)	65 (56-71)	61 (40-76)
ISS, n (%)		
1	5 (33)	3 (14)
2	2 (13)	3 (14)
3	1 (6)	9 (41)
Unknown	7	7
High risk cytogenetics, n (%)	4 (27)	4 (18)
Therapy lines before ASCT, n (%)		
1	9 (60)	17 (77)
2	4 (27)	4 (18)
3 +	2 (13)	1 (5)
HDM dose (mg/m^2), n (%)		
110	0	3 (14)
140	12 (80)	11 (50)
200	3 (20)	8 (36)
Uncorrected GFR, ml/min; median (range)	47 (33-57)	45 (26-59)
Uncorrected GFR < 40 ml/min, ml/min, n (%)	2 (13)	7 (32)
Time between HDM and HSCR, hours; median (range)	25 (23-26)	48 (41-49)
HSC dose, CD34 x 10^6/kg; median (range); $p = 0.357$	2.8 (1.9-16.8)	2.7 (1.5-12.1)

Conclusions: Our results suggest a 24 h interval between HDM and HSCR in patients with renal impairment is safe. A 24 hour HSCR facilitates better scheduling and resource utilisation. More data is needed particularly in those with a GFR < 40/min.

Disclosure: Nothing to declare

P410

Outcome of patients with multiple myeloma receiving allogeneic hematopoietic stem cell transplantation in the pre-car t cell era

C. de Ramon Ortiz[1], F. Giannotti[1], A.-C. Mamez[1], Y. Beauverd[1], S. Morin[1], T.-A. Tran[1], M. Mappoura[1], E. Mahne[1], A. Pradier[1], C. Dantin[1], K. Samii[1], S. Masouridi-Levrat[1], F. Simonetta[1], Y. Chalandon[1]

[1]*Geneva University Hospitals, Geneva, Switzerland*

Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is considered the only potentially curative treatment for multiple myeloma (MM). Before the approval of anti-BCMA chimeric antigen receptor (CAR) T cells, HSCT was the only available cellular therapy based on the graft-versus-myeloma effect of adoptively transferred allogeneic T cells. However relapses after HSCT are frequent and its role in MM treatment remains unclear. The aim of this work was to evaluate the outcome of patients undergoing allogeneic HSCT for MM at our institution to generate a reference survival curve for new upcoming cellular therapies such as BCMA-CAR T cells.

Methods: We retrospectively analyzed the outcome of MM patients receiving allogeneic HSCT at our institution between 1990 and 2021.

Results: We included 55 patients in the analysis of which 14% received upfront allogeneic HSCT, while 42% and 38% had a single autologous HSCT and a tandem autologous HSCT prior to allogeneic HSCT respectively. Among patients for which cytogenetics characteristics were available (n = 41), 14% displayed high risk cytogenetics. With a median follow-up for alive patients of 5.6 years(y), the median overall survival (OS) was 3.6y and the median progression-free survival (PFS) was 0.8y. The 5y OS and PFS were 41% (30%-58%) and 17% (9%-31%), respectively. The 5y cumulative incidence of disease progression/relapse was 64%±7% and of non-relapse mortality (NRM)

was 22%±6%. Patients' stratification based on disease status at transplantation, previous autologous HSCT, type of allogeneic HSCT (allo-upfront, tandem auto-allo, later allo), conditioning (MAC, RIC), stem cell source (PBSC, BM), donor type, ATG use, and ex vivo T-cell depletion (TCD) suggested a significant improvement in OS [HR 0.46 (95% CI 0.21-1); p = 0.05] and PFS [0.46 (0.24-0.88); p = 0.019] associated with ex vivo TCD. We observed a trend not reaching statistical significance toward reduced PFS [2.1 (0.92-4.7); 0.078] in patients who received one or more previous autologous HSCT. Use of grafts from HLA-matched unrelated donors (MUD) was associated with a significantly reduced OS [2.6 (1.3-5.2); 0.0095] and PFS [3.1 (1.7-5.9); p = 0.00037] compared with grafts from HLA-identical siblings. The 5y OS for patient receiving grafts from SIB donors was 55% (40%-75%) and the 5y PFS was 26% (15%-47%) compared with a 16% (5%-53%) 5y OS and a 0% PFS for patients receiving grafts from MUD. Multivariable analysis considering previous autologous HSCT and ex vivo TCD confirmed the negative impact of grafts from MUD on both OS [2.13 (0.99, 4.59); 0.05] and PFS [2.65 (1.32, 5.32); 0.006] while the impact of previous autologous HSCT and ex vivo TCD was not confirmed. Use of grafts form MUD was associated with a trend not reaching statistical significance towards an increased cumulative incidence of both relapse and NRM.

Conclusions: Our study identifies a subset of MM patients, receiving grafts from SIB donors, displaying an improved long-term outcome after allogeneic HSCT, suggesting the curative potential of this treatment approach for a fraction of patients. Our results may help to evaluate the impact of new cellular therapies, including BCMA-CAR T cells, for relapsing/refractory MM.

Disclosure: Nothing to disclose.

COI Yves Chalandon : consulting fees from MSD, Novartis, Incyte, BMS, Pfizer, Abbvie, Roche, Jazz, Gilead, Amgen and travel support from MSD, Roche, Gilead. Amgen, Abbvie, Janssen, AstraZeneka, Jazz.

P411

Response to lenalidomide maintenance in patients diagnosed with multiple myeloma after autologous transplantation. Modifications during treatment plan due to its toxicity

E. Fort Casamartina[1], C. Muñoz Sanchez[1], A. Sancho Artes[1], J.A. Esteban Gonzalez[1], C. Bleda Perez[1], J. Prats Jimenez[1], A. Sureda Balari[1], V. Clapes Puig[1], C. Baca Cano[1], S. Fontanals Martinez[1]

[1]Hospital Duran y Reynals, Hospitalet Llobregat, Spain

Background: Consolidation therapy with lenalidomide (LEN) after induction therapy and transplantation is one strategy that improves outcomes in patients with multiple myeloma (MM). Toxicity due to LEN could lead to delays or reductions in initial dose treatment plan.

The objective was to evaluate modifications in the initial treatment plan during maintenance with LEN after autologous transplant (ASCT) in patients with MM (dose reductions or delays due to its toxicity), and analyze differences on long-term outcome.

Methods: Retrospective observational study in an oncohematological hospital between June/2018–October/2020. Patients diagnosed with MM who were treated with LEN after ASCT were included: Treatment data were obtained with prescription software system: starting date, LEN dose in each cycle, preplanned delays in cycles (yes or not), dose reductions (yes or not) and dose intensity. Clinical and demographic data were obtained by means of a electronic medical record software. X2 test was used to analyze categorical variables, T-student test for quantitative variables, progression free survival was calculated by means of the Kaplan Meyer Test.

Results: 29 patients were included, length of LEN treatment was 15.47 months (range 0.1–33). Most frequent starting dose was 10 mg, treatment delay was needed in 14 patients and dose reduction in 13 patients. Most patients reduced to 5 mg per day (69.2%). A second reduction was needed in 5 patients.

Median dose intensity administered was 78.3% (range 34%–101%); progression was detected in 5 cases (17.2%). Median dose intensity was 80.76% and 64.55% (p = 0.092) in patients without/with progressive disease after transplant. Delayed therapy and dose reductions had also a non-significant impact on disease progression [26.6% vs 7.1%, p = 0.164 and 23% vs 12.5%, p = 0.453, respectively].

Conclusions: In most cases, patients needed a LEN dose reduction of 50% (from 10 to 5 mg po daily). Dose reduction of LEN maintenance therapy seemed to be associated to a non-significant increase in disease progression, probably due to the low sample size. More studies are needed to evaluate if dose intensity could be an independent predictive factor for survival in this setting.

Disclosure: Nothing to declare

P412

Epidemiological profile of patients with multiple myeloma who developed pulmonary complications after hematopoietic stem cell transplantation

J. Chacón[1], D. Cano[1,2], F. Bolivar[3,2], J. Rey[1], L. Salazar[1,4], A. Peña[1,5], S. Jimenez[4,5], M. Rosales[4,5], J. Diaz[1], J. Alvarez[4], A. Prada[1], G. Vesga[1], S. Grandas[1], M. Ochoa[1], M. Chacón[4], C. Sossa-Melo[1,4]

[1]Universidad Autónoma de Bucaramanga, Floridablanca, Colombia, [2]Instituto Neumológico del Oriente, Floridablanca, Colombia, [3]Universidad Industrial de Santander, Bucaramanga, Colombia, [4]Clínica FOSCAL, Floridablanca, Colombia, [5]Programa para el Tratamiento de Enfermedades Hemato-Oncológicas de Santander-PROTEHOS, Floridablanca, Colombia

Background: Multiple myeloma (MM) is a neoplastic entity for which Hematopoietic Stem Cell Transplantation (HSCT) is a therapeutic option. Between 30–60% of patients managed with HSCT have pulmonary complications (PC). The aim of this study was to identify the clinical and sociodemographic characteristics associated with the incidence of PC in patients with MM after HSCT (post-HSCT) at Clinica FOSCAL.

Methods: An observational, descriptive, retrospective cohort study was carried out in adults with a diagnosis of MM post-HSCT in a clinic in Colombia, between July 2013 and April 2020. Sociodemographic, clinical and hematological variables related to post-HSCT were established. All patients had a chest image (X-ray or Computed Tomography) prior to HSCT

Results: A total of 73 patients were included. 54.8% were women, with a mean age at the time of HSCT of 58 years, and a mean time between diagnosis and HSCT of 2 years. As a history of lung disease, it was found that 15% had presented pneumonia, 6.8% asthma, 5.5% Chronic Obstructive Pulmonary Disease, and 1.4% both bronchitis and pulmonary hypertension. 56.2% had a normal chest image. The overall incidence of PC post-HSCT was 19.2%, with 8.2% occurred before day 100 post-HSCT and were entirely infectious complications, and 10.9% occurred after 100 days post-HSCT, 9.5% being infectious and 1.4% not infectious (asthma).

Of the total sample, patients who developed PC post-HSCT corresponded to 18% and 20% of men (RR = 0.98) and women

(RR = 1.02) respectively, with a mean age of 62.7 years (RR = 1.02), and 18.2% of patients were from urban areas. In the medical history, these patients with PC post-HSCT corresponded to 20.4% of the patients with normal BMI (RR = 0.94) and 18.2% of those who were overweight (RR = 1.05). Regarding comorbidities, 20.8% had chronic kidney disease (RR = 1.13), 17.8% had hypertension (RR = 1.39) and 7.4% had dyslipidemia (RR = 1.14). Likewise, 25.9% of the smokers/ex-smokers (RR = 1.1) and 20% of those who reported alcohol consumption (RR = 1.36) had PC post-HSCT. Regarding the hematological variables, it was observed that 21% of the patients with MM IgG Lambda (RR = 0,.7), 19.4% with MM IgG Kappa (RR = 1.05), 22.8% in stage 3 according to ISS (RR = 5.7) and 21.3% with Durie Salmon II (RR = 1.75) developed PC post-HSCT, as well as 19.1% of patients with MM who received myeloablative conditioning (RR = 1.8) and 22.2% who received Cybord (Bortezomib + Cyclophosphamide + Dexamethasone) (RR = 0.88). None of these results showed statistically significant differences.

Conclusions: This study allowed to identify an incidence of PC of 19.2% in MM patients post-HSCT in a university Clinic in Colombia, without statistically significant relative risk for socio-demographic, clinical, or hematological variables.

Clinical Trial Registry: N/A

Disclosure: N/A

P413

Multiple myeloma characteristics correlated to serum free light chain ratio at diagnosis and association with early renal damage

D. De Novellis[1], A. Carobene[1], R. Fontana[1], B. Serio[1], I. Ferrara[1], M.C. Martorelli[1], L. Mettivier[1], R. Guariglia[1], S. Luponio[1], I. Ruggiero[1], V. Giudice[1], C. Selleri[1,2]

[1]University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy, [2]Surgery and Dentistry "Scuola Medica Salernitana" University of Salerno, Baronissi, Italy

Background: Serum free light chain (FLC) ratio is a sensitive method to detect light chain hyper-production and is a biomarker of Multiple Myeloma (MM) progression from premalignant conditions.

We investigated the relationship between FLC ratio at diagnosis and clinical/MM characteristics and the predicting role of FLC ratio in influencing progression-free (PFS) and overall survival (OS).

Methods: A total of 33 MM patients who underwent autologous stem cell transplantation after induction therapy at the Hematology and Transplant Center, University Hospital "San Giovanni di Dio e Ruggi d'Aragona" of Salerno since 2015, was included in this retrospective study (Table 1). Quantification of FLC ratio at diagnosis was performed by nephelometric assays and standardized (sFLC) as follows: involved/uninvolved chain. Correlations between sFLC ratio and clinical/MM parameters were investigated by univariate and multiple linear regression models, while the influence of sFLC ratio on PFS and OS was analyzed by Mantel-Cox proportional hazard regression model.

Characteristics	**N = 33**
Median age, years (range)	62 (40-73)
Gender, n (%)	
Male	18 (55)
Female	15 (45)
Chromosome 17 deletion, n (%)	
Yes	4 (12)
Not available	5 (15)
M-protein type, n (%)	
IgG	20 (61)
IgA	7 (21)
IgD	1 (3)
Micromolecular	4 (12)
Not secerning	1 (3)
Light chain type, n (%)	
Kappa	17 (52)
Lambda	16 (48)
Median serum M-protein, gr/dl (range)	2.7 (0-5.9)
Median flow cytometry plasma cell, % (range)	6 (0.25-41)
Median sFLC ratio (range)	15.4 (1-3640)
Median β -2 microglobulin, mg/dl (range)	3.3 (1.4-19)
Median albumin, g/dl (range)	3.3 (2-4.9)
Median LDH, mU/ml (range)	395 (217-900)
Median glomerular filtration rate, ml/min (range)	93 (4-120)
Median PFS, months (range)	26 (2-95)
Median OS, months (range)	43 (6-104)

Results: Effects of gender (male, $P = 0.28$), age ($P = 0.75$), MM type (micromolecular, $P < 0.005$), M-protein level ($P = 0.05$), free light chain type (lambda, $P = 0.34$), β-2 microglobulin ($P < 0.005$), LDH ($P = 0.66$), albumin ($P = 0.9$), flow cytometry plasma cell count ($P = 0.62$), and extramedullary disease (yes, $P = 0.76$) on sFLC ratio were investigated by univariate linear regression analysis. By multiple linear regression, only micromolecular MM ($P = 0.05$) and β-2 microglobulin ($P < 0.005$) were significantly associated to sFLC ratio. Furthermore, sFLC ratio inversely correlated with glomerular filtration rate at diagnosis (r = -0.45; P = 0.009) by Pearson analysis. No influences on PFS [median PFS 26 months; HR:0.93 (CI: 0.85-1.03); p = 0.21] and OS [median OS 43 months; HR:0.97 (CI:0.92-1.02); p = 0.27] by sFLC ratio were observed.

Conclusions: Diagnostic and predictive roles of serum sFLC ratio in MM has been largely evaluated in recent years. In our study, sFLC ratio was significantly associated with micromolecular MM and β-2 microglobulin likely due to a delay in MM diagnosis ultimately leading to higher disease burden, especially without heavy chain M-protein at serum electrophoresis. Furthermore, the inverse correlation between sFLC ratio and glomerular filtration rate might be related to an early damage of FLC excess on renal tissue.

In conclusions, our preliminary results confirmed the importance of early sFLC evaluation for diagnosis of micromolecular and lower disease burden MM, reducing the risk of renal damage. However, further validation on larger and prospective studies are needed.

Disclosure: Nothing to declare

P414

Tandem ASCT or amyeloablative ALLO-SCT in patients high risk with multiple myeloma: A phase 3 biological assignment trial

B. Huang[1], X. Wang[2], H. Huang[3], X. Du[4], B. Wu[5], X. Xu[6], J. Li[1]

[1]First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, [2]Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China, [3]Affiliated Hospital of Nantong University, Nantong, China, [4]Shenzhen Second People's Hospital, Shenzhen, China, [5]Shunde Hospital of Southern Medical University, Foshan, China, [6]The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, China

Background: Novel drugs induction followed by autologous stem cell transplantation (ASCT) is the standard regimen for transplant-eligible patients with multiple myeloma (MM). However, approximately 20% of patients will have early relapse within 2 years after ASCT, which are defined as high risk myeloma. Tandem ASCT or allogeneic stem cell transplantation (allo-SCT) may overcome the poor prognosis of high risk myeloma. However, prospective controlled studies evaluating the role of tandem ASCT and allo-SCT in high risk myeloma are lacking. Thus we aimed to assess effectiveness of tandem ASCT with allo-SCT.

Methods: In our phase 3 biological assignment trial, we enrolled patients with multiple myeloma attending 8 transplant centers in China. Patients (<70 years old) with adequate organ function who had completed four to six cycles of systemic antimyeloma therapy were eligible for inclusion. We assigned patients to receive an myeloablative allo-SCT or tandem ASCT on the basis of the availability of an HLA-matched sibling donor. We used the Kaplan-Meier method to estimate differences in time-to progression survival (TTP; primary endpoint) and overall survival (OS) between the two groups.

Results: Between Jan 1, 2018 and Jun 30, 2021, we enrolled 49 patients, of whom 40 were enrolled to tandem ASCT group and 9 were enrolled to allo-SCT group. In intention to treat population, Kaplan-Meier estimates of TTP (not reach and 15.0 months, $p = 0.010$) and OS (not reach and 17.3 months, $p < 0.0001$) were better in Tandem ASCT group. TTP of those received double ASCT in Tandem ASCT group was better than those received only one time of ASCT (33.5 months and 25.3 months, $p = 0.037$). Cumulative nonrelapse mortality after allo-SCT ($n = 2$, because of GVHD) was higher than tandem ASCT ($n = 1$, because of infection), $p = 0.012$.

Conclusions: Tandem ASCT is effective that myeloablative allo-SCT for patients with high-risk multiple myeloma.

Clinical Trial Registry: ChiCTR2100046510; http://www.chictr.org.cn/index.aspx.

Disclosure: Nothing to declare

P415

Allogeneic hematopoetic cell transplantation in patients with myeloma – unicentric study

T. Kriz[1], A. Jungova[1], D. Lysak[1], M. Karas[1], M. Hrabetova[1], J. Sramek[1], P. Jindra[1]

[1]Faculty Hospital Pilsen, Pilsen, Czech Republic

Background: Standard treatment of MM consists of induction chemotherapy followed by autologous hematopoetic cells transplant (autoSCT), but this scheme doesn't present a curative potential. The only one modality with curative potential remains allogeneic hematopoetic cells transplant (aloSCT). With the knowledge of high mortality & morbidity related to the tratment (TRM) in comparison to tratment with novel drugs, there is no consensus in indication of aloSCT in MM, also identification of ideal patients profiting from this method is difficult. Therfore a retrospective unicentric study of patients after aloSCT for MM was performed.

Methods: 36 consecutive patients with MM transplanted in University hospital in Pilsen between years 2000-2020. Median of age 52 (38-63), 26 men (72%), 19pts transplanted between 2000-2010 including (52,8%). Median of previous regimens 2 (1-5), 92% of pts underwent autoSCT after induction, in 9 patients (25%) elective auto-alo tandem. 12 patients (33,3%) transplanted with resistant disease. Novel drugs before aloSCT in 16pts (44,4%). Conditioning mostly non-myeloablative (Flu-Mel, $n = 33$, 91,7%), non-related donors ($n = 20$, 56%), identical related donors ($n = 14$, 38,9%), haploidentical ($n = 2$, 5,5%).

Results: With median follow up of 85 months (8-178) 27 patients (75%) died: TRM in 11 patients (31%), relaps in 16 pts (44%). 9 patients alive, 6 of them with relaps/profression. OS/PFS medians 30 (10-60), respectively 15 months (11-175). OS in 1 and 5 years 55% and 30,3%. Patients transplanted without resistant disease had statistically significantly prolonged OS (HR 0,43, 95%CI 0,18-1,01, $p = 0,05$), not proven in PFS (HR 0,75, 95%CI 0,25-2,21, $P = 0,57$). Neither period of tranplant (2000-2010 vs 2011-2020), nor previous treatment with novel drugs showed the impact on survival.

Conclusions: Accordingly to international litarature, our data prove curative potential of aloSCT in some carefully selected high risk patients, it proves the potential to prolong survival in these patients even if with active disease, but not derogating the QoL significantly. GvM efect shows like potential platform for following therapy. Even though we cant precisely define patients profiting from alo SCT, we should still consider aloSCT as an efective treatment in suitable high risc patients.

Disclosure: No disclosures

P416

Salvage autologous stem cell transplantation is a cost-effective treatment option for multiple myeloma relapsing after prior asct: A single-center experience in China

L. Kuang[1], W. Zou[1], J. Liu[1], B. Huang[1], J. Gu[1], M. Chen[1], X. Li[1], J. Li[1]

[1]First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: We aimed to evaluate the outcome and cost-effectiveness of salvage ASCT (sASCT) for multiple myeloma (MM) relapsing after prior ASCT in a cohort of patients from China.

Methods: Thirteen patients relapsing after upfront ASCT retreated with sASCT were enrolled. The outcome and cost-effectiveness were compared with those of patients retreated without sASCT.

Results: The median age of the patients at the first and second ASCT were 52.0 and 55.0 years. Twelve patients (92.3%) achieved a response of VGPR or above after sASCT. Compared with patients relapsing during the same period who were retreated with novel agents (NAs) ($n = 26$)or with conventional cytotoxic drugs (CCs) ($n = 4$), sASCT patients had longer PFS (37.800 months in the sASCT group vs 10.533 months in the NA group vs 1.933 months in the CC group, $P < 0.001$) and longer OS (45.867 months in the sASCT group vs 15.633 months in the NA group vs 1.933 months in the CC group, $P < 0.001$). The sASCT group demonstrated lower cost-effectiveness ratio (¥179126 per life year) than those of patients retreated without sASCT (¥330474 per life year,

$P = 0.049$). Eight (61.5%) patients used cryopreserved stem cells from the first ASCT for sASCT, all of which achieved successful engraftment. Three (60.0%) of the 5 remobilized patients failed to collect sufficient stem cells, 2 of which failed hematopoietic reconstruction.

	Initial ASCT	sASCT
Mobilization regimen		
High dose cyclophosphamide + G-CSF	12/13 (92.3%)	5/13 (38.5%)
G-CSF	0	0
Bone marrow collection	1/13 (7.7%)	2/13 (15.4%)
Cryopreserved stem cells (collected before initial ASCT)	-	8/13 (61.5%)
Mobilization failure	0	3/5 (60.0%)
Engraftment failure		
Granulocytic graft failure	0	1/13 (7.7%)
Megakaryocytic graft failure	0	2/13 (15.4%)

Conclusions: sASCT is a cost-effective treatment option for MM patients relapsing from upfront ASCT. Reserved stem cells from the first ASCT are of significance for hematopoietic reconstruction of sASCT.

Disclosure: Nothing to declare

P417

Autologous stem cell transplantation in al amyloidosis: A single centre experience

I. Santos Marques[1], E. Aguiar[1], R. Bergantim[1], J. Cancela-Pires[1], I. Tavares[1], F. Trigo[1]

[1]Centro Hospitalar Universitário São João, Porto, Portugal

Background: Amyloid light chain amyloidosis (ALA) is characterized by the pathologic production of fibrillar proteins comprised of monoclonal light chains which deposit in tissues and cause organ dysfunction. The therapeutic approach is based on the use of drugs widely used in the treatment of multiple myeloma and performing autologous stem cell transplant (ASCT). Although the median survival of patients undergoing ASCT is quite relevant (10 years), only 20% of patients are eligible for ASCT due to delayed diagnosis and strict eligibility criteria for ASCT.

Methods: Retrospective review of ALA patients submitted to ASCT in one institution (2017-2021). The overall survival (OS) and progression-free survival (PFS) was estimated by the Kaplan-Meier method. ASCT toxicity was evaluated by CTCAEv5.0.

Results: A total of 6 patients had undergone ASCT (male = 1, 16.7%), with a median age of 66 years (51-68) and ECOG performance status 0-1. Median visceral organ involvement at diagnosis was 2.5 (1-4). All patients receive induction treatment before ASCT with cyclophosphamide/bortezomib/dexamethasone and peripheral blood progenitor cells (PBPCs) mobilization was accomplished with granulocyte-colony stimulating factor (G-CSF) alone (n = 5, 83.3%) or G-CSF plus cyclophosphamide (n = 1, 16.7%). After induction treatment, haematological complete remission (CR), very good partial response (VGPR) and partial (PR) response were 16.7%, 66.7% and 16.7% respectively, whereas organ response was 66.7%. All patients received melphalan as conditioning [200mg/m^2 (n = 3, 50%) and 140mg/m^2 (n = 3, 50%)]. Median inpatient stay during ASCT was 24 days (17-52). All patients received supportive care specific for ALA: infusion of PBPC performed through peripheral venous access; graft syndrome prophylaxis with 0.5mg/kg/day prednisolone from day +7 until neutrophils ≥500/mm^3 and eviction of G-CSF after PBPC infusion. Toxicity was frequent and severe. All patients developed febrile neutropenia; median time until neutrophils>500/mm^3 was 11 days (10-15). Two (33.3%) patients had gastrointestinal mucositis (grade 2-3), and all had grade ≥2 oral mucositis. Three patients developed renal failure requiring renal replacement therapy. The four patients with cardiac involvement at diagnosis, developed cardiac complications (two during hyperhydration of the conditioning regimen). One patient died from sepsis and multiple organ failure. At day +100 post-ASCT, haematological CR and VGPR were 60% and 40% respectively. During monitoring period (9-60 months) median OS and PFS was not achieved. Two patients relapsed after 4 and 9 months after ASCT and one patient died without apparent cause 31 months after ASCT.

Conclusions: ASCT in ALA was first performed in our institution in 2017. Therefore, the number of patients included in this analysis is limited, which does not allow us to make comparisons with studies already carried out in this area, nor to establish logistic regression models to assess the clinical factors that may have an impact on transplant success in our population. Although the number of patients, our real-life results demonstrate that ASCT appears to be an effective therapy for patients with ALA, with durable response rates. Additionally, despite the strict eligibility criteria for ASCT, the occurrence of serious complications is still noticed, so these patients must always be guided by a dedicated and trained team.

Disclosure: Nothing to declare.

MYELODYSPLASTIC SYNDROMES

P419

Influence of donor type and r-ipss stratification on outcomes from myelodysplastic syndrome bone marrow transplantation latin american registry

F.B. Duarte[1], T.E. Sousa[2], V.A.M. Funke[3], V.A.R. Colturato[4], N. Hamerschlak[5], N.C. Villela[6], M.C.M.d.A. Macedo[7], A.C. Vigorito[8], R.D.d.A. Soares[9], A. Paz[10], M. Stevenazzi[11], A.E. Hallack Neto[12], G. Bettarello[13], B.M. Gusmão[14], M.A. Salvino[15], R.F. Calixto[16], M.C.R. Moreira[17], G.M. Teixeira[18], E.J.d.A. Paton[19], V. Rocha[20], A. Enrico[21], C. Bonfim[22], C.C. Silva[5], R.P.G. Lemes[2], Y.D.O. Garcia[2], R. Chiattone[23], A.J. Simioni[4], C. Arrais[24], E.O.d.M. Coelho[25]

[1]University Hospital Walter Cantídio, Hematology, Fortaleza, Brazil, [2]Hematology Research Laboratory - Federal Universityof Ceara, Fortaleza, Brazil, [3]Federal University of Paraná, Bone Marrow Transplantation, Curitiba, Brazil, [4]Hospital do Câncer Amaral Carvalho - Fundação Amaral Carvalho, Bone Marrow Transplant, Jaú, Brazil, [5]Hospital Israelita Albert Einstein, Bone Marrow Transplant, São Paulo, Brazil, [6]Hospital de Câncer Infantojuvenil de Barretos, Bone Marrow Transplant, Barretos, Brazil, [7]Instituto Brasileiro de Controle do Cancer, Bone Marrow Transplant, São Paulo, Brazil, [8]Universidade Estadual de Campinas - UNICAMP/ Hemocentro, Bone Marrow Transplant, Campinas, Brazil, [9]Natal Hospital Center, Bone Marrow Transplant, Natal, Brazil, [10]Hospital das Clínicas de Porto Alegre, Bone Marrow Transplant, Porto Alegre, Brazil, [11]Centro TPH-SMI Serviço Médico Integral, Bone Marrow Transplant, Montevideo, Uruguay, [12]Hospital Universitário Universidade Federal de Juiz de Fora, Bone Marrow Transplantation, Juiz de

Fora, Brazil, [13]Unidade de Transplante de Medula Óssea Pietro Albuquerque - ICDF, Bone Marrow Transplantation, Brasilia, Brazil, [14]Hospital São José, Bone Marrow Transplantation, São Paulo, Brazil, [15]Hospital Universitário Prof. Edgard Santos, Bone Marrow Transplantation, Salvador, Brazil, [16]Real Hospital Português de Beneficência em Pernambuco, Bone Marrow Transplantation, Recife, Brazil, [17]CEMO-INCA, Bone Marrow Transplantation, Rio de Janeiro, Brazil, [18]Hospital das Clínicas - Universidade Federal de Minas Gerais - Transplante de Medula Óssea, Belo Horizonte, Brazil, [19]ONCOBIO Serviço de Saúde S.A., Bone Marrow Transplantation, Nova Lima, Brazil, [20]Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Bone Marrow Transplantation, São Paulo, Brazil, [21]Hospital Italiano La Plata, Bone Marrow Transplantation, La Plata, Argentina, [22]Hospital Pequeno Principe, Bone Marrow Transplantation, Curitiba, Brazil, [23]Hospital Samaritano de São Paulo, Bone Marrow Transplantation, São Paulo, Brazil, [24]Hospital Sírio Libanês, Bone Marrow Transplantation, São Paulo, Brazil, [25]Hospital Santa Joana, Bone Marrow Transplantation, Recife, Brazil

Background: The role of mutations in diagnosis, prognosis, treatment and even follow-up post HSCT in MDS has become increasingly relevant from a diagnostic point of view, especially in cases with cytopenias without blasts. The presence of mutations, epigenetic regulation or splicesseosome regulation can be of great diagnostic value. In treatment, the presence of the SF3B1 mutation indicates the possibility of treatment with luspatercept; in the case of TP53 mutation, the possibility of using APR-246 or even Venetoclax associated with Vidaza can be very efficient, opening up a great discussion of a more rational therapy. Regarding HSCT, despite being a single curative therapy, its precise indication is essential, because even in the best centers, morbidity and mortality is still necessary, and a fundamental aspect is to select the best donor, cell source and type of conditioning, which force us to define post-HSCT goals. In view of these considerations, we decided to study two aspects of this work in patients from the Latin American HSCT registry in MDS: donor type and the correlation of stratification with R-IPSS with overall survival, considering that we do not have molecular analysis as a tool, just like most places in Latin America.

Methods: We analyzed data from 331 patients with MDS from the transplant registry of 32 centers in Latin America from 1989 to 2021. Statistics were performed using SPSSv.23.1, considering a significant $p < 0.05$.

Results: There was a predominance of males (59%) and whites (87%). The median age was 46 years. According to the Prognosis Scoring System (IPSS-R), patients were classified as very low (0.6%), low (10.6%), intermediate (24,1 %), high (18.7%) and very high risk (5.1%). About 40% did not have IPSS-R data. In myeloablative conditioning (MAC) (73,7%), the regimens were bulsulfan/fludarabine (39,58 %), bulsulfan/cyclophosphamide (30,51%) and regimes with total body irradiation (7,85%). At reduced intensity/non-myeloablative regimen (RIC) (26,3%) were bulsulfan/fludarabine (40,79%), fludarabine/melphalan (44,71%) and regimens based on total body irradiation (11,48%). The cell source was bone marrow (BM) (54,08%), peripheral blood (PB) (44,11%) and umbilical cord blood (1.8%). In 69,18% of cases, donor was related, 22,96% unrelated and 7,85% haploidentical. The main post-HSCT complications were infections (92.1%) of which 48,8% included CMV infection. Frequency of death was 39,88%($n = 132$). When comparing the donor type, haploidentical group had higher Overall Survival (OS) but there was no statistical difference in HSCT for haploidentical (63,30%) related (59,90%) and unrelated (58,70%) $p = 0.9614$. Regarding R-IPSS stratification, the 5-OS was 57.1%, 50%, 50.5% and 16.4% for Low, Intermediate, High and Very High Risk, respectively.

Conclusions: Haplo-hematopoietic stem cell transplantation is a valuable alternative in the absence of an HLA-compatible donor in patients with myelodysplastic disease. R-IPSS stratification is a useful prognostic tool in HSCT, especially in those centers where molecular analysis is not yet a reality.

Disclosure: Nothing to declare

P420

Preliminary results of bone marrow transplantation in hypocellular variant myelodysplastic syndrome from the latin american registry

F. Duarte[1], T.E.J.S. Sousa[2], V. Funke[3], V. Colturato[4], N. Hamerschlak[5], N. Vilela[6], M.C.MA. Macedo[7], A.C. Vigorito[8], R.D.A. Soares[9], A. Paz[10], M. Stevenazzi[11], A.E. Hallack Neto[12], G. Bettarello[13], B.M. Gusmão[14], M.A. Salvino[15], R.F. Calixto[16], M.C.R. Moreira[17], G.M. Teixeira[18], E.J.A. Paton[19], C.C. Silva[5], R.P.G. Lemes[2], Y.D.O. Garcia[2], V. Rocha[20], A. Enrico[21], C. Bonfim[22], R. Chiattone[23], A.J. Simioni[4], C. Arrais[24], E.O.M. Coelho[25], L. Diaz[11]

[1]University Hospital Walter Cantídio, Hematology, Fortaleza, Brazil, [2]Hematology Research Laboratory - Federal Universityof Ceara, Fortaleza, Brazil, [3]Federal University of Paraná, Bone Marrow Transplantation, Curitiba, Brazil, [4]Hospital do Câncer Amaral Carvalho - Fundação Amaral Carvalho, Bone Marrow Transplant, Jaú, Brazil, [5]Hospital Israelita Albert Einstein, Bone Marrow Transplant, São Paulo, Brazil, [6]Hospital de Câncer Infantojuvenil de Barretos, BoneMarrowTransplant, Barretos, Brazil, [7]Instituto Brasileiro de Controle do Cancer, Bone Marrow Transplant, São Paulo, Brazil, [8]Universidade Estadual de Campinas - UNICAMP/Hemocentro, Bone Marrow Transplant, Campinas, Brazil, [9]Natal Hospital Center, Bone Marrow Transplant, Natal, Brazil, [10]Hospital das clínicas de Porto Alegre, Bone Marrow Transplant, Porto Alegre, Brazil, [11]Centro TPH-SMI Serviço Médico Integral, Bone Marrow Transplant, Montevideo, Uruguay, [12]Hospital Universitário Universidade Federal de Juiz de Fora, Bone Marrow Transplantation, Juiz de Fora, Brazil, [13]Unidade de Transplante de Medula Óssea Pietro Albuquerque - ICDF, Bone Marrow Transplantation, Brasilia, Brazil, [14]Hospital São José, Bone Marrow Transplantation, São Paulo, Brazil, [15]Hospital Universitário Prof. Edgard Santos, Bone Marrow Transplantation, Salvador, Brazil, [16]Real Hospital Português de Beneficência em Pernambuco, Bone Marrow Transplantation, Recife, Brazil, [17]CEMO-INCA, Bone Marrow Transplantation, Rio de Janeiro, Brazil, [18]Hospital das Clínicas -Universidade Federal de Minas Gerais- Transplante de Medula Óssea, Belo Horizonte, Brazil, [19]ONCOBIO Serviço de Saúde S.A., Bone Marrow Transplantation, Nova Lima, Brazil, [20]Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Department of Bone Marrow Transplantation, São Paulo, Brazil, [21]Hospital Italiano La Plata, Bone Marrow Transplantation, La Plata, Argentina, [22]Hospital Pequeno Principe, Bone Marrow Transplantation, Curitiba, Brazil, [23]Hospital Samaritano de São Paulo, Bone Marrow Transplantation, São Paulo, Brazil, [24]Hospital Sírio Libanês, Bone Marrow Transplantation, São Paulo, Brazil, [25]Hospital Santa Joana, Bone Marrow Transplantation, Recife, Brazil

Background: Hypocellular variant myelodysplastic syndrome (Hypo MDS) accounts for approximately 10 to 20% of all MDS cases. Diagnosis can be challenging due to clinical and laboratory similarities with aplastic anemia. Some studies indicate a better response to treatment and a better prognosis in this group of individuals. Allogeneic HSCT is indicated for patients with high risk R-IPSS or transfusional dependence. The objective was to evaluate the HSCT results in patients with Hypo MDS from 32 centers in Latin America.

Methods: It is multicenter study of Brazil, Uruguay and Argentina. Data of 331 patients (both sexes) from 1989 to 2021 were analysed. Patients were stratified according to the Revised International Prognostic Classification System (R-IPSS).

Conditioning regimen and supportive treatment were performed according to the protocol of each institution. Statistical analysis by GraphPad Prism version 5.0 and SPSS software v.23.1 and v.24, considering significance of $p < 0.05$.

Results: The mean age was 46,29 years. There was a predominance of male patients (n = 194; 59%) e Caucasian (n = 288; 87%). Prevalence of Hypo MDS was 11,1% (n = 37). According to R-IPSS patients were Intermediate (24,17%), High risk (18,73%), very hig risk (5,14%) and low risk/very low risk (11,17%). No response was observed in 40,79% cases. The Conditioning regimen used was Myeloablative (244; 73,72%) and Reduced Intensity/ Nonmyeloablative (87;26,28%). Most donor type was Related (229; 69,18%). Cell sources were: bone marrow (179; 54,08%), peripheral blood (146; 44,11%) and umbilical cord (6; 1,81%). Treatment Prior to HSCT was performed in 217 (65,56%) cases with predominant use of Chemotherapy (134; 61,75%). Overall survival in 5 years was 28,4%. According to the cell source, OS was higher when used peripheral blood compared to bone marrow and umbilical cord ($p < 0,001$). There was no difference in overall survival according to treatment prior to HSCT, type of donor and conditioning regimen. Hypo MDS patients had a better 3-years OS with a tendency of statistical significance ($p = 0, 07$). Specific data analysis is in progress to better understand the factors that may influence these results.

Conclusions: Patients with Hypo MDS seemed to present a tendency to better OS. Absence of blasts and the molecular profile as other specific aspects may be the differentials in this response to treatment. Further specific studies need to be carried out to confirm these observations.

Disclosure: Nothing to declare

P422

Prognosis and results of allogeneic hematopoietic stem cell transplantation in patients with primary and therapy–related myelodysplastic syndrome

E. Morozova[1], P. Kotselyabina[1], N. Tcvetkov[1], K. Jurovskaya[1], T. Gindina[1], I. Moiseev[1], A. Kulagin[1]

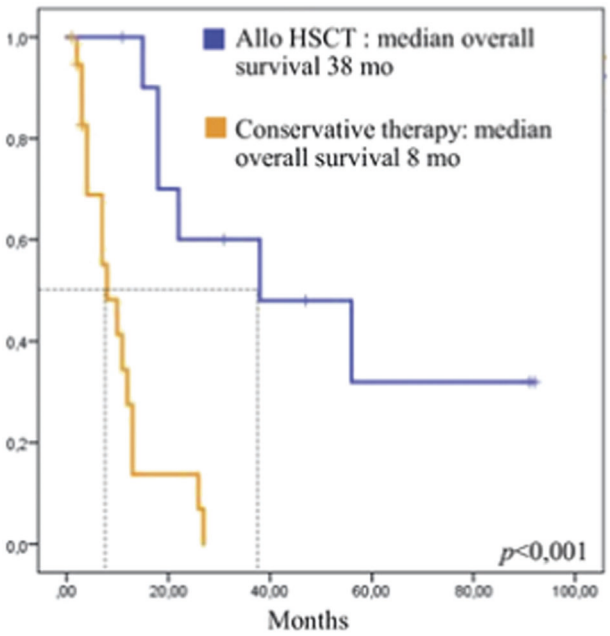
[1]RM Gorbacheva Research Institute, Pavlov University, St. Petersburg, Russian Federation

Background: Patients with secondary myelodysplastic syndrome (t-MDS), developing after previous chemoradiation therapy, have a more unfavorable course and prognosis compared to patients with initially diagnosed MDS (de novo MDS).

Methods: A single-center retrospective cohort study included 60 patients: 30 with t-MDS (therapy –related myelodysplastic syndrome),30 with de novo MDS. A group of 30 patients (10 m/20 f) with t-MDS who developed after chemotherapy or radiation therapy of a previous malignant neoplasm (MNO) was analyzed. The control group included 30 patients (10 m/20 f) with de novo MDS, matched by age at the time of MDS diagnosis, sex and risk in accordance with IPSS-R and WPSS.Overall survival (OS) was assessed, which was defined as the time from diagnosis of MDS to death from any cause

Results: All patients were included in the analysis. Median OS for t-MDS was significantly shorter than for de novo MDS (13 and 48 months, respectively, $p = 0.03$). The frequency of transformation into acute myeloid leukemia (AML) didn't differ significantly in the t-MDS and de novo MDS groups (33% and 30%, respectively, $p = 0.7$). The median time to transformation into AML in the t-MDS group was 2.6 months, and in the de novo MDS group - 8.6 months ($p = 0.27$). Risk factors have been analyzed in patients with t-MDS.

The structure of previous malignant neoplasms included classical Hodgkin's lymphoma 30% (n = 9), non-Hodgkin's lymphomas 23% (n = 7), breast cancer 20% (n = 6), acute leukemia 7% (n = 2), chronic lymphocytic leukemia 7 % (n = 2) and other solid tumors 13% (n = 4). Therapy for previous malignant neoplasms included chemotherapy in 37% (n = 11), radiation therapy in 3% (n = 1), and combination therapy in 50% (n = 15). There was no effect of the type, status, and treatment option of prior cancer on OS in patients with t-MDS. At the same time, the predictive value of risk stratification proposed by the MD Anderson Cancer Center group for t-MDS (TPSS) was demonstrated. Allo-HSCT was performed in 37% of patients (n = 11) with t-MDS. The median OS for patients without allo-HSCT was significantly shorter than for patients undergoing allo-HSCT (8 and 38 months, respectively, $p < 0.001$). There was a tendency to an increase in OS in patients with allo-HSCT in the first year after diagnosis compared with patients who underwent allo-HSCT at a later date, but the statistical significance of the differences was not confirmed, probably due to the small sample size (median OS 38 and 22 months, respectively, $p = 0.8$).



Conclusions: Patients with t-MDS have a significantly poorer prognosis compared to patients with comparable risk with de novo MDS, which makes it inappropriate to use standard prognostic scales for patients with t-MDS.Allo-HSCT increases the survival rate of patients with t-MDS and requires an earlier time frame.

Disclosure: Nothing to declare

MYELOPROLIFERATIVE NEOPLASM

P423

Partial embolization of splenic artery (PESA) - novel method for spleen size and splenic activity reduction in patients with myelofibrosis undergoing HSCT

P. Sobieralski[1], M. Bieniaszewska[1], A. Sadowska-Klasa[1], B. Baścik[1]

[1]Medical University of Gdańsk, Gdańsk, Poland

Background: The study aims to investigate the applicability of a novel method for spleen size reduction and splenic activity down-regulation in patients with myelofibrosis. Partial embolization of splenic artery (PESA), in comparison with conventional methods, such as surgical splenectomy or splenic

irradiation, is hypothesized to minimize the risk of known complications - bleeding, thrombosis and infection with encapsulated bacteria - therefore improving outcomes and reducing mortality.

Methods: A total of 12 patients were referred for PESA. Two patients with suspected hypersplenism-impaired engraftment had PESA in post-transplantation setting as a salvage procedure with the purpose of maintaining the graft function. Next, seven transplant-eligible patients underwent PESA because of splenomegaly and/or hypersplenism to reduce risk of graft failure. In three transfusion-dependent patients with massive splenomegaly and portal hypertension, PESA was conducted as a preparation for otherwise high-risk surgical splenectomy. The procedure has been evaluated regarding perioperative recommendations, occurrence of infections, bleeding and thrombotic events, management of complications and hospitalization time.

Results: PESA causes necrosis of 70-80% of splenic tissue and is associated with severe pain in the following days after the procedure. Successful pain management was achieved by the use of patient controlled analgesia (PCA) with the use of oxycodone and administration of coanalgesics.

PESA requires access to splenic artery. Intravascular catheter manipulation within the pancreatic area is suspected to cause symptoms similar to acute pancreatitis, inducing inflammation and thrombosis in splenic and portal vein. All patients received a prophylactic dose of anticoagulant starting 12 hours after the procedure. To maintain anticoagulant treatment in patients with thrombocytopenia, PLT count >30 G/l was sustained through daily platelet transfusion. Two thrombotic events were recorded. One patient, who had PESA with subsequent splenectomy, developed massive splenic vein thrombosis after surgery, ultimately leading to the rupture of the vein, intra-abdominal bleeding and death in hypovolemic shock. We recommend the use of therapeutic dose of anticoagulants in patients that are referred for PESA as a preparation for splenectomy. Additionally, we believe it's reasonable to keep the patient on the stable dose of JAK-inhibtor throughout the procedure.

All patients presented with a rapid increase in inflammatory markers over the first two days after the procedure. One patient has been discharged shortly after the procedure with the use of oral antibiotic prophylaxis only and required rapid rehospitalization due to sepsis. In remaining patients, an i.v. antibiotic (meropenem) was maintained until normalization of inflammatory markers and no detectable source of infection has been identified. We recommend the use of broad-spectrum antibiotics (preferably carbapenem) as a perioperative prophylaxis.

The median time of hospitalization for PESA was 22 days.

Notably, successful engraftment has been achieved in all patients who had PESA either prior or post transplantation procedure.

Conclusions: We revealed several applications of PESA and prepared a management algorithm to ensure patient's safety. However, the applicability of PESA, including proper patient selection, timing in relation to allo-SCT and long-term outcomes remains to be further investigated.

Disclosure: Nothing to declare

P424

Does fibrosis persist after allogeneic HSCT in patients with myelofibrosis, who are otherwise negative for driver mutations, with full donor chimerism?

F. Sora[1], P. Chiusolo[1], L. Laurenti[1], S. Giammarco[1], I. Innocenti[1], E. Metafuni[1], F. autore[1], E. Galli[1], S. Sica[1], A. Bacigalupo[1]

[1]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Background: Allogeneic HSCT is capable of inducing a significant proportion of patients with MF into a clinical and molecular remission. Less clear is the role of bone marrow morphology beyond 6 months from transplant. We aimed to correlate clinical, hematologic, molecular, chimerism data with marrow morphology from bone marrow biopsies, in MF patients 6-48 months post-allogeneic HSCT

Methods: Data were derived from an electronic database into which patient, disease, and transplantation characteristics had been entered prospectively. All patients provided written informed consent for research studies using forms approved by the Institutional Review Board. Eligible for this study were patients with a negative driver mutation and full donor chimerism. Forty two, out of 50 consecutive MF allografts, met the inclusion criteria. They are 21 male and 21 female, median age was 59 years (41-71 range); 7 patients had diagnosis of primary myelofibrosis and 35 secondary MF, 19 had high and 23 intermediate-2 risk disease (DIPSS) 29 have JAK positive disease. Before transplant all the patients showed severe (MF3) in bone marrow biopsy. Median follow up was 642 days (range 210-1907). All patients underwent a routine bone marrow biopsy between 6-24 months post-HSCT.

Results: Bone marrow biopsies were scored as follows: moderate severe fibrosis (MF2-MF3), n = 19, 45%; normal or minimal fibrosis (MF0-1), n = 17, 40%; not evaluable n = 4 (10%), non performed n = 2 (5%). When stratified by interval from transplant, the proportion of MF2-MF3 was 53%, 50%, 50% and 29% at <365, 366-730, 731-1095 and >1095 days from transplant **(Table 1)**. Two patient (5%) showed a poor graft function at the time of bone marrow biopsy, all other patients had normal/near to normal blood counts . Nintyfive percent of these patients were off immunosuppressive therapy at the time of bone marrow biopsy.

Conclusions: A significant proportion of patients with negatifve driver mutations, complete donor chimerism, and normal blood coutns, still exhibit marrow fibrosis long term post transplant: there seems to be a trend for a reduction of MF2-MF3 patients with time. Additional investigation in these patients may highlight the pathogenesis of fibrosis in patients with MF.

Table 1. Driver mutation, Chimerism and Bone marrow fibrosis at differet time after allogeneic transplantation.

Days from transplant	<365	365-730	731-1095	>1095
Driver mutation	0%	0%	0%	0%
Chimerism	100%	100%	100%	100%
MF0-1	47%	50%	50%	71%
MF2-3	53%	50%	50%	29%

Disclosure: none

P425

Molecular annotation of extramedullary and bone marrow primary myelofibrosis relapse after allogeneic hematopoietic stem cell transplantation

M.V. Barabanshikova[1], D.S. Bug[1], E.A. Izmailova[1], I.M. Barkhatov[1], N.V. Petukhova[1], V.V. Baykov[1], J.J. Vlasova[1], I.S. Moiseev[1], E.V. Morozova[1], A.D. Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, Saint-Petersburg, Russian Federation

Background: Allogeneic stem cell transplantation (alloHSCT) is currently the only treatment option with curative potential in patients with PMF. Relapse prevention and treatment remains a challenge in these patients. Here were report a case of extramedullary relapse of myelofibrosis and its molecular profile after alloHSCT.

Methods: A 39-years old female was diagnosed with CALR type 1-positive PMF, 46XX, IPSS low risk, DIPSSplus intermediate -2 risk, four years before alloHSCT. During 12 months the patient received therapy with pacritinib in clinical trial which was accompanied by reduction of spleen volume and transfusion requirements. Just before alloHSCT splenectomy was performed. After short course of ruxolitinib alloHSCT from 10/10 –HLA matched related donor with peripheral stem cells (10.5 x 109 CD34 + cells/kg) was performed. Conditioning regimen consisted of fludarabine (180 mg/m2), busulfan (10 mg/kg p.o.). Post-transplant cyclophosphamide was administered at 100 mg/kg at day +3, +4, and ruxolitinib 15 mg was used from D + 5 till D + 100 as graft versus host disease (GVHD) prophylaxis.

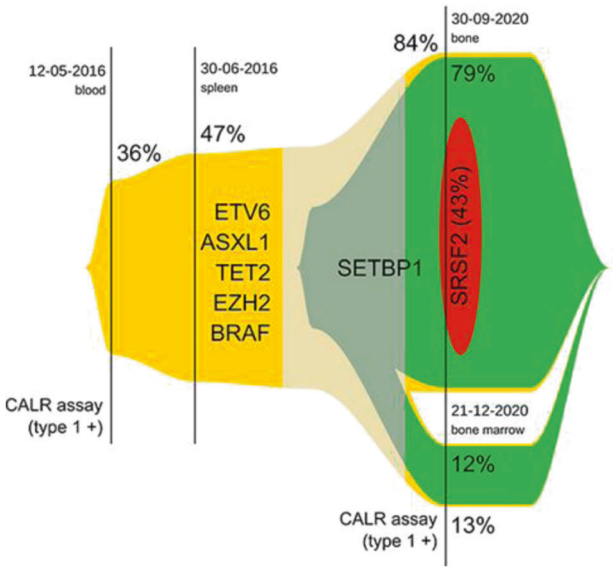
Library for next-generation sequencing was created with QIAact Myeloid DNA UMI Panel, sequencing itself was performed on Illumina MiSeq System. We used our in-house script based on GATK Best Practices for primary data analysis. All variants with population frequency exceeding 1%, confirmed by less than 100 UMI, or with allele frequency less than 2% were filtered out. We used PyClone with standard parameters to infer clonal evolution.

Results: Platelet and neutrophil engraftment was documented at D + 35 and D + 38 and full donor chimerism and molecular remission was achieved. Acute GVHD grade 3 with liver (2) and skin (1) evolvement at D + 50 was documented and resolved after cyclosporine A administration. Bone marrow fibrosis regression from grade MF 3 to MF 0-1 was documented at D + 749. At D + 1045 the patient experienced mild pain and additional mass in her right shin. At D + 1344 PET/CT revealed additional metabolic active mass (SUV = 8.66) 38 x 27 x 63 mm with cortical thinning and destruction. Histological examination documented PMF relapse with reactive osteoblasts proliferation. At D + 1401 thrombocytopenia 30-14 x 10^9/l, anemia – 92 g/l, peripheral blasts – 5%, bone marrow blasts – 5% were documented. Due to hematological and extramedullary relapse fludarabine and cytosine arabinoside – containing chemotherapy was started. However, patient died due to infection complications after chemotherapy completion.

Targeted next-generation sequencing was carried out in four samples: (1) blood taken during the onset, (2) spleen after splenectomy, (3) extramedullary hematopoiesis elements in bone in the course of late bone marrow remission, and (4) bone marrow in relapse.

Clonal reconstruction revealed three relevant clones: the first, which was present in the onset, contained six mutations: ETV6:-p.Asn227fs, ASXL1:p.Glu635fs, TET2:p.His1737fs, EZH2:p.Glu726Lys, EZH2:p.Lys665_Tyr666insValTyrAspLys, and BRAF:p.Asp594Asn. It was discovered in all samples. The second emerged in the third timepoint with SETBP1:p.Ser869Asn mutation, and was also present in the fourth sample. The third clone, characterized by SRSF2:p.Pro95Arg mutation, appeared only in the bone sample (figure 1).

Figure 1. Fish plot showing clonal evolution in patent with bone marrow and extramedullary PMF posttransplant relapse



Conclusions: Bone marrow and extramedullary PMF relapse after alloHSCT may be characterized by diverse mutational profile. Extended genetic sequencing of PMF relapses may help to identify new therapeutic strategies in case of treatment failure following allo-HSCT.

Disclosure: This work was done as a part of Russian Science Foundation grant № 17-75-20145-P.

P426

Allogeneic hematopoietic stem cell transplantation in myelofibrosis: Our 15-years experience

J. Zanabili Al-Sibai[1], L.R. Morais Bras[1], M.d.P. Palomo Moraleda[1], A.J. González Huerta[1], S. González Muñiz[1], A.P. González Rodríguez[1]

[1]Hospital Universitario Central de Asturias, Oviedo, Spain

Background: Primary myelofibrosis (PMF) or post-essential thrombocytosis/polycytemia vera myelofibrosis (SMF) is one of the Philadelphia-negative myeloproliferative neoplasms which has a poor prognosis with a survival of 6 years, approximately. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) can cure a substantial number of patients (pts) but is still not universally applicable due to toxicity which leads to therapy-related morbidity and mortality.

Methods: This is a retrospective study to analyze variables associated with pts' overall survival (OS) after allo-HSCT. The study population included 16 pts who were diagnosed of myelofibrosis from January 2005 to December 2020 and sent to Hospital Universitario Central Asturias to assess allo-HSCT. Nine (56.3%) were male. Median age was 51 years old (range: 32-66). Seven pts

(43.75%) received cells from matched siblings, 7 from unrelated donor and the remainder haploidentical-HSCT. Stem cell source were: peripheral blood (n = 14) and bone marrow (n = 2).

Results: Only 7 pts (43.75%) had PMF; 6 pts (37.5%) progressed from ET and 3 from PV to SMF with a median time of 12.6 and 13.6 years, respectively. Median time from PMF diagnosis to allo-HSCT was 12.5 months. All pts had one of the driver mutations; 13 pts JAK2 mutation (81.25%) and 3 pts CALR mutations, none MPL or triple-negative. Fourteen pts (87.5%) presented constitutional symptoms and all had splenomegaly with a mean spleen size of 19.3 cm before allo-HSCT. Thirteen (81.25%) pts had anemia (hemoglobin <10g/dL); 3 of them (23%) with transfusion dependency. Ten pts (62.5%) had circulating blasts ≥1%, 2 pts (12.5%) leukocytes higher than 25 × 10^9/L and another 2 pts (12.5%) platelets lower than 100 × 10^9/L.

Since ruxolitinib is approved for MF, the drug was used in 11 pts (68.75%) before allo-HSCT.

Six pts (37.5%) developed poor graft function or graft failure. Median time to achieve 500 and 1.000 neutrophils/μL and 20.000 and 50.000 platelets/μL were 19, 21, 24 and 48 days, respectively. Thirteen pts reached complete chimerism with a median time to achieve it of 7.3 months. Bone marrow biopsy could be performed at day 100 in thirteen pts and 5 (38.46%) had grades 0 or 1 fibrosis.

The most frequent complications were GVHD, 62.5% and 18.75% of pts developed aGVHD (≥grade II) and cGVHD, respectively. Six pts (37.5%) died, 3 out of 6 due to aGVHD, remainder due to progression, second neoplasm and sepsis.

Median and maximum follow-up were 51 and 131 months, respectively. Overall survival at 5 years was 54%. When using IPSS, one year survival was 100% for intermediate-1, 79% for intermediate-2 and 25% for high risk group, but differences were not significant maybe due to the low number of cases.

Conclusions: In our series of pts, only 7 pts had PMF and the remainder were SMF developed more than 10 years after PV/ET. Most patients had constitutional symptoms and splenomegaly that were treated in 68.75% of cases with Ruxolitinib. The most frequent complication of transplantation was GVHD that was involved in 66.7% of deaths.

Disclosure: none

P427

Allogeneic hematopoietic stem cell transplantation in primary myelofibrosis: About 6 cases

F. Mehdid[1], M. Benakli[1], M. Baazizi[1], N. Rahmoune[1], D. Ait Ouali[1], H. Bouarab[1], S. Akhrouf[1], S. Zerkout[1], F. Louar[1], F. Harieche[1], R.-M. Hamladji[1], R. Ahmed Nacer[1]

[1]Pierre and Marie Curie Center, Algiers, Algeria

Background: Primary myelofibrosis (PM) is a malignant hematologic disease, characterized as chronic myelopriferative disorder. Allogeneic hematopoietic stem cell transplantation (allo–HSCT) is the only therapeutic option with curative potential, but remains reserved for a minority of patients (pts).We report the results of a series of 6 pts who underwent this procedure over a period of 206 months.

Methods: between May 2002 and July 2019, allo-HSCT performed in 6 pts with PM. The median age is 37 years (5-48) of which one of them 5 years. The sex-ratio (M/F): 1. The average delay diagnosis-transplant is 29 months (12-89). Four pts (66,6%) had a history of red blood cells (RBC) transfusions, including 1 (16.6%) with more than 20 RBC units. Two pts were splenectomized before the transplant and 2 pts received a previous treatment based on Hydroxyurea. According to the DIPSS score: Intermediate-2 (5 pts), high (1 pt). Conditioning regimens based on Busulfan were used in all pts. Prophylaxis GVHD consisted on Ciclosporin–Methotrexate. The grafts used are peripheral blood stem cells with an average rate of CD 34+ cells: 8,89 x 10^6/kg (6,11-12,9). At July 2021, the minimal follow-up was 24 months and maximal was 206 months.

Results: Aplasia was observed in all pts with median day of neutrophils engraftment was 12 days (8-15). Early rejection was observed in one patient. Grade IV Acute GVHD occurred in one pt (25%). CMV reactivation is noted in 3 pts (60%). After a median follow-up of 30 months (24-36), 2 pts are alive with a strictly normal blood count and 4 pts (66.6%) died within 3 (50%) from TRM (severe infection:2, GVHD:1) and one patient following early rejection.

Conclusions: Allo–HSCT remains the only curative treatment in PM, which can restore hematopoiesis on the one hand and prevent progression to acute leukemia on the other. The Fludarabine-Busilvex-antilymphocyte conditioning regimen is well tolerated and seems to give better results (50%).

Disclosure: Nothing to declare

NEW DRUGS- AND CELL-BASED IMMUNE THERAPIES

P428

A tri-specific killer engager (triKE®) against b7-h3 (gtb-5550) enhances nk cell mediated killing of multiple myeloma

A. Merino[1], H. Hamsher[1], N. Zorko[1], G. Berk[2], M. Felices[1], J. Miller[1]

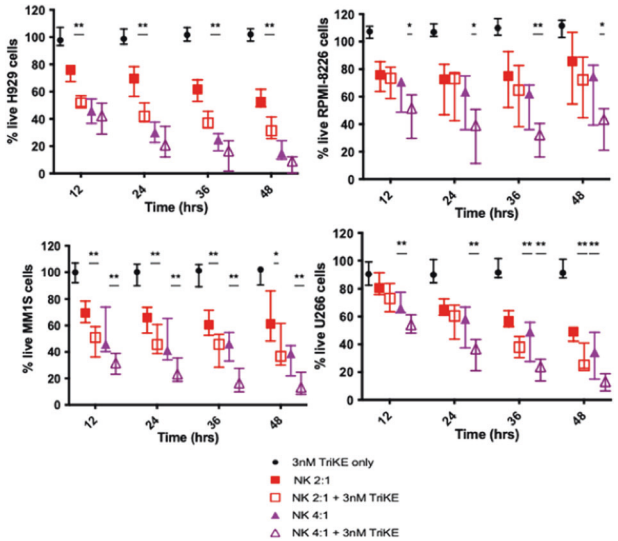
[1]University of Minnesota, Minneapolis, United States, [2]GT Biopharma, Beverly Hills, United States

Background: Natural Killer (NK) cell-based therapies hold great promise in treating multiple myeloma. One method to enhance NK cell specificity against myeloma is antibody dependent cellular cytotoxicity through CD16 receptor. We targeted B7-H3 (CD276) because its expression in myeloma is associated with decreased progression free survival, it exhibits low expression on healthy tissue, and it is expressed on myeloid derived suppressor cells (MDSC), which promote myeloma growth.

Methods: We developed a tri-specific killer engager (TriKE) with camelid single-domain antibody (sdAb) fragments against B7-H3 and CD16, linked by IL-15, to enhance NK cell killing of myeloma. Delivery of IL-15 by TriKE supports NK cell proliferation while avoiding off-target effects on T cells. We found high expression of B7-H3 on the myeloma lines RPMI-8226, U266, and MM1S and relatively low expression on H929 by flow cytometry. We compared the ability of peripheral blood NK cells with or without B7-H3-TriKE to kill myeloma cells in live imaging IncuCyte Zoom assays with escalating doses of TriKE. Maximal killing occurred with 3 nM concentration. We also tested the efficacy of B7-H3-TriKE with the proteasome inhibitor bortezomib (10nM) and the immunomodulatory drug lenalidomide (5mM). Cytotoxicity curves were compared by repeated measures ANOVA and performed in triplicate. We developed MDSC from $CD33^+$ myeloid cells from healthy donors using IL-6 and GM-CSF and these cells suppressed T cell proliferation. MDSC were used at 1:1 ratio with targets in cytotoxicity assays.

Results: We found a statistically significant increase in NK cell mediated killing of all four myeloma lines when 3nM B7-H3-TriKE was added. Against U266 and MM1S, B7-H3-TriKE significantly enhanced killing at effector:target (E:T) ratios of 1:1, 2:1 and 4:1. RPMI-8226 showed relatively high resistance to NK cell cytotoxicity but B7-H3-TriKE enhanced killing at E:T of 4:1. H929 cells were more potently killed in the presence of B7-H3-TriKE at E:T of 1:1 and 2:1 but there was no difference in killing at E:T 4:1 likely due to high natural cytotoxicity in both groups. We compared degranulation (CD107a) and cytokine production by flow cytometry after NK

cells were incubated with healthy donor NK cells at an E:T of 2:1 with or without 3 nM B7-H3-TriKE. There was an increase in degranulation with TriKE compared to NK cells alone after four hours but no significant change in cytokine production. Combination therapy with B7-H3-TriKE, NK cells, and lenalidomide showed synergistic killing of H929 cells but combination with bortezomib did not further enhance killing compared to NK cells and TriKE alone. Addition of MDSC to cytotoxicity assays enhanced myeloma cell growth but was overcome by B7-H3 TriKE + NK cells. We examined MDSC from a relapsed myeloma patient and found 81% B7-H3 expression on $CD14^+CD11b^+$ cells suggesting B7-H3 is highly expressed on myeloma-derived MDSC.



Conclusions: In conclusion, B7-H3-TriKE significantly enhances NK cell mediated killing of myeloma cells, even in the relatively low B7-H3-expressing H929 line. Our data also shows it can reverse MDSC-induced myeloma growth. Commercial manufacturing of B7-H3 TriKE (GTB-5550) has begun and a phase I trial will begin enrollment in 2022.

Disclosure: Greg Berk: Employee GT Biopharma

Martin Felices: Royalties: GT Biopharma

Jeffrey Miller: Royalties; Fate Therapeutics, Inc. Fate Therapeutics, Inc. GT Biopharma. Royalties; GT Biopharma. Vycellix. Vycellix. ONK Therapeutics. Honoraria; ONK Therapeutics. Honoraria; Nektar. Nektar. Wugen. Wugen. Magenta. Magenta. Sanofi. Sanofi.

P429

Pre-clinical development and characterisation of a decitabine-induced regulatory $HLAG^+CD4^+$-T cell-enriched cell product against GVHD

M. Lysandrou[1], D. Kefala[1], P. Christofi[1,2], C. Pieridou[3,4], P.G. Papagianni[1,2,5], N. Savvopoulos[1], M. Kyriakou[3,4], P. Stamou[1], A. Papadopoulou[2], P. Costeas[3,4], E. Yannaki[2,6], A. Spyridonidis[1]

[1]University of Patras, Patras, Greece, [2]Gene and Cell Therapy Center, George Papanikolaou Hospital, Thessaloniki, Greece, [3]Center for the Study of Hematological and other Malignancies, Nicosia, Cyprus, [4]Cyprus Cancer Research Institute (CCRI), Nicosia, Cyprus, [5]Aristotle University of Thessaloniki, Thessaloniki, Greece, [6]University of Washington, Seattle, United States

Background: Graft-vs-host-disease (GvHD) is a life-threatening complication of allogeneic hematopoietic cell transplantation (allo-HCT) with limited approved therapies. HLA-G is an immunosuppressive molecule playing a central role in the acceptance of the semi-allogeneic foetus during pregnancy, the expression of which is epigenetically regulated. We have previously reported the small-scale generation of $HLAG^+CD4^+FOXP3^-$ regulatory T-cells through hypomethylation exerting potent suppressive function in vitro (Stamou et al, 2017). Herein, we aimed to produce and characterise a clinical scale $HLAG^+$ product (iG-Treg), assess its safety profile and elucidate the molecular mechanisms of $HLAG^+CD4^+$ T cell-mediated suppression.

Methods: Peripheral blood mononuclear cells from healthy donors were enriched for T cells through monocyte depletion and were activated with CD3/CD28 beads for 3 days and followed a 3-day decitabine treatment ($n = 9$). The final product was tested for immunophenotype, expression of exhaustion markers and ability to produce effector cytokines following 4-hour stimulation with PMA/ionomycin via flow cytometry ($n = 3$) as well as for cytokine secretion in supernatants during production using a multiplex magnetic bead-based immunoassay ($n = 9$). Sorted $HLAG^+CD4^+$ T-cells and $HLAG^-CD4^+$ were analysed by RNA-seq and the expression of the key differentially genes were validated via RT-PCR and/or flow cytometry.

Results: The iG-Treg product ($n = 9$) contains 95,8% CD3 + of which 58,6% are CD4 + and 37,8% are CD8 + . Compared to untreated controls (PBS), iG-Tregs are enriched for $HLAG^+CD4^+$ T-cells (25.6% vs 0,7%, $p < 0,0001$), are PD-1 + (61.25% vs 20.46%, $p = 0.04$), with impaired ability to produce effector cytokines as was evident by diminished intracellular IL-2 (38.1%, vs 63.3% $p = 0.0176$), IFNγ (45.8% vs 59%, $p = 0.008$) and IL-17a (2.94% vs 5.87%, $p = 0.0368$). Assessment of culture supernatants interestingly displayed increased production of IL-13 (653.3pg/ml vs 291pg/ml, $p = 0.0496$) without concomitant increase of other Th1/Th2 cytokines ($p =$ ns). RNA-seq revealed that $HLAG^+CD4^+$ T cells have a distinct and uniform gene expression profile compared to $HLAG^-CD4^+$ with highly differentially expressed IDO-1, CCL17, CCL22 and CXCL9 transcripts ($\log_2$(fold change)>1.5 & $q < 0.05$), findings whch were validated via RT-PCR. Notably, the expression of IDO-1 on $HLAG^+CD4^+$ cells was further validated with flow cytometry ($p = 0.02$).

Conclusions: Our data indicate that iG-Tregs, which are enriched in $HLAG^+CD4^+$ T cells, can be effectively produced through a short and GMP-compatible protocol. iG-Tregs demonstrate a favourable safety profile as depicted in the exhausted phenotype associated with high levels of PD-1, the impaired ability to produce effector cytokines that are typically associated with GvHD exacerbation and the absence of Th1/Th2 polarized cytokine secretion in supernatants despite the increase in IL-13. Moreover, we describe, for the first time, the presence of the predominantly myeloid suppressor gene IDO-1 on regulatory $HLAG^+CD4^+$ T cells. The exact effect on immunosuppression mediated through IDO-1 remains to be assessed through functional. In parallel, iG-Tregs are being evaluated for their GVHD and GVL effect in in vivo models. Collectively, iG-Tregs constitute a well-characterized and safe immunosuppressive product able to be administered against GvHD in the initiated phase I clinical trial (EUDRACT number: 2021-006367-26).

Clinical Trial Registry: N/A

Disclosure: Nothing to declare

P430

Pembrolizumab for the treatment of relapsed and refractory classical hodgkin lymphoma after autologous transplant and in transplant-naïve patients

334

K. Halahleh[1], I. Muradi[2], S. Al-Sawajneh[3], Y. Saleh[3], F. Barakat[1], I. Sultan[1]

[1]King Hussein Cancer Center and Foundation, Amman, Jordan, [2]Al-Ahliyya Amman University, Al-Salt, Jordan, [3]King Hussein Cancer Center and foundation, Amman, Jordan

Background: Pembrolizumab demonstrated significant efficacy in R/R cHL, resulting in high ORR, prolonged PFS in patients, who relapse after or are ineligible for autotransplant, including patients with chemorefractory disease.

Methods: Retrospective cohort study.55 patients included (JAN 2016 to March 2021). Primary objectives were OS, PFS. Secondary objectives ORR, CR, and toxicity (IRAE). patients demographics are detailed in Table-1.

Patients Characteristics (N-55)	
Age, median, range	28 y (range:16-62y)
Median follow-up under Pembrolizumab, range	15.3 mo (range:0.23-48.5mo)
Male/ female	28 (50.9%)/28 (50.9%)
ECOG status 1	ECOG status 1
Comorbidities	46 (83.6%)
Stage 3–4 diseases	37 (67%)
Extranodal involvement	33 (60%)
B symptoms	43(78%)
Bulky disease	18 (32.7%)
Response to first line ABVD	18 (32.7%)
Number of therapies before pembrolizumab,Median, range	3(range:1-10)
Prior use of brentuximab vedotin (BV)	1(1.8%)
Pembrolizumab cycles, median and range	6 (range: 1 -32)
Auto-SCT prior to Pembrolizumab	14/55 (25.5%)
Auto-SCT after Pembrolizumab	12/55 (27.3%)
No Auto-SCT	02/55 (3.6%)
Allo-SCT after pembrolizumab	09/55 (16.4%)
Allo-SCT with no prior Auto-SCT	02/09 (22%)
Response to Intervening chemotherapy after pembrolizumab(N-15)	
ORR	15/15(100%)
CR	7 (46.6%)
PR	7 (46.6%)

Results: 55 included,14/55 (25.5%) received pembrolizumab AFTER Auto-SCT, 41(74.5%) as bridge to auto-SCT. Median pembrolizumab cycles 6 (range: 1-32). Median number to CR 4(range:2- 8). 41(74.5%) had ORR;35 (85.3%) continued response;18(32.7%) went into CR;17 PR-VGPR(30%);4(7.3%) had no response and 15(27.3%) progressed at the end of pembrolizumab. 12/41 (29.2%) received auto-SCT,02/41(4.87%) had no Auto-SCT, 9 (22%) allo-SCT; 2 had no prior auto-SCT(mobilization failure1, short response 1)

Six out of 18 patients (11%), who achieved CR remained on pembrolizumab at last encounter with median duration of 7.5mo (range, 2-20.5mo); among patients who discontinued therapy, median treatment duration 3mo (range,1-21mo). DP was the most common reason for pembrolizumab discontination,23/49 (47%), followed by pneumonitis, 5 /49(10%), auto-SCT 9/49 (18.4%), 9/49(18.4%) went to allo-SCT,1 patient based on physician preference.

At median FU of 15.3 mo(range: 0.23-48.5mo), MOS and MPFS was NR, 12.5 mo (95% CI, 94.3-35.8mo) respectively. 1-year OS and PFS 92% (95% CI: 76–95%),and 51% (95% CI, 39-67%) respectively, Fig. 1. 1-year PFS for patients who achieved CR or PR or PD was 88%(95% CI:07-75%); PR 60%(95%CI:21-29%) and 5%(95%CI: 5-0%). MPFS for patients in CR and PD was 26.1mo(9.6-NR) and 4.5mo(3.4-7.8mo) respectively.

Patients, who received auto-SCT consolidation after Pembrolizumab(n-12), had 1-year OS 100% (95%CI:0-100),PFS of 93%(6-82%), respectively. Only 2 patients had no Auto-SCT, continue to survive and disease free at last follow up. Patients who received allo-SCT(n-9) after failure of auto-SCT in 7 patients had 1-year OS 88% (955CI:10-70),PFS 66% (15-42). 11 (20%) patients deceased at the end of the study. Death attributed to DP in 7,sepsis 1, GvHD 2, and unknown 1 patient

Adverse events reported in 26(47%);25(45.5%) IRAEs. Most common were hypothyroidism 10(18%),pneumonitis 9(14.5%). Auto-allo-SCT group had the highest AE(25%).11(20%) required steroids;3(4.5%) discontinued pembrolizumab. All recovered, no deaths attributed to pembrolizumab. 8 out of 9(88.9%) developed aGvHD, 6(75%) cGvHD. 2 patients died due to severe lung and gut GvHD with TRM 22%.

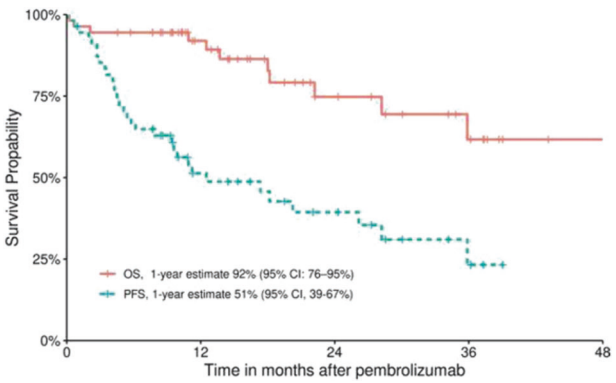


Figure: OS and PFS for the whole cohort(N-55)

Conclusions: Pembrolizumab demonstrated high remission rates at reasonable follow up time, improved survival outcomes, especially in patients who attained CR and received SCT consolidation with acceptable safety profile.

Clinical Trial Registry: NA

Disclosure: All authors has no conflict to disclose

P431

HLA-mismatched stem cell microtransplantation as a treatment option for de novo and relapsed/refractory AML/MDS in elderly patients

R. Alonso Trillo[1], M.E. Martínez-Muñoz[2], A. De Laiglesia[2], J.L. Bueno[2], G. Bautista[2], N. Panadero[2], M. García[2], C. Vilches[2], F. Rafael[2], F.R. Duarte[1,2,3]

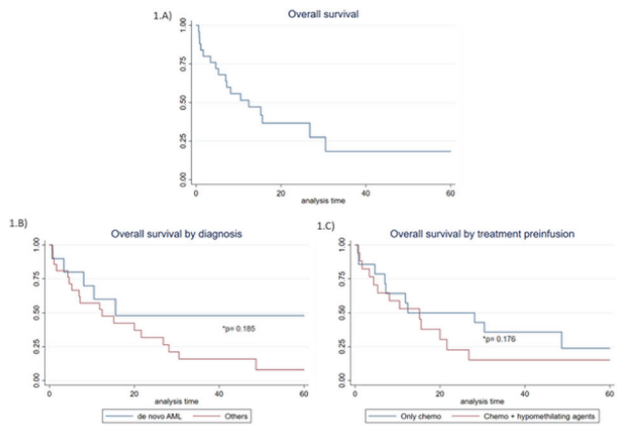
[1]Fundación para la Investigación Biomédica Hospital Universitario Puerta de Hierro, Majadahonda, Spain, [2]Hospital Puerta de Hierro,

Majadahonda, Spain, [3]Universidad Autónoma de Madrid, Madrid, Spain

Background: HLA-mismatched stem cell microtransplantation (MST), pioneered by Huisheng Ai, is a non-engrafting stem cell immunotherapy for elderly patients with AML/MDS not eligible for allogeneic HSCT, in whom it provides high response rates and survival in *de novo* AML primed with conventional chemotherapy [Guo M, *et al*. JAMA Oncology 2018]. Evidence is lacking in more advanced forms of AML/MDS and in elderly patients treated with hypomethylating agents.

Methods: Retrospective analysis of all consecutive adult patients with AML/MDS who had HLA-mismatched related PBSC donors available (haplo or lower matching), were not eligible for allogeneic HSCT and underwent MST at our center between 2012 and 2020.

Results: Twenty-five patients (19 male; median age 69, 53-77; 10 *de novo*, 8 relapsed/refractory, 4 secondary AML, and 3 advanced MDS) received 31 MST procedures, including 6 patients who had a second MST upon AML relapse. DRI was high/very high in 18 patients (72%). Ten patients received a first course of chemotherapy without stem cell infusion and initiated them with their second course, when donors were available. Sixty-seven MST infusions were carried out in these series (median 2 per procedure, 1-3, approximately two months between infusions). Most of these infusions were primed with hypomethylating agents either alone (23; 34%) or combined with chemotherapy (13; 19%) or FLT3-inhibitors (2; 3%), and 29 infusions were primed with intensive chemotherapy alone (43%). Overall, patients received 6.16 (2.16-10.7) mononuclear cellsx10^8/kg, 2.72 (0.64-3.96) CD3 + cellsx10^8/kg and 6.01 (1.13-15.65) CD34 + cellsx10^6/kg per MST procedure. Haploimmunostorm symptoms occurred in all patients after the first MST infusion, fever being the commonest (94.03%), followed by skin rash (24%), although only nine (13%) required specific treatment with corticosteroids or anti-IL6. Tolerance overall was good with a low rate of opportunistic infections (18; 27%) and a mortality at 28 days after any infusion of only 7%. Four patients died before the response to MST could be evaluated. Among 21 evaluable patients, 16 achieved complete remission following MST (76%) and five did not respond. Median overall survival (OS) after the first MST was 12 months (range 0-100), with two-year OS of 37% (IC95% 17.7-55.9%; Figure 1A). Five out of six patients who underwent a second MST procedure achieved a complete response, with a median OS of 20 months and 47.12% (IC 95% 25.51-64.49%) at one-year. Median progression-free survival in our population was 10 months. Finally, despite statistical limitations in this small population, it is worth mentioning that the novel use of MST in patients with refractory and secondary AML (Figure 1B), in those primed with hypomethylating agents (Figure 1C), and even as a second MST following prior progression were not associated with worse response rates of survival.



Conclusions: MST can be used in combination with hypomethylating agents, in advanced forms of AML/MDS, and can also be offered to patients a second time with good outcomes and no evidence of increasing toxicity, hereby becoming a safe and effective immunotherapy for a broad spectrum of elderly patients with AML/MDS that are not candidates for allogeneic HSCT.

Disclosure: Nothing to declare

P432

Use of venetoclax in combination with hypomethylating agents in patients with acute myeloid leukemia relapsing after allogeneic hematopoietic stem cell transplantation

C. Ozturk[1], U. Sahin[2], G.C. Seval[1], S.C. Bozdag[1], S.K. Toprak[1], M.K. Yuksel[1], P. Topcuoglu[1], M. Ozcan[1], G. Gurman[1], O. Ilhan[1], O. Arslan[1]

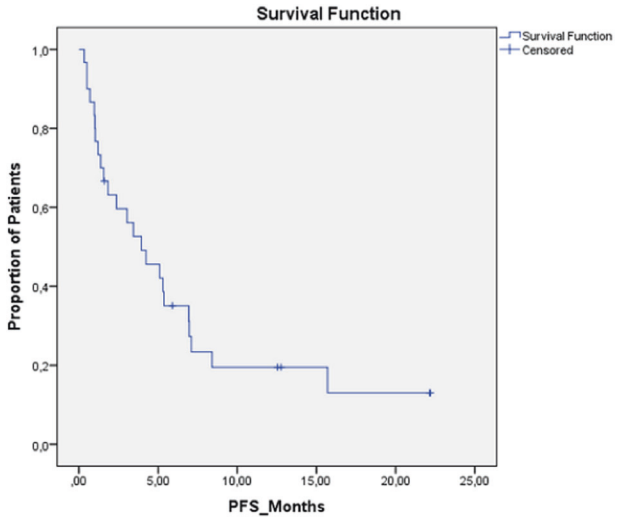
[1]Ankara University, Ankara, Turkey, [2]Medicana International Ankara Hospital, Ankara, Turkey

Background: There is no standardized therapeutic approach for relapsed acute myeloid leukemia (AML) following allo-HSCT. A growing body of evidence exists about the efficacy of venetoclax (VNC) based therapies in AML. VNC is a bcl-2 inhibitor that has shown a composite complete remission rate of 66.4% in treatment-naïve elderly AML patients. There are scarce data about the efficacy of VNC based therapies in patients who relapsed after allo-HSCT. In this study, we retrospectively analyzed the data of relapsed AML after allo-HSCT treated with the combination of VCN and a hypomethylating agent.

Methods: In total, 30 patients were included in this study between February 2019 and October 2021. The median age was 43.1 years (range, 20-69). Sixteen (53.3%) patients were female and 14 were male (46.7%). Before transplant 23 (76.7%) patients had de-novo and seven (23.3%) had secondary AML. The distribution according to ELN 2017 risk category was 8 (26.7%) adverse, 20 (66.7%) intermediate, and 2 (6.7%) favorable. At the time of the transplant, 18 patients were in CR1, 2 patients were in ≥CR2, and 10 were with persistent disease. Among 30 patients, 28 received azacytidine (75mg/m^2 for 7 days, subcutaneously), and the remaining 2 received decitabine (20mg/m^2 for 5 days, intravenously) in combination with VNC . Nine patients (30%) had a history of prior HMA exposure. The median cycle of VNC was 3 (1-6). The targeted VNC dose was 400mg/d reached by rump-up dosing schema. The median maximal VNC dose was 400mg per day (range, 100-400mg). In total, 23 patients achieved at least one cycle of VNC based therapy. Seven patients were excluded from treatment response analysis who failed to complete at least one cycle of VNC.

Results: The median time from diagnosis to allo-HSCT was 7.3 (2.5-125) months.The median time from allo-HSCT to relapse was 8.5 (1.7-47.8) months. Fourteen patients (46.7%) relapsed within six months after transplant. The median duration of follow-up was 5.3 (1-22) months. Among 23 patients who were evaluable for assessment, the overall response rate (ORR) was 56% (7/23 CR, 3/23 CRi, 3/23 PR). None of the patients developed clinical tumor lysis syndrome. The median time to best response was 2.1 (0.6-4.4) months.). Median PFS was 3.9 months (95% CI 1.2-6.6) (Figure 1) . Median overall survival (OS) was 5.3 (2.6-8.0) months. Two patients who attained a negative measurable residual disease CR had a survival of more than 20 months despite the interruption of the VNC based therapy after six cycles. At the time of the data cut-off, 6 patients (26%) were alive, and the remaining 17 (74%) had died. None of the patients experienced new-onset acute or chronic GVHD during the VNC based therapy. In total, 5 patients received second allo-HSCT. The vast majority of patients experienced

grade2-4 neutropenia (82%) and thrombocytopenia (78%) at any time of the treatment.



Conclusions: The combination of VNC and HMA is an effective and safe therapeutic option for adult AML patients who relapsed after allo-HSCT.

Disclosure: Nothing to disclose.

P433

Retrospective comparison of the amicus blue™ online ecp system to current offline and online ECP methods, focus on agvhd

T. Kanouni[1], S. Bouhya[1], P. Ceballos[1], J.J. Tudesq[1], N. Fegueux[1]

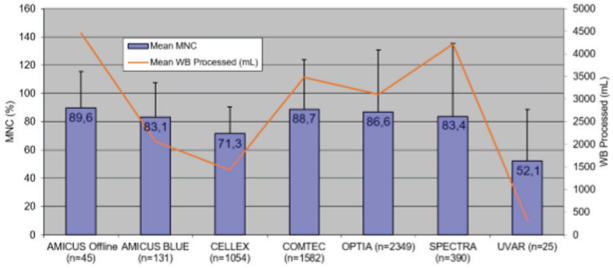
[1]*CHU Montpellier, Montpellier, France*

Background: The therapeutic apheresis department at CHU Montpellier has performed ECP therapy since 2010 using both offline and online methods. We perform ca. 500 procedures annually to treat GvHD, CTCL, heart and lung transplant rejection. In 2019, the online Amicus Blue™ ECP System (Fresenius Kabi, Germany) was CE marked and introduced in Europe. We have used the Amicus since 2012 for MNC, TPE and RBCx, and so evaluated the new ECP procedure. A retrospective comparison to historical data from our other ECP systems was performed.

Methods: We evaluated the system in routine use from November 2020 through October 2021 (n = 131 procedures) for collected cell yield and procedure time in adult patients prescribed ECP. Amicus Blue was incorporated into their existing treatment regimen. Amicus v6.0, Phelix v2.0 and double-needle disposable kits were used. All patients used peripheral access. A 12:1 whole blood (WB) to ACD-A anticoagulant ratio was used, 1.24 mg/kg/min citrate infusion rate, and the default 2000ml WB processed. Hematology counts were performed on patient WB and the treated MNCs.

Historical data was summarized for all ECP procedures performed since 2010. For online ECP, we use Cellex (Mallinckrodt, UK) and in years past, its predecessor, UVAR. Offline ECP is performed with UVA-PIT (PIT Medical Systems, Germany) and Macogenic (Macopharma, France) in conjunction with cells collected using standard MNC procedures. The cell separators used include COBE Spectra and Spectra Optia (Terumo BCT, USA), and COM.TEC and Amicus (Fresenius Kabi).

Results: For Amicus Blue, no adverse events were reported, and mean total procedure time including collection, photoactivation and reinfusion was 93 minutes. Cellex mean procedure time was 127 minutes, however 50% of these procedures were single-needle. The mean concentration of MNCs collected for each system type is presented in the graph. Amicus Blue had a higher concentration than Cellex, and comparable levels to offline methods even though less WB was processed. Lymphocyte proliferation measured for Amicus Blue system qualification was >90%.



We did a subset analysis of ECP methods in aGVHD patients, as they are often lymphopenic. The data indicate that total lymphocytes collected is related to the volume of WB processed. Amicus Blue's flexible programming allows processing of up to 4000ml WB. Although the optimal cell dose is unknown, this feature is appreciated especially for lymphopenic patients.

Device	n	WB Total Lymph (109)	WB Processed (mL)	Total Lymph Collected (109)
Amicus Blue	39	0,27	2013	0,43
Cellex	88	0,36	1544	0,24
COM.TEC	155	0,36	3056	1,1
Optia	264	0,56	3283	1,02

Conclusions: Results for cell yields are comparable to our historical data for online and offline systems. We observed no differences in clinical response compared to previous ECP treatment. A multi-procedural platform like Amicus Blue provides better return on investment for apheresis departments that require flexibility. Our staff prefer the Amicus Blue ECP for its shorter, predictable procedure time and for its friendly use. We will expand its use when the single-needle option becomes available (in development).

Disclosure: tarik kanouni: Hospitalty fees fromFresenius Kabi

P434

Effective lysis of MOLM-13 and AML blasts by triplebody spm-2 (cd123-16-33) in combination with subsets of nk cells

C.-P. Maier[1], F. Heubach[2], S. Herrmann[2], P. Kümmerle[2], A.-M. Arendt[2], A. Rabsteyn[2], G.H. Fey[3], M. Peipp[4], C. Lengerke[1], W. Bethge[1], R. Handgretinger[2], P. Lang[2]

[1]*University Medical Hospital Tuebingen, Tuebingen, Germany,* [2]*University Children's Hospital Tuebingen, Tuebingen, Germany,* [3]*University of Erlangen, Erlangen, Germany,* [4]*University Medical Hospital Kiel, Kiel, Germany*

Background: Although complete remissions can be achieved in 60-80% of AML patients by conventional chemotherapy, more than half of them experience relapse. Since relapses are thought

to evolve from leukemic stem (AML-LSCs) or progenitor cells persisting despite repetitive chemotherapeutic cycles, innovative therapies preferably targeting AML-LSCs leading to deep and long-lasting remissions are highly desirable.

SPM-2 is a triplebody carrying single-chain variable fragments, dually targeting CD33 and CD123. The combined surface density of CD33 and CD123 is far greater on AML-LSCs than on non-malignant hematopoietic stem cells. Therefore, SPM-2 seems to be a promising therapeutic agent.

Here, we analyze the specific lytic capacity of SPM-2 utilizing different NK cell preparations against MOLM-13 and primary AML blasts.

Methods: ADCC mediated by SPM-2 was fluorometrically assessed in calcein release assays. Targets (T): calcein-labeled MOLM-13, blasts from pediatric AML patients. Effectors (E): PBMCs, lymphokine-activated killer (LAK) cells, expanded NK (eNK) cells, cytokine-induced memory-like (CIML) NK cells (CD3-depleted/CD56-enriched). Expression of CD25, CD69, NKG2D (effectors) and of CD33/CD123 (targets) were determined by FACS and/or QIFI Kit.

Results: We evaluated the capacity of different effector cell preparations to lyse tumor cells in concert with SPM-2.

Using patients' PBMCs (E:T 30-40:1), specific lysis mediated by SPM-2 (500-1500 pM) against MOLM-13 ranged from 30-40%. LAKs were generated by incubating PBMCs with OKT-3 (10 ng/ml; d1-5) and IL-2 (500 U/ml; d1-21). Lysis capacity of LAKs varied markedly among donors with a maximum of 30% (E:T 20:1; SPM-2 500 pM). eNKs were produced by co-stimulation of PBMCs with IL-2 (50-100 U/ml) and irradiated feeder cells (K562-mbIL15-4-1BBL). Concentrations of SPM-2 paralleled specific lysis of MOLM-13, plateauing at 50% (E:T 10:1). eNKs also lysed (range: 15-50%; 4 donors; E:T 10:1) $CD33^{+}CD123^{+}$AML blasts in the presence of SPM-2 (500 pM).

Cytokine combinations were used to generate CIML-NKs without the need for feeder cells which is of high relevance for potential clinical application:

CIMLs stimulated for 16h with IL-12/15/18 (10/50/50 ng/ml) ("triples"); CIMLs stimulated with IL-15 high (10 ng/ml), boosted with IL-21 (25 ng/ml) on days 9-12 ("boosts"); NKs stimulated with IL-15 high and low dose (10 and 1 ng/ml) ("controls").

"Triples" showed a high natural cytotoxicity (55-70%), only slightly increased by SPM-2 (70-75%; 16h). In contrast, "controls" showed low natural cytotoxicity (3-25%), whilst specific lysis was drastically enhanced by SPM-2 (60-80%; 16h) (500 pM; E:T 5-10:1). NKG2D was increased in all three subsets after 16h, whereas relevant expression of CD25 and CD69 was limited to "triples" (100%). "Boosts" displayed robust, but donor-dependent ADCC even at d + 25.

Conclusions: SPM-2 mediates efficient lysis of tumor cells in the presence of PBMCs, even without additional NK cell transfer. SPM-2-mediated specific lysis was substantially increased using mono-stimulated (IL-15) NK cells. Thus, SPM-2 appears to be a potent new agent in AML treatment, combining targeted with immunotherapy. Whether highly preactivated CIMLs are also clinically beneficial due to their enhanced natural cytotoxicity should be investigated in vivo.

Disclosure: Nothing to declare.

P435

Daratumumab-containing regimen in the treatment of relapsed hematological malignancies in children after allogeneic stem cell transplantation

Z. Li[1], X. Wang[1], X. Wen[1], J. Li[1], F. Wu[1], T. Wu[1]

[1]Beijing Boren Hospital, Beijing, China

Background: To investigate the safety and efficacy of daratumumab-containing regimen in the management of relapsed hematological malignancies in children after allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Methods: From January 2019 to November 2021, thirteen children with refractory/relapsed hematological malignancies who relapsed after myeloablative allo-HSCT in our hospital were enrolled. Diagnosis included acute myeloid leukemia (AML, 5 cases), T-lymphoblastic lymphoma/leukemia (T-LBL/L, 6 cases), and B-acute lymphoblastic leukemia (B-ALL, 2 case). The median age was 10(5-18) years old. The disease status pre-HSCT was either non-remission (7 cases) or minimal residual disease (MRD) positive (6 cases). The fusion genes of recurrence were amL1-ETO positive in 3 cases, MLL gene rearrangement in 2 cases, HOX11 positive in 2 cases, BCR-ABL1 positive in 1 case and no special gene in 5 cases. The expression of CD38 antigen in their tumor cells was all positive by flow cytometry. Five AML patients received at least 1 cycle of chemotherapy or donor lymphocyte infusion (DLI) and failed. Daratumumab-containing regimen was consisted of daratumumab 400mg x 1, cytarabine 100mg/d x 3-5d, etoposide 100mg/d x 3-5d, and venetoclax 10mg bid x 14d.

Results: All patients were tolerant this regimen well. The main adverse events during daratumumab infusion were runny nose, cough, chest tightness, transient decrease of blood oxygen saturation. They all experienced pancytopenia for 2-3 weeks. No life-threatening infections and bleeding were noted. One AML patient underwent the second allo-HSCT after complete remission (CR) with daratumumab-containing regimen. With the median follow-up 218 (30-617) days, CR was achieved in 4/6 T-LBL/ALL, 3/5 AML, and 0/2 B-ALL. The disease-free survival rate was 46.2%, and the overall survival rate was 53.8%.

Conclusions: The prognosis of refractory/relapsed patients with hematological malignancies who relapsed after allo-HSCT is extremely poor, and effective therapeutic regimens are very limited. Our pilot study has shown that daratumumab-containing regimen is feasible and effective in half of CD38 positive hematological malignancies in children who relapsed after allo-HSCT. It seems that better response is found in the patients with T-LBL/ALL. More patients and longer follow-up are warranted.

Disclosure: Nothing to declare

P436

Driving cell therapy in treatment of mrd-positive acute pediatric lymphoblastic leukemia after allogeneic-sct: Blinatumomab + dli

S. Vitiello[1], E. Rossitti[2], F. Cacace[3], V. Caprioli[3], D. De Novellis[4], M.R. D'Amico[3], W.G. Wierda[5], K.M. Mahadeo[5], G. De Simone[3], F.P. Tambaro[3]

[1]Federico II, Napoli, Italy, [2]Università Federico II, Naples, Italy, [3]AORN Santobono - Pausilipon, Napoli, Italy, [4]Hospital San Giovanni di Dio e Ruggi D'Aragona, Salerno, Italy, [5]The University of Texas- MD Anderson Cancer Center, Houston, United States

Background: Persistence of Measurable Residual Disease (MRD > 10^{-4}) in Acute Lymphoblastic Leukemia (ALL) is high risk for relapse after allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) which has a very dismal prognosis. The role of donor lymphocytes in the treatment of MRD-positive ALL is still debated, while favorable results have been observed with treatment of MRD-positive relapse with the CD3-CD19 bi-specific T cell engager, blinatumomab.

Pts	Age (y)	DLI dose per infusion (CD3 + cells/kg)	Blina Dose	# Blina + DLI	# DLI Alone	Best response	End of treatment Chimerism %	FU from post -SCT MRD + (weeks)	Status
1	17	$5x10^6$/kg	15 mcg/m^2/ kg/28 days	4	3 (pre Blina-DLI)	MRD - CR	100	28	CNS relapse
2	16	$6x10^6$/kg	15 mcg/m^2/ kg/28 days	1	3 (Post Blina-DLI)	MRD - CR	100	8	CR
3	3	$5x10^6$/kg	15 mcg/m^2/ kg/28 days	3	3 (Pre Blina-DLI)	MRD - CR	100	44	CNS relapse

Methods: Three pediatric patients with high risk B-ALL, were treated according to AEIOP ALL 2009 and AIEOP ALL 2017 protocols and referred for allo-HSCT.

Patients all were MRD-positive after allo-HSCT and received Blinatumomab + DLI.

Results: Patient 1, a 17 years old male was primary refractory to 2 lines of chemotherapy and blinatumomab, received 2 courses of inotuzumab and achieved an MRD-positive complete remission (CR). Patient 2, a 16 years old female, had secondary ALL who achieved CR1 after 1 course of chemotherapy and subsequently received 2 courses of blinatumomab, due to treatment chemotherapy-associated toxicity and achieved MRD-negative CR1. Patient 3 developed CNS relapse during maintenance, then received salvage therapy according to the INTREALL HR 2010 and 1 course of blinatumomab, achieving MRD-positive CR1. All patients proceeded to allo-SCT and were MRD-positive at 14, 31 and 8 weeks post-allo-SCT, respectively. All patients discontinued immunosuppressive therapy and received 3, 1 and 4 courses of DLI + blinatumomab respectively . Blinatumomab was started one week after each dose of DLI. Only patient 1 experienced Grade 2 liver GVHD. None of the patients experienced serious adverse events needing Blinatumomab discontinuation . All 3 patients reached an MRD-negative complete remission (CR). One patient is still in CR and 2 patients presented MRD-positive and CNS relapse. All patients still present MRD- Bone Marrow disease.

Conclusions: The role of cellular therapy with DLI is still debated ALL. Blinatumomab directs T cells to bind CD19 present on malignant B cells and engages CD3 on T cells causing activation and inducing cytotoxicity against the ALL cells. The use of blinatumomab allowed recruitment of fit donor-derived T lymphocytes (not exposed to immune suppressive agents) against ALL B cells. This hypothesis is supported by the fact that patient 1, who received blinatumomab pre-HSCT and had disease progression, (probably due to lack of T cells showed by flow cytometry), achieved MRD-negative response after receiving DLI + blinatumomab post transplant. All patients reached MRD-negative status and 2 subsequently developed CNS relapse; none received CNS prophylaxis post-HSCT. We hypothesize that blinatumomab + DLI is able to clear the hematological disease, but it is not effective in preventing CNS relapse.

Disclosure: Nothing to declare.

NON-HAEMATOPOIETIC STEM CELLS AND REGENERATIVE MEDICINE

P437

Clinical application of mesenchymal stem cells from wharton's jelly in patients with cerebral palsy

M. Piątek[1], I. Zdolińska-Malinowska[1], E. Semenova[1], M. Chrościńska-Krawczyk[2], D. Boruczkowski[1]

[1]Polski Bank Komórek Macierzystych, Warsaw, Poland, [2]Uniwersytet Medyczny w Lublinie, Lublin, Poland

Background: Cerebral palsy (CP) is the most common motor disorder in children in which Wharton Jelly Mesenchymal Stem Cell (WJMSC) infusions has become a promising therapeutic strategy for patients with this disease. Our earlier work has shown that application of mesenchymal stem cells derived from Wharton's Jelly seems to be safe and an effective procedure that improves gross motor functions, muscle tension, communication, attention, and cognitive functions in children with CP. Here we obtain results from a population of patients with cerebral palsy. This population of patients with cerebral palsy was taken from a larger study where patients with neurological/genetic diseases were treated with at least two doses of WJMSC coming from PBKM.

Methods: The WJMSC were derived from umbilical cords obtained from unrelated third party donors. The intravenous injections of WJMSC were used as a treatment for 123 patients with CP, who have received at least two infusions of mesenchymal stem cells in dose 20-30 x 10^6 cells/infusion. The median age of the studied participants at the initiation of the therapy was 6 years of age. Each procedure had an individual bioethical committee approval. The patients were evaluated by the same neurologist both before the first treatment dose and during the subsequent administrations using scales testing for motor and neurological abilities such as GMFM (Gross Motor Function Measure), GMFMS (Gross Motor Function Classification System) scale test, 6MWT (6-minute walk test), Up & Go test, and the CGI (Clinical Global Impression) scales test. The results were analysed using the Wilcoxon Test for pairs of observations.

Results: Among 123 patients with CP, there was a statistically significant improvement in motor skills as measured by the GMFM scale, with the median score increasing from 19.5 points before therapy to 24.5 points after therapy ($p < 0.05$). Also, the 6MWT and Up & Go test results showed statistically significant improvement in 19 and 18 patients, respectively, who were tested before and after umbilical cord mesenchymal stem cell infusion. The median distance walked by pediatric cerebral palsy patients increased from 120 meters (range min 38 m max 220 m) to 180 meters (range min 110 m to max 300 m) $p = 0.00025$. The median time for children to stand up after hearing a command decreased from 12 seconds (range min 7 sec to max 22 sec) to 10 seconds (range min 8 sec to max 17 sec) $p = 0.0005$ after cell administration. There were observed no serious adverse events related to WJMSC application

Conclusions: The infusion of third party donor WJ-derived MSC is a safe procedure with clinical effects that significant improves CP patients health status in all assessed scales despite the lack of changes in muscle strength. The results from this and our previous studies allow us to predict that the therapeutic effect of WJMSC administration will increase with subsequent infusions of the WJMSC cells.

Disclosure: The authors of abstracts are workers of Bank providing cells and Medical Center where cell infusions took place.

P438

Clinical application of mesenchymal stem cells from wharton's jelly in patients with neurological/genetic diseases

M. Piątek[1], I. Zdolińska-Malinowska[1], E. Semenova[1], M. Chrościńska-Krawczyk[2], D. Boruczkowski[1]

[1]Polski Bank Komórek Macierzystych, Warsaw, Poland, [2]Uniwersytet Medyczny w Lublinie, Lublin, Poland

Background: In recent years, extensive pre-clinical and clinical experimental data have suggested that mesenchymal stem cells derived from Wharton Jelly (WJMSC) have unique properties that not only invoke minimal immune reactivity, but also possess secretion ability, modulatory and anti-inflammatory effects. As a result, WJMSCs can provide an interesting therapeutic option in the treatment of many neurological/genetic diseases. In this abstract we obtained results from medical experiments where patients with various neurological/genetic diseases were treated with at least two doses of a WJMSC from an unrelated third party from the Polish Stem Cell Bank (PBKM).

Methods: The intravenous injections of WJMSC (dosage: 20-30 x 10^6 cells/infusion) were used as a treatment for 38 patients with spina bifida (SB), 12 with global developmental disorder, and 40 with other neurological disorders (including 8 with neuroinfections, 6 with encephalopathy, 6 with intellectual disability, 5 with malformations, 3 patients with brain injuries, 2 with spinal cord hernia with brain trauma, 2 diagnosed with myasthenia gravis, 2 with epilepsy, and 1 patient each with dystonia, systemic developmental disorders, optic nerve disc disorder, arthrogyposis with myopathy, and 3 diagnosed with other disorders) and 26 patients with genetic defects (including 4 patients with muscular dystrophy, 4 with adrenoleukodystrophy, 4 with leukodystrophy, 2 patients with Down syndrome, 2 with Wolf-Hirschoma syndrome, and 1 patient each with Cornelli de Lange syndrome, Phelan McDermid Pitt syndrome chromosome 3 deletion, propion aciduria, ceroidolipofuscinosis, genetically determined epilepsy, and 3 patients with unspecified defects. Each WJMSC infusion procedure had an individual bioethical committee approval. The patients were evaluated by scale testing motor and neurological abilities such as GMFM (Gross Motor Function Measure), GMFCS (Gross Motor Function Classification System),scale test 6MWT (6-minute walk test), Up & Go test, and the CGI (Clinical Global Impression) scale test. The results were analysed using the Wilcoxon Test for pairs of observations.

Results: Among the 33 patients with SB from whom follow ups were obtained, the median GMFM motor ability rating scale showed significant (statistically) improvement upon treatment, where the median value before therapy was 48 points (range 12 -96) and after therapy it increased to 50 points (range 16-99), $p = 0.002$. Similar results were observed in a group containing 12 patients with global developmental disorder, where, the median GMFM score showed a significant (statistically) increase from 82 points (11-95) to 85 (18-97) $p = 00764$. There was also a significant increase in the distance that patients were able to walk in 6 minute during the 6MWT test after infusion of WJMSCs compared to their scores before therapy. The median distance increased by almost 60 meters; patients went from 100 meters before therapy to 158 meters after therapy $p = 0.025$. Among the 20 patients who suffered from other neurological disorders and 16 with genetic disease from whom follow ups was obtained to the present day, there was a statistically significant improvement in GMFM and CGI scales.

Conclusions: WJ-MSC administration is promising for the improvement of motor skills, cognitive functions, in patients with various neurological and genetic disease.

Disclosure: Authors of abstract are working in stem cell bank and medical center where cells infusion took place

NON-INFECTIOUS EARLY COMPLICATIONS

P439

The defifrance registry study: Effectiveness and safety of defibrotide in patients with veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) following chemotherapy

I. Yakoub-Agha[1], D. Blaise[2], J.-H. Dalle[3], M. Labopin[4], R. Peffault de Latour[5], S. Chantepie[6], A. Petit[7], K. Asubonteng[8], F. Duchêne[9], M. Mohty[4]

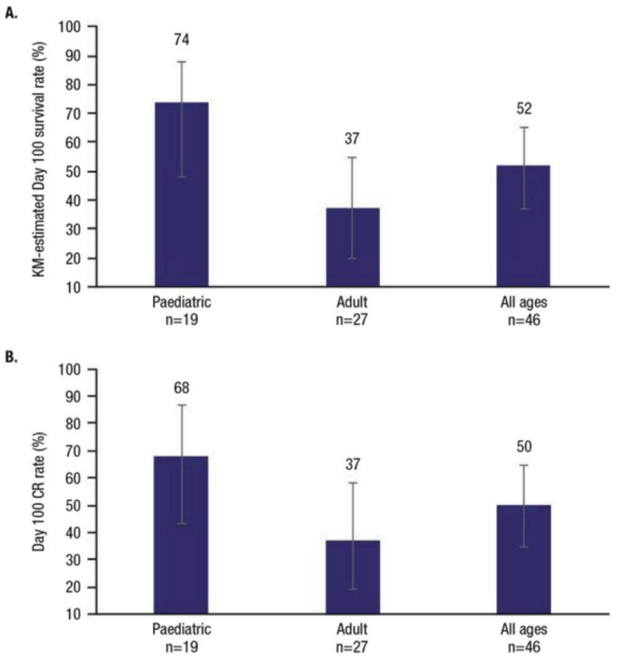
[1]CHU de Lille, Université Lille, Lille, France, [2]Institut Paoli-Calmettes, Aix Marseille Univ, Marseille, France, [3]Hôpital Robert-Debré, GHU APHP Nord and Université of Paris, Paris, France, [4]Hôpital St Antoine, Sorbonne University, Paris, France, [5]Hôpital Saint-Louis, Paris, France, [6]Institut d'Hématologie de Basse Normandie, Caen, France, [7]Hôpital Armand Trousseau, APHP, Paris, France, [8]Jazz Pharmaceuticals, Philadelphia, United States, [9]Jazz Pharmaceuticals, Lyon, France

Background: VOD/SOS is a potentially life-threatening complication of haematopoietic cell transplantation (HCT) that can also occur after high-dose chemotherapy. Defibrotide is approved for the treatment of severe hepatic VOD/SOS post-HCT in patients aged >1 month in the EU. The DEFIFrance study collected real-world data on the effectiveness and safety of defibrotide from HCT centres across France. This analysis presents outcomes in patients who received defibrotide treatment for VOD/SOS post-chemotherapy.

Methods: This post-marketing registry study collected retrospective and prospective real-world data on patients receiving defibrotide at 53 HCT centres in France. VOD/SOS diagnosis was per the investigator's typical clinical practice. Disease severity was categorised using adult EBMT severity criteria in adults; paediatric patients (<18 years) were retrospectively/prospectively categorised using paediatric EBMT severity criteria. Survival and complete response (CR; total serum bilirubin <2 mg/dL and multiorgan failure [MOF] resolution per investigator's assessment) rates by Day 100 post-VOD/SOS diagnosis were calculated. Treatment-emergent serious adverse events (TESAEs) of interest were haemorrhage, coagulopathy, injection-site reactions, infections, and thromboembolic events, irrespective of relationship to treatment.

Results: Overall, 46 patients (19 [41%] paediatric and 27 [59%] adults) received defibrotide for VOD/SOS post-chemotherapy. Median age was 5.8 years (range: 2, 17) in paediatric patients and 56.6 years (range: 18, 72) in adults. Paediatric patients were more likely than adults to have a primary diagnosis of ALL (paediatric: 53%; adult: 22%) or neuroblastoma/solid tumour (32%; 0%), while AML (11%; 63%) was more common in adults. Paediatric patients were less likely to have prior exposure to gemtuzumab ozogamicin and inotuzumab ozogamicin (11% and 0%, respectively) than adults (41% and 15%). VOD/SOS was severe/very severe in all paediatric patients and 22 (81%) adults. MOF was present in 5 (26%) paediatric patients and 10 (37%) adults, including renal failure (paediatric: 60%; adult: 70%), respiratory failure (100%; 80%), and cerebral failure (20%; 70%). By Day 100 post-VOD/SOS diagnosis, the Kaplan-Meier (KM)–estimated survival rate was 74% in paediatric patients and 37% in adults (**Figure**

1A), and the CR rate was 68% in paediatric patients and 37% in adults (**Figure 1B**). Of 5 paediatric patients who died within 100 days of VOD/SOS diagnosis, all 5 had very severe VOD/SOS. Of 17 adults who had died by Day 100, 10 had very severe VOD/SOS. By Day 100, 2 paediatric patients and 6 adults had died due to relapse/progressive disease and there were no VOD/SOS-related deaths. TESAEs of interest occurred in 15% of patients with VOD/SOS post-chemotherapy (paediatric: 11%; adult: 19%), including infection and haemorrhage (each 9% in the overall group).



Conclusions: In this real-world DEFIFrance study, the majority of patients who received defibrotide for VOD/SOS post-chemotherapy had severe/very severe VOD/SOS and a notable proportion had MOF, indicating advanced disease in this patient population. Over half of adult patients had received ozogamicin-containing therapy. These data indicate that VOD/SOS is a concern outside the HCT setting and suggest a need for continuous vigilance for VOD/SOS among those monitoring patients after chemotherapy, especially for signs and symptoms to improve earlier diagnosis.

Disclosure: IY-A, DB, J-HD, ML and RPL have received honoraria from Jazz Pharmaceuticals. SC and MM have received honoraria and research funding from Jazz Pharmaceuticals. KA and FD are employees of and hold stock and/or stock options in Jazz Pharmaceuticals. AP has no conflicts to disclose.

P440

The role of conjugated monoclonal antibodies in development of post-transplant veno-occlusive disease: Single center study

M.M. Kanunnikov[1], D.Z. Rakhmanova[1], N.P. Volkov[1], O.V. Paina[1], J.J. Vlasova[1], E.V. Morozova[1], L.S. Zubarovskaya[1], S.N. Bondarenko[1], I.S. Moiseev[1], A.D. Kulagin[1]

[1]RM Gorbacheva Research Institue, Pavlov University, St. Petersburg, Russia, Saint-Petersburg, Russian Federation

Background: The conjucated monoclonal antibodies (c-mABs), inotuzumab ozogamycin (Ino) and gemtuzumab ozogomycin (GO), are novel treatment options for relapsed/refractory acute lymphoblastic and myeloid leukemia, respectively. Nonetheless, they are known to cause sinusoid obstructive syndrome/veno-occlusive disease (SOS/VOD), especially in allogeneic stem cell transplantation recipients (alloHSCT) after bridging with these agents. Currently there is limited data on the incidence and risk factors of SOS/VOD after c-mABs and alloHSCT, as well as no recommended approach to allograft patients after these agents.

Methods: A total 82 patients (56 adults and 26 children) with acute leukemia (acute myeloid leukemia (AML) n = 33, acute lymphoblatic leukemia (ALL) n = 49) were included in this study. The treatment consisted of median 2 (range 1-3) cycles Ino for ALL and all AML patients received 1 cycle of GO-FLAG prior to allo-HSCT. Allo-SCT was performed from a matched related (n = 13), unrelated (n = 15) or haploidentical donor (n = 54) between 2017 and 2021. The disease status before allo-SCT were: remission I (n = 8, 9.8%), remission II + (n = 55, 67.1%) and active disease (n = 19, 23.2%). Median time from c-mABs to SOS/VOD development was 75 days (39-287).

Results: In 26 patients (32%) we observed SOS/VOD in the posttransplant period: 1 mild (1.2%), 9 moderate (11%), 7 severe (8.5%) and 9 very severe (11%) based on EBMT criteria. Median time to development VOD was 15 days (7-100).

Ino therapy in ALL was associated with significantly higher SOS/VOD incidence than GO in AML 41% (n = 19) vs 33% (n = 7) (HR 3.75, 95%CI 1.43-9.8, p = 0.007). Also calcineurin inhibitors (CNIs) in graft-versus-host prophylaxis regimen was strongly associated with increased SOS/VOD incidence (HR 5.58, 95%CI 1.53-20.3, p = 0.009). Other factors as busulfan in conditioning regimen, time interval between c-mABs course and alloHSCT, type of donor, HLA-mismatch between recipient and donor, myeloablative conditioning were not associated with high VOD/SOS incidence.

In multivatiative analysis, VOD severity (HR 2.2, 95%CI 1.07-4.67, p = 0.032) and disease status (HR 3.99, 95%CI 1.25-12.76, p = 0.019) were associated with survival differences, while type of disease was not predictive (HR 1.089, 95%CI 0.33-3.56, p = 0.88). In patients developed PT-VOD 1-year OS was 36% (95%CI 17%).

Conclusions: The incidence of SOS/VOD is high after c-mABs bridging to alloHSCT. The only potential intervention we identified to reduce the risk of SOS/VOD after c-mABs is to use CNI-free GVHD prophylaxis regimens. Severe SOS/VOD is a negative prognostic factor for survival in this group of patients.

Disclosure: M.K. received lecturer fees from Pfizer. I.M. received lecturer and consulting fees from Novartis, J&J, Celgene, BMS, Takeda, Sobi.

P441

Easix predicts veno-occlusive disease and survival in children who underwent hematopoietic stem cell transplantation

K. Yalcin[1], S. Celen[1], S. Zhumatayev[2], N. Azizova Gurbanzade[3], M.M. Jazazi[4], V. Uygun[5], G. Karasu[3], A. Yesilipek[3]

[1]Bahcesehir University, İstanbul, Turkey, [2]Nazarbayev University, Nur Sultan City, Kazakhstan, [3]Medicalpark Goztepe Hospital, Istanbul, Turkey, [4]Queen Rania Al-Abdullah Children Hospital, Amman, Jordan, [5]Medicalpark Antalya Hospital, Antalya, Turkey

Background: The main clinical challenge of hematopoietic stem cell transplantation (HSCT) is treatment-related mortality (TRM). Endothelial dysfunction plays a crucial role in the pathophysiology of major complications contributing to TRM. In the previous adult studies, the Endothelial Activation and Stress Index (EASIX) score was detected as a predictor for survival after HSCT, and also it was

shown that EASIX scores were associated with biomarkers of endothelial homeostasis.

In this study, we aim to assess if the EASIX might be valuable for the prediction of early HSCT-related complications and survival after pediatric HSCT.

Methods: This study is a retrospective analysis of 343 children who underwent HSCT between January 2018–September 2021 in Medicalpark Göztepe Pediatric Stem Cell Transplantation Unit.

EASIX was calculated as described before by Luft et al. Veno occlusive disease (VOD) was diagnosed according to EBMT recommendations which were described by Corbacioglu et al. and acute graft versus host disease (aGvHD) was diagnosed according to Glucksberg criteria.

Results: The median age of the patients was 81 months (1-248 months), the primary disease was malign in 118 patients and non-malign in 225 patients. According to donor type, 204 transplants were performed from matched unrelated donor (MUD), 73 from match sibling donor (MSD), 23 from match family donor (MFD), and 43 from haploidentical donors. Stem cell source was peripheral blood (PB) for 196 transplants, followed by bone marrow (BM) for 127, combined BM and PB for 12 (for only haplo procedures), and combined BM and cord blood for 8 transplants.

Ninety patients (26%) developed aGvHD. Regarding the severity of aGvHD, 47 patients (13%) developed grade 2, 22 patients (6,4%) developed grade 3, and 21 patients (6,1%) developed grade 4 aGvHD. Twenty-one patients (6,1%) developed VOD. VOD is not a cause of death for any of the patients.

Analyzing the EASIX scores on different time points; median pre-conditioning EASIX was 0,64 (0,11 – 16,16), median day 0 EASIX was 1,48 (0,17 - 107), median day 15 EASIX was 2,6 (0,12 - 148), and median day 30 EASIX was 1,9 (0,29 -71,3). Pre-conditioning EASIX scores were significantly higher for malignancies ($p < 0.001$). Regarding the age, patients over 7 years old had significantly higher EASIX scores on pre-conditioning and day 0 ($p = 0.001$ and $p = 0.009$ respectively).

The pre-conditioning EASIX scores were significantly higher in patients who developed VOD at any time after HSCT ($p < 0.001$). The EASIX scores in any of the time points were not significantly associated with aGvHD. Mortality was significantly higher for the patients with high EASIX scores in any time point and this association was stronger in early time points ($p < 0.001$ for pre-conditioning EASIX, $p < 0.001$ for Day 0 EASIX, $p = 0.03$ for Day 15 EASIX, and $p = 0.05$ for Day 30 EASIX)

Conclusions: In our study, we showed that higher EASIX scores were associated with higher VOD risk and lower survival rates. We propose that EASIX scores be further investigated as an early biomarker for risk-adapted treatment strategies in larger datasets.

Disclosure: Nothing to declare

P442

Risk factors for poor graft function in 231 patients receiving allogeneic hematopoietic stem cell transplantation

F. Giglio[1], I.T. Petralia[1], F. Lorentino[1], T.D. Clerici[1], R. Greco[1], L. Lazzari[1], E. Xue[1], S. Mastaglio[1], S. Piemontese[1], F. Farina[1], S. Marktel[1], A.A. Assanelli[1], C. Corti[1], M.T. Lupo-Stanghellini[1], M. Marcatti[1], M. Bernardi[1], J. Peccatori[1], F. Ciceri[1]

[1]IRCCS San Raffaele Scientific Institute, Milano, Italy

Background: Poor graft function (PGF) is a life-threatening complication following allo-HSCT characterized by bilineage or trilineage cell deficiency with hypoplastic marrow with full chimerism, in the absence of relapse or GVHD. With the increased use of allo-HSCT, PGF has become a growing obstacle to transplant success. Factors involved in PGF include low dose of infused CD34 + cells, donor specific antibody (DSA), viral infections, iron overload, splenomegaly, GvHD, among others. Emerging evidence demonstrates that bone marrow microenvironment is dysfunctional in PGF patients. The PGF pathogenesis risk factors remain largely unknown and treatments are limited. Here we report PGF incidence in a cohort of patients and analyze risk factors to understand how to prevent or limit PGF.

Methods: PGF risk factors investigated were splenomegaly, myelofibrosis, iron overload, DSA, gender mismatch, AB0 mismatch, donor age, viral infections, use of myelotoxic drugs, prophylactic G-CSF and use of cryopreserved graft particularly utilized during COVID-19 pandemic. Other HSCT features were also analyzed (i.e. source, donor, donor age, conditioning, among others).

Results: From 2018 to 2020, we performed 231 allo-HSCT in patients with hematological malignancies, receiving myeloablative or reduced-toxicity conditioning, GvHD prophylaxis consisting of ATG or PT/Cy, coupled with Sirolimus and mycophenolic acid. 127 patients received allo-HSCT for AML, 24 for ALL, 32 for lymphoproliferative disorders, 48 for MDS/MPD. Donors were MRD, MMRD, MUD, UCB in 42, 64, 109, 16 patients respectively. According to the Disease Risk Index, patients were stratified in very high ($n = 18$), high ($n = 63$), intermediate ($n = 130$) or low ($n = 16$) risk. Stem cells were collected from BM ($n = 7$), PB ($n = 208$) and CB ($n = 16$).

We reported 1-year probability of OS 74.8% and PFS 70.5%. 1-year CI of TRM was 15.5%, 1-year CI of relapse was 14%, along with 100-day CI of grade II-IV acute and chronic GvHD of 19.5% and 25.3%, respectively. Platelet engraftment was moderately delayed: 30-day CI was 43.7% and 60-day CI was 68.4%. 30-day CI of neutrophil engraftment was 78.8% and at 60-day was 93.5%. In our cohort, 34 patients developed PGF: 21 with primary PGF and failed to achieve sustained graft function and 13 with secondary PGFdeveloped after complete hematologic recovery. The CI of PGF at 60 days was 6.1% and 15.2% at 180 days. Univariate analysis for PGF risk factors showed significance for cryopreserved graft (HR 3.26; 1.65-6.42; $p = 0.001$) and major ABO mismatch between host and donor (HR 2.43; 1.22-4.86; $p = 0.012$), whereas donor age (HR 1.02; 0.99-1.04; $p = 0.119$) and prophylactic G-CSF (HR 1.86; 0.94-3.69; $p = 0.076$) were borderline significant. Cryopreserved graft (HR 3.59; 1.80-7.2; $p < 0.001$), major AB0 incompatibility (HR 2.38; 1.18-4.83; $p = 0.016$) and donor age ≥35 years (patients median age; HR 2.22; 1.03-4.78; $p = 0.041$) were confirmed using multivariable Cox regression analysis as factors predicting PGF as opposed to the prophylactic G-CSF which didn't show significance.

Conclusions: These findings suggest that donor age ≥35 years, major AB0 mismatch and graft cryopreservation may play a role in PGF onset. This might help to better understand PGF pathogenesis, to establish targeted interventions and to guide risk stratification, excluding donors and transplant with these features when possible.

Disclosure: No relevant conflicts of interest

P443

CD34-selected stem cell boost in pediatric patients with poor graft function after allogeneic stem cell transplantation is associated with durable engraftment and excellent overall survival

E. Fraint[1], S. Farooki[2], E. Klein[3], S. Prockop[4], A. Scaradavou[3], K. Curran[3], M. Cancio[3], G. Spitzer[3], J.J. Boelens[3], J. Oved[3], A. Harris[3], R. O'Reilly[3], N. Kernan[3]

[1]Children's Hospital at Montefiore, Bronx, United States, [2]Charleston Area Medical Center, Charleston, United States, [3]Memorial Sloan

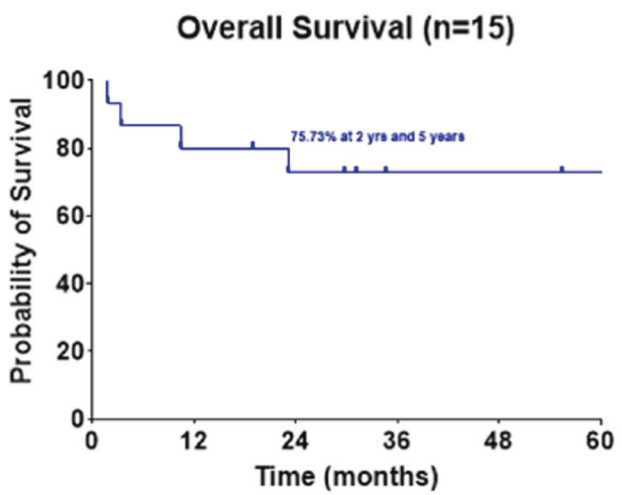
Kettering Cancer Center, New York, United States, [4]Boston Children's Hospital, Boston, United States

Background: Poor Graft Function (PGF) is a life-threatening complication after allogeneic stem cell transplantation (alloSCT). Few outcomes with a CD34-selected stem cell boost (CD34 + SCB) for PGF in pediatric alloSCT recipients have been reported. Here we report on a single center experience from MSK Kids, Memorial Sloan Kettering Cancer Center.

Methods: A retrospective analysis of data was done on all patients who received a CD34 + SCB between 2008-2020 for PGF defined as the need for G-CSF and/or RBC/platelet transfusion support. Peripheral blood stem cells from the original alloSCT donor was the source for CD34 + SCB. Donor chimerism was done by short tandem repeat molecular testing. Patients had bone marrow donor chimerism ≥85%. Complete Recovery (CR) was defined as achievement of ANC > 500x10^6/L without G-CSF support, and Hb ≥7 g/dL and platelets ≥50 x 10^9/L without transfusion support. Additional outcomes of interest included development of GvHD and other toxicities.

Results: 19 consecutive patients (AL/MDS-9, FA-4, SAA-2, SCID-2, CGD-1, WAS-1) received 22 CD34 + SCBs. Median age was 7.8 years (0.4–24.5 years). Donors were MRD (1), MMRD (3), MUD (6) and MMUD (9). Primary alloSCT: 15 patients received CD34 + enriched PB (12) or BM (3) and 4 patients received unmodified BM following MA (16) or RIC (3) regimens. The median CD34 + /kg was 6.38x10^6/kg (2.0-8.08). The median time between alloSCT and CD34 + SCB was 152 days (50-461 days). The median T-cell donor chimerism was 89% (0-100%). At the time of PGF, 13 patients had an associated infection: CMV/adenovirus (9), EBV (2), or mycobacterium (2). Three patients received ATG and 1 patient received ATG plus fludarabine prior to CD34 + SCB. The median CD34 + /kg was 5.46 (2.01-19.07). Following CD34 + SCB, only 1 patient developed aGVHD. Four patients with PGF and autoimmune cytopenias were analyzed separately.

Among the 15 patients without autoimmune cytopenias, 5 of 5 patients with single (3 patients) or two (2 patients) lineage PGF and 7 of 10 patients with trilineage PGF had durable CR (12 total patients). None of these patients required a second CD34 + SCB. The median time for recovery was 20 days (7-166 days). One patient with late ANC engraftment (166 days) had CGD with 66% donor myeloid engraftment. One patient with CR died of new onset aGVHD. Three patients did not achieve CR: 2 patients transplanted for leukemia died (prior aGVHD 1, EBV 1) and 1 patient transplanted for SAA underwent a successful 2nd alloSCT. The overall survival for these patients is 72.7% at 2 years and 5 years (Figure 1).



In patients with autoimmune cytopenias (n = 4), CD34 + SCB aided recovery of other lineages but did not control autoimmune cytopenias despite repeated CD34 + SCBs.

Conclusions: For pediatric allogeneic stem cell transplantation recipients with high donor bone marrow chimerism (≥85%) and PGF associated with infection or of unknown cause, CD34-selected peripheral blood stem cell boost is safe and can provide for durable trilineage engraftment and long-term survival. CD34-selected peripheral blood stem cell boost for autoimmune cytopenias was not effective in this cohort of 4 patients.

Disclosure: Boelens: Consultancy: Race Oncology, Sanofi, Avrobio, BlueRock, Omeros, Advanced Clinical, Equillium, Medexus and Sobi. Not conflicting with content abstract

Curran: Consultancy and support from Novartis

Fraint, Farooki, Klein, Scaradavou, Prockop, Cancio, Spitzer, Oved, O'Reilly, Harris, Kernan – nothing to declare.

P445

Prospective evaluation of upper and lower gastrointestinal endoscopies and biopsies in the diagnosis and management of allogeneic hematopoietic stell cell transplant recipients with persistent diarrhea

A.B. Bocanegra[1], J.M. Mateos[1], A. Alarcón[1], C. De Miguel[1], B. Guiomar[1], M.E. Martínez-Muñoz[1], C. Gonzñalez-Lois[1], M.R. Sánchez-Yuste[1], I. Sánchez-Romero[1], I. Vera-Mendoza[1], M. Calvo[1], M.F. Portero[1], C. Salas-Antón[1], J.L. Calleja[1], R.F. Duarte[1]

[1]Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda, Spain

Background: Diarrhea is common in allogeneic (alloHSCT) recipients and may result from multiple causes, including chemo-radiotherapy, drug toxicity, infections, GVHD and others. Gastrointestinal endoscopies and biopsies are part of the broad differential diagnosis in alloHSCT recipients with persistent diarrhea, but their value to help establish the correct diagnosis and treatment of these patients requires thorough evaluation.

Methods: In June 2016, we initiated a prospective protocol whereby all alloHSCT recipients with persistent diarrhea (>48h) despite supportive treatment and negative screening tests (stool culture, *C. difficile*, adenovirus, rotavirus, norovirus and parasites) would undergo esophago-gastro-duodenoscopy and recto-sigmoidoscopy with serial biopsies of the gastric fundus, duodenum, sigmoid and rectum, and urgent processing with a pathology report in 24-48h to guide management.

Results: Thirty-nine patients (17 males; median age 55, 19-69; 16 HLA-identical siblings, 10 cords, 9 haploidentical, 4 unrelated; 26% of alloHSCT in this period) were included in this protocol at a median day +90 post-alloHSCT (IQR: 54-121). A total of 59 procedures were carried out, including 8 patients who had 20 additional procedures (median 3.5, range 2-5) for recurrent diarrhea and diagnostic uncertainties. A minority of only 14 procedures (24%) in 8 patients (21%) did not complete the full upper/lower endoscopy/biopsy protocol, primarily a physician's decision for patient/clinical circumstances. GVHD was the initial cause of persistent diarrhea in 12 patients (31%): 6 out of 15 patients (40%) with GVHD in other organs (skin or liver) and 6 out of 24 (25%) patients without GVHD elsewhere. The vast majority of alloHSCT recipients with persistent diarrhea had causes of diarrhea other than GVHD (69%), including nonspecific colitis with normal histology or isolated nonspecific changes (10; 26%), infectious colitis (7; 18%) including 3 cases of CMV disease (8%), gastritis (6; 15%), pharmacologic diarrhea (3; 8%) and acute pancreatitis (1; 3%). This had major relevance for treatment decision-making to avoid immunosuppressive treatment and its complications in

many patients with other causes of diarrhea. Repeated endoscopy/biopsy procedures helped the management and choice of treatment for patients with diagnostic uncertainties or recurrent episodes of persistent diarrhea (Figure 1). Diagnoses may change over time, from nonspecific colitis to CMV disease (#8) or to other infections and GVHD (#16). Some patients may have recurrent episodes of nonspecific, infectious, or pharmacologic colitis over the course of months without GVHD (#9, #23), and others have GVHD alone (#29, #35) or associated with other complications at different time-points (#26, #34). Of clinical relevance, patients with a confirmed diagnosis of GVHD may evolve over time to a pattern of nonspecific regenerative changes without signs of active GVHD (#34, #35), which also helps modulating immunosuppressive intensity and patient management.

Conclusions: The prospective, systematic assessment of upper/lower gastrointestinal endoscopies and biopsies in alloHSCT recipients with persistent diarrhea shows that beyond GVHD, most patients have other causes of diarrhea, even among those with GVHD in other organs. These findings have major implications in patient management and treatment decision-making. Repeated endoscopies/biopsies in cases with recurrent episodes of persistent diarrhea are useful to clarify diagnostic uncertainties and improve patient management.

Disclosure: None of the authors have conflicts of interest to declare.

P446

Cytokine release syndrome during atg/atlg serotherapy for GVHD prophylaxis before allogeneic HSCT: Incidence and early clinical impact according to astct grading criteria

J. Cserna[1], T. Rottner[1], C.K. Baumann[1], H. Knaus[1], M. Mitterbauer[1], A. Schulenburg[1], W. Rabitsch[1], P. Wohlfarth[1]

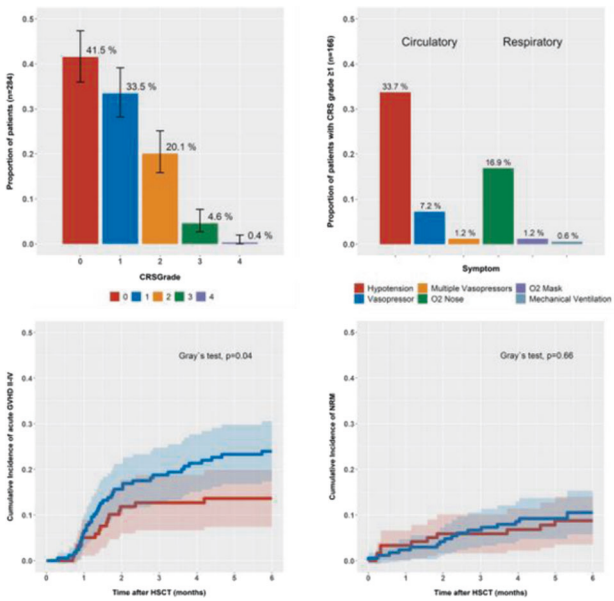
[1]Medical University of Vienna, Vienna, Austria

Background: Anti-thymocyte globulin (ATG)/Anti-T-lymphocyte globulin (ATLG) enhances graft-versus-host disease (GVHD) prophylaxis in HLA-matched related and unrelated donor hematopoietic stem cell transplantation (HSCT). Its use is frequently accompanied by systemic infusion reactions attributable to cytokine release syndrome (CRS), but current data on this complication are lacking.

Methods: Retrospective single-center analysis including consecutive allogeneic HSCT recipients treated with ATG/ATLG to prevent GVHD at the Medical University of Vienna, Austria, between January 1, 2014, and August 15, 2021. Multivariate regression models were constructed to explore risk factors of CRS and its association with clinical outcomes (acute GVHD II-IV, clinically significant cytomegalovirus infection, non-relapse mortality, overall survival) six months after HSCT.

Results: A total of 284 patients (median age: 54 [interquartile range: 45-61] years; f:m = 120:164) were included in the study. ATLG was used in 222 (78%) patients, ATG in 62 (22%) patients. 166 (58%) patients developed CRS grade ≥1 according to ASTCT criteria (Lee et al., BBMT 2019) during any ATG/ATLG administration day despite prophylaxis with high-dose systemic steroids (250 mg prednisone) on all infusion days. CRS was mostly mild, with 92% of the cases having experienced grade 1-2 (Figure). Thirteen (5%) patients had CRS grade 3, one patient CRS grade 4, and no CRS-related death (grade 5) was observed. Patients with CRS showed a pronounced systemic inflammatory response as measured by inflammatory markers (i.e., C-reactive protein, interleukin-6, procalcitonin). In multivariate analysis, lymphoma as the underlying disease (subdistribution hazard ratio [sHR]: 4.93 [95% confidence interval: 1.50-22.37]; p = 0.02), high ATG/ATLG dose level (sHR 3.01 [95%CI: 1.42-6.78], p < 0.01) and body weight (sHR 1.02 [95%CI: 1.00-1.04] per kg, p = 0.03) were statistically significantly associated with CRS. Patients with CRS grade ≥1 had a higher 6-month incidence of acute GVHD II-IV than non-CRS patients (24% vs. 14%, p = 0.04) (Figure). This effect remained statistically significant only for CRS grade 3-4 (sHR 3.70 [95%CI: 1.58-8.68]; p < 0.01) after adjusting for relevant confounders (Table). Other clinical outcomes were not affected by the occurrence of CRS.

Figure



Upper Panels: Distrubution of CRS grades and symptoms.

Lower Panels: Cumulative incidence of acute GVHD II-IV and NRM according to CRS grade ≥1 (blue = yes, red=no).

Table

	Hazard ratio	95% CI	p-value
Acute GVHD II-IV			
Age	1.00	0.98-1.03	0.72
Donor type (MSD reference)			
MUD	2.35	0.84-6.58	0.10
MMUD	4.57	1.42-14.77	0.01
CMV R+	1.19	0.64-2.23	0.58
CRS (Grade 0 reference)			
Grade 1-2	*1.55*	*0.84-2.86*	*0.16*
Grade 3-4	*3.70*	*1.58-8.68*	*<0.01*

Conclusions: In our cohort, CRS defined by ASTCT grading was a frequent but mostly mild complication following ATG/ATLG

administration for GVHD prophylaxis. Our results suggest a possible interaction of CRS with GVHD risk. Further studies should be conducted to define this relation, as it might be amenable to additional prophylactic interventions (e.g., tocilizumab).

Disclosure: Nothing to declare.

P447

Relationship of pre-transplant body composition and bone mineral density assessed by dual energy x-ray absorption with early complications after hematopoietic stem cell transplantation

P. Jablonowska[1], D. Jedrzejuk[1], M. Majcherek[1], A. Szeremet[1], M. Karasek[1], A. Czyz[1], T. Wrobel[1]

[1]Wroclaw Medical University, Wroclaw, Poland

Background: There are growing evidence in the literature on the influence of body composition, especially sarcopenia and body fat mass, on overall mortality in various patient groups, including patient with hematological malignancies. The aim of our study was to assess the relationship between complications after allogeneic (allo) or autologous (auto) hematopoietic stem cell transplantation (HCT) and body composition, as well as bone mineral density.

Methods: We evaluated total bone mineral density (BMD) and body composition in all consecutive patients who underwent autologous or allogeneic HCT between October 2019 and November 2021 in our center. The data on patients and disease characteristics, as well as the transplant details and outcomes were prospectively gathered. To assess total BMD and body composition, a densitometry using dual-energy x-ray absorptiometry (DXA) method was performed (Horizon A, Hologic, USA, 2017). The BMD was expressed in T score and Z score. Regarding the total body densitometry reports on body composition, the measured and calculated body fat values were: % body fat, fat mass index (FMI), androidal fat deposit (AFD), gynoidal fat deposit (GFD), androidal/gynoidal ratio. The measured and calculated body free fat mass values were free fat mass index (FFMI) and appendicular lean mass index (ALMI).

Results: A study group consisted of 209 patients (116 male and 83 female), including 126 patient treated with autoHCT and 83 with alloHCT. The median age of autoHCT and alloHCT patients was 57 years (range, 20-73) and 56 years (range, 18-73), respectively (p ns). The median follow-up time of survivors was 6 months (range, 1-28). No patients died in the autoHCT group during the follow-up time. The non-relapse mortality rate in alloHCT group was 9.6% (8/83 patients), with no association between NRM and BMD or body fat values. With regard to non-infectious complications, no grade 3-4 complications were observed in the autoHCT group. In the alloHCT group grade 3-4 non-infectious complications (including mucositis, toxic diarrhea, cardiac arrhythmia, heart arrest, and orthostatic hypotension) were observed in 22 out of 83 patients (26.5%) with significantly lower BMD Z-score, android/gynoid ratio, FFMI, and ALMI found in this group compared to patients without serious toxicities. Regarding the infectious complications after autoHCT, the significantly lower BMI (27.1 vs 23.1; $p = 0.009$), as well as lower total fat values and free fat values (i.e. % Fat Trunk/% Fat Legs, FFMI, and ALMI) were observed in the group of patients with febrile neutropenia (FN) in comparison to non-FN patients. In alloHCT group, FN was associated with significantly lower BMI and lower FMI.

Conclusions: The patients with post-transplant serious non-infectious complications present with lower values of fat mass and free fat mass, as well as lower BMD compared to patients without these complications. Our preliminary results suggest that fat tissue and lean tissue adjusted to height, as well as android/gynoid ratio might serve as new predictors of early non-infectious complications.

Disclosure: Nothing to declare

P448

Defibrotide causes decreased expression of inflammatory genes and proteins by activated primary human pulmonary microvascular endothelial cells

A. Laberko[1], A. Gardner[1], I. Haq[1], G. Nelson[1], M. Brodlie[1], A.R Gennery[1]

[1]Newcastle University, Newcastle upon Tyne, United Kingdom

Background: Hematopoietic stem cell transplantation (HSCT) is curative for many disorders of impaired hematopoiesis, immunity and malignancies. The number of patients undergoing HSCT has grown and incremental improvements have been made in HSCT techniques. However, among HSCT complications, endothelial cell (EC) damage syndromes remain some of the most serious complications causing severe morbidity and mortality, with limited therapies available. They include liver veno-occlusive disease (VOD) and renal thrombotic microangiopathy (TMA). The pathogenesis of the potentially fatal HSCT complication, idiopathic pneumonia syndrome (IPS), is poorly understood, however the role of EC injury may be pivotal. Defibrotide is a drug that has revolutionized the prevention and treatment of VOD, and there is growing evidence of its effectiveness in TMA. This study aimed to elucidate effects of defibrotide on pulmonary EC to evaluate its possible use in treating IPS.

Methods: Primary human pulmonary microvascular EC (HPMEC, Promocell) from 3 donors were cultured under recommended conditions and treated as follows: 1) human recombinant tumor necrosis factor alpha (TNFa) (Thermo Fisher Scientific) 20ng/mL for 24hr for HPMECs activation; 2) defibrotide (Jazz Pharmaceuticals) 20-100µg/mL for 24hr; 3) either TNFa or 4) defibrotide at the above concentrations for 24h followed by co-treatment with TNFa and defibrotide for 24h; 5) EC medium alone for 24h as a negative control. Cell viability analysis in HPMEC supernatants was performed using the CyQUANT LDH Cytotoxicity Assay (Thermo Fisher Scientific). Quantitative real-time PCR (TaqMan gene assay, Thermo Fisher Scientific) was used to investigate mRNA gene expression in treated HPMECs for *VWF, VCAM1, NOS3, CASP3, BAX* and *BCL2* compared to controls by DCt method. Expression of endothelial nitric oxide synthase (eNOS; Abcam) and vascular cell adhesion molecule 1 (VCAM1; R&D Systems) proteins were assessed in treated HPMECs using immunofluorescence microscopy and quantified by measuring fluorescence intensity mean of single cell cytoplasm mean in 20 cells per sample, compared between the samples (Nikon NiE microscopy; Fiji J software).

Results: HPMEC viability was not significantly affected by TNFa exposure and defibrotide treatment alone or before/after TNFa exposure. TNFa activation of HPMECs caused upregulation of both inflammatory (*VWF, VCAM1, NOS3)* and apoptotic (*CASP3, BAX, BCL2*) gene expression. Defibrotide treatment in HPMECs at the above concentrations before and after TNFa application caused downregulation of inflammatory and apoptotic gene expression to levels comparable with controls. Defibrotide treatment before and after TNFa activation reduced expression of VCAM1 and eNOS proteins in HPMEC cultures derived from 2 of the 3 donors investigated.

Conclusions: These results demonstrate downregulatory effects of defibrotide on inflammatory gene and protein expression in HPMECs in response to TNFa activation. This suggests a possible

mechanism for the effect of defibrotide on IPS in HSCT recipients that is worthy of further investigation.

Disclosure: AL received a non-restrictive educational grant from JAZZ Pharmaceuticals

P449

Use of emapalumab in the peri-transplant period to prevent graft failure in patients at risk

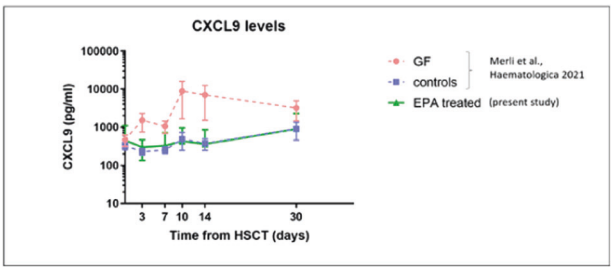
P. Merli[1], S. Ryhänen[2], F. Del Bufalo[1], S. Mielke[3], F. Quagliarella[1], M.G. Cefalo[1], P. Byström[3], M. Sundin[3], M. Algeri[1], A. Pitisci[1], F. Galaverna[1], L. Strocchio[1], T. Corsetti[1], P. Ljungman[3], F. Locatelli[1]

[1]Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, [2]University of Helsinki and Helsinki University Hospital, Helsinki, Finland, [3]Karolinska University Hospital Huddinge, Stockholm, Sweden

Background: Since graft failure (GF) is associated with dismal outcomes, novel strategies aimed at prevention/pre-emptive treatment of this complication are desirable. Several studies showed that IFNγ might have an important pathogenic role in immune-mediated GF [Merli, 2019]. We hypothesized that inhibition of this cytokine through emapalumab, an anti-IFNγ monoclonal antibody approved in US for refractory/relapsed primary hemophagocytic lymphohistiocytosis (HLH) [Locatelli, 2020], may improve engraftment in patients at risk for GF.

Methods: We retrospectively collected HSCT data from different centers who treated patients with emapalumab (on a compassionate use/off-label basis) in the peri-HSCT period to reduce the risk of GF. Patients at risk of GF were defined based on one or more of the following criteria: previous GF, disease know at risk for GF [e.g., primary HLH], use of reduced-intensity or non-myeloablative conditioning, T-cell depletion, and HSCT from a haploidentical donor. All patients who received at least 1 dose of emapalumab between day -1 and +28 were considered eligible. Patients were treated either during a second HSCT after experiencing a first episode of GF or upfront during the first HSCT. Treatment schedule varied in terms of dose (median 3 mg/kg/dose, range 1-10 mg/kg/dose) and frequency/number of administrations. Five patients underwent monitoring of CXCL9 (a chemokine specifically induced by IFNγ and used as marker of IFNγ neutralization) levels during the first 28 days after HSCT.

Results: Between 07/2016 and 01/2021, 10 patients were treated at 3 centers (Bambino Gesù Children's Hospital in Rome, Helsinki University Central Hospital and Karolinska Institutet in Stockholm). Main indication for treatment was primary hemophagocytic lymphohistiocytosis (n = 8); two patients affected by leukemia (T-ALL and JMML) were treated because of previous GFs. Most of patients were transplanted from a haploidentical donor after ex-vivo T cell depletion. Emapalumab was well tolerated with no infusion reactions reported. Adverse events recorded, including infectious complications, did not differ from common toxicities encountered after HSCT in pediatric patients; no treatment-related emergent adverse events were noted. Eight out of ten patients engrafted at a median of 17 days; platelet recovery was fast (median 10 days). Chimerism at day +28 was full donor in all patients who engrafted. Two patients developed chronic GVHD; 4 patients suffered from CMV infection and 1 had adenovirus infection. The patient with T-ALL engrafted, while that with JMML rejected and was rescued with a fourth allograft; none experienced relapse. However, one of the leukemia patients succumbed due to uncontrollable adenovirus infection. With a median follow-up of 40.3 months (range 10.0-65.1), 9/10 patients are alive and well. In patients who engrafted the levels of CXCL9 resembled those of the control group (i.e., that of patients who achieved sustained engraftment) of our previous report (Merli, 2019; Figure 1).



Conclusions: Emapalumab seems to have a good safety profile also when used in the setting of HSCT. Preliminary data from this small cohort suggests that emapalumab may be effective in promoting engraftment. A prospective clinical trial is ongoing (#NCT04731298).

Disclosure: PM: Advisory board: Sobi, Speaker's bureau: Bellicum. Honoraria: Jazz.

RS: Honoraria from Amgen and Novartis (advisory board)

SM: personal fee (consultancy): MSD; Speaker's bureau: Celgene, Kiadis, Jazz, Miltenyi.

PL,:personal fees from AiCuris and grants from Astellas, Oxford Immunotech, Takeda (Shire), and MSD.

FL: Research support: Bellicum; Speaker's bureau: Miltenyi, Bellicum, Amgen, Medac, Neovii, Novartis, Sanofi, Gilead, bluebird bio; Advisory board: Bellicum, Amgen, Neovii, Novartis, Sanofi.

P450

Efficacy of recombinant human thrombopoietin for the treatment of secondary failure of platelet recovery after allogeneic HSCT

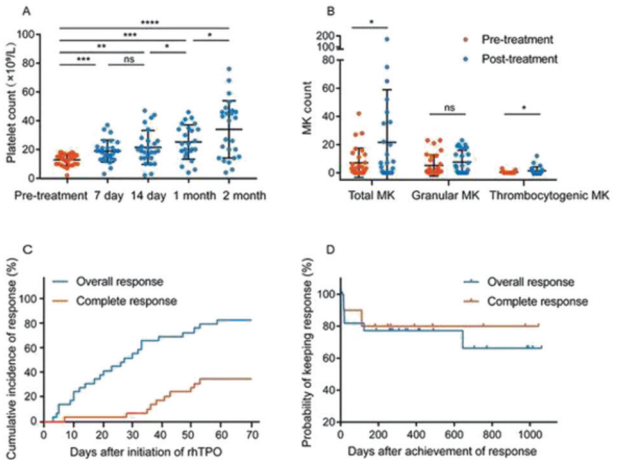
M. Wang[1], Y. Cao[1], B. Shen[1], A. Pang[1], E. Jiang[1]

[1]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China

Background: Secondary failure of platelet recovery (SFPR) is a life-threatening complication that may affect up to 20% of patients after allogeneic hematopoietic stem cell transplantation (HSCT). The effect of recombinant human thrombopoietin (rhTPO), a naturally occurring glycosylated peptide growth factor, in treating SFPR after allo-HSCT has not been reported in detail yet. Here, we describe a single center experience with rhTPO for the treatment of SFPR.

Methods: In this study, to evaluate the efficacy of rhTPO, we retrospectively analyzed 29 patients who received continuous rhTPO for the treatment of SFPR. SFPR is defined as a decline of platelet counts below 20 $\times 10^9$/L for 7 consecutive days or requiring transfusion support to maintain a platelet count above 20 $\times 10^9$/L after achieving sustained platelet counts $\geq 50 \times 10^9$/L without transfusions for 7 consecutive days after HSCT. Between January 2017 and April 2020, 741 patients underwent allo-HSCT in our institution. 29 patients who consistently received rhTPO for the treatment of SFPR were analyzed in this study. Patients who did not develop SFPR or developed SFPR but received other therapy or different schedule of rhTPO were excluded. RhTPO was injected at 300

IU/kg/day for 42 consecutive days at most or until platelet counts were ≥50 × 10^9/L, independent of platelet transfusion. Overall response (OR) and complete response (CR) was defined by platelet ≥ 20 × 10^9/L and ≥50 × 10^9/L for 7 consecutive days without platelet transfusion support within 2 months after initiation of rhTPO, respectively. Patients did not meet the criteria of response were defined as "no response".



Results: Patients were treated with rhTPO immediately after diagnosis of SFPR. The median duration of rhTPO treatment was 18 days (range, 8-42 days). The platelet count in peripheral blood significantly increased after 7 days post-rhTPO initiation. Of note, platelet counts continued to increase when compared 14-day vs 1-month (21.46 ± 2.32 vs 25.21 ± 2.426 ×10^9/L, P = 0.03) and 1-month vs 2-month (25.21 ± 2.426 vs 34 ± 3.983 ×10^9/L, P = 0.01). In addition, the number of total megakaryocytes and thromocytogenic megakaryocytes in bone marrow was significantly higher after rhTPO treatment (7.03 vs 21.58, P = 0.04; 0.31 vs 1.35, P = 0.048). In total, 24 (82.8%) patients responded to rhTPO treatment and 10 (34.5%) patients further achieved CR. The 30-day and 50-day cumulative incidence of OR was 55.2% and 72.4%, respectively, and of CR was 7.0% and 28.5%, respectively, since the start of rhTPO treatment. Multivariate analysis indicated that CR to rhTPO was associated with higher $CD34^+$ cells (≥3 × 10^6/kg) infused during HSCT (HR:7.22, 95% CI: 1.53-34.04, P = 0.01) and decreased ferritin after rhTPO treatment (HR: 6.16, 95% CI: 1.18-32.15, P = 0.03). Importantly, rhTPO was well tolerated in all patients without side effects urging withdrawal and clinical intervention.

Conclusions: Our results emphasize the essential role of rhTPO as a safe and effective treatment option for SFPR after HSCT. Further prospective randomized comparative studies are required to make accurate assessment on the efficacy of rhTPO for treating SFPR.

Disclosure: Nothing to declare.

P453

Safety proof of romiplostim immediately after cord-blood transplantation: Results of a phase 1 trial

N. Kurita[1], Y. Maruyama[1], Y. Suehara[1], K. Hattori[1], T. Sakamoto[1], T. Kato[1], Y. Yokoyama[1], N. Obara[1], K. Maruo[1], K. Hashimoto[1], M. Sakata-Yanagimoto[1], H. Nishikii[1], S. Chiba[1]

[1]University of Tsukuba, Tsukuba, Japan

Background: High rate of graft failure and delayed hematologic recovery are the major limitations of cord-blood transplantation (CBT), which lead to high morbidity and mortality. Prolonged thrombocytopenia may cause long-term transfusion dependency and hospitalization. Romiplostim, a thrombopoietin receptor agonist (TPO-RA), has shown to promote not only megakaryopoiesis in chronic ITP but also tri-lineage hematopoiesis in aplastic anemia. After allogeneic stem cell transplantation (AlloSCT), it has been tested for delayed platelet recovery and secondary thrombocytopenia in some previous studies. However, whether romiplostim promotes hematopoiesis if administered early after CBT is poorly understood. Here, we conducted a phase 1 trial in order to investigate the safety of starting romiplostim immediately after CBT with 6 adult patients.

Methods: This study was a phase 1, open-label, single center, dose escalation study (PROMPT-1; UMIN000033799). Adult patients with hematologic malignancy in remission undergoing single-unit CBT as the first AlloSCT were eligible for this study. Patients were excluded if they had impaired organ function, donor-specific anti-HLA antibody, prior history of thrombosis, or bone marrow fibrosis. Romiplostim was administered a day after CBT and then once a week for 14 weeks or until platelet recovery. The initial dose of romiplostim was 5 μg/kg (first 3 patients) or 10 μg/kg (subsequent 3 patients), and could be escalated to maximum 20 μg/kg. The primary endpoint was the incidence of any adverse events related to romiplostim. Secondary endpoints included hematologic recovery, incidences of relapse, non-relapse mortality, thrombosis, bone marrow fibrosis, and romiplostim-specific antibody.

Results: Seven patients were enrolled between April 2019 and August 2020, and romiplostim was administered except for a patient who met the exclusion criteria. The median age of the evaluable 6 patients was 40 years (range, 19–57). The diagnoses were AML (2), ALL (3), and MDS (1). Four patients received myeloablative conditioning and two received reduced-intensity conditioning. Tacrolimus and mycophenolate mofetil were used as GHVD prophylaxis. The median number of romiplostim administration was 5.5 (range, 3–15), and the maximum dose was 20 μg/kg. The administration was terminated due to platelet recovery in 5 patients, and due to non-relapse death in 1. The events possibly related to romiplostim were bone pain in 3 patients, and injection site reaction in 1. A total of 10 serious adverse events were reported in 5 patients: febrile neutropenia (4), acute GVHD (2), pneumonia (1), HHV6 encephalitis (1), CMV antigenemia (1), and arrhythmia (1). Relapse, thrombotic complications, or bone marrow fibrosis were not observed. All achieved neutrophil recovery, in whom the median day was 14 (range, 12–32). Platelet recovery was recorded in all patients except for one who died of pneumonia on day 48. The median days for platelet ≥ 50×10^9 /L was 34 (range, 29–98). Anti-romiplostim antibody was detected in 1 of 6 patients, which did not have neutralizing activity.

Conclusions: Romiplostim can be safely administered in the early phase of CBT. Further investigation with a larger prospective trial is warranted to evaluate its safety and efficacy.

Clinical Trial Registry: UMIN000033799

Disclosure: Romiplostim was provided by Kyowa Kirin. Mamiko Sakata-Yanagimoto has received research funding from Eisai, Bristol Myers Squibb, and Otsuka. Shigeru Chiba has received research funding from Kyowa Kirin, Chugai, Ono, Astellas, Beyer, Eisai, and Thyas.

P454

Pure red cell aplasia among abo mismatched hematopoietic stem cell transplant recipients: A 10 years retrospective study

E. Metafuni[1], M.A. Limongiello[1], S. Giammarco[1], F. Sorà[1], E. Galli[1], M. Bianchi[1], G. Massini[1], N. Piccirillo[1], R. Putzulu[1], L. Teofili[1], C.G. Valentini[1], F. Frioni[2], M.T. Busnego Barreto[3], R. Maggi[2], I. Pasini[2], A. Bacigalupo[1], P. Chiusolo[1], S. Sica[1]

[1]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, [2]Università Cattolica del Sacro Cuore, Rome, Italy, [3]Hospital Universitario Nuestra Senora de Candelaria, Santa Cruz de Tenerife, Spain

Background: Pure red cell aplasia (PRCA) is a possible complication after allogeneic stem cell transplantation (HSCT) with major ABO incompatibility. Patients experience a delayed engraftment of the erythroid series, with prolonged transfusion dependent anemia and iron overload.

Methods: We conducted a retrospective study, over the last 10-years, which included all consecutive major ABO mismatched HSCT performed in our unit, with the aim to assess PRCA prevalence and response to different treatment. One hundred-four patients received a major ABO mismatched transplant between May 2010 and August 2020. For each patients data about demographic and transplant characteristics, engraftment, blood transfusion and possible treatment received for transfusion dependent anemia were collected.

Results: A total number of 17 cases (12%) of PRCA were diagnosed: group A donor for group 0 recipient (n = 12), group A donor for group B recipient (n = 1) and group B donor for group 0 recipient (n = 4). Stem cell source was bone marrow from haploidentical donor in 10 cases, bone marrow from HLA matched donor in one case and peripheral blood from matched donor in 6 cases. IgG antibodies titer was available as dilution ratio before conditioning start for 13 patients: 1/64 (n = 1), 1/128 (n = 4), 1/256 (n = 2), 1/512 (n = 1), 1/1024 (n = 3), 1/2048 (n = 1), 1/4096 (n = 1). Four patients did not received specific treatment but only transfusion and recombinant erythropoietin (rEPO), with a median time to reticulocytes engraftment of 91 days (61 to 92). Median number of red cells packets received during the first three months was of 19.5 (18 to 21). Six patients had received peripheral plasmapheresis before transplantation, with a median number of 2 procedures (1 to 3). Among these, one patients did not receive specific treatment other than rEPO and transfusions after transplant. The other five patients received 4 weekly administration of rituximab without obtaining a response, followed by 6 procedures of plasmapheresis each other days combined with double dose of rEPO in a week. Three patients were treated with 4 weekly administration of rituximab, two of whom were then submitted to 6 procedures of plasmapheresis each other days combined with double dose of rEPO. Three patients received only 6 procedures of plasmapheresis each other days combined with double dose of rEPO in a week and another patient received only steroid therapy and rEPO. Among patients who received specific treatment, median time to reticulocytes engraftment was of 189 days (68 to 308) and median number of infused red cell packets was of 26 (14 to 80) in the first three months after transplant. All but one patients resolved PRCA with sensitive reduction in IgG antibodies dilution ratio (p = 0.07).

Conclusions: PRCA occurred in 12% of ABO mismatched patients, with a moderate prevalence among patients who had received bone marrow as stem cell source and haploidentical donor. Even if PRCA does not directly affect survival, it impacted strongly the quality of life of the affected patients. Specific treatments are needed for patients with prolonged PRCA duration and heavy transfusion support.

Disclosure: Nothing to declare

P456

HSCT-associated endothelial damage in real life: Retrospective analysis in 155 consecutive patients

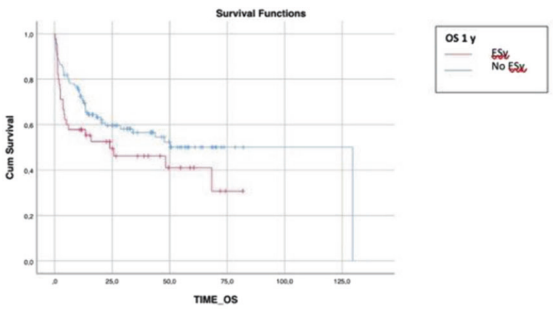
G. Mancini[1], I. Federici[1], I. Scortichini[1], F.R. Colaneri[2], S. Guerzoni[2], B. Puglisi[2], A.F. Lotito[2], A. Fiorentini[1], F. Saraceni[1], I. Scortechini[1], M. Moretti[1], S. Angeletti[1], R. Passera[3], A. Olivieri[1]

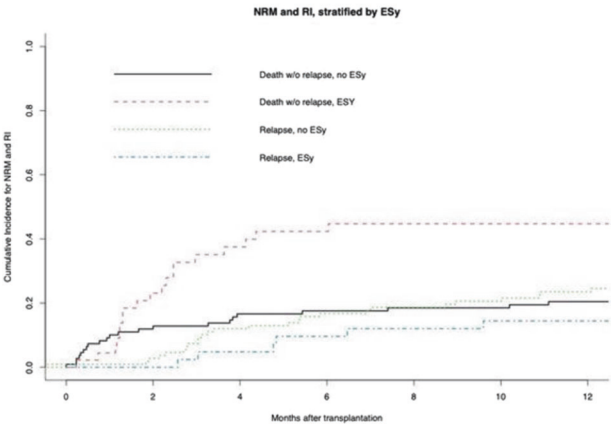
[1]Azienda OspedaliероUniversitaria Ospedali Riuniti, Ancona, Italy, [2]Università Politecnica delle Marche, Ancona, Italy, [3]Università degli Studi di Torino, Torino, Italy

Background: Endothelial syndromes (ESy) is emerging as a common but often underdiagnosed complication of hemopoietic stem cell transplantation (HSCT), with a relevant impact on morbidity and mortality; the most frequently reported ESy are: TA-TAM, Diffuse Alveolar Hemorrhage (DAH), Engraftment syndrome (ES) and VOD.

Moderate-severe arterial hypertension, renal failure, neurological symptoms and capillary leak syndrome or fluid overload have been commonly recognized as recurrent clinical pictures (here defined as major signs) of endothelial damage (ED), outside of diagnostic criteria for specific ESy; they are often associated with laboratory alterations (here defined as minor signs) such as LDH increase and albuminuria, PLT drop and haptoglobin consumption. We performed a retrospective study to evaluate the incidence of damage and endothelial syndrome in our center. This study has been approved by our IRB.

Methods: We retrospectively evaluated 155 consecutive patients (pts) underwent HSCT from January 2015 to December 2020. Characteristic of pts: median age 52 y (20-70 y); M/F recipient sex 57,4%-42,6%, conditioning MAC/RIC 54,5%-42,5%; ATG 56%, PTCy 39%, donor sibling 22,5%, MUD 46,5%, haploidentical 31%; source PBSC 62,5% and BM 37,4%. The median follow up was 31 months (14-54).





Results: We observed 45 (29%) ESy (13 TA-TAM, 15 VOD, 1 DAH, 16 ES) with a median onset of 39 days; 121 ED (79,2%) of wich 84 without ESy (median onset: 7,5 days) and 37 associated with ESy (median onset: 31 days).

We observed 69,7% aGVHD (17% grade 3-4); the aGVHD prevalence was 77,8% in ESy vs 66,4% in no Esy; 70,5% in ED vs 65,6% in no ED.

The OS was 48,3, 24 and 129,5 months in whole cohort, in ESy and in no ESy setting respectively (p-value 0.109).

The one year overall NRM was 27,2% with a RI of 21%; in ESy we observed NRM of 44,7% versus 20,5% in no ESy (p-value 0.003); pts developing ED without ESy, did not show increased NRM at 1 y (27,9% versus 22% in no ED.

At univariate analysis, the significant risk factors for NRM were: the presence of ESy, PBSC source, aGVHD, PTCy prophylaxis, value of bilirubin; for OS: stem cell source, donor type, PTCy prophylaxis, G-CSF administration, bilirubin value, VOD, DAH and capillary leak syndrome.

Conclusions: We have analyzed here both the incidence of ESy and the incidence of ED in a real life contest; ESy and ED are often underdiagnosed complications of HSCT that represent an important risk factors for OS and NRM. Both clinical signs and some simple biomarkers alterations of ED, in some cases may anticipate the ESy; although the identification of ED seems not to have a significant impact on OS, it represents a complication to be taken into account in the usual management of the transplant patient and should be captured in a prospective fashion in order to better correlate its real impact on the HSCT outcome.

Disclosure: Nothing to declare

P458

Severe GI regimen related toxicities increase with age in patients receiving autologous transplant for lymphoma

G. Shouse[1], A. Frank[2], E. Kavalerchik[3], S. Aggarwal[3], J. Fraser[3], P. Finnegan[3], B. Fakhri[2]

[1]City of Hope, Daurte, United States, [2]University of California San Francisco, San Francisco, United States, [3]Angiocrine Bioscience, San Diego, United States

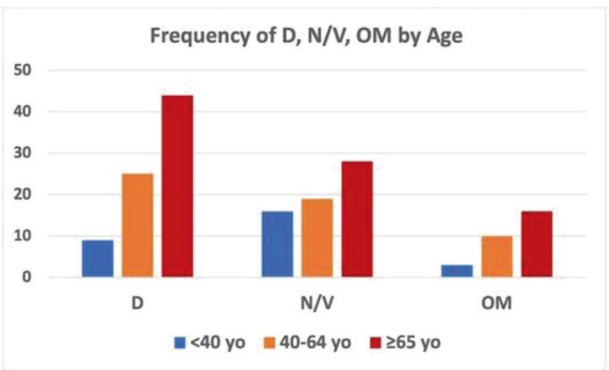
Background: High-dose chemotherapy (HDT) and autologous hematopoietic cell transplant (AHCT) is the standard-of-care (SOC) therapy for patients with aggressive lymphoma. Reporting of severe toxicities is sparse in literature but suggests high rates that increase with age despite improvements in supportive care. Clinically, severe toxicities involving the gastrointestinal (GI) tract lead to breakdown of the mucosa and translocation of the normal GI flora into circulation, increasing the risk of febrile neutropenia (FN) and severe infections. This may limit the use of the life-prolonging HDT-AHCT in older adults. Therefore, this study was conducted to document the extent of the GI toxicities in a rapidly aging population.

Methods: We conducted a retrospective analysis of 143 adults from 2 academic transplant centers undergoing HDT carmustine or bendamustine with etoposide, cytarabine, melphalan (BEAM or BeEAM) followed by AHCT for aggressive lymphoma between 2018 and 2020. Severe GI Regimen Related Toxicities (GI SRRT) were defined as grade 3 or higher (≥G3) oral/GI toxicities (NCI CTCAE v5).

Results: The median age of all patients was 58 years (yr) (range, 20–77). 69% were male with HL (29%) and NHL (71%). Median prior lines of therapy were 2 (1-4). BEAM was used in 99% of patients. GI SRRT occurred in 45% of patients overall. The most common GI SRRTs were diarrhea (D) (26%), nausea/vomiting (N/V) (20%), and oral mucositis (OM) (10%). GI SRRT rate increased with age: <40 (N = 32), 40-64 (N = 79), ≥65 (N = 32) yr from 31% to 44% and 63%, respectively. Frequency of D (9%, 25%, 44%), N/V (16%, 19%, 28%), and OM (3%, 10%, 16%) increased with age. When compared to the youngest group <40 yr, patients ≥65 yr had significantly higher risk of GI SRRT (OR 3.67, p = 0.0227), D (OR 7.50, p = 0.0046), and a trend towards more N/V and OM. Older patients were more likely to experience 2 or more GI SRRTs (9%, 13%, 25%). FN occurred in 66% of patients overall, increasing with age: 56%, 67%, 75% in respective age groups. Patients with GI SRRT developed FN more frequently than those without SRRT (74% vs 60%, OR = 1.86, p = 0.088).

	<40 yo (N = 32)	40-64 (N = 79)	≥65 y (N = 32)
GI SRRT, n (%) OR, p-value	10 (31)	35 (44)	20 (63)
		1.75 (p = 0.291)	3.67 (p = 0.0227)
Diarrhea (G3+)	3 (9)	20 (25)	14 (44)
		3.27 (p = 0.105)	7.50 (p = 0.0046)
Nausea/Vomiting (G3+)	5 (16)	15 (19)	9 (28)
		1.26 (p = 0.88)	2.11 (p = 0.361)
Oral mucositis (G3+)	1 (3)	8 (10)	5 (16)
		3.4 (=0.401)	5.7 (p = 0.198)
Febrile Neutropenia	18 (56)	53 (67)	24 (75)
		1.58 (p = 0.390)	2.33 (p = 0.188)

Age group 40-64 and ≥65 yo compared to <40 yo



Conclusions: We demonstrate that in a contemporary cohort of patients receiving HDT-AHCT, rates of GI SRRT and FN remain high and increase in frequency with age, despite advances in supportive care. The study provides support that GI SRRT and FN may be linked. The findings underscore the need for a new therapy that could prevent or reduce these clinically meaningful toxicities so that HDT-AHCT, a potentially curative therapy, can be provided to a broader group of older adults where toxicity concerns remain paramount.

Disclosure: Geoffrey Shouse has nothing to declare.

Annabel Kate Frank has nothing to declare.

Edward Kavalerchik is currently employed by and a current holder of stock options in Angiocrine Bioscience.

Sanjay K. Aggarwal is a current holder of stock options in Angiocrine Bioscience.

John K Fraser is currently employed by and a current holder of stock options in Angiocrine Bioscience.

Paul Finnegan is currently employed by and a current holder of stock options in Angiocrine Bioscience.

Bita Fakhri has nothing to declare.

P459

Lectin pathway inhibitor for transplant-associated thrombotic microagangiopathy

P.J Ganatra[1], M. Kakunje[1], V. Mishra[1], A. Pandrowala[1], P. Hiwarkar[1]

[1]Bai Jerbai Wadia Hospital for Children, Mumbai, India

Background: Transplant-associated thrombotic microangiopathy (TA-TMA) is a complement activation disease, considered to be caused by "multiple hits" that includes abnormal genetics of alternative pathway, calcineurin inhibitors, conditioning regimens, infections and graft-versus-host disease. It is characterized by thrombocytopenia, microangiopathic anemia with schistocytes on the blood smear, and varying organ impairment such as renal failure and gastrointestinal symptoms. Mannose residues on fungi and viruses activate mannose-binding lectin pathway, and hence activation of lectin pathway could be the prime reason for infection-driven TA-TMA. Narsoplimab, a human monoclonal antibody targeting MASP-2 is a potent inhibitor of lectin pathway. Hence, it could be an effective way to treat infection-driven TA-TMA.

Methods: We describe the transplant course of a pediatric patient who developed TA-TMA following Candida-driven Macrophage activation syndrome that was treated with Narsoplimab. The data collection was performed prospectively.

Results: Six-year old girl without HLA matched donor underwent haploidentical transplant for severe aplastic anaemia. Transplant conditioning included John Hopkins protocol with post-transplant cyclophosphamide and cyclosporine as graft-versus-host disease prophylaxis. In the second week of transplant, the patient developed macrophage activation syndrome necessitating treatment with steroids and intravenous immunoglobulin (IVIg). USG abdomen and blood fungal PCR revealed the diagnosis of a hepatosplenic candidiasis (Candida tropicalis) at a later date. Although macrophage activation and Candida infection was controlled with steroids, IVIg and caspofungin, the clinical course was further complicated by thrombotic microangiopathy. Patient developed hypertension in the 2nd week, followed by high LDH (1010 U/L), schistocytes (5 per hpf), low haptoglobulin (<5 mg/dl), thrombocytopenia and anaemia in the 3rd week. Ciclosporine was stopped and the patient was treated with 10 days of defibrotide without any response. The course was further complicated by microangiopathy of the gastrointestinal tract and kidneys. She had per rectal bleeding with frequent but low volume stools and severe abdominal pain, and hypoalbuminemia (1.8 g/dl) and proteinuria with high urine protein:creatinine ratio (2.8). Narsoplimab was started in the 5th week. A dramatic fall in LDH was observed after starting Narsoplimab (Figure 1). This was followed by resolution of gastrointestinal symptoms, proteinuria and recovery of cytopenia.

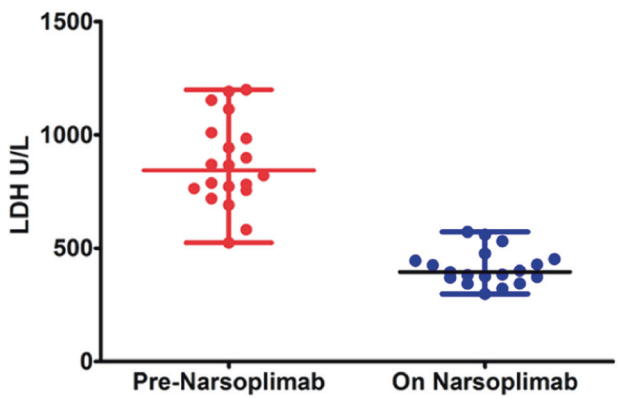


Figure 1 LDH levels before and after starting Narsoplimab

Conclusions: Lectin pathway inhibition could be useful in treating the fatal complication of TA-TMA. Lectin pathway inhibitor should be considered in Infection-related TA-TMA since lectin pathway is activated by viral and fungal infections.

Clinical Trial Registry: Not Applicable

Disclosure: No conflicts of the interest to declare.

P460

Extracellular DNA in children with venoocclusive disease after hematopoietic stem cell transplantation treated with defibrotide

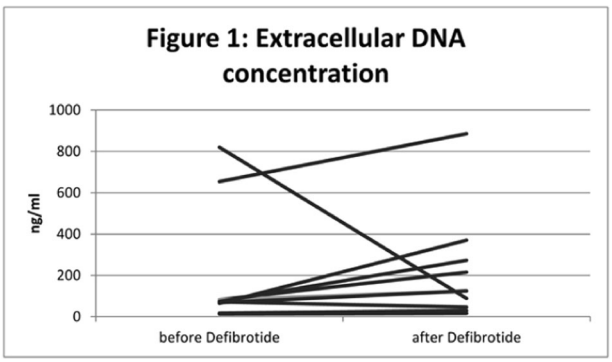
P. Svec[1,2], M. Fussiova[1], M. Janíková[2], M. Pastorek[2], J. Horakova[1], I. Bodova[1], A. Panikova[1], J. Adamcakova[1], T. Sykora[1], D. Doczyova[1], V. Dobsinska[1], M. Pozdechova[1], B. Vlkova[2], A. Kolenova[1,2], P. Celec[2]

[1]National Institute of Children's Diseases, Bratislava, Slovakia, [2]Comenius University, Bratislava, Slovakia

Background: The mechanism of action of DNA-containing drug defibrotide in venoocclusive disease (VOD) after HSCT is not precisely known despite its proven clinical efficacy. Extracellular DNA (ecDNA) has been implicated to play a role in pathopysiology of several disorders associated with endothelial dysfunction. We aimed to test the hypothesis that defibrotide increases total, but decreases patient-derived ecDNA in VOD.

Methods: Plasma samples from 10 pediatric VOD patients were collected before and shortly after initiation of defibrotide therapy. Plasma samples were collected at various timepoints between 3 hours to 48 hours since the first defibrotide infusion. Defibrotide was administered at standard dose of 25mg/kg/day divided in four 2-hours infusion per day. The underlying diagnoses included 7 neuroblastoma, 1 B-ALL, 1 JMML and 1 MDS patient. The VOD diagnosis was established based on updated pediatric EBMT criteria for VOD. EcDNA was isolated from double-centrifuged EDTA plasma and quantified using Qubit fluorometry. Nuclear (ncDNA) and mitochondrial (mtDNA) ecDNA was assessed using real time PCR. Wilcoxon non-parametric related sample test was used to compare pre- and post-defibrotide ecDNA concentrations.

Results: The interindividual variability in plasma ecDNA (13-820 ng/ml), ncDNA (38-204724 genome equivalents (GE)/ml) and mtDNA (5493-367409 GE/ml) was very high already before treatment. The median concentrations of ecDNA, ncDNA and mtDNA before and after defibrotide administration were 73 vs. 124 ng/ml ($p = 0.14$), 4287 vs. 9203 GE/ml ($p = 0.07$, 53062 vs. 118142 GE/ml ($p = 0.96$). The pre- and post-defibrotide concentrations of total ecDNA did not follow a uniform pattern (Figure 1), similarly to ncDNA and mtDNA (data not shown). Only one of ten patients showed a steep decrease of ecDNA, ncDNA and mtDNA concentrations in plasma after start of defibrotide therapy.



Conclusions: The results of this small but focused study do not suggest that defibrotide in VOD after HSCT does affect plasma ecDNA. Further analyses shall test ecDNA, its fractions and its metabolism as potential prognostic biomarkers but should also prove whether ecDNA has a role in the pathogenesis of VOD, as it does in sepsis and acute liver injury.

Disclosure: Nothing to declare

P461

Weight loss post allogeneic stem cell transplant is associated with increased transplant related mortality

K. Madsen[1], K. Lee[1], S. Chen[1], C. Chen[1], A. Law[1], A. Gerbitz[1], F. Michelis[1], W. Lam[1], A. Viswabandya[1], D. Kim[1], R. Kumar[1], I. Pasic[1], J. Lipton[1], J. Mattsson[1]

[1]Princess Margaret Cancer Centre, Toronto, Canada

Background: Allogeneic Stem Cell Transplant (allo-SCT) patients often experience weight loss as a result of impaired oral intake from gastrointestinal toxicities, taste dysfunction, and psychological effects. To date, there is currently no study in Canada examining the clinical impact of weight loss on allo-SCT outcomes.

Methods: A retrospective review of 246 patients transplanted at Princess Margaret Cancer Centre from 2016-2018 was performed. Patients were categorized into <10% weight loss or > =10% weight loss from SCT to 3 months and SCT to 6 months post-transplant Clinical outcomes included 2-y rate of OS (overall survival), transplant related mortality (TRM), and relapse free survival (RFS). Cox PH and Fine and Gray's models [CS1] examined the associations between weight loss and survival outcomes.

[CS1]Cox PH models and Fine-Gray's models.

Results: The overall incidence of patients who experienced weight loss of ≥10% from SCT to 3 months post-transplant was 45.9% and from SCT to 6 months was 56.6%. In univariate analysis, there was no difference in 2-y OS in patients who had ≥10% weight loss at both 3 and 6 months post transplant compared to those who did not, $p = 0.11$ and $p = 0.27$, respectively. Similarly, there was no difference in RFS in patients who had ≥10% weight loss at both 3 and 6 months post transplant compared to those who did not, $p = 0.22$ and $p = 0.31$, respectively. However, patients with ≥10% weight loss at 3 months post transplant had significantly higher 2-y TRM, 36% versus 17%, $p = 0.0007$. This was also found in patients with ≥10% weight loss at 6 months post transplant, with TRM rates of 22% versus 8%, $p = 0.0034$. In multivariate analysis, weight loss of more ≥10% remained statistically significant for increased TRM at both 3 months (HR = 1.91 (95% CI: 1.13-3.22)), $p = 0.015$ and at 6 months post-transplant (HR = 3.29 (1.47-7.35)), $p = 0.004$.

Conclusions: Patients who experienced ≥10% weight loss at 3 and 6 months post allo-SCT had significantly higher 2-year TRM. Ongoing monitoring of weight and nutritional status pre and post-transplant is imperative to allow for early intervention. More prospective studies are needed to examine specific strategies to address this potentially modifiable risk factor.

Disclosure: Nothing to declare.

P462

Compassionate use narsoplimab to treat transplant associated thrombotic microangiopathy in a pediatric patient with multi-organ failure

M. Schoettler[1], E. Bryson[1], L. Deeb[1], M. Qayed[1], B. Watkins[1], S. Chandrakasan[1], S. Chonat[1], K. Williams[1]

[1]Emory University, Atlanta, United States

Background: Multi-organ failure due to transplant associated thrombotic microangiopathy (TA-TMA) is often fatal after hematopoietic cellular therapy (HCT). Narsoplimab is a human monoclonal antibody which inhibits MASP-2, the effector enzyme of the lectin pathway of the complement system. In a phase 2 trial (NCT NCT02222545), 61% of adults with TA-TMA responded to narsoplimab. While experience in children is limited, we initiated treatment in an infant with refractory TA-TMA complicated by diffuse alveolar hemorrhage (DAH).

Methods: While experience in children is limited, we initiated treatment in an infant with refractory TA-TMA complicated by diffuse alveolar hemorrhage (DAH) via a compassionate use eIND.

Results: A 9-month-old girl with leukemia (KMT2A-MLL) underwent a 10/10 unrelated bone marrow transplant conditioned with busulfan and cyclophosphamide, complicated by anicteric veno-occlusive disease (day + 16). Despite treatment with defibrotide, she required a peritoneal drain, ventilator support, and renal replacement therapy (CRRT). On day +18 she was diagnosed with high-risk TA-TMA (proteinuria, elevated sC5b-9 multiorgan dysfunction) and started on eculizumab. Her hematologic parameters and organ function improved on eculizumab; she was extubated and recovered renal function. On day +34 she developed acute respiratory failure requiring re-intubation and was diagnosed with diffuse alveolar hemorrhage (DAH). She was started on inhaled tranexamic acid, and CRRT again. While her CH50 remained appropriately suppressed and eculizumab level was appropriate, she had evidence of worsening microangiopathy and organ dysfunction including recurrent DAH. She was treated with meropenem and vancomycin though her infectious work up was unrevealing. She demonstrated elevated C3a and Bb, confirming activation of the alternative pathway of complement. After obtaining an eIND, the family enrolled in a single patient protocol to use narsoplimab 4mg/kg IV starting on day + 57 (eculizumab discontinued to prevent additional risk of infections). Hematologic markers of TMA improved, she was extubated without any recurrent pulmonary bleeds, CRRT was stopped, and her proteinuria is improving. She continues twice weekly dosing (received 6 weeks). Narsoplimab was well tolerated. While there are no standard MASP2 pathway complement markers, after 3 weeks of treatment, she had normalization of Bb, C3a, C5a, and sC5b-9, and decreasing platelet and hemoglobin transfusion needs, suggesting the rapid reversal of organ dysfunction seen in this child was likely from lectin pathway blockade. As of the most recent follow up, day +91, she is on ¼ L nasal cannula for oxygen support and is working toward discharge home.

Conclusions: We describe an infant who developed severe TA-TMA that progressed on adequate blockade of terminal pathway using eculizumab, who had an excellent response to narsoplimab, emphasizing the role of lectin pathway activation in the pathophysiology of TA-TMA. Additional clinical trials of narsoplimab to treat pediatric TA-TMA are warranted.

Disclosure: Nothing to declare

P463

Incidence and impact on survival of sinusoidal obstruction syndrome/veno-occlusive disease in adult patients after allohct - retrospective palg analysis. Validation of ebmt severity scoring system

P. Mensah-Glanowska[1], A. Piekarska[2], A. Sadowska-Klasa[2], M. Sobczyk-Kruszelnicka[3], B. Nasilowska-Adamska[4], M. Tormanowska[4], A. Tomaszewska[5], A. Lojko-Dankowska[6], B. Piatkowska-Jakubas[1], T. Sacha[1], M. Bieniaszewska[2], J.M.

Zaucha[2], K. Halaburda[4], G. Basak[5], L. Gil[6], T. Wrobel[7], T. Czerw[3], S. Giebel[3], A. Czyz[7]

[1]Jagiellonian University Medical College, Krakow, Poland, [2]Medical University of Gdansk, Gdansk, Poland, [3]Maria Sklodowska-Curie National Research Institute of Oncology Gliwice Branch, Gliwice, Poland, [4]Institute of Hematology and Transfusion Medicine, Warsaw, Poland, [5]Medical University of Warsaw, Warsaw, Poland, [6]Poznan University of Medical Sciences, Poznan, Poland, [7]Wroclaw Medical University, Wroclaw, Poland

Background: Hepatic sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) is a life-threatening complication following allogeneic hematopoietic cell transplantation (alloHCT). The reported incidence of SOS/VOD in the literature ranges widely depending on conditioning regimen, type of transplant, patient characteristics and other factors. The aims of the study were to identify retrospectively the incidence of SOS/VOD, estimate its impact on survival and, finally, validate EBMT severity scoring in population of Polish adult transplant patients.

Methods: To identify SOS/VOD patients, pilot survey study was undertaken within Polish adult transplant centers aligned within the Polish Acute Leukemia Group (PALG). Based on review of institutional medical records, we have gathered the detailed data on SOS/VOD patients who underwent alloHCT from January 2012 to November 2021 in PALG centers. EASIX pretransplant and day 0 scores were assessed using EASIX calculator. SOS/VOD severity was evaluated using novelized EBMT criteria.

Results: As a result of a pilot survey study, the data was obtained from 7 centers. A total of 56 cases of SOS/VOD in 55 patients were reported, resulting in a SOS/VOD incidence rate of 1.8%. Thirty-three patients were conditioned with myeloablative regimens (59%), 21 with reduced intensity (37.4%) and 2 with non-myeloablative conditioning (3.6%). Thirty-five patients were conditioned with chemotherapy-based regimen (62.5%), and 21 patients received radiation-containing conditioning (37.5%). The median EASIX pretransplant, and EASIX 0 score were 2.59 (range 0.67-138.82) and 7.325 (range 0.95-685.15), respectively. According to EBMT grading system, 49 patients (87.5 %) presented with severe/very severe SOS/VOD. Regarding the SOS/VOD treatment, defibrotide was used in 13 out of 56 SOS/VOD cases (24%) – all these patients were classified as severe or very severe. Other therapeutic modalities included fluid and sodium restriction, diuretics, heparin, UDCA, steroids, and tocilizumab. More than two EBMT risk factors were present in almost all cases (54/56). Half of all SOS/VOD patients presented with platelet refractoriness (28 cases). Similarly, multi-organ failure (MOF) was observed in 51.7% of patients (29 cases). After the median follow-up time of 38 months (range 1-102), the outcomes were poor, with the overall survival (OS) rate of 33% (95%CI 21.8-46.5) at 2 years, and corresponding cumulative incidence (CI) of non-relapse mortality (NRM) of 65.1% (95% CI 53.6-79.6). Of note, CI_NRM was significantly lower in patients with mild/moderate SOS/VOD compared to patients with severe/very severe disease according to EBMT score (20.0% vs. 71.1%, $p = 0.032$). In univariate survival analysis, good performance status, low disease risk index (DRI), non-severe/very severe EBMT severity score and low EASIX scores were associated with longer OS. In a multivariate Cox proportional *hazard model*, a good performance status before transplantation remained an independent prognostic factor for OS.

Conclusions: The incidence of SOS/VOD in adult patients after alloHCT is low, however, prevalence of severe and very severe disease in the analyzed cohort might suggest that SOS/VOD is still underdiagnosed in adults. EBMT severity scoring allows adequate NRM risk assessment. Furthermore, pretransplant performance status, DRI, and EASIX scores might predict survival in SOS/VOD patients, with performance status confirmed in our study as an independent prognostic factor.

Disclosure: The study is supported by grant JAZZ Pharmaceuticals IST 10682

P464

Easix and endothelial cell dysfunction in allogeneic stem cell transplantation

L. Pardo Gambarte[1], M. López Pérez[1], S. Ramos Cillán[1], J.C. Caballero Hernáez[1], J.L. López Lorenzo[1], J. Cornago Navascúes[1], L. Solán Blanco[1], P. Llamas Sillero[1]

[1]Fundación Jiménez Díaz University Hospital, Madrid, Spain

Background: Allogeneic stem cell transplantation (alloSCT) is a curative treatment option for patients with many malignant and non-malignant hematological diseases, being the high treatment-associated mortality the main clinical challenge to overcome.

Endothelial dysfunction plays a crucial role in major complications of alloSCT, such as the graft-versus-host disease (GvHD), sinusoidal obstruction syndrome (SOS/VOD) and transplant-associated microangiopathy (TA-TAM).

The Endothelial Activation and Stress Index (EASIX) is a marker of endothelial damage that has been recently validated to identify a patient population at high risk for SOS/VOD and to predict the risk of death after acute GvHD (aGvHD).

The study's primary end-point was to test the capacity of EASIX and modified EASIX (m-EASIX) to predict these alloSCT complications

Methods: We performed a retrospective cohort analysis of 72 adult alloSCT recipients at a single Spanish transplant center (Fundación Jiménez Díaz University Hospital) between January 2017 and December 2020.

EASIX was calculated by the formula: LDH (U/l) x Creatinine (mg/dL)/Thrombocytes (nL), and modified EASIX (m-EASIX) was calculated replacing creatinine with CPR. Both scores were assessed prior to conditioning in all patients.

To analyze the differences between the values pre-transplant and the onset of complications, we use the U-Mann-Whitney Test and the independent T-test. All the statistical analysis were done with SPSS program 25.0.

Results: The baseline patient characteristics by cohort are given in Figure 1A.

Median PRE-EASIX values were 1.22 (interquartile range [IQR] 0.74 to 2.10). Median PRE-m-EASIX values were 0.60 (IQR 0.14 to 1.98).

SOS/VOD was diagnosed in 7 patients (9.7%, median onset day +14). Median EASIX in patients who develop SOS/VOD was higher than in patients who did not develop VOD/SOD (4.48 vs. 1.15, $p < 0{,}014$). There were no differences in the m-EASIX values.

Grade II-IV aGvHD was diagnosed in 19 patients (26.4%, median onset day + 71). Median EASIX in patients who develop aGvHD was higher than in patients who did not develop aGvHD (1.58 vs. 1.08, $p < 0{,}034$). There were no differences in the m-EASIX values.

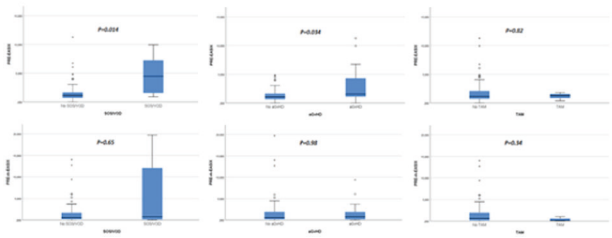
TA-TAM was diagnosed in 3 patients (4.2%, median onset day +46). There were no differences both in EASIX and m-EASIX values between patients who develop TAM and who did not develop TA-TAM (Figure 1B).

Figure 1A). Baseline characteristics of the patient cohort.

	n=72
Age (years) at alloSCT (median, range)	53 (41-59)
Recipient sex, n (%)	
Male	43 (60)
Female	29 (40)
Donor, n (%)	
MRD	29 (40)
MUD/MMUD	13 (18)
Haplo/MMRD	30 (41)
Disease, n (%)	
AML, MDS	40 (56)
ALL	10 (14)
Lymphoma, CLL	16 (22)
Others	6 (8)
EMBT Risk Score criteria, n (%)	
< 5	42 (60)
≥ 5	29 (40)
HCT-CI Score, n (%)	
< 3	54 (75)
≥ 3	17 (24)
Stem cell source, n (%)	
Peripheral blood	71 (99)
Bone marrow	1 (1)
Conditioning, n (%)	
RIC	37 (51)
MAC	35 (49)

Abbreviations:
ALL: acute lymphoblastic leukaemia, AML: acute myelogenous leukaemia, CLL: chronic lymphocytic leukaemia, MAC: myeloablative conditioning, MDS: myelodysplastic syndrome, MMUD: mismatched unrelated donor, MUD: matched unrelated donor, MRD: matched related donor, RIC: reduced intensity conditioning, SCT: stem cell transplantation, MMRD: mismatched related donor

Figure 1B). Association between PRE-EASIX and PRE-m-EASIX and allo-SCT complications.



Conclusions: In our cohort, higher PRE-EASIX values were associated with the development of SOS/VOD and grade II-IV aGvHD. No association was found between PRE-EASIX values and TA-TAM. We did not find differences between PRE-m-EASIX values.

Disclosure: The authors declare no conflicts of interest.

P465

Veno-occlusive disease after high-dose busulfan–melphalan in neuroblastoma: A 10 year single centre experience (2011-2021)

A. Deshpande[1], Y. Gupta[1], J. Patel[1], D. Hobin[1], S. Lawson[1], A. Norton[1], S. Gatz[2]

[1]Birmingham Women's and Children's NHS Foundation Trust, Birmingham, United Kingdom, [2]Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, United Kingdom

Background: Neuroblastoma is the most common paediatric extra-cranial solid tumour and accounts for 12% of cancer-related deaths in children. Autologous stem cell transplant following Busulfan-Melphalan (Bu-Mel) conditioning has shown superior survival compared to other regimens and is currently the standard of care for high-risk (HR)-neuroblastoma. High incidence of Veno-occlusive disease (VOD) of up to 38% has been reported in patients undergoing this treatment. To identify potential new factors associated with VOD, we undertook a single centre analysis, assessing incidence as well as selected clinical and laboratory parameters.

Methods: A retrospective analysis of all patients undergoing Bu-Mel conditioning with autologous stem cell return for HR-Neuroblastoma over a 10 year period (August 2011-2021) was performed. VOD was defined as per modified Seattle criteria. All patients received intravenous Busulfan and prophylactic Ursodeoxycholic acid. The following variables were extracted: age, sex, percentile of weight at start of conditioning, presence of liver impairment (ALT/AST/Bilirubin)/liver metastasis at time of starting conditioning, CD34 cell count, number of stem cell bags transfused (to account for DMSO content), number of days over which stem cells were infused, platelet counts on day 0 and day 8 along with platelet refractoriness (≥1 platelet transfusion/ day for 3 consecutive days to achieve a platelet count > 20x 10^9/L or control bleeding), parenteral nutrition required in immediate post-transplant period (yes/no); duration of Defibrotide therapy and VOD related mortality within 100 days of transplant. For numerical factors median, range and percentages were tabulated. Appropriate statistical tests were performed and significance calculated.

Results: Of a total of 44 patients 19 (43%) fulfilled the diagnostic criteria for VOD and received Defibrotide. Two novel factors were identified in our cohort which showed significant correlation with VOD:

1) platelets <20 x 109/l within 8 days of stem cell return (14/19 in the VOD group versus 10/25 in the No-VOD group, $p = 0.031$);

2) weight <25th percentile (9/19 in VOD group versus 3/25 in No-VOD group, $p = 0.014$).

No statistical correlation was identified for other factors as outlined above. Interestingly, 63% (12/19) of VOD patients were platelet refractory 7 days prior to starting Defibrotide but reversal of portal flow on doppler was only seen in 52% (10/19) at time of diagnosis. Defribotide treatment was started at a median of 20 days (range: 7-27) after stem cell return and was administered for a median of 14 days (range: 4 -25). VOD related mortality was 6.8% (3/44).

Conclusions: Compared to previous studies, we report a higher incidence of VOD in our patient cohort. We report a clinical association of early drop in platelet count within 8 days post autologous transplant and VOD development. If proven significant in larger studies, this might be beneficial for early diagnosis of VOD.

Further, we identified for the first time a weight <25th percentile as a potential factor contributing to VOD. Optimizing patient weight prior to transplant might be beneficial. More data including assessment of other measures of nutritional status are needed to better assess the potential clinical association and a larger multi-centre cohort study is required.

Disclosure: Nothing to declare

P466

A real-world evidence systematic literature review (slr) of the metrics used to detect veno-occlusive disease/sinusoidal obstruction syndrome (vod/sos) after haematopoietic cell transplantation (hct)

J. Angus[1], L. Rutherford[2], L. Moubarak[2], K. Roussi[2], A. Martin[2]

[1]Jazz Pharmaceuticals, Oxford, United Kingdom, [2]Crystallise Ltd, Essex, United Kingdom

Background: VOD/SOS is a potentially fatal complication of HCT. Its diagnosis is challenging, due to the many patient- and transplant-related VOD/SOS risk factors, and the dynamic presentation of symptoms. This study identifies the clinical manifestations of VOD/SOS post-HCT and determines how these relate to the features that comprise standard VOD/SOS diagnostic criteria using an SLR.

Methods: Medline and Embase were searched up to 4 March 2021 for studies of VOD/SOS post-HCT and were supplemented with guidelines on VOD/SOS diagnosis and management. English

Patients, n (%)b	Ascites	Hepatomegaly	Hyperbilirubinaemia	RUQ pain	Weight gain
First manifestation (n = 55)[c]	11 (31)	17 (44)	19 (39)	12 (50)	14 (40)
Second manifestation (n = 55)[c]	17 (47)	15 (38)	22 (45)	5 (21)	17 (49)
Third manifestation (n = 26)[c]	4 (11)	7 (18)	7 (14)	7 (29)	4 (11)
Fourth manifestation (n = 5)[c]	4 (11)	0 (0)	1 (2)	0 (0)	0 (0)
Total occurrences	36 (100)	39 (100)	49 (100)	24 (100)	35 (100)

language reports of observational and database studies were included if they studied adults or children with any HCT-related disease, therapies aimed at preventing/treating VOD/SOS, or HCT-associated VOD/SOS outcomes. Publications were evaluated based on inclusion of patients with features related to VOD/SOS diagnostic criteria and changes in diagnostic features over time; reports were categorised by specific subgroups within inclusion criteria. In cohort studies, an unweighted mean was calculated for the proportion of patients with each VOD/SOS feature; for case studies, the number of case reports where the feature was present was divided by the total number of cases where any features were reported.

Results: Overall, 204 publications were included in the SLR. Among cohort studies (n = 22,121 patients receiving HCT), the mean proportion of patients with reported VOD/SOS features was: weight gain (any) 87%, hyperbilirubinaemia 82%, hepatomegaly 76%, thrombocytopaenia 70%, ascites 61%, and right upper quadrant [RUQ] pain 61%. Among case studies (n = 280 patients), the proportion of patients with each reported feature was: hyperbilirubinaemia 79%, ascites 59%, hepatomegaly 47%, RUQ pain 21%, thrombocytopaenia 9%, and weight gain (>5%) 6%. There was no consistent pattern on which VOD/SOS feature appeared first (**Table**), although there was a trend for hepatomegaly and RUQ pain as early manifestations, with hyperbilirubinaemia, weight gain and ascites observed subsequently, consistent with the pathology of progressive VOD/SOS. VOD/SOS features changed rapidly in some patients after the first symptoms developed.

Conclusions: Presentation of VOD/SOS symptoms post-HCT in individual patients is heterogeneous, underscoring the difficulty in VOD/SOS diagnosis. VOD/SOS features are not reported in a distinct sequence, requiring a high index of suspicion for VOD/SOS and continuous vigilance by those involved in patient monitoring post-HCT.

Table. Typical VOD/SOS features[a] in case reports by order of occurrence

[a]For each report, ≥1 feature could count as a first/subsequent manifestation (e.g., if a report listed ascites and hepatomegaly as the first manifestations, both were counted as first).

[b]The denominator was the total number of occurrences of each feature.

[c]Total number of cases that reported a first, second, third, or fourth manifestation of VOD/SOS.

Disclosure: JA is an employee of and holds stock ownership/stock options in Jazz Pharmaceuticals. LR and KR are employees of Crystallise Ltd., which received funding from Jazz Pharmaceuticals to conduct this literature review. LM was an employee of Crystallise Ltd. at the time this study was conducted. AM is a director and employee of Crystallise Ltd.

P467

Low rates of testing and high prevalence of vitamin d deficiency before and after transplantation at an australian transplant centre

J. Perram[1,2], N. Hamad[1,2], J. Moore[1,2]

[1]St Vincent's Hospital, Darlinghurst, Australia, [2]University of New South Wales, Kensington, Australia

Background: The importance of vitamin D deficiency to transplant outcomes is largely unknown, however vitamin D is known to be critical for bone health and has known immunomodulatory roles. Several retrospective analyses have been performed examining the association between vitamin D deficiency and transplant outcomes, with variable findings related to overall survival, rates of graft-versus host disease (GVHD), CMV disease, and relapse risk. In addition to contradictory evidence, there is variability in the definition of deficiency, and the optimal marker of clinically significant deficiency remains unknown. A recent EBMT study of practices relating to peri-transplant vitamin D supplementation showed a lack of consensus regarding optimal management and absence of guidelines in this area. In New South Wales, it is recommended to maintain vitamin D levels above 75nmol/L following allogeneic stem cell transplant, for optimal bone health.

Methods: A retrospective audit of peri-transplant vitamin D levels in patients undergoing allogeneic stem cell transplant at St Vincent's Hospital in Sydney between January 2016 and December 2020 was performed. Rates of testing within 60 days pre-transplant and 100 days post-transplant were assessed. The incidence of vitamin D deficiency (defined as 25-hydroxyvitamin D level <50nmol/L) pre and post transplant were calculated. Testing and deficiency rates at any time post transplant were also assessed and the proportion with vitamin D < 75nmol/L was determined.

Results: A total of 209 transplants were performed in the five year study period. Rates of pre transplant vitamin D testing increased each year over the study period, being performed in 26% of patients undergoing transplant in 2020. Post transplant testing rates were higher than pre-transplant rates across all years, varying between 24-66%. Rates of pre-transplant deficiency generally decreased over time, whilst rates of post transplant deficiency remained high across the study period at 50-70%.

As pre-transplant testing increased, the rate of vitamin D deficiency decreased, however post-transplant vitamin D deficiency was seen in 50-70% of patients across the study period.

Of the 209 patients included in this analysis, 154 (74%) had at least one vitamin D level tested post transplant. Of these, 131 (85%) were deficient relative to local guidelines recommending a vitamin D level of >75nmol/L for maintenance of optimal bone health.

Conclusions: The importance of vitamin D deficiency to transplant outcomes remains controversial with little prospective research to date. Most studies focus on pre-transplant deficiency, however the development or worsening of vitamin D deficiency in the acute post transplant period has received little attention, despite this likely being a critical period for development of GVHD and infection. Our findings suggest that even in Australia, a country with long sunlight hours by global standards, pre and post transplant vitamin D deficiency is common. While the importance of this to transplant outcomes remains to be determined with prospective research, there is an existing mandate for supplementation due to the impacts of vitamin D deficiency on bone health.

Disclosure: No funding sources or conflicts of interest to declare.

P468

Systematic literature review of the natural history of hematopoietic stem cell transplant-associated thrombotic microangiopathy in adults

S. Whitaker[1], N. Nangia[1], E. Ng[2], K. Sotolongo[1], W. Pullman[1]

[1]Omeros Corporation, Seattle, United States, [2]Pacific Northwest Statistical Consulting, Seattle, United States

Background: Hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA) is a serious and potentially fatal complication of HSCT with no approved treatment. Frequent co-existing transplant complications can affect outcomes for patients with HSCT-TMA. A systematic literature review was conducted to better understand outcomes in this patient population. This literature review describes the natural history of HSCT-TMA in adults who have not received any specific pharmacological treatment for this condition, and the impact of co-existing complications on that history.

Methods: A protocol-driven, retrospective systematic literature review was conducted by searching PubMed for unique, English-language articles published between 2000 and 2020 using specific and relevant search terms. The criteria for including patient data from the articles identified were: age ≥18 years; diagnosis of HSCT-TMA following allogeneic HSCT; and had identifiable patient-level data that included any of the following: 1) any relevant laboratory or clinical variable (i.e., platelet count, lactate dehydrogenase [LDH], organ function, or transfusions) OR 2) report of "response" AND at least one risk factor (i.e., graft versus host disease [GVHD], neurological dysfunction, infection, pulmonary dysfunction, renal dysfunction, gastrointestinal dysfunction, or relapse or persistence of underlying malignancy). To assess the natural history of HSCT-TMA, patients from the published literature were excluded if they received pharmacological treatment for HSCT-TMA.

Data from the literature were subjected to meta-analysis statistical methods using random effects logistic regression. Resolution of HSCT-TMA was defined as 1) evidence in the article of reported "response" OR 2) improvement in platelet count, LDH, and either organ function or transfusion burden, if reported in the article. Unreported measures in all articles were imputed as improvement. Rates of HSCT-TMA resolution and 100-day survival from HSCT-TMA diagnosis were estimated with 95% confidence intervals (CI).

Results: The literature search identified 459 articles that were subsequently reviewed in duplicate by independent medically qualified reviewers, with adjudication by a physician. Twenty-five articles, which included 149 distinct patients, met the predefined criteria. Patient counts in these 25 studies ranged from 1 to 22 with a median of 4 patients.

Median patient age was 41.5 years (range, 18–66 years). Fifty-one percent were male, 39% were female, and sex was not reported for 10% of patients. Median time from HSCT to TMA diagnosis was 48 days (range, 1–2500 days). The overall HSCT-TMA spontaneous resolution rate from the identified articles was 23.3% (95% CI, 15.1–34.2%); in patients with co-existing GVHD or infection, HSCT-TMA resolution rates were 20.8% and 12.7%, respectively. The overall 100-day survival following HSCT-TMA diagnosis was 37.3% (95% CI, 22.8–54.6%).

Conclusions: This systematic literature review provides a comprehensive approach for determining the natural history of adult patients with HSCT-TMA in a real-world setting. HSCT-TMA resolution rates and 100-day survival in the absence of pharmacological treatments are generally low, highlighting the unmet medical need for an approved treatment for HSCT-TMA.

Disclosure: Steve Whitaker, Narinder Nangia, Kathy Sotolongo, William Pullman: Employment (Omeros Corporation); **Edmund Ng:** Consultant (Omeros Corporation)

P470

Outcomes related to pediatric intensive care unit admission in the first 100 days post hematopoietic cell transplantation

H. Hashem[1], A. Awais[1], Y. Nser[1], E. Khattab[1], M. Abu Shanap[1], Z. Alzebin[1], R. Rihani[1], I. Sultan[1]

[1]King Hussein Cancer Center, Amman, Jordan

Background: Hematopoietic cell transplantation (HCT) represents the only curative choice for children with certain malignant and non-malignant diseases. Nevertheless, HCT remains a high-risk procedure, and can lead to severe complications, requiring transfer to pediatric intensive care unit (PICU)

Methods: We retrospectively reviewed the medical charts of pediatric patients who underwent HCT between January 2014 and August 2020 and required PICU admission in the first 100 days after HCT at King Hussein Cancer Center (KHCC). The aim of our study is to describe incidence, causes, and outcomes related to PICU admission in the first 100 days post-HCT

Results: From January 2014 to August 2020, 530 children and young adults (0-19 years) underwent HCT at KHCC. Thirty seven patients (7%) were admitted to PICU in the first 100 days post-HCT for a total of 46 PICU admissions. The main causes of PICU admission were respiratory failure (32%), septic shock (21%), Gastrointestinal bleeding (19%), multiorgan failure (MOF) (16%), and seizure (11%). The overall 100-day cumulative probability of survival after PICU admission was 84% and six patients died. Causes of death were sepsis and MOF in 4 of the 6 patients, 1 with pulmonary hemorrhage, and one with acute respiratory distress syndrome (ARDS). Five of the 6 patients who died within 100 days after PICU admission were admitted within 10 days of stem cell infusion and 3 of the 6 patients had severe aplastic anemia. Seven patients (19%) required invasive ventilation and only 1 patient died. Four patients (11%) required dialysis and 1 died. On univariate analysis, only MOF had a negative impact on survival ($p = 0.02$)

Conclusions: These findings may provide support for the clinical decision making process on the opportunity of PICU admission for severely immunocompromised patients after HCT

Clinical Trial Registry: NA

Disclosure: Nothing to declare

P471

The recipient-specific antibodies (RSA) in mismatched related donors may affect transplant-related complications

A. Sadowska-Klasa[1], A. Dukat-Mazurek[2], H. Zielińska[2], J. Dębska-Zielkowska[2], G. Moszkowska[2], J.M. Zaucha[1]

[1]Medical Univeristy of Gdańsk, Gdańsk, Poland, [2]Medical Univeristy of Gdańsk, Gdańsk, Poland

Background: The presence of donor-specific antibodies (DSA) has a known impact on graft rejection and delayed immune recovery. However, it is unknown if recipient-specific antibodies (RSA) affect transplant-related complications. Here we present the incidence and impact of RSA on transplant outcomes in 17 consecutive pairs of recipients and their mismatched related donors.

Methods: At the donor selection, we checked both donors (D) and recipients (R) for the presence of DSA and RSA. Cytometric Luminex screen was performed as a first step. If any anti-HLA antibodies were detected, the next test involved a Luminex single antigen beads array (SAB) in determining the type of DSA/RSA. The results were presented as a mean fluorescence intensity value (MFI). All patients received a myeloablative conditioning regimen, peripheral blood stem cells (except one bone marrow), the same type of immunosuppression with post-Cy and tacrolimus/MMF, except one treated with sirolimus.

Results: The majority of patients, 15/17, were transplanted from haploidentical donors, two from mismatched related donors (1 mismatch). DSA were detected in 2 recipients (2/9; 22% patients with positive screen) whereas RSA in six donors (6/9; 66%). There was no difference in sex between DSA and RSA groups – R: 1 man/1woman, D: 3men/3women. We didn`t find differences in MFI values. Among 3 RSA-positive female donors, two were pregnant in the past. None of the donors had a prior blood transfusion history.

The median follow-up was 141 days (13-401); 3 patients are still in the early post-transplant period (before engraftment) and were excluded from further analyses. Among the remaining 14 cases, two patients didn`t have engraftment and finally died due to transplant complications, 4 had poor graft function. Ten out of 14 patients (71%) experienced CMV reactivation; in 11/14, transplant-associated thrombotic microangiopathy (TA-TMA) was diagnosed, acute graft-versus-host disease (GvHD) was observed in 5/14 cases (36%). There was no impact of RSA on graft failure/poor graft function; none of the patients with aGvHD had the RSA positive donor. RSA were observed more often in the TA-TMA group, however with no statistical significance.

All data, including demographic characteristics and antibodies, are summarized in table 1.

	Recipient		Donor	
Age	37 (19-68)		44 (17-69)	
Female (pregnancy history)/ male	9 (5)/8		5 (4)/12	
Blood transfusions	17/17		0/17	
	Recipient	**MFI median (range)**	**Donor**	**MFI median (range)**
Anti-HLA screen	9/17		9/17	
Class I	5/17	150 (40-9042)	5/17	748 (170-4602)
Class II	6/17	446 (44-1970)	6/17	432 (300-13946)
MIC	2/17	907 (596-1221)	3/17	702 (120-1219)
DSA / RSA	2/9	826 (629-1024)	6/9	757 (122-20087)

Conclusions: Our preliminary findings indicate that the incidence of anti-HLA-positive donors with RSA is relatively high despite the lack of transfusion history. The impact of RSA on transplant-related complications remains unknown, however, the association between RSA and TA-TMA requires further testing.

Disclosure: Nothing to disclose

P472

Clinical factors associated with red blood cell and platelet transfusion after hematopoietic stem cell transplantation

L. Pardo Gambarte[1], J. Cornago Navascues[1], C. Martínez Ingelmo[2], L. Solán Blanco[1], J.L. López Lorenzo[1], B. Pérez de Camino Gaisse[1], M.S. Sánchez Fernández[1], P. Llamas Sillero[1]

[1]Fundación Jiménez Díaz University Hospital, Madrid, Spain, [2]Autonomous University of Madrid, Madrid, Spain

Background: The vast majority of allogeneic hematopoietic stem cell transplant (allo-HSCT) patients require red blood cell (RBC) and platelets transfusion during the preengraftment phase after HSCT. Both RBC and platelets transfusion had been associated with adverse effects, including transfusion reactions or transmissible diseases. It had been shown that allo-HSCT patients who received more RBC transfusions after transplantation had a higher risk severe acute graft-versus-host disease (aGvHD) and had worse overall survival.

The principal aim of this study was to identify the principal clinical factors that are associated with RBC and platelets transfusions in order to identify possible interventions that can reduce transfusion requirements.

Methods: We retrospectively reviewed a cohort of 72 adult patients who had undergone alloSCT at a single Spanish transplant center (Fundación Jiménez Díaz University Hospital) between January 2017 and December 2020.

Patient demographics and transplant-related data were extracted from the clinical history of the patients. It was collected the number of RBC and platelets units transfused before the HSCT, between day +0 and +30 post-transplant and between day +30 and +100 post-transplant.

All the statistical analyses were done with SPSS program 25.0.

Results:

A total of 13 patients (18%) did not require RBC transfusion in the first 30 after alloSCT. Median pretransplant Hb was 13.2 gr/dl in patients not transfused and 11.2 gr/dl in those transfused ($p < 0.01$).

There were no differences between the underlying disease, the conditioning regimen or ABO groups and the amount of RBC or platelets transfusions required.

Low pretransplant hemoglobin (Hb) level, the use of erythropoietin (EPO) prior to transplantation and the development of veno-occlusive disease (VOD/SOS) have been identified with increase RBC requirements in the first 30 days. Acute graft-versus-host disease (aGvHD) increased transfusion needs in the period from day +31 to +100.

Prior autologous HSCT, the development of VOD/SOS and grade III-IV mucositis were associated with increased platelet requirements in the first 30 days after transplantation. GvHD was associated with higher platelets transfusions on days +31 to +100.

Conclusions: Anemia, the use of EPO, VOD/SOS and aGvHD are factors associated with higher RBC requirements, while prior autologous HSCT, grade III/IV mucositis, VOD/SOS and aGvHD are associated with platelets transfusion.

The identification of factors that avoid RBC and platelets transfusions may allow the development of strategies aimed at reducing RBC and platelets transfusions requirements and improving outcomes after allo-SCT.

Clinical Trial Registry: Anemia, the use of EPO, VOD/SOS and aGvHD are factors associated with higher RBC requirements, while prior autologous HSCT, grade III/IV mucositis, VOD/SOS and aGvHD are associated with platelets transfusion.

The identification of factors that avoid RBC and platelets transfusions may allow the development of strategies aimed at reducing RBC and platelets transfusions requirements and improving outcomes after allo-SCT.

Disclosure: The authors declare no conflicts of interest

P473

Role of N. Acetyl cysteine in reducing the mucositis in bone marrow transplantation

C.S. Ranjit Kumar[1], A. Aribandi[1]

[1]*American Oncology Institute, Hyderabad, India*

Background: Oral mucositis [OM] is a complications of high dose chemotherapy which is frequently observed in hematopoietic stem cell transplant settings. Antioxidants line N acetyl cysteine [NAC] proposed to prevent the OM. In the present observational study to evaluate the effects of NAC on OM incidence and severity.

Methods: The current study includes both pediatric and adult patient who were enrolled for both autologous and allogenic SCT received high dose chemotherapy or Myeloablative chemotherapy. Total 10patients were enrolled as observational study. NAC was given as parenteral route until the conditioning therapy complete and there after prescribed oral NAC until the engraftment.OM score was monitored during transplant period until engraftment.

Results: In this observational study total 10 patient were included, five were children less than 18years old and remaining five were adults. Four were autologous SCT and six were allogenic SCT[2 were haploidentical SCT;4 Matched related donor].underlying diagnosis- Multiple myeloma(n = 1)-High dose melphalan 200mg/m2],Relapsed Lymphoma(n = 2)-BEAM conditioning,Neuroblastoma(n = 1)- BuMel conditioning, Severe aplastic anemia(n = 3)-Fluderabine + Cyclophosphamide and ATG, Hyper IgE syndrome (n = 1)-Flu + CTx +Bu+ TBI with PT/Cy, Congenital Amegakaryocytic thrombocytopenia (n = 1) -Flu + CTx +Bu +TBI with PT/Cy, All patient received high dose chemotherapy.OM Maximum grade observed was grade 2 in 4 patient remaining 6 had only erythema as grade 1.All patient were engrafted, no mortality was seen until day +100 post transplant.

Conclusions: The NAC significantly reduces the OM in high dose chemotherapy setting, which may reduces the bacterial translocation and therefore gram negative sepsis, NAC did not affect engraftment and transplant outcomes. We also observed reduced stool volume in case of Gut GVHD and faster recovery when used for gut GVHD, though numbers were small may need larger study to confirm this.

Clinical Trial Registry: The NAC significantly reduces the OM in high dose chemotherapy setting, which may reduces the bacterial translocation and therefore gram negative sepsis, NAC did not affect engraftment and transplant outcomes. We also observed reduced stool volume in case of Gut GVHD and faster recovery when used for gut GVHD, though numbers were small may need larger study to confirm this.

Disclosure: nothing to declare

P474

Hepatic venoocclusive disease as main complication of autologous stem cell transplantation

M.A. Pimentel Villar[1], F. Almagro Torres[1], J.A. López López[1]

[1]*Haematological Service, Jaen University Hospital, Jaen, Spain*

Background: Hepatic venoocclusive disease (HVOD) is a potentially severe complication of high-intensity chemotherapy (HIC) for hematopoietic stem cell transplantation (HSCT). The development of HVOD can be rapid and unpredictable, thus the recognition of the main HVOD risk factors and close monitoring of them are essential for the optimal complication management. The HVOD diagnosis has traditionally been based on the Baltimore or modified Seattle criteria, which assess the common signs and symptoms of HVOD, that typically takes part during the first three weeks after transplantation. The symptoms of HVOD are dynamic, variable and can be progressive. This complication is relatively frequent after HIC used for allogeneic HSCT; however, it is unusual in an autologous HSCT.

Methods: The first of the cases is a 43-years-old woman with a diagnosis of IgA multiple myeloma ISS IIIA/ISS-R 2, who received autologous tandem transplantation after induction chemotherapy with two cycles of Bortezomib + Cyclophosphamide + Dexamethasone and five cycles of Carfilzomib + Lenalidomide + Dexamethasone due to progression. In the first transplant she arrived with a partial response, BUMEL conditioning was used. On day +25 she presents signs compatible with HVOD: hepatomegaly, ascites with increase in weight and hyperbilirubinemia. Defibrotide® was administered during 23 days, and condition improves. Subsequently, a second autologous HSCT was carried out with disease progression. A conditioning with MEL200 was used and the patient did not present signs compatible with HVOD.

Secondly, a 29-year-old man with acute promyelocytic leukemia diagnosis achieved complete remission (CR) after induction treatment. However, three years later he presented clinical and molecular relapse, for this, rescue chemotherapy treatment was administered reaching CR again. He was admitted to autologous HSCT, performing BEA regimen conditioning. On day +13, he presented worsening of liver analytical parameters with increased bilirubin and transamintases, severe hydropic decompensation with weight gain of more than five kilos, and painful hepatomegaly. Due to the high suspicion of HVOD and the clinical and analytical worsening with bilirubin 8.6 mg/dL, Defibrotide® is applied assuming hemorrhagic risk, because at that time he presents severe thrombopenia and coagulopathy, in consequence a prophylactic transfusion of platelets and antithrombin is prescribed during the first days; Ursodeoxycholic Ac is also associated. After these measures and 21 days of Defibrotide® treatment, the patient presented a favorable evolution.

Results: In both cases It can be observed as risk factors for the HVOD development: Busulfan administration as conditioning and the performance of an autologous HSCT.

Conclusions: Identifying patients with higher risk of HVOD could be the key for the early diagnosis and unanticipated treatment with Defibrotide®, which is also associated with better results. Some investigators have suggested that drug treatment should begin with the first possible HVOD signs/symptoms, even if patients do not already meet all the criteria for a complete diagnosis. Furthermore, although the review data indicate that this complication occurs more frequently after allogeneic transplantation, recent studies in adult and pediatric patients with autologous HSCT reported an increasing incidence of this complication.

Disclosure:
Conflict of Interest: None

NON-INFECTIOUS LATE EFFECTS, QUALITY OF LIFE AND FERTILITY

P475

How to improve quality of life in allogeneic transplant patients with a telemedicine-based protocol: Mandatory during covid-19 crisis, an opportunity for the future

M. Cabrero[1], E. Perez-Lopez[1], A.A. Martin[1], M. Baile[1], A. Avendaño[1], A. Cabero[1], B. Portal[1], M. García-Blazquez[1], B. Rey[1], M. Fonseca[1], L. Lopez-Corral[1], F. Sanchez-Guijo[1], L. Vazquez[1], M. González[1], D. Caballero[1]

[1]*Hospital Universitario de Salamanca-IBSAL, Salamanca, Spain*

Background: SARS-CoV-2 outbreak has challenged Spanish health system, with most of health care facilities exclusively dedicated to COVID-19 during the first wave. This situation forced Hematology departments to defer non-urgent procedures or visits to the hospital. In allogeneic stem cell transplant (AlloSCT) patients, this recommendation conflicts with the need of close follow-up due to potential complications, particularly related to graft versus host disease (GVHD). In the COVID-19 scenario, we had to balance optimal care of AlloSCT patients with minimization of their risk of exposure in the hospital. Telemedicine emerged then as a fundamental tool that could be implemented from now on to improve patients quality of life.

Methods: We elaborated a Telemedicine protocol based on daily review of scheduled appointments to evaluate the need of presenting visit, phone consultations and home-delivery drugs system developed by Pharmacy Department.

To evaluate our protocol, we prospectively collected data of medical consultations for March 16th to April 31st, both in-person or by phone, and compared it with the same period from 2019. To validate the protocol, we specifically checked: 1) percentage of presential visits after a phone evaluation; 2) rate of chronic GVHD diagnosed.

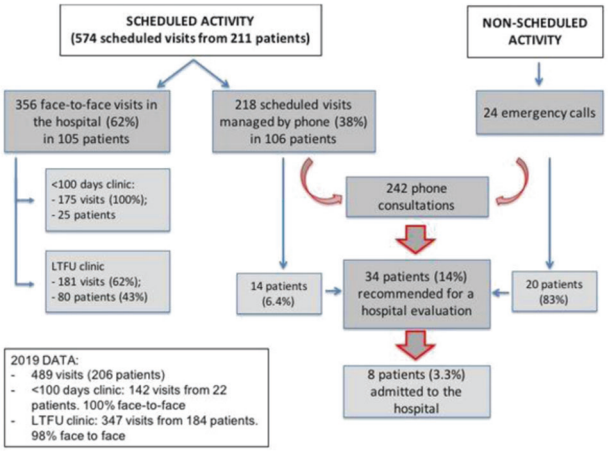
Results: From March 16th to April 30th, 574 out of 635 scheduled appointments were implemented, with 90% of assistance maintained during the outbreak peak. A total of 211 patients were attended: 25 patients in the first 100 days after AlloSCT with 100% face-to-face assistance (175 visits) and 186 patients from long-term follow-up (LTFU) clinic (399 consultations) with 43% face-to-face assistance. Regarding these LTFU consultations, we observed that 19 patients with GVHD, cytopenias or relapse represented 61% of face-to-face evaluations.

When comparing to our control group from 2019 (206 patients, 489 consultations), we observed a reduction in a 55% of face-to-face visits in LTFU patients, whereas those in <100 days after AlloSCT maintained 100% in-person assistance.

A total of 218 scheduled appointments (117 patients) were managed by phone; face-to-face evaluation was recommended in 14 cases due to infection (n = 2), suspected GVHD (n = 10) or suspected progression (n = 2). Twenty-four emergency calls were managed with a recommendation of face-to-face evaluation in 20 of them due to infectious disease (n = 16), suspected GVHD (n = 3) or symptoms consistent with cytopenias (n = 2) or thrombosis (n = 1). Among those patients managed by phone and considered not candidates for a face-to-face consultation, no cases of later hospital admission have been documented after a follow-up period of 28 to 70 days

Chronic GVHD rate was similar in patients managed by phone in 2020 and those with presential evaluation in 2019 (9.8% vs 8.5%; $p = 0.44$).

Results are summarized in Figure 1.



Conclusions: Our telemedicine based protocol allowed us to maintain 90% of activity during 1st wave of covid-19 pandemic, limiting visit to the hospital to those in real need.

Telemedicine proved to be a feasible tool for AlloSCT patients follow-up and it allows to diagnose common complications when applied by a trained Hematologist.

Telemedicine implementation for AlloSCT patients would improve their quality of life by decreasing the number of visits to the hospital.

Disclosure: Nothing to declare.

P476

Secondary neoplasms after umbilical cord blood transplantation. On behalf of eurocord and the european group for blood and marrow transplantation

H. Rafii El Ayoubi[1,2], A. Ruggeri[3,1], C. Kenzey[1,2], J. Sanz[4], R. Peffault De La Tour[5], J. Sierra[6], G. Michel[7], P. Chevallier[8], M.T. Rubio[9], J Cornelissen[10], M. Michallet[11], F. Volt[1,2], G.M. Scigliuolo[2,1], B. Cappelli[2,1], V. Rocha[12,1], E. Gluckman[1,2]

[1]*Eurocord, Hopital Saint Louis APHP, IRSL, EA3518, Université de Paris, Paris, France,* [2]*Monacord Centre Scientifique, Monaco, Monaco,* [3]*Haematology and Bone Marrow Transplant Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy,* [4]*Hospital Universitario La Fe, Valencia, Spain,* [5]*Bone Marrow Transplant Unit, Saint Louis Hospital, APHP, Paris, France,* [6]*Hospital de la Santa Creu i Sant Pau, Barcelona, Spain,* [7]*Hopital pédiatrique de la Timone, Marseille, France,* [8]*Hospital Hotel Dieu, Nantes, France,* [9]*CHRU Nancy, Nancy, France,* [10]*Erasmus MC-Daniel den Hoed Cancer Centre, Rotterdam, Netherlands,* [11]*Centre Leon Berard, Lyon, France,* [12]*Clinics Hospital, University of São Paulo Medical School, São Paulo, Brazil*

Background: Secondary neoplasms (SN) represent serious late complications in long-term survivors after hematopoietic stem cell transplantion. With improved outcomes and better post-transplant care, the number of long-term survivors is continually increasing. The risk of developing SN is the result of a complex interaction of factors related to treatment, recipient and immunosuppression drugs. This study aims to describe the SN reported in patients who received umbilical cord blood transplantations (UCBT).

Methods: We performed a retrospective analysis of cases of SN in recipients of UCBT reported to Eurocord and to the European Group for Blood and Marrow Transplantation (EBMT) registries.

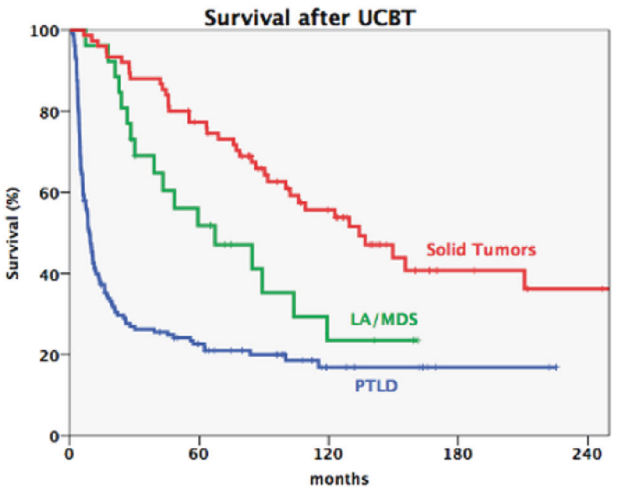
Results: From October 1988 to December 2018, 253 cases of SN (2,4%) were reported within the cohort of 10358 patients who received UCBT. Graft sources of the 253 UCBT which resulted in SN included single (n = 159), double (n = 80), expanded (n = 2) UCB

and UCB associated with other stem cell sources (n = 12). Patients with a follow-up less than 2 years (y) were excluded. Three main subgroups of SN were identified : post-transplant lymphoproliferative disorders (PTLD, n = 153, 60%), secondary leukemia/myelodysplasia (SL/MDS, n = 26, 10%) and solid tumors (n = 75, 30%).

One hundred fifty-two patients developed PTLD within a median time of 3 months (0.3-9.6) after UCBT and had a median age at UCBT of 27y (0.3-68). Primary disease was hematological malignancy in 120 patients (79%). Ninety patients (59%) received myeloablative conditioning (MAC), 68 patients (45%) received total body irradiation (TBI) and 120 patients (79%) received anti-thymocyte globulins (ATG). Eigty-five patients (56%) died of PTLD. At last follow-up, 31 patients (20%) were alive with a probability of 5y-survival after the diagnosis of PTLD of 21 ± 3%.

Twenty-six patients developed SL/MDS within a median time of 27 months (15-50) after UCBT, including 16 acute myeloid leukemia (AML), 2 acute lymphoblastic leukemia (ALL), 4 donor-derived AML and 4 MDS. The median age at UCBT was 22y (1-62). Twenty-three patients (88%) were transplanted for malignant diseases [ALL (9); AML (4); Myeloproliferative disease (4); Lymphoma (6)], two patients for bone marrow failure and one patient for hemoglobinopathy. Thirteen patients (52%) received MAC regimen, 10 patients (40%) received TBI and 13 patients (52%) ATG. At last follow-up, 9 patients (35%) were alive with a probability 5y-survival after the diagnosis of SN of 19 ± 14%.

Seventy-five patients (developed 83 solid tumors within a median of 57 months (32-99) after transplantation. The median age at UCBT was 45y (0.5-67). Thirty one patients (42%) received MAC, 47 (63%) received TBI and 36 (52%) received ATG. The most frequent tumor sites included lung (12), bone/soft tissue (11), thyroid (9), gastrointestinal (8), oral cavity (7) and skin (7 basal cell carcinoma BCC; 4 non-BCC), in addition to less common sites (20). Thirty-seven (49%) patients were still alive at last follow-up; the probability of 5y-survival after the diagnosis of solid tumors was 48 ± 6%.



Conclusions: Recipients of UCBT are at risk to develop both early and late onset SN with poor outcome. Identification of risk factors and life-long screening for early detection of solid tumors are mandatory to improve overall survival.

Clinical Trial Registry: Not applicable

Disclosure: Nothing to declare.

P477

Late effects: Patient-reported and proxy-reported outcomes among pediatric allogeneic hematopoietic stem cell transplantation for non-malignant diseases – what doesn't kill you, makes you stronger

J.E. Bense[1], L. Haverman[2], E.G.J. von Asmuth[1], M. Louwerens[1], M.AJ Luijten[2], A.M Stiggelbout[1], A.C. Lankester[1], A.P.J. de Pagter[1]

[1]Leiden University Medical Center, Leiden, Netherlands, [2]Amsterdam University Medical Center, Amsterdam, Netherlands

Background: Insight into the long-term patientreported outcomes (PROs) after pediatric hematopoietic stem cell transplantation (HSCT) for non-malignant diseases is lacking but essential for optimal shared decision-making, counseling and improving care.

Methods: In this single-center cohort study PROs were evaluated from December 2020 – March 2021 among patients ≥2 years after pediatric allogeneic HSCT for non-malignant disease from the Leiden University Medical Center. Validated age-appropriate PRO measures (PedsQL™ 4.0 and PROMIS item-banks) were selected based on availability in Dutch and optimal international reference. Patients aged ≥8 years completed self-report, if aged <8 years parents completed the proxy version. Mean PedsQL™ scores and PROMIS T-scores were compared to Dutch reference data using independent t-tests. Variables associated to PROMIS T-scores were determined using univariate regression analysis.

Results: 119 of 174 patients participated in this study (68% response rate), median age was 15.8 years (range 2-49), of whom 72 males. Median follow-up duration after HSCT was 8.7 years (IQR 4.2-15.4). Indications for pediatric HSCT were inborn errors of immunity (IEI, N = 41), hemoglobinopathies (HB, N = 37), bone marrow failure (BMF, N = 41). Conditioning regimens were mainly treosulfan-based (41%), busulfan-based (34%), and cyclophosphamide-based (17%).

Significant lower scores compared to the Dutch population were found on the following PedsQL™ 4.0 subscales: Physical Health (children (5-7 years) and adolescents), Psychosocial health (adolescents), School Functioning (children (5-12 years) and adolescents). Young adults (18-30 years) reported no significantly different scores.

Table 1 presents mean delta PROMIS T-scores compared to Dutch reference data, if available, per age category.

PROMIS item	5-7 years	8-18 years	19-30 years	>30 years
	N = 15	N = 57	N = 28	N = 9
Anger[1]	-	1.2 (±11.2)[b]	-	-
Anxiety[1]	-	1.4 (±7.6)	-1.4 (±6.5)[d]	2.6 (±8.0)
Depressive Symptoms[1]	*-4.3 (±7.4)*	0.4 (±9.3)	*-4.3 (±6.2)	-1.7 (±6.3)
Fatigue[1]	*-7.2 (±7.5)*	*-8.0 (±11.2)*	-2.8 (±7.2)[d]	3.6 (±6.7)
Pain Interference[1]	-	*-7.2 (±8.1)*	*-2.9 (±7.3)[d]	*-8.3 (±9.7)
Sleep Disturbance[1]	*-1.0 (±7.7)*	*3.1 (±8.0)[b]	*-5.3 (±8.2)[d]	1.1 (±8.1)
Cognitive function[2]	*-4.4 (±8.9)[a]*	*-0.6 (±7.3)[c]*	-	-
Mobility^[2]/Physical Function[2]	-	*0.4 (±7.8)^*	*-3.1 (±6.7)[d]	*-8.3 (±8.1)
Peer Relationships^[2]/ Satisfaction with Social Roles and Activities[2]	*-2.0 (±6.1)^*	*2.7 (±7.3)^[b]	*5.4 (±7.5)[d]	4.8 (±6.8)

*p < 0.05; [a]N = 14; [b]N = 56; [c]N = 52; [d] N = 27

[1]Higher scores indicate more symptoms; [2]Higher scores indicate better functioning.

USA reference (mean T-score = 50; SD = 10) was used if Dutch reference was not available.

Young adults (19-30 years) show the most favorable scores compared to Dutch reference in the PROMIS item-banks. Univariate regression analysis showed significantly worse scores for HB compared to IEI on *Pain Interference*, *Physical Functioning*, and *Satisfaction with Social Roles and Activities*. Significantly better scores were seen on *Pain Interference, Fatigue, and Mobility* in patients with busulfan-based compared to treosulfan-based regimen. Higher age at HSCT showed significantly worse scores on *Pain Interference, Satisfaction with Social Roles and Activities*, and *Fatigue*.

Conclusions: This study showed normalization of long-term PROs in patients after pediatric HSCT for non-malignant diseases. More attention is needed for physical health, school, and cognitive functioning. Children and adolescents seem most vulnerable, indicating the need for early supportive care to prevent long-term impaired quality of life.

Disclosure: Nothing to declare.

P478

A mobile phone application and physician dashboard for real time remote monitoring of symptoms, vital sign and activity in patients after allogeneic stem cell transplantation

E. Al-Shaibani[1], A. Quirke[2], S. Takkar[3], A. Gerbitz[1,4]

[1]Princess Margaret Cancer Centre, UHN, Toronto, Canada, [2]University of Toronto, Toronto, Canada, [3]Reknowldge Inc., Kitchener, Canada, [4]Curetrax. Inc, Toronto, Canada

Background: Spending less inpatient time on transplant wards has been shown to improve quality of life and outcomes after allogeneic stem cell transplantation (aHSCT). One of the major obstacles for early discharge after aHSCT is aside from frailty the high risk for infections and the need for monitoring of graft versus host disease. This requires frequent hospital visits which is in times of Covid19 often a challenge and patients express reluctancy due to the higher risk of disease transmission in congested outpatient clinics. Furthermore, structured data acquisition is missing, especially in the home care setting.

Methods: We have developed a mobile phone application for aHSCT patients that allows for specific symptom reporting and, in combination with a wearable device for online monitoring of major vital signs in real time. The application captures currently more than 50 data points relevant for aHSCT and infectious disease monitoring. It is based on REACT/NATIVE and JSON coding and enables specific designs based on requirements. Data captured by the wearable devices and manual symptom reporting are displayed in a close to real time fashion on a browser-based dashboard to the physician in a comprehensive fashion to allow for trend assessment of all transplant relevant information. It provides a photo function to capture skin images which are displayed on the physicians dashboard. Daily symptom reporting can be performed as often as necessary by the patient and data from wearable device are obtained multiple times every hour. The mobile phone application runs on android and iOS devices. The physicians dashboard includes several decision buttons that capture time stamped diagnosis or treatment decisions to enable machine learning and pattern recognition.

Results: Data from symptom reporting and wearable device are displayed on a dashboard to the responsible health care provider with only a minor time delay. With this platform we capture and display in addition to vital signs (pulse, breathing rate, oxygen saturation of the peripheral blood, body weight) and simple GvHD related symptom reporting information on the patient's physical activity, food intake, fluid intake, sleeping patterns, blood pressure and body temperature. The dashboard displays all transplant relevant information (HLA match, conditioning regimen, ABO incompatibility, CMV/EBV/Toxoplasmosis serology etc.) of the patient and of the donor and allows for a quick connection to the patient in case trends are reason for concern. It displays all data longitudinally over several days and therefore allows to observe trends and developments. Access to the dashboard is centre specific and secured by a dual verification process. Patient data are stored in HIPAA/PHIPA compliant fashion but storage can be adapted to country specific requirements.

Conclusions: This application enables remote home monitoring of patients after aHSCT. It has been designed to improve quality of life by enabling more controlled home care and potentially earlier discharge. Both front ends are developed in a modular fashion and can easily be adapted to specific requirements for example after CD19 CAR T cell therapy or after autologous transplantation.

Disclosure: Sudeep Takkar is founder of Reknowledge Inc.
Armin Gerbitz is founder of Curetrax Inc.

P479

Pulmonary function is a strong predictor of 2-year overall survival and non-relapse mortality after allogenic hematopoietic cell transplantation

F. Schierbeck[1], N.S. Andersen[1], L.S. Friis[1], B.T. Kornblit[1], S.L. Petersen[1], I. Schjødt[1], H. Sengeløv[1]

[1]Rigshospitalet, Copenhagen University Hospital, København Ø, Denmark

Background: Prescence of comorbidity prior to allogenic hematopoietic cell transplantation (aHCT) impairs overall survival (OS) and increases the rate of non-relapse mortality (NRM). Therefore, predictive tools for assessing OS and NRM prior to transplant are much warranted.

Methods: In this retrospective single-center study of 663 consecutive adult HCT recipients, we investigated the predictive value of pulmonary impairment prior to allogenic hematopoietic cell transplantation by stratifying patients by the three scores defined in the commonly used HCT-CI; (low-risk group, no pulmonary impairment (DL_{CO} and/or $FEV_1 > 80\%$); intermediate-risk group, moderate pulmonary impairment (DL_{CO} and/or FEV_1 66-80%); high-risk group, severe pulmonary impairment (DL_{CO} and/or $FEV_1 \leq 65\%$)). The predictive value of this pulmonary impairment index (PI-I) was compared to HCT-CI (low-risk group, HCT-CI score 0; intermediate-risk group, HCT-CI score 1-2; high-risk group, HCT-CI score ≥3).

Results: 241 patients (36%) had moderate pulmonary impairment and 142 patients (21%) had severe pulmonary impairment. In the group of myeloablative conditioning (MAC) patients, the frequencies were 107 patients (38%) and 46 patients (16%), respectively, and in the non-myeloablative (NMA) conditioning group, the frequencies were 134 patients (35%) and 96 patients (25%), respectively. In univariate analysis, both the HCT-CI and the PI-I were associated with OS after transplantation when comparing patients in high-risk groups with patients in low-risk groups. Using the PI-I, the HRs of the 2-year OS in the entire population and in the MAC group were 1,98 ($P < 0,001$) and 3,27 ($P < 0,001$), respectively, whereas the HRs using the HCT-CI were 1,83 ($P < 0,001$) and 2,57 ($P = 0,002$), respectively. None of the indexes showed significance in the NMA group.

Using the HCT-CI without scores for pulmonary disease, we found that this index showed no significance separating risk groups within the groups of MAC and NMA patients.

In multivariate analysis, stratified for age and conditioning regimens, comparing high-risk groups to low-risk groups, the HRs of 2-year OS using the PI-I and the HCT-CI were 1,88 ($P < 0,001$) and 1,72 ($P = 0,002$), respectively.

The 2-year NRM incidence in the three risk-groups using the PI-I and the HCT-CI was 10% (95% CI 7%-14%), 13% (95% CI 9%-17%), and 24% (95% CI 17%-31%) ($P < 0,001$), respectively and 12% (95% confidence interval CI 8%-17%), 10% (95% CI 7%-14%), and 19% (95% CI 14%-24%) ($P = 0,003$), respectively. In the MAC group, the 2-year NRM was significant using the PI-I ($P = 0,003$), but not using the HCT-CI ($P = 0,23$).

Conclusions: In conclusion, our single-center study suggest that pulmonary function alone is a strong predictor of 2-year OS and NRM after aHCT. A pulmonary function test is readily accessible in most centers, and the result is easily translated into a risk score.

Clinical Trial Registry: In conclusion, our single-center study suggest that pulmonary function alone is a strong predictor of 2-year OS and NRM after aHCT. A pulmonary function test is readily accessible in most centers, and the result is easily translated into a risk score.

Disclosure: Nothing to declare

P480

Relapse and severe graft-versus-host-disease have a negative impact on long-term symptoms and quality of life of patients three years after allogeneic haematopoietic stem cell transplantation

S. Oerlemans[1], F. Verheij[2], T. Nagtegaal-de Wit[2], K. Nijssen[2], L. Kramer-Smittenberg[2], L. Schoonhoven-Bos[2], A. Van Rhenen[2], L. Van Hussen-Daenen[2], L. Van der Wagen[2], M. De Witte[2,3], J. Kuball[2,3]

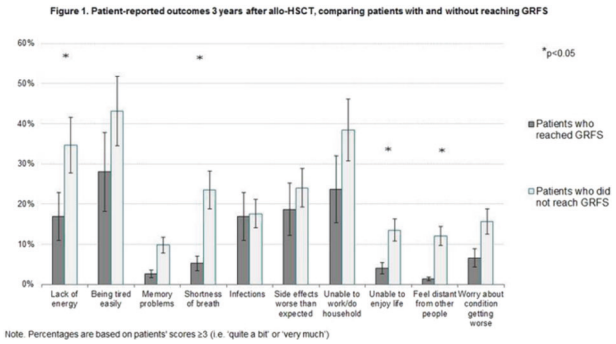
[1]Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, Netherlands, [2]University Medical Centre Utrecht, Utrecht, Netherlands, [3]University Medical Centre Utrecht, Laboratory of Translational Immunology, Utrecht, Netherlands

Background: Graft-versus-Host Disease (GvHD) relapse free survival (GRFS) is increasingly used as composite endpoint to evaluate allogeneic haematopoietic stem cell transplantation (allo-HSCT). To our knowledge, GRFS is not systematically linked to (long-term) patient-reported outcomes (PROs). The aim of this study was therefore to investigate the impact of GvHD and/or Relapse according to the refined GRFS definition (i.e. being alive with neither grade III–IV acute GvHD nor severe cGvHD and without disease recurrence or death) on the prevalence of substantial symptoms and health-related quality of life (HRQoL) of patients three years after allo-HSCT.

Methods: Since 2013, patients admitted for allo-HSCT in the UMC Utrecht were approached by their nurse to complete questionnaires at regular time-points after transplantation (yearly ± 50 patients). The Functional Assessment of Cancer Therapy General and Bone Marrow Transplantation (FACT-G and BMT) were used to assess HRQoL and symptoms. Patients graded items on a 5-point Likert scale:'0: Not at all', '1: A little bit', '2: Somewhat', '3: Quite a bit', '4: Very much'. FACT-subscales were calculated. To evaluate long-term PROs, all patients alive at three years after allo-HSCT were selected who also completed a questionnaire. Questionnaire data were linked to clinical data as reported to the EBMT-registry. Prevalence rates of substantial symptoms were computed based on patients scores ≥3, and were compared between patients meeting and not meeting GRFS criteria. Multivariable linear regression models were performed to study differences on physical, emotional, social and functional well-being and HSCT-related issues, including demographic (age, sex) and clinical (donor type, conditioning) covariates. P < .05 was considered statistically significant and mean differences >0.5SD were considered clinically relevant based on Norman's rule of thumb.

Results: From 130 included patients the median age was 54 years at time of transplantation and 59% were male. Donor type was matched sibling (23%), matched unrelated (55%) or mismatched unrelated (22%). Conditioning consisted of ATG/busulfan/fludarabine with ex vivo T-cell depletion (48%) or fludarabine/TBI without ATG (9%) or with ATG (18%) or other (24%). Median time since allo-HSCT was 36.5 months. 60% of this selection reached GRFS. Reasons for failures (n = 52) were relapse (n = 18), grade III-IV aGVHD and/or cGvHD (n = 27), or both (n = 7). No statistically significantly differences were observed on these characteristics between patients with or without GRFS.

Patients meeting criteria of GRFS less frequently reported substantial symptoms and consequences of emotional wellbeing (Figure 1). Statistically significant differences were observed for lack of energy (16.9% versus 34.6%), shortness of breath (5.2% versus 23.5%), being unable to enjoy life (4.0% versus 13.5%) and feeling distant from other people (1.3% versus 12.0%). Functional well-being (mean (SD): 20.6(5.1) versus 17.9(5.2)) and BMT-related well-being (29.5(5.9) versus 25.4(7.2)) as FACT-G total (87.7(12.0) versus 77.4 (14.5)) were statistically significantly and clinically relevantly higher for patients reaching GRFS, independent of the covariates.



Conclusions: Patients reaching GRFS reported a higher HRQoL and lower symptom levels 3 years after allo-HSCT when compared to those who did not reach GRFS. These data underline that GRFS should be the primary long-term outcome to address the success of allo-HSCT.

Disclosure: JK is shareholder of Gadeta (www.gadeta.nl), patent holder on multiple patents dealing with genetic engineering and received research grants from Novartis, Miltenyi Biotech and Gadeta. Other authors have nothing to declare.

P481

The timing of ratg matters: MSD-pbsct patients receiving 2d-atg regimen have lower cumulative incidence of relapse and better dfs than those receiving 4d-atg regimen

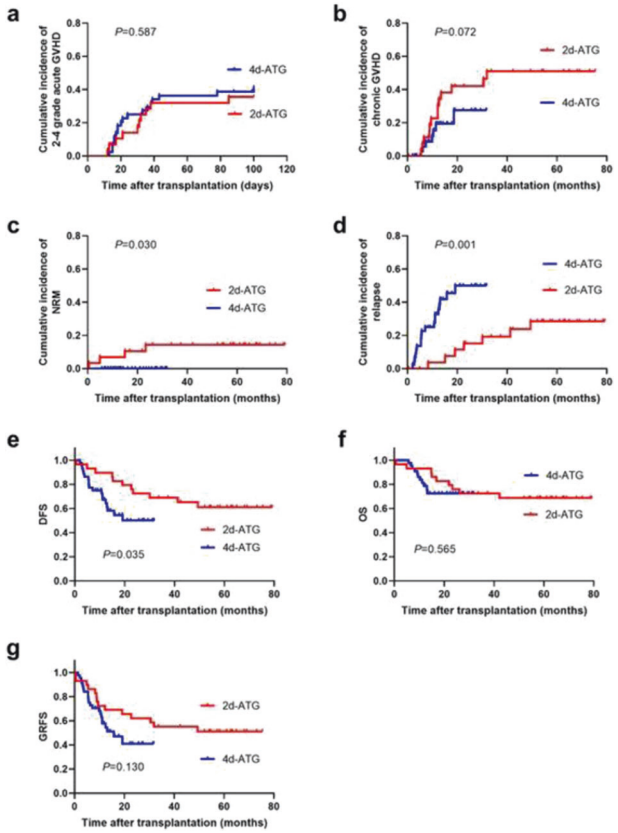
N. Wang[1], H. Wang[1], S. Fang[1], J. Du[1], K. Qian[1], S. Huang[1], J. Yang[1], H. Wang[1], Y. Wen[1], Y. Jiao[1], L. Dou[1], D. Liu[1]

[1]Chinese PLA General Hospital, Beijing, China

Background: The optimal timing of rabbit anti-thymocyte globulin (rATG) for prevention of graft-versus host disease (GVHD) in matched sibling donor peripheral blood stem cell transplantation (MSD-PBSCT) remains to be elucidated.

Methods: In this retrospective study, consecutive patients received MSD-PBSCT with rATG as GVHD prophylaxis in our hospital were enrolled. Twenty-nine patients were assigned to 2d-ATG group and forty-four to 4d-ATG group respectively according to the timing of rATG (2d-ATG regimen, a 5 mg/kg total dose divided from days −5 to −4; 4d-ATG regimen, a 5 mg/kg total dose divided from days −5 to −2).

Results: There was no significant difference between the two groups in the cumulative incidences (CI) of grades 2-4 acute GVHD (aGVHD) at day 100 after transplantation (34.5% *vs* 40.9%, $p = 0.587$). The 2-year CI of severe chronic GVHD was higher in the 2d-ATG group than that in the 4d-ATG group without statistical significance (10.3% *vs* 2.6%, $p = 0.311$). The 2-year cumulative incidence of relapse (CIR) in the 2d-ATG group was lower than that in the 4d-ATG group, and 2-year disease-free survival (DFS) was better in 2d-ATG group (CIR: 13.8% *vs* 50.0%, $p = 0.001$; DFS: 72.4% *vs* 50.0%, $p = 0.035$). 4 patients in 2d-ATG group died of non-relapse causes, whereas non in 4d-ATG group. Multivariate analyses suggested that 2d-ATG regimen was an independent influence factor for lower CIR (HR: 0.212, $p = 0.0008$) and better DFS (HR: 0.421, $p = 0.003$).



Conclusions: This study indicated that different timing of rATG affected the transplant outcomes of MSD-PBSCT patients, and 2d-ATG regimen had lower CIR and better DFS.

Disclosure: Nothing to declare.

P482

Emergency department consultation in allogeneic HSCT recipients - data from the vienna HSCT program

C.K. Baumann[1], J. Cserna[1], H. Knaus[1], M. Mitterbauer[1], A. Schulenburg[1], W. Rabitsch[1], P. Wohlfarth[1]

[1]Medical University of Vienna, Vienna, Austria

Background: Allogeneic hematopoietic stem cell transplantation (HSCT) recipients are at risk for various complications during their post-transplant follow-up. Acute events may lead to emergency department (ED) consultation in an unknown proportion of patients.

Methods: We performed a retrospective analysis of all consecutive adult (≥18 years) patients who underwent allogeneic HSCT at the Medical University of Vienna between 01/2013 and 08/2021. The primary objective was to analyze the rate of ED admissions after allogeneic HSCT. Secondary objectives included the temporal distribution, reasons, and outcome of ED admissions. Data cut-off for individual follow-up was October 19, 2021.

Results: 394 patients (median age: 51.58 [IQR: 40.44-59.63] years; f:m = 156:238) were included in the analysis. The median follow-up for the entire cohort was 1.57 [0.66-3.45] years. We recorded 142 ED admissions in 91/394 (23%) patients. 55 (60%), 21 (23%), and 15 (16%) patients presented once, twice, and ≥3 times to the ED during their follow-up.

Time from HSCT to ED presentation was 0-6 months in 45 (32%), 6-12 months in 26 (18%), 12-24 months in 40 (28%), and >24 months in 31 (22%) patients, respectively. ED admissions were primarily recorded on Sundays (n = 27; 19%), Saturdays (n = 26; 18%) and Tuesdays (n = 23; 16%). Most ED consultations occurred between 12 p.m. and 6 p.m. (n = 57; 40%), followed by 6 p.m. to 12 a.m. (n = 38; 27%).

The symptoms reported at ED consultation were pain (n = 89, 63%), reduced general condition (n = 72, 51%), fever (n = 63, 44%), diarrhea/vomiting (n = 41, 29%), and dermal symptoms (n = 31, 22%). An infection had been clinically or microbiologically documented in 64 (45%) ED visits. Hospitalization was required in 89 (63%) of 142 ED admissions, 10 (1%) patients were transferred to an ICU. The in-hospital mortality rate was 11/89 (12%).

In univariate analysis, risk for ED admission was greater in patients with acute GVHD (34% vs. 19%, $p < 0.01$), chronic GVHD (42% vs. 18%, $p < 0.01$), and in males (27% vs. 17%, $p = 0.02$). Age, underlying disease, and donor type were not associated with ED consultation.

Conclusions: Almost every fourth HSCT recipient in our cohort presented to the ED at least once during the individual post-transplant follow-up. Patients reported various symptoms and frequently required hospitalization, associated with a 12% mortality rate. Acute and chronic GVHD appear to be the major risk factors for requiring ED admission.

Disclosure: Nothing to declare.

P483

Long-term psychosocial impact of pediatric hematological stem cell transplantation for non-malignant diseases: A qualitative study

J.E. Bense[1], L. ter Welle[1], M. Schimmel[1], M. Louwerens[1], A.C. Lankester[1], A.H Pieterse[1], A.P.J. de Pagter[1]

[1]Leiden University Medical Center, Leiden, Netherlands

Background: Understanding the long-term psychosocial impact of pediatric hematological stem cell transplantation (HSCT) for non-malignant diseases is needed in order to optimize pre-HSCT counseling, supportive care, and long-term follow up programs after HSCT for this group of patients and caregivers.

Methods: In this qualitative study 14 patients transplanted for a non-malignant disease during childhood at the Leiden University Medical Center, The Netherlands were included. Inclusion criteria were HSCT two or more years ago and ≥12 years of age. In-depth

interviews were conducted online to explore patients' perspectives on the long-term psychosocial impact of HSCT on their current lives. Using a Grounded Theory approach four main themes were identified.

Results: Patients' median age at HSCT was 10 years (range 0.5-17 years, date of HSCT 1987-2018) and median age at time of interview was 19 years (range 14-49 years). Half of the patients was male. Indications for HSCT were inborn errors of immunity (n = 4), hemoglobinopathies (n = 4), or bone-marrow failure syndromes (n = 6). The main themes of psychosocial impact of HSCT that were uncovered, were: *'Doing okay', 'Experiencing persistent involvement of healthcare services', 'Influence on relationships with loved ones'*, and *'Impact on patient's life course'*.

Almost all patients reported recovery and curation after HSCT, feeling good, and the current ability to pursue their ambitions. Furthermore, they had been able to put the HSCT event behind them at some point. Patients reported health limitations due to side effects of the HSCT (e.g., fatigue, compromised fertility, growth restrictions, epilepsy) leading to necessary adjustments in daily life. Many patients reported a sense of vulnerability, feeling more susceptible to diseases than their peers, and fear of new complications or disease recurrence. Frequent hospital visits and check-ups reinforced the sense of vulnerability. However, many patients also reported to have accepted the side-effects, hospital visits, and the HSCT itself. For most patients family-relations had been affected, both positively (more parent-child equality) and negatively (increased dependency in family relationships). The impact of a family donor ranged from experiencing a positive intense connection, to the feeling of being indebted. For most patients the HSCT did not affect friendships. Patients reported that the HSCT had influenced their social-emotional development. For some patients, the HSCT had impacted (school)career choices. Since patients had faced major life decisions at a young age, they experienced gratefulness and did not take life for granted. Most patients mentioned that the previous HSCT did not influence how they envisioned the future.

Table 1. Illustrative quotations.

Subtheme	Sex	Age	Quotation
Doing Okay	♂	26	*"Yes, I'm actually doing really well. I am feeling comfortable in my own skin and I don't experience consequences of the transplantation."*
Sense of vulnerability	♀	20	*"I've seen how fragile life can be and that's still stuck in my head. Still, the possibility of that happening again scares me."*
Development of own identity	♀	17	*"I'm really trying to find my identity. I am looking for who I am without the disease or who I am without the process of transplantation."*

Conclusions: This study is one of the first qualitative studies characterizing the long-term psychosocial impact experienced by patients after pediatric HSCT for non-malignant diseases. Patients showed active coping strategies and resilience after this intensive treatment. The key themes emerging from our data highlights the need of optimal patient-adjusted supportive care in the long-term outpatient clinic.

Disclosure: Nothing to declare.

P484

Endocrinopathies in long-term follow-up after autologous hematopoietic stem cell transplantation

E. Arrieta-Lopez[1], B.L. Acosta-Maldonado[1], L. Rivera-Fong[1], L.M. Valero-Saldaña[1], I.K. Pellon-Tellez[1], M.A. Tapia-Bravo[1], F.E. Ahumada-Cordoba[1]

[1]Instituto Nacional de Cancerología, Mexico City, Mexico

Background: Late endocrine disorders are among the most common complications in survivors after autologous and allogenic stem cell transplantation (HSCT). There is evidence to suggest that long-term cancer survivors may be at high risk for premature development of metabolic syndrome, have higher fasting plasma glucose and insulin levels, impaired glucose tolerance, hypertriglyceridemia, low HDL cholesterol level. survivors of allogeneic HCT were 3.65 times (95% confidence interval [CI], 1.82-7.32) more likely to report diabetes than healthy people but recipients of autologous HCTs were no more likely than healthy people to report diabetes in a few series. The aim of this study is to evaluate the incidence of endocrine complications after autologous HSCT, stratified by hematological neoplasms diagnosis.

Methods: Observational, analytical, retrospective cohort study in patients undergoing autologous stem cell transplantation (ASCT) at the National Cancer Institute of Mexico (INCAN), with survival greater than 1 year and followed for 10 years. The data were analyzed using SPSS statistical software.

Results: 249 autologous transplants were carried out between 2011 and 2020. Patients with a survival less than 1-year or with institutional follow-up lower than 12 months were excluded, at the end, 188 patients were analyzed. The cumulative incidence of endocrine complications was 57.4% (n = 108), occurring in 55.3% of men and 61.1% of women, without difference by gender, (p = 0.43). Stratifying by diagnosis, the incidence of endocrine complications was 60.5% (n = 49) of Non-Hodgkin's Lymphoma (NHL), 55.4% (n = 36) of multiple myeloma (MM) and 54.8% (n = 23) of Hodgkin's Lymphoma (HL) (p 0.762). Post-transplant diabetes was higher in patients with MM 52.3% (n = 34) p 0.001, the incidence of post-transplant dyslipidemia was higher in patients with NHL 30.3% (n = 23), p 0.003, the incidence of hypothyroidism post-transplantation was higher in patients with HL 12 (60%) 0.043. There was no difference in the incidence of osteopenia and osteoporosis stratified by diagnosis, but there was a trend towards more osteoporosis in the HL group. The overall survival of patients with endocrine complications was equal to patients without endocrine complications p: 0.538, with median survival not yet reached. 70.5% (n: 31 pct) had post-transplant endocrine and cardiovascular disease p: 0.046, with 44.4% of HL, 75.5% of NHL and 81% of multiple myelomas developing the 2 disorders, with patients with multiple myeloma those that developed the most cardiovascular and endocrine complications simultaneously p: 0.053.

Conclusions: Results of this study suggest that patients undergoing autologous transplantation also have an increased risk of post-transplant endocrine complications (incidence of 57%) and, especially, patients with multiple myeloma are more likely to develop diabetes and post-transplant endocrine and cardiovascular complications.

Disclosure: No conflict interest

P486

The impact of thrombopoietin receptor agonists on bone marrow fibrosis in allogeneic stem cell transplant recipients

B. Bostankolu Değirmenci[1], Z.A. Yegin[1], A. Dikyar[1], L. Aydın Kaynar[1], Z.N. Özkurt[1], P. Uyar Göçün[1], N. Akyürek[1]

[1]Gazi University, Ankara, Turkey

Background: Prolonged thrombocytopenia and poor graft function are significant causes of transplant related morbidity and mortality based on a multifactorial etiological landscape. Although thrombopoietin receptor agonists (TPO-RA), particularly Eltrombopag, have been reported to be efficacious in these clinical conditions, potential long-term adverse effects still remain to be elucidated.

Methods: This retrospective study was performed to analyse the efficacy and side-effect profile of TPO-RAs in allogeneic hematopoietic stem cell transplant (allo-HCT) recipients who developed post-transplant prolonged thrombocytopenia and/or poor graft function. A total of 27 patients [median age: 55(21-73) years; male/female: 15/12] were included.

Results: Eltrombopag was started on day 110(33-670) after transplant. Median initial dose was 25(25-50) mg/day perorally and increased properly to a maximum dose of 75(50-100) mg/day. Duration of the treatment was median 120(31-377) days. Overall response rate was 59.3% in the study population. Time-to-treatment response was 42(3-170) days. A positive correlation was demonstrated between treatment response and pre-treatment platelet count ($p = 0.007$; $r = 0.538$) with an adverse association with pre-treatment bone marrow megakaryocyte reserve ($p = 0.047$, $r = -0.428$), respectively. Bone marrow biopsies were performed in 25 patients before treatment and post-treatment biopsies were repeated in 22 patients. Mild-to-moderate bone marrow fibrosis (BMF) [median grade 1.5(1-2)] was detected in the post-treatment biopsies of 12 patients (54.5%), 9 of whom did not represent any grade of myelofibrosis in their inital biopsies. Median 1(1-2) grade improvement was observed in BMF after the cessation of the drug in 7 patients. Pre-treatment existence of BMF had a significant impact on the severity of post-treatment fibrosis ($p = 0.049$). The grade of treatment-related fibrosis was significantly increased when time-to-treatment response was longer ($p = 0.008$).

Age (years) [median (range)]	55 (21-73)
Gender (male/female) (n)	15/12
Diagnosis [n(%)]	
Acute myeloid leukemia	12 (44.5)
Acute lymphoblastic leukemia	10 (37)
Non-Hodgkin lymphoma	3 (11.1)
Multiple myeloma	1 (3.7)
Primary myelofibrosis	1 (3.7)
Pre-transplant Disease Status [n(%)]	
CR	20 (74.1)
PR	3 (11.1)
PD	3 (11.1)
SD	1 (3.7)
Donor Type [n(%)]	
MRD	15 (55.6)
MUD	1 (3.7)
MMRD	1 (3.7)
MMUD	5 (18.5)
Haploidentical	5 (18.5)
Neutrophil Engraftment (days) [median (range)]	15 (10-32)
Platelet Engraftment (days) [median (range)]	16 (9-146)
Previous Cytomegalovirus Reactivation [n(%)]	23 (85.2)
Previous Acute GvHD [n(%)]	13 (48.1)
Post-transplant Day [median (range)]	55 (21-134)
Grade [median (range)]	2 (1-4)
Previous Chronic GvHD [n(%)]	6 (22.2)
Post-transplant Day [median (range)]	188 (126-586)
Stage	
Limited [n(%)]	4 (66.7)
Extended [n(%)]	2 (33.3)

Conclusions: The therapeutic efficacy of TPO-RAs in prolonged thrombocytopenia and poor graft function was confirmed in the present study as previously published. Besides multiple underlying factors which may have an impact on BMF in allo-HCT recipients, long-term use of TPO-RAs should also be kept in mind to be considered as a potential cause of myelofibrosis in this particular group of patients.

Clinical Trial Registry: N/A

Disclosure: Authors have no conflict of interest to declare.

P487

Allogeneic stem cell transplant recipients surviving at least 2 years without relapse. Outcome and risk-factors

B. Linder Grønvold[1,2], M.M. Ali[2], T.Å. Myklebust[3,4], A. Lenartova[2], M. Remberger[5,2], I.W. Abrahamsen[2], G.E. Tjønnfjord[1,2], A.E. Myhre[2], Y. Fløisand[6], T. Gedde-Dahl[1,2]

[1]University of Oslo, Institute of clinical medicine, Oslo, Norway, [2]Oslo University Hospital, Oslo, Norway, [3]Cancer Registry Norway, Oslo, Norway, [4]Møre and Romsdal hospital trust, Ålesund, Norway, [5]Uppsala university hospital, Uppsala, Sweden, [6]University of Oslo, center for cancer cell reprogramming, Oslo, Norway

Background: Most deaths after Allogeneic haematopoietic stem cell transplantation (HSCT) occur within the first 2 years. In 2-year survivors, the long term survival is good, but life expectancy remains lower than expected. Outcomes of 2-year survivors undergoing allo-HSCT at Oslo University Hospital were assessed.

Methods: We retrospectively studied the outcomes of 421 patients with malignant haematological disease, age 18-72 years, who underwent transplantation from 2005 to 2019 and were alive and free of disease after 2-years. Data were reported from The OUS-HSCT registry. Median follow-up was 6.2 years (2.0-16.1), and 232 patients (55%) were observed for 5 years or more.

Results: The probability of being alive 5 and 10 years after HSCT was 86% and 76%. The primary risk factors for late death included initial diagnosis of lymphoma or chronic lymphocytic leukaemia (CLL), previous blood stream- or invasive fungal infection (BSI, IFI), and extensive chronic graft-versus-host disease (cGVHD). Transplant-related mortality (TRM) and relapse at 5 years was 9.0% and 7.7%, respectively. Two factors were associated with the latter: CMV seronegative donor and CLL. Compared with the age and gender matched Norwegian general population, life expectancy was lower for each disease, except for CML.

Conclusions: The prospect for long-term survival is good for 2-year survivors of allogeneic hematopoietic stem cell transplantation. However, life expectancy remains inferior to the age- and gender matched general population. Optimizing prophylaxis and treatment for chronic GVHD, BSI and IFI is needed along with improved adherence to guidelines for early detection of secondary malignancies. Measures to improve immune reconstitution, possibly the microbiota, and the use of CMV seropositive donors regardless of recipient sero-status may be warranted and should be addressed in further studies.

Table 2. Results from multivariate analyses of factors affecting outcome in patients alive without relapse two years after HSCT. Hazard Ratio (HR), 95% confidence interval (CI) and p-value are displayed for the various variables.

Factor	MVA OS	MVA TRM	MVA RI
Age ≥ 60y vs < 60y	1.73, 1.02-2.96, 0.044	2.94, 1.60-5.40, <0.001	-
Donor CMV sero – vs +	2.21, 1.29-3.77, 0.004	-	4.42, 1.74-11.2, 0.002
Lymphoma	1.82, 1.03-3.21, 0.038	3.52, 1.92-6.46, <0.001	-
CLL	5.16, 2.00-13.3, <0.001	8.14, 2.64-25.1, <0.001	4.14, 1.28-13.4, 0.018
BSI vs no BSI	2.35, 1.20-4.61, 0.01	2.31, 1.02-5.23, 0.045	-
IFI vs no IFI	2.70, 1.57-4.66, <0.001	3.27, 1.75-6.12, 0.001	-
Ext cGVHD vs no + limited*	3.68, 2.14-6.35, <0.001	6.14, 2.85-13.2, <0.001	-

MVA; multivariate analysis, OS; overall survival, TRM; transplant-related mortality, RI; relapse incidence, BSI; blood stream infection, IFI; invasive fungal infection, CLL; chronic lymphocytic leukaemia, GVHD; graft-versus-host disease, Ext; extensive. *analysed as a time-dependent variable.

Disclosure: Nothing to declare

P488

Cumulative incidence of thyroid disorders in patients undergoing HSCT at the foscal clinic in the period 2009 – 2019

F. Arias[1], E. Wandurraga[1,2], M. Rosales[3,4], A. Peña[1,3], L. Salazar[1,4], S. Jimenez[3], M. Ochoa[1], J. Alvarez[3], E. Arias[1], M. Luna-Gonzalez[1,4], C. Sossa-Melo[1,3]

[1]Universidad Autónoma de Bucaramanga, Floridablanca, Colombia, [2]Endocrinólogos del Oriente (ENDORIENTE), Floridablanca, Colombia, [3]Clínica FOSCAL, Floridablanca, Colombia, [4]Programa para el Tratamiento de Enfermedades Hemato-Oncológicas de Santander - PROTEHOS, Floridablanca, Colombia

Background: Hematopoietic stem cell transplantation (HSCT) is an increasingly used therapeutic option to treat hematological and autoimmune diseases, making it important to have proper knowledge of its related comorbidities. Our objective was to evaluate thyroid function and the incidence of thyroid disorders associated with HSCT during a 10-year period within an institution.

Methods: A secondary analysis of an anonymized database which had patients over 18 years old who underwent HSCT at FOSCAL clinic was performed (2009-2019), patients who had previous thyroid disease were excluded. The incidence of thyroid disorders was determined at 1 and 3 years of follow-up from the moment the HSCT was performed.

Results: A total of 278 patients were included, 54.7% were male, with a mean age of 45.8 years, 33.9% were overweight or obese, a Karnofsky score average of 92.7 points and had an average Charlson comorbidity index of 2.64. Patients were taken to HSCT as a therapeutic option for multiple myeloma (30.6%), lymphoma (29.1%), acute leukemia (22.3%) and chronic leukemia (8.3%). Prior to HSCT, 11.2% of the patients underwent to the external radiotherapy, performed in abdomen and pelvis (41.9%) and in the chest area (38.7%). Two patients received thyroid ablation with radioactive iodine prior to HSCT. The patients received cyclophosphamide near the HSCT were 20.5% and 19.8% of them received a myeloablative regimen. Most of the HSCT were autologous (70.9%). The average time elapsed from diagnosis to HSCT was 1.7 years. Ciclosporin post-HSCT was used in 22.8% of the patients. The average TSH level at 1year post-HSCT was 3.2 mU/L, while at 3 years it rose to 4.7 mU/L. Regarding FT4, the average lab results were 1.2ng/dL at 1 year and 1.3 ng/dL at 3 years. Finally, the cumulative incidence of hypothyroidism at 1 and 3 years after HSCT was 18% and 40.3% respectively, while the cumulative incidence of hyperthyroidism at 1 and 3 years post-HSCT was 6.6% and 12.8% respectively.

Conclusions: The high incidence of thyroid gland disorders in patients who underwent HSCT makes it necessary to systematically search and identify these alterations through timely clinical and biochemical follow-up.

Clinical Trial Registry: N/A

Disclosure: N/A

P489

Incidence of male hypogonadism after hematopoietic stem cell transplantation: Experience of a referral center

E. Wandurraga[1,2], F. Arias[1], M. Rosales[3,4], L. Salazar[1,3], A. Peña[1,4], M. Luna-Gonzalez[1,4], D. Reyes[1,3], M. Ochoa[1], E. Arias[1], S. Jimenez[3,4], C. Sossa-Melo[1,3]

[1]Universidad Autónoma de Bucaramanga, Floridablanca, Colombia, [2]Endocrinólogos del Oriente (ENDORIENTE), Floridablanca, Colombia, [3]Clínica FOSCAL, Floridablanca, Colombia, [4]Programa para el Tratamiento de Enfermedades Hemato-Oncológicas de Santander - PROTEHOS, Floridablanca, Colombia

Background: Hematopoietic stem cell transplantation (HSCT) is a potentially curative option which is being increasingly used in multiple hematological and autoimmune diseases; Being of our interest the study of endocrinological morbidity, the objective of this study was to evaluate the gonadal function and the incidence of hypogonadism in males undergoing HSCT at a 1-year follow-up

Methods: A secondary analysis of a database was used, which consisted of patients older than 18 years who underwent HSCT (2009-2019) at Clinica FOSCAL, without previous hypogonadism. In addition to the extraction of clinical variables, an analysis of total testosterone levels was made before transplantation (pre-HSCT) and 1 year after the of transplant during follow-up (post-HSCT). A single testosterone value less than 300ng/dL was considered hypogonadism. The general, and subgroup incidence was estimated according to the intensity of the conditioning regimen and other socio-demographic, clinical, and HSCT-related variables.

Results: Thirty-six men with a mean age of 41.2 ± 14.6 years were included in the analysis 70.9% had received an autologous HSCT. The mean total testosterone in the study population was 520 ± 270 ng/dL pre-HSCT and 560 ± 350 ng/dL at 1-year post-HSCT. An incidence of hypogonadism of 28.6% was found at the

1-year mark and 8.6% the patients presented testosterone values <200ng/dL. No association was found between age or conditioning therapy with the development of hypogonadism.

Conclusions: One out of every 3 to 4 men undergoing HSCT presented hypogonadism at the1-year follow-up. This incidence suggests a systematic and early search for this complication.

Disclosure: N/A

P490

Incidence of primary ovarian insufficiency after hematopoietic stem cell transplantation: Experience of a reference center

E. Wandurraga[1,2], F. Arias[1], M. Rosales[3,4], L. Salazar[1,3], A. Peña[1,4], M. Luna-Gonzalez[1,4], D. Reyes[1,3], L. Sanchez[1], S. Jimenez[3], M. Ochoa[1], C. Sossa-Melo[1,3]

[1]Universidad Autónoma de Bucaramanga, Floridablanca, Colombia, [2]Endocrinólogos del Oriente (ENDORIENTE), Floridablanca, Colombia, [3]Clínica FOSCAL, Floridablanca, Colombia, [4]Programa para el Tratamiento de Enfermedades Hemato-Oncológicas de Santander - PROTEHOS, Floridablanca, Colombia

Background: Hematopoietic stem cell transplantation (HSCT) is a potentially curative option that is on rise in multiple hematological and autoimmune diseases; being for our interest the study of endocrinological morbidity, the objective of this study was to evaluate the incidence of hypogonadism in women less than 40 years who underwent HSCT at one year follow-up.

Methods: A secondary analysis from a database of women between 18 and 40 years old who underwent HSCT (2009-2019) was performed at the Clinica FOSCAL, without previous hypogonadism. In addition to the clinical variables, an analysis of levels of FSH was made one year after transplantation(posHSCT). Primary ovarian insufficiency was considered an FSH value greater than 25 mU/mL in the presence of amenorrhea. The general incidence and between subgroups were estimated according to the intensity of the conditioning regimen and other variables like sociodemographic, clinics and relationated with HSCT.

Results: Twenty-four women under 40 years were included in the analysis, with 71% being autologous HSCT. An incidence of 62.5% of primary ovarian insufficiency was found at 1year posHSCT. There was not found association between the aged or the conditioning therapy with the development of hypogonadism.

Conclusions: Six out of ten women undergoing HSCT had primary ovarian insufficiency at 1 year of follow-up. This incidence suggests a routine evaluation of gonadal function and timely handling.

Clinical Trial Registry: N/A

Disclosure: N/A

PAEDIATRIC ISSUES

P491

Hematopoietic stem cell transplantation for inherited immune disorders: 30-year italian single- center experience

G. Dell'Orso[1], F. Bagnasco[2], S. Giardino[2], F. Pierri[2], M. Miano[2], S. Volpi[2], M. Faraci[2]

[1]IRCCS Istituto G. Gaslini, Genova, Italy, [2]IRCCS- Istituto G. Gaslini, Genova, Italy

Background: Currently, more than 400 monogenetic inherited immune disorders (IID) have been identified. Overtime, outcome of hematopoietic stem cell transplantation (HSCT) for IID has significantly improved. In clinical practice, distinction of IID between Primary Immune Deficiency Disorders (PIDD) and Primary Immune Regulatory Disorders (PIRD) has been increasingly used.

Methods: All children with IID who underwent allogeneic HSCT from 1989 to 2021 at IRCCS Istituto G. Gaslini were included in the study. HSCTs have been retrospectively described with the aim of reporting the outcome in terms of overall survival (OS), graft failure (GF) and Graft-versus-Host Disease (GvHD)

Results: 65 patients, 30 affected by a PIDD and 35 by a PIRD, received 71 allogeneic HSCTs. In 7 patients, 8 (11.3%) HSCTs were complicated by GF (5 primary and 3 secondary); 4 patients underwent 2 HSCTs, 1 patient underwent 3 HCTs. According to the year of HSCT (≤2006 vs >2006), the number of transplants was 20 and 51, respectively. Median age at transplant was 2.5 years (IQR, 0.9-5.5), 42 (59.2%) HSCTs were performed at ≤3 years of age, 29 (40.8%) at >3 years of age.

The donor was a matched-unrelated (MUD) in 34 (47.9%) HSCTs, matched-related (MRD) in 19 (26.8%), and haploidentical in 18 (25.3%). Among haploidentical HSCTs, 17 were performed according to T cell receptor (TCR) αβ/CD19 depletion platform and 4/17 (23.5%) were complicated by GF. Overall, 8/71 HSCTs were complicated by GF.

Conditioning regimens (CR) were Busulfan-based in 24 (33.8%) HSCTs, Treosulfan-based in 39 (54.9%) and 8 (11.3%) received different CRs.

The 1-, 3-, and 20-year OS was 89.2% [95%CI (78.6-94.7)], 83.4% [95%CI (71.1-90.7)] and 83.4% [95%CI (71.1-90.7)] respectively. OS was significantly higher in patients transplanted after 2006 (3 year OS: 65.0% ≤2006 and 92.5% >2006, $p = 0.006$).

After a median follow-up of 4 years (max 20 years), 10 patients were dead: 6 died during the first 42 days after HSCT (4 before engraftment and 2 after primary GF) and 4 died within 3 years. OS was higher, but not significantly, among patients with PIRD (3-year OS: 79.7% for PIDD and 86.8% for PIRD, $p = 0.418$), for patients transplanted at > 3 years of age (3-year OS: 78.4% for ≤3 years and 90.9% for >3 years, $p = 0.135$) and in Treosulfan-based CR HSCTs (3-year OS: in Busulfan 72.9% and 90.8% in Treosulfan, $p = 0.079$).

Overall, 31 HSCTs were complicated by acute GvHD (aGvHD), 12 (38.7%) by grade 3-4 aGvHD. Considering year of HSCT (≤ 2006 vs >2006), the distribution of grade 3-4 aGvHD was statistically different between ≤2006, 61.5%, and >2006, 22.2% ($p = 0.027$). In haploidentical TCR αβ/CD19 depleted HSCTs, grade 3-4 aGvHD was absent

Conclusions: Our experience supports that HSCT represents an effective strategy in treatment of IID. In last years, outcome of HSCT for IID has significantly improved. Treosulfan and haploidentical TCR αβ/CD19 depleted HSCT represent promising strategies in this setting.

Disclosure: Nothing to declare

P492

Hematopoietic stem cell transplantation is an effective therapeutic modality for the infants with high-risk acute leukemia

L. Shelikhova[1], R. Khismatullina[1], M. Klimentova[1], A. Livshits[1], D. Balashov[1], I. Kalinina[1], V. Fomynih[1], A. Kazachenok[1], M. Fadeeva,[1], E. Zerkalenkova[1], A. Popov[1], N. Miakova[1], G. Novichkova[1], A. Maschan[1], M. Maschan[1]

[1]"Dmitry Rogachev Federal Research Centre of Pediatric Hematology, Oncology and Immunology", Moscow, Russian Federation

Background: Infant acute leukemia is a rare but aggressive disease. Standard approaches are curative in a minority of patients. Most treatment failures are due to relapse, treatment-related mortality and life-limiting late effects in survivors are also problematic.

Among such approaches, allogenic stem cell transplantation, may offer the greatest potential for improving cure rates.

Methods: A total of 63 pts with infant leukemia (AML- 37, BP-ALL-26, 30 female, 33 male, median age at the moment of diagnosis 0,6 years (0-1), at the moment of HST 1,2 years (0,5-3,9), underwent allogeneic HSCT between May 2012 and July 2021. Forty pts received haploidentical graft, 12 a graft from matched unrelated donor, 11 from matched related. Disease status at transplant was CR1 in 45 pts, >CR1 in 10 pts and AD (all AML) in 8 pts. Thirty-three (52%) pts had MLL gene–rearranged (ALL n = 23, AML n = 10). Fourteen pts with ALL received target therapy before HSCT. All pts received treosulfan-based myeloablative preparative regimen either melphalan (n = 30), thiotepa (n = 26) or vepesid (n = 7) were added as a second agent.

TCR αβ + /CD19 + depletion of HSCT with CliniMACS technology was implemented in 51 (80%) cases. The median dose of CD34 + cells was 10 x10^6/kg (range 4,3-21). Median time of follow-up for survivors was 4,5 years (range: 0.3 – 9,4).

Results: Primary engraftment was achieved in 59 of 63 pts (1 pt died due septic event, 3 non-engraftments received successful 2nd HSCT), the median time to neutrophil and platelet recovery was 14 and 16 days, respectively. All engrafted pts had verified morphologic remission and achieved sustained complete donor chimerism by day +30. Transplant-related mortality was 3 % (95% CI: 0,8-12): one pt died due septic event before engraftment, one in CR due viral infection and GvHD. Cumulative incidence of aGVHD grade II-IV was 13% (95% CI, 8 - 24), grade III-IV was 3% (95% CI, 0,08 - 12). No correlation between donor type, serotherapy and GvHD was noted.

The cumulative incidence (CI) of relapse at 4,5 years was 25% (95% CI:16-38 for the whole cohort. Among patients with AML CI of relapse was 22 % (95%CI:12-40), as compared to ALL group, with CI of relapse of 30 % (95%CI:16-57), p = 0,7. CI of relapse in MLL + group was lower 17% (95%CI:7-37), in contrast in MLL- group 33 %(95%CI:20-55), p = 0,1. All patients with MLL + AML (n = 10) are alive.

EFS at 4,5 years was 67% (95%CI: 55-79), OS –76% (95%CI:65-88). Statistically there was no significant difference in event-free or overall survival probabilities between leukemia type, remission status, donor type or GvHD-prophylaxis regimens. EFS in MLL + group was high 77% (95% CI 63 - 92) vs in MLL- group 56 % (95% CI 39 - 74), p = 0,056

Conclusions: We confirm that allogenic stem cell transplantation ensures high engraftment rate and low TRM. All major outcomes were equivalent between transplantation from unrelated, haploidentical and related donor. Improvement of anti-leukemic activity will require further refinement of target therapy, preparative regimen and post-transplant strategy of disease control.

Disclosure: no

P493

Plasma levels of MRP-8/14 associate with neutrophil recovery, engraftment syndrome and bacterial blood stream infections following pediatric allogeneic HSCT[

K. Kielsen[1], M.B. Kammersgaard[1], C.H. Nielsen[1], M. Ifversen[1], K.G. Müller[1,2]

[1]Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark, [2]University of Copenhagen, Copenhagen, Denmark

Background: Neutrophil engraftment is essential for a successful outcome after allogeneic HSCT, but neutrophils are also thought to promote engraftment syndrome and aGvHD. Neutrophil status is assessed by neutrophil counts in peripheral blood, but the function of these circulating cells, including activation and migration to sites of injury or infection, requires further analyses. Myeloid-related protein (MRP)-8/14 is expressed in granulocytes during inflammatory conditions and secreted as a stress response, inducing production of pro-inflammatory cytokines and increasing leukocyte recruitment and activation.

In this study, we investigated associations between MRP-8/14 levels, neutrophil recovery, and clinical outcomes after pediatric HSCT.

Methods: We included 73 children undergoing allogeneic HSCT between 2010-2017 for ALL ($n = 21$), AML ($n = 10$), other malignancies ($n = 10$) and benign disorders ($n = 32$). Median age was 8.0 years (range: 1.1-17.2 years). Donors were either MSD ($n = 22$) or MUD ($n = 51$). BM ($n = 69$) and PB ($n = 4$) were used as stem cell source. All conditioning regimens were myeloablative and based on TBI ($n = 17$), busulfan (n = 32) or other chemotherapy (n = 20). ATG was administered to 75% of patients as GvHD-prophylaxis. Six blood donors with a median age of 20 years (range: 18-20) were included as healthy controls.

MRP-8/14 was measured by ELISA in blood samples collected prior to conditioning, at the day of HSCT before graft infusion, and at day +7, +14, +21, +28, +90 and +180 post-transplant.

Results: All patients engrafted at median 22 days (10-30 days) after HSCT. Plasma level of MRP-8/14 decreased from pre-conditioning levels to nadir at day +7, before rising significantly until day +28 and then gradually declining. The rise in MRP-8/14 levels preceded the rise in circulating neutrophil counts, reflected into an increased MRP-8/14 to neutrophil ratio early post-transplant, indicating increased activation of emerging neutrophils.MRP-8/14 levels were significantly higher at day +14 in patients with acute leukemias compared with other diagnoses (0.50 mg/mL vs. 0.20 mg/mL, p = 0.023) and lower in patients receiving ATG for MUD transplants (0.20 mg/mL vs. 0.92 mg/mL, p = 0.00019). We further investigated whether MRP-8/14 levels were predictive of neutrophil recovery. Indeed, reduced levels of MRP-8/14 levels were observed at day +14 and +21 in patients with delayed neutrophil engraftment occurring after day +21 and in patients receiving G-CSF treatment to promote engraftment (P = 0.030 and P < 0.0001, respectively).

Engraftment syndrome occurred in 8 patients (11.0%) and was associated with elevated MRP-8/14 levels at day +7 and +21 and increased neutrophil counts from day +9 to +25 (P = 0.0005-0.016). Patients who developed bacterial blood stream infections in the early post-transplant period (n = 13) had significantly lower MRP-8/14 at day +14 and +21, but comparable neutrophil counts during this period. In general, MRP-8/14 levels and neutrophil counts were comparable in patients with and without aGvHD.

Conclusions: A rise in MRP-8/14 levels precedes the appearance of neutrophils, and MRP-8/14 may serve as predictor for delayed neutrophil recovery, bacterial blood stream infections and engraftment syndrome after HSCT. Thus, MRP-8/14 measurement could be be a useful marker to distinguish bacterial infections from engraftment syndrome and to guide commencement of G-CSF therapy.

Disclosure: Nothing to declare

P494

Allogeneic hematopoietic stem cell transplantation from matched related and unrelated donors in children with hematologic malignancies using "naïve" (CD45RA +) t-cell-depleted grafts

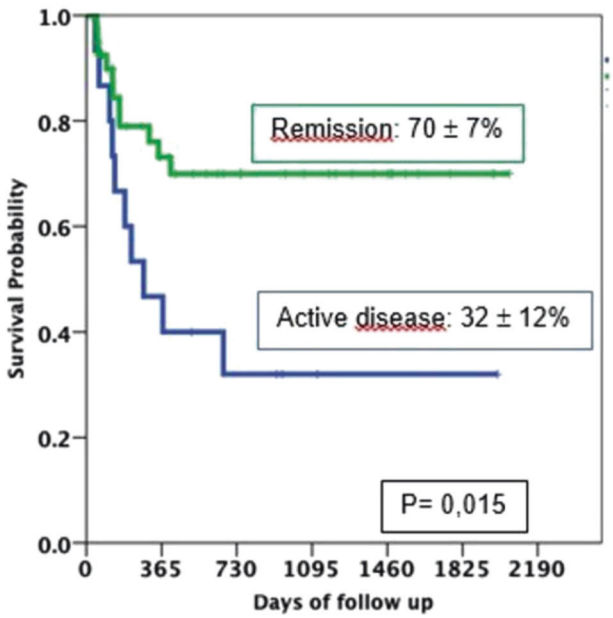
B. Molina Angulo[1], I. López Torija[1], M. González Vicent[1], J. Zubicaray Salegui[1], J. Sevilla Navarro[1], E. Sebastián Pérez[1], J. Iriondo Alzola[1], S. Vinagre Enríquez[1], M.A. Diaz Perez[1]

[1]Hospital Niño Jesús, Madrid, Spain

Background: In allogeneic hematopoietic stem cell transplantation, T lymphocytes play a decisive role in promoting hematopoiesis, transferring immunity to pathogens, and acting as mediators of the graft-versus-leukemia effect (GVL). However, they are also responsible for graft-versus-host disease (GVHD), the main cause of post-transplant morbidity and mortality, especially naive T cells (CD45RA +) that cause more severe GVHD than memory T cells. Our hypothesis is that using the new graft-engineering technology in which T naive cells are selectively depleted from the donor graft we would reduce or minimize severe acute and chronic GvHD following allogeneic transplantation.

Methods: We design a prospective observational study in which the patients with high-risk hematologic malignancies receive an allogeneic T naive-cell depleted transplant from a HLA matched related or unrelated donor. A total of 58 children (median age 9 years, range 1-21) diagnosed of acute leukemia ALL (n = 20), AML (n = 22), MDS (n = 8), NHL (n = 4) and other (n = 4) were included in the study between 2016 and 2021. Twenty-one patients were in 1st CR, 19 patients in 2nd CR, 18 in >2nd CR (3th CR or active disease). Median donor age was 18 years (range; 1-51). There were 32 matched related donors (MRD) and 26 matched unrelated donors (MUD).

Results: All patients received two donor cell products on day 0. The first product was given as a primary source of hematopoietic progenitor cell graft. A CD34 + enriched graft containing a median dose of 7,14x10^6/kg (range: 1,51-18). The second one was a CD45RA + depleted product. On day +1, +15 and +30, CD45RA + depleted DLIs were infused with a median cell number of 1 x 10^6/kg (range: 1-13,8). With a median follow up of 24 months (range; 3-60), 54 patients achieved neutrophil engraftment with a median time of 13 (range: 8–27) days. The median time to platelet engraftment was 11 (range: 6-34) days. The cumulative incidence of relapse was 33 ± 6% and the cumulative incidence of NRM was 9 ± 3%. Only 8 patients developed acute GVHD (13%) and 3 patients chronic GVHD (5%). DFS and OS were 58 ± 7% and 70 ± 6%, respectively. On univariate analysis, MDS (88 ± 11%, p = 0,03), CR at transplant (70 ± 7% vs 32 ± 12%, p = 0,015) and CD34 + cell infused (>7 x 10^6/kg, 41 ± 10% vs ≤7 x 10^6/kg, 73 ± 9%, p = 0,018) were associated with DFS. On multivariate analysis, complete remission at transplant (yes vs no, HR:5; 95%CI, 1,7-14-, p = 0,003) and the number of CD34 + cells infused/kg (≤7 vs >7, HR 5; 95% CI,1.7-12,5; p = 0.003) influenced on DFS.



Conclusions: Our results strongly suggest that allogeneic transplant using "naïve" T-cell-depleted grafts from matched related and unrelated donors in children provide a good platform for DLI with very low incidence of GVHD.

Disclosure: Nothing to declare

P495

Matched sibling donor transplant with reduced intensity conditioning has excellent results in pediatric bone marrow failure syndromes

J. Oved[1], C. Elgarten[2], E. Levy[2], D. Monos[2], Y. Wang[2], D. Barrett[2], S. Grupp[2], N. Bunin[2], T. Olson[2]

[1]Memorial Sloan Kettering Cancer Center, New York, United States, [2]Children's Hospital of Philadelphia, Philadelphia, United States

Background: Matched Sibling Donor Bone Marrow Transplantation (MSD-BMT) is the standard of care for pediatric patients with severe acquired Aplastic Anemia (sAAA) or single-lineage bone marrow failure (BMF) syndromes. At our center, standard of care (SOC) MSD-BMT using cyclophosphamide (200mg/kg) and Thymoglobulin (9mg/kg) for sAAA or cyclophosphamide (200mg/kg) and pharmacokinetic (PK) adjusted Busulfan for single-lineage failures yielded a 5-year overall survival of 100%. Given these data, we sought to reduce toxicity associated with conditioning by reducing conditioning intensity.

Methods: CHP14BT057 (NCT02928991) is a prospective, single center, single arm trial for pediatric patients with BMF that utilizes fludarabine to minimize or eliminate cyclophosphamide. Pediatric patients with sAAA or single-lineage BMF with an available, unaffected MSD were eligible. For sAAA, conditioning included: fludarabine 150mg/m2, cyclophosphamide 120mg/kg and Thymoglobulin 9mg/kg. Calcineurin inhibitor +/− methotrexate was used for GVHD prophylaxis. For single-lineage BMF, conditioning included fludarabine 30mg/m2 with PK adjusted Busulfan and Thymoglobulin 9mg/kg with a calcineurin inhibitor and mycophenolate mofetil for GVHD prophylaxis. We used a historical cohort (n = 10) who received MSD-BMT with SOC conditioning regimens as a comparator.

Results: 18 patients enrolled on or were treated per CHP14BT057. Demographics of CHP14BT057 and SOC cohorts are in table 1. Median follow up was 772 days (205-1543). 1 patient with COVID-related sAAA died of vasculopathy during conditioning. Of the 17 patients who received bone marrow infusion, the overall survival was 100%. There were no graft failures compared to 1 in SOC (patient with congenital sideroblastic anemia, successfully salvaged). Acute GVHD was minimal: 1 patient (6%) with grade 2-4 aGVHD compared to 1 patient (10%) in SOC. Limited chronic GVHD occurred in 4 (24%) patients compared to 2 (20%) in SOC. 1 patient on CHP14BT057 had residual PNH clone. Engraftment and immune reconstitution kinetics are shown in figure 1 and similar to SOC. Time to neutrophil and platelet engraftment per CIBMTR criteria was 21 and 30 days, respectively. This compared to 18 and 28 days in SOC. Viral reactivation on CHP14BT057 included: 3/17 CMV, 8/17 EBV, 1/17 BK and 1/17 Varicella compared to 2/10 CMV, 1/10 EBV 1/10 Adenovirus, 1/10 Varicella in SOC arm. No patients required viral specific CTLs or had end organ disease. Other BMT-related complications included: mild VOD (n = 1) and TA-TMA (n = 1) on CHP14BT057 compared to mild VOD (n = 1) and a rhizomucor infection requiring resection (n = 1) on SOC.

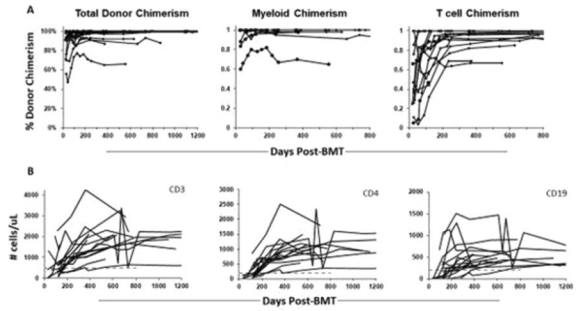


Figure 1: a) Total, myeloid and T cell donor chimerism as a function of time (days) post-transplant in patients treated on or per CHP14BT057. b) CD3+, CD4+ and CD19+ immune reconstitution from CHP14BT057 as a function of time post-transplant.

	14BT057 (18)	SOC (10)
Age at transplant (years), median (range)	10.6 (0.3-20.0)	8 (1.7-11.7)
Female, # (%)	6 (33)	5 (50)
Race/Ethnicity, n (%)		
White, Non-Hispanic	13 (72)	6 (60)
African-American	-	1 (10)
Hispanic	5 (28)	1 (10)
Middle Eastern	-	2 (20)
Disease, n (%)		
Severe Aplastic Anemia (SAA)		
Idiopathic	9 (50)	3 (30)
SAA with >10% PNH	1 (6)	-
Hepatitis associated	2 (11)	4 (40)
Diamond-Blackfan Anemia	1 (6)	1 (10)
Severe Congenital Neutropenia	4 (22)	1 (10)
Congenital Sideroblastic Anemia	-	1 (10)
Amegakaryocytic Thrombocytopenia	1 (6)	-
Time from diagnosis to SCT (years), median (range)	**0.2 (0.1 to 15)**	**0.2 (0.1 to 9.1)**
More than 10 lifetime PRBC transfusions pre-SCT	**1 (6)**	**2 (20)**
Prior treatments n (%)	1 (6)	-
IST for aplastic anemia (hATG/CSA) Steroids for hepatitis/DBA	2 (11)	4 (40)
Chronic RBC/platelet Transfusions	2 (11)	1 (10)
Chronic G-CSF	**4 (22)**	**1 (10)**

Conclusions: Dose reduction of cyclophosphamide in MSD-BMT for pediatric BMF is a safe method to provide curative therapy without compromising efficacy. Patients with large PNH clones and/or other evidence of clonal hematopoiesis may require more intensive conditioning regimens.

Clinical Trial Registry: NCT02928991 clinicaltrials.gov

Disclosure: Ellen Levy is now an employee of Merck
David Barrett is now an employee of Tmunity Therapeutics

P496

Upfront stem cell transplant from matched unrelated donors in newly diagnosed idiopathic severe aplastic anaemia and refractory cytopenia of childhood. The Spanish experience

V. Quintero[1], M.L. Uria-Oficialdegui[2], M. Gonzalez-Vicent[3], C. Fuentes[4], C. Diaz-de-Heredia[5]

[1]Hospital Universitario Ramón y Cajal, Madrid, Spain, [2]Hospital Universitari Vall D'Hebron, Barcelona, Spain, [3]Hospital Infantil Universitario Infantil Niño Jesús, Madrid, Spain, [4]Hospital Universitario y Politécnico La Fe, Valencia, Spain, [5]Hospital Universitary Vall D'Hebron, Barcelona, Spain

Background: Immunosuppressive therapy (IST) had been the recommended treatment in paediatric patients with severe idiopathic aplastic anaemia (SAA) and refractory cytopenia of childhood (RCC) who lacked a matched related donor. IST's response rate is fair, but many patients relapse and become candidates for a stem cell transplant (SCT). The results of matched unrelated donor (MUD) transplants after IST are inferior compared to matched related donor transplants in the first line. In 2015, Dufour et al. published their excellent results treating SAA patients with upfront SCT from MUD, attaining significantly better outcomes than a historical series of patients that had received MUD SCT after IST. Many paediatric centres in Spain have adopted the upfront MUD STC strategy for newly diagnosed SAA and RCC.

Methods: We performed a multicentre retrospective review of children with SAA or RCC that received treatment with upfront MUD SCT in GETMON/GETH associated hospitals.

Results: From 2014 to 2021, 8 patients (6 males/2 females) with SAA (6) and RCC (2) underwent an upfront MUD SCT. At diagnosis, the median age was 11 years old (range, 0.55-17.13). All received bone marrow from MUD 10/10. All had a good performance status (Lansky > 70). None of them had significant cytogenetic anomalies. 7/8 patients were CMV positive, and a mismatched CMV (donor negative and receptor positive) was used in 3 cases. The median time from diagnosis to SCT was 124.5 days (range, 79-210 days). Conditioning regimens were Flu+Cy in 6 patients with SAA and Treo/Bu +Flu+Thio in 2 patients with RCC. All patients received Serotherapy with ATG. GVHD prophylaxis consisted of cyclosporine/methotrexate in 7/8. The mean cell dose was 3.12 x 10e6 CD34 + / kg (SD 1.25). Median neutrophils engraftment was on day +20 and platelet engraftment on day +29. Acute GVHD grade ≥ 2 was seen in 4 (all responded to steroid treatment).

Viral reactivation was common (7/8). All but one patient reached transfusion independence at a median time of 33 days (range, 19-398). No transplant-related mortality (TRM) was registered. Two patients presented increasing receptor's lymphoid chimerism and were successfully treated with augmentation of immunosuppression. All patients are alive without chronic GVHD. One patient experienced poor graft and recovered with CD34 boost. One patient is still platelet dependent and is on treatment with romiplostim. Both had received CD34 dose under 2 x 10e6/kg. The median duration of post-transplant immunosuppressive treatment was 546 days (range, 48-679). EFS was 100% after a median follow up of 33.38 months (range, 2-84).

Conclusions:

- In our experience, upfront MUD SCT offers excellent results with 100% overall survival without chronic GVHD and no graft failure.
- Many patients suffered viral reactivations and other infectious complications accordingly to immunosuppression required for SCT for these conditions.

- Management of mixed chimerism and poor graft remains the principal clinical concern for these patients. Higher cell doses could help to revert these problems.
- Longer follow-up is needed to assess late sequelae and QoL.
- Our data support upfront MUD SCT for newly diagnosed SAA and RCC paediatric patients.

Disclosure: Nothing to declare

P498

Incidence of invasive fungal disease and risk factors in 368 children receiving allogeneic haematopoietic cell transplantation: A UK multi-centre, prospective audit on national anti-fungal guidelines

G. Ottaviano[1], Z. Nademi[2], H. Campbell[3], R. Mottram[4], B. James[4], O. Tatarinova[5], C. Furness[3], K. Patrick[6], O. Ochaya[6], S. Lawson[7], M. Slatter[2], R. Wynn[3], P. Amrolia[1], K. Rao[1], G. Lucchini[1], J. Silva[1], A. Lazareva[1], O. Mirci-Danicar[1,8], A. Warris[1], R. Chiesa[1]

[1]Great Ormond Street Hospital NHS Foundation Trust, London, United Kingdom, [2]Great North Children's Hospital, Newcastle upon Tyne, United Kingdom, [3]Royal Manchester Children's Hospital NHS Foundation Trust, Manchester, United Kingdom, [4]Leeds Teaching Hospital NHS Trust, Leeds, United Kingdom, [5]The Royal Marsden NHS Foundation Trust, London, United Kingdom, [6]Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom, [7]Birmingham Women's and Children's NHS Foundation Trust, Birmingham, United Kingdom, [8]Bristol Royal Hospital for Children, NHS Foundation Trust, Bristol, United Kingdom

Background: Invasive fungal diseases (IFD) represent a significant cause of morbidity and mortality after allogeneic hematopoietic cell transplantation (allo-HCT) in children. The optimal strategy for prophylaxis and treatment is not universally accepted. In 2017, UK guidelines for antifungal management in children receiving allo-HCT were defined and a prospective audit was conducted.

Methods: From March 2017 to December 2019, we prospectively collected data on allo-HCT performed in 7 UK pediatric centers to audit adherence to and effectiveness of national antifungals guidelines. Data on patients/transplants characteristics, antifungal prophylaxis, incidence of new IFD and treatment, prevalence of GvHD were included. Fungal infections were defined as possible, probable, or proven according to EORTC definitions.

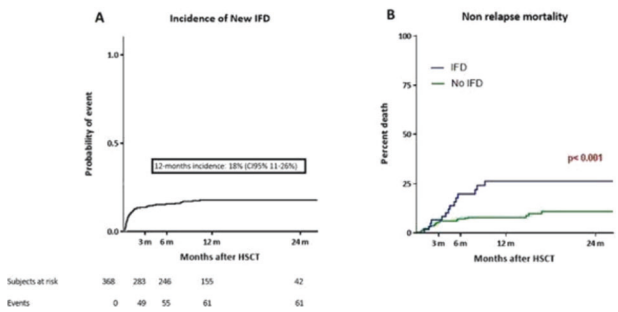
Results: During the study period, 368 children were enrolled, with a median follow-up of 361 days (95%CI 56-1000 days). Baseline characteristics are shown in *Table I*. Before allo-HCT, 64 patients (17%) had a history of IFD, that was probable/proven in 28 (7.5%). At the start of conditioning most patients (301/368, 81%) were on single agent prophylaxis with itraconazole (146, 39%) or liposomal amphotericin B (155, 42%). Twenty-three patients (6%) were on antifungal treatment due to previous IFD. Median length of antifungal prophylaxis was 191 days (range, 17-819). Incidence of new IFD was 18% (95%CI 11-26, 66 events in 61 patients), with 18/66 probable/proven infections (5%). Most IFDs occurred within the first 6 months after transplant (*Figure 1a*). Most patients (83%) with probable/proven IFD received double antifungal agents, while mostly a single drug (77%) was used with possible IFD.

A univariate risk factors analysis showed that primary immunodeficiency (PID) diagnosis, second allo-HCT, HLA mismatched donors, myeloablative conditioning, previous IFD and acute graft versus host disease (aGvHD) were significantly associated with occurrence of new IFD. In multivariate analysis (MVA), only aGvHD was confirmed as a significant risk factor (OR: 2.1, 95%CI 1.1 – 4, $p < 0.05$). Choice of anti-fungal prophylaxis didn't impact on incidence of IFD. Non-relapse mortality (NRM) accounted for 40 deaths. Although only 5 IFD-related deaths were reported, IFD had a significant impact on survival, as children with a new IFD had a higher NRM, compared to patients without IFD post allo-HCT (26 vs 11%, $p < 0.001$) (*Figure 1b*).

Table I.

	Patients 368 (%)
Diagnosis	
Malignancy	159 (43%)
Non-malignant hematology	67 (18%)
PID	121 (33%)
Metabolic	18 (5%)
Other	2 (1%)
Stem cell source	
Bone Marrow	199 (54%)
Peripheral Blood	123 (33%)
Umbilical Cord Blood	46 (13%)
Donor	
Matched	281 (76%)
Mismatched	52 (14%)
Haploidentical	34 (10%)
Conditioning	
Myeloablative	136 (37%)
Reduced toxicity/intensity	193 (52%)
Minimal	34 (10%)
None	5 (1%)
Transplant number	
First	336 (91%)
Second	32 (9%)

Figure 1



Conclusions: This study provides a prospective assessment of incidence and risk factors for IFD in a large cohort of children receiving allo-HCT in the UK, after the adoption of national antifungal guidelines. In MVA, aGVHD was associated with increased risk of IFD, which contributed to increased NRM. Patients with GVHD might benefit from further optimization of anti-fungal prophylaxis and treatment.

Disclosure: The audit received financial support from Gilead.

P499

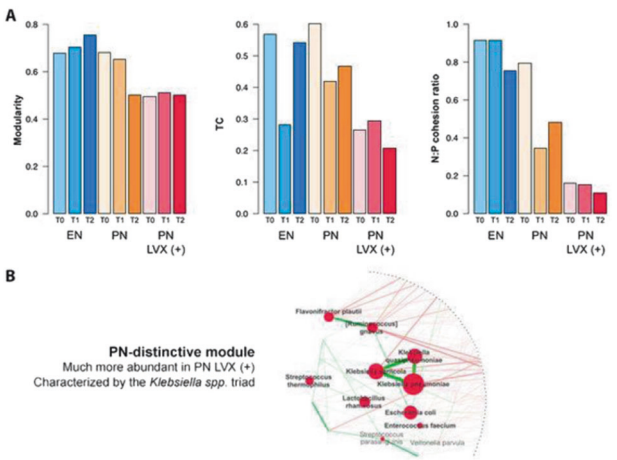
Levofloxacin prophylaxis and parenteral nutrition have a detrimental effect on intestinal microbial networks in pediatric patients undergoing allo-HSCT

M. Fabbrini[1,2], D. Zama[3,4], T. Belotti[3], E. Muratore[3], D. Leardini[3], F. Baccelli[3], F. Gottardi[3], F. D'amico[1,2], S. Turroni[2], P. Brigidi[1], A. Prete[3], R. Masetti[3,4]

[1]University of Bologna, Bologna, Italy, [2]University of Bologna, Bologna, Italy, [3]Pediatric Oncology and Hematology Unit "Lalla Seràgnoli", IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [4]University of Bologna, Bologna, Italy

Background: Levofloxacin (LVX) prophylaxis and nutritional support in pediatric allo-HSCT patients are relevant to clinical outcomes but evidence on their impact on the gut microbiome (GM) is still limited. Here, we longitudinally evaluated GM network architecture and species-level dynamics of pediatric patients before, during and after allo-HSCT.

Methods: A total of 90 stools from 30 pediatric patients underwent shotgun metagenomic sequencing on Illumina Next-Seq platform. Patients were given: i) enteral nutrition (EN); ii) parenteral nutrition (PN); or iii) PN preceded by LVX prophylaxis (PN LVX (+)). Species-level compositional insights were obtained to build correlation networks. Network evaluation (*i.e.*, computing modularity and cohesion) was used to characterize the microbial consortia.



Results: Three network parameters were adopted to describe the GM community: i) modularity, *i.e.*, the measure of connections between and within modules, with high values determining a lower spread of any external stressor, meaning an improved resistance to it; ii) total cohesion (TC), *i.e.*, the quantification of connectivity in terms of positive and negative interactions, with high values denoting a dense and plastic community; and iii) the ratio of negative to positive cohesion (N:P), informative on the reliance of the system on positive interactions, where low values stand for high stress conditions since negative interactions are prevented and disrupted by the pressure of the stressor.

PN LVX (+) resulted in lower modularity, TC and N:P ratio compared to EN, indicative of a less plastic and structurally altered GM, more susceptible to external stressors and less predisposed to prompt recovery. In addition, PN and more markedly PN LVX (+) was associated with the appearance of a module containing bacterial species of concern such as what we named "*Klebsiella* spp. triad" (comprising *K. pneumoniae*, *K. quasipneumoniae* and *K. variicola*), *[Ruminococcus] gnavus*, *Flavonifractor plautii*and *Enterococcus faecium*, which altered the network structure compared to EN-fed patients.

Conclusions: By evaluating GM network properties longitudinally after LVX prophylaxis and PN in pediatric allo-HSCT patients, we found a less plastic community, less able to maintain a dense net of interactions, thus to withstand stress. In particular, we detected the emergence of network modules comprising several potential pathobionts, such as *Klebsiella* spp., *R. gnavus*, *F. plautii* and *E. faecium* that have previously been linked to the production of possibly harmful molecules. Our results shed light on the harmfulness of LVX prophylaxis before allo-HSCT and help support EN as the first-choice nutritional support after allo-HSCT.

Disclosure: Nothing to declare

P500

Sports medicine physicians and exercise scientists in a transplant unit: Precision exercise and beyond

A. Balduzzi[1], W. Zardo[1], G. Prunotto[1], T. Moriggi[1], M. Verna[1], E. Corti[1], F. Vendemini[1], S. Napolitano[1], M. Barbieri[1], E. Villa[1], S. Bonanomi[1], F. Lanfranconi[1]

[1]Università degli Studi di Milano Biccoca, Monza, Italy

Background: Increasing evidences support feasibility and safety of sports in fragile patients, where the concept of inclusion substitutes for the concept of competition.

Methods: Patients undergoing HSCT in a single Institution are offered to participate in the "Sport-Therapy" research project, consisting of precision exercise training by sports medicine doctors and exercise scientists, besides osteopathic treatment, in order to prevent toxicities, derived from bed-resting and treatment.

Three training sessions per week (150'), consisting of aerobic, strength, balance and flexibility exercises, are planned with two operators per session for each patient. The training is held in the patient room, in the ward or in the clinic, in case of preventive isolation, in the gym-hall or in the garden, as soon as the patient may attend small groups (<5).

The training is personalized for each patient, according to the parameters measured at the beginning of the program, by means of multiple performance tests (6-minute-walking, timed-up-and-downstairs, quick motor function, strength tests), and continuously reassessed on the basis of the patient exercise tolerance and vital signs (heart-rate and blood saturation) throughout the training session.

Four sport techniques have been implemented: indoor climbing, no pedal bike, soccer, golf.

Results: Out of 123 consecutive patients 3 years or older (44% ALL, 16% AML, 6% NHL, 3% HL, 32% non malignant disease) transplanted in the period April 2017-October 2021, 93 (76%) started the exercise training during the HSCT hospitalization, at a median of 15 days after HSCT. 30 additional patients, transplanted in the same period or earlier, were enrolled in the later post-HSCT course, mainly due to specific issues, such as osteonecrosis (18 cases).

Both pre- and post-functional assessments are available for 72% of the 123 patients. An adapted Yo-Yo test was performed in the 33% of the patients.

Adherence: 63% of the patients attended more and 22% less than one third of the training sessions, whereas 15% dropped-out, with main reasons being mainly logistical. No accidents occurred. Patient and parental satisfaction, as investigated by questionnaires, exceeded 90%.

The program went beyond the expectations, as four unplanned goals were achieved:

- earlier diagnosis of system impairment, compared with what clinicians could diagnose after a medical visit in bed-rest. The body systems are critically challenged during exercise, which triggers structural weaknesses or damages as well as a reduced cardio-respiratory reserve;
- precise assessment of the range of motion of joints involved by chronic GVHD allowed basal and periodical measurements for treatment efficacy assessment; 8 pts with cGVHD have been longitudinally evaluated;
- timely diagnosis of lung impairment by GVHD by means of routine lung function test upon enrollment and periodical monitoring, with the possibility to anticipate diagnosis and proper GVHD treatment at an earlier stage, ultimately optimizing efficacy
- earlier detection and proper management of osteonecrotic lesions, based on the identification of gait or motion abnormalities or pain. Specifically tailored exercise protocols, upon suspected/diagnosed ON, pre-surgery preservation training, post-surgery rehabilitation.

Conclusions: Personalized exercise programs are feasible and safe since the very early post-HSCT cohort. The project went far beyond the exercise training and improved patient clinical management.

Clinical Trial Registry: Ethical Committee Università degli Studi di Milano Bicocca #284

Disclosure: Nothing to declare

P501

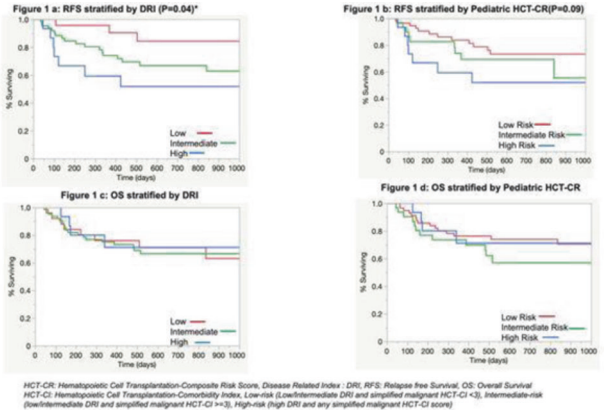
Developing a pediatric hematopoietic cell transplantation-composite risk score to predict outcomes in children with acute leukemia undergoing hematopoietic cell transplantation

M. Lakkaraja[1,2,3], T. John[1,2,3], B. Salem[1,2,3], S. Bhar[1,2,3], E. Doherty[1,2,3], J. Craddock[1,2,3], G. Sasa[1,2,3], D. Steffin[1,2,3], H. Heslop[3,1,2,4], R. Krance[1,2,3], C. Martinez[1,2,3], B. Friend[1,2,3]

[1]Baylor College of Medicine, Houston, United States, [2]Texas Childrens Hospital, Houston, United States, [3]Center for Cell and Gene Therapy (CAGT), Houston, United States, [4]Houston Methodist Hospital, Houston, United States

Background: Pre-transplant risk assessment is an important tool to optimize allogeneic hematopoietic cell transplantation (HCT) outcomes. HCT-comorbidity index (HCT-CI) accounts for patient's organ function, but does not incorporate disease characteristics or inherent resistance to therapy. Disease risk index (DRI) and refined-DRI based on disease-specific characteristics and remission status prior to HCT accurately assess risk of relapse post-HCT, but do not account for patient comorbidities. Two recent studies in adults combined the HCT-CI/Age and refined-DRI scores to develop the HCT-composite risk (HCT-CR) model that better predicts overall survival (OS) in HCT. Our goal was to design a combined pediatric-HCT-CR that can predict outcomes in children with acute leukemia undergoing allogeneic HCT.

Methods: A retrospective chart review of children (<18 years) who underwent their first allogenic HCT for acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) between January 2017 and August 2020 at Texas Children's Hospital was performed. Primary outcome was overall survival (OS) and secondary outcomes were relapse-free survival (RFS) and non-relapse mortality (NRM). Patients were stratified into three risk groups of a combined pediatric-HCT-CR based on pediatric-DRI and simplified-malignant HCT-CI: low-risk (low/intermediate DRI and simplified malignant HCT-CI < 3), intermediate-risk (low/intermediate DRI and simplified malignant HCT-CI > = 3), and high-risk (high DRI and any simplified malignant HCT-CI score), using classification and regression trees analysis for OS and RF. Kaplan-Meier method was used to estimate survival curves and log-rank test to compare curves.



Results: The cohort included 103 children with ALL: 59(57)% and AML: 44(43%). Median age was 10 (range 0-17) years. Donor type included matched related donor: 25(24%), matched unrelated donor: 29 (28%), mismatched unrelated donor: 20(19%), haploidentical: 17(17%), and umbilical cord blood: 12(12%). 92(89%) received myeloablative conditioning. Pediatric-DRI was low in 25 (24%), intermediate in 63 (61%), and high in 15 (15%) patients. Simplified malignant-HCT-CI scores were 0, 1-2, and 3+ in 43 (42%), 24 (23%), and 36 (35%) patients, respectively.OS was 75% (95%CI: 67-83) at 1 year and 66% (95%CI: 56-76) at 3 years. RFS was 77% (95%CI: 69-85) at 1 year and 66% (95%CI: 55-77) at 3 years. NRM was 16% (95%CI: 9-23) at 1 year. Pediatric-DRI was prognostic for RFS, as low, intermediate, and high-risk groups translated to 3-year RFS of 84% (95%CI: 68-100), 63% (95%CI: 49-77), and 52% (95%CI: 37-78), respectively ($p = 0.04$). There was no correlation between pediatric-DRI score and OS ($p = 0.95$). Simplified malignant-HCT-CI > = 3 was suggestive of inferior survival: 3-year OS 72% (95% CI: 60-84) vs. 56% (95%CI: 37-75), $p = 0.16$. The combined pediatric HCT-CR model demonstrated a trend in predicting RFS ($p = 0.09$). The intermediate-risk group of pediatric HCT-CR indicated a lower likelihood of 3-year OS compared to other groups: 57% (95%CI: 38-76) vs. 71% (95%CI: 59-83), $p = 0.19$ (Figures 1a,b,c,d).

Conclusions: The pilot data presented here suggest that combining disease and patient-related factors into a pediatric-HCT-CR may be an important and prognostic tool in pre-transplant risk stratification for children with acute leukemia undergoing allogeneic HCT. A larger analysis of children who received allogeneic HCT at our center is ongoing with a plan to internally refine and validate the model.

Disclosure: Helen Heslop: Equity in Allovir and Marker Therapeutics (both publically traded). Advisory boards for Tessa Therapeutics, Gilead, Novartis, Kiadis, Fresh Wind Biotherapies, Takeda and GSK. Research support from Tessa Therapeutics and Kuur Therapeutics (now Athenex).

Other authors report no conflicts.

P502

Treosulfan-based conditioning regimen in hematopoietic stem cell transplantation in children and adolescents: An analysis of spanish group of hematopoietic stem cell transplantation (GETH)

A. Perez-Martínez[1], C. Belendez Bieler[2], B. Molina Angulo[3], C. Fuentes[4], A. Regueiro Garcia[5], M. Plaza Fornieles[6], A. Margarit Soler[7], M.I. Benitez Carabante[8], R. Olivas Mazón[9], P. Palomo Moraleda[10], A. Pascual Martinez[11], L. Sissini[12], Y. Mozo del Castillo[12], D. Bueno Sanchez[12], A.M. Galera Miñarro[6], L. Alonso Garcia[13], J. Marsal[14], M. Trabazo del Castillo[14], A. Urtasun Erburu[15], J. Rifón[16], M.L. Palacios[16], M.A. Diaz[3], C. Diaz de Heredia[13], J.L. Fuster Soler[6], J.M. Fernandez Navarro[17], M. Gonzalez Vicent[18], J. Rifón[16], M.L. Palacios[16]

[1]*Unidad de Hemato-Oncologia del Hospital Universitario La Paz, Madrid, Spain,* [2]*Hematología-Oncología pediátricas. Hospital G. Universitario Gregorio Marañón, Madrid, Spain,* [3]*Hospital Infantil Universitario Niño Jesús, Madrid, Spain,* [4]*Hospital La Fe, Valencia, Spain,* [5]*Hematología y Oncología Pediátrica Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain,* [6]*Hospital Clínico Universitario Virgen de la Arrixaca, El Palmar, Spain,* [7]*Pediatra - Unitat de Trasplantament Hematopoètic Hospital Sant Joan Déu, Esplugues de Llobregat, Spain,* [8]*Unidad de Trasplante de Progenitores Hematopoyéticos Servicio de Oncología Y Hematología Pediátrica Hospital Universitari Vall d'Hebron, Barcelona, Spain,* [9]*Hospital Clínico Universitario de Valencia, Valencia, Spain,* [10]*Hospital Universitario Central de Asturias, Oviedo, Spain,* [11]*Hospital Universitario Regional de Málaga Carlos Haya, Malaga, Spain,* [12]*Hospital Universitario La Paz, Madrid, Spain,* [13]*Hospital Universitario Valle de Hebrón, Barcelona, Spain,* [14]*Hospital Sant Joan de Déu, Esplugues de Llobregat, Spain,* [15]*Pediatra del Servicio Oncohematología Infantil Hospital Sant Joan de Deu (Barcelona), Esplugues de Llobregat, Spain,* [16]*Clinica Universitaria de Navarra, Pamplona, Spain,* [17]*Hospital Universitario y Politécnico de La Fe, Valencia, Spain,* [18]*Unidad de Trasplante Hematopoyético Hospital Niño Jesús, Madrid, Spain*

Background: Treosulfan properties, as potent cytotoxic, myeloablative and immunosuppressive effect with low organ toxicity are the main strengths to incorporate it as conditioning regimen in vulnerable hematopoietic stem cell transplantion (HSCT) patients as pediatric cohort. To analyze the role of treosulfan-based conditioning in children, the Spanish Group of Hematopoietic Stem Cell Transplantation (GETH) performed a retrospective analysis from 11 centers between the period 2012-2021.

	All	Non-malignant diseases	High risk malignancies	p
Male/female, n	92/68	66/51	26/17	ns
Age (years), median (IQR)	5 (2-10)	4 (2-9)	8 (4-14)	0,00
1st/2nd/3rd HSCT, n	124/31/5	102/12/3	22/19/2	0,000
MRD/MUD/ Haplo/MMUD/ Auto	74/32/39/13/1	67/22/18/10	8/10/21/3/1	0,000
PB/BM/CB	65/88/7	32/80/5	33/8/2	0,000
Conditioning, n FTT/FT/others/ not reported,	109/38/11/2	80/32/3/2	28/6/8/1	0,001
CsA based/ Tacro based/Ex vivo TCD/ others/not reported	81/45/18/4/12	65/35/6/2/9	16/10/12/2/3	0,000
CD34 + x106/ kg cells graft, median (IQR)	6,9 (4,8-9,5)	7 (4,9-9,8)	5,8 (4,7-8,7)	ns
CD4 + > 200 at 3 months, n	48	37	11	ns

Methods: A total of 160 children (median 5 years old, IQR: 2-10) diagnosed with non-malignant diseases (n = 117) or high risk malignancies (n = 43), including 36 (22.5%) patients undergoing second/third hematopoietic stem cell transplantation from matched related (MRD) (n = 74), matched unrelated (MUD) (n = 32), haploidentical (n = 39), mismatch unrelated (n = 13) and autologous (n = 1) donors. The source of progenitor cells included bone marrow (n = 88), mobilized peripheral blood (n = 65) and cord blood (n = 7). Preparative regimens were treosulfan-based according to body surface area in combination with fludarabine and thiotepa (n = 109), only fludarabine (n = 38), other drugs as clofarabine (n = 14), depending on the diagnosis (Table I).

Results: Engraftment was achieved in 91.3%. The median (IQR) myeloid and platelet engraftment was 16 (13-21) and 18 (14-24) days, respectively. The probability of venooclussive disease (VOD) was 8,8 ± 2%. The cumulative incidence of acute graft versus host disease was 39,6 ± 4% for grades I-IV and 30 ± 8% for grades II-IV. The cumulative incidence of overall chronic graft versus host disease was 10,6 ± 3% and 3,6 ± 1% moderate/severe. The 2-year overall survival (OS) was 80 ± 4%, and was significantly lower in malignancies (61 ± 9%) vs no malignancies (87 ± 3%). The 2-year cumulative incidence of relapse and transplant related mortality was 24 ± 7% and 14 ± 3% respectively. In the complete series, the number of $CD4^+$ T cells higher than 200 µL at 3 months impacted favorably in OS with a hazard ratio 0,19 (0,043-0,846). In the non-malignant cohort the VOD with a hazard ratio 5,53 (1,21-25,25), p = 0,005 and in the cohort of malignant disorders the number of $CD34^+$ cells lower than the median in the graft with a hazard ratio 12,6 (1,5-106) p = 0,021, impacted in the OS.

Conclusions: Treosulfan-based conditioning is a safe and effective approach for children with non-malignancies and high risk malignancies. Particularly favorable results were achieved in non-malignant disorders and patients with faster $CD4^+$ T cell reconstitution. Venooclussive disease was not completely avoided and impacted negatively in OS in the non-malignant cohort. The high number of $CD34^+$ cells in the graft impacted negatively in OS in the cohort of malignant diseases.

Disclosure: Nothing to declare

P503

Patient-reported health-related quality of life (HRQOL) following allogeneic stem cell transplantation (SCT) performed early after diagnosis of pediatric chronic myeloid leukemia (CML)

O. Schleicher[1], A. Horndasch*[1], M. Krumbholz[1], S. Sembill[1], A. Karow[1], C. Bremensdorfer[2], D. Grabow[2], M. Metzler*[1], M. Suttorp*[3]*

[1]*Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany,* [2]*Division of Childhood Cancer Epidemiology, Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany,* [3]*Pediatric Hemato-Oncology, Medical Faculty, Dresden, Germany*

Background: *Equally contributed as authors

Prior to 2003, when imatinib was licensed for CML-treatment in minors, SCT as a curative approach was ideally performed soon after diagnosis. The study CML-paed I (1995-2004) recommended SCT from a sibling within 6 months after diagnosis and within 12 months from an HLA-matched unrelated donor (MUD) resulting in 5-year overall survival of 87 ± 11% for sibling SCT but inferior (52 ± 9%) and comparable to adult data for MUD-SCT [Suttorp M et al. 2009]. So far, no data exists on the long-term HRQOL of former pediatric CML patients. We here present patients' self-reporting to a questionnaire sent out to adolescents and young adults (AYAs) formerly enrolled on pediatric CML-SCT trials.

Methods: Eligible patients underwent SCT at German centers and were identified from the records of the Children's Cancer Registry. Following approval by the Institutional Ethical Board and patients' consent, the completed self-assessment questionnaires SF36 and FACT-BMT were mailed back as of Jan 2021.

Results: 111 out of 171 (65%) patients survived long-term. Missing key data resulted in the exclusion of 25 survivors. 37/86 (43%) remaining patients responded to the questionnaire.

In 37 responders, CML was diagnosed at a median time point in Aug 2001 (range 1993-2013, median patient age 11 years (range 1-17, gender N = 24 female (65%)). SCT was performed at a median age of 12 years (range 2-19 years, interval from diagnosis to SCT median 7 months, range 2-46). The questionnaire was filled in 4-27 years (median 19) after SCT at a median age of 29 years (range 18-43).

10 patients (27%) did not participate in regular medical follow-up examinations. Self-reported key findings in the total cohort comprised cGvHD-associated damages (N = 8, 22%) like lung problems, dry eyes (each N = 7, 19%), skin alterations (N = 6, 17%), and hair problems (N = 4, 11%). Conditioning regimen consequences reported frequently comprised hypothyroidism (N = 11, 30%), infertility (N = 9, 24%, 7 female), and sexual dysfunction (N = 3, 9%, 2 female).

Following SCT, 10 patients (27%) experienced 13 CML-relapses at a median interval SCT to relapse of 34 months (range 2-83). Only one patient underwent 2nd SCT when relapse treatment with 2G-TKI failed. Six secondary malignancies (dysplastic melanocytic nevus and ALL, rhabdomyosarcoma, thyroid carcinoma, basal cell carcinoma (N = 2) occurred in five patients (13%).

18 patients (49%) considered the sequelae of SCT an education obstacle. When filling in the questionnaire, N = 20 (54%), N = 7 (19%), N = 5 (14%), and N = 4 (11%) patients worked full time, part- time, were unemployed or had not yet finalized their education, respectively.

20 unmarried patients (54%) lived as singles, 8 patients (22%) lived in a partnership, 6 patients (16%) were married, and 3 patients (8%) had been divorced. Four patients (11%) reported on a total number of 7 children.

Conclusions: This assessment of HRQOL in AYAs transplanted because of CML two decades ago demonstrates self-reported satisfactory well-being only in the absence of cGvHD. Adherence of the whole group to regular (annual) physical examinations is insufficiently low. While relapse of CML nowadays is treated primarily with TKIs, secondary cancers due to conditioning require careful lifelong monitoring.

Disclosure: Nothing to declare

P504

Plasma ST2 levels are associated with agvhd severity and treatment response in pediatric HSCT

N. Gadanehzadeh[1,2], S. Weischendorff[1,2], C. Enevold[2], M. Ifversen[3], D. Bønk Elbæk[1,2], K. Kielsen[1,2], K. Müller[1,3,2]

[1]*Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark,* [2]*Institute for Inflammation Research, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark,* [3]*Insitute of Clinical Medicine, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark*

Background: The pathogenesis of acute graft-versus-host disease (aGvHD) is initiated by innate immune activation due to conditioning-induced tissue damage, leading to activation of cytotoxic donor T lymphocytes and increased tissue damage.

The soluble IL-33 receptor, known as suppressor of tumorigenesis 2 (ST2), is thought to be released from Th1 and Th17 cells and has been reported as a promising biomarker for aGvHD-related outcomes, although studies in children are sparse. In this time course study, we investigated the prognostic value of plasma ST2 levels in monitoring aGvHD development and treatment response after pediatric HSCT.

Methods: We included 117 children undergoing HSCT between 2010-2020 in Denmark. Median age was 8.9 years (range: 1.1-17.9). Diagnoses included ALL (n = 29), AML (n = 18), other malignancies (n = 25), and benign disorders (n = 45). Donors were either MSD (n = 33) or MUD (n = 84). BM (n = 112) or PB (n = 5) was used as stem cell source. All patients received a myeloablative conditioning regimen based on TBI (n = 23) or chemotherapy alone (n = 94). GvHD prophylaxis consisted of cyclosporine A, either alone or in combination with methotrexate.

ST2 was measured by ELISA in consecutive plasma samples collected before conditioning and at day 0, +7, +14, +21, +30, +60, +90 and +180 post-transplant. Plasma samples from 17 healthy young adults (aged 17-20 years) were included for comparison.

Results: Plasma levels of ST2 in the patients were comparable to those in healthy controls (median: 16760 pg/mL *vs*. 16323 pg/mL) before conditioning but increased early after transplantation reaching a maximum around day +30 ($P < 0.0001$) (figure).

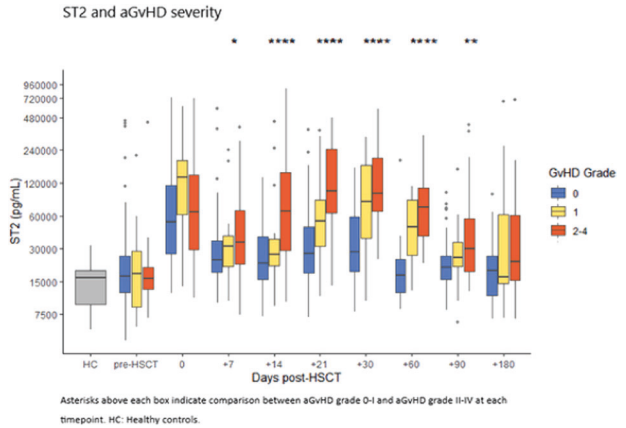
Patients with malignant diagnoses had significantly higher ST2 levels before start of conditioning compared to patients with benign diseases (median: 18121 pg/mL vs. 14754 pg/mL, $P = 0.007$). Furthermore, busulfan-based conditioning was associated with elevated ST2 levels from day 0 to +21 (all $P < 0.05$).

Thirty-eight patients (32.5%) developed aGvHD grade II-IV (MAGIC criteria) with median onset at day +17 (range: 5-35). These patients had significantly higher levels of ST2 from day +7 to +90 compared to patients with aGvHD grade 0-I, correlating with severity (figure). This was confirmed in a multivariable analysis adjusted for malignant diagnosis, donor type and busulfan-based conditioning (ST2 day +14: OR = 1.95 per doubling in ST2, $P = 0.0003$).

Forty-nine patients (41.9%) received glucocorticoid treatment for aGvHD. The cumulative prednisolone equivalents dose for patients with aGvHD from diagnosis to day +365 (median 0.23 mg/kg/day (range: 0-10.7)) correlated significantly with the ST2 levels measured at the time of aGvHD diagnosis (rs = 0.27, $P = 0.04$). Moreover, ST2 levels tended to be elevated in patients with steroid resistant/ dependent aGvHD (n = 10) at all timepoints

between day +14 and +180 compared to steroid responsive patients, reaching significance at day +90 ($P = 0.01$). ST2 levels were, however, similar in the two groups at the timepoint of aGvHD diagnosis.

Conclusions: Our findings support the use of ST2 as a prognostic biomarker of aGvHD after pediatric HSCT. We demonstrate that ST2 has not only a prognostic value in terms of predicting aGvHD but may also predict aGvHD severity and treatment response.



Disclosure: Nothing to declare

P505

Preliminary data from an early phase trial in children using pooled granulocytes to generate transient t-cell expansion after cord blood transplant in high-risk leukaemia

R. Borrill[1], H. Campbell[1], L. Kusyk[1], H. Lee[1], N. Diaz Burlinson[1], S. Morton[2,3], S. Stanworth[4,5], K. Poulton[1], J. Konkel[6], R. Wynn[1]

[1]Manchester University NHS Foundation Trust, Manchester, United Kingdom, [2]NHS Blood and Transplant, Birmingham, United Kingdom, [3]University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom, [4]NHS Blood and Transplant, Oxford, United Kingdom, [5]Oxford University Hospitals Foundation Trust, Oxford, United Kingdom, [6]University of Manchester, Manchester, United Kingdom

Background: Haematopoietic stem cell transplantation (HSCT) has a role to cure leukaemia that is refractory to chemotherapy. This is principally mediated by a graft versus leukaemia (GVL) effect of donor-derived T-cells, directed at the recipient leukaemia. Reduction of relapse has been reported after cord blood (CB) HSCT with augmented GVL since the graft is T-cell replete with frequent donor/recipient HLA mismatch. Although acute graft versus host disease (GVHD) can be significant, chronic GVHD is uncommon. Xenograft studies have reported that CB CD8 + T-cells can mediate GVL but T-cell reconstitution after CB transplant is CD4 + biased and CD8 + recovery is late. We have previously reported very early, unprecedented CD8 + T-cell expansion in a small number of T-cell replete, CB recipients receiving concomitant pooled granulocyte infusions in the early post-transplant period for refractory infection management. These CD8 + T-cells were polyclonal, activated, cytotoxic and had switched from an infused naïve to memory phenotype. These cells may mediate an enhanced GVL effect. We now report initial results of an investigator-led study of children with very high-risk leukaemia, receiving pooled granulocytes after unrelated donor CB HSCT.

Methods: Patients aged <16 years with high-risk leukaemia were recruited following referral from the UK national leukaemia multidisciplinary team. Transplants were performed at Royal Manchester Children's Hospital using T-replete, HLA-mismatched (5/8 – 7/8) unrelated CB donors. Patients received daily infusions of pooled granulocytes in the peri-transplantation period. 7 daily doses of granulocytes were transfused (each 10 ml/kg to a maximum of 200ml). We collected and assessed clinical data including tolerability of granulocytes, cytokine release syndrome (CRS), disease response, transplant related mortality and rates of acute and chronic GVHD. Assessment of T-cell immunophenotypic profile using fluorescence-activated cell sorting was performed during lymphocyte expansion to characterise cell populations.

Results: We report data from 2 fully evaluable patients with 3 further patients currently scheduled to receive transplant shortly. All 5 patients had high-risk, chemo-refractory, relapsed AML and had received a previous transplant. In the evaluable patients, the pooled granulocyte product was well tolerated with grade 1-2 CRS. Both patients entered morphological, cytogenetic and flow MRD disease remission (molecular awaited). Acute GVHD was seen in both patients. 1 patient died of transplant related toxicity. Early lymphocyte expansion and contraction was seen, with both CD4 + and CD8 + T-cell populations following this pattern within days of receiving granulocyte infusions. The majority of CD8 + T-cells seen were activated with $CD38^+$/HLA-DR^+ expression and were cytotoxic with granzyme B and perforin expression. They produced interferon-gamma in response to stimulation and there was a notable switch in phenotype from $CD45RA^+$/$CCR7^+$ naïve to $CD45RA^-$/$CCR7^-$ effector memory and $CD45RA^+$/$CCR7^-$ TEMRA T-cells.

Conclusions: CB transplant reduces leukaemia relapse after HSCT compared to other cell sources. This GVL effect is mediated by CB-derived T-cells, likely of CD8 + phenotype. We have initiated an investigator-led clinical trial of granulocytes to induce early, CB graft-derived T-cells to augment GVL effect in patients at the highest risk of leukaemia relapse. We report safety and early clinical response data in conjunction with T-cell data in this patient cohort.

Disclosure: Nothing to declare

P506

Upfront alternative donor HSCT for pediatric patients with acquired severe aplastic anemia

H.J. Im[1], E.S. Choi[1], S.H. Kang[1], H. Kim[1], K.-N. Koh[1]

[1]Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea, Republic of

Background: We compared the outcomes of allogeneic hematopoietic cell transplantation (HSCT) from alternative donors between unrelated donor (URD) and haploidentical family donor (HFD).

Methods: Between March 2003 and October 2021, 66 patients with acquired severe and very severe aplastic anemia (32 SAA, 34 vSAA) received upfront allogeneic HSCT from alternative donors (URD 30, HFD 36) at Asan Medical Center Children's Hospital. For HSCT from HFD (HSCT-HFD), 5 patients received CD3-depleted PBSC and 31 received TCRαβ-depleted graft. Conditioning regimens consisted of cyclophosphamide, fludarabine and r-ATG for URD and TBI (4-6 Gy), fludarabine, cyclophosphamide and r-ATG for HFD.

Results: Of 66 patients, 2 patients, who received HHCT-HFD, experienced primary graft failure (GF) and the remaining 34 achieved engraftment of neutrophil at a median of 11 days (range, 9-20 days). The median days of neutrophil engraftment was faster

in HSCT-HFD compared to HSCT-URD at 10 days and 12 days, respectively. (P < 0.001). Additional 2 patients from HFD experienced graft rejection and one from URD developed poor graft function. The cumulative incidences (CI) of any graft failure were 11.1% for HFD and 3.8% for URD (P > 0.05). The CI of grades 2-3 and grades 3 acute GVHD were 33% and 11%, respectively, which were not different between HHCT-URD and HHCT-HFD. No patient developed grade 4 acute GVHD. Two patients from URD developed severe chronic GVHD with CI of 7.4%, while no patients from HFD developed moderate/severe chronic GVHD (P > 0.05). One patient from URD died of GF and three patients from HFD died of transplant-related causes (GF, CMV pneumonia and TMA 1 each), leading to TRM of 5.6% for URD and 9.0% for HFD, respectively (P > 0.05). All survived 62 patients were transfusion independent. At a median follow-up of 4.7 years (range,0.2-18.8 years), 3-year estimated overall survival, failure-free survival, and mod/severe cGVHD-free and failure-free survival were 94%, 96%, and 89% for URD and 91%, 83% and 83% for HFD.

Table 1. Characteristics of patients with SAA.

	URD (N = 30)	HFD (N = 36)
Age at transplantation, median (range, years)	8.0 (1.1-18.7)	12.5 (1.4-22.6)
Conditioning regimens		
CyATG	2	
FluCyATG		3
TBIFluCyATG	28	33
Depletion of T cells		
None		
CD3/TCRαβ	30	5/31
GVHD prophylaxis		
Cyclosporine/MTX	30	
Cyclosporine or tacrolimus/MMF		10
MMF		14
None		12

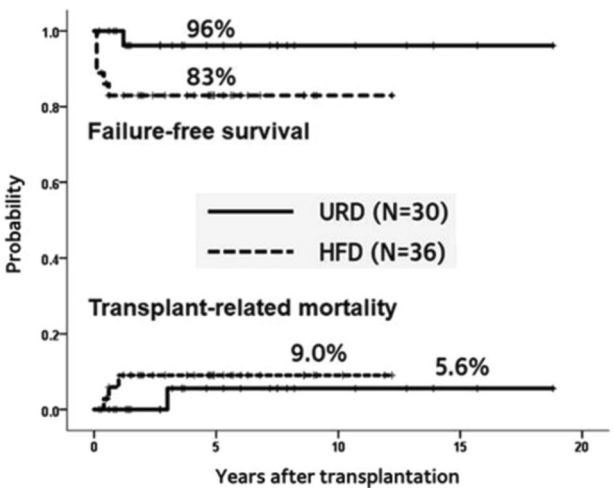


Figure 1. Outcomes of alternative donor HSCT for pediatric patients with SAA

Conclusions: Our study is another emerging evidence of upfront haploidentical HSCT for pediatric patients with SAA in terms of low TRM and moderate/severe chronic GVHD with favorable failure-free survival.

Clinical Trial Registry: NCT 01759732

Disclosure: Authors have no personal or financial interests to declare.

P507

Relapse after transplantation in children with acute lymphoblastic leukemia in cellular therapies era. A retrospective analysis of grupo español de trasplante hematopoyetico (geth) pediatric committee

M. Gonzalez Vicent[1], J.L. Fuster[2], D. Bueno[3], M. Panesso[4], B. Molina[1], Y. Mozo[3], R. Olivas[5], C. Fuentes[6], M. Lopez Duarte[7], A. Regueiro[8], P. Palomo[9], I. Lopez[1], A. Perez Martinez[3], C. Diaz de Heredia[4], M.A. Diaz[1]

[1]Hospital Niño Jesus, Madrid, Spain, [2]Hospital Virgen de la Arrixaca, Murcia, Spain, [3]Hospital La Paz, Madrid, Spain, [4]Hospital Vall de Hebrón, Barcelona, Spain, [5]Hospital Clinico, Valencia, Spain, [6]Hospital La Fe, Valencia, Spain, [7]Hospital Marques de Valdecilla, Santander, Spain, [8]Hospital Clinico de Santiago, Santiago de Compostela, Spain, [9]Hospital Central de Asturias, Oviedo, Spain

Background: Acute lymphoblastic leukemia (ALL) is the main indication for allogeneic transplantation in the pediatric age. An important proportion of these patients achieve long-term remission after transplant and can be considered cured. However, relapse after transplant still is the main cause of transplant failure and the leading cause of death. For many years, relapsed ALL patients have been considered candidates for a second transplant. This landscape has changed since advent of immunotherapy and CAR-T cell therapy.

Methods: A total of 29 children (18 female) with ALL (median age 7 years; range; 1-15) who relapsed after an allogeneic transplant since 2013 to 2020 were included in this retrospective study. Median time to relapse was 4 months (range; 2-24). Twenty-three out of 29 patients were in CR and MRD negative at time of first allogeneic transplant. Previous transplants were from a MUD in 12 cases, Haploidentical Donor in 8, MSD in 7 and CBU in 2. Four out of 29 (14%) patients had previous chronic GvHD.

Results: CAR-T cell therapy was used in 12 patients (10 preceded by bridge chemotherapy and 2 by monoclonal antibody). Second allogeneic transplant was performed in a total of 5 patients (using a different donor of first transplant), 2 with identical unrelated donors and 3 with haploidentical donors. The other patients progressed before they could receive consolidation therapy.

CR was obtained in all 12 CAR-T patients (100%) and in 4 out of 5 (80%) patients after transplant. One patient died of TRM.

With a median follow-up for survivors of 2 years (range; 1-8), 6 patients relapsed again after obtain CR: 5 after CAR-T cell therapy and 1 after transplant. Thirteen patients are alive, 3 of them with active disease, with an overall survival of 21 ± 5%. Ten patients are alive in CR (7/12: 58% after CAR-T and 3/5: 60% after transplant). There are no differences in terms of DFS between therapy groups: 7/12 (58%) after CAR-T and 3/5 (60%) after transplantation.

Conclusions: Despite small sample size, our results suggest that treatment of relapsed ALL patients after allogeneic transplant is moving to cellular and immunotherapies rather a second allogeneic transplant. The role of transplantation as consolidation of the CAR-T cell therapy. must be established, since half of the patient relapse after CAR-T.

Disclosure: Nothing to declare

P508

Non-osteopenic bone pathology post-hematopoietic stem cell transplant (HSCT) in patients with inborn errors of immunity (IEI)

Z. Golwala[1], C. Booth[1], W. Qasim[1], A. Worth[1], M. Kusters[1], R. Elfeky[1]

[1]*Great Ormond Street (GOS) Hospital for Children NHS Foundation Trust, University College London GOS Institute of Child Health, and NIHR GOSH BRC, London, United Kingdom*

Background: Non-osteopenic bone disease (BD) in children post-HSCT for IEI remain unrecognised. We present post-HSCT long term follow up (LTFU) data from large tertiary paediatric immunology centre.

Methods: Between 2000-2018, 432 children received HSCT for IEI. 342 children were alive at last assessment and included for analysis. Patients' records were checked for BD and potential risk factors; underlying IEI, steroid use/duration, hormonal replacement therapy (HRT); growth and gonadal hormones, weight-for-age (centiles) and donor engraftment at onset of BD. Exclusion criteria included decreased bone density, fractures, anomalies due to underlying IEI, short stature without other BD. BD was divided into 5 categories; Bone tumors; Congenital defect with late diagnosis; Avascular necrosis (AVN); Evolving bone deformities; Slipped upper femoral epiphysis (SUFE).

Results: 27/342 (7%) children developed BD at a median of 7.7 years post-HSCT (29 HSCTs in 27 children). Conditioning regimen included Treosulfan- (n = 20), Fludarabine/Melphalan- (n = 7) and Busulfan- (n = 2) based conditioning. Donors were 10/10 HLA matched (n = 15), 7-9/10 mismatched (n = 13) and haplo-identical (n = 1). Underlying IEI included severe combined immune deficiency (SCID) (n = 9); Wiskott Aldrich Syndrome (WAS) (n = 7), other non-SCID (n = 11). Six patients have >1 category. Two patients had HRT, 17/27 (63%) had steroid therapy > 6 months. Of note, 4/8 patients with benign bone tumor had WAS. Eight developed AVN at a median of 7 years post-HSCT; 6/8 had steroid use >12 months. Seven had genu valgum at a median of 8.1 years post-HSCT; 6/7 had steroid use >6 months and 1/7 received HRT 11 months ahead of BD. Six patients developed SUFE; 5/6 boys; 1/6 overweight and all presented at 10 years or below.

Conclusions: Non-osteopenic BD post-HSCT for IEI are not rare and should be actively looked for in LTFU clinic. Prolonged steroid use (>6 months) is associated with increased rates of BD including AVN, genu valgum and benign bone tumors. Increased rates of BD among WAS warrants investigation to understand potential mechanism in context of specific IEI.

Disclosure: Nothing to declare

P510

Endothelial injury impact on the results of ex vivo t-cell-depleted haploidentical hematopoietic cell transplantation in pediatric patients with malignant hemopathies

I. López Torija[1], B. Molina Angulo[1], M. González Vicent[1], S. Vinagre Enríquez[1], J. Zubicaray Salegui[1], J. Iriondo Alzola[1], E. Sebastian Pérez[1], J. Sevilla Navarro[1], M.Á. Díaz Pérez[1]

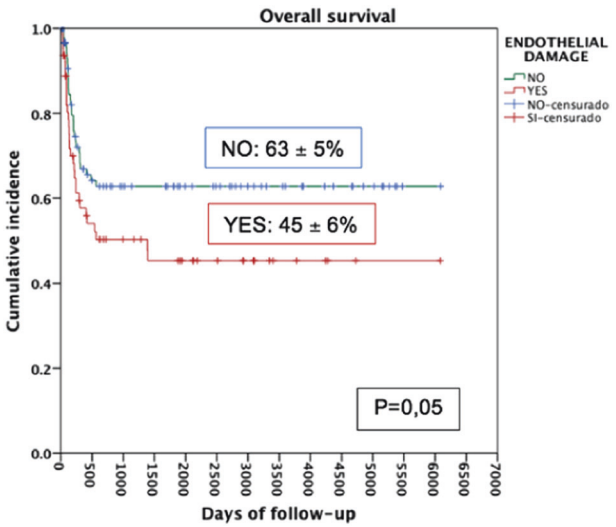
[1]*Hospital Infantil Universitario Niño Jesús, Madrid, Spain*

Background: Endothelial injury (EI) is the common trigger of numerous posttransplant complications. Little has been published about complications secondary to EI in the ex vivo T-cell-depleted haploidentical hematopoietic cell transplantation platform, and even less when considering pediatric population.

The primary end point is to analyze incidence, outcome and survival rates of complications secondary to EI in pediatric patients, both in general terms and specifically for each pathology. As secondary outcome, the possible relation between the complications secondary to EI and graft versus host disease (GVHD) will be studied.

Methods: A total of 159 patients (106 males) diagnosed from hematological malignancies that underwent allogenic HSCT from haploidentical donors using ex vivo T-cell depletion between 2005 and 2020 were included. Seventy-nine patients were diagnosed of AML and 80 patients of ALL. Forty-eight transplants were in 1stCR, 55 in 2ndCR and 56, beyond 2ndCR or with active disease at time of transplant.Donors mean age was 40 (range 2–54) years. All patients received myelo-ablative conditioning and total-body irradiation was not used in any case. A P-value ≤0.05 was considered statistically significant.

Results: The cumulative incidence of EI was 45 ± 5%, with a follow-up median of 7 (1,7-17) years. Patients developing these complications have an incidence of transplant-associated mortality (TAM) of 40 ± 7% compared to 12 ± 4% in patients that did not develop them (p = 0,0001). Regarding overall survival rates (OS), clinical and statistically relevant differences were found (p = 0,05): patients that developed complications had 45 ± 6% OS compared to 63 ± 5% OS in patients that did not. OS for the whole group was 60 ± 4%.



Descriptive statistics for each complication related (sinusoidal obstruction syndrome, engraftment syndrome, [ARL1] thrombotic microangiopathy, diffuse alveolar hemorrhage and posterior reversible encephalopathy syndrome) to are collected in Table 1.

In the multivariate analysis of the results, it was found that having any complication related to EI increases up to 4 times the risk of developing acute GVHD (being EI present the hazard ratio (HR) is: 4,1, CI95%: 2,1-8,1, p = 0,0001).

TABLE 1	SOS	ES	TMA	DAH	PRESS
Incidence	8.80%	22.60%	11.30%	3.10%	3.10%
OS					
• Ψεσ	60 ± 4%	57 ± 5%	64 ± 4%	60 ± 4%	57 ± 4%
• No	31 ± 12%	59 ± 8%	10 ± 8%	20 ± 17%	60 ± 21%
	p = 0.002	p = n.s	p = 0,0001	p = 0,003	p = n.s
TAM					
• Ψεσ	20 ± 3%	22 ± 4%	14 ± 3%	20 ± 3%	23 ± 4%

TABLE 1	SOS	ES	TMA	DAH	PRESS
• No	57 ± 14%	29 ± 8%	88 ± 10%	80 ± 17%	40 ± 21%
	P = 0.001	p = n.s	p = 0,0001	p = 0,0001	p = n.s

Conclusions: From the results obtained in the study, we can infer that complications related to EI affect the outcome of ex vivo T-cell-depleted haploidentical hematopoietic cell transplantation in pediatric patients with malignant hemopathies, resulting in an decreased of OS and increased TAM. Additionally, EI is directly related to other complications that associates high morbidity and mortality rates such as GVHD.

Scientific and clinic efforts should be directed to recognize risk factors for developing EI, that will consequently allow to establish early diagnosis, early treatment and better prevention measures for EI.

Disclosure: No disclosures.

P511

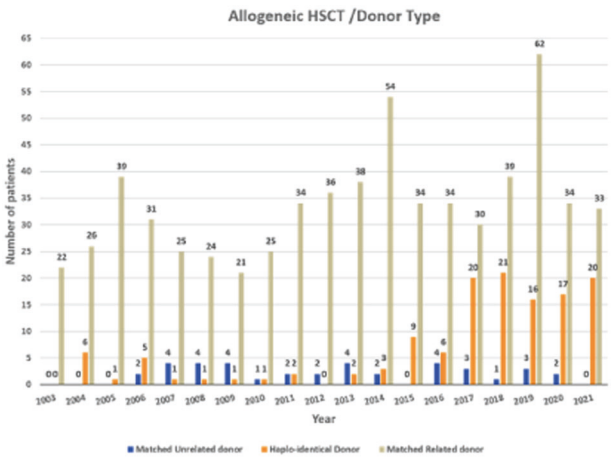
Hematopoietic stem cell transplantation for children in jordan 2003-2021: Activity and trends

R. Rihani[1], H. Hashem[1], M. Abu Shanap[1], E. Khattab[1], A. Tbakhi[1], I. Sultan[1]

[1]King Hussein Cancer Center, Amman, Jordan

Background: Hematopoietic stem cell transplantation (HSCT) is a curative modality for variable malignant and non-malignant conditions. The first comprehensive state of the art pediatric HSCT program in Amman-Jordan was established in 2003 at The King Hussein Cancer Center (KHCC). We describe the pediatric HSCTs activities and trends by The Pediatric HSCT Program at KHCC which performs a significant number of HSCTs reaching 100 per year.

Methods: Data collected since the start of the program in 2003 to date, from medical files and electronic medical records, were retrospectively reviewed and analyzed, after obtaining Institutional Review Board Approval.



Results: Between January, 2003 and October 2021, a total of 1051 HSCTs were performed for pediatric patients with a median age of 8 years (0.13-31), of which 58% were males and 72 % were Jordanian (n = 758). Median follow-up time was 2.9 years (0.087-12.5 years). Allografts accounted for the majority of HSCTs (77%; n = 811); whereas, autografts accounted for 23 %(n = 240). Allogeneic HSCTs included full-matched family/related donors in 79% (n = 641), haploidentical HSCTs in 16% (n = 132) and unrelated donors in 5% (n = 38). Stem cell sources included PBSCs in 75% (n = 788), BM 21% (n = 221) and CBUs 4% (n = 38) of the HSCTs. Myeloablative and reduced intensity (mainly for non-malignant disorders) conditioning regimens were employed in 71 % and 27% of the HSCTs, respectively; and no conditioning was given in 2%. Malignant conditions were the main indications for HSCTs (56%; n = 591), whereas, non-malignant conditions accounted for 44% (n = 460). The most common indication for allogeneic HSCTs were leukemia (37%; n = 297), followed by hemogloinopathies in 26% (n = 212), bone marrow failure syndromes in 17% (n = 137) and immune deficiencies in 11% (n = 88); while solid tumors (69%; n = 165), followed by lymphomas (41%; n = 99) were the main indications for autologous HSCTs. The 5-year OS and EFS for all HSCTs were 81% ±2.3 and 75%±3.4, respectively; and for allogeneic HSCTs 84%±3.1 and 77% ±2.2. Cumulative incidence of TRM at 1 year for allogeneic HSCTs was 1.9%, compared to 5% in the previous treatment era (before 2010), p = 0.004). Whereas, that for autologous HSCT was 0.54%. Disease progression/ relapse of underlying condition was the main cause of mortality (76%).

Conclusions: HSCTs have provided long-term disease-free survival and cure for a wide spectrum of malignant and non-malignant conditions in children. Referral to a dedicated pediatric HSCT center and implementing contemporary practices such as refinement of conditioning regimens, high resolution patient and donor typing, expertise of the treating teams and robust supportive care services have contributed to significant improvement in outcomes of pediatric HSCTs at KHCC. In recent years, a constant increment in the total number of pediatric HSCTs performed at KHCC is evident. In particular, haploidentical HSCTs are increasingly employed as they constitute a readily available alternative donor option, similar to international practices.

Disclosure: no conflict of interest

P512

Re-visit of the applications of granulocyte colony-stimulating factor in pediatric patients undergoing autologous high dose chemotherapy with stem cell rescue – single center experience

P. Manku[1], X. Zhang[1], D. Wall[1], K. Chiang[1], A. Koo[1]

[1]The Hospital for Sick Children, Toronto, Canada

Background: Patients undergoing autologous high dose chemotherapy with stem cell rescue (aHDC-SCR) commonly receive granulocyte colony-stimulating factor (GCSF) to reduce the duration of neutropenia. Timing of GCSF administration after aHDC-SCR is varied and has been analyzed in adult studies. These have shown mixed results when assessed for time to neutrophil recovery, duration of hospitalization, infection rates and cost. There is a paucity of data in pediatrics.

Methods: A single-center, retrospective pediatric study was conducted at a tertiary care academic institution, The Hospital for Sick Children. Patients who received aHDC-SCR were reviewed to determine the primary outcome of days to neutrophil >500/μL, and secondary outcomes duration of hospitalization, proportion of patients with febrile neutropenia, infection, engraftment syndrome and cost of GCSF. Variation in neutrophil recovery was analyzed using the Mann-Whitney U test and other secondary endpoints used Chi-Squared test comparing cohorts of patients treated with varying approaches to GCSF administration.

Results: This retrospective sequential cohort of 61 pts (102 transplants) who were aged 0.5-21 years and who underwent aHDC-SCR for treatment of neuroblastoma, brain tumors, lymphoma and other solid tumors. Three groups were identified based on the timing of GCSF administration: A) early GCSF, given

on day 0/+1 post-transplant (N = 72), B) delayed GCSF (N = 7) where GCSF was started d 5-10 post HSCT, C) no GCSF (N = 13) and D) those that were not planned to receive GCSF, but received due to a clinical reason (N = 10). There was no difference in neutrophil recovery between group A and B (10.7 and 10.9 days respectively). However, neutrophil recovery was delayed ($p < 0.001$) in those not planned to receive GCSF (group C & D) (14.5 days). The mean neutrophil recovery was similar irrespective of primary diagnosis and $CD34^+$ cell dose (mean 8.6, range 9 – 21 $x10^6$ /kg) infused. The proportion of patients with febrile neutropenia, infection and engraftment syndrome were similar regardless of administration and timing of GCSF. The duration of hospitalization was not different between groups who received and not received GCSF (36.1 days and 26.4 days, respectively). This resulted in no difference in the cost of hospitalization (per diem charges) between groups who received GCSF and no GCSF group. However, the cost difference per transplant was closed to $35,000 higher in those who received early GCSF.

Conclusions: Time to neutrophil recovery was reduced with post-transplant GCSF administration. The duration of hospitalization was not shorter if GCSF was given. The episodes of fever and neutropenia, infection and engraftment syndrome were similar. The cost of hospitalization was higher due to the cost of GCSF. Further studies are needed to confirm findings and assess cost-benefit of GCSF in this patient population.

Disclosure: Nothing to declare.

P513

Analysis of allogeneic hematopoietic cell transplantation in the tyrosine kinase inhibitor era: A multicenter, prospective study on pediatric chronic-phase chronic myeloid leukemia (JPLSG CML-08)

C. Tono[1], A. Tanizawa[2], A. Watanabe[3], M. Ito[4], H. Shima[5], Y. Yuza[6], H. Muramatsu[7], M. Okada[8], H. Shimada[5]

[1]Iwate Prefectural Chubu Hospital, Iwate, Japan, [2]Sugita Genpaku Memorial Obama Municipal Hospital, Fukui, Japan, [3]Niigata Cancer Center Hospital, Niigata, Japan, [4]Fukushima Medical University School of Medicine, Fukushima, Japan, [5]Keio University School of Medicine, Tokyo, Japan, [6]Tokyo Metropolitan Children's Medical Center, Tokyo, Japan, [7]Nagoya University Graduate School of Medicine, Nagoya, Japan, [8]Nagasaki University School of Medicine, Nagasaki, Japan

Background: The timing of allogeneic hematopoietic cell transplantation (HCT) for pediatric patients with chronic-phase chronic myeloid leukemia (CML-CP) is controversial in this tyrosine kinase inhibitor (TKI) era.

Methods: A subanalysis was conducted on 14 patients (18%) from the nationwide, prospective, multicenter, observational study (CML-08, UMIN 00000258, n = 78) that was carried out by the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG). These patients were under 18 years of age and diagnosed with BCR-ABL1-positive CML-CP between October 2009 and September 2014. All had been treated according to the modified European LeukemiaNet 2009 recommendations and opted for HCT during the 10-year observation period.

Results: In total, there were 10 males and four females. The median diagnostic age was 12 (range: 3–16) years, with six patients younger than 10. The median observation period from diagnosis to the last follow-up was 66 (range: 26–110) months. All patients were initially treated with imatinib (IM), except for one who was administered nilotinib. As a pre-transplant therapy, two patients received IM, other patients received two to four different TKIs. Twelve patients received HCT for inadequate responses to TKIs, one did it for intolerance, and one did it for her young age. Two had progressed to the blast phase during treatment with TKIs but achieved a second CP (CP2) before HCT. The median duration from diagnosis to HCT was 24 (range: 8–86) months. HLA-matched sibling donors (MSD) were available for five patients. Among the first CP (CP1) patients, all but one received a reduced-intensity conditioning regimen. Five-year overall survival and event-free survival were 86% and 59%, respectively. One patient had an engraftment that initially failed, yet later succeeded upon the second HSCT.

Graft-versus-host disease (GVHD), at a grade III to IV acute GVHD or an extensive/ severe chronic GVHD, was experienced by one (7%) and two (14%) patients, respectively. Two patients, a CP1 transplanted from an HLA mismatched related donor and a CP2 transplanted from an MSD, died from post-transplant complications within a year. Five patients received a TKI and/or donor lymphocyte infusions following HCT treatment, besides those who received a retransplantation for graft failure. Short stature was observed in a patient who suffered from severe chronic GVHD. On the other hand, HCT enabled some young patients to recover from impaired growth that had been induced by TKIs. At the last follow-up, all surviving patients were in deep molecular responses, and their performance status scores were zero, except the one with short stature.

Conclusions: HCT is still an alternative for CML-CP patients who do not maintain an optimal response with TKIs. In this study, HCT was successful in most patients even without MSD, but by no means all. We should carefully consider each patient's situation and circumstances before administering HCT.

Disclosure: Nothing to declare

P514

Reduced intensity conditioning regimen in children with non-malignant diseases: High incidence of mixed chimerism without impact on overall survival and disease free survival

M.I. Benitez Carabante[1], D. Bueno Sanchez[2], L. Valero Arrese[1], M. Silva Hernandez[2], M.L. Uria Oficialdegui[1], L. Alonso Garcia[1], L. Sisinni[2], Y. Mozo del Castillo[2], A. Pérez Martínez[2], C. Diaz de Heredia Rubio[1]

[1]Hospital Universitario Vall d'Hebron, Barcelona, Spain, [2]Hospital Universitario La Paz, Madrid, Spain

Background: The use of reduced intensity conditioning (RIC) regimens in patients with non-malignant diseases has allowed hematopoietic stem cell transplantation (HSCT) in children with moderate or severe comorbidities. However, this practice has been associated with a higher incidence of mixed chimerism (MC). The objective of this study is to analyze the incidence of MC in patients with non-malignant diseases who received a RIC regimen and to demonstrate that its presence does not have an impact on overall survival (OS) and disease-free survival (DFS).

Methods: Retrospective study where children who received a first HSCT following a RIC regimen for non-malignant diseases between 2013 and 2019 were included. Primary endpoint: disease free survival. Secondary endpoint: engraftment, graft failure, incidence of MC, acute and chronic graft versus host disease (GvHD) and OS.

Results: With a median follow up of 28 months, 78 patients were included (median 5 years old, IQR: 0.2-17), with primary immunodeficiency (n = 41,52.6%), severe aplastic anemia (n = 23,29.5%) and bone marrow failure (n = 14,17.9%). Fifty patients (64.1%) underwent a first HSCT from a matched donor (unrelated n = 32 /related n = 18) and twenty eight (35.9%) from a mismatched donor (unrelated n = 19/haploidentical n = 7/related n = 2). The source of stem cells included bone marrow (n = 57,73.1%), peripheral blood (n = 12,15.4%) and cord blood (n = 9,11.5%). Most used conditioning regimen included Cyclophosphamide and Fludarabine (n = 32, 42.3%), Busulfan and Fludarabine (n = 23, 29.5%), Treosulfan and Fludarabine (n = 9, 11.6%) and Fludarabine and Melphalan (n = 7, 9%). All patients except one received T cell depletion (98.7%): in vivo (n = 66, 84.6%) and ex vivo (n = 11, 14.1%). Median time for neutrophil engraftment was 19 days, IQR 14-22. Seven patients had primary graft failure (9%). A total of 40 patients (51%) presented MC, of whom 5 (12%) had secondary graft failure. The incidence of grade III-IV aGvHD at D + 100 was 19.5% (95% CI 11.39 - 32.33%), the incidence of cGvHD at 2 years was 15% (95% CI 8.31-26.19%). The OS at 1 and 3 years post HSCT were 83% (95% CI 72.6-89.8%) and 77.% (95% CI 66-85.2%). The EFS at 1 and 3 years post HSCT were 78.72% (95% CI 67.6-86.4%) and 70.5% (95% CI 58-79.8%). Overall, 18 patients (23%) died, of whom 4 after primary graft failure and 5 after a secondary graft failure. The causes of death were infections (n = 9), transplant-associated thrombotic microangiopathy (n = 3), diffuse alveolar hemorrhage (n = 1), liver (n = 1) and respiratory (n = 1) failure, multi organ failure (n = 1) and not documented/ unknown (n = 1). There were no significant differences in terms of OS and EFS in patients with mixed chimerism and patients with full donor chimerism [OS 87% (95% CI 71.8-94.4%) vs 72% (95% CI 52-85.1%) p 0.25; EFS 82% (95% CI 66.5-90.9%) vs 72% (95% CI 52.0-85.1%) p 0.49]. Patients who received a matched donor, bone marrow as stem cell source and in vivo T cell depletion presented a better OS and DFS.

Conclusions: Children with non-malignant diseases have a high incidence of MC when receiving a RIC regimen. The presence of MC does not have a negative impact on OS and DFS.

Disclosure: Nothing to declare

P515

Primary immunodeficiencies: HSCT experiences of a single pediatric center in Argentina

M.D. Iglesias[1], G. Gonzalez[1], G. D`Angelo[1], S. Diaz[1], D. Cabanillas[1], L. Regairaz[1], D. Di Giovanni[2], S. Formisano[1]

[1]Hospital Sor Maria Ludovica, La Plata, Argentina, [2]Hospital de Niños Gutierrez, Ciudad de Buenos Aires, Argentina

Background: Primary immunodeficiency diseases (PID) are characterized by the occurrence of frequent infections and are caused by many genetic defects. Hematopoietic stem cell transplantation (HSCT) is a curative treatment option for the majority of PID.

We want to present our experience about HCST in PID in a single pediatric center in Argentina.

Methods: Retrospective study on HSCT in PID collected from clinical charges from January 1999 to June 2021.Donor type, demographic data, stem cells source, conditioning regimen (CR) and outcome were evaluated.

Results: 16 patients were included in this study and 17 transplants were performed. 6 were female and 10 male.The median age was 4.98 years (range 2 months- 15.16 years) . The diagnosis were SCID 5 patients, CID 3 patients (1 non characterized; 1 CD40 ligand deficiency 1 and PNP deficiency) HLH 5 patients (2 grisceli, 1 chediak and 2 non characterized), 2 CGD and 1 IPEX. Related donor (RD) were used in 10 transplants(haplo 5 and 5 Match related donor) and Unrelated 7 transplants. The source used was BM 10, PB 6 and 1CB.

Graft failures were presented in 5 patients. Primary were presented in 3 patients (17.64%), secondary ocurred in 2 patients, both of them caused by CMV reactivation. 3 of the 5 patients are dead.

The GS was 70.6% and TRM was 11.76%.

Acute GVHD happened in 4 patients (23.5 %) Grade III/IV 1 (5.8%) and Chronic GVHD none.

Viral reactivation presented in 9 transplants (52%), CMV 5, VEB 4 and others 4. Some of them had coinfections . 3 of them used ATG and 3 Alemtuzumab for GVH prophylaxis.

Conditioning regimen used were 12 MAC, 2 RIC and 2 without conditioning.

11 patients are alive (and 9 are cured of their PID).

Conclusions: The transplantation procedures appear to have provided a permanent cure in nine PID patients. Early diagnosis and prompt performance of SCT with an optimal donor and conditioning regimen contributed to the favorable outcomes that were similar to reported in literature. Virus reactivation is a frequent complication and contributes to graft failure. New and better viral treatments and alternatives GVH prophilaxys strategies may contribute to improve outcomes.

Disclosure: Nothing to declare

P516

Successful haploidentical stem cell transplant with post transplant decitabine for 3 patients with high risk juvenile myelomonocytic leukaemia

F. Yeap[1], K.L. Cing[1], D. Tan[1], P.L. Tan[1]

[1]National University Hospital Singapore, Singapore, Singapore

Background: Allogenic haematopoietic stem cell transplantation (HSCT) remains the only proven curative therapy for juvenile myelomonocytic leukaemia (JMML). Despite that, leukaemia relapse remains the major cause of treatment failure in 30-60% of children with JMML and tends to occur within the first year after the allograft.

Methods: We report on 3 high risk JMML patients (age > 2 years, PLT < 30 x 109/L, somatic PTPN11 mutation) who all underwent haploidentical peripheral blood HSCT with CD3/CD45 RA T- cell depletion followed by post-transplant Decitabine as pre-emptive therapy to prevent relapse. All 3 patients were diagnosed in their home country and presented to our institution for a second opinion. Patient 3 in particular had been diagnosed as relapsed mixed phenotype acute leukaemia whilst receiving maintenance therapy as per COG protocol when her unique features of monocytosis, monosomy 7 and PTPN11 prompted the diagnosis of Acute JMML. All 3 patients had peripheral blasts >5%, BM blasts >15% and patient 1 and 2 also had an elevated HbF > 20% at diagnosis. They all had poor response to various initial therapy and achieved cCR only after combination therapy with Etoposide +AraC +Aza. All 3 patients underwent pre-HSCT splenectomy with the hope of reducing tumor burden at the time of HSCT to reduce the risk of recurrence.

Diagnostic Features and Transplant conditioning/

All 3 patients had PTPN11 somatic mutation (samples sent to C Niemeyer, Uni Freiberg)

ADE: Cytarabine, Daunorubicin, Etoposide (AML like therapy), Aza: Azacytidine

[1]cCR: clinical complete response based on criteria for evaluating response and outcome in clinical trials for children with JMML (C Niemeyer et al, 2015)

	Age (years)/ Gender	Platelet Count x10^9/L/ Transfusion dependence	Karyotype	Chemo prior to transplant	No. of cycles of Aza	Disease status at transplant[1]	Time from diagnosis to transplant (months)	Donor type	Conditioning Regimen
Patient 1	4.4/M	25/Y	46,XY,inv(9) (p11q13)	ADE Low dose Cytarabine (AraC) Etoposide + AraC Aza + AraC	7	cCR	9.1	Father	Flu+Treo +Thio +Mel
Patient 2[2]	6.3/M	29/Y	47,XY, + 11[4]/ 48, idem, +X[3]/ 46 XY[13]	Etoposide +AraC + Aza	4	cCR	5.4	Mother	Flu +Bu +Thio +Mel
							7.3	Father	Flu+Treo +Thio +Mel
Patient 3	7.0/F	23/Y	45,XX,-7[18]/ 46,XX[2]	Metrononic Etoposide Venetoclax + Aza Etoposide +AraC +Aza	6	cCR	9.0	Father	Flu+Treo +Thio +Mel

[2]Patient 2 failed his first haploidentical maternal stem cell transplant and required a second transplant

Results: All 3 patients are alive and remain disease free at a median of 31.5 months from time of HSCT. There were no reported aGVHD or cGVHD and all 3 patients received 6 cycles of monthly decitabine from as early as 1 month post HSCT. Patient 2 required a second transplant due to early graft rejection with macrophage activation syndrome from suspected central line infection with acute decline in counts and fall of donor chimerism. He was successfully re-transplanted with a 2nd haploidentical HSCT despite multiple infections including Klebsiella and Sternotrophomonas maltophilia sepsis with a rapidly progressing thigh cellulitis which required debridement and skin grafting. All the patients achieved neutrophil engraftment (ANC > 0.5) between 9-15 days and platelet engraftment (PLT > 50) before 20 days and GVHD prophylaxis was only in the form of CD3/CD45RA T-cell depletion.

Conclusions: Our small experience in treating this high risk group of patients has been encouraging and the use of post transplant Decitabine appears to be beneficial in preventing early relapses without additional GVHD. Splenectomy should also be considered in this high risk group.

Clinical Trial Registry: NA

Disclosure: Nothing to declare

P518

Iron overload after pediatric allogeneic hematopoietic stem cell transplantations: Varies by disease type, improves over time. A single center experience

A. Gefen[1], V. Kagan[1], N. Mandel[1], S. Ash[1]

[1]*Rambam Medical Center, Haifa, Israel*

Background: Iron-overload (IO) is a late complication of HSCTs, mainly investigated in chidren transplanted for hemoglobinopathies. We present factors associated with IO, with emphasis on the differences between disease groups: hemoglobinopathies, leukemia, and other nonmalignant disorders, and the trend of change over time before and after transplant.

Methods: All children allo-transplanted between 2009-2019, with ≥2 years follow-up, were included. IO was assessed by blood-ferritin level at different time points. The values at 2-years post-HSCT were used to determine statistical significance (ANOVA & t-test) between different disease-groups and other factors.

Statistical analysis was conducted by SPSS software (Chicago, IL); mean ferritin values were log-transformed. Study was approved by IRB.

Results:

Forty eight allo-transplanted children (52% males, median age at HSCT 9.1 years) were included. Indications for HSCT were non-malignant disorders in 28 children (58%), mainly Hemoglobinopathies (15 patients), and Leukemia in th e other 20 (42%).

Median follow-up after HSCT was 4 years (range: 2-12.8); all but 3 patients (6%) were alive at last follow-up. The incidence of chronic GVHD was 31%.

All but 2 patients were exposed to RBCs-transfusions, mostly (75%) before transplant. Number of transfused RBCs units was 22.6/patient (mean) for all cohort, and was significantly different between the disease-groups: 32 and 9, for the hemoglobinopathies & leukemia, versus other nonmalignant disorders, respectively ($p < 0.001$). After transplant, no chelation-therapy nor phlebothomy were given to any patient, including hemoglobinopathies.

Ferritin levels before HSCT were 1145 ng/mL (mean); and after transplant, at the following time-points: 1-year post HSCT, 2-years post HSCT, and at last follow-up, were: 708, 474, and 268 ng/mL, respectively. The hemoglobinopathies & leukemia groups had significant higher levels vs. other nonmalignant disorders-group ($p < 0.001$).

Higher age at HSCT, higher number of RBCs-units transfused, and disease-group: hemoglobinopathies & leukemia vs. other nonmalignant disorders ($p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively), but not chronic GVHD ($p = .982$), were correlated with higher 2-year-ferritin level (Table 1).

Table 1: Factors correlated with higher blood-ferritin level 2-years post-Allo-HSCT in children.

variable		Statistics	M(SD)	CI	P value
HSTC Age (Higher vs. lower)		r = .312	8.79(6.28)	.130-.560	**<.05**
Number of RBCs-units transfused		r = .715	22.59†	.522-.838	**<.01**
Ferritin-level (ng/dL) according to diagnosis	**Other nonmalignant disorders** a	$F_{(2,40)}$=7.58	110.58 ng/dL†	246-288	**<.001**
	Leukemia b		457.48 ng/dL†	205-1017	**<.001**
	Hemoglobinopathies b		908.77 ng/dL†	557-1480	**<.001**
Chronic GVHD		t-test=0.137			N.S.
(yes vs. no)					=.982

† back transformed note: categories not sharing subscript are significantly different

Conclusions: These retrospective data show that in children: 1. post-HSCT IO is correlated mainly with pre-transplant factors; 2. non-malignant indications for HSCT other than hemoglobinopathies are associated with lower level of IO, presumably due to

lower burden of pre-HSCT blood-transfusions; 3. and spontaneous improvement without intervention is excpected. Collavorative prospective studies about the role of pos-transplant-celation would be valuable.

Disclosure: Nothing to declare

P519

Haploidentical stem cell transplant in paediatric patients with recurrent or treatment-refractory severe aplastic anaemia and refractory cytopenia of childhood

V. Quintero[1], D. Bueno-Sanchez[2], Y. Mozo-Del Castillo[2], M. Lopez-Duarte[3], J.M. Perez-Hurtado[4], J.I. Fuster[5], L. Sisinni[2], M. Gonzalez-Vicent[6], C. Diaz-de-Heredia[7]

[1]Hospital Universitario Ramón y Cajal, Madrid, Spain, [2]Hospital Universitario La Paz, Madrid, Spain, [3]Hospital Universitario Marqué de Valdecilla, Santander, Spain, [4]Hospital Universitario Virgen del Rocio, Sevilla, Spain, [5]Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain, [6]Hospital Infantil Universitario Infantil Niño Jesús, Madrid, Spain, [7]Hospital Universitari Vall D'Hebron, Barcelona, Spain

Background: Children with acquired severe aplastic anaemia (SAA) or refractory cytopenia of childhood (RCC) who relapsed or are refractory after conventional therapy and lack a suitable donor urgently need novel therapies. Haploidentical stem cell transplant (Haplo) offers a curative option, but the experience is limited. We review our experience with Haplo for this indication.

Methods: We carried on a multicentre retrospective review of paediatric patients treated with Haplo for relapsed or refractory SAA/RCC that lack suitable donors in Grupo Español de Trasplante de Medula Osea en Niños (GETMON)/ Grupo Español de Trasplante hematopoyetico (GETH) associated centres.

Results: Between 2017 and 2020, 9 patients (4 females/5 males) with refractory SAA (7) and RCC (2) were treated with Haplo in five centres. Most of them were heavily pretreated patients, refractory to immunosuppressive treatment (8/9) and eltrombopag (7/9). Iron overload was common, and most of the patients had ferritin above 1500 ng/ml. The median age at Haplo was 11.20 years (range, 8.99-16.94). All had good performance status with Lansky > 70. The median time from diagnosis to Haplo was 10.54 months (range, 2.14-56.61). Lymphodepletion strategies were post-transplant cyclophosphamide (3), α/β CD19 depletion (2), and CD45 RA depletion (4). Conditioning was based on fludarabine+cyclophosphamide combination in all SAA patients and was myeloablative with busulfan/treosulfan + fludarabine+thiotepa in RRC patients. In all SAA (7/9), reduced dose TBI or nodal irradiation was part of the conditioning. Mean CD34 cells dose was 5.62 x 10e6/kg (SD 2). All patients engrafted (medians: neutrophils day + 13 and platelets day + 13) and all reached transfusion independence (median 15 days, range, 10-82). Viral reactivation was common (6/9), and three patients developed post-transplant microangiopathy. 5/9 developed acute GVHD ≥ 2 (3 were grade 4) that evolved to chronic in 2 (1 severe). All patients achieved sustained full chimerism. One patient developed progressive receptor chimerism that was reverted with donor lymphocyte infusions (DLI) but developed severe autoimmune cytopenia requiring intensive immunosuppressive treatment. Two patients died of transplant-related complications (microangiopathy and respiratory failure). Overall survival was 76.2% (SD 14.8) with a median follow up of 36 months (range, 10-50). There was no secondary graft failure.

Conclusions:

- Haplo transplant offers a relatively successful therapeutic opportunity for refractory SAA/RIC, a subset of patients with limited curative alternatives.
- We observed excellent engrafting rates likely related to the addition of low dose radiotherapy to the conditioning.
- TRM was acceptable, and transplant-related microangiopathy was involved in the two cases. However, it is important to work forward to reducing transplant toxicity.
- We still face a significant rate of severe acute GVHD and, to a lesser degree, cGVHD that should be improved.
- The limited number of cases precludes us from assessing which Haplo platform is best suited for these patients.
- Longer follow-up is needed to assess QoL in patients treated with Haplo.

Disclosure: Nothing to declare

P520

Very low day-100 and 1-year transplant-related mortality (trm) in the pediatric hematopoietic cell transplantation program at king hussein cancer center

H. Hashem[1], D. Darabseh[1], R. Rihani[1], E. Khattab[1], M. Abu Shanap[1], A. Tbakhi[1], N. Hussein[1], I. Sultan[1]

[1]King Hussein Cancer Center, Amman, Jordan

Background: Survival at 100 days post-transplant is a critical point followed by transplant centers to assess the quality of their transplant program. Deaths within 100 days post-transplant that are not due to relapse or progression of disease are set to be transplant-related (TRM). TRM are presumed to be due to toxicities of pre-transplant conditioning (chemotherapy, radiation) and its associated complications.

Methods: We retrospectively collected data of all first allogeneic HCT at KHCC between 2003 to 2019. Data were collected for both HLA-matched related (MRD) and haploidentical HCT. We calculated TRM at day-100 and at 1 year post HCT.

Results: Over the period of 2003-2019, 629 first allogeneic HCTs were performed (547 MRD, 82 haploidentical). Referrals from surrounding countries account for 26% of all transplants (165/629). HCT was performed in 50% of patients for non-malignant disorders. Day 100 and 1 year TRM were very low at 2.2% (14/629) and 3.8% (24/629), respectively. We observed significant reduction in Day-100 and 1 year TRM over time (TRM at day-100 and 1 year decreased from 3% and 6% in 2003-2011 to 1.5% and 2.4% in 2012-2019). Causes of death were mostly sepsis (14/24), bleeding (4/24), GvHD (3/24)

Conclusions: In a high-volume single center experience where referrals from surrounding countries account for one forth of transplants, there was a very low day-100 and 1 year TRM compared to benchmarks. Our data suggest that a specific transplant infrastructure with a highly experienced team, staff training and retention, strict infection control measures, better venous access care, excessive pre transplant screening, and great vigilance in detecting and treating early infections, including sepsis and CMV likely contributes to a better transplant outcomes

Clinical Trial Registry: NA

Disclosure: Nothing to declare

P521

Favourable evolution of a hematopoietic stem cell transplant in a cbl syndrome patient after splenectomy and immunosuppression suspension

L. Català[1], S. Redondo[2], L. Garcia Marzo[1], A. Català[3], S. Brió[1], M. Torrent[1], N. Brun[1], I. Badell[1]

[1]Hospital de la Santa Creu I Sant Pau, IIB-Sant Pau and Universitat Autónoma de Barcelona, Barcelona, Spain, [2]Hospital de la Santa Creu i Sant Pau. IIB-Sant Pau and José Carreras Leukemia Research Institutes. Universitat Autónoma de Barcelona, Barcelona, Spain, [3]Hospital Sant Joan de Déu, Barcelona, Spain

Background: CBL syndrome is caused by germline heterozygous mutations in the CBL gene. It is a rare and heterogeneous genetic disease that clinically overlaps with the phenotypic features of Noonan syndrome. It presents as dysmorphic features, congenital heart defects and increased risk of cerebral vasculopathy. Paediatric management and treatment can vary from a "wait and watch" strategy to allogeneic hematopoietic stem cell transplantation (HSCT).

Methods: We report a paediatric patient diagnosed with CBL syndrome in 2020 from a Spanish tertiary University Hospital with cerebral vasculitis that underwent a HSCT.

Clinically she presented with persistent splenomegaly, thrombocytopenia, progressive episcleritis and persistent monocytosis. The diagnosis of CBL syndrome was carried out by whole exome sequencing (WES). Cerebral vasculitis was treated with steroids, cyclophosphamide and required ventriculoperitoneal shunting. In order to prevent the progression of the central nervous system vasculitis and the risk of developing juvenile myelomonocytic leukemia (JMML) the patient was submitted to an allogeneic bone marrow transplantation from an unrelated donor with 9/10 HLA compatibility. She received a conditioning regimen based on treosulfan, fludarabine, thiotepa and rabbit anti-thymocyte globulin. Tacrolimus and methotrexate were used as graft versus host disease (GVHD) prophylaxis.

Results: Amongst the multiple complications the patient presented severe hepatic veno-occlusive disease which led to a 10 day stay in the Intensive Care Unit. She also developed a *Pseudomona* septicaemia and GVHD grade III-IV with pulmonary, intestinal and hepatic involvement. Previous to the discharge she presented 100% chimerism in both lymphocytes and granulocytes.

Four months after transplant, transfusion dependency and severe neutropenia were observed together with hypersplenism and severe splenomegaly that complicated oral feeding; so a splenectomy was performed.

Despite that, the bicitopenia persisted and the patient lost the donor granulocyte chimerism. (See Figure 1). Immunosuppressive drugs were withdrawn. Bone marrow biopsy showed bilineal dysplasia and acquisition of t(1;11(q21;q23) with affection of KMT2A gene, but without monocytosis.

Within the following month after immunosuppression stop and splenectomy, the patient showed a spontaneous hematologic recovery. Total donor chimerism in myeloid and lymphoid series was observed, and a repeated bone marrow biopsy showed normalization of the three series with loss of the CBL1 and KMT2A mutations.

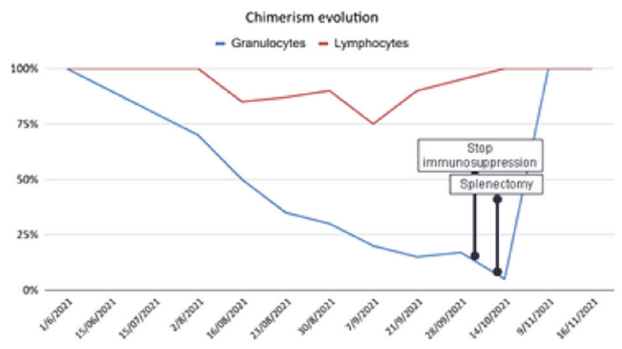


Figure 1

Conclusions: We would like to highlight the important role that has played in the haematological recovery of our patient both the immunospurression stop and the splenectomy.

CBL is a rare syndrome and very few transplant cases have been reported, but data suggests that HSCT not only can prevent developing JMML but it also improves cerebral vasculitis. Further investigation should be conducted on this topic.

Disclosure: Nothing to declare

P522

Nontuberculous mycobacterial infection among paediatric hematopoietic stem cell transplant recipients

M. Ascunce[1], Y. Mozo[1], T. Del Rosal[1], C. Toro[1], I. Falces[1], L. Sisinni[1], D. Bueno[1], D. Corral[1], F. Baquero[1], A. Pérez-Martínez[1,2]

[1]La Paz University Hospital, Madrid, Spain, [2]Universidad Autónoma de Madrid, Madrid, Spain

Background: Infections are one of the main causes of morbidity and mortality after hematopoietic stem cell transplant (HSCT). Incidence of nontuberculous mycobacteria (NTM) infections has raised during the past few years, especially in immunosuppressed hosts such as HSCT recipients in which cell-mediated immunity is compromised until immune reconstitution after HSCT occurs. Nevertheless, there are still few studies on the incidence, severity and management of NTM infections in paediatric HSCT recipients.

Methods: We performed a retrospective study of NTM infections in children with HSCT of all consecutive paediatric patients from 2013 to 2020 in a single-centre setting. We included HSCTs performed for both malignant and non-malignant diseases. Epidemiological and clinical data were recorded from the medical history.

Results: A total of 242 HSCT were performed during the study period, with 1.65% of NTM infection. 4 patients were included, three females and one male. The median age at the time of transplantation was 11 years (range, 5-16 years). The median time to infection after HSCT was 7 months (range, 3.5-11 months). All patients had graft-versus-host disease (GvHD) at the time of infection and 3 out of 4 had CD4 + counts <200/mm^3. The only patient with CD4 + above 200/mm3, was at that time admitted in the ICU with respiratory failure due to lung GvHD and severe infection caused by *E. Coli* and *Klebsiella sp*., and has received prolonged immunosuppressive therapy. All the infections in this series were caused by *Mycobacterium avium complex* (MAC): two by *M. avium* and two by *M. intracellulare*. Two patients developed a disseminated infection and the other two had a pulmonary disease. All patients received combined antimicrobial therapy without significant side effects. With a median follow-up of 4 months (range, 2-40 months), 50% of the patients are alive; none of the deaths was attributed to mycobacterial infection.

aGvHD: acute graft vs host disease; AML: acute myeloid leukemia; BAL: bronchoalveolar lavage; cGvHD: chronic graft vs host disease; gi: gastro-intestinal; haplo: haploidentical; HSCT: hematopoietic stem cell transplant; IEI: inborn error of immunity MDS: myelodysplastic syndrome; MMUD: mismatched unrelated donor; MUD: matched unrelated donor.

Conclusions: NTM infection is an infrequent but severe complication of HSCT in paediatric patients, affecting mainly those with impaired cell-mediated immunity. All patients in our series had active lung GvHD. The most frequent causative species is MAC.

Disclosure: Nothing to declare.

P523

Donor lymphocyte infusion post haematopoietic stem cell transplantation – fundeni clinical institute experience

C. Jercan[1,2], A.-M. Bică[2], A.-D. Marcu[2], I. Avramescu[2], L. Oprea[2], A. Purnavel[2], C. Călugăroiu[2], A. Ionete[2], C. Popa[1,2], A. Dragomirișteanu[3], I. Constantinescu[1,2], A. Colită[1,2]

[1]*Carol Davila University of Medicine and Pharmacy, Bucharest, Romania,* [2]*Fundeni Clinical Institute, Bucharest, Romania,* [3]*RNDVCSH, Bucharest, Romania*

Background: Allogeneic hematopoietic stem cell transplant (HSCT) is a curative approach for hematological malignancies and non-malignant diseases. Disease relapse is associated with poor prognosis and survival, therefore carefully post-HSCT monitoring is required. Donor lymphocyte infusions (DLI) are used preemptively for patients with mixed donor chimerism (MDC) to enhance the graft-versus-leukemia effect, for high-risk patients as a prophylactic measure to prevent relapse and in relapsed patients along/without salvage chemotherapy.

Methods: We performed a retrospective study to analyse pediatric patients with allo-HSCT and DLI procedures between February 2016 and November 2021, in Fundeni Clinical Institute. Patients' diagnosis was: acute myeloid leukemia (AML)–6/16, chronic juvenile myelomonocytic leukemia (JMML)-3/16, acute lymphoblastic leukemia (ALL)-5/16, non-malignant disease-2/16. Conditioning regimens used for HSCT were accordingly to the disease. All patients were monitored with chimerism evaluations at 1, 3, 6, 9, 12 months and before every DLI. Chimerism analysis was performed using short tandem repeats (STR) technique. MDC was considered if less than 100%. Patients were divided into 3 groups: preemptive (MDC), prophylactic (high-risk AML/ALL) and treatment for relapse. DLI was administered using escalating doses.

Results: We identified 16 patients, 13M:3F, who received 55 DLI. Median age at HSCT was 8.4 years, 3/16 patients with matched sibling donor, 2/16 with haploidentical donor(father), 8/16 with matched unrelated donor(MUD) and 4*/16 with mismatched MUD (1* previous haplo-HSCT). 6/16 received preemptive DLI (1 patient with 2 HSCT, DLI in both cases), 2/16 patients with prophylactic DLI and 8/16 patients received DLI at relapse. Median doses: 1x10^5/kg, 5x10^5/kg, 5 x10^5/kg, 1x10^6/kg and >1 x10^7/kg subsequent doses. Median donor chimerism at DLI was 48%, median days from transplant to first DLI was 86 days, median DLI administration was 2, for patients with preemptive DLI. 2/6 patients received Azacytidine, 1/6 patient developed graft-versus host disease (GvHD) post-DLI; 3/6 patients died due to disease progression, 1/6 died due to severe infections following graft loss, 2/6 are alive, one with 82% chimerism, 100% respectively after haplo-HSCT from father. In the prophylactic group 2/2 patients received Azacytidine. One patient with 100% donor chimerism, the other 97% before DLI. Median time from transplant to DLI was 324 days, with a median of 3 DLI. No GvHD, both are alive, with 100% donor chimerism in first case, 98% respectively. In the treatment group, DLI was combined with Azacytidine in 3/8 cases, chemotherapy followed by DLI in 4/8 cases, 1/8 without any salvage treatment. Median time to DLI was 416.5 days, with a median of 3 DLI. GvHD occurred in 3/8 patients. 6/8 patients died due to disease progression, 2/8 patients are alive, with 100% donor chimerism.

Conclusions: Overall survival (OS) was 37.5%. Patients with preemptive DLI had 33,33% OS, patients in treatment group had 25% OS, compared to the prophylactic group (OS 100%). GvHD appeared in 25% of patients. In our study, prophylactic DLI showed better results when compared to both preemptive and treatment DLI, though the number of patients is low. Prophylactic DLI should be considered in high-risk patients to prevent relapse after HSCT. Close monitoring is needed for these patients.

Disclosure: No disclosures.

P524

Modified johns hopkins conditioning protocol for non-malignant haploidentical stem cell transplantation in children

C.S. Ranjit Kumar[1], A. Aribandi[1]

[1]*American Oncology Institute, Hyderabad, India*

Background: The conditioning regimens in pediatric haploidentical transplants not uniform across the world, the results of various conditioning regimens were variable with significant number of toxicities and economic burden in the low and middle income countries, here we are presenting our two case scenarios with different diagnosis using similar conditioning regimen, achieved complete donor chimerism and without any viral reactivation which is a major concern and has financial implication.

Methods: Here we are presenting two case scenarios using same conditioning protocol – Hyper IgE syndrome with homozygous DOCK 8 mutation and Congenital Amegakaryocytic thrombocytopenia[CAMT] with cMPL mutation. We used modified Johns hospkins protocol – using Fluderabine [150mg/m^2], Cyclophosphamide [14.5mg/kg for 2days], Busulfan [3.2mg/kg/day for 3days] with TBI[2Gy],with Post transplant cyclophosphamide[PT/Cy] on day +3 and +4 along with sublingual Tacrolimus and Mycophenolate mofetil as GVHD prophylaxis. We also used N acetyl cysteine infusion during PT/Cy for reducing the risk of mucositis. Two children followed for minimum 100days [range 100days-270days].

Results: Two children attained engraftment neutrophil on Day +16 in hyper IgE syndrome and Day +12 in CAMT, Platelet engraftment on Day+19 in Hyper IgE syndrome and Day+13 in CAMT, Maximum mucositis observed was Grade 2,No microbiologically proven infections, we did not observed Cytokine release storm, two children attained complete donor chimerism on Day+30 of transplant. No viral reactivations were observed, monitored for Cytomegalovirus and Urine for BK virus weekly. Hyper IgE syndrome child IgE level came to normal by Day+180 [2600IU/ml to 340IU/ml].No GVHD was observed in the two children.

Conclusions: In Low and middle income countries viral reactivation is a major challenging in haploidentical stem cell transplantation and it has lot of financial burden on the families, minor modification in the conditioning regimen results in reduction of toxicities and overall outcome would improve, ours was small observational study need to be proved in larger multicentre study.

Disclosure: nothing to declare

Solid Tumours

P525

Autologous hematopoietic stem cell transplantation using 18 mCI/Kg ^{131}i-MIBG and high-dose chemotherapy in high-risk neuroblastoma: A single-center experience

A.A. Hamidieh[1,2], P. Naji[1], M. Behfar[1,2], R. Mohseni[1], E.S. Makki Talehjerdi[1], F. Jafari[1], Z. Nikfetrat[1,2], L. Hejazipour[1,2], L. Jafari[1]

[1]*Pediatric Cell and Gene Therapy Research Center, Gene, Cell and Tissue Research Institute, Tehran University of Medical Sciences,*

Tehran, Iran, Islamic Republic of, [2]Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran, Islamic Republic of

Background: Neuroblastoma (NB) is a sympathetic nervous system malignancy, which predominantly affects children. It has a high relapse rate and causes 15% of cancer mortality in pediatrics. The high-risk NB remains one of the most challenging pediatric solid tumors. Autologous hematopoietic stem cell transplantation (Auto-HSCT) has a significant improvement in the treatment of these patients. Metaiodobenzylguanidine (MIBG) is used as a targeted therapeutic agent, which currently is conducted as part of clinical trials with an increasing number of centers participating with different doses of ^{131}I-MIBG. This study reports the Auto-HSCT outcomes in NB pediatrics, which undergo 18 mCi/Kg ^{131}I-MIBG therapies at Children's Medical Center, the largest pediatric Iranian hospital.

Methods: We report on twenty-three relapsed or refractory NB patients referred to Children's Medical Center; for Auto-HSCT from February 2017 to October 2021. All transplants utilized PBSC sources. All patients received ^{131}I-MIBG (18 mCi/Kg) at day -21, besides a conditioning regimen consisting of Carboplatin (1500 mg/m^2) and Vp16 (1200 mg/m^2) for five consecutive days from day -7. Furthermore, Melphalan (210 mg/m^2) was administered for three consecutive days from day -7.

Results: Eight females and fifteen males NB patients with the mean age at the Auto-HSCT time was six years (range, 2 - 8 years). The mean number of harvested MNC and CD34 + was 6×10^8 cells/kg (range, 2.3 - 14) and 3.4×10^6 cells/kg (range, 0.3 – 8.5), respectively. The median time to neutrophil and platelet engraftment was 12 and 8 days, respectively. With an average 15 months' follow-up (range, 0.5 - 49), 60% overall survival (OS) and 43.4% disease-free survival (DFS) rates were achieved. The death cause was relapsed and transplant-related; infections and VOD; in seven and two patients, respectively.

Conclusions: Different studies have suggested an efficient role of MIBG in NB patients as a pre-transplant conditioning regimen. These patients might rescue with high-dose conditioning regimens alongside the therapeutic MIBG. Finally, our study demonstrates the 18 mCi/Kg ^{131}I-MIBG dose has a similar survival rate without more transplant-related complications, compared with the previous one using a lower 131I-MIBG dosage.

Disclosure: Nothing to declare.

STEM CELL DONOR

P526

Donor KLRC2 deletion genotype is associated with upregulation of alloreactivity pathways with increased GVHD and nrm following t-replete haploidentical HCT

S.R. Jaiswal[1,2,3], A. Saifullah[2], J. Arunachalam[1], M. Soni[2], S. Chakrabarti[1,2]

[1]Manashi Chakrabarti Foundation, Kolkata, India, [2]Dharamshila Narayana Super-speciality Hospital, Research & Development, New Delhi, India, [3]Amity University, Noida, India

Background: NKG2C is an activating receptor expressed on adaptive NK (ANK) cells, encoded by the KLRC2 gene on chr 12p13.2. Early reconstitution of ANK cells has been shown to reduce relapse following both cord blood and haploidentical HCT. In this study, we analysed the impact of donor KLRC2 genotype on transplant outcomes following PTCy-based haplo-HCT.

Methods: 100 patients with malignant (n = 72) and non-malignant(n = 28) diseases were included in the study. The donors were categorised based on KLRC2 sequence as KLRC2 wildtype (wt/wt)[D-KLRC2wt group] and KLRC2 deletion homozygous (del/del) or heterozygous (del/wt) [D-KLRC2del group]. All donors and recipients were CMV seropositive. Gene expression profiling by RNA-seq was carried out on PBMC samples from both donor groups.

Results: Twenty-eight out of 100 donors had KLRC2 deletion (del/wt-26; del/del-2). Even though both groups were similar in pre-transplant, graft characteristics and engraftment kinetics, D-KLRC2del group had increased CMV reactivation (85.7% Vs 49%), CMV viral load (25.8 vs 5.7 x 10^3/ml) as well as persistence (41 days Vs 25 days), [$p < 0.001$].

Acute GVHD gr 2-4 was witnessed only in the D-KLRC2del group (27% vs 0, $p = 0.0001$), with a trend towards higher chronic GVHD as well (25.4% vs 10.3%, $p = 0.09$). Overall non-relapse mortality was 9.6%, but this was 25% in the D-KLRC2del group vs 3.4% in D-KLRC2wt group ($p = 0.0001$), with a marked impact on overall survival (63.4% vs 92.8%, $p = 0.0001$). There was no impact of KLRC2 genotype of the patient on outcomes.

Even though the median donor-ANK (D-ANK) level was lower in D-KLRC2del group (15.5 vs 23%, $p = 0.03$), the ANK levels varied widely (0-67%). D-ANK cells and not D-KLRC2del had the strongest impact on relapse rate (24.4 vs 8.6%), [HR-0.8(95%CI-0.7-0.9) $p = 0.0001$]. Based on recursive partitioning to determine the optimal cut point for absolute counts of ANK cells, relapse was 2.2% in those with D-ANK > 14.5% vs 72.6% in those below 14.5% ($p = 0.0001$).

To understand this dichotomy in the impact of D-KLRC2del genotype on GVHD and NRM, but not relapse, we studied the differential gene expression (with a cut-off for p value of 0.05) based on transcriptome analysis between D-KLRC2wt with D-KLRC2del groups. KLRC1 (NKG2A), SYK, FCER1G, EAT2 and NKp30 were upregulated in the D-KLRC2del group with downregulation of BCL11B, KLRC2, KLRC3 & KLRC4, indicating downregulated ANK and ADCC pathways. However, there was significant upregulation of alloreactive and inflammatory pathways in D-KLRC2del group (NFKB, NLRP3, TLR, TNF-α, IL12, IL17, IL18, IL33, CD28, CD86 and T-BET, JAK2, MAPK), along with downregulation of the regulatory pathways (TGF-β, FOXP3, STAT5, IL-10, IL-12RA, CD73).

Conclusions: Our findings suggest a non-redundant role for adequacy of ANK cells in maintaining homeostasis between pro- and anti-inflammatory alloreactive pathways, along with an anti-leukemia potential independent of T cell derived alloreactivity. While KLRC2 del donor strongly correlated with acute GVHD and NRM, but not relapse, KLRC2wt donor with high D-ANK was associated with low incidences of GVHD, NRM as well as relapse, suggesting that incorporation of KLRC2 genotype and ANK cell repertoire in the algorithm for selection of haploidentical donors, might improve transplant outcomes.

Clinical Trial Registry: NA

Disclosure: Nothing to declare

P527

HLA-mismatched unrelated donor transplantation with post-transplant cyclophosphamide versus HLA-haploidentical transplantation in patients with active acute myeloid leukemia

F. Baron[1], M. Labopin[2], J. Tischer[3], F. Ciceri[4], A.M. Raiola[5], D. Blaise[6], S. Sica[7], J. Vydra[8], R. Fanin[9], J.L. Diez-Martin[10], C.E. Bulabois[11], F. Stölzel[12], A. Busca, P. Jindra[13], Y. Koc[14], P. Chevallier[15], E. Forcade[16], W. Rösler[17], J. Passweg[18], A. Kulagin[19], A.M. Carella[20], C. Simand[21], A. Bazarbachi[22], P. Pioltelli[23], A. Nagler[24], M. Mohty[25]

[1]University of Liege, Liege, Belgium, [2]EBMT Paris Study Office/CEREST-TC, Paris, France, [3]Klinikum Grosshadern, Munich, Germany, [4]IRCCS

San Raffaele Scientific Institute, Dept. of Hematology, Milan, Italy, [5]Ospedale San Martino, Dept. of Haematology II, Genova, Italy, [6]Programme de Transplantation & Therapie Cellulaire, Centre de Recherche en Cancérologie de Marseille, Institut Paoli Calmettes, Marseille, France, [7]Universita Cattolica S. Cuore, Istituto di Ematologia, Rome, Italy, [8]Institute of Hematology and Blood Transfusion, Prague, Czech Republic, [9]Azienda Ospedaliero Universitaria di Udine, Division of Hematology, Udine, Italy, [10]Hospital Gregorio Marañón, Sección de Trasplante de Medula Osea, Madrid, Spain, [11]CHU Grenoble Alpes - Université Grenoble Alpes, Service d`Hématologie, CS 10217, Grenoble, France, [12]Universitätsklinikum Carl Gustav Carus Dresden, Medizinische Klinik und Poliklinik I, TU Dresden, Dresden, Germany, [13]Charles University Hospital, Dept. of Hematology/Oncology, Pilsen, Czech Republic, [14]Medicana International Hospital Istanbul, Bone Marrow Transplant Unit, Istanbul, Turkey, [15]CHU Nantes, Nantes, France, [16]CHU Bordeaux, Hôpital Haut-Leveque, Pessac, France, [17]University Hospital Erlangen, Dept. of Internal Medicine 5, Erlangen, Germany, [18]University Hospital Hematology, Basel, Basel, Switzerland, [19]First State Pavlov Medical University of St. Petersburg, Raisa Gorbacheva Memorial Research Institute for Paediatric Oncology, Hematology, and Transplantation, St Petersburg, Russian Federation, [20]IRCCS, Casa Sollievo della Sofferenza, Dept. of Hemato-Oncology, Stem Cell Transplant Unit, Sgiovanni Rot, Italy, [21]Hematology, ICANS, University Hospital, Strasbourg, France, [22]American University of Beirut Medical Center, Beirut, Lebanon, [23]Ospedale San Gerardo, Clinica Ematologica dell`Universita Milano-Biocca, Monza, Italy, [24]Division of Hematology and Bone Marrow Transplantation, The Chaim Sheba Medical Center Tel Hashomer, Ramat Gan, Israel, [25]Saint Antoine Hospital, Dept. of Hematology, Paris, France

Background: HLA-haploidentical allogeneic hematopoietic stem cell transplantation (Haplo-HCT) is frequently used as treatment for patients with active acute myeloid leukemia (AML). Here, we investigated whether 9/10 HLA-mismatched unrelated donor transplantation (MMUD-HCT) with post-transplant cyclophosphamide (PTCy) is an adequate alternative.

Methods: This is a retrospective study from the acute leukemia working party of the EBMT. Inclusion criteria consisted of adult patients, first HCT with a Haplo donor or MMUD between 2010 and 2020 using PTCy as graft-versus-host disease (GVHD) prophylaxis, and primary refractory or relapsed disease. MMUD patients were pair-matched 1 to 2 with Haplo-recipients. Matching criteria included status at transplantation, conditioning intensity, Karnofsky performance score, and age at transplantation.

Results: A total of 73 MMUD patients met the inclusion criteria. Their data were compared to those of 146 Haplo patients (out of 762 patients meeting the inclusion criteria) in a matched-pair analysis. Median follow-up was 27 months in MMUD patients and 34 months in Haplo recipients. Two-year incidences of relapse and non-relapse mortality (NRM) were 40% and 18% in MMUD patients, respectively, versus 50% ($P = 0.23$) and 24% ($P = 0.3$) in Haplo recipients. Two-year leukemia-free survival (LFS) and overall survival (OS) was 42% and 46% in MMUD recipients, respectively, versus 26% ($P = 0.1$) and 28% ($P = 0.061$) in Haplo-patients.

Conclusions: In AML patients with active disease at transplantation, MMUD-HCT results in at least comparable outcomes to Haplo-HCT when PTCy is applied. These observations could serve as a basis for a phase III trial comparing these two donor types in patients with active AML at transplantation who lack an HLA-matched related or unrelated donor.

Disclosure: No COI to disclose

P528

Excellent 3-year survival in recipients of mismatched unrelated donor transplants using post-transplant cyclophosphamide: Longer term outcomes of a national marrow donor program-sponsored prospective clinical trial

B. Shaw[1], A.M. Jimenez-Jimenez[2], L. Burns[1], B. Logan[3,1], F. Khimani[4], B. Shaffer[5], N. Shah[6], A. Mussetter[7], X.-Y. Tang[1], J. McCarty[8], A. Alavi[9], N. Farhadfar[10], K. Jamieson[11], N. Hardy[12], H. Choe[13], R. Ambinder[14], C. Anasetti[4], M.-A. Perales[5], S. Spellman[7], A. Howard[7], K. Komanduri[2], L. Luznik[14], M. Norkin[15], J. Pidala[4], V. Ratanatharathorn[9], D. Confer[7], S. Devine[7], M. Horowitz[1], J. Bolaños-Meade[14]

[1]CIBMTR® (Center for International Blood and Marrow Transplant Research), Medical College of Wisconsin, Milwaukee, United States, [2]Sylvester Comprehensive Cancer Center, University of Miami, Miami, United States, [3]Division of Biostatistics, Institute for Health and Equity, Medical College of Wisconsin, Milwaukee, United States, [4]H. Lee Moffitt Cancer Center & Research Institute, Tampa, United States, [5]Adult Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, United States, [6]Medical College of Wisconsin, Milwaukee, United States, [7]CIBMTR® (Center for International Blood and Marrow Transplant Research), National Marrow Donor Program®/Be The Match®, Minneapolis, United States, [8]Massey Cancer Center Bone Marrow Transplant Program, Virginia Commonwealth University, Richmond, United States, [9]Blood and Marrow Stem Cell Transplant Program, Karmanos Cancer Institute/ Wayne State University, Detroit, United States, [10]Division of Hematology/Oncology, University, University of Florida College of Medicine, Gainesville, United States, [11]University of North Carolina Hospitals, Chapel Hill, United States, [12]Greenebaum Cancer Center, University of Maryland, Baltimore, United States, [13]James Comprehensive Cancer Center, The Ohio State University Wexner Medical Center, Columbus, United States, [14]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, United States, [15]Baptist MD Anderson Cancer Center, Jacksonville, United States

Background: The use of Post-Transplant Cyclophosphamide (PTCy) as Graft Versus Host Disease (GVHD) prophylaxis has resulted in reductions in GVHD and improved outcomes in allogeneic hematopoietic cell transplant (HCT) using mismatched related donors.

Methods: We performed a multi-center phase II prospective clinical trial using PTCy in mismatched unrelated donors (MMUD). The study met its primary endpoint of >65% overall survival (OS) at 1 year, with an OS of 76% [Shaw et al, JCO, 2021]. Here we report the 3-year outcomes in the study cohort.

Results: 80 patients (40 each receiving myeloablative (MAC) or reduced intensity conditioning (RIC)) were enrolled and transplanted between December 2016-March 2019. The median patient age was 52 (18-70), and 48% were from racial/ethnic minority groups. 95% of patients in the MAC cohort were transplanted for acute leukemia/MDS, compared to 53% in the RIC cohort (the remainder having lymphoma, CLL or non-hodgkins lymphoma). 34% of patients had a KPS < 90 and the HCT-CI was >2 in 54%. HLA match was 4-6/8 in 39% of transplants (43% in RIC, 39% in MAC) and 7/8 in 61%. Median follow up (set date: September 2021) is now 34 months (range 12-46) in RIC and

36 months (range 18-49) in MAC. Three-year outcomes are shown in Table 1. OS in the RIC cohort was particularly good at 70%. Non-relapse mortality was 15%. Rates of chronic GVHD (cGVHD) were low at 20% for all grades and 5% for severe cGVHD, with a relapse rate of 29%. GVHD-/relapse-free survival (GRFS) was 44%. Although 3-year survival in the MAC cohort remained acceptable at 62%, rates of relapse were high at 51%. Non-relapse mortality was 10%. cGVHD occurred in 38% of patients, with 13% reporting severe disease. GRFS in this cohort was correspondingly low at 17%. OS in the 7/8 cohort was 63% and 71% in the 4-6/8 cohort.

	MAC (N = 40)		RIC (N = 40)	
Outcomes	**N (at risk)**	**Prob (90% CI)**	**N (at risk)**	**Prob (90% CI)**
Overall survival	11	62.4 (49.5-74.5)%	11	69.6 (55.8-81.8)%
Non-relapse mortality	9	10 (3.5-19.2)%	9	14.7 (5.7-26.9)%
Relapse	9	50.5 (36.3-64.7)%	9	29.4 (17.7-42.7)%
Progression-free survival	8	39.5 (26.4-53.4)%	8	55.9 (41.6-69.8)%
cGVHD	6	37.5 (25.2-50.6)%	6	20 (10.6-31.5)%
Severe cGVHD	8	12.5 (5.2-22.4)%	12	5 (0.9-12.2)%
GRFS	3	16.9 (8.2-27.8)%	5	44.3 (30.6-58.5)%

Conclusions: Outcomes for patients receiving a MMUD HCT using PTCy-based GVHD prophylaxis remain very good with follow up at 3 years post-transplant. Patients receiving RIC in particular have excellent survival and very low rates of cGVHD. Use of more mismatched donors (<7/8) was not associated with worse outcomes, providing early reassurance that access to transplant can be safely expanded to patients with no 7-8/8 matched donors. While cGVHD and OS remained acceptable in the MAC cohort, the relapse rate was disappointingly high. The predominance of acute leukemia patients in the MAC cohort may explain some of the difference in relapse rate between cohorts, warranting further study and analysis.

Clinical Trial Registry: ClinicalTrials.gov
NCT02793544

Disclosure: Bronwen E. Shaw - OrcaBio, Mallindrodt.

Antonio Martin Jimenez-Jimenez - Research funding from AbbVie.

Stephen R. Spellman -NMDP/Be The Match

Joseph Pidala - Compensation: Consulting and advisory board membership – Syndax, CTI Biopharma, Amgen

Miguel-Angel Perales - Compensation: •Member, Scientific Advisory Board: NexImmune; Ad hoc Advisory Board: Abbvie, Astellas, Celgene, Bristol-Myers Squibb, Incyte, Karyopharm, Kite/Gilead, Miltenyi Biotec, MorphoSys, Nektar Therapeutics, Novartis, Takeda; •Consulting: Merck, Omeros; •Member, DSMB: Cidara Therapeutics, Medigene, Servier: •Research Funding: Incyte (clinical trial), Kite/Gilead (clinical trial), Miltenyi (clinical trial), Novartis (clinical trial)

Payments: > $5,000 for the following; Ad hoc Advisory Board: Bristol-Myers Squibb, Incyte, Kite/Gilead, Novartis; •Consulting: Merck, Omeros; •Member, DSMB: Cidara Therapeutics; •Research Funding: Incyte (clinical trial), Kite/Gilead (clinical trial), Miltenyi (clinical trial), Novartis (clinical trial); Relationships: Member, Board of Directors NMDP

Steve Devine - Full time employee of NMDP/Be The Match, Research support from Magenta, Vor Bio, Orca Bio, Advisor to Janssen, BMS, Sanofi, Orca, Vor Bio

P529

Analysis of unrelated allogeneic hsc donors who tested positive for sars-cov-2 at different donation stages, and the effect on donation outcomes: A donor registry experience

R. Maniusyte[1], G. O'Brien[1], C. Anthias[1], R. Danby[1], A. O'Leary[1], C. Adams-Fairhurst[1]

[1]*Anthony Nolan, London, United Kingdom*

Background: In response to COVID-19 pandemic WMDA, EBMT, BSBMTCT and National Institute of Clinical Excellence (NICE) published recommendations to test donors for SARS-CoV-2 [1-4]. The exact timing and frequency of testing remains in debate and practice varies between donor registries.

This study aims to illustrate COVID-19 testing practice in donors from the Anthony Nolan (AN) register, determine the incidence of COVID-19 within actively donating AN donors, and analyse the delay in donor harvesting and HSC graft infusion.

Methods: AN donors between the 1st October 2020 to 30th September 2021 who had a positive SARS-CoV-2 PCR test at any stage of their donation pathway were included in this retrospective analysis. PBSC, BM and DLI donations were included. Donor age, type of donation, estimated and actual collection, and graft infusion dates were recorded.

Donors were routinely tested for SARS-CoV-2 at medical, and either pre-starting GCSF/pre-admission for BM harvest or before the recipient started conditioning if the donation was to be infused fresh. Donors were also tested for SARS-CoV-2 if they had symptoms or had a contact with a person with COVID-19 infection. AN initially recommended a 3-month deferral when a donor tested SARS-CoV-2 positive, which was reduced to 28 days.

Results: During the study period, 30 donors tested positive for SARS-CoV-2. Six were at verification typing (VT), 16 at pre-medical, 1 at medical, 5 post-medical and 2 on the day of donation (Figure 1A). The median age of the SARS-CoV-2 positive donors were 22 years (range, 19-52).

83% (n = 25) of the SARS-CoV-2 positive donors had been requested for PBSC collections; 3 being subsequent requests. Three requests were for DLI donations and two for BM harvests.

Transplant centres (TC) sought alternative donors in 12 cases and 3 donations were cancelled due to the recipient deterioration. 15 donors who tested positive for SARS-CoV-2 successfully donated after a deferral period (Figure 1B).

In three cases, the collected cells were not infused: on two occasions recipients died and in one case the cells were discarded because the donor had COVID-19 on the day of donation.

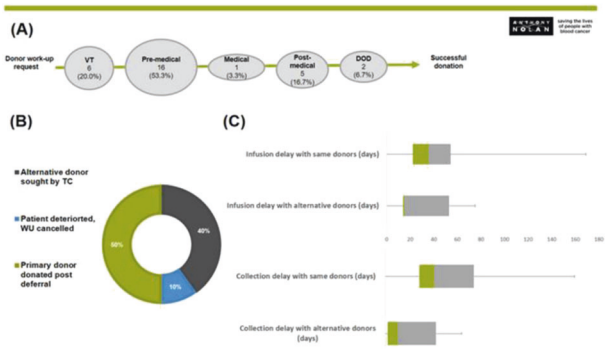
The median delay from the initial proposed cell harvest date was 10.5 days (range, 0-68) when alternative donor was requested and 40 days (range, 0-155) when the same donor donated after the deferral period. The median delay in graft infusion was 15 days (range, 0-75) with alternative donors versus 35.5 days (range, 0-169) days when proceeding with the same donor (Figure 1C).

Figure 1.

(A) Number or donors who tested COVID19 positive at different stages of donation process. VT – verification typing, DOD – day of donation.

(B) Outcomes of the deferred donations due to positive SARS-CoV-2 donor test. TC – transplant centre, WU – work-up

(C) Delay of the HSC graft collection and infusion in days when alternative and the same donors donated.



Conclusions: The incidence of COVID-19 positive donors during active donation stages was 4.7%. Although overall numbers were small, when TC sought alternative donors there was a shorter delay to both HSC collection and infusion. This study highlights the need for robust back up donor.

Clinical Trial Registry: Not applicable

Disclosure: None of the authors have any conflict of interest to declare.

P530

Myeloablative conditioning and peripheral blood stem cells from haploidentical donors offers comparable outcomes to matched donors in allogeneic transplantation for haematological malignancies

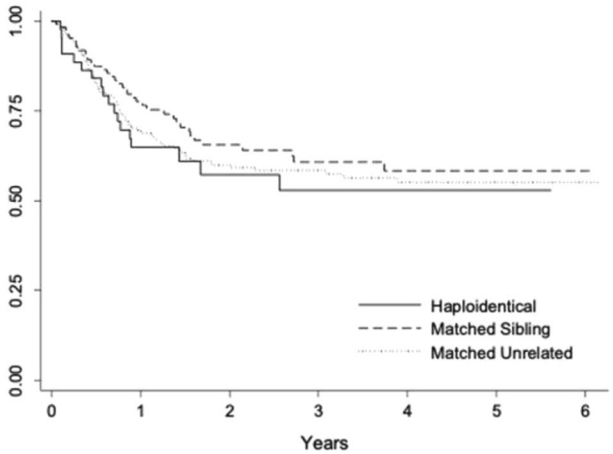
K. Paulson[1,2], G. Popradi[3], D. Wall[4], O. Bucher[2], G. Cuvelier[1], P. Lambert[2], G. Musto[2], E. Richardson[2], M. Seftel[5], D. Szwajcer[1], A. Daly[6]

[1]University of Manitoba, Winnipeg, Canada, [2]CancerCare Manitoba, Winnipeg, Canada, [3]McGill University Health Center, Montreal, Canada, [4]University of Toronto, Toronto, Canada, [5]Canadian Blood Services, Ottawa, Canada, [6]University of Calgary, Calgary, Canada

Background: For patients without matched donors, the use of haploidentical donors with post-transplant cyclophosphamide (PTCy) is often considered. Most studies evaluating this combination have used bone marrow (BM) grafts with reduced intensity conditioning (RIC). The safety and relative efficacy of haploidentical donor transplants performed using peripheral blood stem cells (PBSC) and myeloablative conditioning (MAC) regimens remains less clear.

Methods: We conducted a prospective cohort study at three transplant centres in Canada using the Cell Therapy Transplant Canada registry as a data collection tool. Patients without a matched donor undergoing transplant for a hematologic malignancy were eligible. A CD34 dose of 3-8x10^6/kg was infused following a MAC regimen of fludarabine (200 mg/m2) and busulfan (12.8 mg/kg) (Flu/Bu). At the discretion of the investigator, low dose total body irradiation could be added (200 or 400 cGy). GVHD prophylaxis consisted of PTCy (50 mg/kg on days +3 and +4) in combination with MMF (days 5-35) and tacrolimus (days 5-100). To determine how outcomes compared to matched sibling donors (MSD) and matched unrelated donors (MUD), a comparison was done with controls from the CTTC registry. To provide a more homogenous cohort, this analysis was restricted to patients undergoing transplant for acute myeloid leukemia (AML).

Results: Thirty-four patients were accrued in the prospective cohort, with diagnoses of acute myeloid leukemia (n = 24), acute lymphoblastic leukemia (n = 7), or myelodysplastic syndrome (n = 3). The median age was 55 years (range 10-70). Of these, 52% were men, with a median KPS of 90 (range 80-100). The median HCT-CI was 0, with 4 patients having a HCT-CI of greater than 3. The protocol was well tolerated, with a cumulative incidence of non-relapse mortality of 19% at 2-years and 1 case of veno-occlusive disease (which resolved with therapy). The cumulative incidence of relapse at 2-years was 22%. The incidence of grade III/IV acute GVHD was 6%, and chronic extensive GVHD was 29%. Overall survival at 2-years was 63%. Based on the success of this protocol, it was adapted as the standard for patients undergoing haploidentical transplant at these centres, and an additional 20 patients with AML were transplanted. These 44 patients with AML (24 on the original study, 20 in the expansion cohort) were compared to 128 MSD transplants and 267 MUD transplants done with similar transplant characteristics (AML, MAC Flu/Bu, and PBSC), with data obtained from the CTTC registry. In multivariate analysis, adjusting for age, HCT-CI, KPS, and disease risk (by ELN), no difference in overall survival (OS), disease free survival (DFS), relapse rate, or non-relapse mortality was found between donor sources (Figure 1). Older age was a predictor of inferior DFS and NRM, HCT-CI was associated with NRM, and high-risk disease was associated with a higher relapse rate.



Conclusions: The use of PBSCs from haploidentical donors with MAC appears to be safe and effective, with outcomes comparable to MSD and MUDs, and low rates of acute and chronic GVHD. The feasibility of this combination provides further evidence supporting the use of haploidentical donors outside the previously studied RIC/BM setting.

Clinical Trial Registry: NCT02504047

Disclosure: Nothing to declare.

P531

Personalized strategy for allogeneic stem cell transplantation guided by machine learning: A real-world data analysis of the japanese transplant registry unified management program

H. Okamura[1], H. Nakamae[1], M. Nakamae[1], D. Kabata[1], H. Yoshida[1], A. Shintani[1], N. Uchida[2], N. Doki[3], T. Fukuda[4],

Y. Ozawa[5], M. Tanaka[6], K. Ikegame[7], T. Eto[8], M. Sawa[9], T. Kimura[10], J. Kanda[11], Y. Atsuta[12], M. Hino[1]

[1]Osaka City University, Osaka, Japan, [2]Federation of National Public Service Personnel Mutual Aid Associations Toranomon Hospital, Tokyo, Japan, [3]Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan, [4]National Cancer Center Hospital, Tokyo, Japan, [5]Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Nagoya, Japan, [6]Kanagawa Cancer Center, Yokohama, Japan, [7]Hyogo College of Medicine Hospital, Nishinomiya, Japan, [8]Hamanomachi Hospital, Fukuoka, Japan, [9]Anjo Kosei Hospital, Anjo, Japan, [10]Japanese Red Cross Kinki Block Blood Center, Ibaraki, Japan, [11]Kyoto University, Kyoto, Japan, [12]Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya, Japan

Background: Developments of allogeneic hematopoietic stem cell transplantation (allo-HSCT) procedures such as reduced-intensity conditioning and use of alternative donor sources have expanded eligibility. On the other hand, it has become more complicated to plan the optimal patient-specific strategy among various allo-HSCT procedures. We retrospectively investigated the prognostic effects of a personalized allo-HSCT procedure recommended by machine learning models.

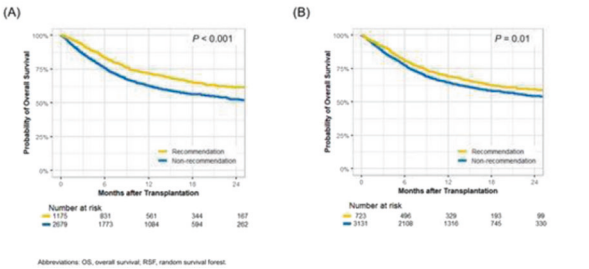
Methods: We analyzed patients who first underwent allo-HSCT between 2009 and 2018 in Japan and used random survival forest (RSF) and DeepSurv as machine learning models. First, we classified ten allo-HSCT procedures based on conditioning intensity, donor source, and post-transplant cyclophosphamide (PTCY) (Table). Second, we split the entire cohort into training and test cohorts chronologically according to the year of allo-HSCT. Third, we trained machine learning predictive models for overall survival (OS) after allo-HSCT. Age, disease, disease status, performance status, hematopoietic cell transplantation-specific comorbidity index (HCT-CI), cytomegalovirus serostatus, and ten allo-HSCT procedures were used as prognostic variables. Fourth, we calculated the predictive probabilities of 1-year OS for ten allo-HSCT procedures in each test patient. Fifth, upon imposing restrictions on donor selection for the recommendation of machine learning because some donors were unavailable depending on the patients in clinical practice, we defined the procedure with the highest predictive probability of 1-year OS as the allo-HSCT procedure recommended by machine learning. Sixth, we divided the test cohort into recommendation and non-recommendation groups according to whether the actual allo-HSCT procedure was concordant with that recommended by machine learning. Finally, we compared OS between the recommendation and non-recommendation groups.

Table. Classification of allo-HSCT procedures.

1	Reduced-intensity conditioning	MRD	Non-PTCY
2		MUD	
3		UCB	
4		Haplo	PTCY
5			Non-PTCY
6	Myeloablative conditioning	MRD	
7		MUD	
8		UCB	
9		Haplo	PTCY
10			Non-PTCY

Results: In total, 17,449 patients were analyzed (training cohort, 13,595; test cohort, 3,854). In a log-rank test, the recommendation groups showed higher OS than the non-recommendation groups in both machine learning ($P < 0.001$ for RSF, $P = 0.01$ for DeepSurv, Figure). In multivariate analysis, the recommendation group using RSF was an independent favorable prognostic factor for OS, but not using DeepSurv (HR: 0.84, $P = 0.01$ for RSF; HR: 0.92,$P = 0.42$ for DeepSurv). Furthermore, in the subgroup transplanted from alternative donors, the recommendation group using RSF was independently associated with a significantly better prognosis than the non-recommendation group.

Figure. Kaplan–Meier OS curves of the recommendation and non-recommendation groups in RSF (A) and DeepSurv (B)



Abbreviations: OS, overall survival; RSF, random survival forest.

Conclusions: These findings suggest that the patient-specific recommendation of the allo-HSCT procedure using RSF may improve prognosis. A further prospective randomized controlled trial is required to confirm the clinical value of the intervention based on machine learning models in the allo-HSCT field.

Disclosure: Ayumi Shintani received honorarium from Shionogi.

Naoyuki Uchida received honorarium from Chugai, Astellas, Otsuka, Sumitomo Dainippon, and Novartis.

P532

Donor specific anti-HLA (DSA) antibodies in HSCT and desensitization strategies

U. La Rocca[1], M.P. Perrone[2], A. Piciocchi[3], P. Cinti[2], W. Barberi[1], L. Laurenti[2], P. Gesuiti[2], M. Shafii Bafti[2], M. Gozzer[2], C. Cavallari[2], L. Quattrocchi[1], F. Gentilini[1], C. Masucci[1], R. Ricci[1], S. Coluzzi[2], A. Angeloni[2], M. Martelli[1], A.P. Iori[1]

[1]Sapienza University, Hematology, Rome, Italy, [2]Sapienza University, Immunohematology and Transfusion Medicine, Rome, Italy, [3]GIMEMA Foundation, Rome, Italy

Background: In the setting of mismatched-hematopoietic stem cells transplantation (mmHSCT), the detection of antibodies directed against donor-specific HLA allele(s) or antigen(s) (DSA) represents a barrier for stem cell engraftment. Thus, it is necessary to plan an immunosuppressive strategy, or to select an alternative donor. This prospective study aimed at evaluating the efficacy of our strategy for testing DSAs and the efficacy of the desensitization strategy (DS) employed in patients candidates for a mmHSCT between November 2017 and November 2020 at Sapienza University of Rome.

Methods: Anti-HLA Abs research was performed with Luminex bead assays (Lifecode ID and LSA I/II-Immucor). Results were expressed as MFI (MFI > 1000 positive). If the patient had DSAs and no alternative donors, a DS was employed, with Rituximab (day -15), 2 single-volume plasmapheresis (PP; days -9 and -8), intravenous immunoglobulin (day -7) and infusion of HLA selected platelets for DSA absorption, if persistent DSAs were directed

against class I HLA. DS was scheduled with or without PP, according to DSAs MFI (>1000 or <5000) and FCXM (flow cytometry cross-match).

Results: Twenty-two out of 126 patients (17.46%) showed anti-HLA Abs, 5 of them DSAs (22%, 3.9% of total). One out of 5 patients died before receiving HSCT, due to disease progression; 3 patients received DS obtaining engraftment; 1 patient showed no DSAs and negative FCXM before starting the conditioning regimen, and DS was not necessary. Female sex ($p = 0.033$) and a history of previous pregnancies or abortions ($p = 0.009$) showed a statistically significant impact on alloimmunization. Factors associated with delayed PMN engraftment were patient's female gender ($p = 0.039$), bone marrow as stem cell source ($p = 0.025$), and a high HSCT-specific comorbidity index ($p = 0.028$). None of the analyzed variables, including the DSA's detection, influenced engraftment.

Conclusions: Our analyses confirm the importance to test DSAs in mmHSCT. Our DS proved successful in removing DSAs. Prospective multicenter studies are needed to better define and validate consensus strategies on DSAs management in HSCT.

Disclosure: Nothing to declare

P533

Retrospective analysis of the impact of recipient-donor HLA-disparity on viral reactivation after hematopoietic stem cell transplantation (HSCT)

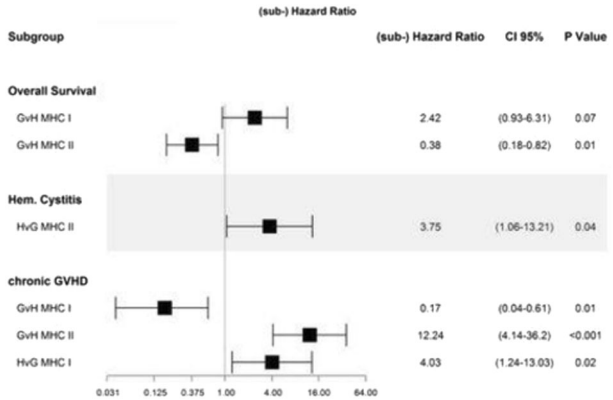
A. Habermehl[1,2], A. Nikoloudis[1,2], M. Wiesinger[1,3], J. Clausen[1,2]

[1]Ordensklinikum Linz Elisabethinen, Linz, Austria, [2]Johannes Kepler University Linz, Linz, Austria, [3]Medical University of Vienna, Vienna, Austria

Background: Viral infections are a common complication after HSCT and significantly contribute to non-relapse mortality (NRM). While it has been recognized that HLA mismatching (MM) between donor and recipient increases the risk for viral infections or reactivation after HSCT, the impact of HLA class I versus II MM and their respective vectors (HVG versus GVH) is largely unknown.

Methods: 2w?>We retrospectively evaluated 140 patients undergoing HLA mismatched (MM) HSCT from haploidentical family ($n = 127$) or MM unrelated ($n = 13$) donors using post-transplant cyclophosphamide based immunosuppression, between August 2014 and May 2021 at a single institution. To assess the impact of recipient-donor HLA-disparity on viral reactivation, individual GVH- and HVG-directed MHC class I (A, B, C) and class II (DR, DQ, DP) mismatches were quantified and dichotomized as 0-1 MM versus 2-3 MM per class and vector, and were assessed for their impact on the incidence of BK-virus associated hemorrhagic cystitis (BKV-HC) and significant CMV reactivation, and on other major HSCT outcomes.

Results: By multivariable analysis, presence of 2-3 (versus 0-1) HVG-directed class II MM was significantly associated with occurrence of BKV-HC (sub-hazard ratio (sHR) 3.75; 95%CI 1.06-13.21; $p = 0.04$). In contrast, no individual class/vector MM was predictive for CMV reactivation. Interestingly, despite its impact on BKV-HC, HVG class II MM was associated with reduced NRM (sHR 0.35; 95%CI 0.12-0.97; $p = 0.04$). Class I MM GVH was associated with lower risk for moderate/severe cGVHD (sHR 0.17; 95%CI 0.04-0.61; $p = 0.01$). In contrast, HVG class I MM (sHR 4.03; 95%CI 1.24-13.03; $p = 0.02$) and GVH class II MM (sHR 12.24; 95%CI 4.14-36.2; $p < 0.001$) were associated with increased moderate/severe cGVHD. Finally, GVH class II MM also associated with a lower risk for overall mortality (sHR 0.38; 95%CI 0.18-0.82; $p = 0.01$), while for GVH class I, an opposite trend for overall mortality was observed (sHR 2.42; 95%CI 0.93-6.31; $p = 0.07$).



Conclusions: The greater importance of HLA MM for BKV as compared to CMV replication may be due to the recipient origin of BKV harbouring cells (urinary tract), while CMV infects lymphocytes, which are predominantly of donor origin after engraftment. The latter may result in a diminished role of an HLA barrier for antiviral immunity in case of CMV. Furthermore, the differential effects of HLA-MM in class I vs II on various HSCT outcomes illustrate the complexity of cellular immunity after PTCy based HSCT across HLA barriers.

Disclosure: Nothing to declare.

P535

Chronic GVHD after mismatch unrelated donor stem cell transplantation (9/10) may be associated with PIRCHE (predicted indirectly recognizable HLA epitopes) calculated from six loci HLA

M. Grabowska[1], D. Moskalik-Kierat[1], M. Brzoza[1], A. Wasilewska[1], P. Rusicka-Krzewska[1], R. Machowicz[1], P. Kacprzyk[1], L. Chmielewska[1], J. Biliński[1], P. Boguradzki[1], E. Karakulska-Prystupiuk[1], W.W. Jędrzejczak[1], A. Tomaszewska[1], G.W. Basak[1]

[1]University Clinical Center of the Medical University of Warsaw, Warsaw, Poland

Background: Hematopoietic stem cell transplantation from HLA-mismatched donors leads to an increased risk of acute and chronic graft-versus-host disease (GvHD). There is no established algorithm for selection of mismatched unrelated donors and we can use a model in silico that predicts the numbers of peptides derived from mismatched HLA alleles that can be presented by shared HLA (PIRCHE- Predicted Indirectly ReCognizable HLA Epitopes). Direct recognition of HLA-DPB1 mismatches can be predicted using the TCE (T-cell epitope) model but we can also predict indirect recognition of HLA-DPB1 mismatches using the model of PIRCHE. Considering the important role of indirect T-cell alloreactivity after transplantation, PIRCHE model can be one of the methods to identify the permissibility of HLA mismatches.

The aim of this study is to explore whether the PIRCHE algorithm including match in DPB1 locus can be used to identify permissive and non-permissive HLA-mismatches in 9/10 HLA matched stem cell transplantations.

Methods: We performed a retrospective study of 18 adult patients transplanted with single HLA-mismatched unrelated donors (9/10 mMUD) in our Department. Unambiguous 4d high resolution HLA-A, B, C, DRB1, DQB1 and DPB1 typing data were available for all donors

and recipients. High-resolution HLA typing was performed by reverse sequence-specific oligo, or sequence-specific primer methods (One Lambda, USA). We retrospectively scored PIRCHE numbers (version v3.3.27, available at https://pirche.com), including DPB1 match/mismatch not available at time of transplantation.

Results: PIRCHE Score cut-off points were generated by receiver operating characteristic (ROC) curves with regard to OS. The one with the highest area under curve (AUC 0,958; SE 0,0589; 95%CI 0,652 - 1,000, p = 0.5346) was used to define cut-off between low and high indicators. The cutoffs that yielded the highest area under the curve were used to define low PIRCHE-I/-II/-score and high PIRCHE-I/-II/-score [PIRCHE-I: 0–6 (low) vs. >6 (high); PIRCHE-II: 0–10 (low) vs. >10 (high); PIRCHE score: 0-18 (low) vs. >18 (high)].The detection of low score of PIRCHE was associated with a lower cumulative incidence of chronic GvHD (OR 0,0338 95% CI: 0,0014 – 0,7949; p = 0.035) but not with acute GVHD. Additionally in the group with 9/10 match we compared of survival according to number of epipoes [class I: 0-5 (low) vs. >5 (high) ; II: 0-2 (low) vs. >2 (high) and score: 0-10 (low) vs. >10 (high)], derived from mismatched allogeneic HLA peptides that are subsequently presented by HLA molecules shared between the donor and recipient. In this case we did not add any predictive value [(HR (95% CI): 1,6795 (0,3293 - 8,5646) P = 0,5328].

Conclusions: These preliminary data suggest that low PIRCHE scores including DPB1 locus may be used to identify permissible HLA mismatches within single HLA-mismatched hematopoietic stem-cell transplantations.

Clinical Trial Registry: These preliminary data suggest that low PIRCHE scores including DPB1 locus may be used to identify permissible HLA mismatches within single HLA-mismatched hematopoietic stem-cell transplantations.

Disclosure: Nothing to declare

P536

Higher donor age with a cut-off of 50 years is associated with increased non-relapse mortality after allogeneic hematopoietic cell transplantation for acute myeloid leukemia

Y. Kadri[1], M. Phan[1], J. Bergeron[1], N. Bambace[1], L. Bernard[1], S. Cohen[1], J.-S. Delisle[1], T. Kiss[1], S. Lachance[1], D.-C. Roy[1], J. Roy[1], G. Sauvageau[1], O. Veilleux[1], I. Ahmad[1]

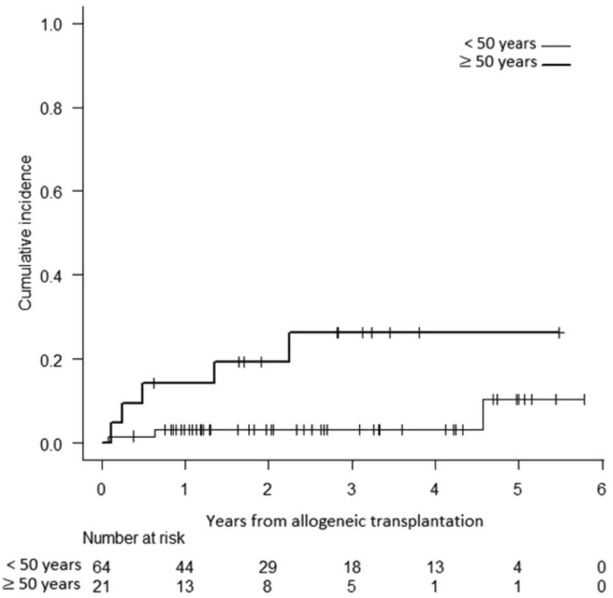
[1]Institut universitaire d'Hémato-Oncologie et de Thérapie cellulaire - Hôpital Maisonneuve-Rosemont - Université de Montréal, Montreal, Canada

Background: In retrospective studies, the association of donor age (DA) and hematopoietic cell transplantation (HCT) outcomes is equivocal. We sought to determine this association in adult acute myeloid leukemia (AML) patients.

Methods: Data from a single-centre cohort of adult AML patients transplanted between 01/07/2015 and 30/06/2020 was analysed retrospectively. Baseline characteristics and outcomes were extracted, and Fine-Gray regression was used to determine the association of DA and cumulative incidence of non-relapse mortality (NRM), and graft-versus-host disease. DA groups using decades were studied in Fine-Gray multivariable models. Patient age-adjusted HCT-Comorbidity Index (aaHCT-CI), patient Karnofsky performance score (KPS), donor type (related matched, haploidentical, matched unrelated), conditioning regimen intensity and acute graft-versus-host disease (aGVHD, time-dependent) were used as covariates to adjust for confounding, and model selection techniques were applied.

Results: In this cohort of 89 transplanted AML patients, median follow-up was 2.7 years (interquartile range: 0.9-3.2) and cumulative incidence of NRM was 16% at 5 years (95% confidence interval: 6-30). DA was independently associated with NRM incidence as a continuous variable (HR = 1.08, p = 0.0008). Decade-based cut-offs yielded ≥ 50 years as a statistically significant and independent predictor of NRM (HR 8.9, p = 0.004). Other independently associated variables were grade 3-4 aGVHD and KPS < 90 (HR 14.8, p = 0.01 and HR = 3.8, p = 0.07, respectively). No association was found between NRM incidence and aaHCT-CI, donor type and conditioning regimen intensity. Univariate graphical association between DA > 50 years and NRM incidence is shown in Figure 1. No association was found between the above-mentioned variables and incidences of acute and chronic GVHD.

Figure 1 – Incidence of NRM according to donor age



Conclusions: In adults with AML, higher donor age with a cut-off of ≥ 50 years is associated with a higher risk of NRM across donor types, conditioning regimen intensities and patient age, comorbidities, and performance status. The mechanisms behind the association of DA and NRM remain to be elucidated.

Disclosure: Nothing to declare.

P537

Research on the effects of transplantation of clonal hematopoiesis of indeterminate potential on recipients

B. Shen[1], E. Jiang[1]

[1]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China

Background: Hematopoietic stem cell transplantation (HSCT) is the only way to cure hematological malignancies, but finding HLA matched hematopoietic stem cell donors has always been a difficult problem. With the development of the research on haploid hematopoietic stem cell transplantation, this problem has been effectively solved and has become the main way of HSCT. However, some donors are found carrying Clonal hematopoiesis of indeterminate (CHIP), and the patients have no other donors to choose from, so they can only transplant donor hematopoietic stem cells who are carrying chip.

Methods: The healthy donors tested in the Institute of Hematology & Blood Diseases Hospital, Chinese Academy of

Medical Sciences from August 2015 to August 2020 were screened for blood system tumor gene mutation, the situation of the donors carrying the mutant gene was analyzed, the graft implantation time, survival time and the incidence of acute graft-versus-host disease between chip recipients and non chip recipients were compared, and the data were analyzed by SPSS 22.0.

Results: 1. From August 2015 to August 2020 in our hospital, 351 cases of blood tumor genetic testing were performed among all donors, including 223 males (63.53%) and 128 females (36.47%). 147 people (41.88%) were positive for gene mutations, and 204 (58.12%) were negative for gene mutations. Among the patients with gene mutation positive, 93 were males, which constituted 41.70%; 54 were females, which constituted 42.18%. 2. 10 people with FAT1 mutation (11.11%), 8 people with SETBP1 mutation (8.89%), 4 people with TET2 mutation (4.44%), 10 people with NOTCH1 mutation (11.11%), 5 people with DNMT3A mutation (5.56%), 8 people with RELN mutation People (8.89%), 5 people (5.56%) with JAK2 mutation, and 6 people (6.67%) with KMT2D mutation. 3. The distribution of gene mutations of donors in different age ranges is as follows: 66.67% for ≤10 years old; 25.86% for 11-20 years old; 21.59% for 21-30 years old; 24.62% for 31-40 years old; 27.08% for 41-50 years old; and over 51 years old 26.31%. 4. Survival of patients after hematopoietic stem cells with genetic mutations and without genetic mutations, the cumulative survival rates of the two groups were 79.70% vs 80.10% and 77.40% vs 70.90%, $p = 0.609$; the two groups The median survival time was 15.19 ± 11.93 months and 13.70 ± 10.98 months, $p = 0.387$; the median time of granulocyte implantation in the two groups was 13.21 ± 2.7 days vs 13.19 ± 2.65 days, $p = 0.964$; platelet implantation time, respectively It was 23.18 ± 25.32 days vs 19.64 ± 16.72 days, $p = 0.275$; input of hematopoietic stem cells carrying gene mutations had no significant effect on the patient's aGVHD, $p = 0.293$. 5. Survival analysis was performed on the gene mutations carried by the donor, and the results were It shows that JAK2 and KMT2D have poor prognosis for patients (P values are 0.026 and 0.048, respectively); TET2 gene is associated with disease recurrence, $p = 0.028$.

Conclusions: About 42% of healthy people in China; CHIP exists in all age groups, and donors carrying JAK2/KMT2D/TET2 mutations are associated with poor prognosis.

Disclosure: NO conflict of interest

P538

Allogeneic stem cells and lymphocyte donations: Responding to the sars-cov-2 challenge

C. Tassi[1], E. Sergio[1], S. Manfroi[1], A. Zanetti[1], F. Barbato[2], E. Dan[2], V. Randi[3]

[1]Policlinico Sant'Orsola-Malpighi IRCCS, Bologna, Italy, [2]Istituto di Ematologia Seragnoli, Policlinico Sant'Orsola-Malpighi IRCCS, Bologna, Italy, [3]SIMT AM.BO Ospedale Maggiore, Bologna, Italy

Background: Since SARS-CoV-2 outbreak, WMDA, EBMT and IBMDR (Italian Donor Registry) have invited centers involved in transplantions to try hard to ensure "treatment continuity" of patients at risk of disease relapse or progression. Every donation center had to create a protected process ensuring: a) fast and safe selection of donors; b) continuity of donation procedures; c) safe release of the collected products.

Methods: The cell collection facility of the Transfusion Center of the Policlinico Sant'Orsola- Malpighi IRCCS, Bologna, Italy, has been JACIE, CNT/CNS and WMDA accredited to assess the eligibility to cell donation of related and unrelated donors, and to collect cell products for transplantation or immunotherapies. In the SARS-CoV-2 "era", our facility has adopted severe safety measures to implement the international, national and regional guidelines. In particular, donors are visited in protected spaces, blood and instrumental exams are performed concurrently, to expedite eligibility assessment and limit donor discomfort. Each donor is subjected to molecular SARS-CoV-2 swabs at least at the first visit, 48 hours before the G-CSF mobilization and on the day of cell collection: negative results are a prerequisite for continuing the donation program. To facilitate this pre-donation path, special agreements with the external facilities involved in this program have been reached.

From March 2020 to December 2021, 65 CSE and 11 DLI donors have been referred to our facility. CSE donors are mobilised with Filgrastim, 10ug/BWKg for five days and subjected to collection if the CD34 + circulating cells are found above the 20/ul threshold by our Immunology Laboratory. The collected products are delivered to the Seragnoli Institute Processing Laboratory, the Tissue Establishment of the Bologna Transplantation Program, for internal use or external shipment.

Results: Main donor demographics, donation type and mobilization data are shown in Table 1.

Conclusions: The SARS-CoV-2 pandemia has not only significantly challenged the activity related to collection procedures, by requiring the adoption of a series of stringent safety measures, but also increased their need.

In spite of the emergency situation, our center succeeded in positively responding to the approximate 10% increment of demand from national and international transplantation units. In particular, we would like to stress that: a) all requested products were collected, provided that the donor was found eligible; b) no SARS-CoV-2 product contaminations or donor infections have been reported.

This positive rtesults was due to a series of factors: the collaboration of both related and unrelated donors, the flexibility of all the actors involved in the process, and the validity of the guidelines issued by WMDA, EBMT, IBMDR and by our Regione Emilia Romagna.

Disclosure: Nothing to declare

P539

Impact of graft cd3 lymphocyte cell dose on clinical outcomes in pediatric patients undergoing haploidentical peripheral blood stem cell transplantation with post transplantation cyclophosphamide

U. Karthik[1], D. Thakkar[1], A. Tiwari[1], S. Pabbi[1], A. Yadav[1], S. Arora[1], N. Rastogi[1], G. Aggarwal[1], A. Marik[1], S.P. Yadav[1]

[1]Medanta, The Medicity Hospital, Gurugram, India

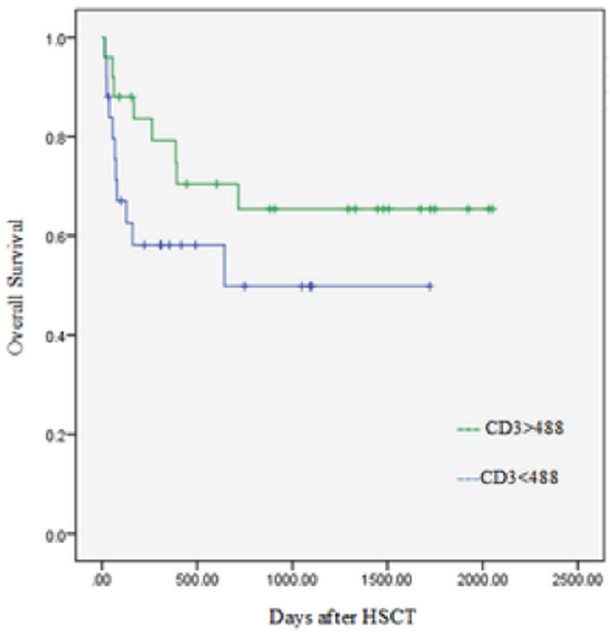
Background: Haploidentical Hematopoietic Stem Cell Transplantation(HSCT) with Post-transplant cyclophosphamide(PTCy) is a curative option for several conditions in children. PTCy is used for in-vivo T-cell depletion in the graft. Higher CD3-lymphocytes in peripheral blood stem cell(PBSC) graft may cause more chronic graft versus host disease(GvHD). We aimed to study the impact of graft CD3-lymphocyte cell dose on clinical outcomes in this group of patients at our center.

Methods: Medical records of all children who underwent unmanipulated haploidentical PBSC transplant with PTCy from May2016 to August2021 were retrospectively analyzed. Donor received subcutaneous G-CSF@10ug/kg/day from day -4 to -1. PBSC were harvested on day0 and transfused to the patient. CD34/CD3 counts were enumerated in the final product by Flowcytometry. All patients received PTCy@50mg/kg/day on day +3,+4 as GvHD prophylaxis. Patients were divided into 2groups based on median CD3count and were analyzed for duration for engraftment, GvHD, Cytomegalovirus(CMV) reactivation, rejection, survival. Also, data was analyzed for significant difference in

N° Donor/ Source	M/F Age yrs Min-Max	Eligible/ N°Donor	Ineligibility causes	Donations/ N°Eligible	Not Donation Causes	AE	Mean collected CD34/BW Kg Recipient	Target not reached at the first collection
Aplo HPCA 10	6/4	10/10		7/10	3 other	0	5.5	1donor:
	52yrs				donor		3.8-11	3 collections needed
	29-66							
Related	9/5	12/14	2 high Omocistein	12/12	0	0	6.8	1donor:
HPCA 14	46yrs						4-16	2 collections needed
	40-59							
Unrelated HPCA 41	28/13	38/41	2 anaemia	37/38	1 recipient	0	5.4	3 donors:
	27yrs		1 active EBV		death		3.8-18	2 collections needed
	20-47							
Related	4/2	6/6		5/6	1 recipient	0	NA	NA
DLI 6	46yrs				death			
	27-66							
Unrelated	4/1	5/5		5/5	0	0	NA	NA
DLI 5	23yrs							
	22-24							
Overall 76	51/25	71/76	5/76	66/71	5/71	0	6	5/66
	39yrs						3.8-18	
	20-66							

Notes: age significantly lower in the unrelated group

median CD3count among those who did or didn't develop GvHD, CMV-reactivation, rejection, malignancy relapse, treatment related mortality(TRM). Statistical analysis was conducted with IBM-SPSS version 21.0.p < 0.05 was taken to be significant.



Results: Kaplan-Meire OS Analysis of the 2 groups.

Parameters	CD3 < 488 (N = 25) (%)	CD3 > 488 (N = 25) (%)	P-value
Mean duration of engraftment			
Neutrophil	19.71days	19.73days	0.985
Platelet	18.14days	18.87days	0.827
Incidence of			
aGvHD	6(25%)	8(32%)	0.588
cGvHD	5(20%)	6(24%)	0.733
CMV-reactivation	13(52%)	10(40%)	0.395
Rejection	3(12%)	5(20%)	0.440
OS	14(56%)	17(68%)	0.177
EFS	14(56%)	11(44%)	0.561

Status of post-transplant events/parameters amongst the groups

Our cohort comprised of 50children(males-35,females-15), aged 5months-18years(median 7.5years). Transplant indications were: Hematological malignancies-21, solid tumors-2,

Hemoglobinopathies-13, Bone marrow failure-10, primary immunodeficiency-3, others-1. Median CD3cell dose- 488million/Kg(range:117.8- 2588.2), CD34cell dose-8.37million/kg(range:3.5-29.8). The cohort was divided into 2groups based on CD3count. There was a statistically significant positive correlation between graft CD3 and CD34count ($p = 0.001$). On analysis, there was no statistically significant difference in the time to neutrophil/platelet engraftment, occurrence of acute/chronic GvHD, CMV-reactivation, graft rejection, overall-survival(OS), event-free survival(EFS) among the 2groups(Table1). Though not statistically significant, the OS was better in the group which had higher than the median CD3count(Figure1). When we divided the cohort based on presence or absence of GvHD, CMV-reactivation, rejection and malignancy relapse; the median CD3count difference was statistically significant for CMV-reactivation ($p = 0.044$), but not for the rest. Those who didn't have CMV-reactivation had a higher median CD3count. At a median follow-up of 13-months(range:14days- 68months), 31/50 patients were alive. Causes of death were relapse of cancer-6 and treatment related mortality-13.

Conclusions: Our data from a small cohort of children undergoing haploidentical PBSCT with PTCy showed that CD3-lymphocyte dose in the graft did not have significant impact on clinical outcomes except that those who didn't have CMV-reactivation had received higher median CD3count. A bigger cohort is needed to confirm our findings.

Disclosure: Nothing to declare

P540

Unrelated hematopoietic peripheral blood stem cell donors' experience; results on 880 donors of the ezer mizion israeli national bone marrow donor registry

R. Zisser (Diamant)[1], I. Yaniv[1], S. Manor[1], B. Zisser[1]

[1]Ezer Mizion Bone Marrow Donor Registry, Petach Tikva, Israel

Background: The Ezer Mizion Bone Marrow Donor Registry, consists of more than 1 million volunteer adult donors, serving Israeli and international patients who need an allogeneic HSCT. Peripheral blood stem cells donation is performed after administration of Filgrastim (Granulocyte Colony-Stimulating Growth Factor) with well-described adverse events.

The primary aim of this study was to explore whether there is any correlation between the occurrence and severity of donors' adverse events during the days of injections and their physical and emotional status at the point of short and long-term follow-up. Moreover, we investigated if there is a correlation between injections' adverse events and CD34 + and WBC counts before collection.

Methods: The dataset included 880 donors with self-reported questionnaires completed on the donation day, up to 30 days after donation (short-term follow-up), and 1 year after donation (long-term follow-up). WBC and CD34 + cell counts were also analyzed.

Results:

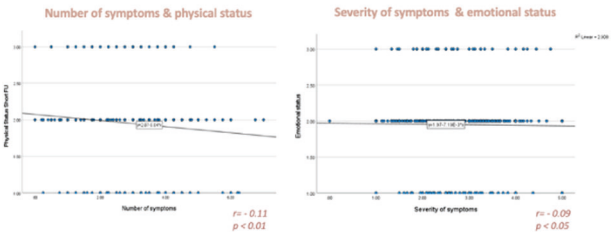
The short term follow-up results have shown that young age was positively related to better emotional status ($r = -.10$, $p < .05$); Worse self-reported physical status correlated with high incidence of symptoms ($r = -.11$, $p < .01$), while high severity of symptoms correlated with poor emotional status ($r = -.09$, $p < .05$). These correlations were still significant at long-term follow up ($-.14 < r < -.10$, $p < .01$).

Short term follow-up (7-30 days post-donation)				Long term follow-up (1-year post-donation)		
	M	SD	Median	M	SD	Median
Physical status	1.96	0.43	2.00	2.12	0.39	2.00
Emotional status	2.43	0.53	2.00	2.29	0.47	2.00

Note: Physical and emotional status was measured by a three-point score and are presented in the table: 1- Worse than normal, 2-Normal, 3- Better than normal

Conclusions: Filgrastim adverse events were shown to influence donors' physical and emotional status both at the short and long term follow-up, affecting donor recovery and manifesting the long term influence of donors' experience during injections days. Many symptoms during injections were related to worse physical status, while more severe symptoms were related to worse emotional status both at the short and the long-term follow-up. However, WBC count and CD34 + cells did not correlate significantly with symptoms. It is reassuring that on long-term follow up donors exhibit full recovery. Based on these data we have suggested possible interventions to improve overall donors' physical and emotional experience such as better management of pain and closer attention during questionnaires compilation.

Figure 1: Correlation between symptoms during injections and physical and emotional state



Disclosure: The authors have no conflicts of interest to declare.

P541

Transplant activity in Mexico during the covid19 pandemic: On the way to recovery

A. Gomez-De Leon[1], L. Gil-Flores[1], P.R. Colunga-Pedraza[1], C. Bourlon-de los Rios[2], C.O. Vargas-Serafin[2], M.d.l.A. Del Campo-Martínez[3], S. Baltazar-Arellano[4], G. Gonzalez-Villarreal[4], G.J. Ruiz-Argüelles[5], X.J. González-Leal[6], L.M. Valero-Saldaña[7], M.M. Contreras-Serratos[8], L. Vega-Vega[9], M. Alvarado-Ibarra[10], A. Olaya-Vargas[11], U. Pérez-Lozano[12], A. Garcia Soto[13], A. Morales-Maravilla[14], G. Cardoso-Yah[15], L.F. Amador-Medina[16], S. Inclán-Alarcón[17], D. Cruz-Contreras[18], C. Chavez Trillo[19], J.A. Flores-Jiménez[20], M. Solano-Genesta[21], C.S. Cruz-Medina[22], R. Ovilla-Martinez[23], E. Gómez-Morales[24], J.A. Badell-Luzardo[25], G.I. Barranco-Lampón[26], R.M. Navarro-Martin del Campo[27], M.d.L. Gutiérrez-Rivera[8], A.A. Ceballos-López[28], A. Milán-Salvatierra[29],

I. Castorena-Villa[30], A.C. Rodríguez-Zúñiga[1], A. Sánchez-Arteaga Carretero[1], D. Gómez-Almaguer[1]

[1]Universidad Autónoma de Nuevo Leon. Facultad de Medicina y Hospital Universitario Dr. José Eleuterio González, Monterrey, Mexico, [2]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [3]Instituto Mexicano del Seguro Social, Mexico City, Mexico, [4]Unidad Médica de Alta Especialidad No. 25. Instituto Mexicano del Seguro Social., Monterrey, Mexico, [5]Centro de Hematología y Medicina Interna, Clínica Ruíz, Puebla, Mexico, [6]Clinica Gomez Almaguer. Instituto Tecnológico de Estudios Superiores de Monterrey, Tec Salud., Monterrey, Mexico, [7]Instituto Nacional de Cancerología, Mexico City, Mexico, [8]Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City, Mexico, [9]Hospital Infantil Teleton Oncología, Querétaro, Mexico, [10]Centro Médico Nacional 20 de Noviembre, Mexico City, Mexico, [11]Instituto Nacional de Pediatria, Mexico City, Mexico, [12]Centro Médico Nacional Manuel Avila Camacho, Instituto Mexicano del Seguro Social, Puebla, Mexico, [13]Centro Médico Nacional La Raza, Instituto Mexicano del Seguro Social, Mexico City, Mexico, [14]Hospital Angeles Puebla, Puebla, Mexico, [15]Hospital Central Militar, Mexico City, Mexico, [16]Hospital Regional de Alta Especialidad del Bajio, Leon, Mexico, [17]Centro Médico ABC, Mexico City, Mexico, [18]Doctors Hospital, Monterrey, Mexico, [19]Hospital Central Universitario, Chihuahua, Mexico, [20]Hospital Puerta de Hierro Sur, Guadalajara, Mexico, [21]Instituto Oncológico del Noroeste, Guadalajara, Mexico, [22]Hospital para el Niño Poblano, Puebla, Mexico, [23]Hospital Angeles Lomas, Mexico City, Mexico, [24]Centro Médico Naval, Mexico City, Mexico, [25]Centro Médico del Noroeste, Hermosillo, Mexico, [26]Hospital Ángeles Acoxpa, Mexico City, Mexico, [27]Hospital Civil de Guadalajara "Juan I. Menchaca", Guadalajara, Mexico, [28]Clínica de Mérida, Mérida, Mexico, [29]Hospital Juárez de México, Mexico City, Mexico, [30]Hospital Infantil de México Federico Gómez, Mexico City, Mexico

Background: Mexico's hematopoietic stem cell transplantation (HSCT) activity remains well below other middle-income countries in Latin-America such as Brazil and Argentina. The effects of the COVID19 pandemic on transplant center (TC) activity in our country are unknown. Therefore, we developed a nationwide survey on behalf of the Mexican Transplant and Cell Therapy Working Group (TCTMX) to account for its effects and perform a situational analysis.

Methods: We performed a comprehensive cross-sectional study including active TCs interrogating HSCT activity from 2019 through September 2021. An electronic survey was sent to TCs during October-December 2021 and consisted of items regarding the number and characteristics of procedures performed and were compared yearly. Changes to their institutions' transplant policies and practices during the COVID19 pandemic were also documented. At the time of writing, of 50 centers invited to participate, 31 had responded (62%) including all high-volume TCs, 28 with complete data included in this analysis.

Results: Most TCs belong to the public health system (64%) and have a mixed pediatric and adult population (46.4%) and almost half concentrated in Mexico City (42.9%). Five centers performed exclusively autologous transplants (17.8%). The number of HSCTs decreased from 767 in 2019 to 460 in 2020 ($p < 0.001$), representing a 40% reduction in transplant activity. In 2021, 462 HSCTs have been performed reaching a monthly transplant rate of 51.3 compared to 38 in 2020, and close to the 63.9 reference in 2019 ($p = 0.002$). All types of HSCTs were diminished with the notable exception of those from haploidentical donors which have surpassed matched sibling donors. On the other hand, only 15 unrelated donor and 2 umbilical cord blood grafts were performed during the 3-year period studied. Most institutions have treated patients with COVID19 (78.6%) and experienced some form of reconversion (67.9%), which was higher in public centers (64.3% vs, 40%: $p = 0.03$). HSCT activity stopped completely in 19 TCs (68%) with a median duration of closure of 10 months (range 1-19), higher in public vs. private centers (median of 13 vs. 6 months; $p = 0.09$); 10% of TCs remained closed, all in the public setting. The most frequent motives behind TC closures were hospital reconversion in 11 (57.9%), precautionary measure in 4 (21.1%) and lack of resources in 4 (21%). Follow-up outpatient visits were totally or partially suspended in 10.7% and 39.3% of TCs, respectively, and were modified in 71.4% most frequently by telemedicine through videocalls. Reported modifications in conditioning regimens, immunosuppression or maintenance strategies specifically due to the pandemic were not common (10.7%, 14.3% and 10.7%, respectively), and most centers continue to treat patients with COVID19 (88%).

Conclusions: The limited transplant activity in Mexico decreased significantly during the pandemic but is recovering and nearly at pre-pandemic levels. A notable exception were haploidentical grafts which remained stable throughout this period and have become the most common donor source in allogeneic transplantation. Most TCs were severely affected with a higher impact in public centers reflecting the fragility of our healthcare system.

Clinical Trial Registry: None

Disclosure: The authors declare no conflict of interest.

P542

No impact of donor type on allogeneic transplantation (alohct) outcomes in patients with myeloid malignity ≥60 years old

V. Schneiderová[1], P. Jindra[1], M. Karas[1], D. Lysák[1], K. Steinerová[1], J. Šrámek[1], A. Jungová[1], M. Hrabětová[1]

[1]University Hospital Pilsen, Plzeň, Czech Republic

Background: Older patients with high risk myeloid malignancies (AML/MDS) have dismal prognosis and the only curative option is alloHCT. HLA identical siblings (SIB) or a matched unrelated donors (MUD) are preferred, however, for some patients only so-called alternative donors – partially matched unrelated (PMUD) or haploidentical donors (HID) are available. However, these have historically been associated with higher transplant related mortality (TRM). We investigated whether those donors i.e. PMUD and HID are an adequate alternative.

Methods: Methods: Retrospective single centre analysis of 140 consecutively transplanted patients ≥60 years with AML ($n = 123$) or MDS ($n = 17$) in the period 10/2001-07/2020. GRFS "event" defined as aGvHD ≥ gr.III, extensive cGvHD, relapse or death during follow-up (whichever occurred first).

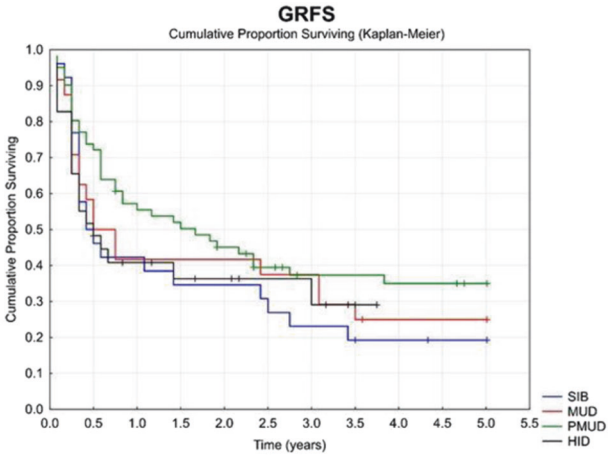
Results: Median age 64 (60-74), SIB donors (26, 19%), MUD (61, 44%), PMUD (24, 17%) and HID (29, 21%). 32 patients (35%) with advanced disease (>CR1/PR1). Disease risk index (DRI): low /medium 52% of patients, high 48%. There were no significant differences between the groups with different donors, except for older age in patients with HID (median 67 years, $p = 0.0006$) and older age of donors in SIB ($p < 0.0001$).

With a median follow-up of 54 months (6-171), 46 (33%) patients are alive. The 1-year/5-year probabilities of OS/GRFS were 59%/48% and 33%/28%, respectively. The cumulative incidences of TRM and relapses were 47% and 23%, respectively. OS and GRFS in individual donor groups were comparable ($p = 0.1392$), Fig1.

In the multivariate analysis for GRFS, advanced disease was the most significant (HR 2,445, 95% CI 1,454-4,113, $p = 0.0008$)

followed by CMV match (HR 2,167, 95% CI 1,320-3,556, p = 0.0022). The same factors together with aGVHD ≥ gr.III (HR 2.546, 95% CI 1.049-6.179, p = 0.0388) were associated for adverse OS in the multivariate analysis. No impact of donor type was detected.

Conclusions: A significant portion of selected elderly patients with AML/MDS achieve long-term OS/GFRS after AloHSCT regardless of donor type. The key factor for outcome is risk of the underlying disease. In these patients, therefore, transplantation in the early stages of the disease is crucial, and any best available donor should be accepted.



Disclosure: Nothing to declare

P543

A report on unmanipulated haploidentical hematopoietic stem cell transplantation for pediatric patients with acute leukemia at the largest children's medical hospital in Iran

M. Behfar[1], L. Jafari[1], Y. Karamlou[1], M. Mardani[1], P. Naji[1], A. Rahmani[2], F. Jafari[1], Z. Nikfetrat[1], R. Mohseni[1], E. Maki[1], A.A. Hamidieh[1]

[1]Pediatric Cell and Gene Therapy Research Center, Gene,Cell and Tissue Research Institute,Tehran University of Medical Science, Tehran, Iran, Islamic Republic of, [2]Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran, Islamic Republic of

Background: Hematopoietic stem cell transplantation (HSCT) is an imperative treatment modality for high-risk acute leukemia patients. Donor availability is one of the main challenges in transplantation. Only 30% of patients have an available matched sibling donor (MSD) and matched unrelated donor (MUD) is an alternative for some of the remaining patients; However, none of these options are available to almost 30% of patients. Over the last decade, haploidentical HSCT (HID-HSCT) has dramatically evolved as an alternative option, with the merit of being available to all patients. The aim of this study is to report the outcome of HID-HSCT in acute leukemia pediatric patients

Methods: From October 2016 to September 2021, 109 pediatric acute leukemia patients underwent HSCT; Of which 59 were ALL patients (median age: 4.5years) and 50 AML patients (median age: 7 years). Overall, from the 26 patients (17 male and 9 female) who received HID-HSCT, 17 were ALL patients (65.38%) and 9 were AML (34.61%), 3 of which (33.3%) had secondary AML. The graft source in all patients was peripheral blood stem cells. The median doses of CD34 + and CD3 + cells, in AML, were 5.5 × 10^6/kg and 364 × 10^6/kg, respectively; while, in ALL, they were 6.1 × 10^6/kg and 345 × 10^6/kg, in the same order. The conditioning regimen consisted of intravenous Busulfan, cyclophosphamide and rabbit anti-thymocyte globulin (ATG).

Cyclosporin, metotheroxate and post-transplant cyclophosphamide were also administrated as a GVHD prophylaxis. In patients without signs of acute graft versus host disease (aGvHD), one dose of donor lymphocyte infusion (10^7cells/kg) was administrated from the same donor as a means to decrease the probability of rejection.

Results: Engraftment transpired in all patients, with two patients (one ALL and one AML) experiencing secondary graft failure; although, both underwent successful HID-HSCT for their second transplantation. From amongst all 26 HID patients, overall survival (OS) rate was 53.84% with 33.3% pertaining to AML and 64.7% to ALL patients. Disease-free survival (DFS) was 49.2%, the rate in AML and ALL patients was 30% and 59.3%, respectively. Acute GvHD occurred in 46.15% of patients, which included 44.4% of AML and 49.2% of ALL patients. The leading cause of death in HID cases were relapse and aGvHD, sequentially; the former occurred in 6 (35.2%) ALL and 4 (44.4%) AML patients.

Conclusions: Studies have illustrated that Haploidentical transplantation demonstrates a stronger graft vs. leukemia effect in pediatric acute leukemia; thus, it may be considered as the optimal choice for high-risk acute leukemia patients. The high incidence of acute GvHD, however, has been the main obstacle in Haploidentical transplantation. Our results, in corroboration with the previous findings, indicate that ALL haploidentical recipients showed auspicious results; we speculate that the low OS and DFS rates in AML patients was probably pertinent to secondary AML.

Clinical Trial Registry: -

Disclosure: Nothing to declare

P544

Comparison of the long-term outcomes of HLA-mismatched unrelated donor transplantation and single unrelated cord blood transplantation after reduced intensity/toxicity conditioning

M. Kuno[1], H. Koh[1], Y. Makuuchi[1], N. Harada[1], T. Takakuwa[1], H. Okamura[1], A. Hirose[1], M. Nishimoto[1], Y. Nakashima[1], M. Nakamae[1], M. Hino[1], H. Nakamae[1]

[1]Osaka City University, Osaka, Japan

Background: The recent advancement of transplantation procedures allows allogeneic hematopoietic cell transplantation (HCT) for patients who are ineligible for standard myeloablative conditioning due to older age and comorbidities. Little information is available on the alternative donor selection strategy for these patients without HLA-matched related or unrelated donors.

Methods: We retrospectively compared the outcomes of 50 consecutive patients with hematological malignancies who underwent first allogeneic HCT from 1- or 2-locus HLA-mismatched unrelated donors (MMUD) (n = 15) or single unrelated cord blood (CB) (n = 35) after reduced intensity/toxicity conditioning in our institute between 2007 and 2019.

Results: The median age at HCT was 58 years (range, 33-65 years) in patients who underwent MMUD transplants and 60 years (range, 23-72 years) in those who underwent CB transplants. The common indications for HCT were acute leukemia or myelodysplastic syndrome in both the MMUD group and the CB group (60% vs. 71%). As a rule, we have used uniform transplantation procedures and supportive care with the manual of our institute, reducing the potential bias from patient heterogeneity in a retrospective study. All patients received fludarabine-based

reduced intensity or reduced toxicity conditioning and graft-versus host disease (GVHD) prophylaxis with calcineurin inhibitors plus methotrexate or mycophenolate mofetil. In the MMUD group, the graft source was bone marrow in 14 of 15 (93%) patients and either anti-thymocyte globulin or bortezomib was added to the GVHD prophylaxis in 8 of 15 (53%) patients. Four (27%) of 15 patients received HLA 6/8 MMUD and 26 (74%) of 35 received HLA 4/6 CB. The patient characteristics of the two groups, including the disease risk index, HCT-CI score, performance status, and donor coordination times, did not differ to a statistically significant extent.

With a median follow-up of 102 months, the MMUD group showed better overall survival in comparison to the CB group (5-year OS: MMUD group, 62%; CB group, 31%, $p = 0.021$). The relapse rates of the MMUD and CB groups were similar (at 5 years: MMUD group, 27%; CB group, 33%, $p = 0.68$). The MMUD group tended to show a lower rate of non-relapse mortality and a low incidence of grade III-IV acute GVHD in comparison to the CB group (at 2 years: MMUD group, 7%; CB group, 40%, $p = 0.12$ and, at day100: MMUD group, 7%; CB group, 29%, $p = 0.079$, respectively). The cumulative incidence of extensive chronic GVHD in the MMUD group was significantly higher than that in the CB group (at 5 years: MMUD group, 40%; CB group, 9%, $p < 0.01$). In a multivariable Cox model adjusted for disease risk and patient age, MMUD was associated with lower overall mortality than CB (hazard ratio 0.38, 95% CI 0.15-0.95, $p = 0.038$).

Conclusions: From the viewpoint of long-term survival, in comparison to CB, MMUD may be a preferred donor source for patients who are ineligible for standard myeloablative conditioning and who do not have HLA-matched donors. Better management of chronic GVHD, including prophylaxis with post-transplantation cyclophosphamide, could improve the long-term outcomes of MMUD transplantation.

Disclosure: Hideo Koh: research funds (Takeda Pharmaceutical and AstraZeneca) and honoraria (Sumitomo Dainippon Pharma, MSD and Novartis). Teruhito Takakuwa: research funds (AbbVie, Celgene, Incyte Biosciences Japan and Bristol-Myers Squibb) and honoraria (Bristol-Myers Squibb, Sanofi, Janssen Pharmaceutical, Novartis and ONO PHARMACEUTICAL). Hiroshi Okamura: honoraria (NIPPON SHINYAKU). Mitsutaka Nishimoto: research funds (Astellas Pharma and Zenyaku Kogyo) and honoraria (Otsuka Pharmaceutical and CSL Behring). Yasuhiro Nakashima: research funds (Astellas Pharma, Celgene, AbbVie, Novartis, Bristol-Myers Squibb and Chugai Pharmaceutical) and honoraria (Amgen, Novartis, Chugai Pharmaceutical and SymBio Pharmaceuticals). Mika Nakamae: research funds (VERITAS) and honoraria (which family member received, see Hirohisa Nakamae's disclosure). Masayuki Hino: research funds (JCR Pharmaceuticals, Asahi Kasei, Abbott, TEIJIN PHARMA, Kyowa Kirin, Otsuka Pharmaceutical, TAIHO PHARMACEUTICAL, DAIICHI SANKYO, Chugai Pharmaceutical, Takeda Pharmaceutical, Celgene, Labcorp Drug Development and TOSOH) and honoraria (CSL Behring, Meiji Seika Pharma, MSD, Astellas Pharma, AstraZeneca, Otsuka Pharmaceutical, ONO PHARMACEUTICAL, Kyowa Kirin, Sanofi, Celgene, Takeda Pharmaceutical, Chugai Pharmaceutical, NIPPON SHINYAKU, Novartis, Pfizer Japan, Bristol-Myers Squibb, Janssen Pharmaceutical, AbbVie, and Sumitomo Dainippon Pharma). Hirohisa Nakamae: research funds (Alexion, Bristol-Myers Squibb, Novartis and CMIC HOLDINGS) and honoraria (Astellas Pharma, Otsuka Pharmaceutical, Sumitomo Dainippon Pharma, Novartis and Bristol-Myers Squibb). All other authors have no conflicts of interest to disclose.

P545

Impact of abo incompatibility on haploidentical hematopoietic stem cell transplant. A single center retrospective study

B. Astibia Mahillo[1], K. Velázquez Kennedy[1], L. Carballeira Seoane[2], C. López Prieto[3], P. Herrera Puente[1], A. Chinea Rodríguez[1], V. García Gutiérrez[1], A. Luna De Abia[1], A. Jiménez Martín[1], A. Vallés Carboneras[1], M.C. Tenorio Núñez[1], F.J. López Jiménez[1], G. Moreno Jiménez[1]

[1]Hospital Universitario Ramón y Cajal, Madrid, Spain, [2]Complejo Hospitalario de Pontevedra, Pontevedra, Spain, [3]Hospital Universitario de Getafe, Madrid, Spain

Background: The effect on clinical outcome of ABO incompatibility in haploidentical hematopoietic stem cell transplant (HSCT) is not well defined in a decade in which this procedure has spread worldwide. In this single center retrospective study, we investigate the influence of ABO mismatch on haploidentical HSCT.

Methods: Patients receiving an haploidentical HSCT at our center between January'13-October'21 were selected ($N = 112$). We retrospectively analysed these cases and collected information about leukocyte, platelet, and red cell (RC) engraftment (Hb > 8g/dL for at least 14 days without transfusion support), red blood cell (RBC) concentrates until RC engraftment, treatment with erythropoietin (EPO) and thrombopoietin receptor agonists, post-transplant haemolysis, acute graft-versus-host disease (GVHD) incidence and overall survival.

Results: Our cohort included 78 ABO-matched patients and 34 ABO-mismatched patients (18 with major, 14 with minor and 2 with bidirectional ABO mismatching). The clinical and demographic characteristics of patients are presented in Table 1. There were no significant differences between average time to leucocyte, platelet, and RC engraftment between both groups: 20 (±4) days, 28 (±17) days and 42 (±20) days respectively in ABO-matched group; 19 (±4) days, 24 (±8) days and 34 (±19) days respectively in ABO-mismatched group. RBC concentrates until RC engraftment were comparable between groups: 8 (±7) vs 7 (±6). The percentage of patients receiving treatment with EPO or Eltrombopag was similar in ABO-matched and ABO-mismatched transplants. 5/112 patients (4.46%) experienced graft failure (3 from the ABO-matched group, 1 with major mismatch and the other with bidirectional mismatch). One patient in the ABO-mismatched group developed pure red cell aplasia. The prevalence of post-transplant haemolysis was significantly higher in ABO-mismatched patients (44.1% vs 18.9%, $P = 0.006$). No association was found between ABO compatibility and the development of acute GVHD or acute GVHD grade III-IV. There were no differences in overall survival between ABO-matched and mismatched patients: 50 (35-66) months vs 49 (37-60) months, respectively.

VARIABLE	ABO-MATCHED (n = 78)	ABO-MISMATCHED (n = 34)	SIG.
Age	52 (+/− 13)	47 (+/−16)	0.1
Sex			
-Male	49 (62.8)	22 (64.7)	0.85
-Female	29 (37.2)	12 (35.3)	
Baseline disease			
-AML	41 (52.6)	9 (26.5)	
-ALL	5 (6.4)	1 (2.9)	0.036
-Lymphoma	18 (23.1)	12 (35.3)	
-Other	14 (17.9)	12 (35.3)	
Conditioning			

VARIABLE	ABO-MATCHED (n = 78)	ABO-MISMATCHED (n = 34)	SIG.
-MA	25 (33.8)	12 (35.3)	0.4
-RIC	49 (66.2)	22 (64.7)	
-RIC (sequential)	4 (5.1)	0 (0)	
GVHD prophylaxis			
Cyclophosphamide	73 (96.1)	30 (88.2)	0.19
-ATG	4 (5.1)	2 (5.9)	1
Number of infused cells ($x10^6$/Kg)	6.11 (1.4)	5.68 (1.2)	0.14

Table 1. Clinical and demographic characteristics of ABO-matched and ABO-mismatched patients. All patients received GVHD prophylaxis with cyclosporine and mycophenolate mofetil.

Conclusions: ABO incompatibility did not have an influence on engraftment or red cell requirements in the setting of haploidentical HSCT in our study. We found no significant difference in acute GVHD development and overall survival between ABO-matched and mismatched patients. ABO mismatch was associated with a higher incidence of post-transplant haemolysis.

Disclosure: Nothing to declare

P546

Impact of ABO mismatch on survival and engraftment in haploidentical hematopoietic stem cell transplantation

B.J. McCormick[1], R. Mohty[1], M. Alhaj Moustafa[1], M. Iqbal[1], R. Parrondo[1], E. Ayala[1], J. Foran[1], V. Roy[1], B. Savani[2], M.A. Kharfan-Dabaja[1], H.S. Murthy[1]

[1]Mayo Clinic Florida, Jacksonville, United States, [2]Vanderbilt University Medical Center, Nashville, United States

Background: Given that a significant proportion of hematopoietic stem cell transplants (HCT) are performed with ABO blood group mismatched donors and the impact of ABO mismatch on survival outcomes and engraftment remain controversial, we aimed to explore retrospectively the impact of ABO mismatch in haploidentical transplant (haplo-HCT) recipients at Mayo Clinic Florida.

Methods:

Using data from patients without prior history of allogeneic HCT who underwent haplo-HCT at Mayo Clinic Florida between 2012 and 2020, comparative analysis between patients who received ABO-matched versus ABO-mismatched transplant was conducted for common clinical endpoints, including survival outcomes, engraftment kinetics, and graft-versus-host disease (GVHD). Bone marrow and peripheral blood chimerism studies were obtained 30 days post-transplant when possible. Neutrophil engraftment was defined as absolute neutrophil count ≥ $0.5x10^9$/L for 5 days without colony-stimulating factor administration. Platelet engraftment was defined as platelets ≥ $20x10^9$/L for 3 days without transfusion. Time to red blood cell (RBC) transfusion independence was defined as hemoglobin ≥ 7.0 g/dL for 7 days without transfusion.

Results: Our study cohort included 60 patients at Mayo Clinic Florida who underwent haplo-HCT with median follow-up duration of 413 days, including 41 ABO-matched and 19 ABO-mismatched patients (2 bi-directional mismatches, 3 major mismatches, and 14 minor mismatches). There was no significant difference in baseline demographics, clinical characteristics, or disease between ABO-matched and ABO-mismatched groups. A median overall survival of 412 days was observed in the ABO-matched group compared to 421 days in the ABO-mismatched group [hazard ratio (HR) 0.50; 95% confidence interval: 0.19-1.34; P = 0.17]. Non-relapse mortality, disease free survival, and time to progression were also comparable between ABO-matched and ABO-mismatched groups. There was no significant difference in grade II-IV acute GVHD [HR 0.74; 95% confidence interval: 0.14-3.83; P = 0.72] or chronic GVHD [HR 0.95; 95% confidence interval: 0.31-2.94; P = 0.93] between groups. Finally, there was no significant engraftment difference between groups, including donor chimerism 30 days post-transplant, time to platelet and neutrophil engraftment, and time to RBC transfusion independence (Table 1).

Table 1. Engraftment per ABO incompatibility group.

Variable	All Patients	ABO Matched	ABO Mismatched	p-value
Graft failure, %	3.30%	4.90%	0%	1
Donor Leukocyte Infusion (DLI), number	6	5	1	0.654
Time to neutrophil engraftment in days, mean (95% CI)	19.3 (16.2-21.5)	20.7 (18.1-32.4)	16.4 (12.89-19.9)	0.054
Time to platelet engraftment in days, mean (95% CI)	21.7 (18.7-24.8)	22.7 (18.7-26.8)	19.7 (15.0-24.4)	0.362
Time to RBC transfusion independence in days, mean (95% CI)	20.0 (16.7-23.3)	20.8 (16.4-25.2)	18.4 (13.5-23.3)	0.595
Donor chimerism at Day + 30, mean % (95% CI)				
Bone marrow	90.3 (83.6-96.9)	88.0 (78.7-97.2)	95.0 (87.1-103.0)	0.321
Peripheral CD3	94.2 (88.1-100.3)	94.1 (86.4-101.7)	94.5 (83.4-105.5)	0.948
Peripheral CD33	90.1 (83.0-97.2)	88.1 (78.5-97.7)	94.0 (83.3-104.6)	0.442

Conclusions: In conclusion, ABO incompatibility has no apparent clinical impact on survival or engraftment kinetics in haploidentical hematopoietic stem cell transplant recipients. This study is limited by the small sample size and low number of patients with major/bidirectional ABO mismatch.

Disclosure: nothing to declare

P547

Haploidentical hematopoietic stem cell transplantation: A single center experience

398

I. Iturrate[1], A. Puchol[1], C. Mayor[1], S. Díaz[1], B. Aguado[1], A. Alegre[1], Á. Figuera[1]

[1]*Hospital Universitario de La Princesa, Madrid, Spain*

Background: Haploidentical Hematopoietic Stem Cell Transplantation (HaploHSCT) has spread rapidly worldwide because HLA-haploidentical donors are highly available and cyclophosphamide is effective.

Methods: We retrospectively analyzed 44 patients with hematological malignancies who received HaploHSCT between 2013-2020 in our center (patient's characteristics on table 1). Most of them received myeloablative conditioning (93.2%), based on fludarabine and busulfan with association in some cases with cyclophosphamide or thiotepa. Three patients received bone marrow as source of stem cells. Fourteen patients (31.8%) had a previous transplant: 9 (64.3%) allogeneic, 5 (35.7%) autologous. All recipients were screened for donor-specific antibodies (DSA) and donors who had HLA alleles targeted by DSA were avoided. The standard GVHD prophylaxis consisted of cyclophosphamide (50 mg/kg/day on days 3 and 4) and cyclosporine plus mycophenolate mofetil starting on day 5.

	N (%)
Gender	
Male / Female	26 (59.1%)/18 (40.9%)
Age	
Median age	56 (21-71)
HCT-CI	
0/1-2/≥3	19 (43%)/14 (32%)/11 (25%)
Hematological malignancies	
Acute myeloid leukemia (AML)	24 (54.5%)
Acute lymphoblastic leukemia (ALL)	7 (15.9%)
Myelodysplastic syndrome (MDS)	5 (11.4%)
Hodgkin lymphoma (LH)	3 (6.8%)
Non-Hodgkin lymphoma LNH)	3 (6.8%)
Myelofibrosis	1 (2.3%)
Plasma cell leukemia (PCL)	1 (2.3%)
Recipient/donor CMV serology	
Positive/positive	32 (72.7%)
Positive/negative	11 (25%)
Negative/negative	1 (2.3%)
Previous transplant	
Autologous	9 (64.3%)
Allogeneic	5 (35.7%)
Disease status	
First complete remission	15 (34.1%)
Second complete remission	8 (18.2%)
Third complete remission	2 (4.5%)
Partial remission	19 (43.2%)
Conditioning regimen	
Myeloablative	41 (93.2%)
Reduced-intensity	3 (6.8%)
Donor gender	
Male / Female	26 (59.1%)/18 (40.9%)
Donor age	
Median age	35 (20-71)
ABO incompatibility	
ABO compatible	30 (68.2%)
Minor incompatible	10 (22.7%)
Major incompatible	4 (9.1%)
Median number infused CD34 + /kg	6 x 10^6 (1.5 - 7.7)
Median number infused CD3 + /kg	238.8 x 10^6 (26.2 – 858)

Results: Neutrophil engraftment was achieved in 82% patients with a median of 20 days. Six of 44 patients (13.6%) experienced delayed engraftment. For platelets, 61% achieved engraftment with a median of 28 days. The incidence of acute GVHD was 34% (grades I-II 73.3%; grades III-IV 26.7%), and for chronic 9% (all cases limited). Thirty-three patients (75%) had CMV reactivation, one of them developed CMV disease.

With a median follow up of 32.1 months, median overall survival was 41%. In the group of AML, 54.2% of patients remain alive 6 months after transplantation. For patients with lymphoma, 6-months survival was 67%. For ALL, 6-months survival was 71.4%. Eight patients (18.2%) relapsed (4 AML, 2 ALL, 1 PCL, 1 LNH) at a median of 131.5 (98-301) days.

Conclusions: These results demonstrate Haplo-HSCT in our center achieves comparable clinical outcomes compared to literature reports. This study has several limitations: heterogeneity between patients and indications for transplant, and reduced sample size. HaploHSCT is one treatment option for adults with hematological malignancies because of high availability of donors. However, prospective randomized studies are needed to compare donor type (haploidentical vs matched unrelated donor).

Disclosure: Nothing to declare

P548

Proposal of the diagnostic workup of *plasmodium* spp. Seropositive allogeneic stem cell donors

R. Machowicz[1], A. Tomaszewska[1], M. Grzybek[2], P. Kacprzyk[1], J. Bilinski[1], L. Chmielewska[1], K. Baranowicz[2], E. Karakulska-Prystupiuk[1], M. Król[1], E. Urbanowska[1], G. Basak[1]

[1]*Medical University of Warsaw, Warsaw, Poland,* [2]*Institute of Maritime and Tropical Medicine, Medical University of Gdańsk, Gdynia, Poland*

Background: Transfer of *Plasmodium* spp. from hematopoietic stem cell (HSC) donor poses a serious threat to the recipient. The World Marrow Donor Association (WMDA) finds it unacceptable to recruit donors who report travel to a malaria-risk area within the past three years and do not present negative malarial antibodies

to exclude the risk of sub-clinical malaria infection. The previously recruited donor, who before the procedure, is found to have a positive result, can be accepted at the discretion of the requesting transplant centre. Still, there is no suggestion of risk mitigation strategy other than analysis of the exposure history.

Methods: Here we propose a diagnostic workup minimizing the risk of *Plasmodium* spp. transfer with hematopoietic stem cells based on the case of a transplant from a seropositive donor.

Results: A 21-year old woman required allogeneic hematopoietic stem cell transplantation (alloHSCT) due to AML with myelodysplasia-related changes. At the initial presentation, she had hyperleukocytosis of 307 G/l. The cytogenetic risk was high: hyperdiploid complex karyotype with KMT2A rearrangement without KMT2A-MLLT3 fusion gene. After the DAC induction and after consolidation therapy, MRD was found (0.4% and 0.2%, respectively). Therefore, relapse risk was high despite obtaining complete remission, and alloHSCT was indicated.

The patient's 28-year old sister was fully matched and was available as a donor. Thirteen months before the planned procedure, the donor spent eight days at Zanzibar (malaria-endemic region). She took prophylactic treatment, applied repellents, and did not experience any febrile episodes during or soon after that trip. However, the antibody test against *Plasmodium* spp. was positive. Polymerase Chain Reaction (PCR) against *Plasmodium* spp., antigen test, and thick blood smear were performed to rule out ongoing sub-clinical malaria – all with negative results. The same three tests were repeated from peripheral blood on the day of apheresis to rule out potential malaria reactivation due to immune system changes during G-CSF mobilization. Samples for those three tests were also taken from apheresis product; the product was frozen and released when negative results were obtained.

FluBu4 conditioning was used with cyclosporin A and methotrexate GvHD prophylaxis. The post-transplant period was complicated only with mild engraftment syndrome presenting with skin rash. In samples taken on days 7, 14, and 21 *Plasmodium* spp. DNA was not found. Consolidation with eight cycles of post-transplant azacitidine was used. After 365 days from transplant patient remains in complete remission and did not experience any infectious complications (except mild SARS-CoV-2 infection).

Conclusions: The proposed testing procedure may help establish a systematic approach to *Plasmodium* spp. seropositive hematopoietic stem cell donors, provide a risk mitigation strategy, and therefore facilitate transplants from this donor group.

Disclosure: Nothing to declare

P549

A single center experience of haploidentical stem cell transplantation with unmanipulated graft - case series of eleven patients

I. Micheva[1], V. Gerov[1], S. Dimitrova[1], Y. Petrov[1], I. Resnick[1]

[1]Clinic of Hematology, UMHAT "Sveta Marina" – Varna, Medical University, Varna, Bulgaria

Background: Haploidentical stem cell transplantation (haplo-SCT) is considered a clinical therapeutic option for patients who are indicated for allogeneic stem cell transplantation. The number of patients transplanted with a haplo-relative increases each year worldwide due to its feasibility and accessibility. The recent advances in the field of haplo-HSCT allow a large number of patients with high risk hematological diseases to benefit from this treatment despite not having a matched donor.

Methods: We present 11 patients (female/male: 1/1.2; mean age 46 years (28-62), 6 with acute myeloid leukemia, 4 with acute lymphoblastic leukemia, and 1 with idiopathic aplastic anemia) who underwent SCT from a haploidentical donor for a period of 3 years.

Results: In 10 of the patients it was a first transplantation, and in one - second. 54.5% of patients were transplanted in first complete remission (CR1), 27.3% - in second complete remission (CR2), and one - in progressive disease. The stem cell source in all patients was peripheral stem cells. In 81.8% we performed myeloablative conditioning regimen, in 18.2% - conditioning with reduced intensity. As part of prophylaxis of graft-versus-host disease (GvHD) we administered post-transplant cyclophosphamide to 10 patients and antithymocyte globulin to 1 patient. The mean number of transfused CD 34 (+) cells was 6.53 x 106/kg (3.76-9.73). All patients achieved engraftment – of the neutrophils on D + 19 (13-25) and of the platelets on D + 22 (14-35). 36.4% of the patients had acute GvHD grade II-IV, 18% - grade IV. At the time of the analysis, 72.2% of patients were alive. 45.5% achieved remission of the disease, 27.3% developed relapse. Graft failure was observed in one patient. Causes of death included acute myocardial infarction, BKV encephalitis and relapse.

Conclusions: Haploidentical SCT is an acceptable option in absence of a compatible donor and necessity of well-timed treatment. With all available strategies, virtually no patient who needs an allogeneic transplant should be excluded by the absence of a donor.

Disclosure: Nothing to declare

STEM CELL MOBILIZATION, COLLECTION AND ENGINEERING

P550

No added benefit from high-dose cyclophosphamide stem cell mobilization in multiple myeloma in first complete remission after bortezomib-based induction therapy

P. Baptista[1], P. Chorão[1], M. Henriques[1], A.A. Pardal[1], P. Monteiro[1], I. Machado[1], S. Teixeira[1], L. Gonçalves[1], R. Bergantim[1], E. Aguiar[1], J.C. Pires[1], F. Trigo[1]

[1]Centro Hospitalar Universitário de São João, Porto, Portugal

Background: Autologous stem cell transplant (ASCT) is a widely recognized essential therapeutic step in eligible patients with newly diagnosed multiple myeloma (NDMM), but the optimal strategies for stem cell mobilization are still a matter of debate. High-dose cyclophosphamide with filgrastim (HD-Cy+G-CSF) might be used for its greater apheresis yield of $CD34^+$ peripheral blood progenitor cells (PBPC) and potential anti-tumour effect, while filgrastim alone (G-CSF) may be preferred for its greater predictability and safety profile. The aim of this study was to compare these regimens on mobilization efficacy, cell grafting and transplant outcomes on NDMM patients submitted to ASCT.

Methods: We retrospectively analysed NDMM patients submitted to ASCT with melphalan conditioning, between 2011 and 2020, in first complete remission (CR) after induction with bortezomib, cyclophosphamide and dexamethasone (VCD) or bortezomib, thalidomide and dexamethasone (VTD). Plerixafor was used pre-emptively before apheresis if the $CD34^+$ count was $<10x10^6$ cells/l. EBMT definitions for neutrophil and platelet grafting were used.

Results: A total of 73 patients in CR were mobilized, 20 with HD-Cy+G-CSF and 53 with G-CSF. Patients in the first group were younger (56 vs 64 years; $p = 0.003$). The induction treatment regimen was VCD in 21% and VTD in 79%, while post-transplant maintenance therapy was used in 58%, with no significant differences between groups. During mobilization, 70% of patients in the HD-Cy+G-CSF group had at least one episode of fever requiring antibiotics, in contrast with 6% in the G-CSF group

($p < 0{,}001$). HD-Cy allowed greater PBPC collection (8.39 vs 4.66x10^6 CD34$^+$ cells/kg; $p < 0{,}001$), less apheresis sessions (2 or less in 85% vs 51%; $p = 0.004$) and less frequent need for pre-emptive plerixafor administration (15% vs 40%; $p = 0.046$), compared to G-CSF. The number of CD34$^+$ cells infused was significantly higher in the HD-Cy+G-CSF group (4.20 vs 2.52x10^6 CD34$^+$ cells/kg) but no differences were seen regarding neutrophil (median 12 vs 12 days) or platelet (median 16 vs 17 days) engraftment. Likewise, febrile neutropenia episodes, grade III-IV mucositis or number of transfused units of platelets or erythrocytes was similar between groups. There were also no differences between HD-Cy+G-CSF and G-CSF-mobilized patients regarding CR rates on day +100 post-transplant (80% vs 85%, respectively) or on 3-year time to next treatment survival probability (67% vs 61%, respectively).

Conclusions: In NDMM achieving CR after induction with a bortezomib-based treatment, mobilization with G-CSF alone, despite having a smaller PBPC apheresis yield and greater need for pre-emptive plerixafor, shows less toxicity than HD-Cy and grants equally effective grafting after ASCT. This suggests HD-Cy +G-CSF may compromise the marrow microenvironment or cause significant toxicity to the PBPC collected, preventing the enhanced number of cells infused to translate into a more advantageous graft with better post-transplant outcomes. Choosing G-CSF as the preferred mobilization regimen may avoid possible infectious complications seen with HD-Cy+G-CSF without compromising ASCT outcomes in this specific group of NDMM with a favourable response to induction therapy.

Disclosure: Nothing to declare.

P551

Effect of CD34 + cell dose on clinical outcomes after allogeneic hematopoietic stem cell transplantation with post-transplant cyclophosphamide

A. Pedraza[1], M.Q. Salas[1], L.G. Rodríguez-Lobato[1], P. Charry[1], M. Suárez-Lledo[1], N. Martinez-Cibrian[1], A. Doménech[1], M.T. Solano[1], J. Arcarons[1], N. Llobet[1], J. Cid[1], M. Lozano[1], L. Rosiñol[1], G. Gutiérrez-García[1], A. Urbano-Ispizua[1], F. Fernández-Avilés[1], M. Rovira[1], C. Martínez[1]

[1]Institute of Hematology and Oncology, Hospital Clínic de Barcelona, IDIPAPS, Josep Carreras Institute, Barcelona, Spain

Background: Graft cell dose may play a crucial role affecting not only engraftment but also non-relapse mortality (NRM) and survival after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Most studies performed so far, considered allo-HSCT using standard GVHD prophylaxis, while the high-dose post-transplant cyclophosphamide (PTCy) setting has not been extensively studied yet. Currently, PT-Cy is widely used in clinical practice not only for haploidentical allo-HSCT but also for related and unrelated transplants. The objective of this retrospective study was to assess the impact of CD34 + cell doses in peripheral blood stem cells (PBSC) grafts, on the outcome of allo-HSCT using PTCy-based GVHD prophylaxis.

Methods: We included a total of 193 consecutive adult patients with hematological malignancies who underwent allo-HSCT at the Hospital Clinic of Barcelona between 2014-2021. T-cell repleted PBSC grafts were infused in all cases and the maximum CD34 + cell dose was capped at 8×10^6/kg. Based on the binary partitioning method, an optimal cut-off of CD34 + cell dose value was proposed to separate the cohort in two groups in terms of our main outcome variable (overall survival, OS).

Results: Patient characteristics are shown in Table 1. Median CD34 + cell dose was 5.86×10^6/kg (IQR: 4.49-7.16). One-hundred and thirty-one patients received a high-dose defined as ≥5x10^6/kg and 62 a low-dose defined as <5x10^6/kg. A total of 12 patients experienced graft failure without differences between groups. Median time to neutrophil engraftment was 19 (IQR 16-23) for high-dose and 20 days (IQR 18-23) for low-dose ($p = 0.04$). Median time to platelets recovery was 16 (IQR 13-26) and 20 days (IQR 13-28) ($p = 0.2$), respectively. No differences between groups were observed in the cumulative incidence of day +100 aGVHD (grade II-IV 24% for high-dose vs. 23% for low-dose, $p = 0.68$; and grade III-IV 5% vs. 3%, respectively, $p = 0.4$), or 2-year cGVHD (moderate/severe 11% vs. 4%, respectively, $p = 0.1$). NRM was significantly lower for high-dose group (1-year: 9% vs. 21%, respectively, $p = 0.04$), with comparable relapse rate (1-year: 19% vs. 19%, respectively, $p = 0.98$). After a median follow-up of 34 months, patients receiving a high-dose had better 1-year OS (82% vs. 67%, $p = 0.03$), with a not significant trend towards a better disease free survival (72% vs. 59%, $p = 0.09$). GVHD-free/relapse-free survival was comparable between groups (64% vs. 56%, $p = 0.4$). The multivariate analysis confirmed the negative association between the infusion of a CD34 + low-dose in OS (HR 1.7, $p = 0.049$). Age ≥ 60 years (HR 2.1, $p = 0.04$), KPS ≤ 80% (HR 2.4, $p = 0.002$), and HCT-CI score > 3 (HR 1.96, $p = 0.02$) were additionally found to be significant risk factors for OS.

Conclusions: Our results show that the infusion of CD34 + cell PBSC dose ≥5 ×10^6/kg had prolonged survival, mainly due to a reduced NRM rate. No differences were observed in relapse rate, suggesting that the infusion of CD34 + cell doses ≥5 ×10^6/kg did not protect from disease relapse. High-CD34 + dose did not increase the risk of GVHD. Taken together, these results suggest that, in the setting of PTCy allo-HSCT, an infusion of a CD34 + dose ≥5 ×10^6/kg could be beneficial.

Clinical Trial Registry: No

Disclosure: Nothing to declare

P552

Prolonged infusion time of cyclophosphamide is more effective as a stem cell mobilization regimen in newly diagnosed multiple myeloma patients: A retrospective monocentric report

Y. Li[1], M. Chen[1], J. Liu[1], B. Huang[1], J. Gu[1], J. Li[1]

[1]First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: Cyclophosphamide (Cy) in combination with granulocyte-colony stimulating factor (G-CSF) is typically used for peripheral blood stem cells mobilization in myeloma patients. The aim of this study was to evaluate the mobilization efficacy and safety of two different infusion times of Cy plus G-CSF for peripheral blood stem cells mobilization in newly diagnosed multiple myeloma (NDMM) patients.

Methods: We retrospectively analyzed the mobilization efficacy and safety of "24 hours continuous infusion" (24 hours group) versus "short time (4-6 hours) infusion" (control group) cyclophosphamide in 156 (68 vs. 88) NDMM patients who receive Cy plus G-CSF mobilization and auto-stem cell transplantation (ASCT) in our department between September 2008 and May 2020.

Results: Among 156 patients, the demographic characteristics including sex, age, hemoglobin, plasma cells percentage, type of myeloma, cytogenetics risk, international staging system, and serum creatinine, serum calcium, lactate dehydrogenase level were similar between two groups. The median numbers of collected CD34 + cells in 24 hours group and control group were 6.78 and 4.48×10^6/kg ($p < 0.0001$). However, the mean number of apheresis was 2.26 in 24 hours group and 1.51 in control group ($p < 0.0001$). The median numbers of collected CD34 + cells of one

apheresis in 24 hours group and control group (2vs.45) were 11.57 and 4.79×10^6/kg ($p = 0.493$). The median numbers of collected CD34 + cells of two apheresis in 24 hours group and control group (49vs.40) were 8.04 and 4.16×10^6/kg ($p < 0.0001$). The median numbers of collected CD34 + cells of three apheresis in 24 hours group and control group (14vs.2) were 4.53 and 3.23×10^6/kg ($p = 0.427$). Target number of CD34 + cells/kg (defined as ≥6 × 10^6/kg) was collected from 55.9% patients in 24 hours group vs. 29.9% in control group ($p = 0.001$). The rate of patients who need secondary mobilization and bone marrow transplant was 1.5% in 24 hours group and 14.8% in control group ($p = 0.004$). The day of neutrophil engraftment after transplantation was 10 in 24 hours group and 11 in control group ($p < 0.0001$), and the day of platelet engraftment was 11 in 24 hours group and 12 in control group ($p = 0.272$). No differences of hematologic toxicity, non-hematologic toxicity and the cost in hospital were observed between two groups.

Conclusions: 24 hours continuous infusion of Cy is effective with equivalent toxicity for stem cell mobilization in patients with newly diagnosed myeloma and could be considered in MM patients with expected secondary or tertiary transplantations.

Disclosure: Nothing to declare

P553

Upregulated expression of SIRT5, SIRT6 and SIRT7 is associated with higher number of CD34 + cells collected at first apheresis

M. Nowicki[1], A. Wierzbowska[1,2], E. Stec-Martyna[3], D. Kulczycka-Wojdala[3], G. Nowicki[4], A. Szmigielska-Kapłon[1,2]

[1]Copernicus Memorial Hospital in Lodz Comprehensive Cancer Center and Traumatology, Łódź, Poland, [2]Medical University of Lodz, Łódź, Poland, [3]Central Scientific Laboratory, Medical University of Lodz, Łódź, Poland, [4]Georgetown University, Washington, United States

Background: Sirtuins are members of the NAD + -dependent class III histone deacetylase family, involved in the post-translational modification of proteins. They participate in the fate of HSC, their metabolism, stress response, differentiation, aging and migration. Mobilization of hematopoietic stem cells (HSC) from the bone marrow niche into the peripheral blood is a crucial step in the treatment of lymphoproliferative neoplasms with autologous hematopoietic stem cells transplantation (auto-HSCT). The aim of this study was to explore SIRT1, SIRT2, SIRT3, SIRT4, SIRT5 SIRT6 and SIRT7 levels during HSC mobilization. Sirtuins were investigated in the context of CD34 + cells mobilization efficacy with different chemotherapy regimens.

Methods: Fifty patients were enrolled in the study (24 F, 26 M). The median (Me) age was 60 years. The investigated group consisted of thirty-nine multiple myeloma (MM), seven non-Hodgkin lymphoma (NHL) and four Hodgkin lymphoma (HL) patients. Sirtuins expression was evaluated in peripheral blood (PB). The blood serum samples were collected at two time points: before hematopoietic stem cell mobilization chemotherapy (day 0) and on the day of the first apheresis (day A). Sirtuins expression was evaluated by ddPCR method.

Results: Our study revealed positive correlation between SIRT5, SIRT6 and SIRT7 expression on day A and the number of CD34 + cells collected at the first apheresis ($R = 0.34$, $p = 0.02$), ($R = 0.31$, $p = 0.03$), ($R = 0.47$, $p < 0.001$), (Figure 1). To evaluate the influence of sirtuins expression on the number of CD34 + cells on day A, patients were divided into "high" and "low" expression groups according to median sirtuins levels on day of first apheresis (above and below median). The group of SIRT7 "high expressors" collected more CD34 + x10^6/kg cells on day A than "low expressors" (5.01 vs 1.68 CD34 + x10^6/kg, $p = 0.003$).

To assess the effect of the administrated mobilization chemotherapy on the level of sirtuins on the day of the first apheresis, we divided the patients into two groups: the first group received mobilization chemotherapy containing alkylating agents (cyclophosphamide/ifosfamide): Cyclophosphamide, DCEP, ICE, R-ICE, ($n = 39$), (Alk group). The second group consisted of patients mobilized with Cytarabine, DHAP, R-DHAP or GCS-F in monotherapy, ($n = 11$), (non-Alk group).

The Alk group had a lower SIRT1, SIRT2, SIRT3 and SIRT5 level on the day of first apheresis than non-Alk group (Me = 300.53 vs 621.94 copies/200µL, $p = 0.002$), (Me = 628.95 vs 1493.02 copies/200µL, $p < 0.001$), (Me = 137.84 vs 304.77 copies/200µL, $p = 0.02$) and (Me = 202.95 vs 482.01 copies/200µL, $p = 0.02$) respectively.

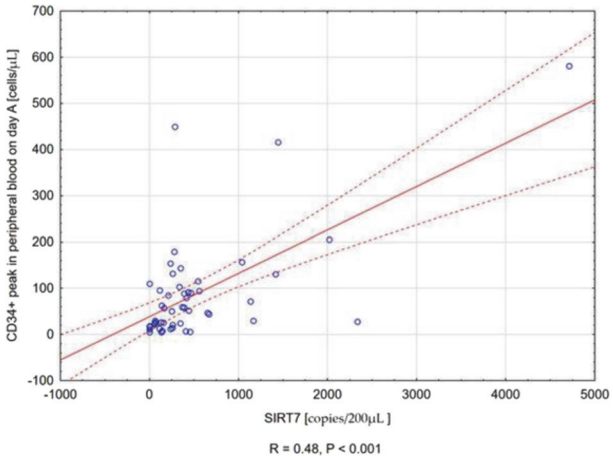


Figure 1. Scatter plots illustrating the positive correlation between SIRT7 expression on day A and CD34 + peak in peripheral blood.

Conclusions: In conclusion, we observed that sirtuins influence HSC migration and hematopoietic landscape in the bone marrow niche during CD34 + cell mobilization for autologous transplantation. SIRT5, SIRT6 and especially SIRT7 play an important role in this process. Moreover, we noticed that alteration in sirtuins expression during first apheresis depends on whether the chemotherapy contains alkylating agents.

Disclosure: Nothing to declare.

P554

Stem cell apheresis: Accuracy of the prediction of the stem cell yield using pre-apheresis cd34$^+$ cell count

M. Hornung[1], J. Gärtner[1], K. Wendelin[1], S. Dressler[1], F. Kerache[1], K. Schaefer-Eckart[1]

[1]Klinikum Nuernberg, Paracelsus Medical University Nuernberg, Nürnberg, Germany

Background: Accurate prediction of the stem cell yield is essential for planning and executing of the PBSC leucapheresis procedure. Calculation based on pre-apheresis peripheral CD34$^+$ cell count usually shows a good correlation between predicted and actually collected cell count, however slight underestimation and over-estimation occurs.

Methods: We calculated the predicted CD34$^+$ yield with the following method:

Predicted $CD34^+x10^6/kg$ = (benchmark collection efficacy x processed blood volume x peripheral $CD34^+$ count per µl)/(patient's weight x metric conversion factor).

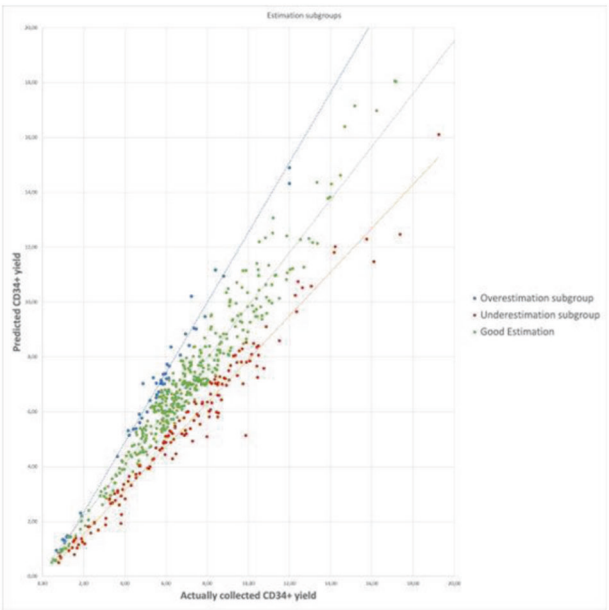
Data were retrospectively analyzed and divided into 3 subgroups, based on their accuracy of the calculated $CD34^+$ yield compared with the actually collected $CD34^+$ count.

The results of the 3 subgroups which were underestimated (UE, 15% below predicted $CD34^+$ yield), overestimated (OE, 15% above predicted $CD34^+$ yield) and good estimation (GE, within +/− 15%) were compared with an ANOVA analysis. Additionally, multiple clinical and laboratory data were evaluated.

Results: We investigated 607 apheresis (569 donors) procedures during the years 2019-2020.

The mean value of the prediction coefficient for all apheresis procedures was 1.06. The Spearman's correlation coefficient (r) between calculated and actually collected CD34 cells per kg bodyweight recipient was 0.9126 ($p < 0.01$), which indicates a very reliable prediction over this 2 years.

Most of the collections (66%) showed a very good correlation between predicted and finally collected stem cell count. The OE subgroup consisted of only 8% apheresis procedures and the UE subgroup of only 26%. The mean prediction coefficient of the UE was 1.29 and of the OE subgroup 0.81. The analysis of clinical and laboratory data revealed a significantly lower $CD34^+$/µl pre apheresis count in the UE group, as well as a trend to lower ferritin blood levels. The underestimation leads to slightly higher results than estimated, so these collections resulted in more than sufficient products.



Conclusions: Our method of calculating the stem cell yield is highly predictive of the number of $CD34^+$ cells actually collected, making planning and adjusting of the apheresis procedure very reliable.

For donors with low pre apheresis CD34 + count and who are critical to meet the threshold for a successful apheresis, the calculation tends to underestimate the $CD34^+$ yield which leads to a better than calculated collection.

On the contrary, the clinical more adverse overestimation occurred predominately in the range of more than sufficient apheresis.

For clinical practice, in case the donors estimated stem cell yield is just below the threshold for a successful collection, we maximize the processed blood flow volume using higher inlet flow rates and longer procedure times. On the other hand, in the event of a more than sufficient stem cell yield calculation, reducing the procedure time turned out to be safe and reliable.

Disclosure: Nothing to declare

P555

Handling of allogeneic related and unrelated hpc grafts during the covid-19 pandemic – a survey from the infectious diseases and cellular therapy & immunobiology working party

N. Worel[1], P. Ljungman[2], I. Sánchez-Ortega[3], J.D. Hoogenboom[4], N.S. Knelange[4], V. Verheggen[4], D.-J. Eikema[5], A. Ruggeri[6], D. Averbuch[7], R. de la Camara[8], C. Chabannon[9]

[1]Medical University Vienna; Dept. of Blood Group Serology and Transfusion Medicine, Vienna, Austria, [2]Dept. of Cellular therapy and Allogeneic Stem Cell Transplantation, Karolinska Comprensive Cancer Center, Karolinska University Hospital Huddinge and Div. of Hematology, Dept. of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden, [3]EBMT Executive Office, Barcelona, Spain, [4]EBMT Leiden Study Unit, Leiden, Netherlands, [5]EBMT Statistical Unit, Leiden, Netherlands, [6]Ospedale San Raffaele s.r.l., Haematology and BMT, Milan, Italy, [7]Faculty of Medicine, Hebrew University of Jerusalem; Hadassah Medical Center, Jerusalem, Israel, [8]Hospital de la Princesa, Madrid, Spain, [9]Institut Paoli-Calmettes, Centre de Lutte Contre le Cancer; Centre d'Investigations Cliniques en Biothérapie, Université d'Aix-Marseille, Inserm CBT 1409, Marseille, France

Background: For nearly two years, the COVID-19 pandemic has had detrimental impact on medical practices. Because of its intrinsic complexity, the delivery of allogeneic haematopoietic cell transplantation (HCT) in this context represents an enormous challenge. Transplant centres have adapted promptly and developed strategies to enable safe HCT, by introducing significant changes in their procedures, e.g. through an unprecedented use of cryopreservation for allogeneic haematopoietic progenitor cell (HPC) grafts.

Methods: To explore how centres modified their strategies in terms of donor selection and implementation of new procedures (e.g. cryopreservation), a 14-item survey was disseminated by the EBMT-IDWP & CTIWP between January 2020 and June 2021. The survey was sent to 509 EBMT-affiliated allogeneic HCT centres and open between September 20th and October 15th, 2021.

Results: Eighty-four of 509 (17%) centres from 24 countries responded. Of these, 68% hold a JACIE accreditation. Seventy-four percent of centres introduced COVID-19 mitigation measures for their donors (e.g. physical and social distancing) to minimize the risk of infection. Forty-one percent of centres changed their donor search strategy, and favoured recruitment of related haploidentical donors over unrelated donors (URD). In addition, 33% and 55% of centres searched for a backup donor in the related and URD settings, respectively. Only 10% of centres considered cord blood (CB) as an alternative source to URD.

Before COVID-19, only six percent were routinely cryopreserving HPC products, whereas this percentage increased to 92% during the pandemic. In details, 53/77 (69%) of centres cryopreserved both, related and URD grafts, 21 (27%) only URD and 3 (4%) related grafts only. In the majority of centres, changes in policies were introduced based on EBMT recommendations (60/75; 80%) and/or national guidelines (45/75; 60%). Bone marrow (BM) grafts were avoided by 33 (39%) centres. In the study period, a total of 2,502 related and 2,680 URD transplants have been reported. Of these transplants, 60% (n = 1,491) related and 78% (n = 2,098) of URD grafts have been cryopreserved pre-emptively and infused in the vast majority of cases. Three percent (n = 50) related and 4%

(n = 79) URD cryopreserved products have not been infused during the observation period. Release criteria for cryopreserved products in terms of COVID-19 were based on a negative SARS-CoV-2 test (not further specified) in 35/77 (46%), interview of the donor (medical history) in 3/77 (4%), and both in 20/77 (26%). Related donors were tested for SARS-CoV-2 during donor work-up in 27/56 (48%) and during mobilization in 35/56 (63%) centres. Test strategies for URD where not covered by the survey.

Conclusions: These data are limited by the low number of respondents, but show a historical increase in cryopreservation of allogeneic HPC grafts during the first three waves of the SARS-CoV-2 pandemic, more in URD than in related donors grafts. The use of BM decreased, and CB grafts were not used as an alternative at most centres. A significant proportion of cryopreserved products (3-4%) were not infused. The clinical impact of allogeneic cryopreserved HPCs will be analysed in the ongoing second part of this study.

Disclosure: Nothing to declare.

P556

Cryopreservation of allogeneic stem cells may be associated with increased early relapse compared with fresh product: A cohort study of irish patients

C. Armstrong[1], H. Foy-Stones[1,2], N. Gardiner[1,2], P. Hayden[1], E. Conneally[1], C. Flynn[1], C.L. Bacon[1], E. Vandenberghe[1], P. Browne[1], N. Orfali[1]

[1]St. James' Hospital, Dublin, Ireland, [2]St. James' Cryobiology Laboratory Stem Cell Facility, Dublin, Ireland

Background: Due to COVID-19 restrictions, many centres have rapidly changed practice regarding processing of stem cell products. We sought to examine the impact of graft cryopreservation on transplant outcomes at the Irish National Stem Cell Transplant programme.

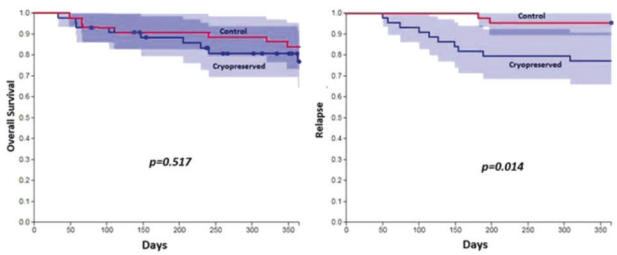
Methods: We reviewed 44 patients undergoing allogeneic transplantation with cryopreserved products from 2020 compared to 44 using fresh product immediately prior to the pandemic. The cohorts were matched for age, stem cell source/type, disease, disease risk index, HCT-CI, ABO compatibility, HLA antigen mismatch status and conditioning regimen/intensity. Release specification of stem cell products including TNC, $CD34^+$ viability, $CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/8^+$ content were examined. Clinical outcomes included time to engraftment, chimerism at 100 days, GVHD incidence, relapse and death within 1 year.

Results: The majority of our cohort received PBSC grafts. The median TNC, $CD34^+$ and $CD3^+$ infusion dose was similar in both groups. T-cell content of grafts was similar, with no significant difference in T-cell subsets ($CD3^+$, $CD4^+$, $CD8^+$, $CD4/8^+$). In the cryopreserved group median $CD34^+$ viability at the time of thawing was 90.66% (53.37-97.36). In vitro progenitor assays showed the median CFU-GM in the fresh cohort was $36x10^4$/kg and $48x10^4$/kg post-thaw in cryopreserved products(*Table1*).

Neutrophil engraftment was slightly delayed with cryopreservation (18.8 vs. 16.6 days, $p = 0.089$). There were no cases of primary graft failure. Time to platelet engraftment was similar in both groups ($p = 0.29$). Platelet engraftment failed in 3 patients with cryopreservation and 4 without. D100 chimerism did not differ between groups. Acute and chronic GVHD incidence was similar between groups.

Interestingly, we identified an increased risk of relapse at 1-year post-transplant in the cryopreserved cohort despite matching for age, disease/risk, conditioning intensity and stem cell source. 10 patients relapsed within 1 year compared to 2 in the non-cryopreserved group ($p = 0.014$). Overall survival at 1 year was similar in both groups ($p = 0.517$) (*Graph1*).

	Control(n = 44)	**Cryopreserved(n = 44)**
Median Age(y)	**51.5**	**55.5($p = 0.15$)**
Disease risk index: *High*	**15**	**11**
Intermediate	**18**	**20**
Low	**11**	**13**
Unrelated donor	**24**	**31**
PBSC	**42**	**42**
Reduced intensity	**35**	**35**
Median HCT-CI	**1**	**1**
HLA mismatch	**2**	**3**
Median $CD34^+x10^6$/kg	**5.0**	**4.77($p = 0.76$)**
Median $CD3^+x10^6$/kg	**14.88**	**14.20($p = 1.0$)**
Median CFU-GM$x10^4$/kg	**36.46**	**48.58(@thaw) ($p = 0.56$)**
Median BFU-E$x10^4$/kg	**38.06**	**61.66(@thaw) ($p = 0.004$)**
GVHD		
Acute	**29**	**21 ($p = 0.085$)**
Chronic	**13**	**6 ($p = 0.069$)**



Conclusions: Large-scale adoption of cryopreservation of allogeneic stem cell products due to COVID-19 provided an opportunity to examine the impact of this practice in our patient cohort. Our data show that graft content is reliably maintained compared to fresh infusion in terms of $CD34^+$ viability, T-cell counts and engraftment times.

Although overall survival was not affected, we identified an increased rate of relapse within 1 year in patients with cryopreserved products, despite similar graft characteristics and matching for categorical variables. Considering similar T-cell quantity in both graft cohorts, functional rather than quantitative T-cell defects may explain this outcome. Indeed, the GVL effect could also be compromised by other variables, such as NK and monocyte alterations. Further and longitudinal review to explore this finding is required, in particular as global logistical restrictions continue.

Clinical Trial Registry: N/A
Disclosure: Nothing to declare

P557

Extracorporeal photopheresis - comparison of the in-line and off-line system

M. Lanska[1], J. Radocha[1], B. Visek[1], A. Zavrelova[2], J.M. Horacek[1], J. Stevkova[1], P. Zak[1]

[1]University Hospital, Hradec Kralove, Czech Republic, [2]University Hospital, Hradec Králové, Czech Republic

Background: Extracorporeal photopheresis (ECP) is an effective treatment for graft versus host disease (GVHD) and cutaneous T cell lymphoma (PTCL). Two types of systems are currently possible for this therapy: in-line or off-line. The advantage of the in-line system includes a shorter procedure time, a lower risk for contamination, and a reduced risk of improper infusion. The off-line system benefits from the lower extracorporeal volume and the higher amount of processed whole blood. However, it is a multistep procedure for which the laminar airflow cabinet and sterility testing are needed. A new type of in-line system has been developed to combine the benefits of both types of systems.

Methods: The objective of this study was to compare two methods of ECP. Twelve patients (7 women and 5 men, median age 53.5 years) with PTCL (3 patients) or GVHD (9 patients) were treated with ECP 2 consecutive days in one cycle. A procedure was performed in standard off-line system - combination of Spectra Optia for collection and photoactivation by Macogenic G2 (Macopharma, Mouvaux, France). The second procedure in the same patient in this cycle was performed using a new system. Spectra Optia (Terumo BCT, Lakewood, U.S.) was used for mononuclear cell (MNC) collection and an accessory device UVA PIT System (PIT Medical Systems GmbH, Cadolzburg, Germany) for photoactivation as a functionally closed in-line multistep system. Apheresis procedure was in both systems the same with using of continuous MNC (CMNC) collection protocol. In the off-line system 8-methoxypsoralen (8-MOP) was added to the MNC bag in the laminar airflow cabinet and after photoactivation the cells were reinfused. In the in-line system 8-MOP was added to MNC bag using sterile tubing connections between the two systems, after photoactivation cells were reinfused due to the connected system to the patient infusion line. The patient remained connected to the Spectra Optia throughout the entire procedure. Sterility of all products was examined before administration.

Results: 48 procedures (24 off-line/24 in-line) were performed in 12 patients. The processed total blood volume (TBV) was similar in each pair, 1.4 - 1.8fold of TBV (7093 ml vs. 7105 ml). No contamination was detected. The time of the entire procedure (from the beginning of MNC collection to the end of reinfusion) was measured. The average time in the off-line group was 280.9 (median 275) minutes and 201.2 (median 200) minutes in the in-line group. We did not observe any severe side effects except mild ACD-A toxicity (hypocalcemia), all procedures were finished completely except one (insufficient peripheral vein in the off-line group). No worsening of the disease was detected.

Conclusions: The new in-line system provides a functionally closed procedure enabling treatment at the bedside with a low risk of cross-contamination, infection and infusion errors. It allows processing the same TBV as in off-line methods. The time of the entire procedure was considerably shorter. The procedure was safe and well-tolerated without bacterial contamination or worsening of the disease.

Disclosure: The authors have nothing to declare.

P558

Prediction of cost-effective calculation of apheresis blood volume achieving target cd3+ cell number for the manufacturing of car-t cells – a single center cohort study

E. Rosenbaum[1], R. Ram[1], O. Amit[1], M.S.W. Springer Weitzman[1], G. Gilben[1], L. Lipshtein[1], J. Kounio[1], E. Udin[1], R. Gold[1], R. Eshel[1]

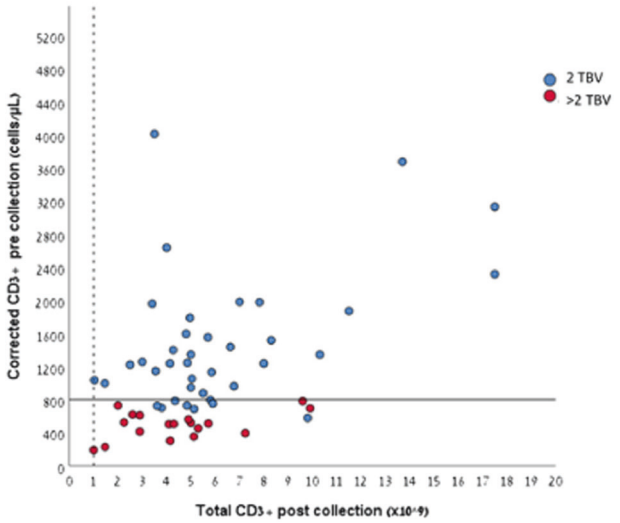
[1]Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv, Israel

Background: Characteristics of the collection material are the first to predict the end-product evaluation of anti-CD-19 CAR-T cells bag. This process starts when patient's cells are collected in the apheresis unit, transferred to the cell processing lab and cryopreserved. Manufacturing eligibility requires viable total nucleated cells (TNC) ≥ 2x10^9, total CD3 + cell ≥ 1x10^9 and % T cells ≥ 3. Pre-collection peripheral blood analysis of %CD3 by flow cytometry is recommended to calculate the minimum total blood volume (TBV) to be processed and to achieve the required number of CD3 + cells. The analysis is both time consuming and costly. Thus, we aimed to further improve calculation of sufficient TBVs based on pre-apheresis blood samples.

Methods: We retrospectively analyzed data from all consecutive patients that underwent leukapheresis and processing of collection material for the production of tisagenlecleucel between March, 2019 and December, 2021 in the Tel Aviv Sourasky Medical Center. We compared the percentage of lymphocytes in the cell count to the %CD3 + cells by Flow Cytometer analysis using Pearson correlation. Based on the correlation to precisely determine the minimum TBV needed for successful collection, we developed a novel equation based exclusively on peripheral blood cell count aiming to minimize TBV processed by the apheresis machine.

Results: We analyzed data of 75 patients with DLBCL (standard group, $n = 56$ and early collection group, $n = 19$). Median age was 69 (range, 21-85) years with 46 patients (61%) having ECOG > = 2. median number of prior lines in the non-early collection group was 2 (range 2-5). All patients, except 2 were collected in 1 day. Median number of collection cycles was 2 (range, 2-6). All collected products were eligible for manufacturing according to NOVARTIS recommendations. Six (8%) products were manufacturing out-of-specification and 2 (2.7%) were not infused. Pre-collection, there was a statistically significant correlation between %CD3 and %lymphocytes among both patients in the standard group ($r = 0.86$) and those in the early-collection group ($r = 0.95$) with a linear equation of $Y = 0.76X\text{-}1.2$ and, $Y = 0.76X + 2.08$, respectively. While there were no correlations between both the pre-collection peripheral blood %CD3 or WBC, and the total collected CD3 + cells, when we applied the linear equation based on both pre-collection %CD3 and WBC, we identified that patients with > 800 lymphocytes/μl required at most 2 TBVs, **Figure**. Receiver operating curve utilizing pre-collection lymphocyte number of 800/μl predicted TBVs with an area under the curve of 0.978 ($p < 0.001$) with sensitivity of 81.6% and specificity of 100%, while those with less than 800, required more than 2 TBVs and to precise calculate the number of TBVs, addition parameters were required. These parameters included

– the maximum number of cryobags in the vapor ship and logistics domains.



Conclusions: We identified a pre-collection peripheral blood lymphocyte level of 800/µl as sufficient for THE collection with 2 TBVs. In cases of less than 800, additional parameters are required to calculate the required TBVs. This enables a high degree of collection-effectiveness.

Disclosure: R.R received honoraria from Novartis

P559

Modifications of a standard ara-c mobilization protocol for ambulatory conditions

M. Dutka[1], A. Irga[1], A. Szymańska[1], M. Kurlapski[1], P. Sobieralski[1], M. Bieniaszewska[1], G. Moszkowska[1], J.M. Zaucha[1], D. Zielińska[1], P. Skowrońska[2]

[1]Medical Universyty of Gdansk, Gdansk, Poland, [2]University Clinical Center, Gdansk, Poland

Background: The safety of autologous hematopoietic cell transplantation (auto-HCT) depends on the number of infused CD34(+) cells. The optimal mobilization schema should be outpatient and result in the collection of a sufficient number of CD34(+) cells within the shortest time. Standard mobilization protocol: Cytosine arabinoside (Ara-C) total 1600mg/m^2 given 400mg/m^2 iv bid for two days requires hospitalization. Here we launched a prospective study aimed at modifying it for ambulatory conditions.

Methods: The design of the study was based on a 3 + 3 protocol performed in the reversed (de-escalation) direction. Standard mobilization schema: (Control Group) was modified and/or de-escalated to 4 schedules (table 1). G-CSF (5ucg/kg bid) was given 72 hours after the last dose of Ara-C until the first apheresis (day + 14). The minimal target dose (MTD) was 5x10^6 of CD34(+) cells/kg. If the MTD was not achieved in one apheresis in 1 patient at least 3 more patients were treated using the same schema, if in more than 2 the group was closed. The effectiveness of each schema was scored as follows: achievement of MTD in 1 apheresis 3 points, in 2 aphereses - 2, in 3 and more - 1, 0 - if MTD was not achieved. The group with the best scoring will be expanded. The primary endpoint is the total (highest) number of CD34(+) cells/kg collected in one leukapheresis. The secondary endpoints are the number of apheresis days, the total number of CD34(+) cells in the 2 best aphereses.

Results: Between 04/21-11/21, 42 patients were randomly enrolled in scheduled groups. The patient clinical characteristics and results are shown in Table 1. In the Control Group and Groups 1, 2, 3 the MTD was achieved by all except 1 patient each in Control, 1 and 2 group. In group 4 none of the patients achieved MTD in 1 leukapheresis therefore the study wasn't continued with this schema. The highest score (3) per patient was achieved in Group 3 which is not different from the Control Group (2,67). Similarly, the highest number of CD34(+) cells in one apheresis, as well as the highest total number of collected CD34(+) cells in 2 aphereses were documented in the Control Group and Group 3. Also in these groups, cells were collected in one apheresis in most patients.

Conclusions: The dosage of Ara-C at 800 mg/m^2 once a day for two days followed by standard G-CSF seems to be sufficient for collecting MTD in 1 leukapheresis. However, for the target dose of more than 10 x10^6/kg of CD34 cells a standard schedule of Ara-C dosing might be preferred.

Disclosure: Nothing to declare

P560

Plerixafor. A fixed dose of 12 mg for rescuing poor mobilizer patients with myeloma or lymphoma

A. Karduss-Urueta[1,2], A. Trujillo[3], A. Cardona[1], G. Ruiz[4], R. Perez[4,2]

[1]Instituto de Cancerologia- Clinica las Americas, Medellin, Colombia, [2]University of Antioquia, Medellin, Colombia, [3]Instituto de Cancerologia - Clinica las Americas, Medellin, Colombia, [4]Instituto de Cancerologia, Medellin, Colombia

Background: The use of plerixafor can rescue about 70-75% of poor mobilizer patients(1). This drug comes in 24 mg vials, the standard dose is 0.24 mg/kg, equivalent to 18 mg for a 75 kg

Table 1.

Group	AraC dose mg/m^2 iv [day 1/day 2]	No.patient Sex [F/M]	Age Med.[MIN/MAX]	Diagnosis [MM / LYMPH.]	AraC dose mg Avg [SD]	No.Aph. MED.[MIN/MAX]	Aph.max.CD34x10^6/kg MED.[MIN/MAX]	2xAph.CD34x10^6/kg MED.[MIN/MAX]	Score/patient
Control	2x400/2x400	21 [14/7]	61 [28/71]	15 / 6	2832 [472]	1 [1/3]	10 [1,3/48]	10,3 [1,9/48]	2,67
1	1x1600 / 0	7 [4/3]	50 [22/66]	4 / 3	2940 [415]	2 [0/3]	3,9 [0-11,8]	6,3 [0/11,8]	1,43
2	2x800 / 0	7 [4/3]	61 [47/69]	5 / 2	2940 [388]	2 [1/3]	4,4 [0,61-12,8]	8,1 [0,6/12,8]	1,86
3	1x800/1x800	4 [2/2]	66 [64/68]	3 / 1	3072 [227]	1 [1/2]	8,5 [5,8-18,8]	8,5 [5,8/18,8]	3
4	2x400 / 0	3 [0/3]	62 [49/69]	3 / 0	1536 [56]	2 [2/2]	2,9 [2,4-3,8]	5,6 [4,4/7,2]	1,33

patient, leaving a remnant of 6 mg per vial. Plerixafor has a stability of up to 84 days (2) allowing the remnants to be used during that time. We report the results of emergency and compassionate use of a fixed dose of 12 mg to rescue poor mobilizers.

Methods: We reviewed the records of all patients with myeloma or lymphoma who received an ASCT at our center (Jan 2020 - Nov 2021, were included those who needed emergency use of plerixafor, and in whom, for logistical or administrative reasons, the standard dose was not available and received 12 mg using remnants stored aseptically at room temperature. The definition of poor mobilizer used was that recommended by EBMT consensus (1): CD34 blood count on day 4 of mobilization less than 10 per uL or failure to obtain, after one apheresis, half the number of CD34 expected for transplantation. Mobilization and harvest consisted of filgrastim 7.5 mg/kg BID for 5 days, and one to three large volume apheresis. All patients consented to plerixafor application.

Results: I- Sixteen patients met the inclusion criteria, 7 were female, median age was 54.5 years (R: 31-68), mean weight; 66.5 kg (R: 48-80). Six had myeloma, 5 of them were exposed to lenalidomide, 2 were heavily treated; 10 had lymphoma; 3 of them received HyperCVAD, five had two or more lines of treatment, and 3 had radiotherapy to pelvis or abdomen. Thirteen out of 16 cases had a blood CD34 count on day 4 of mobilization less than 10/uL, X: 3.23 (R: 2-8), three had an insufficient CD34/kg count after the first harvest. Twelve received one dose of plerixafor and four received two. The main adverse events were grade I-II diarrhea and myalgias (65%), there were not any cases of infection associated with the use of reminder of plerixafor.

II- The mean number of apheresis was 1.6 (R: 1-3), the mean CD34 obtained was 2.28 million/kg (R: 0.5-3.42). Twelve out of 16 patients reached a CD34 number of 2.0 million/kg or more and another two: 1,6 and 1,75 million/kg respectively, all these 14 were transplanted. Two did not reach enough number of CD34 positive cells after three apheresis

All patients were given myeloablative conditioning and filgrastim post-transplantation. All cases had a hematopoietic recovery, the average days for autonomous neutrophil and platelet production was 11.14 (R 10-12) and 14.0 (R 12-25) respectively. Transplant-related mortality was zero, and after a median follow-up of 7 months (R: 2-17), all are alive without loss of hematopoiesis.

Conclusions: A fixed-dose of 12 mg of plerixafor, using the remnants of it, was effective (87%), and safe in rescuing poor mobilizers

Considering the stability of the product and its cost, it is worth carrying out a dose optimization study.

1. Bone Marrow Transplantation (2014) 49: 865
2. Pharm. Technol. Hosp. Pharm. 2016; 1(2): 73

Disclosure: The authors did not have disclosures

P561

Adopting plerixafor in a limited resource scenario: Clinical and pharmacoeconomic comparison of hematopoietic stem cell mobilization strategies

L. Mariano[1], R. Alencar[2], F. Moreira[2], L.J. Otuyama[2], V. Rocha[2]

[1]Hospital das Clinicas da Faculdade de Medicina da USP, Sao Paulo, Brazil, [2]Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil

Background: Failure rate of hematopoietic stem cell mobilization (HSC) with traditional protocols described in literature ranges between 10-25%. Current evidence suggests a beneficial use of plerixafor in selected cases, with a reduction in mobilization failure rate to 3%. However, its high cost is the major limiting factor for routine use, with a scarcity of studies in Latin America evaluating the cost-benefit of this drug. Thus, the need to assess cost-effectiveness of using plerixafor in public health services in an emerging country is meaningful.

Methods: Retrospective observational study with patients over 18 years of age who underwent hematopoietic stem cell mobilization between January 2014 and December 2020. Clinical and pharmacoeconomic effectiveness of HSC mobilization protocols adopted over 03 different periods were evaluated: pre-Plerixafor protocol (Period 1), use of Plerixafor in mobilization failure (Period 2) and preemptive use of Plerixafor (Period 3). HSC mobilization failure was defined as collection of less than 2.0 x 10^6 $CD34^+$ cells/kg after a mobilization protocol. The cost values used were based on SIGTAP (Brazilian public health cost chart) and on hospital cost of the drugs used.

Results: Of the 623 patients evaluated, 51.7% (322) were diagnosed with Monoclonal Gammopathies and 42.5% (265) with Lymphomas. 49.9% (311) of this cohort underwent mobilization with G-CSF while 50.1% (312) received G-CSF and chemotherapy. HSC mobilization failure rate was 13.43%. 96.5% (517) of patients who successfully mobilized needed only 1 apheresis session to collect HSC. Success rate of HSC mobilization with only 1 collection was of 89% in Period 1, 82.7% in Period 2 and 85.5% in Period 3. Main factors associated with failure rate of HSC mobilization was age older than 32 years ($p = 0.013$), pre-mobilization white blood count less than 5,800 ($p = 0.007$) and previous use of Fludarabine, Lenalidomide or alkylating agents ($p = 0.017$). Such factors did not show statistical significance after analysis by multivariate logistic regression. Cost per patient was of R$1,556.83 in Period 1; R$3,820.77 in Period 2; R$4,278.09 in Period 3. Incremental cost-effectiveness ratio for a 10% benefit with the use of Plerixafor was of R$24,160.63.

Conclusions: The incorporation of plerixafor in a Brazilian public health service did not reduce the rate of HSC mobilization failure in the analyzed periods, although it significantly increased the cost per patient. Evaluation of variables related to time until transplantation and associated morbidity can contribute to define the best use of new drugs.

Disclosure: Nothing to declare.

P562

The impact of cryopreservation of peripheral blood stem cells (PBSC) on early clinical outcome after allo-hsct

A. Ciomber[1], I. Mitrus[1], W. Fidyk[1], M. Wilkiewicz[1], A. Smagur[1], A. Chwieduk[1], M. Głowala-Kosińska[1], P. Borzdziłowska[1], S. Giebel[1]

[1]Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland

Background: Before the March 2020, cryopreservation of allo-HSCT grafts was restricted only to exceptional situations. Since the begining of the COVID-19 pandemic, it is strongly recommended, to have secured stem cell cryopreserved product before the start of patient conditioning.

The aim of the study was to evaluate the impact of cryopreservation of PBSC on clinical outcome after allo-HSCT.

Methods: Study group: The study group consisted of 131 patients who underwent allo-HSCT at the Department of Bone Marrow Transplantation and Oncohematology, National Research Institute of Oncology, Gliwice Branch, Poland. We retrospectively investigated the clinical outcomes of 66 allo-HSCT performed with cryopreserved PBSC (from 03.2020 to 02.2021) and compared to 64 patients transplanted with unfrozen PBSC (from 01.2019 to

03.2020). The study groups did not statistically differ with regard to the diagnosis, age, conditioning regimen, type of donor and the number of transplanted cells.

Methods: The PBSCs were cryopreserved with 5% DMSO solution within 72 hours after collection and stored in liquid nitrogen (median storage time 22 days; min 5, max 152). In the control group PBSC were infused within 72 hours after leukapheresis.

The time to leukocyte and neutrophil recovery was defined as the first of 3 consecutive days, on which absolute cell count in peripheral blood was higher than 1×10^9/L and 0.5×10^9/L, respectively. We have compared two points in the time to platelet recovery, defined as the first of 3 consecutive days, on which platelet count in peripheral blood was higher than 50×10^9 and 100×10^9 respectively.

The frequency of GvHD (grade 0 and I–III), CMV reactivation and donor chimerism level were also compared between groups.

Statisitics: The differences between groups with regard to numerical variables were evaluated using Mann-Whitney U-test, chi-squared test was used in case of categorical variables. Time to hematopoietic recovery was estimated using the Kaplan–Meier method (observations were censored in case of death). The groups were compared with log-rank test ($p < 0.05$ was considered as statistically significant).

Results: There were no statistically significant differences in the median days of leukocyte, neutrophil and platelet recovery between groups. The groups do not differ significantly in terms of GvHD, CMV reactivation and chimerism level. The results are presented in Table 1.

	Cryopreserved HSCT	Fresh HSCT	p
Day of leukocyte recovery (WBC > 1 G/L) (median,range)	15 (10-28)	14 (10-30)	0.06
Day of neutrophil recovery (ANC > 0.5 G/L) (median,range)	16 (12-26)	15 (10-30)	0.50
Day of platelet recovery (PLT > 50 G/L) (median,range)	13 (10-50)	14 (10-35)	0.58
Day of platelet recovery (PLT > 100 G/L) (median,range)	15 (13-42)	16 (11-31)	0.67
Acute GvHD			
Grade 0	44	46	0.69
Grade I	15	13	
Grade II-III	7	5	
CMV reactivation			
Yes/No	41/25	42/22	0.45
Donor chimerism level (30th day after HSCT > 95%)			
Yes/No	65/1	63/1	0.25

Conclusions: Cryopreservation of unrelated donor products does not appear to negatively affect early clinical outcomes after allo-HSCT. On the other hand, the safety of transplant procedure is increased by the guaranteed availability of PBSC when recipient conditioning is started.

Disclosure: Authors declare no conflict of interest

P563

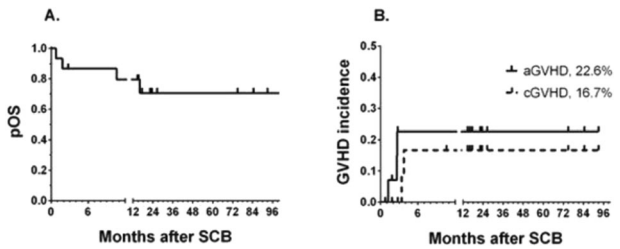
Hematopoietic recovery with manageable complications after stem cell boost with immunomagnetic selection in the therapy of allogeneic poor graft function

J. Fraczkiewicz[1], M. Majcherek[2], A. Szeremet[2], R. Ryczan-Krawczuk[1], B. Rybka[1], T. Wróbel[2], A. Czyż[2], M. Ussowicz[1]

[1]Wroclaw Medical University, Wroclaw, Poland, [2]Wroclaw Medical University, Wroclaw, Poland

Background: Poor graft function (PGF) is a rare, life threatening complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT), characterized by protracted multilineage cytopenia with dominant (>95%) allogeneic chimerism. We analyzed the outcomes of CD34-enriched or T-cell depleted (TCD) stem cell boost therapy (SCB) without preceding chemotherapy for PGF in 16 patients transplanted in Wroclaw Medical University stem cell transplant centers in years 2002-2021.

Methods: The median age at SCB was 15.24 years (range 0.8-66 years). Patients were transplanted for malignant (14 patients: ALL-5, MDS-EB/AML- 4, other - 5) or nonmalignant (2 patients) diseases. One of the treated patients was after 6 months of unsuccessful eltrombopag therapy for PGF. Donor types were matched unrelated (7/16), and haploidentical donors (9/16). The median time from allo-HSCT to SCB was 126 days (range: 19 to 1085 days). Immunomagnetic selection was performed with Miltenyi CliniMacs Plus or Prodigy: CD34 enrichment in 11 patients, alpha-beta T-cell depletion in 4 patients, and combination of both procedures in 1 patient. The median SCB dose was 5.88 x 10^6 CD34 cells/kg (range, 1.34-32 x 10^6 CD34 cells/kg). The median T-cell dose/kg was 0.33 x 10^4 in CD-34 enrichment (range 0.04-13.1 x 10^4 cells/kg), and median alpha-beta T-cell/kg 1.31 x 10^4 in alpha-beta TCD (range 0.88-2.65 x 10^4 cells/kg). The post-SCB immunosuppressive treatment consisted of mofetil mycophenolate (MMF, 3 patients), MMF + tacrolimus (4 patients), none (6 patients), or other (3 patients). Filgrastim was administered in 9/16 patient for a median of 15 days (10-22).



Results: Three lineage hematopoietic recovery was achieved in 14/16 patients. Absolute neutrophil count >500/uL was reached at median of 11 days after SCB (range 4-17 days). After a median follow-up of 17 months (range 2-84.5 months), the probability of OS was 70.6% (figure A.). The incidence of acute and chronic GVHD after SCB was 22.6% and 16.7% (figure B.), respectively. Non-relapse mortality was reported in 3/16 patients, and death due to relapse was observed in 1 patient.

Conclusions: The SCB represent effective treatment for PGF with manageable complications and rapid neutrophil recovery, as reported in standard allo-HSCT. The major limitation is the need for cell processing facility equipped with specialistic equipment and availability of the allo-HSCT donor. Of interest, the efficacy and safety of TCD SCB product is worth further studies.

Disclosure: Nothing to declare

P564

A comparison of mobilization regimens in autologous stem cell transplantation for multiple myeloma

T. Chandler[1], F. Seymour[1], C. Parrish[1], M. Karakantza[2], D. Pawson[2], J. Carmichael[1], G. Cook[1]

[1]Leeds Teaching Hospitals NHS Trust, St James's Institute of Oncology, Leeds, United Kingdom, [2]National Health Service Blood and Transplant, Barnsley, United Kingdom

Background: Harvesting of peripheral blood haematopoietic stem cells (PBSC) in multiple myeloma entails mobilisation with granulocyte colony stimulating factor alone (G-CSF) or in combination with chemotherapy, typically cyclophosphamide (Cyclo-G). Whilst historically Cyclo-G has been the technique of choice, more recently there has been a shift toward chemotherapy-free mobilisation. This retrospective study evaluates the mobilisation strategies utilised by a single regional comprehensive cancer centre.

Methods: 83 patients underwent a total of 86 mobilisation procedures between January 2016 and September 2021. While a minimum of $2x10^6$ $CD34^+$/kg per autologous stem cell transplant (ASCT) is required for safe engraftment, higher doses of $3\text{-}5x10^6$/kg are associated with optimal engraftment. It is common practice to collect sufficient PBSC for two ASCTs. Therefore our $CD34^+$ minimum target was $>4x10^6$/kg, with an optimal target of $>8x10^6$/kg. The outcomes measured were stem cell yield, days of harvesting, rescue plerixafor use and mobilisation complications. Groups were compared using the Mann-Whitney or Chi-squared test.

Results: 66 harvests used Cyclo-G mobilisation (Cyclophosphamide $2g/m^2$ then G-CSF 5mcg/kg for 10 days), and 20 used G-CSF (10mcg/kg for 5 days). 93.02% of harvests collected the minimum dose. The failure rate of Cyclo-G was 4.5% in comparison to G-CSF which was 15%.

Patients receiving Cyclo-G yielded higher $CD34^+$ doses (8.94 *vs.* 4.88 x 10^6/kg, $p = <0.0001$) and collected with fewer days of apheresis (1.6 *vs.* 2.4 days, $p = 0.007$). Harvests attaining the optimal collection target were more frequently seen with Cyclo-G (62% *vs.* 11%, $p = 0.0001$). Mobilisation with G-CSF resulted in a higher percentage of patients requiring salvage plerixafor (35% *vs.*13.6%, $p = 0.0407$).

$CD34^+$ yields were lower in patients who received IMiD containing induction regimens prior to mobilisation (5.18 *vs.* 8.98 $x10^6$/kg, $p = 0.00003$) and the use of Cyclo-G mobilisation did not overcome this negative impact (5.8 *vs.* $4.8x10^6$/kg, $p = 0.34$).

There were no recorded infective complications relating to mobilisation with G-CSF. Five patients receiving Cyclo-G were hospitalised, including one who required treatment for neutropenic sepsis.

	Cyclo-G	G-CSF	
Number	66	20	
Age (years)	60	61.5	$p = 0.571$
1st line treatment (%)	89	90	$p = 0.938$
Cycles of induction pre-apheresis (number)	5.3	4.1	$p = 0.0021$
CD34 dose > 4x106/kg (%) (1st line patients only)	97	83	$p = 0.045$
CD34 dose > 8x106/kg (%) (1st line patients only)	62	11	$p = <0.0001$

Conclusions: Patients receiving Cyclo-G mobilisation achieved larger stem cell harvests in fewer days, and required fewer doses of salvage plerixafor than G-CSF-only mobilisation. IMiD containing induction negatively impacted on $CD34^+$ yield. Infectious complications rates were low. In the era of IMiD based induction and continuous IMiD maintenance, these data highlight the negative impact of IMiD treatment on $CD34^+$ mobilisation and the importance of optimising the stem cell collection in the first line setting to ensure sufficient cells are collected for subsequent ASCTs. Incorporation of additional novel agents (e.g. daratumumab) into induction regimens has been shown to further compromise stem cell harvest yields, and consideration should be given to re-adoption of Cyclo-G as a standard of care for stem cell mobilisation.

Disclosure: Nothing to declare

P565

Clinico-laboratoristic aspects of cryopreservation of peripheral blood stem cells (PBSC) in match unrelated transplant

G. Facchin[1], C. Savignano[2], M.L. Battista[2], U. Pizzano[1], C. Rosignoli[1], M. Cerno[2], A. Bertone[2], G. De Cecco[2], M. Isola[1], G. Barillari[2], R. Fanin[1,2], F. Patriarca[1,2]

[1]University of Udine, Udine, Italy, [2]Azienda Sanitaria Friuli Centrale, Udine, Italy

Background: Pandemic SARS-CoV-2 has increased the use of cryopreserved hematopoietic-stem-cells(HSC) in MUD transplants. The impact of unrelated donor graft freezing on outcome of allo-HSCT in terms of hematological recovery, acute graft-versus-host-disease(GVHD) and survival is still controversial.

Methods: we evaluate the impact of variables related to cryopreservation on the viability of HSCs and engraftment in all MUD transplants performed at our Center using cryopreserved PBSC (CryoPBSC) from January 2020 to July 2021. The variables considered were: time between apheresis and freezing(t1), buffy composition, viability on satellite tube (48 hours after freezing) and bag (Trypan Blue and 7-AAD). We also compare graft composition, clinical characteristics, and outcome of 23 allo-HSCT from Cryo-PBSC (Cryo-Group) with 23 from fresh-PBSC (Fresh-Group) performed at the same period.

Results: Tab.1 resume characteristics of 31Cryo-PBSC-MUD-transplants performed.

MEDIAN DONORS AGE	30 (19-21)
SEX PATIENTS:	
Male	13/31 (42%)
Female	18/31 (58%)
SEX DONORS:	
Male	24/31 (77%)
Female	7/31 (23%)
MEDIAN PATIENTS WEIGHT (kg)	76 (49-100)
MEDIAN DONOR WEIGHT (kg)	(54-103)
PATIENTS DISEASE	
Acute Leukemia	22/31 (71%)
Other	9/31 (29%)

DISEASE STATUS	
Complete remission	16/31 (52%)
Relapsed/Refractory	11/31 (35%)
Other	4/31 (13%)
HLA COMPATIBILITY	
10/10	22/31 (71%)
Others	9/31 (29%)
ABO COMPATIBILITY	
Major incompatibility	13/31 (42%)
Minor incompatibility	13/31 (42%)
Compatibility	5/31 (16%)

Mean t1 was 43.5hours(23.8-53.5). Leukocytes on buffy were $245x10^3$uL($128x10^3$-$484x10^3$) with 24%(4-75) neutrophils(PMN). Median TB viability was 76(54-97) on freeze and 61%(27-89) on satellite tube. Mean time from freezing to reinfusion was 12.6 days(5.5-26.6). The post thawing 7-AADviable CD34s were 66%(29-89). Univariate analysis showed a tendency to inverse correlation between t1 and post thawing TB($p = 0.057$, Spearman's rho -0.3509). t1 correlated with PLT engraftment($p = 0.0036$) while t1 didn't correlate with neutrophil recovery ($p = 0.2416$). Buffy composition didn't impact on post thawing viability. Hematological recovery occurred after 14days(10-17) for PMN > 500uL and 16days(11-30) for PLT > 20.000uL without cases of graft failure.

The comparing sub-analysis between Cryo(complete data aviable only for 23 transplants) and Fresh group(23 transplants) shows no significant differences in clinical characteristics of patients, donors and transplants. In Cryo-Group median time from apheresis to cryopreservation was 1.78 days(0.99-2.23) while median time from cells collection and reinfusion was 15.04 days(7.66-25.45). In the Fresh Group median time from apheresis to reinfusion was 1.57 days (0.89-2.4). Viable CD34 + cells infused were significantly lower in Cryo-Group($4.98x10^6$/kg vs $7.02x10^6$/kg; $p = 0.001$). All patients engrafted with no statistical differences in neutrophils and platelets recovery. No differences in transfusion needs and acute GVHD ≥ 2 incidence(36%Cryo-Group vs 39% Fresh-Group;$p = 0.463$) were recorded. All patients were alive 100-days after transplant in Cryo-Group. Two out 23 patients in Fresh-Group died due to infections.

Conclusions: In our series, TB on freezing seems to be influenced by t1 even though it doesn't reach statistical significance. Viability 48hours after cryopreservation is a good indicator of post thawing viability. No differences between Cryo and Fresh groups were found in engraftment, acute GVHD ≥ 2 incidence and 100-days survival, despite a lower CD34 + infused dose in Cryo-Group.

Disclosure: Nothing to declare

P566

Autologous stem cell transplantation in a patient with red cells agglutination in low temperature

I. Mitrus[1], W. Fidyk[1], M. Wilkiewicz[1], A. Smagur[1], A. Ciomber[1], P. Borzdzilowska[1], A. Chwieduk[1], M. Glowala-Kosinska[1], M. Sadus-Wojciechowska[1], M. Sobczyk-Kruszelnicka[1], S. Giebel[1]

[1]Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland

Background: Successful autologous hematopoietic stem cell transplantation depends on safe cryopreservation and storage of the cellular product. Any problems during these steps could result in cellular material loss.

Methods: Clinical case: 35-year-old man diagnosed with Hodgkin's lymphoma, initially treated with six cycles of BEACOPP and three cycles of BGD (Bendamustine, Gemcytabine, Dexamethasone) chemotherapy, was referred for autologous HSC transplantation. The patient was in CR phase. His blood type was A, RhD positive. Mobilization of HSCs was performed using ID-ARA C (total dose 3200 mg) on days 1 and 2, combined with G-CSF at a dose of 10μg/kg/day for 5 days, starting at +9 day. As a result of the apheresis, $22.5×10^6$ per kg CD34-positive cells was obtained. According to the local protocol, cellular product was stored in 4°C, with shaking, until cryopreservation. Next day, the appearance of cell suspension has changed – the red blood cells were clumped. When the product has been transferred into temperature room, the aggregates disappeared, without hemolysis. After cooling, the cells clumped again. Despite this situation, the cells were frozen in 4 cryopreserved bags, in a mixture containing 5% DMSO, and stored in liquid nitrogen vapor.

If the aggregates had not dissolve after thawing of the transplant material, the infusion of HSCs would be impossible. To check for clumping post-thaw, one bag was thawed and heated to room temperature 1 week after freezing. No aggregates of cells were seen, and the 200μm filter was not blocked during the transfer of the cell suspension into the transfer bag. Based on this result, the material was considered suitable for transplantation.

Results: The patient underwent conditioning chemotherapy before autologous transplantation with BeEAM (bendamustine, etoposide, cytarabine, melphalan), and the transplant material was successfully infused. The viability of cells was low (65%). They were no adverse effects during the infusion, and no post-transplant complications occured. WBC engraftment (WBC > 1.0G/L) and ANC engraftment (WBC > 0.5 G/L) was achieved on day 9, and platelet engraftment (Ptl > 20G/L, without platelet transfusion for 7 days during seven preceding days) on day 13.

Conclusions: This case report presents safe autologous transplantation in patient with reversible agglutination. This phenomenon could be associated with cold agglutinin disease (CAD), which may occur in lymphomas. CAD is often not clinically important, however, there is limited information about cryopreservation of cell suspension in this kind of situtation. We have found only two case reports concerning the successful transplantation of HSCs in patient with cold agglutinins, however, in both patients the red cells clumped in room temperature [Crowther et al, 2006; Badami et al., 2017].

HSCs from patient with CAD may be used for transplantation, however, checking the quality of the material by thawing one cryopreserved bag before conditioning is recommended to assure its viability.

References: Badami et al. Autologous peripheral blood stem cell harvest and transplant in a patient with cold agglutinin disease secondary to lymphoma. *Transfus Med*. 2017;27:222-224.

Crowther t al. Successful autologous peripheral blood stem cell harvest and transplant in a patient with cold agglutinins. *Bone Marrow Transplant*. 2006;37:329-30

Disclosure: N/A

P567

Factors limiting the access to performing an autologous hematopoietic stem cell transplant in candidates. A single center experience in Mexico

M.A. Tapia Bravo[1], B.L. Acosta Maldonado[1], L.M. Valero Saldaña[1], L. Rivera Fong[1], E. Arrieta López[1], I.K. Pellón Tellez[1], F.E. Ahumada Córdoba[1]

[1]Instituto Nacional de Cancerología, Mexico City, Mexico

Background: Autologous hematopoietic stem cell transplantation (ASCT) is widely used as a consolidation therapy in non-Hodgkin's lymphoma (NHL), recurrent or refractory classic Hodgkin's lymphoma (HL), Multiple Myeloma (MM) and other malignant diseases. However, in Mexico and other countries in Latin America, about 26% of general population do not have health insurance and there is a limited number of centers which performing ASCT; these factors hinder the access to this treatment in patients with hematological cancer.

Considering the financial and infrastructure limitations, it is imperative to create strategies to carefully select patients for the transplant program, to reduce the risk of exclusion during the process and optimize the resources. This study aims to identify those factors that directly exclude patients with hematological and non-hematological malignancies for ASCT in a single center in Mexico.

Methods: A retrospective study was conducted in patients with hematological and non-hematological diseases, candidates. for ASCT as consolidate therapy, at the Instituto Nacional de Cancerología (INCan), in Mexico, between January 2010 and. December 2020.

The data was analyzed using. SPSS statistical software v23.

Results: A total of 334 patients with hematological and non-hematological neoplasm who were candidates for an ASCT were analyzed.

284 (84%) received an ASCT (Multiple Myeloma n = 131, HL n = 64, NHL n = 133 and Germ cell tumor n = 5), while 50 patients (15%) failed to complete ASCT process. Causes that directly led the exclusion of this patients were identified and are summarized in table 1.

The characteristics of patients not being able to continue to an ASCT were a median age 52 years (range 18-70), male predominance (54%). Most of the patients excluded had the diagnosis of Multiple Myeloma n = 21 (42%), followed by Non Hodgkin's lymphoma n = 20 (40%) and Hodgkin's lymphoma n = 9 (18%). The most common causes of exclusion was the relapse of the disease and peripheral blood stem cell mobilization failure.

There were non-statistical significant differences results between both groups.

Table 1. Exclusion cause for ASCT.

	n = 50 (%)
Relapse disease	19 (38)
Mobilization failure	16 (32)
Socio-cultural beliefs	7 (14)
Infection	5 (10)
Socioeconomic status	1 (2)
Non hematological death	1 (2)
Other	1 (2)

Conclusions: The Instituto Nacional de Cancerología (INCan) is one of the few centers in Mexico performing HSCT. While 85% of the patients who are candidates for an ASCT, 15% of the patients fail to proceed with the transplant program. The main causes of failure to reach an ASCT are the relapse of the disease and peripheral blood stem cell mobilization failure, both constitute more than half of the situations that excluded these patients.

Strategies to prevent the identified causes of exclusion from the transplant program have to focus on an earliest referral of the patients, reducing the waiting time to perform the transplant, and to have access to better mobilization therapies.

Disclosure: Nothing to declare.

P568

Mobilization of hematopoietic stem cells with lenograstim in multiple myeloma patients with minimal residual disease

J.M. Byun[1], E.H. Jung[2], D.-Y. Shin[1], Y.R. Do[3], H. Kim[4], S.H. Bae[5], S.-J. Kim[6], J.-Y. Kwak[7], S.M. Lee[8], S.-S. Yoon[1]

[1]Seoul National University Hospital, Seoul, Korea, Republic of, [2]Seoul National University Bundang Hospital, Seongnam, Korea, Republic of, [3]Dongsan Medical Center, Keimyung University School of Medicine, Daegu, Korea, Republic of, [4]Gachon University Gil Medical Center, Incheon, Korea, Republic of, [5]Daegu Catholic University School of Medicine, Daegu, Korea, Republic of, [6]Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, Republic of, [7]Chonbuk National University Medical School, Jeonju, Korea, Republic of, [8]Busan Paik Hospital, Inje University, Busan, Korea, Republic of

Background: Current guideline suggest using filgrastim or tbo-filgrastim for mobilization of hematopoietic progenitor cells in autologous setting. However, previous studies have suggested other forms of granulocyte colony stimulating factor (G-CSF) are equally efficacious, possibly with fewer aphereses required. Thus, we prospectively studied the efficacy of lenograstim, a glycosylated recombinant form of G-CSF, in multiple myeloma (MM) patients.

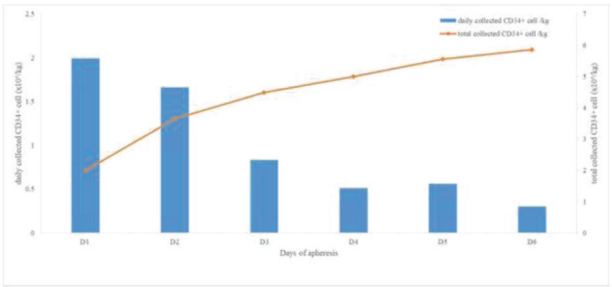
Methods: From November 2011 to January 2020, 98 MM patients undergoing autologous stem cell transplant (ASCT) from 8 academic centers in Korea were enrolled. Donors were mobilized with subcutaneous lenograstim (Neutrogin®) with fixed doses of 10 ug/kg for four days. There was no dose adjustment of G-CSF during mobilization. The collection was performed on day 5, with goal of collecting 5 x 10^6 CD34 + cells/kg body weight. This study was carried out according to the Helsinki Declaration, and was approved by Institutional Review Board of each participating study center. All patients gave their informed consent.

Results: Most of patients (N = 90, 91.8%) achieved targets of ≥ targets of 2 x 10^6 CD34 + cells/kg body weight and more than half of MM patients (N = 57, 58.2%) reached target of 5 x 10^6 CD34 + cells/kg body weight. Among those attaining of 2 x 10^6 CD34 + cells/kg, 48.0% (N = 47) patients met target requirement in a single leukapheresis. The median number of apheresis required for optimal collection of 5 x 10^6 CD34 + cells/kg was 2 (range 1-5). Half of patients (N = 49, 50.0%) showed optimal collection success within third apheresis. The mobilization failure rate was 8.2% (N = 8). The median number of CD34 + cell/kg using G-CSF only was 5.25 x 10^6/kg (range 0.49-13.47). There were ten patients (10.2%) with adverse events during the mobilization. The most frequently reported adverse event was bone pain (N = 6, 6.1%). Other side effects included diarrhea (N = 1, 1.0%), fever (N = 2, 2.0%), and abdominal pain (N = 1). Out of 98 patients, 93 were able to undergo ASCT. The median infused dose of CD34 + cell/kg body weight was 3.42 (range 1.80-11.00). Neutrophil engraftment was observed in all patients, and platelet engraftment was observed in 89 (95.7%) patients. The median time to neutrophil and platelet engraftment was 10 days (range 1-21 days) and 10 days (range 1-37 days), respectively.

Table. Baseline characteristics and collection outcomes.

Characteristics	N = 98
Age (median, years)	59.0 (35-70)
Median no. of apheresis procedures (median, range)	3 (0-6)
Median of total collected PB CD34 + cells (median, range, x 106/kg)	5.25 (0.49-13.47)
No. of patients with transfusion during apheresis, N (%)	
RBC	5 (5.1%)
Platelet	51 (51.5%)
Complication during apheresis, N (%)	10 (10.1%)
Neutrophil engraftment for autologous stem cell transplant	93 (93/93, 100%)
Time to neutrophil engraftment, days (median, range)	10 (1-21)

Figure. Change of daily and total collected CD34 + cell count after starting apheresis



Conclusions: Lenograsim can safely and effectively mobilize stem cells in MM autologous setting.

Disclosure: Neutrogin® was provided by JW Pharmaceutical

P569

Safety of bone marrow hematopoietic stem cell collection from a sars-cov-2 positive donor: A single experience during the Italian pandemic

G. Magliano[1], B. De Marco[1], G. Bertani[1], L. Pezzetti[1], L. Intropido[1], G. Travi[1], E. Volpato[1], G. Grillo[1], R. Cairoli[1]

[1]*ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy*

Background: The worldwide pandemic caused by SARS-CoV-2 virus has brought significative burden to the Health Care system, including programs performing allogeneic hematopoietic stem cell transplantation (HSCT). The true impact on the whole procedure is still to be determined.

We present the case of a safe bone marrow collection procedure from a SARS-CoV-2 positive donor.

Methods: A 54 year-old woman, who came to our attention in September 2020 for pancytopenia, was diagnosed with severe aplastic anemia. The 55 year-old patient's brother was selected as a potential HLA haploidentical donor. His past medical history was not significant.

Pre-donation screening exams were permissive.

Despite a first negative molecular test on nasopharyngeal swab, a new pre-operative test, performed on the basis of hospital policy, revealed positivity for SARS-CoV-2. The donor was completely asymptomatic.

Considering the urgent need to treat our patient, as the general clinical conditions were rapidly worsening due to infectious complications, we decided not to stop the transplant procedure.

Conditioning regimen was cyclophosphamide 300 mg/mq + fludarabine 30 mg/mq (days -6 to-3), GvHD prophylaxis was antithymocyte globulin 3,75 mg/Kg (days -1 and 0), total body irradiation (TBI) 400 cGy (day -1).

Results: Bone marrow harvesting was performed in an operating room which provided airborne infection isolation routine. The involved medical team wore enhanced personal protection equipment. The procedure was free from clinical and anesthesiological complications.

SARS-CoV-2 RNA on the product was found negative in real-time PCR.

In the absence of any symptom, the donor was discharged the day after the procedure and was put in home isolation.

Our patient received the processed product, which consisted in CD34+ cells 3.54 x 10^6/kg, total nucleated cells (TNC) 3.54 x 10^6/kg, CD3+ cells 0.285 x 10^8/kg, in 270 ml.

The recipient was negative for SARS-CoV-2 on nasopharyngeal swab after stem cell infusion.

Conclusions: Our case enlightens a successful bone marrow harvesting procedure from a SARS-CoV-2 positive donor, which was organised in urgent clinical need.

It demonstrates that transplantation from asymptomatic positive donors is feasible and safe, as viral transmission did not happen, since the stem cell product was RT-PCR negative for SARS-CoV-2.

Although EBMT does not recommend stem cell donation from positive individuals, donor care and selection in this pandemic era should be revisited, as SARS-CoV-2 swab positivity itself might not be an exclusion criteria for bone marrow donation.

Further data are needed to assess whether harvested marrow could transmit SARS-CoV-2.

Specific measures are also needed to provide the safety of the bone marrow collection medical team.

Disclosure: Nothing to declare.

P570

The impact of dara-vrd on stem cell mobilisation and successful engraftment; a real world case series

J. Patel[1], W. Toscano[1], I. Gabriel[1], M. Streetly[1], J. Topping[1], M. Kazmi[1]

[1]*London Bridge Hospital - Private Care at Guy's, London, United Kingdom*

Background: Following the GRIFFIN trial data publication, we reviewed the use of D-VRd induction (4 cycles) and consolidation (2 cycles) as the new standard of care in transplant eligible newly diagnosed multiple myeloma (NDMM) patients and our ability to successfully mobilise stem cells compared with a historic cohort of patients who were treated with RVd and having SCM as part of planned first line treatment for Myeloma. GRIFFIN trial data showed a median $CD34^+$ cell yield of 8.2 x 10^6/kg with the common requirement of plerixafor and the time to engraftment was indifferent in both arms.

Methods: All patients were treated with D-VRd Induction (4 cycles) prior to the stem cell collection, and all patients who were mobilised were all given Cyclophosphamide 1.5g/m2 and GCSF. Historic data of patients who were treated with RVd Induction was collected in order to compare the SCM yield time to neutrophil engraftment and times.

	D-VRd n = 12	RVd n = 5
Age, y, median (range)	55 (37-66)	61.4 (56-67)
Male, n (%)	8 (66.6)	3 (60)
Female, n (%)	4 (33.3)	2 (40)
ISS Disease stage 1, n (%)	5 (42)	4 (80)
ISS Disease stage 2, n (%)	6 (50)	1 (20)
ISS Disease stage unknown, n (%)	1 (8)	0

Results: 7 patients have been successfully mobilised. 1 patient is currently undergoing mobilisation and 4 patients are still on induction therapy. Of this 1 patient had to be mobilised twice due to failed first harvest and only 1 patient required plerixafor to successfully mobilise stem cells. The median $CD34^{+}x10^{6}$/kg yield was 4.07 (1.4-6.94) and the median day to neutrophil engraftment was 12.4 (range 12-14).

Of the above patients, 5 have completed their AHSCT and median $CD34^{+}$ x 10^{6}/kg yield was 4.64, median day to neutrophil engraftment was 12.4 and the median $CD34^{+}$ x 10^{6}/kg dose reinfused was 2.68. When compared to our historic data of patients who completed induction (4 cycles) with RVd the median $CD34^{+}x10^{6}$/kg yield was 5.69, median day to neutrophil engraftment was 11.2 and median $CD34^{+}$ x 10^{6}/kg dose reinfused was 4.10.

Conclusions: Quadruplet therapy is now becoming the standard of care in NDMM. Patients can be successfully mobilised after DVRd 4 cycles with good engraftment kinetics. However, there was a trend to lower yields (18.4%), 1 day longer median time to engraftment and a lower quantity of cells being reinfused (34.6% less). It is important to schedule in stem cell collection after no more than 4 cycles of induction therapy assuming the disease is responding to reduce the risk of sub optimal collection in particular if a tandem procedure is being planned.

Disclosure: Nothing to declare

P571

Efficacy of plerixafor plus g-csf in patients with multiple myeloma and lymphoma who have had mobilization failure with at least two regimens. A retrospective study

V. Ozkocaman[1], F. Ozkalemkas[1], İ.E. Pınar[1], T. Ersal[1], M. Buldu[1], V. Gursoy[1]

[1]Bursa Uludag University School of Medicine, Bursa, Turkey

Background: Plerixafor is a valuable stem-cell mobilizer for use in combination with G-CSF in patients with lymphoma or multiple myeloma, particularly those who are poor mobilizers. This study aimed was to evaluate the real-life impact of plerixafor+G-CSF mobilization regimen in cases where mobilization failed with at least two regimens for autologous stem-cell mobilization for patients MM and lymphoma.

Methods: Between August 2009 and December 2021, 513 stem-cell transplants were performed in our center. It could be collected with a plerixafor+G-CSF regimen in 21 of 373 cases. Patients received G-CSF 10 µg/kg in the morning (at 06:00) for four consecutive days, then a single subcutaneous injection of plerixafor 0.24 mg/kg in the evening of day 4 (at 23:00). Aphereses was begun in all patients on the 5th day. Accepted the target CD34 + cells yield was ≥ 4 x 10^{6}/kg. Continue G-CSF and plerixafor up to 4 aphereses until 4x10^{6} CD34 + cells /kg were collected. We can perform all apheresis collections with central venous access.

Results: The patient's characteristics are summarized in Table 1. 62% of the cases requiring plerixafor+G-CSF were due to lymphoma. The number of cases diagnosed with MM was six, 29%. A total of 75% of plerixafor+G-CSF patients reached target after two aphereses; only one patient required three procedures. Neutrophil engraftment of 16 autologous transplants was +12 to > 500 median day was reached (69 %). Platelet engraftment was +17.day arrived (50%). Plerixafor+G-CSF was well tolerated. The most common plerixafor-related adverse events were diarrhea (4.7%) and nausea (4.7 %). In this study, the addition of the results of plerixafor+G-CSF leads to increased stem cell collection in a shorter with no concomitant increase in adverse events.

Table 1. Patient Characteristics.

Period	August 2009-December 2021
n: 21	Total tx: 513
	Autologous tx: 373 (MM + Lymphoma)
	MM: 274
	Lymphoma: 99
	Mob regimen(G-CSF/ Chemotherapy+G-CSF): 252
	Required third step mob. regimen: 21/373 (7.6%)
Age, median (min-max)	51 (21-66)
Female/Male	6/15 (29%/ 71 %)
Diagnosis	
MM:	6 (29%)
Lymphoma:(NHL + HD): (12 + 3)	15 (71%)
Day 1,CD34 + cells count (post-plerixafor)	32 (5.8-92)
Median days of apheresis (day)	2 (2-3)
1	0
2	12 (75 %)
3	1
Total Yield CD34 + x 10^{6} cells/kg	
(min-max)	4.72 (1.3-7.17)
Not processed:	4 (19%)
<2 :	2 (9.5 %)
>2-4:	4 (19 %)

>4-6:	11 (52.3%)
Successful mobilization	16 (76 %)
Mobilization failure	5 (24 %)
Patients undergoing transplantation	16 (76 %)
Median time to engraftment (day), (min-max)	
Neutrophil> 500: 12 (9-17)	11/16 (69 %)
Platelet > 20 000: 17 (12-30)	8/16 (50 %)
Platelet > 50 000: 35 (17-95)	7/16 (44 %)
Adverse events	
Diarrhea	1 (4.7 %)
Nause	1 (4.7 %)

MM: multipl myeloma, NHL: non-Hodgkin lymphoma, HD: Hodgkin Disease

Conclusions: In conclusion, our data suggest that patients who were failing an initial mobilization attempt, in particular, can use those with lymphoma, and MM or ıt can be used at an earlier stage in severely treated patients.

Disclosure: No conflict of interest

P572

Haematopoetic stem cell transplant collections during the covid-19 pandemic in south africa

T.N. Glatt[1], R. Cockeran[1]

[1]South African National Blood Service, Johannesburg, South Africa

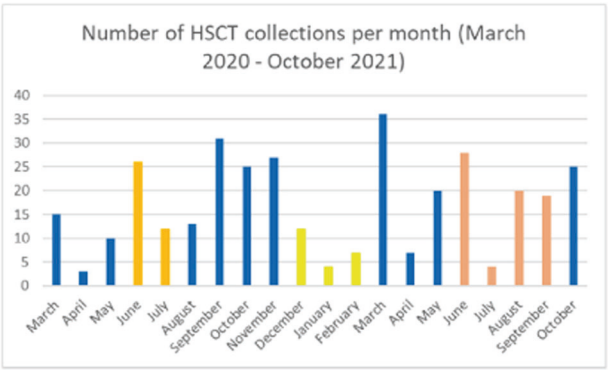
Background: South Africa reported its first two SARS CoV-2 positive cases on 2 March 2020. To date there have been over 250 million infections and three periods of increased transmission: wave 1 (June-July 2020), wave 2 (December 2020 to February 2021) and wave 3 (June 2021 to September 2021).

The South African National Blood Service (SANBS) provides a haematopoietic stem cell transplant (HSCT) service to 18 public and private clinical facilities across South Africa. In 2019 we performed a total of 329 HSCT collections, averaging 27 per month. Due to the pandemic, HSCT scheduling was disrupted. Reasons for this include governmental lockdown levels during specific periods of heightened infections, restricted availability of hospital beds for non-Covid-19 diseases and local and international recommendations on HSCT during the pandemic.

Methods: All paediatric and adult HSCT collections performed by SANBS from March 2020 to October 2021 were analysed. The HSCT collections during and between the three Covid-19 waves were analysed in conjunction with demographic data including gender, age, diagnosis, type of transplant and type of facility.

Results: During the 15 month period, 1st March 2020 to 31st October 2021, 344 HSCT collections were performed on 201 patients. The median age was 48 years, females accounted for 44.5% (n = 153) of HSCT collections and 95.9% (n = 330) were autologous HSCT collections. Indications for HSCT collections include multiple myeloma (n = 185), Non Hodgkin Lymphoma (n = 48), acute leukaemia (n = 39), Hodgkin Lymphoma (n = 34), neuroblastoma (n = 28), multiple sclerosis (n = 6), amyloidosis (n = 2), retinoblastoma (n = 1) and meduloblastoma (n = 1). 40.4% (n = 139) of HSCT collections were performed in public facilities.

The number of HSCT collections per month are shown in Figure 1. The orange colour variants express waves 1, 2 and 3 respectively. The average(range) number of HSCT collections per month was 17(3-36). The average(range) number of HSCT collections in wave 1, 2 and 3 were 19(12-26); 7.6(4-12); 17.8(4-28) respectively, compared to 19.3(3-36) during 'non-wave' months.



Conclusions: Covid-19 resulted in an overall decrease in HSCT collections at SANBS. Despite many challenges, HSCT collections at SANBS were performed during the three Covid-19 waves however they were decreased in comparison to 'non-wave' months. Wave 2 showed a marked decrease in HSCT collections with a rebound directly after.

Clinical Trial Registry: N/A

Disclosure: Nothing to declare

P573

Predictive factors of poor mobilization in multiple myeloma patients

N. Soyer[1], F. Keklik Karadag[1], A. Arslan[1], T. Pashayev[1], B. Sevgili[1], F. Sahin[1], M. Töbü[1], M. Tombuloglu[1], G. Saydam[1], F. Vural[1]

[1]Ege University, Izmir, Turkey

Background: High dose chemotherapy followed by autologous stem cell transplantation (ASCT) is the standart treatment approach for multiple myeloma (MM) patients. Peripheral blood stem cells (PBSCs) have become the most common prefered source for ASCT however nearly 15% of MM patients experienced poor PBSCs mobilization due to many factors such as higher age, previous chemotherapies and radiation. Our aim is define the factors of poor mobilization in patients with MM.

Methods: In total, 110 MM patients who underwent autologous PBSC collection at Ege University Department of Hematology between january 2017 and December 2020 were evaluated retrospectively in our study. The patients were divided into two groups (patients with successful PBSC mobilization and patients who had poor PBSC mobilization) and risk factors were compared between these groups.

Results: The median age was 58 (range, 31-71 years) years at the time of diagnosis and 59.1% (65/110) of patients were male. The median time from diagnosis to mobilization date was 7 months (range, 1-137 months). Number of patients who received G-CSF or cyclophosphamide plus G-CSF before peripheral stem cell harvesting were 73 (66.4%) and 37 (33.6%) respectively. In 98 of 110 patients (89.1%, $\geq 2 \times 10^6$/kg CD34 + PBSCs were

collected at first apheresis. Twelve patients (10.9%) had poor mobilization and most of them (11/12) of them were male ($p < 0.0001$). Three of 12 patients were previously treated with ASCT. Immunomodulatory drugs (thalidomide or lenalidomide) were most commonly used in patients with poor mobilization ($p < 0.012$).

Conclusions: Mobilization failure was observed more frequently in males, patients with previous ASCT and treated with immunomodulatory drugs.

Disclosure: no conflict of interest

P574

Predicting the success of peripheral blood progenitor cells collection with CVC

D. Machado[1], S. Lopes[1], A. Salselas[1], S. Roncon[1]

[1]Instituto Português de Oncologia do Porto, Porto, Portugal

Background: The collection of hematopoietic progenitor cells (HPC) by apheresis is a routine procedure for hematopoietic cell transplant. Although usually performed with peripheral venal access, a central venous catheter (CVC) is sometimes required, particularly in the autologous setting. Placing a CVC not only carries risk for the patient but also increases the cost of the procedure, as it requires the patient to be admitted and the use of ultrasonic guidance. The main risks are venous thrombosis and catheter-related blood infections. Predicting the success of the harvest is thus extremely helpful in avoiding health risk and cost overruns. Measuring circulating CD34 + cells/ µl in the mobilized peripheral blood (PBCD34) is the most widely used method to predict the success of the harvest, defined as a minimum of $2x10^6$ CD34 + /kg of the patient. A minimum count of 10 to 20 PBCD34 is usually recommended. The usefulness of total leukocytes counts in the PB (PBWBC) for this purpose has also been investigated, but it appears not to be a good indicator of successful harvesting.

Our goal was to determine a threshold of CD34 + and total leukocytes in the peripheral blood (PB), capable of predicting a successful HPC collection by apheresis, prior to a CVC placement.

Methods: We retrospectively analysed all apheresis collections performed via CVC in our Institution from 2017 to August 2021, in a total of 176 patients. PBWBC and PBCD34 counts on the first day of collection and the total dose of HPC/kg of the patient collected were registered. Individuals mobilized with Plerixafor were excluded from this study. HPC collection yelding more than $2x10^6$ CD34 + cells/kg were considered as good efficacy.

Results: We observed a high percentage of good efficacy harvests (93%) with a minimum of 5 PB CD34. On the other hand, on patients with less than 5, we only observed 5% of good efficacy collections. We found no threshold of total leukocyte counts capable of predicting collection success, in accordance with the literature.

In Portugal, our Institution included, the use of ultrasound-guided peripheral vein cannulation is not usually performed, so a CVC placement is the available alternative, with a placing cost of 700€. Using this threshold, we identified 45 patients who did not achieved a good successful collection, which corresponds to an increase of 31.500€ to the cost of mobilization, collection, processing and cryopreservation of the grafts.

Conclusions: Considering that a PBCD34 count can be obtained in less than an hour, that the placement of a CVC carries risks to the patient and increases the cost of the procedure, we recommend that every patient proposed to apheresis HPC collection via CVC should perform a PBPD34 count before the CVC placement, and the collection cancelled if less than 5 PBCD34 is obtained. The frequently suggested threshold of 10-20 PBCD34 excludes many good efficacy collections, in patients that might miss a future chance for collection. This strategy allows the identification of patients not likely to achieve a good harvest and that should not proceed to catheterization, avoiding cost overruns and exposer to unnecessary health risk.

Disclosure: Nothing to declare

STEM CELL SOURCE

P575

Comparison of the clinical outcomes of haplo versus cord blood transplantation in pediatric AML. A retrospective analysis on behalf of GETH

L. Sisinni[1], J.M. Pérez Hurtado[2], M. Panesso[3], P. Palomo[4], C. Fuentes[5], J.L. Fuster[6], J. Verdu[7], A. Regueiro[8], C. Belendez[9], D. Bueno[1], Y. Mozo[1], A. Pascual[10], I. Badell[11], A. Pérez Martínez[1], J.M. Fernandez[5], C. Díaz de Heredia[3], M. Gonzalez Vicent[12]

[1]HSCT Unit, Hematologia y Oncología Pediatrica. La Paz University Hospital, Madrid, Spain, [2]Unidad de Hematologia Pediatrica. UGC Hematologia.Hospital Virgen del Rocío, Sevilla, Spain, [3]Servicio de Oncología y Hematología Pediátricas. Hospital Universitari Vall d'Hebron, Barcelona, Spain, [4]Hematología Pediatrica, Hospital Universitario Central de Asturia, Oviedo, Spain, [5]Hematologia Pediatrica, Hospital La Fe, Valencia, Spain, [6]Hematologia Pediatrica, Hospital Arrixaca, Murcia, Spain, [7]Hematologia Pediatrica, Hospital Clinico, Valencia, Spain, [8]Hematología y Oncología Pediátrica, Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain, [9]Hematologia Pediatrica, Hospital Gregorio Marañon, Madrid, Spain, [10]Hematología, Hospital de Malaga, Malaga, Spain, [11]Unidad pediátrica HSCT, Hospital Santa Creu i Sant Pau, Barcelona, Spain, [12]Unidad HSCT, Hematología-Oncología Pediatrica, Hospital Niño Jesús, Madrid, Spain

Background: Haploidentical transplantation (Haplo-SCT) and cord blood transplantation (CB-SCT) are both effective alternative treatments in patients suffering from Acute Myeloid Leukemia (AML) and lacking an identical HLA donor. In the last years, many centers have abandoned CB-SCT mostly due to concern about poorer immune recovery. In this multicenter study we compared the results using both alternative approaches in AML.

Methods: We included data from 12 spanish centers. A total of 128 consecutive cases (92 Haplo-SCT and 36 CB-SCT) from 2009 to 2019 were collected. Median age at HSCT was 6.7 (0.4-20.3) years. Positive MRD was detected at HSCT in 44 cases and a previous HSCT was performed in 41 cases. In 75 Haplo-SCT patients, some kind of ex-vivo lymphocyte depletion (CD34 + enrichment or CD3/CD19 +, alfa/beta/CD19 + or CD45RA + selection) was performed. Cy-post was used in the other Haplo-SCT. The median infused cellularity was 8.0 x10^6/kg CD34 and 71.4 x10^7/Kg TNC for haplo-SCT and 1.5 x10^5/Kg CD34 and 5.7 x10^7/Kg TNC for CB-SCT.

Results: At median follow up of 13 months (0.26-140) 79 patients (61.7%) are alive. The overall survival was 57% at 8 years of follow up for both procedures. The TRM at day +100 was 10.9% for haplo and 16.7% for CBT. Relapse was observed in 22 cases (22.8%) for Haplo-SCT and in 7 cases (19.4%) for CB-SCT. Graft rejection was reported in 14 cases (15.2%) for haplo and in 5 cases (13.9%) for CBT. Severe acute GvHD (grade III-IV) was observed in 22.8% and 13.9% for haplo and CB respectively. Chronic GvHD was reported in 20.7% and 8.3% in haplo and cord respectively. Relapse and chronic GvHD free survival were 52.7% for haplo and 56.7%, at 8 years of follow up, for CBT with no significant difference. Immune recovery was faster for Haplo-SCT in the first 3 months with a median of 178 CD4/mm3 for haplo compared with a median of 83 CD4/mm3 for CBT at day +90, although the

median of NK cells count was higher in CB (501 cell/mm3 vs 198 cells/mm3). At 6 months the median CD4/mm3 was 280 and 431 for haplo and CB respectively.

Conclusions: Our study supports that both haploidentical transplantation and cord transplantation show similar results in pediatric AML patients. We obtained comparable survival rates, although CB-SCT shows a trend to decrease rates of relapse and chronic GVHD, demonstrating that it should still be considered a valuable option, particularly for pediatric patients.

Disclosure: No conflict of interest to declare

P576

Optimal cord blood unit selection results in good engraftment and low TRM and relapse, but conditioning intensity matters

C. Anthias[1,2], S. Easdale[1], I. Evseeva[2], M. Potter[1], C. Arias[1], M. Ethell[1], E.K Nicholson[1]

[1]Royal Marsden Hospital, Sutton, United Kingdom, [2]Anthony Nolan, London, United Kingdom

Background: With less stringent HLA-matching requirements, rapid graft acquisition, and excellent anti-tumour effects, UCB is in many ways an ideal graft source; but slow engraftment and high early TRM have historically limited its use.

Methods: We conducted a retrospective single centre analysis to determine the outcomes of UCBTs between 1/1/05 and 1/11/20 in 81 adults with haematological malignancies. Data from 10 further patients transplanted 1/11/20-1/8/21 were included in analyses for engraftment and aGVHD. Cords were selected with the Anthony Nolan Graft Identification and Advisory Service and followed UK (Shaw, 2009; Hough, 2016) and international cord selection guidelines, prioritising FACT-accredited banks.

Results: The median age at transplant was 43 years (range 18-70). 46 patients had AML, 16 ALL, five MDS, 10 lymphoma, 3 MPDs and 1 MM. 45 patients received RIC (fludarabine/cyclophosphamide /2GyTBI), 32 patients received MAC (fludarabine /cyclophosphamide/14.4 GyTBI) and 4 had "Midi" conditioning (fludarabine /cyclophosphamide/thiotepa/4Gy TBI). Median age in MAC and RIC groups were 29.5 and 52.5 respectively. GVHD prophylaxis consisted of ciclosporin and mycophenolate and 2 patients received ATG. Median weight was 75kg (range 47-139). 29 patients received a single UCBT, and 62 double UCBT.

Pre-thaw median TNC infused per patient was 4.39x10^7/kg (range 2.0-7.13) and median CD34 dose per patient was 2.35x10^5/kg (range 0.12-6.32). 8 of 9 patients with a CD34 dose <1x10^5/kg were transplanted prior to publication of 2016 UK recommendations including CD34 dose as a selection criterion. All patients received mismatched cords with HLA matching 3/8, 4/8, 5/8,6/8, 7/8 (in 2, 13, 60, 48, 19 cords respectively (data unavailable in 46 patients)).

Neutrophil engraftment occurred at median 20 days in the whole cohort (22 days in UCBTs pre-2017 and 18 days in UCBTs 2017-2021, ($p = 0.19$). 3 patients had delayed engraftment and 5 patients (5.4%) failed to engraft.

In 81 patients eligible for survival analyses the median follow-up was 24 months (range 12-135). OS at 2 and 5 years was 59.8% and 53.1% respectively and was superior in recipients of MAC UCBT compared to RIC (5-year OS 72.9% vs 40.0%, $p = 0.02$). This was due to a reduction in relapse in the MA group (5-year relapse 8.5% vs 26.3%; $p = 0.035$) with no difference in NRM (2-year NRM 18.2% vs 30.6%;$p = 0.18$). 5-year OS in patients aged 60 or older was equivalent to younger patients (50.4% vs 53.9%; $p = 0.71$) and MRD positive acute leukaemia patients had no survival deficit compared to those who were MRD-negative (52% vs 60% $p = 0.88$).

aGVHD grade I-IV and III-IV occurred in 53% and 13% of those alive at day 100 respectively. cGVHD and severe cGVHD occurred in 12% and 4.6% of those alive at one year respectively.

Conclusions: Our data show that optimal CBU selection leads to excellent engraftment, and OS equivalent or superior to many matched donor analyses, but importantly with very low incidence of severe cGVHD. Patients receiving MAC derive particular benefit, and increasing the intensity of RIC for fitter older patients using midi regimens where possible may further improve outcomes. In the context of the COVID19 pandemic CBU also offers secure and rapid donor access.

Disclosure: The authors declare no conflicts of interest

P577

Impact of allo PBSC cryopreservation on graft function and acute GVHD

M. Gambella[1], A.M. Raiola[1], A. Bo[1], A. Ghiso[1], R. Varaldo[1], A. Dominietto[1], C. Di Grazia[1], F. Gualandi[1], S. Bregante[1], L. Giannoni[1], N. Di Felice[1], S. Luchetti[1], A. Serio[1], S. Geroldi[1], E. Angelucci[1]

[1]Ematologia e Terapie Cellulari. IRCCS Ospedale Policlinico San Martino, Genova, Italy

Background: Cryopreservation has become a risk-mitigation strategy for allogeneic transplant during the COVID-19 pandemic. Nevertheless, cryopreservation may adversely impact transplant outcomes. Previous experiences are non-conclusive, with some suggesting a detrimental impact on engraftment, chimerism, and GVHD (Maurer 2021; Hsu 2021), and others, especially in the haploidentical setting, which do not identify differences (Hamadani 2020).

Tb.1 Patients characteristics (n)	Fresh (67)	Cryopreserved (45)	P
Median Age (range), yr	57 (21–73)	58 (20–75)	0.1
Diagnosis, n(%) AML	42 (63)	24 (53)	0.3
Status at transplant, n(%) 1°CR	34 (51)	18 (40)	0.2
Donor, n(%) Sibling HLA id.	17 (25)	5 (11)	0.3
Haplo	27 (41)	23 (51)	0.3
MUD	19 (28)	14 (31)	0.8
MMUD	4 (6)	3 (7)	0.9
Conditioning, n(%) MAC	51 (76)	31 (69)	0.3
Median FU (range), days	629 (74 – 1567)	160 (15 – 949)	0.04

Methods: Here we report a retrospective analysis on 112 patients transplanted from allogeneic peripheral blood stem cells (PBSC) from 1° January 2016 to 1° September 2021. Forty-five patients received cryopreserved grafts and 67 fresh PBSCs. Both the groups were balanced in terms of age, diagnosis, disease status at transplant, conditioning regimen intensity, and donor source (Tab.1). Median follow-up was 504 days from transplant (range: 21

- 1530). GVHD prophylaxis consisted of high-dose post-transplant cyclophosphamide, cyclosporine, and mycophenolate-mofetil in the familiar haploidentical setting; pre-transplant Thymoglobulin®, cyclosporin and a short course of methotrexate for HLA-identical sibling, matched (10/10) and mismatched (9/10) unrelated donor (MUD and MMUD). Engraftment was defined as a ≥ 95% donor chimerism at day +30 in the presence of neutrophil-engraftment.

Results: Despite a superimposable time to neutrophil-engraftment (defined as 500/mcl for 3 consecutive days) for cryopreserved vs fresh (median 18 days vs 16 days, $p = 0.1$), graft failure was significantly higher for cryopreserved products (13% vs 3%, $p = 0.03$). No differences could be depicted for grade 2-4 aGVHD (26% vs 15%, $p = 0.1$), cGVHD (15% vs 16%, $p = 0.9$), TRM (17% vs 12%, $p = 0.4$), relapse (11% vs 21%, $p = 0.2$), 2-years OS (73% vs 75%, $p = 0.1$). However, when data were stratified for the donor-source, incidence of grade 2-4 aGVHD resulted significantly higher for cryopreserved vs fresh in the HLA-identical setting (HLA-identical sibling and unrelated donor) (42% vs 3%, $p < 0.001$). Chronic GVHD, relapse, NRM and OS were similar in these two groups of patients. No significative differences emerged in patients receiving graft cryopreserved or fresh from haploidentical donor.

Conclusions: Taken together, our data suggest a donor-independent, increased risk of graft failure with cryopreserved cells and a higher probability of aGVHD, which is limited to the HLA-identical donor. Cryopreservation may adversely impact engraftment due to a suboptimal post-thawing cell recovery, while the impact on lymphocytes' fitness and the hypothetical selection of specific subpopulations is currently unknown. Further investigations in a larger multicentre setting, to explain the biological assumptions are urgently needed.

Disclosure: Nothing to declare

P578

Does HLA tissue group change after granulocyte transfusion?

A. Ünal[1], M. Baydar[1], M.Y. Köker[1], M. Keklik[1], K. Fidan[1], Z.T. Güven[1], S. Çelik[1], E. Yildizhan[2], S.S. Durusoy[3], N. Taşer Kanat[1]

[1]Erciyes University, Kayseri, Turkey, [2]Kayseri City Hospital, Kayseri, Turkey, [3]Sanko University, Gaziantep, Turkey

Background: Granulocyte transfusion has been shown to reduce infection-related mortality in neutropenic patients.

Objective: We detected an erroneous change in the HLA tissue type of the patient with granulocyte transfusion (GTX) given to patients diagnosed with Acute Myeloblastic Leukemia (AML) in the neutropenic period.

Methods:

Results: Case Report 1:

A 26-year-old female patient was diagnosed with AML. The HLA tissue group of the patient was examined. The patient was given 7 + 3 (ARA-C + Dounoromisin) chemotherapy with the diagnosis of AML. In the bone marrow examination performed on the patient, myeloblast was detected with a rate of 70% compatible with AML in the flow cytometry. Gemtuzumab + FLAG (Fludarabine, ARA-C, G-CSF) were given. On the 8th day of this treatment, due to neutropenic fever and deep neutropenia (WBC: $0.02x10^3$/μL neutrophil: zero), GTX ($4x10^{10}$) was given to the patient. HLA tissue group was studied again from the patient 2 hours after GTX. It was determined that the HLA tissue group studied for the second time was completely different from the HLA tissue group of the patient, which was studied for the first time. In the blood control, it was determined that the HLA tissue group of the patient had transformed into the HLA tissue group of the granulocyte donor.

Case Report 2:

A 32-year-old male patient was diagnosed with AML. The HLA tissue group of the patient was examined. The patient was given 7 + 3 chemotherapy with the diagnosis of AML. The leukocytes returned to normal, and the bone marrow flow cytometric examination revealed 4% myeloid blast, and the patient was considered in remission. Then, High dose ARA-C was given for the 1st and 2nd times. GTX ($5.8x10^{10}$)was given to the patient who had deep neutropenia (WBC: $0.1x10^3$ μL/neutrophil $0.01x10^3$/μL) on the 11th day after high dose ARA-C given for the second time. At the 2nd hour after GTX, blood was drawn again for HLA tissue group control. In the HLA tissue typing examined, there was no agreement with the HLA tissue group detected before the treatment. Tissue group similarity could not be determined exactly.

Conclusions: HLA compatibility is the main criterion for donor selection in hematopoietic stem cell transplantation. Peripheral blood is frequently used for HLA tissue group determination. We checked whether the HLA tissue type from the peripheral blood changes with these foreign DNA containing cells from the peripheral blood after the GTX application to our patients who had deep leukopenia due to chemotherapy. We determined that this could change with the blood sample we took at the 2nd hour after GTX.

In conclusion, HLA tissue typing from peripheral blood should be performed 24 hours after cellular transfusions containing DNA in deeply neutropenic patients given GTX. In this period, if tissue typing is to be examined, sampling should be preferred from regions such as buccal mucosa other than peripheral blood.

Disclosure: Nothing to declare