Bone Marrow Transplantation (2020) 55:22–174
https://doi.org/10.1038/s41409-020-01119-3

ABSTRACTS COLLECTION

The 46th Annual Meeting of the European Society for Blood and Marrow Transplantation: Physicians Oral Session (O010-O173)

29 August - 1 September, 2020 ● Virtual Meeting

Modified and published with permission from https://www.ebmt.org/annual-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

O010.

Allogeneic Transplantation in Patients with HIV-infection: An Updated Pair-Matched Cohort Study by the European Society for Blood and Marrow Transplantation

Rafael F. Duarte[1], María E. Martínez-Muñoz[1], Myriam Labopin[2], Manuela Badoglio[2], Anja van Biezen[3], Stephanie Nguyen[4], José L. Diez[5], Jakob Passweg[6], Lucrecia Yáñez[7], Andy Peniket[8], Jean Y. Cahn[9], Tsila Zuckerman[10], Jenny L. Byrne[11], Gerard Socié[12], Noel Milpied[13], Jan J. Cornelissen[14], Arnon Nagler[15], Selim Corbacioglu[16], Silvia Montoto[17], Jan Styczynski[18], Nicolaus Krogër[19], Mohamad Mohty[20]

[1]Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain, [2]EBMT Paris Data Office, Paris, France, [3]EBMT Data Office Leiden, Leiden, Netherlands, [4]Hopital Pitié-Salpêtrière, Paris, France, [5]Hospital Universitario Gregorio Marañon, Madrid, Spain, [6]Basel University Hospital, Basel, Switzerland, [7]Hospital Universitario Marqués de Valdecilla, Santander, Spain, [8]Churchill Hospital, Oxford, United Kingdom, [9]CHU Michallon, Grenoble, France, [10]Rambam Health Care Campus, Haifa, Israel, [11]Nottingham City Hospital, Nottingham, United Kingdom, [12]Hospital Saint Antoine, Paris, France, [13]CHU Bordeaux Hôpital Haut-Leveque, Pessac, France, [14]Erasmus University Medical Center, Rotterdam, Netherlands, [15]Chaim Sheba Medical Center, Tel-Hashomer, Israel, [16]Children's Hospital, Regensburg, Germany, [17]Barts Cancer Institute, London, United Kingdom, [18]Collegium Medicum, Bydgoszcz, Poland, [19]University Hospital Eppendorf, Hamburg, Germany, [20]Hopital Saint Louis, Paris, France

Background: The introduction of highly active antiretroviral therapy (HAART) in 1996 changed the natural history of HIV-infection. Nonetheless, HIV-infected patients (HIV-pts) remain at an increased risk of hematologic malignancies for which HSCT is standard therapy. While HAART enables HIV-pts to undergo autologous HSCT with comparable results to the general population, the outcome of HIV-pts after allogeneic (allo-) HSCT remains largely unknown, with limited case reports and small series. Here, we present an updated report of the experience of allo-HSCT for hematologic indications in HIV-pts reported to the EBMT Registry.

Methods: This is a retrospective study of HIV-pts receiving a first allo-HSCT from 1997 to 2018. HIV-pts' outcomes were compared with HIV-negative controls (HIV-neg), including a 1:3 case-control matched analysis for the following criteria: diagnosis, disease status, year and age at transplant (both +/− 3 years), gender, previous autologous transplant, donor type, cell source, conditioning regimen (myeloablative vs reduced intensity, TBI vs chemotherapy-based) and ex-vivo manipulation.

Results: We identified 144 HIV-pts who received a first allo-HSCT: AML (n = 59, 41%), CLPD (n = 30, 21%), MDS (n = 21, 15%), ALL (n = 20, 14%), SAA (n = 6, 4%), and others (n = 8, 5%); 96 men (67%), median age 42

(0-69), including 19 pediatric/adolescent cases ≤18 years; matched (72, 50%) and mismatched (15, 10%) related, unrelated (50, 35%) and cord-blood (7, 5%) donors/source; 76 myeloablative conditioning (53%; 35 TBI-based); 10 (7%) with ex vivo TCD; 13 (9%) with a prior autologous transplant. Beyond the matching criteria, cases and controls were also balanced for donor gender and gender mismatch, in vivo TCD and Karnofsky's performance status. Compared to HIV-neg, HIV-pts had lower rates of neutrophil engraftment (92% vs 98%, $p = 0.002$), higher incidence of grade III-IV acute GVHD (18% vs 10%, $p = 0.007$), higher NRM at day 100 (13% vs 7%, $p = 0.022$) and 2 years (32% vs 20%, $p = 0.001$), and similar incidence of relapse (28% vs 24%, n.s.). Overall, HIV-pts had poorer PFS (40% vs 56%; $p < 0.001$, HR=1.80 [1.34-2.41]), GRFS (31% vs 46%; $p = 0.002$, HR=1.54 [1.17-2.03]) and OS (48% vs 61%; $p = 0.001$; HR=1.68 [1.23-2.28]) at 2 years than HIV-neg cases. Outcomes within HIV-pts were comparable across different donor types, stem cell sources or intensity of conditioning regimen (data not shown). Of note, the use of unrelated donors in HIV-pts (40%) remains markedly reduced compared to allo-HSCT standard practice (51%; Passweg, et al. https://doi.org/10.1038/s41409-019-0465-9).

Conclusions: This study reports on the largest series available of allo-HSCT in HIV-pts. Despite the limitations of any retrospective study, the pair-matched design strongly suggests that the outcome of allo-HSCT is poorer in HIV-pts than in the general population, primarily driven by higher NRM, in association with higher severe GVHD, and in keeping with their reduced overall life expectancy despite HAART. Even so, allo-HSCT is feasible in HIV-pts with hematologic indications, with a 48% OS at 2 years. HIV-pts with an indication for allo-HSCT should be considered for the procedure, including those without matched-related donors, who should be granted access to alternative donor search and consideration for transplantation at the same level as HIV-neg candidates.

Disclosure: Nothing to declare.

O011.

Comparable Outcomes of AML Patients Receiving Haplo-HCT with Thiotepa/Busulfan/Fludarabine Conditioning and Post-Transplant Cyclophosphamide Versus a Matched Unrelated Donor with Fludarabine/Busulfan Conditioning, Regardless of Disease Status

Ali Bazarbachi[1], Myriam Labopin[2], Didier Blaise[3], Edouard Forcade[4], Gerard Socié[5], Ana Berceanu[6], Claude Eric Bulabois[7], Nicolaus Kröger[8], Alessandro Rambaldi[9], Patrice Ceballos[10], Stephan Mielke[11], Ibrahim Yakoub-Agha[12], Bipin Savani[13], Alexandros Spyridonidis[14], Arnon Nagler[15], Mohamad Mohty[16]

[1]American University of Beirut Medical Center, Beirut, Lebanon, [2]EBMT Paris Study Office, CEREST-TC, Saint Antoine Hospital, Paris, France, [3]Paoli-Calmettes Institute, Inserm CBT1409, Marseille, France, [4]CHU Bordeaux, Bordeaux, France, [5]Hopital St. Louis, Paris, France, [6]Hopital Jean Minjoz, Besancon, France, [7]CHU Grenoble Alpes - Université Grenoble Alpes, Grenoble, France, [8]University Hospital Eppendorf, Hamburg, Germany, [9]ASST Papa Giovanni XXIII, Bergamo, Italy, [10]CHU Lapeyronie, Montpellier, France, [11]Karolinska Intitutet and University Hospital, Stockholm, Sweden, [12]CHU de Lille, LIRIC, INSERM U995, Université de Lille, Lille, France, [13]Vanderbilt University Medical Center, Nashville, TN, United States, [14]University Hospital of Patras, BMT Unit, Patras, Greece, [15]Chaim Sheba Medical Center, Tel Aviv University, Tel-hosmer, Israel, [16]EBMT Paris Study Office, CEREST-TC, Saint Antoine Hospital, INSERM UMR 938, Université Pierre et Marie Curie, Paris, France

Background: While a HLA matched sibling donor (MSD) represents the first choice for allogeneic hematopoeitic cell transplantation (HCT) in patients with acute myeloid leukemia (AML), most patients do not have a MSD and hence alternative donor sources are used, most frequently matched unrelated donors (MUD) or haploidentical donors (haplo). Multiple studies compared outcomes of MUD and haplo but included patients from different risk groups and with heterogeneous conditioning regimens.

Methods: Here we compared transplant outcomes at EBMT participating centers between 2010 and 2018, of 708 AML patients receiving haploHCT using a homogeneous thiotepa/busulfan/fludarabine conditioning with post-transplant cyclophosphamide (haplo-TBF), to 2083 patients receiving MUD (10/10) using a homogeneous fludarabine/busulfan conditioning and in vivo T-cell depletion (MUD-FB), both being among the most popular regimens in these respective settings. All analyses were stratified according to disease status and cytogenetic risk group for patients transplanted in first complete remission (CR1).

Results: Patients, donors and transplant characteristics are summarized in Table 1. For patients with intermediate cytogenetic risk AML transplanted in CR1 (234 haplo-TBF and 1124 MUD-FB), multivariate analysis (MVA) using the Cox regression method revealed that haplo-TBF significantly increased non-relapse mortality (NRM) (HR 2.1; $p = 0.0006$) but did not affect relapse incidence (RI), leukemia free survival (LFS), overall survival (OS) or graft- versus-host disease free, relapse free survival (GRFS). Older age negatively affected

NRM, LFS, OS and GRFS whereas transplant outcomes were not affected by patient and donor gender or CMV positivity, year of transplant, time from diagnosis to transplant, Karnofsky score, stem cell source, or intensity of conditioning. For patients with high cytogenetic risk AML transplanted in CR1 (79 haplo-TBF and 280 MUD-FB), MVA showed that haplo-TBF significantly increased NRM (HR=2.7; $p = 0.02$), decreased RI (HR=0.45; $p = 0.03$) but had no influence on LFS, OS or GRFS. Again, transplant outcomes were not affected by other patient, donor and transplant characteristics, except lower OS in older patients. For patients with AML transplanted in CR2 (165 haplo-TBF and 440 MUD-FB), haplo-TBF significantly increased NRM (HR=2.36; $p = 0.008$), decreased RI (HR=0.38; $p = 0.005$), but had no influence on LFS, OS or GRFS. Patient age negatively affected NRM and OS whereas a shorter time from diagnosis to transplant negatively affected RI, LFS, OS and GRFS. Transplant outcomes were not affected by other patient, donor and transplant characteristics. Finally, for patients with AML transplanted with active disease (230 haplo-TBF and 239 MUD-FB), haplo-TBF had no influence on transplant outcomes. Older patient age negatively affected NRM and poor performance status negatively affected all transplant outcomes. Other patient, donor and transplant characteristics had no effect on outcomes.

Conclusions: Compared to MUD-FB, haplo-TBF increased NRM, reduced RI in high risk AML, resulting in similar LFS, OS and GRFS. These results support the use of either a matched unrelated donor or a haplo-identical family donor for AML patients lacking a MSD, regardless of disease status at transplant.

Clinical Trial Registry: not applicable.

Disclosure: no disclosures.

O012.

Trends and Predictive Factors for Outcome of Relapsed Acute Myeloid Leukemia After Allogeneic Hematopoeitic Cell Transplant: Improved Survival for Young Patients in Recent Years

Ali Bazarbachi[1], Myriam Labopin[2], Dietrich Beelen[3], Igor Wolfgang Blau[4], Victoria Potter[5], Riitta Niittyvuopio[6], Gerard Socié[7], Didier Blaise[7], Jaime Sanz[8], Fabio Ciceri[9], Alexandros Spyridonidis[10], Gesine Bug[11], Jordi Esteve[12], Bipin N Savani[13], Christoph Schmid[14], Arnon Nagler[15], Mohamad Mohty[16]

[1]American University of Beirut, Beirut, Lebanon, [2]EBMT Paris Study Office, CEREST-TC, Saint Antoine Hospital, Paris, France, [3]University Hospital, Essen, Germany, [4]Charité Universitätsmedizin Berlin, Berlin, Germany, [5]GKT School of Medicine, London, United Kingdom, [6]HUCH Comprehensive Cancer Center, Helsinki, Finland, [7]Institut Paoli Calmettes, Marseille, France, [8]University Hospital La Fe, Valencia, Spain, [9]Ospedale San Raffaele s. r.l., Milano, Italy, [10]University Hospital of Patras, Patras, Greece, [11]Goethe-Universitaet, Frankfurt Main, Germany, [12]Hospital Clinic, Barcelona, Spain, [13]Vanderbilt University Medical Center, Nashville, TN, United States, [14]Klinikum Augsburg, II Medizinische Klinik, Ausburg, Germany, [15]Chaim Sheba Medical Center, Tel-hosmer, Israel, [16]EBMT Paris Study Office, CEREST-TC, Saint Antoine Hospital, INSERM UMR 938, Université Pierre et Marie Curie, Paris, France

Background: Disease relapse represents the main cause of treatment failure after allogeneic hematopoietic-cell-transplantation (allo-HCT) for acute-myeloid-leukemia (AML). Standard treatment modalities include reduction/withdrawal of immunosuppression, chemotherapy or hypomethylating agents with or without donor lymphocyte infusion, a second allo-HCT or even palliative care. More recently, multiple targeted therapies were introduced in that setting. However, little information is available about the global impact of the current standard of care for relapsed AML after allo-HCT and about the predictive factors for outcome.

Methods: Here we compared transplant outcomes at EBMT participating centers of 8162 adult AML patients who relapsed between 2000 and 2018 after allo-HCT performed in first complete remission (CR1). We included patients who received transplants from matched sibling or unrelated donors or haploidentical donors. Patients receiving in vitro T cell depletion were excluded. All outcomes were censored at 2 years after relapse. Median follow up for alive patients was 35 months.

Results: Patients, donors and transplant characteristics are summarized in Table 1. Overall, 692 patients relapsed between 2000-2004, 1734 between 2005-2009, 2856 between 2010-2014 and 2878 between 2015-2018. The 2-year overall survival after relapse was 17%. Original disease was the cause of death in 77% of patients. A second allo-HCT within 2 years after relapse was performed in 17% of patients resulting in a 2-year OS of 37%. For 3630 patients less than 50 years of age at relapse, the 2-year OS after relapse increased from 16% for patients relapsing between 2000-2004 to 18% for 2005-2009, 21% for 2010-2014 and 26% for 2015-2018 ($p = 0.001$). The incidence of second allo-HCT was 23%, 20%, 22% and 32% for the same time periods ($p = 0.001$). In multivariate analysis, OS from relapse was positively affected by the year of relapse after 2010 compared to 2000-2004 (HR 0.82; p< 0.02 for

patients relapsing from 2010-2014 and HR=0.72; $p = 0.0002$ for patients relapsing from 2015-2018), good performance status at transplant and longer time from transplant to relapse but negatively affected by patient age and intermediate or high cytogenetic risk group. Other patient, donor and transplant characteristics had no significant effect. Conversely, for 4532 patients $\geq$ 50 year-old at relapse, the 2-year OS from relapse was not affected by the year of relapse (16% for 2000-2004; 15% for 2005-2009 and 2010-2014 and 14% for 2015-2018; $p = 0.56$) whereas the incidence of second allo-HCT surprisingly decreased from 17% for 2000-2004 to 14% in 2005-2009; 11% in 2010-2014 and 13% in 2015-2018 ($p = 0.006$). In multivariate analysis, OS from relapse was positively affected by the time from transplant to relapse, good performance status and transplant from matched sibling donor while negatively affected by patient age and adverse cytogenetic risk group. Other patient, donor and transplant characteristics had no effect including the year of relapse.

Conclusions: We demonstrate a significant improvement of OS from relapse after 2010 for younger patients, which was more pronounced after 2015. These results likely reflect the efficacy of post-transplant salvage including second allo-HCT. The 2-year OS of 37% after a second transplant probably supports to reconsider this approach in a subset of relapsed patients.

Clinical Trial Registry: not applicable.

Disclosure: no disclosures.

O013.

Anti-cd3/cd33 Bispecific Antibodies Efficiently Redirect Donor T Cells Against HLA Loss Leukemia Relapses

Pier Edoardo Rovatti[1], Laura Zito[1], Eleonora Draghi[1], Monika Herrmann[2], Anetta Marcinek[1,2], Bettina Brauchle[2], Cesare Covino[1], Mattia Di Bono[1], Matteo Giovanni Carrabba[1], Massimo Bernardi[1], Karl-Peter Hopfner[2], Cristina Toffalori[1], Fabio Ciceri[1], Marion Subklewe[2], Luca Vago[1]

[1]IRCCS San Raffaele Scientific Institute, Milan, Italy, [2]Ludwig-Maximilians-Universität, Munich, Germany

Background: Genomic loss of mismatched HLAs ("HLA loss") represents a frequent modality by which acute myeloid leukemia (AML) evades immune recognition from donor T cells after partially HLA-incompatible allogeneic hematopoietic cell transplantation (allo-HCT). Here, we tested the ability of an anti-CD3/CD33 bispecific antibody (BsAb) to circumvent the loss of T cell receptor-HLA interactions and re-target donor T cells towards HLA loss relapses.

Methods: T cells purified from healthy donors were co-cultured with primary patient blasts with or without addition of BsAb and surface expression of early T cell activation markers (CD25 and CD69) was evaluated after 72 hours.

We established mixed lymphocyte cultures (MLCs) between T cells purified from three patients after allo-HCT and primary AML blasts obtained from the same patients at time of diagnosis. After sequential stimulations, co-cultures were tested against respective patient leukemia at diagnosis and at relapse, measuring T cell degranulation (as CD107a expression), antigen-specific activation (as CD137/41-BB expression) and target-specific cytotoxicity (by live cell imaging over a 48-hour time span) in the presence or absence of BsAb.

For in vivo experiments, primary HLA loss samples were infused intravenously into non-irradiated NSG mice, followed by intravenous infusion of T cells and daily administration of BsAb.

Results: First, we reviewed immunophenotypic data of 36 HLA loss relapses documented at our Institution over the last 15 years, verifying robust surface expression of CD33 on relapsed leukemia in 97% of them.

By short-term co-culture experiments between healthy donor T cells and allogeneic leukemia we titrated BsAb concentration and effector:target ratio to be used for subsequent experiments.

T cells collected from patients after HCT robustly responded against patient leukemia at time of diagnosis in terms of degranulation (71,6% mean CD8+CD107+ population). As expected, when tested against HLA loss relapses, T cells failed to recognize target cells (5,9% mean CD8+CD107+ population). Noticeably, when BsAb was added, we detected a strong response, indicating that T cells were effectively re-targeted towards HLA loss variants (84,6% mean CD8+CD107+ population).

Similar results were obtained measuring antigen-specific T cell activation and target cell apoptosis by live-cell imaging: consistent with previous assays, donor T cells recognized and killed leukemia at diagnosis (45% of detection area positive for apoptosis dye) and failed to recognize its HLA loss relapse counterpart (32% of area positive for apoptosis dye). Addition of BsAb to co-cultures drove dramatic cell death of HLA loss blasts (80% of area positive for apoptosis dye), demonstrating that BsAb also, and most importantly, induced target cell killing.

Finally, we modelled BsAb activity in vivo, showing that, whereas the sole infusion of T cells is not able to prevent the leukemia outgrowth in the bone marrow of NSG mice, addition of the BsAb leads to significant disease reduction.

Conclusions: Our results demonstrate that anti-CD3/CD33 BsAbs can effectively redirect donor T cells against HLA loss leukemia variants, resulting in their rapid and

effective killing. Taken together, these promising findings strongly support translation of this approach to clinical trials, to provide a rational therapy for this increasingly recognized but still treatment-orphan modality of post-transplantation relapse.

Disclosure: Fabio, Ciceri: San Raffaele Telethon Institute for Gene Therapy (SR-TIGET). Other (Wiskott-Aldrich Syndrome (WAS) gene therapies was licensed to GlaxoSmithKline (GSK) in 2014. WAS was licensed to Orchard Therapeutics (OTL) in April 2018) and Research Funding

Marion, Subklewe: AMGEN (Consultancy, Honoraria and Research Funding), Roche (Consultancy and Research Funding), Gilead (Consultancy, Honoraria and Research Funding), Miltenyi (Research Funding), Oxford Biotherapeutics (Research Funding), Pfizer (Consultancy and Honoraria), Celgene (Consultancy and Honoraria), Morphosys (Research Funding), Janssen (Consultancy)

Luca, Vago: GenDx (Research Funding), Moderna Therapeutics (Research Funding).

O014.

Polycomb Repressive Complex 2 (PRC2) Emerges as a Key Driver of HLA Class II Negative Post-Transplantation Relapse

Valentina Gambacorta[1,2], Daniela Gnani[1], Laura Zito[1], Stefano Beretta[3], Lucia Zanotti[1], Giacomo Oliveira[1], Davide Cittaro[1], Ivan Merelli[3], Fabio Ciceri[1], Raffaella Di Micco[1], Luca Vago[1]

[1]IRCCS San Raffaele Scientific Institute, Milano, Italy, Milano, Italy, *[2]San Raffaele Telethon Institute for Gene Therapy (SR-TIGET), IRCCS San Raffaele Scientific Institute, Milano, Italy*, *[2]Milano-Bicocca University, Milano, Italy*, *[3]Institute for Biomedical Technologies, National Research Council, Segrate, Milano, Italy*,

Background: Evasion from immune control represents one of the main drivers of acute myeloid leukemia (AML) relapse after allogeneic cell transplantation (allo-HCT). Recently, we and others (Toffalori et al, Nat Med, 2019; Christopher et al, N Engl J Med, 2018) reported that up to 40% of AML relapses display loss of surface expression of HLA class II not explained by genomic alterations. Here, we aim to decipher epigenetic alterations responsible for this immune escape modality.

Methods: We generated patient derived xenografts (PDXs) from diagnosis and relapse samples with non-genomic loss of HLA class II expression and verified that they faithfully recapitulated the original immune-related differences between diagnosis and relapse. Primary and PDX samples were then characterized for gene expression (by RNA-seq), DNA methylation (by RRBS), and chromatin accessibility (by ATAC-seq). All the data were integrated by multi-omics factor analysis (MOFA), followed by gene set enrichment analysis (GSEA). Finally, the immunological effects of epigenetic drugs and recombinant cytokines on primary and PDX-derived AML cells were tested in ex-vivo short-term cultures on a layer of mesenchymal stromal cells.

Results: We verified that PDXs faithfully recapitulate immune-related differences between diagnosis and post-transplantation relapse, including loss of expression of HLA class II molecules. Separate analysis of each of the omics and their integration by MOFA concordantly evidenced that the relapse-specific features were mainly explained by decreased chromatin accessibility in immune-related genes, with a very limited role of DNA methylation. GSEA highlighted that chromatin changes overlapped with known target of EZH2, the enzymatic subunit of the polycomb repressor complex 2 (PRC2), and that this epigenetic signature was shared by a number of patients at relapse. Consistently, we evidenced closed chromatin status at HLA class II genes and their regulators in relapse samples. To revert these changes, relapse samples with downregulated expression of HLA class II were tested in ex-vivo with a panel of compounds targeting different subunits of PRC2. PRC2 inhibition reduced the levels of the repressor mark H3K27me3 and increased the surface expression of HLA class II molecules. Notably, these effects were even more pronounced when PRC2 inhibition was combined with IFN-g treatment, recovering leukemia recognition by $CD4^+$ T cells and suggesting synergism between reverting epigenetic changes and cytokines released by immune cells upon target recognition.

Conclusions: Our results provide mechanistic links between epigenetic regulation and immune escape, and pave the way for testing PRC2 inhibition as an innovative strategy for the treatment of AML post-transplantation relapses.

Clinical Trial Registry: None.

Disclosure: No disclosure.

O015.

Allogeneic HCT for Adults with B-Cell Precursor Acute Lymphoblastic Leukemia Harboring IKZF1 Gene Mutations. A Study by the Acute Leukemia Working Party of the EBMT

Sebastian Giebel[1], Myriam Labopin[2,3], Gerard Socié[4], Ibrahim Yakoub-Agha[5], Stefan Klein[6], Eva Maria Wagner-Drouet[7], Didier Blaise[8], Stephanie Nguyen-Quoc[9], Jean Henri Bourhis[10], Anne Thiebaut[11], Hélène Labussière-Wallet[12], Amandine Charbonnier[13],

Ana Berceanu[14], J L Diez-Martin[15], Nathalie Fegueux[16], Jordi Esteve[17], Arnon Nagler[18], Mohamad Mohty[2]

[1]Maria Sklodowska-Curie Institute, Oncology Center, Gliwice, Poland, [2]Saint Antoine Hospital, INSERM UMR 938, Sorbonne University, Paris, France, [3]EBMT Paris Study Office, Saint Antoine Hospital, Paris, France, [4]Hopital St. Louis, Paris, France, [5]CHU de Lille, LIRIC, INSERM U995, Université de Lille, Lille, France, [6]Universitaetsmedizin Mannheim, III. Medizinische Klinik, Mannheim, Germany, [7]University Medical Center Meinz, Meinz, Germany, [8]Institut Paoli Calmettes, Marseille, France, [9]Universite Paris IV, Hopital la Pitié-Salpêtrière, Paris, France, [10]Gustave Roussy Cancer Campus, Villejuif, France, [11]CHU Grenoble Alpes - Université Grenoble Alpes, Grenoble, France, [12]Centre Hospitalier Lyon Sud, Lyon, France, [13]University of Amiens, CHU Amiens, Amiens, France, [14]Hopital Jean Minjoz, Besancon, France, [15]Hospital Gregorio Marañón, Madrid, Spain, [16]CHU Lapeyronie, Montpellier, France, [17]Hospital Clinic, Barcelona, Spain, [18]Chaim Sheba Medical Center, Tel-Hashomer, Israel

Background: Transcription factor IKZF1 (IKAROS) acts as a critical regulator of lymphoid differentiation and is frequently deleted or mutated in B-cell precursor acute lymphoblastic leukemia (BCP-ALL). *IKZF1* gene defects may be detected in up to 50% of BCP-ALL in adults and are associated with inferior outcome. The goal of this retrospective study based on EBMT registry was to evaluate outcome of allo-HCT in this population and to identify prognostic factors.

Methods: This was a retrospective study based on EBMT registry. Adult patients with ALL harboring *IKZF-1* gene mutations, treated with first allo-HCT between 2015 and 2018 were eligible.

Results: Ninety-five patients transplanted in first (n = 75) or second (n = 20) complete remission (CR) from either HLA-matched sibling (n = 32), unrelated (n = 47) or haploidentical (n = 16) donor, were included in the analysis. Median recipient age was 41 years. Forty-six (48%) patients had Ph(+) ALL. Status of minimal residual disease (MRD) prior to transplantation was reported as positive (n = 42), negative (n = 38) or unknown (n = 15).

The probabilities of the overall survival (OS) and leukemia-free survival (LFS) at 2 years were 55% and 47%, respectively. Relapse incidence was 32% while non-relapse mortality (NRM), 21%. The incidence of grade II-IV acute GVHD and chronic GVHD was 34% and 30%, respectively. The probability of GVHD and relapse-free survival (GRFS) was 35%.

In a univariate analysis the probability of LFS at two years was 71% for patients in molecular remission compared to 23% for those with detectable MRD (p = 0.002), while OS rates were 75% and 40%, respectively (p = 0.02). Relapse incidence at two years according to MRD status equaled 12% vs. 55%, respectively (p = 0.002). Both LFS and OS rates were higher for patients transplanted in CR1 than CR2 (53% vs. 27%, p = 0.003 and 61% vs. 37%, p = 0.02, respectively). LFS rates were comparable for patients with Ph(+) and Ph(-) ALL (55% vs. 41%, p = 0.51).

Multivariate analysis was restricted to 80 patients with known MRD status at allo-HCT. MRD-positive status was associated with decreased chance of LFS (HR=3.15, p = 0.004) and OS (HR=2.37, p = 0.049) as well as increased risk of relapse (HR=5.87, p = 0.003). Disease stage (CR2 vs. CR1) affected all, LFS (p = 0.0003), OS (p = 0.003), GRFS (p = 0.007), the risk of relapse (p = 0.02) and NRM (p = 0.003). In addition, the risk of NRM was decreased with increasing year of transplantation (p = 0.005).

Conclusions: Patients with BCP-ALL and *IKZF1* mutation may benefit from allo-HCT performed in CR1. Results of allo-HCT are enhancing provided that MRD negative status is achieved. Patients with detectable MRD have poor prognosis and therefore require additional intervention prior to transplantation.

Disclosure: Nothing to declare.

O016.

The Value of Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Acute Myeloid Leukemia with and without *ASXL*1-, *RUNX*1- and *TP*53 Mutations

Katharina Heidrich[1], Jan Moritz Middeke[1], Kerstin Schäfer-Eckart[2], Walter E Aulitzky[3], Hermann Einsele[4], Carsten Müller-Tidow[5], Wolf Rösler[6], Mathias Hänel[7], Claudia D Baldus[8], Lars Fransecky[8], Friedrich Stölzel[1], Christoph Röllig[1], Franziska Taube[1], Michael Kramer[1], Sebastian Stasik[1], Andreas Neubauer[9], Andreas Burchert[9], Wolfgang E Berdel[10], Matthias Stelljes[10], Gesine Bug[11], Gerhard Ehninger[1], Martin Bornhäuser[1,12], Christian Thiede[1], Johannes Schetelig[1]

[1]Universitätsklinikum Carl Gustav Carus, Dresden, Germany, [2]Klinikum Nürnberg, Nürnberg, Germany, [3]Robert-Bosch-Krankenhaus, Stuttgart, Germany, [4]Universitätsklinikum Würzburg, Würzburg, Germany, [5]Universitätsklinikum Heidelberg, Heidelberg, Germany, [6]Universitätsklinikum Erlangen, Erlangen, Germany, [7]Klinikum Chemnitz, Chemnitz, Germany,

[8]*Universitätsklinikum Schleswig-Holstein, Kiel, Germany*, [9]*Universitätsklinikum Marburg, Marburg, Germany*, [10]*University Hospital Muenster, Münster, Germany*, [11]*Medizinische Klinik 2, Universitätsklinikum Frankfurt, Frankfurt, Germany*, [12]*National Center for Tumor Diseases, Dresden, Germany*

Background: The ELN guidelines propose risk-adapted consolidation strategies for acute myeloid leukemia (AML) patients with recurrent mutations, e.g. *RUNX*1, *ASXL*1 and *TP*53. The latter were introduced as high-risk mutations into the 2017 revision of the ELN classification. So far, no data has been published whether patients who are only classified as high risk based on mutations in *RUNX*1, *ASXL*1 and *TP*53, benefit from consolidation with allogeneic hematopoietic stem cell transplantation (alloHCT).

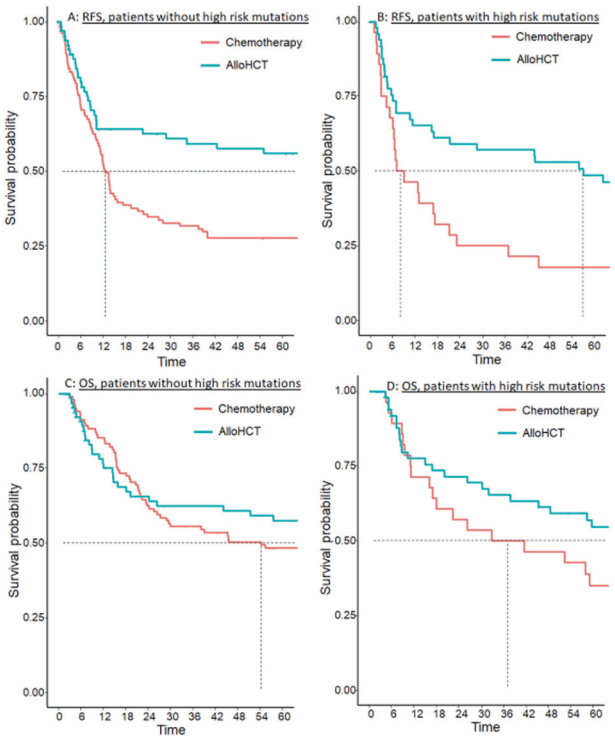
Methods: To address this question, we re-analyzed samples of 312 AML patients who had achieved a first complete remission (CR1) and were classified as intermediate risk based on ELN 2017 criteria, with NGS-based targeted sequencing. Patient age ranged between 18-60 years. All patients were treated within randomized controlled trials on intensive induction chemotherapy of the Study Alliance Leukemia (AML96, NCT 00180115; AML 2003, NCT00180102; SORAML, NCT00893373). Altogether 145 patients received alloHCT in CR1 and 75 patients after hematologic relapse. We performed Cox regression models to compare outcomes of patients with and without *ASXL*1-, *RUNX*1- and *TP*53 mutations. To evaluate the effect of alloHCT on OS and RFS, we tested alloHCT as a time-dependent covariate in a multivariable model including age, white blood cell count, lactate dehydrogenase and AML type (*de novo* versus secondary versus therapy-related myeloid neoplasia) as adjusting covariates and displayed OS and RFS by means of Simon-Makuch-Plots.

Results: We identified 77 cases of AML with high-risk mutations (35 *RUNX*1-, 22 *ASXL*1-, 12 concordant *ASXL*1- and *RUNX*1-, and eight *TP*53-mutant cases of AML). These patients were re-classified as high-risk according to ELN 2017.

At 5 years from study inclusion, both RFS (38%, 95% CI 28 to 50%, versus 37%, 95%CI 31 to 44%) and OS (47%, 95%CI 37 to 60%, versus 50%, 95%CI 44 to 57%) did not differ significantly between patients with and without high-risk mutations irrespective of postremission treatment.

For patients with AML and *ASXL*1-, *RUNX*1-, or *TP*53 mutations who received alloHCT in CR1, we observed a statistically significant benefit in terms of RFS (HR 0.4, 95%CI 0.23 to 0.69, p=0.001) and a trend towards better OS (HR 0.56, 95%CI 0.31 to 1.01, p=0.053) compared with postremission chemotherapy. Patients with AML without these high risk mutations also benefited from alloHCT in terms of RFS (HR 0.47, 95%CI 0.33 to 0.66, p=0.001) and showed a trend to better OS (HR 0.73, 95% CI 0.51 to 1.05, p=0.093).

Conclusions: Our data supports the recommendation to offer alloHCT as consolidation therapy for fit patients with ELN 2017 intermediate risk and high-risk AML in CR1. Further studies in larger cohorts are warranted to study the effect of *ASXL*1-, *RUNX*1-, or *TP*53 mutations outside the context of high-risk karyotype abnormalities.



[Simon Makuch Plots on relapse free (RFS) and overall survival (OS).]

Clinical Trial Registry:
AML96 https://clinicaltrials.gov/ct2/show/NCT00180115
AML 2003 https://clinicaltrials.gov/ct2/show/NCT00180102
SORAML https://clinicaltrials.gov/ct2/show/NCT00893373
Disclosure: Nothing to declare.

O017.

Allogeneic Stem Cell Transplantation in Patients with Acute Myeloid Leukemia and Karnofsky Performance Status Score Equal or Lower Than 80%. A Study from the ALWP-EBMT

Francesco Saraceni[1], Myriam Labopin[2], Edouard Forcade[3], Nicolaus Kröger[4], Gerard Socié[5], Riitta Niittyvuopio[6], Jan Cornelissen[7], Hélène Labussière-Wallet[8], Didier Blaise[9], Goda Choi[10], Jenny Byrne[11], Gaelle Guillerm[12], Thierry Lamy[13], Jordi Esteve[14], Ali

Bazarbachi[15], Bipin Savani[16], Arnon Nagler[17], Mohamad Mohty[18]

[1]Ancona University Hospital, Ancona, Italy, [2]EBMT Paris Study Office, Saint Antoine Hospital, Paris, France, [3]CHU Bordeaux, Hôpital Haut-Leveque, Bordeaux, France, [4]University Hospital Eppendorf, Hamburg, Germany, Hamburg, Germany, [5]Hopital St. Louis, Paris, France, [6]HUCH Comprehensive Cancer Center, Helsinki, Finland, [7]Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, Netherlands, [8]Centre Hospitalier Lyon Sud, Lyon, France, [9]Institut Paoli Calmettes, Maarseille, France, [10]University Medical Center Groningen (UMCG), Groningen, Groningen, Netherlands, [11]Nottingham University, Nottingham, United Kingdom, [12]CHRU de Brest, Brest, France, [13]Centre Hospitalier Universitaire de Rennes, Rennes, France, [14]Hospital Clínic, Barcelona, Spain, [15]American University of Beirut Medical Center, Beirut, Lebanon, [16]Vanderbilt University Medical Center, Nashville, TN, United States, [17]Chaim Sheba Medical Center, Tel-Hashomer, Israel, [18]Saint Antoine Hospital, Paris, France

Background: We report here the results of a retrospective study designed to evaluate outcome of patients with AML with KPS score≤80% undergoing allo-SCT.

Methods: The analysis included patients with AML aged ≥18 years, undergoing allo-SCT in first remission between 2000 and 2018, with a KPS score at the time of transplant between 50% and 80%.

Results: A total of 2,963 patients were identified. Median age at transplant was 55 years (18-77 years). The KPS score was 80% in 85% of the patients and < 80% in 15% of the patients. Cytogenetic risk was good, intermediate or poor in 6%, 68% and 26% of the patients, respectively. Donor type was sibling (MSD), matched (10/10 UD), mismatched (9/10 UD) unrelated, haploidentical (haplo) or cord blood (CB) in 47%, 35%, 8%, 6% and 4% of patients, respectively. Conditioning was myeloablative (MAC) or reduced-intensity (RIC) in 42% and 58% of patients, respectively. Stem cell source was PBSC or BM in 84% and 14% of the patients, respectively. Non-relapse mortality (NRM) and relapse incidence (RI) at 2 years were 19% and 27%, respectively. Notably, in the subgroup of patients with KPS < 80% NRM rate was as high as 27% (23-31%). Leukemia-free survival (LFS), overall survival (OS) and GVHD-free, relapse-free survival (GRFS) rates were 54%, 59% and 41%, respectively. On multivariate analysis, transplant from a MSD was associated with a reduced risk of aGvHD ($p < 10^{-4}$) and NRM ($p < 10^{-3}$) as compared to all other donor types. Transplant from 10/10 UD was associated with lower GRFS (HR 1.2, $p = 0.03$), while 9/10 UD predicted inferior LFS, OS and GRFS ($p < 0.001$) as compared to MSD. Patients with KPS score of 80% had significantly lower NRM and improved survival as compared to patients with KPS< 80% (NRM: HR 0.6, $p < 10^{-4;}$ OS: HR 0.7, $p < 10^{-4}$). Notably, administration of ATG was associated with reduced risk of developing grade II-IV aGVHD ($p < 10^{-4}$), cGVHD ($p < 10^{-4}$), severe cGVHD ($p < 10^{-4}$) and with improved GRFS ($p < 0.01$). In the group of patients with a KPS score of 80%, a RIC regimen was associated with higher RI ($p < 0.01$), higher incidence of severe cGVHD ($p < 0.001$), and inferior GRFS ($p < 0.001$) as compared to MAC. NRM was not significantly different following RIC or MAC in this population. In contrast, in patients with a KPS score < 80%, RIC was associated with lower NRM ($p < 0.0001$) and better LFS ($p < 0.01$), OS ($p < 0.0001$) and GRFS ($p < 0.01$) as compared to MAC.

Conclusions: Allo-SCT is feasible in patients with AML in CR1 and KPS score ≤ 80%, with acceptable NRM and survival rates. As for the conditioning regimen, in patients with a KPS score of 80% a MAC regimen was associated with lower relapse rate, similar NRM and better GRFS as compared to RIC, while in patients with a KPS score lower than 80% RIC was associated with reduced NRM and improved OS as compared to MAC. In addition, transplant from a MSD was associated with reduced risk of NRM and aGVHD rates as compared to other donor types. Finally, administration of ATG correlated with reduced acute and chronic GVHD and improved GRFS.

Disclosure: Nothing to declare.

O018.

RIC Combined with Anti-Thymocyte Globulin and Post-Transplant Cyclophosphamide Provides Higher GVHD-Free/Relapse Free Survival in Fit Young Adults with Acute Myeloid Leukemia

Maria Queralt Salas[1,2], Shiyi Chen[2], Wilson Lam[1,2], Zeyad Al-Shaibani[1,2], Dennis (Dong Hwan) Kim[1,2], Fotios V Michelis[1,2], Ivan Pasic[1,2], Armin Gerbitz[1,2], Auro Viswabandya[1,2], Jeffrey Howard Lipton[1,2], Jonas Mattsson[1,2], Arjun D. Law[1,2]

[1]University of Toronto, Toronto, Canada, [2]Princess Margaret Cancer Center, Toronto, Canada

Background: An ideal conditioning platform should maximize anti-leukemia cytotoxicity and potentiate the graft-versus leukemia effect while minimizing transplant-related toxicity. The selection of the intensity of the conditioning regimen is tailored according to age and comorbidities. However, the optimal age cut-off is not well determined because age is an imprecise determinant of medical fitness. Moreover, with the refinement of HLA-typing, GVHD

prophylaxis and supportive care, TRM in patients with comorbidities has decreased.

We aim to compare the outcome of alloHCT in adults with AML transplanted with RIC combined with dual T-cell depletion using anti-thymocyte globulin (ATG) and post-transplant cyclophosphamide (PTCy) for GVHD prophylaxis with patients transplanted receiving myeloablative conditioning (MAC) regimens combined with standard GVHD prophylaxis.

Methods: All adults with AML in complete remission who underwent MAC alloHCT ($N = 111$) between January 2013 to December 2018 were included in the analysis. Those adults younger than 60 years with an HCT-CI score < = 3 who underwent RIC alloHCT in combination with ATG-PTCY-CsA ($N = 79$) during the defined period of time were included in the analysis. Data was collected retrospectively and updated in July 2019.

A propensity score matching was applied between both cohorts to reduce section bias and approximate a randomized trial. The goal was that both cohorts and matched individual pairs will have well balanced characteristics. Age, CD34 dose, frozen/fresh, disease stage (CR1, CR2-3), donor type and disease risk index (DRI) were entered into the multiple logistics regression (with group membership as the outcome) to create propensity score, which is the predicted probability of receiving RIC. 8à1 digit match technique was performed to find matched pairs.

All together 55 pairs of patients ($N = 110$) were finally included in the analysis. Paired t-tests were used to compare continuous variables and McNemar's tests were used to compare categorical variables, taking into account the correlations between matched pairs. Cox proportional hazard models were used to compare two groups in terms of OS, RFS and GRFS, whereas Fine and Gray competing risk models were used to compare outcomes including NRM and CIR.

Results: Figure 1 summarizes baseline characteristics of patients included in the analysis and comparison over the two cohorts after applying the propensity score matching analysis. Results suggest that the two groups were very balanced after matching.

The cumulative incidence of acute and chronic GVHD was significantly lower in patients who deceived RIC alloHCT with ATG-PTCY-CsA.

Patients who underwent RIC alloHCT combined with ATG-PTCY-CsA had a non-significant trend to better OS ($p = 0.08$) and RFS ($P = 0.07$), and a significantly lower NRM ($P = 0.002$) in comparison with patients who underwent MAC alloHCT. The differences on CIR between both approaches were not statistically significant ($p = 0.51$). Those patients who underwent RIC alloHCT with ATG-PTCY-CsA had a significantly higher GRFS ($P < 0.001$).

Conclusions: Dual T-cell depletion for GVHD prophylaxis in RIC alloHCT reduces clinically relevant GVHD improving GRFS in AML patients.

Both strategies provided comparable overall survival and cumulative incidence of relapse. However, RIC alloHSCT resulted in lower NRM in AML patients.

Clinical Trial Registry: No applicable.

Disclosure: Nothing to declare.

O019.

Low-Dose Memory Donor Lymphocyte Infusion After αβ T Cell-Depleted HSCT Among Children with High-Risk Leukemia: Results of a Prospective Randomized Single-Center Trial

Zhanna Shekhovtsova[1], Maria Dunaikina[1], Larisa Shelikhova[1], Elena Osipova[1], Dmitriy Pershin[1], Dmitriy Balashov[1], Elena Kurnikova[1], Alexei Kazachenok[1], Yakov Muzalevskii[1], Maria Ilushina[1], Rimma Khismatullina[1], Julia Starichkova[1], Galina Novichkova[1], Alexei Maschan[1], Michael Maschan[1]

[1]*Dmitriy Rogachev National Medical Research Centre of Pediatric Hematology, Oncology and Immunology, Москва, Russian Federation*

Background: Depletion of αβ T lymphocytes is an established method of graft manipulation. Delayed recovery of adaptive immunity remains is an unresolved issue. To accelerate the recovery of immunity we proposed to use low doses of donor memory lymphocytes. We have report the results of a prospective randomized trial that tested safety and efficiency of low-dose memory DLI after αβ T cell-depleted HSCT among children with hematologic malignancies.

Methods: A group of 149 patients were enrolled. Indications for HSCT were acute lymphoblastic leukemia ($n = 91$), acute myeloid leukemia (AML) ($n = 39$), other high-risk malignancies ($n = 19$). Median age was 8.6 years (0.5-18) and m:f ratio was 1.5:1. Donors were haploidentical family among 137 (91%) cases and matched among 13 (9%) cases. Conditioning regimen included either treosulfan at Σ42 g/m^2 ($n = 65$) or total body irradiation at Σ12Gy($n = 84$). All patients received thiotepa at Σ10mg/kg, fludarabine at Σ150mg/kg and bortezomib at 1.3mg/m^2 on days -5,-2, +2,+5. Anti-thymocyte globulin serotherapy was abandoned. Tocilizumab at 8 mg/kg at day 0 and abatacept at 10 mg/kg at days 0,7,14 and 28 were administered instead. Grafts were derived from G-CSF-mobilized peripheral blood and split into two parts. Part I was used to produce the primary graft by αβTCR/19+ depletion. Part II was depleted of CD45RA+ population to produce memory DLI. Patients were randomized at enrollment either to

experimental or control arm. Experimental arm ($n = 77$) were scheduled to receive 25×10^3 CD3+CD45RO+ cells at day 0 and monthly infusions of $50x10^3$ CD3+CD45RO+ on days 30, 60 and 90. Control arm ($n = 73$) received standard care. The primary endpoints were the cumulative incidence of acute GVHD grade II-IV and the cumulative incidence of CMV viremia.

Results: One patient died due to septic shock before engraftment. A total of 148 patients were evaluable for engraftment at day 30. Engraftment rate was 98%, 97% (control) and 99%(experimental). The cumulative incidence of aGVHD grade II-IV was 14% in total population, 15% (experimental) and 14%(control), p-ns. The incidence of grade III-IV aGVHD was 8% (experimental) and 6% (control), p-ns. The cumulative incidence of CMV viremia was 55% in the control arm and 45% in the experimental arm, Gray's, $p = 0,3$. The incidence of chronic GVHD was 6%, 5%(experimental) and 6%(control). The cumulative incidence of relapse was 21%, 22% (experimental) and 20% (control). Non-relapse mortality was 2%, 1% and 3% in the control and experimental arm, respectively. At a median follow-up of 1.5 years the event-free survival for all patients was 77 ± 4% and overall survival was 89 ± 3%. In the experimental arm the EFS and OS were 75% and 91%, while in the control arm EFS and OS were 79% and 87%, $p =$ ns. There was a trend towards faster recovery of CMV-specific immunity in the experimental arm in a subcohort of CMV-seropositive recipients

Conclusions: Low-dose CD45RA-depleted DLI commenced at day of grafting were safe but insufficient to prevent CMV viremia. Overall αβ T cell depleted HSCT among children with high-risk leukemia was associated with very low non-relapse mortality, which we ascribe to overall refinement of the regimen, specifically to replacement of polyclonal lymphodepleting serotherapy with targeted immunomodulation

Clinical Trial Registry: NCT02942173.

Disclosure: MM recieved lecturer's fee from Miltenyi Biotec.

O020.

The Brazilian Experience with Haploidentical Hematopoietic Cell Transplants (Haplo-HCT) with Post-Transplant Cyclophosphamide (PTCy) in Pediatric Patients with Hematological Malignancies

Carmem Bonfim[1], Leonardo J. Arcuri[2], Vergilio Colturato[3], Victor G. Zecchin[4], Cilmara C. Kuwahara[5], Lisandro L. Ribeiro[6], Roseane Gouveia[7], Juliana F. Fernandes[8], Rita Tavares[9], Liane E. Daudt[10], Luiz G. Darrigo Jr[11], Mair P. de Souza[3], Vanderson Rocha[12], Neysimelia C. Villela[13], Livia C. B. Mariano[14], Valeria C. Ginani[15], Gisele Loth[1], Alessandra A. Gomes[16], Antonella Zanette[17], Nelson Hamerschlak[18], Mary E. Flowers[19]

[1]Federal University of Parana - Hospital De Clinicas, Curitiba-PR, Brazil, [2]Instituto Nacional de Cancer, Rio de Janeiro, Brazil, [3]Hospital Amaral Carvalho, Jau-SP, Brazil, [4]Instituto Oncologia Pediatrica - GRAACC, Sao Paulo, Brazil, [5]Hospital Infantil Pequeno Principe, Curitiba, Brazil, [6]Hospital Nossa Senhora das Graças, Curitiba-PR, Brazil, [7]Hospital Samaritano, Sao Paulo, Brazil, [8]Instituto da Criança do Hospital das Clínicas da FMUSP, Sao Paulo, Brazil, [9]Instituto Nacional de Cancer, Rio de Janeiro-RJ, Brazil, [10]Federal University of Rio Grande do Sul - Hospital de Clinicas, Porto Alegre, Brazil, [11]Ribeirão Preto Medical School - University of Sao Paulo, Ribeirao Preto, Brazil, [12]Hospital Sirio Libanes, Sao Paulo, Brazil, [13]Hospital do Câncer de Barretos, Barretos, Brazil, [14]Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [15]Hospital Sao Camilo, Sao Paulo, Brazil, [16]Hospital Nove de Julho, Sao Paulo, Brazil, [17]Hospital Erasto Gaertner, Curitiba-PR, Brazil, [18]Hospital Israelita Albert Einstein, Sao Paulo, Brazil, [19]Fred Hutchinson Cancer Research Center, Seattle, WA, United States

Background: The use of haplo-HCT with PTCy has significantly expanded the donor pool worldwide but results of this approach in children with hematological malignancies is limited.

Methods: We retrospectively evaluated major outcomes of first haplo-HCT with PTCy in children with hematological malignancies (HM). All 149 consecutive first haplo-HCT with PTCy (50mg/kg on D+3 and D+4) reported by the 17 Brazilian participating centers of the Pediatric Working Group transplanted for HM were included.

Results: The median age was 10 (0-18) years and 86 were transplanted for ALL, 58 for AML and 5 for MDS. HCTdonors were father (N=82), mother (N=51), or siblings (N=16). Most patients were in second complete remission (CR2; N=57) and in CR1 (N=38) followed by CR3+ and active/refractory disease (N=27 each). Most received a myeloablative conditioning (87%). In addition to PTCy, all patients received mycophenolate mofetil with either cyclosporine (79%) or tacrolimus (21%) for GVHD prophylaxis. Bone marrow (BM) was the stem cell source in 57%. Median follow up for surviving patients is 16 (5-84) months. Most achieved neutrophil engraftment (96%). Primary and secondary graft failure occurred in 5 and 4 patients respectively, and all received BM grafts. The cumulative incidence (CI) of non-relapse mortality at D +100 was 7.4%. At a median of 170 days after HCT, 38% of patients relapsed. The 1-year PFS was 52%: 70% in CR1, 50% in CR2 and 42% in CR3+ or active disease ($p =$

0.006). CI of acute GVHD grades II-IV was higher after PB grafts (45%) than after BM grafts (27%), ($p = 0.02$). CI of chronic GVHD at 1 year was higher after PB grafts from female (75%) than from male (21%) donors, as well as after BM from female (24%) than male donors (13%), both $p < 0.001$. The risk of cGVHD was higher after PB grafts than after BM grafts from a female donor (Hazards Ratio (HR) 3.4; $p < 0.01$). In a multivariable analysis, risk associated with death were female donor (HR=1.9; $p = 0.02$) and disease status ($p<0.001$) and increased risk for cGVHD was the use of PBSC from a female donor (HR=6.9; $p<0.001$). The 1-year overall survival was 62% (95% CI, 54 to 70). Disease progression was the main cause of death (66%). Early mortality after haplo-HCT with PTCy in children with hematological malignancies was low. The 1-year PFS was above 50% with higher rates for those with lower disease risk. The use of PB grafts from female donors increased the risk of acute and of cGVHD.

Conclusions: Our results show that Haplo-HCT with PTCy for children without an HLA-matched donor is an alternative curative intervention for hematological malignancies. A retrospective comparative study of all allogeneic HCT performed in Brazil between 2014 and 2018 and reported to the CIBMTR from HLA matched sibling, unrelated and haploidentical donors is underway. Prospective studies using haploidentical donors with PTCy are necessary to determine if current HCT practices will be changed.

Disclosure: All authors declare no conflict of interest related to this abstract.

O021.

Better Leukemia-Free Survival with Allogeneic Than with Autologous HCT in AML Patients with Isolated Trisomy 8: A Study from the ALWP of the EBMT

Frederic Baron[1], Myriam Labopin[2], Didier Blaise[3], Maija Itälä-Remes[4], Gérard Socié[5], Edouard Forcade[6], Ibrahim Yakoub-Agha[7], Norbert Claude Gorin[8], Jordi Esteve[9], Arnon Nagler[10], Mohamad Mohty[8]

[1]University of Liege, Liege, Belgium, [2]EBMT Paris Study Office, Paris, France, [3]Institut Paoli Calmettes, Marseille, France, [4]HUCH Comprehensive Cancer Center, Stem Cell, Helsinki, Finland, [5]CHU Saint Louis, Paris, France, [6]CHU Bordeaux, Pessac, France, [7]CHU de Lille, LIRIC, INSERM U995, Lille, France, [8]Saint Antoine Hospital, Paris, France, [9]Hospital Clínic, Barcelona, Spain, [10]Chaim Sheba Medical Center, Tel Aviv University, Tel-Hashomer, Ramat-Gan, Israel

Background: The indication of performing an allogeneic hematopoietic cell transplantation (allo-HCT) in patients with isolated trisomy 8 AML in first complete remission (CR) has remained debated. Here we compared outcomes of such patients given either allo-HCT or autologous (auto)-HCT.

Methods: Inclusions criteria consisted of adult patients, de novo AML, isolated trisomy 8, first HCT between 2000 and 2018, CR1 at transplantation, and either auto-HCT or allo-HCT with a HLA-identical sibling donor (MSD) or a 10/10 HLA-matched unrelated donor (MUD).

Results: A total of 401 patients met the inclusion criteria. They were given auto-HCT ($n = 81$), allo-HCT with a MSD ($n = 186$) or allo-HCT with a MUD ($n = 134$). Median patient age was 52 years in auto-HCT recipients, 52 years in MSD recipients, and 55 years in MUD recipients. Median time from diagnosis to transplantation was 5.3 months in auto-HCT recipients, 4.5 months in MSD recipients and 5 months in MUD recipients ($P = 0.001$). At 3-year, nonrelapse mortality, relapse incidence, and leukemia-free survival (LFS) were 5%, 59%, and 37%, respectively, in auto-HCT recipients; 14% ($P = 0.04$), 31% ($p < 0.001$), and 55% ($p = 0.033$), respectively, in MSD recipients and 13% ($P = 0.15$), 29% ($P < 0.001$), and 59% ($P = 0.03$), respectively, in MUD recipients. The 180-day incidence of grade II-IV acute GVHD was 22% in MSD versus 35% in MUD ($P = 0.01$) while 42% of MSD versus 43% of MUD recipients experienced chronic GVHD. In multivariate analysis, in comparison to auto-HCT, each MSD and MUD were associated with a lower risk of relapse (HR = 0.47, $P < 0.001$ and HR=0.40, $P < 0.001$, respectively) translating to better LFS (HR=0.69, $P = 0.04$ and HR = 0.60, $P = 0.03$, respectively). There was also a similar trend for overall survival (HR=0.73, P=12 and HR=0.65, $p = 0.08$).

Conclusions: In AML patients with isolated trisomy 8, allo-HCT in first CR with either a MSD or a MUD results in better LFS than auto-HCT, due to significantly lower risks of disease relapse.

Clinical Trial Registry: NA.

Disclosure: NA.

Aplastic anaemia

O022.

LNP023 - A New Oral Complement Factor-B Inhibitor Normalizes Hemoglobin in Paroxysmal Nocturnal Hemoglobinuria Patients with Poor Response to Eculizumab, Both as Add-on and Monotherapy

Antonio M Risitano[1], Alexander Roth[2], Juliette Soret[3], Camilla Frieri[1], Flore Sicre de Fontbrune[4], Luana Marano[1], Izabella Rozenberg[5], Julie Milojevic[5],

Peter End[5], Prasanna K Nidamarthy[6], Guido Junge[5], Regis Peffault de Latour[3,4]

[1]Federico II University, Naples, Italy, [2]University Hospital, Essen, Germany, [3]Hopital Saint Louis, Paris, France, [4]Frence Reference Center for AA & PNH, Paris, France, [5]Novartis Institutes for Biomedical Research (NIBR), Basel, Switzerland, [6]Novartis Institutes for Biomedical Research (NIBR), Hyderabad, India

Background: The treatment of hemolytic paroxysmal nocturnal hematuria (PNH) is based on anti-C5 antibodies resulting in control of intravascular hemolysis (IVH), leading to reduction of thromboembolic events and improved survival. However, 20-50% of patients remain transfusion-dependent due to persistent extravascular hemolysis (EVH), and further 20-40% exhibit different degree of residual anemia. LNP023 is a new, oral, selective and potent first-in-class factor B inhibitor, expected to block both IVH and EVH.

Methods: CLNP023X2201 (NCT03439839) is a multicenter, open-label, sequential 2-cohort trial to assess the safety, efficacy, tolerability, and pharmacokinetics/-dynamics (PK/PD) of LNP023 in PNH patients with active hemolysis despite treatment with eculizumab. The primary objective is defined as the effect of LNP023, given add-on to eculizumab, on the reduction of hemolysis. Other endpoints include changes in hemoglobin (Hb), reticulocytes, C3-positive red blood cell (RBC), various hemolysis and complement markers, as well as PK/PD and safety/tolerability assessments. At 13 Weeks, patients could enter into a long-term study extension, which also included the possibility of modifying/discontinuing eculizumab treatment.

Results: N=10 (3/7 female/male) PNH patients (25-79 years) with active hemolysis were enrolled and received LNP023 twice daily (BID) concomitant to eculizumab for at least 13 weeks. LNP023 was well tolerated; no treatment discontinuation, no treatment-related serious adverse event (SAE) nor thromboembolic events have been reported. All patients required RBC transfusions prior to LNP023 therapy. At baseline (prior to LNP023 treatment) mean values for LDH (539 U/L), reticulocytes (199 10^9/L), bilirubin (39.2 umol/L), free hemoglobin (28.7 g/L) were increased, while values for Hb (97.7 g/L), RBC (2.7 10^12/L), and haptoglobin (<0.2 g/L) were decreased. At week 13, LNP023 demonstrated meaningful improvement of LDH in all patients with a reduction of 34-81%, and transfusion-free Hb normalization in all (100%) female subjects and 71% males achieved Hb >120 g/L (mean Hb change from baseline 31.9 g/L; 90% CI 23.4-40.3), and normalization of all biomarkers of hemolytic disease activity. The remarkable effect on both IVH and EVH was confirmed by disappearance of C3 deposition on, and increased size of the PNH RBC population (48.4 ± 32.3 *vs*. 92.5 ± 34.9 %RBC at BL *vs*. Week 13), confirming the prolonged survival of affected RBC. All patients entered into the LNP023 extension treatment; with a mean LNP023 exposure of 241 (92-392) days, no patient required RBC transfusion. At the time of the data lock point, 5 patients have already discontinued eculizumab treatment: even on LNP023 monotherapy, all of them retained their hemoglobin levels, with no change in any biomarker of disease activity and no sign/symptom of breakthrough hemolysis.

Conclusions: LNP023 is a new, well-tolerated oral factor B inhibitor that blocks IVH and EVH in patients with hemolytic PNH with poor response to eculizumab, leading to marked improvement up to normalization of Hb and all biomarkers of disease activity. The observed efficacy was retained even in monotherapy, demonstrating the redundancy of terminal complement inhibition in presence of complete and sustained proximal complement inhibition. These data anticipate that oral, single-agent, treatment with LNP023 represents an emerging therapeutic option aiming to change the treatment paradigm of hemolytic PNH.

Clinical Trial Registry: NCT03439839

Disclosure: Antonio Maria Risitano and Regis Peffault de Latour have received consultancy, honoraria and research funding from Novartis.

Izabela Rozenberg, Julie Milojevic, Peter End, Prasanna K. Nidamarthy and Guido Junge, MD are Novartis employees.

O023.

Epigenetic Aging After Hematopoietic Stem Cell Transplantation is Associated with Poor Survival in Patients with Severe Aplastic Anemia: Results from DNA-Methylation Grimage

Rotana Alsaggaf[1], Shilpa Katta[1], Stephen Spellman[2], Tao Wang[3], Belynda D. Hicks[1], Youjin Wang[1], Sharon A. Savage[1], Bin Zhu[1], Stephanie J. Lee[4], Steve Horvath[5], Shahinaz M. Gadalla[1]

[1]National Cancer Institute, National Institutes of Health, Bethesda, MD, United States, [2]Center for International Blood and Marrow Transplant Research, Minneapolis, MN, United States, [3]Medical College of Wisconsin, Milwaukee, WI, United States, [4]Fred Hutchinson Cancer Research Center, Seattle, WA, United States, [5]University of California Los Angeles, Los Angeles, CA, United States

Background: Biological aging in hematopoietic cell transplantation (HCT) is important in the context of immune

reconstitution and age-related complications. Several DNA-methylation (DNAm) based biomarkers of aging known as "epigenetic clocks" have been introduced as novel tools to predict biological age. Most recently, the DNAm "GrimAge" (DNAm-GrimAge) clock, a composite biomarker of seven lifespan-associated plasma proteins, smoking pack-years, and chronological age, has been shown to outperform previous DNAm clocks in predicting mortality. Here, we explored the possible associations of donor pre-HCT DNAm-GrimAge and early post-HCT changes in DNAm-GrimAge with post-HCT survival among severe aplastic anemia (SAA) patients.

Methods: This study is part of the Transplant Outcomes in Aplastic Anemia (TOAA) Project, an ongoing collaboration between the Center for International Blood and Marrow Transplant Research and the National Cancer Institute aiming to identify molecular predictors of transplant outcomes in patients with SAA. This study included 732 patients who underwent unrelated-donor HCT and for whom donor pre-HCT blood samples were available; 41 patients had a post-HCT sample collected at day 100. We used Illumina Infinium whole-genome MethylationEPIC array data to calculate DNAm-GrimAge and DNAm-GrimAge acceleration (a measure of the deviation from expected biological age relative to chronological age). For statistical analyses, we used Cox proportional hazards regression models.

Results: Median donor chronological age was 33.6 years (interquartile range [IQR]=14.2). Donor DNAm-GrimAge was highly correlated with chronological age ($R^2 = 0.7$, $p < 0.001$). In multivariable analyses adjusted for recipient age and race, transplant year, conditioning regimen, Karnofsky performance score (KPS), HLA match, and disease subtype, the effects of donor chronological age and pre-HCT DNAm-GrimAge on post-HCT survival were similar (hazard ratio [HR]=1.01, 95% confidence interval [CI]=1.00-1.03, $p = 0.07$ and HR = 1.01, 95% CI = 1.00-1.03, $p = 0.08$, respectively). Results from DNAm-GrimAge acceleration showed a small deviation from expected (median = -0.5, IQR=5.1 years), with no statistically significant linear relationship with post-HCT survival (HR = 1.00, 95% CI = 0.97-1.04, $p = 0.80$) after further adjusting for donor chronological age. Notably, though we observed no statistically significant association between extreme donor DNAm-GrimAge acceleration (10+ years) and survival post-HCT (HR = 1.39, 95% CI = 0.67-2.86, $p = 0.39$), the elevated HR warrants further exploration. In patients with a post-HCT sample at day 100, a significant increase in DNAm-GrimAge post-HCT was noted (median difference post-HCT *vs*. pre-HCT=12.5 years, IQR=7.0). Increased DNAm-GrimAge post-HCT (15+ years) was associated with inferior survival (HR=4.57, 95%CI=1.81-11.51, $p = 0.001$) after adjusting for donor age, conditioning regimen and KPS. The excess mortality risk was most significant in the first year post-HCT (HR at < or = 12 months=17.07, 95% CI=2.09-139.69, $p = 0.008$; HR at >12months=2.07, 95% CI=0.52-8.18 $p = 0.30$). Patients whose DNAm-GrimAge increased 15+ years post-HCT were more likely to die of infection (33% *vs*. 11%) and primary disease (17% *vs*. 0%) compared with those with < 15 years of aging. Exploratory analyses suggested donor sex, recipient sex, and KPS may be associated with accelerated post-HCT aging.

Conclusions: Donor DNAm-GrimAge pre-HCT did not provide a better prediction of survival post-HCT over chronological age in patients with SAA. Significant DNAm aging post-HCT was associated with poor survival, predominantly within the first year post-HCT.

Disclosure: Nothing to declare.

O024.

GVHD and Relapse Free Survival (GRFS) After Allogeneic Transplantation for Idiopathic Severe Aplastic Anemia: An Analysis from the Saawp Data Quality Initiative Program of EBMT

Raynier Devillier[1], Dirk-Jan Eikema[2], Paul Bosman[3], Carlo dufour[4], Mahmoud Aljurf[5], Depei Wu[6], Alexei Maschan[7], Boris Afanasyev[8], Joan Hendrik Veelken[9], Matthew Collin[10], John Snowden[11], Yves Bertrand[12], Arnold Ganser[13], Karl-Walter Sykora[13], Brenda E. Gibson[14], Johan Maertens[15], Maija Itäla-Remes[16], Andrea Biondi[17], Jan Cornelissen[18], Martin Bornhäuser[19], Mercedes Colorado Araujo[20], Hakan Ozdogu[21], Antonio risitano[22], Regis Peffault de la Tour[23]

[1]Paoli Calmettes Institute, Marseille, France, [2]EBMT Statistical Unit, Leiden, Netherlands, [3]EBMT Data Office, Leiden, Netherlands, [4]Gaslini Children Research Hospital, Genova, Italy, [5]King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, [6]First Affiliated Hospital of Soochow University, Suzhou, China, [7]Federal Research Center for Pediatric Hematology, Moscow, Russian Federation, [8]Pavlov First State Medical University of St. Petersburg, St Petersburg, Russian Federation, [9]Leiden University Hospital, Leiden, Netherlands, [10]Adult HSCT Unit, Newcastle, United Kingdom, [11]Sheffield Teaching Hospitals NHS Trust, Sheffield, United Kingdom, [12]Institut d`Hematologie et d`Oncologie Pediatrique, Lyon, France, [13]Hannover Medical School, Hannover, Germany, [14]Royal Hospital for Children, Glasgow, United Kingdom, [15]University Hospital Gasthuisberg, Leuven, Belgium, [16]Turku University Hospital, Turku, Finland, [17]Centro Trapianti di Midollo Osseo, Monza, Italy, [18]Erasmus MC Cancer Institute, Rotterdam, Netherlands, [19]Universitaetsklinikum Dresden, Dresden, Germany, [20]Hospital U. Marqués de

Valdecilla, Santander, Spain, [21]*Baskent University Hospital, Adana, Turkey*, [22]*Federico II University of Naples, Napoli, Italy*, [23]*Hopital St. Louis, Paris, France*

Background: Survival after Allo-HSCT for severe idiopathic aplastic anemia (SAA) has improved over past 20 years, approaching 75% at 5 years. However, beyond survival, a SAA-adapted composite endpoint GVHD and relapse free survival (GRFS) may more accurately assess patient outcomes, becoming a meaningful study endpoint. We analyzed GRFS aiming to identify risk factors and specific causes of GRFS failure.

Methods: This retrospective analysis from the SAAWP Data Quality Initiative (DQI registry database) program of EBMT included patients with: diagnosis of idiopathic SAA; first Allo-HSCT from 2005 to 2016; and matched related (MRD) or unrelated donor (UD) (no cord blood). Relevant events for Kaplan-Meier calculation of GRFS were: relapse (including primary and secondary graft failure); grade 3-4 acute GVHD; extensive chronic GVHD; and death. In addition, we used a competing-risk model to analyze cumulative incidences of specific causes of GRFS failure.

Results: We analyzed 580 patients (385 adults and 195 younger than 18 years), with a median age of 23 years (< 0.1-77). Donor was matched related and unrelated in MRD and 243 patients, respectively. Median time from diagnosis to Allo-HSCT was 6 months (<1-444) and 310 (53%) patients underwent Allo-HSCT without prior treatment. GRFS at 5 years was 69% (65-73) in the whole cohort. Median follow up was 59 months (2-165). Multivariate cox model including age (continuous), graft source, conditioning intensity, sex mismatch, CMV-serostatus, donor type, time from diagnosis to Allo-HSCT (< vs. > 6 months) and previous treatment before Allo-HSCT showed that age (HR=1.02, [1.01-1.03], p < 0.001) and CMV serostatus other than negative-donor to negative-recipient [D-/R-] (HR=1.51, [1.02-2.23], $p = 0.041$) were the only independent factors associated with worse GRFS. Using cause specific cox model, we analyzed the risk of the different causes of GRFS failure and found that CMV-serostatus other than D-/R- was associated with higher risk of graft failure/relapse (HR=2.88, [1.12-7.38], $p = 0.028$) while age influenced the risk of grade 3-4 acute GVHD (HR=1.03, [1.00-1.05], $p = 0.043$), extensive chronic GVHD (HR=1.03, [1.01-1.06], $p = 0.008$) and death without prior failure (HR=1.03, [1.01-1.04], p < 0.001).

Among the 209 patients who underwent upfront Allo-HSCT from a MRD, 5-year GRFS was 77% (71-84). In multivariate analysis, time from diagnosis to Allo-HSCT (HR=2.64, [1.38-5.03], $p = 0.003$) and age (HR=1.03, [1.00-1.05], $p = 0.039$) independently influenced GRFS. When investigating the causes of GRFS failure in this subset of patients who underwent upfront MRD Allo-HSCT, time from diagnosis to Allo-HSCT was the only remaining factors significantly associated with the risk of death without prior failure (HR=0.29, [0.10-0.84], $p = 0.022$). No factor was found specifically associated with any other causes of GRFS failure.

Conclusions: We observed 5-year GRFS of 69%, meaning that most of patients who underwent Allo-HSCT for idiopathic SAA are cured without experiencing severe forms of acute and chronic GVHD. In the context of upfront MRD Allo-HSCT, GRFS was even more promising (77%). In this particular setting, time from diagnosis to Allo-HSCT was the most important factor influencing GRFS, suggesting the need to proceed to Allo-HSCT as quick as possible when a MRD is available.

Disclosure: Regis Peffault de la Tour: research grant and honorarium speaker fees from alexion, novartis, amgen and pfizer.

O025.

Outcome of Haematopoietic Cell Transplantation in Children with Fanconi Anaemia: A Study on Behalf of the EBMT SAAWP and PDWP

Su Han Lum[1], Sujith Samarasinghe[2], Robert Wynn[3], Dirk-Jan Eikeman[4], Paul Bosman[5], Serap Aksoylar[6], A. Ghavamzadeh[7], M. Bierings[8], Yves Bertrand[9], V. Kitra-Roussou[10], F. Smiers[11], Brigitte Strahm[12], M. Faraci[13], A. Schulz[14], S. Robinson[15], G. Krivan[16], M. Taskinen[17], Amal ALseraihy[18], John Snowden[19], Maija Itäla-Remes[20], Fanette Bernard[21], N. Kröger[22], F. Bambi[23], Susana Riesco[24], Antonio Risitano[25], Carlo Dufour[26], Selim Corbacioglu[27], Regis Peffault de Latour[28]

[1]Great North Children's Hospital, Newcastle upon Tyne, United Kingdom, *[2]Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom*, *[3]Royal Manchester Children's Hospital, Manchester, United Kingdom*, *[4]EBMT Statistical Unit, Leiden, Netherlands*, *[5]EBMT Data Office, Leiden, Netherlands*, *[6]Ege University, Izmir, Turkey*, *[7]Shariati Hospital, Tehran, Iran, Islamic Republic of*, *[8]Princess Maxima Center, Utrecht, Netherlands*, *[9]IHOP Lyon, Lyon, France*, *[10]St. Sophia Children's Hospital, Athens, Greece*, *[11]Leiden University Hospital, Leiden, Netherlands*, *[12]University of Freiburg, Freiburg, Germany*, *[13]Institute G. Gaslini, Genova, Italy*, *[14]Klinik für Kinder- und Jugendmedizin, Ulm, Germany*, *[15]Bristol Royal Hospital for Children, Bristol, United Kingdom*, *[16]Central Hospital of Southern Pest, Budapast, Hungary*, *[17]University of Helsinki, Helsinki, Finland*, *[18]King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia*, *[19]Sheffield Teaching Hospitals NHS Trust, Sheffield, United Kingdom*, *[20]Turku University Hospital, Turku, Finland*,

[21]*Great Ormond Street Children's Hospital, London, United Kingdom*, [22]*University Hospital Eppendorf, Hamburg, Germany*, [23]*Azienda Ospedaliero Universitaria Meyer, Florence, Italy*, [24]*Hospital Clinico, Salamanca, Spain*, [25]*University of Naples, Naples, Italy*, [26]*IRCCS Istituto G. Gaslini - Ospedale Pediatrico, Genova, Italy*, [27]*Children's Hospital Regensburg, Regensburg, Germany*, [28]*Hospital St. Louis, Paris, France*

Background: SAAWP and PDWP of the EBMT performed a retrospective registry study on the largest cohort of 130 children (1 to 16 years of age) with Fanconi anaemia (FA) undergoing haematopoietic cell transplantation (HCT) between 2001 and 2015.

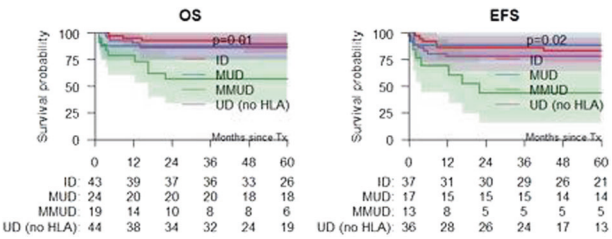
Methods: Patients who did not receive serotherapy and had haploidentical donor transplant were excluded. Primary endpoints were overall survival (OS) and event-free survival (EFS). EFS was defined as survival without graft failure, relapse and post-transplant malignancy. Secondary endpoints were grade II-IV acute GvHD (aGvHD), chronic GvHD (cGvHD) and graft failure. Subgroup differences in OS and EFS were evaluated by log-rank test. Competing risks methods were used for the cumulative incidence of acute and chronic GVHD, with competing events death, graft failure, relapse and second transplant. Subgroup differences in cGvHD and aGvHD were evaluated by Gray's test. All estimates are reported with 95% confidence intervals.

Results: Median age at transplant was 8 years (range, 1-16) and median follow-up was 5.7 years (5.2 - 6.3). Median interval between diagnosis and HCT was 2.4 years (range, 0.03-12.7). Eleven patients (8%) had pre-transplant malignancy (3 acute leukaemia; 8 MDS/MPD). Conditioning regimen was Fludarabine/Cyclophosphamide (n = 95; 73%), Busulfan/Cyclophosphamide/Fludarabine or others (n = 35, 27%). Ten (7.7%) received TBI. Donors were matched family (MFD; n = 43, 33%), matched unrelated (MUD; n = 24, 19%), mismatched unrelated (MMUD; n = 19; 14%) or unrelated donor with no HLA results (UD; n = 44, 34%). Stem cell source was bone marrow (n = 83, 65%), peripheral blood (n = 22, 17%) or cord blood (CB; n = 18, 14%) or BM and CB (n = 5, 4%). The CI of primary or secondary engraftment failure was 9% (4-14%). CI of secondary malignancy at 5-year post-HCT was 2% (0-4%).

The 5-year OS and EFS were 83% (95% CI, 77-90%) and 77% (69-85%). Increasing age was associated with lower OS (HR: 1.14, 1-1.29, p=0.05) and EFS (HR 1.11, 0.98-1.26, p = 0.1). MMUD (56%, 34-79%) was associated with inferior 5-year OS compared to MFD (90%, 81-99%), MUD (88%, 74-100%), UD (86%, 75-96%) (p=0.006). MMUD (43%, 15-71%) was associated with significantly lower EFS versus MFD (83%, 71-9%) or MUD (88%, 73-100%) or UD (78%, 64-91%). CB was associated with lower OS (60%, 35-85% vs BM: 85%, 77-93% vs PB: 86%, 72-100%) (p=0.07) and EFS (51%, 25-78% vs BM: 79%, 68-89% vs PB: 84%, 68-100%) (p=0.07). Conditioning had no association with OS and EFS.

CI of grade II-IV aGvHD at day 100 and cGvHD at 1 year were 38% (29-43%) and 14% (8-20%). Younger age had higher rate of aGvHD (HR=0.91 (0.83-1.0), p = 0.05) but had no association with cGvHD (HR 1.07, 0.93-1.22, p=0.33). Rate of aGvHD was significantly lower in MFD (20%, 8-32% vs MUD: 59%, 39-80% vs MMUD: 44%, 21-67% vs UD: 40%, CI 26-55%) (p=0.04). Donor type had no impact on cGvHD. FluCy had lower rates of aGvHD (28%, 19-37% vs FluBuCy/others: 64%, 47-80%, p< 0.001) and cGvHD (11%, 4-17% vs FluBuCy/others (35%, 19-51%), p=0.002). Stem cell source was not associated with aGvHD and cGVHD.

Conclusions: Younger age was associated with better survival. MFD and MUD had comparable survival in children with FA.



[Figure OS and EFS according to donor type]

Clinical Trial Registry: Not application

Disclosure: REgis PEFFAULT DE LA TOUR: Alexion, Amgen, Novartis and Pfizer: Grant for research and speaker honorarium for symposium.

O026.

Reduced Intensity Conditioning is Effective for Hematopoietic stem Cell Transplantation in Patients with Diamond-Blackfan ANEMIA

Shun Koyamaishi[1], Takuya Kamio[1], Akie Kobayashi[1], Tomohiko Sato[1], Ko Kudo[1], Shinya Sasaki[1], Rika Kanezaki[1], Daiichiro Hasegawa[2], Hideki Muramatsu[3], Yoshiyuki Takahashi[3], Yoji Sasahara[4], Hidefumi Hiramatsu[5], Harumi Kakuda[6], Miyuki Tanaka[7], Masataka Ishimura[8], Masanori Nishi[9], Akira Ishiguro[10], Hiromasa Yabe[11], Kenichi Yoshida[5], Hitoshi Kanno[12], Shouichi Ohga[8], Akira Ohara[13], Seiji Kojima[3], Satoru Miyano[14], Seishi Ogawa[5], Tsutomu Toki[1], Kiminori Terui[1], Etsuro Ito[1]

[1]*Hirosaki University, Hirosaki, Japan*, [2]*Prefectural Kobe Children's Hospital, Kobe, Japan*, [3]*Nagoya University,*

Nagoya, Japan, [4]Tohoku University, Sendai, Japan, [5]Kyoto University, Kyoto, Japan, [6]Chiba Children's Hospital, Chiba, Japan, [7]Shinshu University, Matsumoto, Japan, [8]Kyushu University, Fukuoka, Japan, [9]Saga University, Saga, Japan, [10]National Center for Child Health and Development, Tokyo, Japan, [11]Tokai University, Isehara, Japan, [12]Tokyo Women's Medical University, Tokyo, Japan, [13]Toho University, Tokyo, Japan, [14]University of Tokyo, Tokyo, Japan

Background: Diamond-Blackfan anemia (DBA) is an inherited bone marrow failure syndrome characterized by red cell aplasia and congenital anomalies. Patients with transfusion-dependent DBA who are unresponsive to corticosteroids can undergo allogeneic hematopoietic stem cell transplantation (HSCT) as a curative therapy. Successful results were recently reported in DBA patients who underwent HSCT using a reduced-intensity conditioning (RIC) regimen. However, there are limited data for determining the optimal conditioning regimen for patients with DBA.

Methods: The aims were to evaluate the outcomes of myeloablative conditioning (MAC) versus RIC regimens in DBA patients in Japan. To evaluate the clinical course of DBA, we sent questionnaires to the physicians of the DBA patients enrolled in our cohort between 2000 and 2018.

Results: Our DBA cohort consists of 187 patients. We performed genetic analysis in all 187 patients, of whom 117 (62.6%) had heterozygous mutations in one of the ribosomal genes. Completed questionnaires were returned from the physicians of 165 of the patients (88.2% response rate). The median age of these 165 patients at the time of diagnosis was 0.917 (range 0-47) years. The median follow-up duration after diagnosis was 7.33 years, and 13 patients (7.9%) were observed for more than 25 years. HSCT was performed in 27 patients (16.4%), of whom 25 (92.6%) became treatment independent. The median age at the time of HSCT was 3.58 (range 1.08-11.7) years. The median follow-up time after HSCT was 3.33 (range 0.667-12.8) years. Transplantation sources were bone marrow in 25 patients (from HLA-matched sibling donors in 5, HLA-mismatched related donors in 2, HLA-matched unrelated donors in 13, and HLA-mismatched unrelated donors in 5) and cord blood in 2 patients (from HLA-mismatched unrelated donors). MAC regimens were used in 13 patients, and RIC regimens with and without busulfan in 2 and 12 patients, respectively. Engraftment was successful in all 27 patients who underwent HSCT. One patient achieved neutrophil recovery and transfusion independency despite secondary graft failure. One patient with mixed chimerism became transfusion dependent, and one patient developed myelodysplastic syndrome (MDS) after HSCT. Three patients who underwent HSCT using a MAC regimen developed sinusoidal obstruction syndrome (SOS). Acute (Grade II-IV) and chronic graft versus host disease (GVHD) incidences were 48.1% and 40.7%, respectively. The 3-year overall survival (OS) and failure-free survival (FFS) rates post-transplantation were 95.2% and 92.6%, respectively, and showed no significant differences between the MAC and RIC regimens (OS: 100% vs. 92.3%, $p = 0.433$; FFS: 92.3% vs. 92.9%, $p = 0.979$).

Conclusions: Our data suggest that HSCT using a RIC regimen is effective to obtain engraftment with a low toxicity and excellent FFS for DBA patients.

Disclosure: Nothing to declare.

Autoimmune diseases

O027.

Beam vs Cyclophosphamide-Based Conditioning Regimen in Aggressive Multiple Sclerosis: A Retrospective Analysis of European Blood and Marrow Transplantation Society

Riccardo Saccardi[1], Manuela Badoglio[2], Joachim Burman[3], Grzegorz Helbig[4], Chiara Innocenti[1], Majid Kazmi[5], Giovanni Luigi Mancardi[6], John Moore[7], Paolo Muraro[8], Basil Sharrack[9], Marek Smilowski[10], Maria Pia Sormani[6], John A. Snowden[11]

[1]Careggi University Hospital, Florence, Italy, [2]EBMT Paris Study Office, Paris, France, [3]Uppsala University Hospital, Uppsala, Sweden, [4]Haematology and Bone Marrow Transplantation, Katowice, Poland, [5]Guy's & St. Thomas' NHS Trust Southwark Wing Guy's Hospital, London, London, United Kingdom, [6]University of Genova, Genova, Italy, [7]St. Vincents Health Network, Darlinghurst, AUS, Darlinghurst, Australia, [8]Imperial College London, London, United Kingdom, [9]Royal Hallamshire Hospital, Sheffield, United Kingdom, [10]Medical University of Silesia, Katowice, Poland, [11]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK, Sheffield, United Kingdom

Background: Multiple Sclerosis (MS) is a chronic, immuno-mediated disease of Central Nervous System (CNS), mostly affecting young adults and frequently resulting in a progressive, irreversible disability despite the administration of approved Disease Modifying Treatments (DMTs). Autologous HSCT was shown to induce a high rate of sustained, treatment-free remissions in cases of aggressive MS. Optimal intensity of Conditioning Regimen

(CR) in terms of both toxicity and efficacy is still to be clarified. In EBMT Registry the most frequently used CR were BEAM + ATG (BEAM) or HD-Cyclophosphamide + ATG (CYC). Overall TRM was low (1.4%), but slightly higher in BEAM over CYC. Here we retrospectively analyzed the neurological outcome of 603 MS patients who underwent autologous HSCT following either BEAM or CYC regimens.

Methods: Patient data were extracted from both the EBMT database and a disease-specific database developed by the EBMT Autoimmune Diseases Working Party (ADWP). Patients were selected for having received either BEAM or CYC and the availability of major neurological variables at both baseline and follow-up. MS forms at HSCT were reported as Relapsing-Remitting (RR), Secondary Progressive (SP), Primary Progressive (PP) and Progressive-Relapsing (PR). The impact of variables related to both patients (age, gender, EDSS at HSCT) and MS form at HSCT were also evaluated. Endpoints were failure to maintain a NEDA (Non-Evidence of Disease Activity) status, incidence of clinical relapses and/or progression of disability.

Results: Number of CYC procedures was higher (331 vs 272, respectively). Gender distribution was similar (p=ns), whilst mean age was higher in CYC patients over BEAM (38.3 vs 36.5, $p = 0.02$). RR forms at baseline were more frequent in CYC group ($p = 0.004$) as well as incidence of Gd-enhancing lesions at baseline (47.2% vs 35.5%, $p = 0.004$). Mean disability at baseline, assessed through the EDSS index, was significantly higher in BEAM over CYC (5.1±1.7 vs 4.8±1.7, $p = 0.03$), with no differences in the number of relapses in the 2 years before HSCT (0.41±0.49 vs 0.39±0.48, p=ns). Analysis of NEDA failures didn't show any significant differences between the two groups, also when RR and Progressive patients were analyzed separately. Comparison of relapse incidence was also not significant whilst CYC-treated patients showed an advantage over BEAM in progressive patients in terms of both overall disability worsening ($p = 0.01$) and continuous progression after HSCT ($p = 0.01$).

Conclusions: The non-myeloablative regimen CYC-ATG has become the most common conditioning regimen despite a lack of comparative data with more intense regimens. In our retrospective analysis of the two most frequent conditioning regimens in the EBMT Registry, there was no significant difference in terms of prevention of relapses, whilst the CYC regimen showed a slight advantage over BEAM in Progressive patients in terms of disability progression. The overall low incidence of relapses and the retrospective character of this analysis prevent to draw conclusions in terms of capability of the two conditioning regimens to restore the self-tolerance in MS. A prospective comparative trial is likely needed in order to provide a reliable information for this still unanswered question

Disclosure: No disclosures.

O028.

A Novel Targeted Approach to Achieve Immune System Reset: CD45-targeted Antibody Drug Conjugates Ameliorate Disease in Preclinical Autoimmune Disease Models and Enable AutoHSCT

Geoffrey Gillard, Jennifer Proctor, Melissa Brooks, Tahirih Lamothe, Sharon Hyzy, Sean McDonough, Nicholas Clark, Rahul Palchaudhuri, Anjali Bhat, Ganapathy Sarma, Prashant Bhattarai, Pranoti Sawant, Bradley Pearse, Charlotte McDonagh, Anthony Boitano, Michael Cooke

Magenta Therapeutics, Cambridge, MA, United States

Background: Resetting the immune system through autologous hematopoietic stem cell transplant (autoHSCT) is a highly effective treatment in selected patients with autoimmune diseases. AutoHSCT can induce long-term remission (up to 15 years) with 80% progression free survival in multiple sclerosis patients (Muraro 2017, Burt 2019). Likewise, use of autoHSCT in scleroderma patients has achieved superior outcomes in two randomized studies compared to standard of care (Tyndall 2014, Sullivan 2018). These impressive results are achieved by a combination of the eradication of autoreactive immune effector cells and re-establishment of self-tolerance, i.e., immune system reset. However, only a small fraction of eligible patients undergo autoHSCT, largely due to toxicity associated with current conditioning protocols.

Methods: As part of our goal to reduce the toxicity of transplant conditioning, we have generated novel anti-human CD45 ADCs that cross react with nonhuman primates (NHP) and evaluated these for the ability to deplete hematopoietic and immune cells in vitro and in vivo in humanized NSG (hNSG) mice and NHPs. To model the transplant approach in mouse models of AID, we generated an anti-mouse CD45 ADC and evaluated the capacity of this ADC to enable immune reset and ameliorate autoimmune disease.

Results: The anti-human CD45-ADC showed efficient killing of human BM $CD34^+$ (EC50 2.44×10^{-9} M) and peripheral CD3+ cells from a healthy donor (EC50 7.6×10^{-10} M) and patients with MS (EC50 1.5×10^{-10} M) (Fig. 1A). In hNSG, single doses of the CD45-ADC were

well-tolerated and led to substantial (>95%) depletion of human cells. (Fig. 1B). In NHPs, single doses of CD45-ADC were well tolerated and achieved >90% peripheral lymphocyte depletion and >80% depletion of HSCs (Fig. 1C). Finally, administration of a single dose of anti-human CD45-ADC to hNSGs with sclerodermatous xenoGVHD resulted in depletion of human T cells and resolution of symptoms (Fig. 1D).

A single-dose of the anti-mouse CD45-ADC enabled full myeloablation (>99% depletion of LT-HSCs) and complete donor chimerism with congenic HSCT (>90% chimerism at 16 weeks). In a murine model of MS, EAE, a single dose of the CD45-ADC followed by congenic HSCT enabled full donor chimerism; treatment prior to disease onset significantly delayed disease onset and reduced disease severity. In a murine model of arthritis, proteoglycan-induced arthritis (PGIA), therapeutic treatment with a single dose of the CD45-ADC followed by congenic HSCT enabled complete donor chimerism and halted disease progression, comparable to what was achieved with repeated doses of anti-TNFα. These data demonstrate that CD45-ADC conditioning followed by congenic HSCT is sufficient for full myeloablation and immune reset. Additional experiments are ongoing, and evaluation of this ADC in a murine model of diabetes will be presented.

Conclusions: These results suggest that targeted immune depletion with a single dose of CD45-ADC may be sufficient to enable auto-HSCT and immune reset in multiple AID indications without toxic side effects. Targeted conditioning with CD45-ADC may represent a better tolerated approach for removing disease-causing cells as part of immune reset through autoHSCT and may significantly reduce the morbidity and mortality associated with current conditioning.

Disclosure: All authors are employees and hold equity in Magenta Therapeutics.

O029.

Long Term Follow up of Systemic Sclerosis French Patients Included in the Astis Trial Using Scot Trial Global Rank Composite Score (GRCS)

Nassim Ait Abdallah[1,2], Mianbo Wang[3], Zora Marjanovic[2,4], Pauline Lansiaux[1,2], Catney Charles[2], Fanny. Urbain[1], Mary Hudson[3,5,6], Dominique Farge[1,2,7]

[1]Hôpital Saint Louis, Paris, France, [2]MATHEC, Centre de Référence Maladies Auto-immunes Systémiques Rares d'Ile-de-France, Paris, France, [3]Lady Davis Institute, Montreal, Canada, [4]Hôpital Saint Antoine, APHP, Paris, France, [5]McGill University, Montreal, Canada, [6]Jewish General Hospital, Montreal, Canada, [7]Université de Paris, Paris, France

Background: Autologous Hematopoietic Stem Cell Transplantation (AHSCT) is the only treatment so far which improved mortality in severe Systemic Sclerosis (SSc) (level I EBMT-evidence). The largest ASTIS (phase III)[1] and SCOT (phase II)[2] randomised trials used similar inclusion criteria and control arms, but different primary endpoints to assess the overall response with respectively: the ASTIS event-free survival (EFS) at 2 years and the SCOT global rank composite score (GRCS) at 54 months.

Objective: To asses the 5 year efficacy of AHSCT vs iv pulse Cyclophosphamide in all French patients initially included in ASTIS after extended follow-up in the MATHEC cohort using the SCOT-GRCS.

Methods: All French patients randomized (1:1, stratification according to centre) in the multicenter open-label ASTIS trial from 2001 to 2019, followed in parallel-groups until October 31, 2013 were subsequently included in the MATHEC cohort for extended follow-up with at least yearly evaluation with data collection up to last visit. Primary endpoint was the GRCS comparing participants with each other, based on a hierarchy of disease features assessed at 5 years 60 months: death, EFS (survival without respiratory, renal, or cardiac failure), forced vital capacity (FVC), the Scleroderma Health Assessment Questionnaire Disability Index score (SHAQ) and the modified Rodnan skin score (mRSS). Secondary endpoints were: EFS, overall survival (OS) and functional status. Delta values were calculated between 5 years and baseline. All analyses have been done by intention to treat.

Results: The 49 MATHEC patients initially randomly assigned in ASTIS to AHSCT ($n = 26$) or cyclophosphamide ($n = 23$) showed no significant difference at baseline regarding: age (46vs 42years), female predominance(58 vs 65%), SSc duration (1.6vs 1.4years), mRSS (25 vs 25), FVC (83vs 80%), CT-scan abnormalities (24/26 vs 18/23), Left Ventricular Ejection Fraction (LVEF%) (66 vs 68), Pulmonary Artery Hypertension (3/26 vs 6/23), creatinemia (66vs 60μmol/ l) and SHAQ (1.2 vs1.3).

At 5 years, comparison between AHSCT versus Cyclophosphamide groups showed median GRCS at 9 versus -19 ($p = 0.018$) with 64% versus 29% improvement using paired comparison ($p = 0.021$). EFS was higher in AHSCT (7 events including 3 deaths) versus Cyclophosphamide group (12 events including 7 deaths) ($p = 0.04$, Hazard ratio = 0.48mRSS improved in both groups, with higher improvement in the AHSCT versus Cyclophosphamide group (delta mRSS: 16 vs -9, $p = 0.02$). SHAQ improved in the AHSCT group only (delta SHAQ = 0.89 versus - 0.2,

$p = 0.05$). No significant difference was observed between the groups in FVC, LVEF and creatinemia.

Conclusions: The ASTIS-France-MATHEC study confirms the efficacy and the superiority of AHSCT versus Cyclophosphamide treatment for severe SSs, after 5 years and using GRCS criteria.

References

[1] van Laar JM, Farge D and Al. Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis: A Randomized Clinical Trial. JAMA 2014;311(24):2490.

[2] Sullivan KM, and al. Myeloablative Autologous Stem-CellTransplantation for Severe Scleroderma. New England Journal of Medicine 2018;378(1):35-47.

Disclosure: Nothing to declare.

O030.

Advances in Multiple Sclerosis (Ms) Treatment: Clinical and Patient-reported Outcomes in Patients Undergoing Autologous Hematopoietic Stem Cell Transplantation

Denis Fedorenko[1], Vladimir Melnichenko[1], Gorgut Zeinalov[1], Tatiana Nikitina[2,3], Natalia Porfirieva[3], Tatiana Ionova[1,2]

[1]National Medical and Surgical Center named after N.I. Pirogov, Moscow, Russian Federation, [2]Saint Petersburg State University Hospital, Saint-Petersburg, Russian Federation, [3]Multinational Center for Quality of Life Research, Saint-Petersburg, Russian Federation

Background: At present high-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation (AHSCT) has been used with increasing frequency as a therapeutic option for MS patients. Here we present the results of single center experience of AHSCT in MS with the analysis of both clinical and patient-reported outcomes (PRO).

Methods: Pts aged >14 y.o. with verified MS, who had indications for AHSCT were involved in a prospective single center study. Reduced-intensity BM/BEAM-like or Cyclophosphamide based conditioning were used. For clinical outcomes neurological assessment using EDSS and MRI scans were performed. Safety was evaluated in accordance with NCI CTCAE v.2.0. Quality of life (QoL) was assessed using RAND SF-36, symptom severity - using CSP-MS-42. Event-free survival (EFS) and progressive-free survival (PFS) after AHSCT were evaluated using Kaplan-Meyer method. For QoL and EDSS comparisons paired t-test, Mann-Whitney test, Wilcoxon test, and ANOVA were used. For comparison of survival log-rank criterion was applied.

Results: 502 MS pts (mean age - 39 years old; male/female -178/324; mean EDSS=4.0; 257 relapsing/remitting MS, 161 - secondary progressive MS and 84 - primary progressive MS) were included in the analysis. Median of MS duration - 5 yrs (0.5-33). Median follow-up after HSCT - 29.5 mo (0.2-111.6). The mobilization and transplantation procedures were well tolerated. Transplant-related mortality - 2 pts (0.4%). Clinical response was observed in the vast majority (99%) of pts. Average time until disease progression - 101.4 mo (95% CI 98.0-104.9). EFS in relapsing-remitting MS was 95%, in progressive - 78%. EFS and PFS were better in younger pts with less EDSS score and less disease duration as well as in those with relapsing-remitting MS ($p < 0.001$). As for QoL it was significantly compromised before AHSCT. In a year after transplantation definite QoL improvement was registered across all the scales of SF-36, except role emotional functioning ($p< 0.01$). At long-term follow-up (median - 24 months) positive QoL changes preserved: QoL scales were significantly higher than at baseline ($p< 0.01$). Further analysis demonstrated that positive QoL and symptom changes after AHSCT were revealed for different patients' subgroups: pts with progressive and relapsing disease; pts with low, intermediate and high disability according to EDSS; pts with MS duration < 5 yrs and pts with longer disease duration. A wide range of disease-related symptoms according to CSP-MS-42 were pronounced before AHSCT. Their severity significantly decreased after transplantation for the majority of scales.

Conclusions: Thus, the risk/benefit ratio of AHSCT in our population of MS pts is very favorable. The vast majority of pts responded to treatment and exhibited clinical improvement or were stable during the follow-up. AHSCT was accompanied by significant improvement in patient's QoL and decrease of symptom burden. AHSCT is beneficial for different subgroups of MS pts, including the unfavorable ones. Information about PROs in MS pts undergoing AHSCT may provide valuable information about patient's perspective about the risks/benefits of treatment, needs for rehabilitation and the degree of the recovery.

Disclosure: Nothing to declare.

O031.

Post Transplantation Cyclophosphamide Improves Outcome After Autologous Hematopoietic Stem Cell Transplantation in Animal Model of Multiple Sclerosis

Kaja Kasarełło[1], Martyna Seta[1], Tomasz Ciesielski[1], Dorota Sulejczak[2], Robert Wrzesień[1], Agnieszka Cudnoch-Jędrzejewska[1], Emilian Snarski[1]

[1]Medical University of Warsaw, Warsaw, Poland, [2]Mossakowski Medical Research Centre, Warsaw, Poland

Background: Experimental allergic encephalomyelitis (EAE) is the animal model of multiple sclerosis (MS), the autoimmunological human disease leading to neurodegeneration.

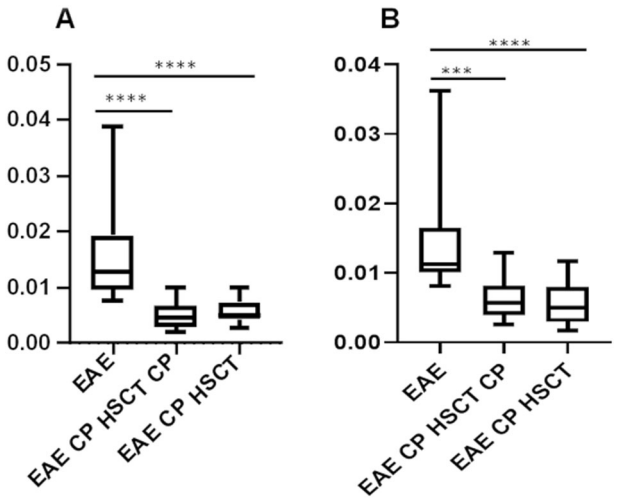
The autologous hematopoietic stem cell transplantation (AHSCT) has recently become the standard treatment for highly-active relapsing remitting MS. Antithymocyte globulin (ATG) which is a typical part of conditioning is thought to eliminate the autoreactive cells, which may persist after the chemotherapy. The other strategies of post-transplantation treatment are neither well developed in animal model nor in clinical transplantation.

In our experiment, we aimed to investigate the effect of AHSCT with the addition of low dose post-transplantation cyclophosphamide (CP) on the disease course in rats with evoked EAE.

Methods: Rats with evoked EAE (day 0) were treated with (a) high-dose (125mg/kg) CP (day +6), followed by AHSCT (day +7) (EAE CP HSCT), or (b) high-dose (125mg/kg) CP, followed by AHSCT (EAE CP HSCT CP), followed by low-dose (20mg/kg) CP (day +10, +11). Clinical symptoms of EAE were observed during the disease course, and after the resolution of symptoms (day +21) rats were euthanized. Spinal cords were collected for further analysis. Histochemical analysis (H+E staining) were performed to assess the intensity of immune cells infiltration to the CNS.

Results: The results showed that both the AHSCT and AHSCT with post-transplant CP reduce the intensity of the inflammatory response in the CNS, in comparison to EAE not-treated rats. Histopathological analysis of cervical and thoracic spinal cord sections has shown significant reduction of the inflammatory infiltrations (% of slice area occupied by infiltrated cells) from 0.015% in EAE non-treated animals to about 0.005% in EAE treated animals (Figure 1). The clinical symptoms reduction was present in both treatment arms ($p = 0.00005$) - however significantly stronger in arm with post-transplantation CP compared to AHSCT alone ($p = 0.03$). The toxicity of both treatment arms was similar: engraftment was complete by day +14 after the AHSCT and there was no transplant related mortality.

Conclusions: Application of the additional post AHSCT low-dose CP improved the results of AHSCT by not only reducing the intensity of inflammation in the CNS but also by significantly reducing the clinical symptoms in treated animals. We provide the experimental rationale that the addition of post transplantation CP could improve outcome of AHSCT in MS.



[Figure 1: Infiltrations in spinal cord in treated animals]

Disclosure: Nothing to declare. Supported by grant no. 2018/02/X/NZ5/01487 financed by the National Science Centre.

CAR-based Cellular Therapy – clinical

O032.

KTE-X19, an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, in Patients with Relapsed/ refractory (R/R) Mantle Cell Lymphoma (MCL): Results from Phase 2 of ZUMA-2

Michael Wang[1], Javier Munoz[2], Andre Goy[3], Frederick Locke[4], Caron Jacobson[5], Brian Hill[6], John Timmerman[7], Houston Holmes[8], Samantha Jaglowski[9], Ian Flinn[10], Peter McSweeney[11], David Miklos[12], John Pagel[13], Marie Jose Kersten[14], Weimin Peng[15], Lianqing Zheng[15], John Rossi[15], Rajul Jain[15], Arati Rao[15], Patrick Reagan[16]

[1]University of Texas MD Anderson Cancer Center, Houston, TX, United States, [2]Banner MD Anderson Cancer Center, Gilbert, AZ, United States, [3]John Theurer Cancer Center, Hackensack, NJ, United States, [4]Moffitt Cancer Center, Tampa, FL, United States, [5]Dana-Farber Cancer Institute, Boston, MA, United States, [6]Cleveland Clinic Foundation, Cleveland, OH, United States, [7]David Geffen School of Medicine at UCLA, Los Angeles, CA, United States, [8]Texas Oncology, Dallas, TX, United States, [9]The Ohio State University Comprehensive Cancer Center,

Columbus, OH, United States, [10]*Sarah Cannon Research Institute, Nashville, TN, United States*, [11]*Colorado Blood Cancer Institute, Denver, CO, United States*, [12]*Stanford University, Stanford, CA, United States*, [13]*Swedish Cancer Institute, Seattle, WA, United States*, [14]*Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands*, [15]*Kite, a Gilead Company, Santa Monica, CA, United States*, [16]*University of Rochester Medical Center, Rochester, NY, United States*

Background: Outcomes with salvage regimens in patients with MCL who progress after Bruton tyrosine kinase inhibitor (BTKi) therapy are poor. Here, we present interim efficacy and safety results from ZUMA-2, the first Phase 2, registrational, multicenter study evaluating KTE-X19 autologous anti-CD19 CAR T cell therapy in patients with R/R MCL.

Methods: Eligible patients (≥ 18 years) with R/R MCL, an ECOG of 0 - 1, and ≤ 5 prior therapies (including chemotherapy, an anti-CD20 antibody, and a BTKi) underwent leukapheresis and conditioning chemotherapy followed by KTE-X19 infusion at 2×10^6 cells/kg. Bridging chemotherapy was permitted. The primary endpoint was objective response rate (ORR [complete response (CR) + partial response]), assessed by an Independent Review Committee per Lugano Classification (Cheson, et al. *J Clin Oncol*. 2014). Interim efficacy endpoints were investigator-assessed using the revised International Working Group Response Criteria for Malignant Lymphoma (Cheson, et al. *J Clin Oncol*. 2007). Key secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), frequency of adverse events (AEs), and blood levels of CAR T cells. Sixty patients received KTE-X19; here, we present results in patients with ≥1 year of follow-up. Updated results for all 60 patients will be reported in the presentation.

Results: As of May 30, 2018, 28 patients received KTE-X19 with ≥ 1 year of follow-up (median, 13.2 months). The median age was 65 years; 43% of patients had an ECOG score of 1; 21% had blastoid morphology; 82% had stage IV disease; 50% had intermediate/high-risk MIPI; 86% received a median of 4 prior therapies; 57% were refractory to last prior therapy. Eight patients received bridging therapy; all had disease present post-bridging. Investigator-assessed ORR was 86% (95% CI, 67% - 96%), with a CR rate of 57% (95% CI, 37% - 76%); 75% of responders remained in response, and 64% of treated patients had ongoing responses. The 12-month estimates of DOR, PFS, and OS were 83% (95% CI, 60% - 93%), 71% (95% CI, 50% - 84%), 86% (95% CI, 66% - 94%), respectively; medians were not reached. The most common Grade ≥3 AEs were anemia (54%), platelet count decrease (39%), and neutropenia (36%). Grade 3/4 cytokine release syndrome (CRS) assessed by Lee et al. (*Blood*. 2014) and Grade 3/4 neurologic events (NEs) were reported in 18% and 46% of patients, respectively (no Grade 5 CRS or NEs). All CRS events and most NEs (15/17 patients) were reversible. There was 1 Grade 5 AE of organizing pneumonia, considered related to conditioning chemotherapy. Median CAR T cell levels as measured by peak and area under the curve were 99 cells/μL (range, 0.4 - 2589) and 1542 cells/μL (range, 5.5 - 27239), respectively. Peak CAR T cell expansion was observed between Days 8 and 15 and levels declined over time.

Conclusions: With ≥1 year of follow-up, KTE-X19 demonstrated significant and durable clinical benefit and a manageable safety profile in patients with R/R MCL for whom there are no curative treatment options.

Clinical Trial Registry: *Clinicaltrials.gov NCT02601313.*

Disclosure: MW: stock/ownership- MoreHealth; honoraria- OMI; consult/advisor- Celgene, MoreHealth, Pulse; testimony- AstraZeneca; research- Novartis, Kite/Gilead, Juno/Celgene, Loxo, VelosBio; honoraria+consult/advisor+research- Pharmacyclics, Janssen, AstraZeneca; travel- Janssen, Pharmacyclics, Celgene, OMI. **JM:** consult/advisor+speaker- Genentech, Bayer, Kite/Gilead, Kyowa, Pharmacyclics, Janssen, SeattleGenetics; consult/advisor- Alexion, Juno/Celgene/BMS, Merck, Pfizer; speaker- Fosunkite, AstraZeneca; research- Celgene, Genentech, Incyte, Janssen, Kite/Gilead, Pharmacyclics, Portola, SeattleGenetics. **AG:** leadership+stock/ownership- COTA; honoraria+consultant/advisor- Kite/Gilead, Janssen, Celgene, Acerta, AstraZenca. **FLL:** consultant/advisor- Kite/Gilead, Novartis, Calibr, GammaDelta, CBMG. **CJ:** honoraria- Kite/Gilead, Novartis; consult/advisor+research- Kite/Gilead, Novartis, Bayer, Precision-Biosciences, Humanigen, Celgene. **BH:** Honoraria +consultant/advisor- Kite/Gilead, Pharmacyclics, Genentech, Abbvie, Astrazeneca, Celgene, SeattleGenetics; research- Pharmacyclics, Genentech, Abbvie, Celgene, Takeda, Amgen. **JT:** consultant/advisor+honoraria+travel+research- Kite/Gilead, BMS; research- Merck, Valor. **HH:** consult/advisor- Kite/Gilead, Bayer, Rigel, Janssen, Juno; speaker- Kite/Gilead, SeattleGenetics, Rigel; research- Kite/Gilead, Unum, Juno, Novartis, Genentech, ADC, SeattleGenetics. **SJ:** consultant/advisor- Kite/Gilead, Juno, Novartis, CRISPR; research- Kite/Gilead, Novartis. **IF:** consultant/advisor- Verastem; research- Infinity, Pharmacyclics/Janssen, Kite/Gilead, Merck, Novartis, Pfizer, Portola, SeattleGenetics, Takeda, TG, Trillium, Verastem. **PM**: consultant/advisor+speaker +honoraria+research- Kite/Gilead; patents/royalties/intellectual property- Fred Hutch. **DM:** consult/advisor +research- Kite/Gilead, Novartis, Celgene/Juno,

Miltenyi, Adaptive, PCYC, Janssen; patents/royalties/intellectual property- PCYC. **JP:** consult/advisor- Gilead, Pharmacyclics. **MJK:** consult/advisor+honoraria +research+travel- Kite/Gilead, Novartis, Celgene, Roche, Miltenyi. **WP:** employment+stock/ownership- Kite/Gilead. **LZ, JR, AR:** employment- Kite/Gilead. **RJ:** employment+stock/ownership- Kite/Gilead, Vida, Amgen; patents/royalties/intellectual property- CAR-T. **PR:** consult/advisor- Kite/Gilead, Curis; research- SeattleGenetics.

O033.

Safety and Efficacy Results From Transcend NHL 001, a Multicenter Phase 1 Study of Lisocabtagene Maraleucel (Liso-cel) In Relapsed/refractory Large B-Cell Lymphoma

Jeremy Abramson[1], M. Lia Palomba[2], Leo Gordon[3], Matthew Lunning[4], Michael Wang[5], Jon Arnason[6], Amitkumar Mehta[7], Enkhtsetseg Purev[8], David Maloney[9], Charalambos Andreadis[10], Alison Sehgal[11], Scott Solomon[12], Nilanjan Ghosh[13], Tina Albertson[14], Jacob Garcia[14], Ana Kostic[14], Daniel Li[14], Yeonhee Kim[14], Tanya Siddiqi[15]

[1]Massachusetts General Hospital Cancer Center, Boston, MA, United States, [2]Memorial Sloan Kettering Cancer Center, New York, NY, United States, [3]Northwestern University, Robert H. Lurie Comprehensive Cancer Center, Chicago, IL, United States, [4]University of Nebraska Medical Center, Omaha, NE, United States, [5]University of Texas MD Anderson Cancer Center, Houston, TX, United States, [6]Beth Israel Deaconess Medical Center, Boston, MA, United States, [7]University of Alabama at Birmingham, Birmingham, AL, United States, [8]University of Colorado, Aurora, CO, United States, [9]Fred Hutchinson Cancer Research Center, Seattle, WA, United States, [10]University of California, San Francisco, CA, United States, [11]University of Pittsburgh Medical Center, Pittsburgh, PA, United States, [12]Northside Hospital Cancer Institute, Atlanta, GA, United States, [13]Levine Cancer Institute, Atrium Health, Charlotte, NC, United States, [14]Juno Therapeutics, a Bristol-Myers Squibb Company, Seattle, WA, United States, [15]City of Hope National Medical Center, Duarte, CA, United States

Background: Liso-cel is an investigational, CD19-directed, defined composition, 4-1BB CAR T cell product administered at target doses of CD8+ and CD4+ CAR+ T cells. We present results from the large B-cell lymphoma (LBCL) cohort of TRANSCEND NHL 001 (NCT02631044).

Methods: Patients aged ≥18 years had relapsed/refractory diffuse LBCL not otherwise specified (including transformed from any indolent lymphoma), high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, primary mediastinal B-cell lymphoma, or follicular lymphoma grade 3B after ≥2 lines of therapy, and ECOG PS of 0–2. Patients with mild/moderate organ dysfunction and secondary CNS lymphoma were eligible. Bridging therapy was allowed with reconfirmed PET-positive disease before lymphodepletion with fludarabine/cyclophosphamide. Liso-cel was given at 1 of 3 dose levels (DLs): 50×10^6 (DL1), 100×10^6 (DL2), or 150×10^6 (DL3) viable CAR+ T cells. DL2 was chosen for dose confirmation. Primary endpoints were treatment-emergent adverse events (TEAEs) and objective response rate (ORR). Secondary endpoints were complete response (CR) rate, duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Cytokine release syndrome (CRS) was graded per 2014 Lee criteria. ORR was assessed by independent review per Lugano criteria.

Results: Of 344 patients leukapheresed, 269 received liso-cel (DL1, $n = 51$; DL2, $n = 177$; DL3, $n = 41$). No product could be manufactured for 2 patients, and 25 patients received nonconforming product. In the optimized manufacturing process, median time from leukapheresis to liso-cel availability was 24 days. Median age was 63 years (range, 18–86 years; ≥65 years, 42%; ≥75 years, 10%). Overall, 26% of patients had ≥4 lines of prior therapy (median, 3; range, 1–8), 67% were chemorefractory, 44% had never achieved CR, and 59% had bridging therapy. Twenty-five patients received liso-cel as outpatients. Outcomes were similar across DLs, so data were pooled. 79% of pts had grade ≥3 TEAEs, mostly cytopenias (neutropenia, 60%; anemia, 38%; thrombocytopenia, 27%). 47% of pts had CRS and/or neurological events (NEs), with late onset (median, 5 and 9 days, respectively). Incidence of grade ≥3 CRS (2%) and NEs (10%) was low. Four grade 5 liso-cel-related TEAEs occurred (diffuse alveolar damage, pulmonary hemorrhage, multiple organ dysfunction syndrome, and cardiomyopathy). Safety was similar among patient subgroups. All primary and secondary efficacy endpoints were met. Of 256 efficacy-evaluable patients, the ORR was 73% (95% CI, 67–78) and the CR rate was 53% (95% CI, 47–59). Responses were similar across patient subgroups (Table). Median DOR was not reached (NR; 95% CI, 8.6–NR) with 12.0 months of median follow-up; median DOR for patients in CR was NR (95% CI, NR–NR). Median PFS was 6.8 months (95% CI, 3.3–14.1). Median OS was 21.1 months (95% CI, 13.3–NR).

Conclusions: Liso-cel showed durable clinical activity with a favorable safety profile across relapsed/refractory LBCL histologic subgroups and in patients with poor prognosis, including chemotherapy refractory, older age, comorbidities, and high tumor burden. Incidence of severe

CRS and NEs was low, with late onset, allowing for outpatient administration.

Clinical Trial Registry: ClinicalTrials.gov identifier NCT02631044.

Disclosure: Funding Statement: This study was funded by Juno Therapeutics, a Bristol-Myers Squibb Company. Medical writing and editorial assistance were provided by The Lockwood Group (Stamford, CT, USA), and was funded by Bristol-Myers Squibb. JSA reports consultancy from Gilead Sciences, Seattle Genetics Celgene, Novartis, Amgen, Juno therapeutics, Karyopharm, Verastem, Bayer, Abbvie, Janssen, Merck, Kite Pharma, Genentech, EMD Serono, Morphosys, research funding from Seattle Genetics, Celgene, Genentech, Juno therapeutics, AI therapeutics; MLP reports Stock/ Royalties/ Honoraria from Seres Therapeutics (immediate family member), Honoraria from Flagship Ventures, Evelo, Jazz Pharmaceuticals, Therakos, Amgen (immediate family member), Honoraria and Consultancy from Merck & Co Inc, Advisory Board from Pharmacyclics, Royalty from Juno Therapeutics (immediate family member), Honoraria from Novartis; LIG reports advisory board from Kite/Gilead and Bayer; ML reports Research Funding from ADC Therapeutics, Celgene, Curis, Janssen Scientific Affairs LLC, Juno Therapeutics, MiRagen, TG Therapeutics, Consultancy from AbbVie, Bayer, Celgene, DAVA, Gilead Sciences Inc, Janssen, Juno Therapeutics, Kite, Novartis, OncLive, Portola, Seattle Genetics, Spectrum, TG Therapeutics, VANIUM, Verastem; MW reports consultancy, honorarium, and advisory board from Janssen, AstraZeneca, Acerta Pharma, Kite Pharma, Pharmacyclics, Loxo Oncology, Celgene, Pulse Biosciences, MoreHealth, Guidepoint Global, Targeted Oncology, Nobel Insights, royalties from MoreHealth, research funding from Janssen, AstraZeneca, Acerta Pharma, Kite Pharma, Pharmacyclics, Loxo Oncology, Celgene, BeiGene, Velosbio, Aviara, Verastem; JA reports advisory board from Regeneron and Celgene/Juno; AM reports consultancy from Pharmacyclics, Celgene, Spectrum, and Imbrium therapeutics, research funding from Roche-Genentech, Incyte, Kite/Gilead, Takeda, Rhizen, ADC therapeutics, Forty Seven Inc, Juno/Celgene, Affimed, Seattle Genetics, Astex, TG Therapeutics, and miRagen, speakers bureau from Kyowa-Kirin, Celgene, Kite/Gilead, Spectrum, Seattle Genetics, and Astra-Zeneca; EP reports salary from Genentech; DGM reports research funding (paid to his institution), patents & royalties (paid to his institution) and honoraria from Juno, a Celgene/BMS company, research funding (paid to my institution) and honoraria from Celgene a BMS company and Kite Pharma, a Gilead company, Honoraria from BioLineRX; Gilead; Novartis; Pharmacyclics, Honoraria and stock options from A2 Biotherapeutics; CA reports Salary from Genentech (spouse), Consultancy from Celgene, Novartis, Gilead, Jazz, ownership interest from Roche, research funding from Novartis, Celgene, Amgen, Merck; AS reports research funding from Juno/Celgene, Kite/Gilead, Merck; SRS reports no conflicts; NG reports research funding, speakers bureau, and consulting from Celgene, research funding, and consulting from T. G. Therapeutics, speakers bureau and consulting from Seattle Genetics, Janssen and Gilead, research funding, speakers bureau, consulting from Pharmacyclics, speakers bureau from Abbvie, research funding from Genentech, research bureau from Forty Seven Inc., and speakers bureau from Astra Zeneca; TA reports salary and ownership interest from BMS; JG reports salary and stock from BMS; AK reports ownership interest and salary from Juno Therapeutics, a BMS Company; DL reports stocks and equity from BMS; YK reports salary and ownership interest from BMS; TS reports consultancy from AstraZeneca, Juno, BeiGene, Kite Pharma, speaker from Pharmacyclic, Jansen, Seattle Genetics, Astra Zeneca.

O034.

CD19/CD22 Dual Targeted (Chimeric Antigen Receptor) CAR-T Therapy for Relapsed or RE Fractory (R/R) B-CELL Non-Hodgkin Lymphoma (B-NHL)

Houli Zhao[1,2,3], Yongxian Hu[1,2,3], Arnon Nagler[4], Alex Hongsheng Chang[5], He Huang[1,2,3]

[1]The First Affiliated Hospital, Zhejiang University, Hangzhou, China, [2]Zhejiang Province Engineering Laboratory for Stem Cell and Immunity Therapy, Hangzhou, China, [3]Zhejiang University, Hangzhou, China, [4]Chaim Sheba Medical Center, Tel Hashomer, Israel, Tel Hashomer, Israel, [5]Shanghai YaKe Biotechnology Ltd, Shanghai, Shanghai, China

Background: Targeted CD19 CAR-T therapy makes great progress in r/r B-NHL with 50% CR. However, another half of patients relapses from a short duration of response or refractory to CAR-T therapy. Antigen escape and heterogeneity of antigen expression are the key mechanisms of anti-CD19 CAR-T therapy failure. A single CAR targeting CD19 and CD22 simultaneously may overcome such obstacles.

Methods: T cells transduced with CD19/CD22 dual targeted CAR lentiviral vectors were infused in patients with R/R B-NHL with CD19 or CD22 positive under fludarabine- and cyclophosphamide-based lymphodepletion. The post-infusion responses, toxicities, and cytokine profiling in enrolled patients were observed and monitored. Cytokine arrays contains 45 different kinds of cytokines related to function of immune cell. Cytokine arrays was performed at the day of CAR-T infusion, day

1-3 after CAR-T infusion, peak of cytokine release syndrome (CRS) according to clinical status and recovery day from CRS.

Results: Baseline characteristics are listed in Table 1. We enrolled 17 patients with r/r B-NHL. The median transduction efficiency of CD19/CD22 CAR-T was 48%. In vitro cytotoxicity assays were conducted and showed prominent anti-lymphoma activities with CD19/CD22 CAR-T. The patients received CD19/CD22 CAR-T infusion at doses of 4.9-9.4×10^6/kg. 11 (64.7%) and 6 (35.3%) patients achieved complete response (CR) and partial response (PR) 1 month after CAR-T infusion. With the median follow-up of 244 days, 1-year overall survival (OS) and 1-year progression free survival (PFS) were estimated at 70.7% and 48.4%, respectively. Among patients who achieved CR 1-year OS and 1-year PFS were estimated at 100% and 83.3% In this trial, all 17 patients experienced CRS. Grade 1, 2, and 3 cytokine release syndrome occurred in 4 (23.5%), 12 (70.6%), and 1 (5.9%) patients respectively. Cytokine arrays showed MIP-3β increase at day 1-3 after CAR-T infusion. CD40 ligand, MIP-1β, GROβ, EGF, PDGF-AB/BB, RANTES, IL-8, TRAIL decrease and PD-L1/B7-H1, MIP-1α, GM-CSF, IL-1ra, IL-3, IL-5, MIP-3β, MCP-1, IP-10 increase were observed at CRS peak. In subgroup analysis, we found patients who achieved CR with lower level of CD40 ligand, FGF basic at day 1-3, and GM-CSF, IP-10 at recovery day than PR patients.

Conclusions: CD19/CD22 dual targeted CAR-T is a promising solution for improving response and prolonging PFS for r/r B-NHL patients with less than grade 3 CRS adverse events. Cytokine profiling showed CD40 ligand, MIP-1β, GROβ, EGF, PDGF-AB/BB, RANTES, IL-8, TRAIL decrease and PD-L1/B7-H1, MIP-1α, GM-CSF, IL-1ra, IL-3, IL-5, MIP-3β, MCP-1, IP-10 increase during CRS. MIP-3β may be a biomarker of early phase of CRS. Lower level of CD40 ligand, FGF basic at early phase of CRS and lower level of GM-CSF, IP-10 when recovery from CRS may be related to good response.

	median		male	female	
age	50	sex	9	8	
prior lines of therapy	3		DLBCL	Burkitt	lymphoblastic lymphoma
		Subtype	14	1	2

[Baseline characteristics]

Clinical Trial Registry: ChiCTR1800015575 www.chictr.org.cn

Disclosure: Nothing to declare.

O035.

An Update of the EBMT Survey on CAR T-Cell Activity in Europe. On Behalf of the Cellular Therapy & Immunobiology Working Party (CTIWP)

Alvaro Urbano[1], Arnon Nagler[2], Gunilla Enblad[3], Susana Rives[1], Michael Hudecek[4], Claire Roddie[5], Peter Dreger[6], Ibrahim Yakoub-Agha[7], Christof Scheid[8], Victoria Potter[9], Franco Locatelli[10], Reuben Benjamin[11], Katharina Fleischhauer[12], Ulrike Koehl[13], Jürgen Kuball[14], Florent Malard[15], Paolo Pedrazzoli[16], Luca Vago[17], Lotte Wietten[18], Rose Ellard[19], Jorinde Hoogenboom[20], Chiara Bonini[17], Annalisa Ruggeri[21], Christian Chabannon[22]

[1]BMT Unit, Barcelona, Spain, [2]Sheba University Hospital, Tel Aviv, Israel, [3]Uppsala University, Uppsala, Sweden, [4]BMT Unit, Wuerzburg, Germany, [5]NHS Christie Trust, London, United Kingdom, [6]BMT Unit, Heidelberg, Germany, [7]CHU Lille, Hôpital Huriez, Lille, France, [8]BMT Unit, Koeln, Germany, [9]NHS, London, United Kingdom, [10]Ospedale Bambino Gesù, Roma, Italy, [11]Kings College Hospital NHS Foundation Trust, London, United Kingdom, [12]BMT Unit, Essen, Germany, [13]Hannover Medical School, Hannover, Germany, [14]BMT Unit, Utrecht, Netherlands, [15]Saint Antoine Hospital, Paris, France, [16]Policlinico San Matteo, Pavia, Italy, [17]San Raffaele Hospital, Milano, Italy, [18]Mastricht Hospital, Mastricht, Netherlands, [19]NHS, Birmingham, United Kingdom, [20]EBMT Data Office Leiden, Leiden, Netherlands, [21]OPBG, Rome, Italy, [22]Paoli-Calmettes Institute, INSERM CBT1409, Marseille, France

Background: The first EBMT survey on CAR T-cell activity in Europe was launched in November 2018 on behalf of the CTIWP. The main aim was to capture the rapidly growing activity in this field and the impact of the first commercial drug products targeting CD19. We were also interested to identify those academic clinical trials promoted by European institutions and currently open for recruitment.

Methods: A questionnaire was prepared by CTIWP to identify CART centers and CART based activity in Europe. Using monkey-survey, the survey was sent to 559 EBMT-centers. We crosschecked the collected information with data available on the ClinTrialsGov and Eudract websites.

Results: The updated survey is based on May 2019 report. As of this latest time point, 549 patients treated with CAR T-cells were reported in Europe. The number

of European centers administering CAR T-cells has nearly doubled in 6 months (from 34 to 56). Only one additional country (from 13 to 14) has started to treat patients with CAR T-cells during this period. There are now many more adult than pediatric patients (71.6% vs 28.4%, respectively). The two most frequent indications for CART treatment were NHL and ALL (46% and 40%, respectively), in line with existing marketing approvals. The third indicationwas MM (6%), a disease for which no approval has yet been granted by EMA. In addition, 39 patients were reported to have received CAR T-cell treatment for CLL, AML, MDS, or solid tumors. Whereas in November 2018, only 9 patients had been treated with marketed CAR T-cells, this figure rose to 90 in May 2019. We have identified at least 42 clinical trials with active recruitment in Europe. Of these, 27 are pharma-sponsored clinical trials, while 15 are academic clinical trials. The great majority of these clinical trials evaluate CAR T-cells targeting CD19 (n = 26) or BCMA (n = 5), with fewer targeting CD20 (n = 1), CD19/22 (n = 1), CD123 (n = 1), or CD33 (n = 1). Focusing specifically on the 15 European academic clinical trials, they evaluate CAR T-cells targeting CD19 (N = 9=, G2D (N = 2), or BCMA, FAP, ErbBR, and ILIRAP (N = 1 each), respectively. Of note, four European institutions fully prepare their own CAR T-cells, manufacturing both the genetic and the cellular product.

Conclusions: These results demonstrate that clinical CAR T-cell activity is rapidly growing at European centers. Adult patients with NHL now represent the most frequent indication for treatment, because of commercial availability of approved products in this indication. The use of marketed CAR T-cells has increased by 10-fold within 6 months, but still represents a minority of the ongoing activity. The existence of 15 active European academic clinical trials shows that Europe is not just a "CAR buyer" but also a "CAR manufacturer". We encourage centers to keep registering patients receiving CAR T-cells, both commercial and investigational, in a timely manner, through the specific Med A Form of the EBMT database. This will be crucial to monitor potential improvements in the procedure over time, similar to the achievements made by EBMT in monitoring patients after hematopoietic stem cell transplantation for more than two decades.

Disclosure: Gunilla Enblad: Member of the Advisory board for Kite/Gilead.

Jurgen Kuball: COI: Scientific cofounder and shareholder of gadeta. Inventor on gdT patents. Research support Miltenyi Biotech and Novartis.

O036.

Third-generation CAR T Cells within the Heidelberg CAR Trial 1 (HD-CAR-1) Display an Excellent Safety Profile and Might Improve Persistence of CAR T Cells

Maria-Luisa Schubert[1], Anita Schmitt[1], Angela Hueckelhoven-Krauss[1], Brigitte Neuber[1], Alexander Kunz[1], Lei Wang[1], Birgit Michels[1], Ulrike Gern[1], Leopold Sellner[1], Susanne Hofmann[1], Petra Pavel[2], Anthony Ho[1], Carsten Müller-Tidow[1], Peter Dreger[1], Michael Schmitt[1]

[1]*University Hospital Heidelberg, Heidelberg, Germany*, [2]*German Red Cross Blood Service Baden-Wuerttemberg-Hessen, Heidelberg, Germany*

Background: The investigator-initiated (IIT) phase I/II clinical CAR trial HD-CAR-1 (Heidelberg CAR trial 1; NCT03676504; EudraCT 2016-004808-60) was initiated in September 2018 and treats patient with B cell malignancies with third-generation chimeric antigen receptor (CAR) T cell (CARTs). Leukapheresis and GMP-conform CART manufacturing are performed in-house at the University Hospital Heidelberg.

Methods: Patients with relapsed or refractory (r/r) acute lymphoblastic leukemia (ALL) and patients with r/r chronic lymphocytic leukemia (CLL) or other non-Hodgkin lymphoma (NHL) including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) or mantle cell lymphoma (MCL) are treated with autologous T lymphocytes transduced with a CD19 targeting CAR retroviral vector (RV-SFG.CD19.CD28.4-1BBzeta). Primary endpoints of HD-CAR-1 are safety and feasibility of escalating CART doses (1-20×10^6 transduced cells/m^2) after lymphodepletion with fludarabine (30 mg/m^2/d; days -4 to -2) and cyclophosphamide (500 mg/m^2/d; days -4 to -2). Patients are monitored for cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) and/or other toxicities. In vivo function, survival and anti-tumor efficacy of CARTs are assessed as HD-CAR-1 secondary endpoints.

Results: To date, 17 patients (8 adult ALL, 2 CLL, 2 MCL, 4 DLBCL (1 transformed from FL), 1 FL) have been enrolled and 15 patients subjected to leukapheresis (2 patients awaiting leukapheresis). CAR products have been manufactured for 14 patients, 1 manufacturing is in process. Mean transduction efficiency of T lymphocytes was 44% (range 19%-61%) and high numbers of CARTs were harvested (52-191 × 10^6 CAR T cells). With regards to subpopulations of CART products, 43% of CARTs were CD8+ and 52% CD4+. The highest proportion of cells (35%) consisted of naïve (CD45RA+

CCR7+) and effector (31%; CD45RA+ CCR7-) CARTs. Twelve patients (4 ALL, 2 CLL, 2 MCL, 4 DLBCL) have received CARTs (6 patients: 10^6 transduced CAR T cells/m^2; 4 patients 5×10^6 CAR T cells/m^2; 2 patient 20×10^6 CAR T cells/m^2); 2 patient are awaiting CART administration. 9 patients have reached end-of-study (EOS) on day 90. No signs of CRS or ICANS > grade 2 have been observed. No neurological side-effects occurred, even not in patients with central nervous system (CNS) involvement. As per quantitative real-time PCR, CARTs were detectable in the peripheral blood (PB) of 10 of 11 analyzed patients. In one ALL patient with CNS involvement, CARTs were detected in the cerebrospinal fluid (CSF). CART frequency reached up to 200.000 copies/µg DNA, in some patients CARTs were detectable beyond EOS. Clinical responses were achieved in 6 of 9 (66%) treated patients (2 CRs, 4 PRs, 3 PDs); 3 patients are not yet available for response).

Conclusions: HD-CAR-1 is the first academic CAR T cell trial in Germany with in-house leukapheresis, CART manufacturing and administration. CART production was feasible for all enrolled patients so far. Patients responded clinically to treatment despite low numbers of administered CARTs. CARTs displayed a highly favorable safety profile, migrated into different compartments and were partly detectable for more than 3 months following administration. HD-CAR-1 accounts for clinical evaluation of third-generation CARTs that might contribute to long-term CART persistence, hence improving responses in treated patients.

Clinical Trial Registry: EudraCT 2016-004808-60; NCT03676504 (clinicaltrials.gov).

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

O037.

Outpatient Treatment with Lisocabtagene Maraleucel in 3 Clinical Studies of Relapsed/Refractory Large B-Cell NHL, Including Second-Line Transplant Noneligible Patients: Transcend NHL 001, Outreach, and PILOT

Carlos Bachier[1], M. Lia Palomba[2], Jeremy Abramson[3], Charalambos Andreadis[4], Alison Sehgal[5], John Godwin[6], Gerhard Hildebrandt[7], Tanya Siddiqi[8], Don Stevens[9], Thalia Farazi[10], Ana Kostic[10], Nikolaus Trede[10], Lei Wang[10], James Lymp[10], Tennille Thelen[10], Ken Ogasawara[11], David Maloney[12]

[1]Sarah Cannon Blood Cancer Network, Nashville, TN, United States, [2]Memorial Sloan Kettering Cancer Center, New York, NY, United States, [3]Massachusetts General Hospital, Boston, MA, United States, [4]University of California, San Francisco, CA, United States, [5]University of Pittsburgh Medical Center, Pittsburgh, PA, United States, [6]Providence Portland Medical Center, Portland, OR, United States, [7]University of Kentucky, Lexington, KY, United States, [8]City of Hope Cancer Center, Duarte, CA, United States, [9]Norton Cancer Institute, Louisville, KY, United States, [10]Juno Therapeutics, a Bristol-Myers Squibb, Seattle, WA, United States, [11]Bristol-Myers Squibb, Summit, NJ, United States, [12]Fred Hutchinson Cancer Research Center, Seattle, WA, United States

Background: CAR T cell therapy has generally been limited to inpatient treatment. Infusion and management of CAR T cell therapy in the outpatient setting may lead to wider use in nonuniversity centers and improved access. We report on patients with relapsed/refractory large B-cell non-Hodgkin lymphoma (NHL) treated with lisocabtagene maraleucel (liso-cel) in the outpatient setting in TRANSCEND NHL 001 (NCT02631044) and 2 phase 2 studies (≥3rd-line therapy: OUTREACH [NCT03744676]; 2nd-line transplant noneligible: PILOT [NCT03483103]).

Methods: Eligible patients had relapsed/refractory large B-cell NHL (TRANSCEND/OUTREACH: ≥2 lines of prior therapy and ECOG PS ≤1; PILOT: 1 line of prior therapy and deemed TNE for autologous HSCT based on age, ECOG PS, or organ function). After lymphodepletion with fludarabine/cyclophosphamide, liso-cel was administered. All studies allowed outpatient treatment at nonuniversity (OUTREACH) or university and nonuniversity medical centers (TRANSCEND/PILOT), with hospitalization at the first sign of fever or neurological events (NEs) per management guidelines.

Results: At data cutoff, 44 patients across studies received liso-cel on study Day 1 and were monitored as outpatients, including patients ≥65 years of age ($n = 18$) and those with SPD ≥50 cm^2 ($n = 12$) or LDH ≥500 U/L ($n = 6$). Results are shown in the Table. Seventeen patients had any-grade cytokine release syndrome (CRS) and 13 had any-grade NEs (20 had CRS and/or NEs). Only 2 patients had grade 3/4 CRS or NEs, which were reversible. Three patients received tocilizumab and corticosteroids for CRS (none received tocilizumab alone; 2 received corticosteroids only). Five patients received corticosteroids for NEs. Overall, 55% of patients ($n = 24/44$; all from TRANSCEND or OUTREACH) required hospitalization at any

time. Of 44 patients, 9 (20%) were admitted on study Day 4 or earlier (for CRS and/or NE) and 2 (5%) required ICU-level care (median length of stay, 4 days). Median time to initial hospitalization after liso-cel infusion was 5 (range, 2–22) days; median length of stay was 6.5 (range, 2–23) days. Across all studies, most patients achieved an objective response (80%), including complete responses (55%).

Conclusions: A subset of patients with relapsed/refractory large B-cell NHL were successfully treated with liso-cel and monitored for CAR T cell-related toxicity in the outpatient setting, including elderly patients and patients with high tumor burden. Incidences of severe CRS, NEs, and early hospitalization were low; 45% of patients did not require hospitalization at any time after liso-cel infusion. Overall, 80% of patients achieved an objective response.

Clinical Trial Registry: ClinicalTrials.gov identifier NCT02631044; ClinicalTrials.gov identifier NCT03744676; ClinicalTrials.gov identifier NCT03483103.

Disclosure: Funding Statement: This study was funded by Juno Therapeutics, a Bristol-Myers Squibb Company. Medical writing and editorial assistance were provided by The Lockwood Group (Stamford, CT, USA), and was funded by Bristol-Myers Squibb. Carlos Bachier reports speakers bureau from Sanofi, and consultancy from Viracyte; M. Lia Palomba reports speakers bureau from Hemedicus (immediate family member), consultancy from Merck (immediate family member) and Noble Insights, equity ownership of Seres Therapeutics (immediate family member) and Evelo (immediate family member), membership on a Board of Directors or advisory committee from Seres Therapeutics (immediate family member), STRAX-IMM (immediate family member), Kite Pharmaceuticals (immediate family member), and Pharmacyclics, patents and royalties from MSK (immediate family member); Jeremy S. Abramson reports no conflicts of interest; Charalambos Andreadis reports research funding from Amgen, Celgene/Juno, Genentech, Merck, and Novartis, consultancy from Astellas, Gilead/Kite, Jazz Pharmaceuticals, and Seattle Genetics, employment and equity ownership from Genentech (immediate family member); Alison Sehgal reports research funding from Celgene/Juno, Gilead/Kite, and Merck; John Godwin reports no conflicts of interest; Gerhard C. Hildebrandt reports equity ownership from Sangamo Bioscience, Celgene/Juno, Kite Pharmaceuticals, Novartis, Insys Therapeutics, AbbVie, GW Pharmaceuticals, Cardinal Health, Immunomedics, Endocyte, Clovis Oncology, Cellectis, Aetna, CVS Health, Celgene, Bluebird Bio, Bristol-Myers Squibb/Medarex, Crispr Therapeutics, IDEXX Laboratories, Johnson & Johnson, Pfizer, Procter & Gamble, Vertex, and Jazz Pharmaceuticals, consultancy from Pfizer, Kite Pharmaceuticals, Incyte, and Jazz Pharmaceuticals, research funding from Takeda, Jazz Pharmaceuticals, and Pharmacyclin, travel, accommodations, or expenses from Kite Pharmaceuticals, Incyte, Pfizer, Falk Foundation, Jazz Pharmaceuticals, and Astellas; Tanya Siddiqi reports consultancy from AstraZeneca, BeiGene, Celgene/Juno, and Kite Pharmaceuticals, speakers bureau from AstraZeneca, Janssen, Seattle Genetics, and PCYC; Don Stevens reports consultancy from Astellas; Ana Kostic, Nikolaus S. Trede, James Lymp, Ken Ogasawara report employment and equity ownership from BMS/Juno; Thalia Farazi, Lei Wang, Tennille Thelen report employment from BMS/Juno; David G. Maloney reports research funding from Celgene/Juno, Celgene, and Kite Pharmaceuticals, honoraria from Celgene/Juno, Celgene, Kite Pharmaceuticals, BioLine RX, Gilead, Genentech, Novartis, and A2 Biotherapeutics, patents and royalties from Celgene/Juno, stock options from A2 Biotherapeutics.

O038.

Correlative Analyses of Patient and Clinical Characteristics Associated with Efficacy iN Tisagenlecleucel-Treated Relapsed/Refractory Diffuse Large B-Cell Lymphoma Patients in the Juliet Trial

Jason Westin[1], Constantine Tam[2], Peter Borchmann[3], Ulrich Jäeger[4], Joseph McGuirk[5], Harald Holte[6], Edmund Waller[7], Samantha Jaglowski[8], Michael Bishop[9], Charalambos Andreadis[10], Stephen Ronan Foley[11], Isabelle Fleury[12], P. Joy Ho[13], Stephan Mielke[14], Takanori Teshima[15], Stephen Schuster[16], Veronika Bachanova[17], Richard Maziarz[18], Koen Van Besien[19], Koji Izutsu[20], Marie Jose Kersten[21], John Magenau[22], Nina Wagner-Johnston[23,24], Koji Kato[25], Paolo Corradini[26], Xia Han[27], Ranjan Tiwari[28], Sergei Agoulnik[29], Lamis Elderjou[27], Lida Bubuteishvili Pacaud[27], Gilles Salles[30]

[1]MD Anderson, Houston, TX, United States, [2]St Vincent's Hospital and University of Melbourne, Peter MacCallum Cancer Center, Melbourne, Australia, [3]Center of Integrated Oncology Aachen, Bonn, Cologne, Düsseldorf, German Hodgkin Study Group, University Hospital of Cologne, University of Cologne, Koln, Germany, [4]Vienna General Hospital, Medical University of Vienna, Vienna, Austria, [5]University of Kansas Health System, Kansas City, KS, United States, [6]Oslo University Hospital, Oslo, Norway, [7]Emory Clinic, Atlanta, GA, United States, [8]Ohio State University, Columbus, OH, United States, [9]University of Chicago, Chicago, IL, United States, [10]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, United States, [11]McMaster University, Hamilton, Canada, [12]University Paris Diderot, Montreal, Canada, [13]Royal Prince Alfred

Hospital, Camperdown, Australia, [14]*University Hospital Wurzbürg, Wurzbürg, Germany*, [15]*Hokkaido University Hospital, Hokkaido, Japan*, [16]*University of Pennsylvania,, Philadelphia, PA, United States*, [17]*University of Minnesota, Minneapolis, MN, United States*, [18]*Oregon Health & Science University, Portland, OR, United States*, [19]*Weill Cornell Medicine, New York, NY, United States*, [20]*National Cancer Center Hospital, Tokyo, Japan*, [21]*Academic Medical Center, Amsterdam, Netherlands*, [22]*University of Michigan, Ann Arbor, MI, United States*, [23]*Johns Hopkins School of Medicine, Baltimore, MD, United States*, [24]*Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, United States*, [25]*Kyushu University Hospital, Fukuoka, Japan*, [26]*Fondazione IRCCS Instituto Nazionale dei Tumori, University of Milan, Milan, Italy*, [27]*Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States*, [28]*Novartis Healthcare Pvt. Ltd., Hyderabad, India*, [29]*Novartis Institutes for Biomedical Research, Cambridge, MA, United States*, [30]*Hospices Civils de Lyon, Lyon-Sud Hospital, Pierre-Bénite, France*

Background: Tisagenlecleucel (autologous anti-CD19 CAR-T cell therapy) has demonstrated durable responses and a manageable safety profile in adult patients with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL).

Methods: Results from JULIET, a global, single-arm, pivotal, phase 2 trial of tisagenlecleucel in adult patients with r/r DLBCL were analyzed to assess the relationship between pre- and post-infusion factors and biomarkers, as well as cytokine release syndrome (CRS; Penn scale)/neurological event (NE, CTCAE v.4.03) severity, with efficacy.

Results: As of December 11, 2018, 115 patients were infused with tisagenlecleucel and evaluable for efficacy. Baseline tumor volume (TV) did not correlate with month 3 response. Median lactate dehydrogenase (LDH) levels at pre-infusion were higher in nonresponders (NRs) compared with patients achieving response. 15/16 patients with pre-infusion grade 3/4 thrombocytopenia ($<50 \times 10^9$/L) were NRs. Pre-infusion C-reactive protein (CRP) levels did not associate with month 3 response. Univariate/multivariate logistic regression analyses showed that high pre-infusion LDH levels (defined as higher than 2-fold the upper limit of normal [ULN]) were independently associated with NRs. Compared with patients with normal levels of LDH at pre-infusion, patients with LDH 1-2-fold or >2-fold above the ULN had poorer progression-free and overall survival (PFS, OS). Patients with pre-infusion platelet levels $< 50 \times 10^9$/L also had significantly worse PFS/OS compared with patients with platelet levels $\geq 50 \times 10^9$/L. Pre-infusion high TV, high CRP, and high ferritin associated with worse OS, but not PFS.

Post-infusion, 13/13 patients with severe NE were NRs. 9/17 patients with grade 3 CRS and 9/9 patients with grade 4 CRS were also NRs. Patients with severe CRS had worse PFS/OS compared with patients with grade 0-2 CRS. Similarly, patients with severe NE had worse PFS and OS compared with patients with grade 0-2 NE. High pre-infusion LDH, pre-infusion grade 3/4 thrombocytopenia, and severe NE, but not severe CRS, were independently associated with poorer PFS in multivariate Cox regression analyses.

Notably, higher median baseline TV, highest levels of serum biomarkers, highest LDH, and lowest platelet counts within 1 month post-infusion were observed in patients with severe CRS who were also NRs, compared with patients with severe CRS who achieved response and patients with grade 0-2 CRS.

Conclusions: Multivariate analyses identified that high levels of pre-infusion LDH (a known marker of tumor burden, metabolic activity, and disease aggressiveness) were associated with NRs at month 3 and worse PFS/OS. Pre-infusion grade 3/4 thrombocytopenia and grade 3/4 NE were also associated with poor efficacy outcomes. The highest serum biomarker profiles post-infusion appeared to associate with patients with severe CRS who were also NRs. These analyses suggest that a subset of patients with aggressive disease at infusion and/or patients with severe CRS/NE had poorer outcomes in the JULIET trial, and may reinforce the rationale for current and future directions of using CAR-T cell therapy in an earlier line of therapy (during less aggressive/less advanced disease), optimizing patient care, and developing interventions to prevent severe CRS and/or NE.

Clinical Trial Registry: NCT02445248

Disclosure: Westin: Genentech: Other: Advisory Board, Research Funding; Novartis; Other: Advisory Board, Research Funding; Curis: Other: Advisory Board, Research Funding; Celgene: Other: Advisory Board, Research Funding; 47 Inc: Other: Research Funding; Juno: Other: Advisory Board; MorphoSys: Other: Advisory Board; Unum: Other: Research Funding; Janssen: Other: Advisory Board, Research Funding; Kite: Other: Advisory Board, Research Funding. Tam: Roche: Honoraria; Pharmacyclics LLC, an AbbVie company: Honoraria; Novartis: Honoraria; BeiGene: Honoraria; Janssen: Honoraria, Research Funding; AbbVie: Honoraria, Research Funding. Borchmann: Novartis: Honoraria, Research Funding. Jaeger: Novartis, Roche, Sandoz: Consultancy; Celgene, Roche, Janssen, Gilead, Novartis, MSD, AbbVie, Sanofi: Membership on an entity's Board of Directors or advisory committees; Amgen, AbbVie, Celgene, Eisai, Gilead, Janssen, Novartis, Roche, Takeda Millennium, MSD, BMS, Sanofi: Honoraria; AbbVie, Celgene, Gilead, Novartis, Roche, Takeda Millennium: Research funding. McGuirk: ArticulateScience, LLC: Other: Assistance with manuscript preparation; Pluristem Ltd: Research Funding; Gamida Cell: Research Funding; Kite Pharmaceuticals: Honoraria, Membership on an

entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; Bellicum Pharmaceuticals: Research Funding; Astellas: Research Funding; Fresenius Biotech: Research Funding; Novartis: Research Funding; Juno Therapeutics: Honoraria, Membership on an entity's Board of Directors or advisory committees; Research Funding. Holte: Novartis: Honoraria, Other: Advisory board. Waller: Novartis: Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; Pharmacyclics: Other: Travel expenses Research Funding; Cerus Corporation: Other: Stock, Patents & Royalties; Chimerix: Other: Stock; Cambium Oncology: Patents & Royalties or other intellectual property; Amgen: Consultancy; Kalytera: Consultancy. Jaglowski: Juno: Consultancy, Other: advisory board; Unum Therapeutics Inc.: Research Funding; Kite: Consultancy, Other: advisory board, Research Funding; Novartis: Consultancy, Other: advisory board, Research Funding. Bishop: Novartis: Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; Juno: Consultancy, Membership on an entity's Board of Directors or advisory committees; CRISPR Therapeutics: Consultancy, Membership on an entity's Board of Directors or advisory committees; Celgene: Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; Kite: Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. Andreadis: Celgene: Research Funding; Juno: Research Funding; Novartis: Research Funding; Genentech: Consultancy, Employment; Kite: Consultancy; Gilead: Consultancy; Jazz Pharmaceuticals: Consultancy; Pharmacyclics: Research Funding; Merck: Research Funding; Roche: Equity Ownership. Foley: Janssen: Speakers Bureau; Amgen: Speakers Bureau; Celgene: Speakers Bureau. Fleury: Gilead: Consultancy, Honoraria; Novartis: Consultancy, Honoraria; Roche: Consultancy, Honoraria; Seattle Genetics: Consultancy, Honoraria; Janssen: Consultancy, Honoraria; AbbVie: Consultancy, Honoraria; AstraZeneca: Consultancy, Honoraria. Ho: Janssen: Other: Trial Investigator meeting travel costs; Celgene: Other: Trial Investigator meeting travel costs; La Jolla: Other: Trial Investigator meeting travel costs; Novartis: Other: Trial Investigator meeting travel costs. Mielke: EBMT/EHA: Other: Travel support; IACH: Other: Travel support; Celgene: Honoraria, Other: Travel support (via institution), Speakers Bureau; Kiadis Pharma: Honoraria, Other: Travel support (via institution), Speakers Bureau; Gilead: Consultancy, Honoraria, Other: Travel (via institution), Speakers Bureau; Miltenyi: Consultancy, Honoraria, Other: Travel and speakers fee (via institution), Speakers Bureau; Jazz Pharma: Honoraria, Other: Travel support, Speakers Bureau; DGHO: Other: Travel support; Bellicum: Honoraria, Other: Travel (via institution); ISCT: Other: Travel support. Teshima: Novartis: Honoraria, Research Funding. Schuster: Novartis: Honoraria, Patents & Royalties: Combination CAR-T and PD-1 Inhibitors, Research Funding; Celgene: Consultancy, Honoraria, Research Funding; Genentech: Consultancy, Honoraria, Research Funding; Merck: Consultancy, Honoraria, Research Funding; Pharmacyclics: Consultancy, Honoraria, Research Funding; Acerta: Consultancy, Honoraria, Research Funding; AbbVie: Consultancy, Honoraria, Research Funding; Nordic Nanovector: Consultancy, Honoraria; Pfizer: Consultancy, Honoraria; AstraZeneca: Consultancy, Honoraria; Loxo Oncology: Consultancy, Honoraria; Gilead: Consultancy, Honoraria, Research Funding. Bachanova: Seattle Genetics: Membership on an entity's Board of Directors or advisory committees; Novartis: Research Funding; Incyte: Research Funding; GT Biopharma: Research Funding; Kite: Membership on an entity's Board of Directors or advisory committees; Gamida Cell: Research Funding; Celgene: Research Funding. Maziarz: Kite: Membership on an entity's Board of Directors or advisory committees; Novartis: Consultancy, Research Funding; Incyte: Consultancy, Honoraria; Celgene/Juno: Membership on an entity's Board of Directors or advisory committees, Research Funding. Van Besien: Miltenyi Biotec: Research Funding. Izutsu: Eisai, Symio, Chugai, Zenyaku: Research Funding; Eisai, Chugai, Zenyaku: Honoraria; Chugai, Celgene, Daiichi Sankyo, AstraZeneca, Eisai, Symbio, Ono, Bayer, Solasia, Zenyaku, Incyte, Novartis, Sanofi, HUYA Bioscience, MSD, Astellas, Amgen, AbbVie, ARIAD, Takeda, Pfizer: Research Funding; Kyowa Kirin, Eisai, Takeda, MSD, Chugai, Nihon Medi-physics, Janssen, Ono, AbbVie, Dainihon, Sumitomo, Bayer, AstraZeneca, HUYA Japan, Novartis, Bristol-Myers Squibb, Mundi, Otsuka, Daiichi Sankyo, Astellas, Asai Kasei: Honoraria; Celgene: Consultancy. Kersten: Bristol-Myers Squibb: Other: Travel grants, honorarium or advisory boards; Gilead: Other; Travel grants, honorarium, or advisory boards; Roche: Consultancy, Research Funding, Travel grants, honorarium, or advisory boards; Amgen: Other: Travel grants, honorarium, or advisory boards; Novartis: Consultancy, Other: Travel grants, honorarium, or advisory boards; Roche: Other: Travel grants, honorarium, or advisory boards; Celgene: Other: Travel grants, honorarium, or advisory boards; Kite: Consultancy, Other: Travel grants, honorarium, or advisory boards; Janssen/Cilag: Other: Travel grants, honorarium, or advisory boards; MSD: Other: Travel grants, honorarium, or advisory boards; Celgene: Consultancy, Research Funding; Takeda: Consultancy, Research funding. Wagner-Johnston: Bayer, ADC Therapeutics, Gilead, Janssen: Membership on an entity's Board of Directors or advisory committees. Corradini: Jazz Pharmaceuticals, KiowaKirin, Kite, Roche, Sanofi, Servier, Amgen, Daiichi Sankyo: Honoraria; Novartis, Takeda,

Celgene: Honoraria, Other: Travel Costs; BMS: Other: Travel Costs; AbbVie: Consultancy, Honoraria, Other: Travel Costs; Janssen, Gilead: Honoraria, Other: Travel Costs. Han: Novartis: Employment. Tiwari: Novartis: Employment. Agoulnik: Novartis: Employment. Eldjerou: Novartis Pharmaceuticals Corporation: Employment. Bubuteishvili Pacaud: Novartis: Employment. Salles: Roche, Janssen, Gilead, Celgene: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Educational events; Amgen: Honoraria, Other: Educational events; BMS: Honoraria; Merck: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; Novartis, Servier, AbbVie, Karyopharm, Kite, MorphoSys: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Educational events; Autolus: Consultancy, Membership on an entity's Board of Directors or advisory committees; Takeda: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Educational events; Epizyme: Consultancy, Honoraria.

O039.

High Activation of BCMA CAR-T Cells Contributes to Increased Response Rate for Patients With Relapsed/Refractory Multiple Myeloma

Yongxian Hu[1], Houli Zhao[1], Alex Hongsheng Chang[2], Arnon Nagler[3], He Huang[1]

[1]Zhejiang University, Hangzhou, China, [2]Shanghai YaKe Biotechnology Ltd, Shanghai, China, [3]Chaim Sheba Medical Center Tel-Hashomer, Tel-Aviv University, Tel Hashomer, Israel

Background: Recently CAR-T cells targeting BMCA (BCMA CAR-T) have demonstrated prominent efficacy in heavily treated R/R MM with overall response (OS) rate of 80-90% and complete remission (CR) rate of 40-70%. Therapy-associated toxicities including cytokine release syndrome (CRS) and neurotoxicity are well tolerable. Despite encouraging results of BCMA CAR-T cells for R/R MM treatment, there are still some unresolved problems. Current clinical trials focused on clinical data about efficacy and toxicities. No detailed studies of corresponding mechanisms have been reported currently.

Methods: Our trial (ChiCTR1800017404) is a phase 1, single-arm, open-label single center study to evaluate the safety and efficacy of autologous BCMA CAR-T treatment for RRMM. Patients were subjected to a lymphodepleting regimen with Flu and Cy prior to CAR-T infusion. BCMA CAR-T cells were administered as a single infusion at a median dose of 3.5 (1 to 6) $\times 10^6$/kg. Profiles of peripheral blood mononuclear cells (PBMCs), frozen BCMA CAR-T aliquots, in vivo CAR-T cell subsets were performed by single-cell mass cytometry.

Results: As of the data cut-off date (December 10th, 2019), 39 patients, median age 60.4 (49 to 75) years old were infused with BCMA CAR-T cells. The median observation period is 8.0 (0.7 to 18) months. ORR was 94.9%. All the patients achieved MRD negative in bone marrow by flow cytometry in 2 weeks after CAR-T infusion. Partial response (6 PR, 15.4%), VGPR (7 VGPR, 17.9%), and complete response (24 CR, 61.5%) within 12 weeks post CAR-T infusion were achieved. Durable responses from 4 weeks towards the data cut-off date (median follow-up time 8.36 months) were found in 25/37 patients (67.6%). All patients had detectable CAR-T expansion by flow cytometry from Day 3 post CAR-T cell infusion. The peak CAR-T cell expansion in CD3+ lymphocytes of peripheral blood (PB) varied from 35% to 95% with a median percentage of 81.8%. CRS was reported in all the 39 patients, including 6 with Grade 1, 15 with Grade 2 and 18 with Grade 3. During follow-up, 1-year progression-free survival (PFS) was 56.6 % and overall survival (OS) was 83.7%. CyTof analysis revealed CAR-T product before infusion have phenotypes of a naïve and central memory T cells. The predominantly CD8+ CAR-T cells present in CRS phase in vivo had acquired a more differentiated and activated effector memory phenotype which might contribute to high response rate.

Conclusions: Our data showed BCMA CAR-T treatment is safe with prominent efficacy. We also observed high activation of BCMA CAR-T cells contribute to potent anti-myeloma activity. These initial data provide strong evidence to support the further development of this anti-myeloma cellular immunotherapy.

Clinical Trial Registry: http://www.chictr.org.cn/index.aspx ChiCTR1800017404.

Disclosure: Nothing to declare.

CAR-based Cellular Therapy – preclinical

O040.

Modulation of Cytosolic CA^{2+} Regulates CAR-T Cell Differentiation and Therapeutic Potency

Mi Shao[1], Xinyi Teng[1], Hao Zhang[1], Yongxian Hu, He Huang[1]

[1]The First Affiliated Hospital of Zhejiang University, Hangzhou, China

Background: Calcium signals play irrefutable role in the regulation of cell activation, differentiation and effector functions, no exception of T cells. The pattern of activation of CAR-T cell is undoubtedly different from T cell. Till now, the answers to the two questions still remain unclear for us: whether the activation of CAR-T cells is accompanied by changes of calcium ions and how do the calcium ions affect the phenotype or effector function of CAR-T cells? Thus, we used the ER Ca^{2+} channel inositol trisphosphate receptor (IP3R) inhibitor to reduce cytosolic Ca^{2+} content and observe the change of differentiation of CART, the expression of activation markers and the anti-tumor effect.

Methods: We activated and harvested human T cells by using CD3/CD28 beads, and then transfected T cells using CAR lentivirus to finally obtain CAR-T cells. In vitro, we detected the Ca^{2+} content in cytoplasm and mitochondria, to assess the dynamic changes in intracellular calcium ions after IP3R inhibitor (2-APB) use. Cytosolic Ca^{2+} (Fluo-4) and mitochondrial Ca^{2+} (Rhod-2) dyes were loaded for 30 minutes, and samples were run directly on flow cytometer. Afterwards, we set up 3 groups: control, 2-APB (5nm) and 2-APB (10nm) group. Then we detected CAR-T cell's subsets, levels of activation (CD25, CD69), exhaustion (PD-1, Tim-3, Lag-3) and apoptosis of each groups. In vivo, we transferred CAR-T cells with/without modulation of Ca^{2+} into nalm6-bearing B-NDG mice, to evaluate the persistence and the antitumor efficacy of CAR-T cells.

Results: Cytosolic Ca^{2+} content could differentiate naïve (CD62L+/CD45RO-), central memory (CD62L+/CD45RO+), effector memory (CD62L-/CD45RO+) and effector (CD62L-/CD45RO-) subsets among CAR-T cell populations, which indicates that cytosolic Ca^{2+} control may be used to modulate CAR-T cell lineage outcomes. In the IP3R-inhibited CAR-T cell group, cytosolic Ca^{2+} was significantly diminished after 24 hours and was related to dosage. After 3 days, CAR-T cells in the presence of 2-APB showed a significantly increased proportion of naïve and central memory (CD62L+) populations when compared to control group. While the expression of CD25 and CD69 did not show significant differences. Based on the effects of calcium ions on CART cell, we made a hypothesis that the using of IP3R inhibitor during cell culture might be beneficial for the persistence of CAR-T cells. To test our hypothesis, we transferred CAR-T cells cultured in the presence of vehicle or 2-APB into GFP-luciferace-nalm6-bearing mice. We found that IP3RI-treated CAR-T cells significantly inhibited tumor growth and extended survival times when compared to control. Besides, the number of CAR-T cell in PB and BM of mice by flow cytometry also showed the longer persistence of CART cells in IP3RI treated group.

Conclusions: The intracellular calcium ion affects the differentiation and antitumor efficacy of CART cells. The ER-modulated cytosolic Ca^{2+} plays a role in defining the CART cell phenotype. The use of IP3R inhibitor helps CAR-T cell maintain in memory state. In addition, CART cells treated with IP3R inhibitors also showed stronger anti-tumor efficacy and longer persistence in vivo.

Disclosure: Nothing to declare.

Cellular Therapies other than CARs

O041.

HLA-Mismatched Mobilized Cellular Therapy (Microtransplant, MST) in Elderly Patients with Acute Myeloid Leukemia and Myelodysplastic Syndromes

María Esther Martínez-Muñoz[1,2], Rafael Forés[1,2], Carmen Regidor[1,2], Jose Luis Bueno[1,2], Yolanda Gutiérrez[1], Miguel García[1], Guiomar Bautista[1,2], Almudena de Laiglesia[1,2], Carlos Vilches[1,2], Cristina Fernández-Maqueda[1,2], Jose Antonio García-Marco[1,2], Emilio Ojeda[1,2], Jose Rafael Cabrera[1,2], Rafael Franciso Duarte[1,2]

[1]Hospital Universitario Puerta de Hierro de Majadahonda, Majadahonda, Spain, [2]Instituto de Investigación Sanitaria Puerta de Hierro-Segovia Arana, Majadahonda, Spain

Background: HLA-mismatched mobilized peripheral-blood hematopoietic cellular therapy (microtransplant, MST) following conventional chemotherapy induces a host-versus-tumour effect through alloreactive graft-rejection and has been pioneered by *Ai et al* as a treatment for elderly patients with *de novo* AML/MDS [Guo et al. JAMA Oncol. https://doi.org/10.1001/jamaoncol.2017.2656]. Here, we present our experience with this procedure in elderly patients with high-risk and advanced AML/MDS, including those treated with hypomethylating agents.

Methods: We have performed 30 MST procedures, in total 63 infusions (11 × 3, 11 × 2 and 8 × 1 infusions), in 24 elderly high-risk AML/MDS patients non-eligible for conventional intensive chemotherapy and allogeneic transplantation (18 men, median age 69 years, range 53-77), including 4 secondary and 8 refractory/relapsed AML. GCSF-mobilized hematopoietic cell products from HLA-mismatched donors (26 haploidentical) included a median of 2.61×10^8/kg MNC (1.37-5.51), 2.80×10^6/kg CD34+ (0.71-6.58) and 1.14×10^8/kg CD3+ (0.35-2.42) cells infused per infusion, and 6.42×10^8/kg MNC (2.11-10.7), 5.76×10^6/kg CD34+ (1.12-15.65) and 2.67×10^8/kg CD3+ (0.64-3.84) cells infused per full MST procedure.

First cell infusions ($n = 30$) were fresh, and all second ($n = 22$) and third ($n = 11$) infusions were cryopreserved. Cells were infused following hypomethylating agents in 34 cases (54%; azacytidine alone in 17, with chemotherapy in 13, and decitabine alone in 4) and following conventional chemotherapy in 29 cases (46%; IA3 + 7, MEC, HDaC or Vyxeos®).

Results: The procedure was generally well tolerated. The commonest side effect was mild and transient "haploimmunostorm syndrome" (fever 90%, rash 27%, edema 14%, diarrhea 13%, raised liver enzymes 10%), which in five patients (17%; 2 cryopreserved, 3 fresh infusions) associated with atrial fibrillation, resolved with standard treatment. Only seven infusions required corticosteroids. Opportunistic infections occurred following 17% of infusions (9 bacterial, including 6 bacteraemia, 2 pneumonia, 1 sepsis; one fungal and one viral infections). Two cases had MST-derived transient chimerism (17% and 39%); only one developed cutaneous grade II acute GVHD that responded to corticosteroids. Non-relapse mortality after MST was 13% (4/30; 2 infections, 1 hemophagocytic lymphohistiocytosis, 1 intracranial haemorrhage). Complete remission (CR) was achieved in 67% of patients (16/24) following a first MST procedure. Fourteen of those achieving CR (87%) relapsed at a median of 9.5 months (1-39). Six patients who relapsed had a second MST, all but one from different donors, and five of them achieved a second CR (83%). Following response to MST, 3 patients underwent an allogeneic transplantation: one died from VOD, two are alive and in CR at 3 and 8 months. Overall survival was 16 months (3-82) for patients that achieved CR after MST, and 1 month (0-7) for non-responders.

Conclusions: Our data shows that MST is well tolerated and effective in elderly patients with high-risk AML/MDS. MST provides remarkably high rates of CR, can be successfully used a second time in patients who relapse, and as a bridge to allogeneic transplantation in selected cases. This novel cellular therapy may be an alternative strategy to improve outcomes in elderly AML/MDS patients not eligible for conventional chemotherapy and allogeneic transplantation, including those with refractory/relapsed disease.

Disclosure: Nothing to declare.

O042.

Donor Lymphocyte Infusions After Haploidentical Stem Cell Transplantation with PTCy: A Study on Behalf of the CTIWP of the EBMT

Nicole Santoro[1], Katya Mauff[2], Raynier Devillier[3], Luca Castagna[4], Zafer Gülbas[5], José Diez-Martin[6], Arancha Bermúdez[7], Concepcion Herrera Arroyo[8], Eric Deconinck[9], Jorge Sierra[10], Manuel Abecasis[11], Hakan Ozdogu[12], Maria Caterina Micò[13], Vanderson Rocha[14], Denis Guyotat[15], Yves Chalandon[16], Edouard Forcade[17], Hans Martin[18], Riccardo Saccardi[19], Sebastian Giebel[20], Mauro Di Ianni[1], Jorinde Hoogenboom[21], Liesbeth C. de Wreede[22], Annalisa Ruggeri[23], Christian Chabannon[24]

[1]Ospedale Civile di Pescara, Pescara, Italy, [2]EBMT Statistical Unit, Leiden, Netherlands, [3]Institut Paoli Calmettes, Marseille, France, [4]Istituto Clinico Humanitas, Milano, Italy, [5]Anadolu Medical Center Hospital, Gebze, Turkey, [6]Gregorio Marañón General University Hospital, Madrid, Spain, [7]Hospital Universitario Marqués de Valdecilla, Santander, Spain, [8]Hospital Reina Sofia Córdoba Hospital, Córdoba, Spain, [9]Hopital Jean Minjoz, Besançon, France, [10]Hospital Santa Creu i Sant Pau, Barcelona, Spain, [11]Instituto Portugues Oncologia, Lisboa, Portugal, [12]Baskent University Hospital, Yüreğir, Turkey, [13]ASST Papa Giovanni XXIII, Bergamo, Italy, [14]Hospital Sirio-Libanes, Sao Paulo, Brazil, [15]Institut de Cancerologie Lucien Neuwirth, Saint Etienne, France, [16]Geneva's University Hospitals and University of Geneva, Gèneve, Switzerland, [17]CHU Bordeaux, Hôpital Haut-leveque, Pessac, France, [18]University Hospital Frankfurt, Frankfurt, Germany, [19]Azienda Ospedaliera Universitaria Careggi, Firenze, Italy, [20]Maria Sklodowska-Curie Institute, Gliwice, Poland, [21]EBMT Data Office, Leiden, Netherlands, [22]Leiden University Medical Center, Leiden, Netherlands, [23]IRRCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, [24]Institut Paoli-Calmettes, Aix-Marseille University, INSERM CBT-1409, Marseille, France

Background: Donor lymphocyte infusion (DLI) is a treatment option to prevent or treat relapse after stem cell transplantation (SCT). While numbers of haplo-SCT are growing rapidly worldwide, taking advantage of rapid availability of potential donors, there remains a need to fully evaluate the safety profile and efficacy of DLI in the setting of unmanipulated haplo-SCT.

Few single center studies analyzed the experience of DLI after haplo-SCT and there is a great variability in clinical practice among centers. Furthermore, there is no available prospective clinical trial that may elucidate the uncertainties around its clinical application.

Methods: We here report efficacy and safety data for 121 patients (median age 47.3 years) who received one or multiple DLI infusion after unmanipulated haplo-SCT with post-transplant cyclophosphamide (PT-CY) at 31 EBMT centers from 2007 to 2017.

A specific questionnaire was sent through the CTIWP-EBMT data office. Main diagnoses were: acute myeloid leukemia (AML, $n = 56$), acute lymphoblastic leukemia

(ALL, $n = 14$), lymphoma ($n = 30$), myelodysplastic syndromes (MDS, $n = 11$), myeloproliferative neoplasm (MPN, $n = 5$), multiple myeloma (MM, $n = 3$).

Reason of DLI was: preemptive for 9 (7%) patients, prophylactic for 26 (22%), therapeutic for 44 (36%) and not specified for 36 (30%) patients.

Results: Median follow-up was 29.9 (12.9-40.4) months, 58% of patients were in complete remission at transplant. Reduced intensity conditioning was used in 49% of patients. Stem cell source was peripheral blood for 80%. The most frequent donor and recipient relationships were child to parent (43%) and siblings (35%).

Median time between haplo-SCT and DLI was 5.1 months (IQR 3-10). The median interval between withdrawal of immunosuppression and DLI was 2.8 months (IQR 1.4-6).

37.8% of patients received chemotherapy pre DLI. The CD3+ T-cell dose ranged from 0.01 to 1x107 mononuclear cell/kg (the dose was 0.1 x107 in 40%).

33% received a single infusion while 47% received multiple infusions ranging from 2 DLI infusion in 35% of cases up to 4 and 6 infusions in 2 and 1 cases, respectively. In 61% of cases the CD3+ cell dose was escalated in the subsequent infusions.

After DLI infusion cumulative incidence (CI) of grade 2-4 acute (a) graft versus host disease (GVHD) and 3 year CI of chronic (c)GVHD was 11% and 28%, respectively. In details, 6 patients experienced grade II, 1 grade III and 4 grade IV aGvHD, and 11 patients had extensive c-GVHD. 48 patients subsequently relapsed after DLI infusion.

In the entire population, 3 year-overall survival (OS) and relapse free survival (RFS) were 41% and 39%, respectively. 3 year-relapse incidence (RI) was 50% and non relapse mortality (NRM) was 11%. The main causes of death were relapse/progression of disease (27%), infection (10%) and GVHD (5%).

Conclusions: Our data showed that there is a great variability in the administration of DLI across responding EBMT centers. While the rate of a-GVHD appears acceptable, survival rates remain relatively low in this small group of patients, with relapses contributing to most deaths. A thorough evaluation of this approach will only be possible in prospective trials using harmonized procedures for cell doses and sequence of infusions.

Disclosure: Nothing to declare.

O043.

Safety, Effectiveness and Persistence of Low-Dose Donor Memory T Cell Infusions After AB T Cell-DEPLETED Hematopoietic Stem Cell Transplantation

Sergey Blagov[1], Ivan Zvyagin[2], Larisa Shelikhova[1], Mariia Ilushina[1], Julia Starichkova[1], Dmitriy Balashov[1], Dmitriy Pershin[1], Elena Osipova[1], Natalia Khripkova[1], Mariia Efimenko[1], Viktoria Fomchenkova[2], Ekaterina Komech[2], Jakov Muzalevskii[1], Alexei Kazachenok[1], Elena Kurnikova[1], Galina Novichkova[1], Alexei Maschan[1], Michael Maschan[1]

[1]Dmitry Rogachev National Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation, [2]Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry, Moscow, Russian Federation

Background: Severe viral infections remain a major source of non-relapse mortality and morbidity in recipients of ab T cell-depleted grafts. As we have shown, infusions of low doses memory T-cells are safe and potentially effective. Here we report the results of a retrospective analysis of an extended cohort with the emphasis on T cell repertoire probing.

Methods: One hundred and thirty-one patient received ab T cell-depleted HSCT from either matched unrelated ($n = 52$), or haploidentical (n = 79), donors between 15.04.2014 and 17.03.2017. Indications for HSCT included hematologic malignancies in 80 cases and non-malignant diseases in 51 cases. Only CMV seropositive donor/recipient pairs were included. After engraftment patients were scheduled to receive 3 infusions at starting doses of 25×10^3/kg (haplo) and 100×10^3/kg(MUD), with monthly 50% increment. Memory T-cells were derived from G-CSF stimulated ($n = 118$), unstimulated ($n = 9$) apheresis or whole blood ($n = 4$) of the original donors. Apheresis product was processed with single-step CD45RA depletion procedure on CliniMACS Plus or Prodigy. CD45RA-depleted fraction was cryopreserved for further use. Beyond monitoring of CMV, EBV and Adenovirus DNA, lymphocyte subset reconstitution, hematopoietic chimerism, pathogen-specific (CMV, EBV, Adeno) T cell activity, we used deep sequencing-based T cell repertoire profiling to track individual T cell clones from donor memory T cells of 16 patients to understand the contribution of donor memory T cells to the recipient repertoire.

Results: Overall 131 patients received 343 memory DLI after engraftment of primary graft. We achieved >4,5 log depletion of CD45RA. Final product contained negligible numbers of CD45RA+ naive T-cells. The cumulative incidence of de novo aGVDH grade II-IV and grade III after DLI was 7% and 2%, respectively. There were no documented cases of grade IV aGVHD. The incidence of TRM was 4% for the whole group. At the last follow-up 106 patients were alive and free from primary disease. According to ELISPOT analysis, among patients with undetectable CMV-specific immune reactivity at baseline (n = 92) expansion of CMV-specific T-cells was detected in 50 (54%) patients at time point 3 (t3, day 120-180 after HSCT). By T cell repertoire profiling after the last infusion (t3) and 6 months later (t4, day 360) we found that both CD4+ and

CD8+ donor memory T cell clones contribute to the patient repertoire. Most importantly, we observed significantly higher number of identical clonotypes in DLI-recipient pairs compared to primary graft-recipient repertoires from patients, who didn't receive DLI: t3 median number 103.0 ($n = 9$) vs 21.5 ($n = 10$) clones; t4 median number 70.5 ($n = 12$) vs 23.0 ($n = 9$) clones; $p < 0.01$). On day 120-180 DLI-derived T cell clones comprise on average 10.2% of patient's peripheral blood T cells (from 2.2% to 35.8%, $n = 9$).

Conclusions: Our data suggest that depletion of ab T cell from the primary graft and with low-dose memory DLI, which are able to transfer pathogen-specific immunity to common infections, can be safely combined to improve the overall results of HSCT from haploidentical and matched donors. We prove by TCR tracking that memory T lymphocytes from CD45RA-depleted DLI contribute to TCR repertoire and are able to persist long-term.

Disclosure: No disclosure.

O044.

Prophylactic Donor Lymphocyte Infusion After T-Cell-Replete Allogeneic HSCT Prevents Disease Relapse and Prolongs Survival in Patients with High-Risk Acute Leukemia

Luxin Yang[1,2], Yamin Tan[1,2], Jimin Shi[1,2], Yanmin Zhao[1,2], Jian Yu[1,2], Yongxian Hu[1,2], Xiaoyu Lai[1,2], He Huang[1,2], Yi Luo[1,2]

[1]The First Affiliated Hospital, Zhejiang University, Hangzhou, China, [2]Zhejiang University, Hangzhou, China

Background: Relapse is the leading cause of treatment failure after allogeneic hematopoietic stem cell transplantation (allo-HSCT) for acute leukemia with high-risk features. Donor lymphocyte infusion (DLI) has been proved to exhibit a strong graft-versus-leukemia (GVL) effect in patients with hematologic relapse after transplantation. However, DLI may also increase the incidence of graft-versus-host disease (GVHD) and treatment-related-mortality. It remains controversial whether patients with high-risk acute leukemia can benefit from prophylactic DLI after allo-HSCT.

Methods: The high-risk features of acute leukemia were defined by the following criteria: (i) primary chemoresistance; (ii) advanced disease at transplantation (beyond the second complete remission or active diasease); (iii) relapse after allogeneic transplantation; (iv) MRD positive at transplantation; (v) unfavorable genetic abnormalities, such as t(4;11), IKZF-1 and TP53; (vi) t (9; 22) or FLT3-ITD mutation without prophylactic target therapy after transplantation. A total of seventy-one patients with high-risk acute leukemia received granulocyte colony-stimulating factor (G-CSF)-mobilized prophylactic DLI and concurrent short-term cyclosporin A after allo-HSCT. For each prophylactic DLI recipient, a control who were matched for diagnosis, primary chemoresistance or not, genetic risk stratification, donor type, disease and MRD status at transplantation, was randomly selected from patients without prophylactic DLI. Altogether forty-four well-matched pairs were identified to analysis the safety and efficacy of prophylactic DLI.

Results: The 3-year overall survival (OS) (78.9% versus 42.7%, $p = 0.005$) and leukemia-free survival (LFS) (76.9% versus 34.6%, $p = 0.001$) of prophylactic DLI group were superior to the control group. A higher GVHD-free/relapse-free survival was found in prophylactic DLI group but without statistical difference (32.6% versus 21.9%, $p = 0.441$). Prophylactic DLI recipients achieved significantly lower 3-year cumulative incidence of relapse (13.8% versus 42.6%, $p = 0.001$). The cumulative incidence of grades II-IV and grades III-IV acute GVHD at 100 days after prophylactic DLI was 20.5% and 9.1%, respectively. Higher 3-year cumulative incidence of chronic GVHD (38.6% versus 12.8%, $p = 0.005$) was observed in prophylactic DLI group while no difference was observed between the two groups concerning non-relapse mortality (41.7% versus 41.4%, $p = 0.672$). Multivariate analysis identified post-transplantation prophylactic DLI as an independent protective factor for LFS ($p = 0.006$, hazard ratio (HR)=0.352), OS ($p = 0.023$, HR = 0.4) and relapse ($p = 0.017$, HR=0.326).

Conclusions: These data indicated that prophylactic DLI after allo-HSCT effectively decreased the risk of relapse and improved survival of patients with high-risk acute leukemia without increasing the risk of acute GVHD or treatment toxicity.

Disclosure: Nothing to declare.

O045.

Baseline Immune Status Predicts Response to Adoptive Therapy with CMV CTLS for Refractory CMV

Vanessa Fabrizio, Irene Rodriguez-Sanchez, Audrey Mauguen, Parastoo Dahi, Ekatarina Doubrovina, Richard J. O'Reilly, Susan Prockop

MSKCC, New York, NY, United States

Background: Adoptive cell therapy using CMV-specific cytotoxic T-cells (CMV CTLs) has demonstrated efficacy in treating CMV in the post HCT setting. However, little is known about the mechanism by which adoptively transferred CTLs exert durable responses. Therefore, we studied the relationship between response and recipient factors.

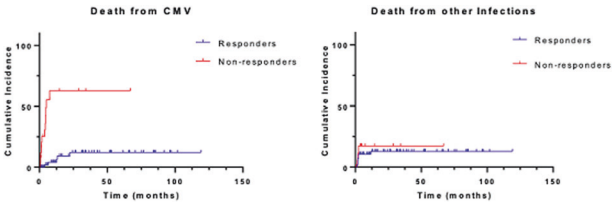
Methods: We retrospectively reviewed pediatric and adult patients (pts) who received primary or 3rd party donor CMV CTLs for the treatment of CMV viremia/disease after HCT between 9/2009 and 1/2018. Outcomes of interest were response to CMV CTLs and death from CMV. We evaluated these in relationship to time to start of CMV CTLs and IR using a CD4 count of 50×10^6/L and of 200×10^6/L as markers of IR. Pts whose CMV response was not attributable to CMV CTLs were excluded from analysis.

Results: Pts ($n = 102$) were transplanted for malignant ($n = 83$) and non-malignant ($n = 19$) disease at a median age of 51.8 (range 0.3-73). Pts were treated with primary ($n = 25$), 3rd party ($n = 74$) and both ($n = 3$) type of donor CMV CTLs. The median time from HCT to treatment was 127 days (range 29-2763). There was no difference in time to IR ($p = 0.4$) or response to CMV CTLs between donor types ($p = 0.17$). However, recipients with a baseline CD4>50×10^6/L were significantly ($p = 0.015$) more likely to respond to CMV CTLs (26/29, 90%) vs those with a baseline CD4<50×10^6/L (30/49, 61%). Responders (48/58, 83%) were more likely to achieve a CD4>50×10^6/L vs non-responding (10/22, 45%) recipients ($p = 0.02$). Using a conventional measure of IR as CD4>200×10^6/L, there was no difference in achieving IR between responders (31/58, 53%) and non-responders (7/22, 32%; $p = 0.14$). Responders ($n = 5$) died less frequently from CMV than non-responders ($n = 12$) (p=< 0.0001). Responders ($n = 7$) died from other infections as frequently as non-responders ($n = 3$) (13 vs 17%, $p = 0.5$).

Conclusions: We demonstrate that adoptive therapy with CMV CTLs may rely on recipient immune components to mediate durable response to therapy. Irrespective of the time from HCT, pts with a baseline CD4< 50×10^6cells/L were less likely to respond to CMV CTLs. Response to CMV CTLs protected from CMV related death but not death from other infections

Patient Characteristics	Primary Donor (25)	3rd Party (74)	Both (3)
Median age in Years(range)	55.9 (0.6 – 73.0)	49.9 (0.3 – 69.7)	62.0 (13.4 – 67.4)
Gender (male/female)	12/13	40/34	1/2
Stem Cell Source Conventional/Cord Blood/ T Depleted	2/0/23	17/9/49	1/0/2
CMV Serostatus D+/R+; D-/R+ Unknown	24/0/1	28/37/9	3/0/0
Median Time (Days) HCT to CMV Reactivation (Range)	28.0 (-4 – 2520)	26.5 (-38 – 483)	24 (19 – 82)
Time (Days) from HCT to CMV CTLs (Range)	116 (76–2763)	130 (29 – 1953)	128 (59 – 385)
Immunosuppression at Start of CTLs	6	40	1
Responder (CR/PR)/ Non-responder (SD/POD) Non-Evaluable	17/4/4	38/21/15	3/0/0
Death from CMV	7	13	1

[Table 1]



[Figure 1]

Clinical Trial Registry: Trial of Third Party Donor Derived CMVpp65 Specific T-cells for The Treatment of CMV Infection or Persistent CMV Viremia After Allogeneic Hematopoietic Stem Cell Transplantation (NCT02136797) Trial of Donor T Cells Sensitized With Pentadecapeptides of the CMV-PP65 Protein for the Treatment of Cytomegalovirus (CMV) Infections Following Allogeneic Hematopoietic Stem Cell Transplants (NCT00674648) and Primary Transplant Donor Derived CMVpp65 Specific T-cells for The Treatment of CMV Infection or Persistent CMV Viremia After Allogeneic Hematopoietic Stem Cell Transplantation (NCT01646645)

Disclosure: Vanessa Fabrizio Nothing to declare.
Irene Rodriguez Sanchez Nothing to declare
Audrey Mauguen Nothing to declare
Parastoo Dahi Nothing to declare
Ekaterina Doubrovina Atara Biotherapeutics
Richard J. O'Reilly Atara Biotherapeutics
Susan Prockop Atara Biotherapeutics and Mesoblast

O046.

Efficacy and Safety of Donor Lymphocyte Infusion After Haploidentical Stem Cell Transplantation: A Retrospective Multicenter Study on Behalf of Geth (Grupo ESPAñOL Trasplante Hematopoyético)

Guillermo Martín Sánchez[1,2], Rebeca Bailén Almorox[3], Miriam Sánchez Escamilla[1,2], Abel Garcia Sola[4], Irene Garcia Cadenas[5], Lucrecia Yañez[1,2], Maria Jesus Pascual

Gascon[4], José Luis DÍez Martín[3], Jordi Sierra[5], Enrique Ocio[1,2], Mi Kwon[3], Aranzazu Bermudez Rodriguez[1,2]

[1]Marques de Valdecilla University Hospital, Santander, Spain, [2]IDIVAL, Santander, Spain, [3]Gregorio Marañon University Hospital, Madrid, Spain, [4]Regional University Hospital of Málaga, Malaga, Spain, [5]Santa Creu i Sant Pau Hospital, Barcelona, Spain

Background: Donor lymphocyte infusion (DLI) after haploidentical hematopoietic stem cell transplantation (HSCT) has been used to reverse mixed donor/recipient chimerism and to prevent or treat relapses showing different results. However, DLI can also induce a strong and potentially lethal graft versus host disease (GVHD). We report the results the results of 83 haploidentical DLI infused in 30 patients from 4 transplant centers, following unmanipulated HSCT.

Methods: Patients included had previously received a T-cell replete peripheral blood ($n = 23$) or bone marrow ($n = 7$) HSCT from haploidentical-related donors, after myeloablative ($n = 17$) or non-myeloablative conditioning regimen ($n = 13$), between June 2011 and April 2019. Median age at transplant was 37 (10-66) years-old. Indications for HSCT were: AML ($n = 16$), Hodgkin lymphoma ($n = 5$), ALL ($n = 4$), MDS ($n = 3$) and non-Hodgkin lymphoma ($n = 2$). GVHD prophylaxis was based on high-dose post-transplant cyclophosphamide in combination with tacrolimus alone ($n = 5$) or mycophenolate mofetil plus cyclosporine ($n = 15$) or tacrolimus ($n = 10$).

DLI were collected from the original donor, without priming agents before the apheresis. Immunosuppresion was discontinued prior to the first DLI and no patients had active GVHD at first DLI infusion. DLI was indicated as relapse prophylaxis in 7 (23%) patients, preemtive therapy in positive MRD in 10 (33%) and treatment of overt relapse in 13 (43%).

Results: The median interval from HSCT to DLI was 223 days (IQL: 117-401) and the median starting dose was 1×10^6 (0,1-1) CD3/kg. The patients received a mean of 2 (1-3) doses reaching a median maximum dose of 5×10^6 (1-10) CD3/kg. Concomitant therapy with DLI was administered in 16 (53%) cases.

Overall 16 patients (53%) developed acute GVHD and 9 (30%) chronic GVHD. Systemic GVHD therapy was required in 14 (47%) of them.

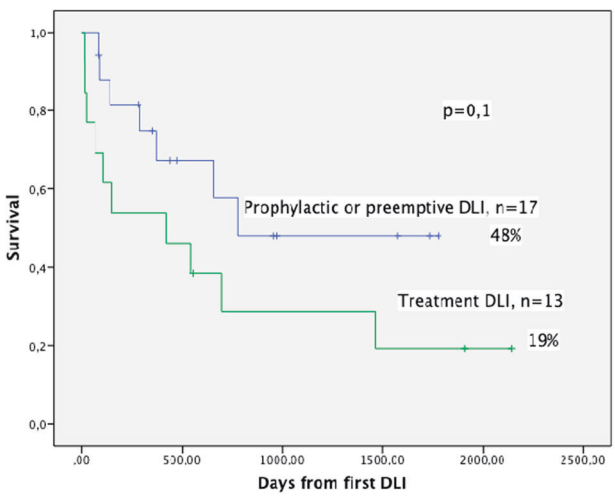
Four patients (57%) did not relapse in the prophylaxis group. Complete response (CR) rates for the preemptive and treatment groups were 40% and 30% respectively. All the patients (40%) in the preemptive DLI group maintained response until last follow up but only two (15%) in the treatment group.

With a median follow-up of 13 months (1-70), overall survival (OS) for all 30 patients was 32% and we found differences between prophylactic / preemptive (48%) versus treatment (19%) groups although not statistically significant. The main causes of death were relapse / progression ($n = 13$; 43%), GVHD ($n = 2$; 7%) and infection ($n = 2$; 7%).

Conclusions: Haploidentical DLI induced long term maintained responses when used prophylactically or pre-emptively. Our study also highlights the difficult to treat patients with overt relapse, who showed very poor results with these approach even in combination with chemo or radiotherapy. GVHD is the main complication after DLI but with low mortality rate.

	Prophylaxis ($n = 7$)	Preemptive ($n = 10$)	Treatment ($n = 13$)
AML / ALL / MDS / HL / NHL	4 / 1 / 1 / 1 / 0	7 / 1 / 1 / 1 / 0	5 / 3 / 1 /3 / 2
Full donor / mixed chimerism pre-DLI	3 / 4	8 / 2	7 / 6
Acute GVHD III-IV	1 (14%)	4 (40%)	2 (15%)
Moderate-severe chronic GVHD	3 (42%)	3 (30%)	1 (8%)
Alive with CR at last follow-up	4 (57%)	4 (40%)	2 (15%)
Median follow up since DLI, months (IQL)	11 (2-31)	18 (7-36)	13 (1-35)

[Characteristics of GVHD and response by DLI indication.]



[OS in prophylaxis and preemptive versus treatment groups.]

Disclosure: Nothing to declare.

O047.

Phase I Study of Adoptive Transfer of Haploidentical Expanded NK Cells

Lucia Silla[1], Vanessa Valim[2], Cristiane Weber[2], Alini Vargas[2], Dayane Catelli[2], Bruna Correa[1], Maria da Silva[3], Bruna Amorin[2], Bruna Zambonato[2], Juliana Nobrega[4], Fernanda Scherer[5], Claudia Astigarraga[6], Lisandra Rigoni[2], Liane Daudt[1], Rosane Bittencourt[2], Mariana Michalowski[1], Fernando Duarte[7], Nelson Hamerschlak[8], Vicente Odone[9], Mariana Jobim[2], Joice Merzoni[2], Samantha Nichele[10], Laura Fogliatto[2], Juliano Perez[2], Raul Rodrigues[1], Nicole Kilian[11], Jeniffer dos Anjos[12], Leo Sekine[2], Alessandra Paz[13], Dean A Lee[14]

[1]*Federal University of Rio Grande do Sul, Porto Alegre, Brazil*, [2]*Hospital de Clinicas de Porto Alegre - HCPA, Porto Alegre, Brazil*, [3]*Hosiptal de Clinicas - HCPA, Porto Alegre, Brazil*, [4]*Privety Sector, Recife, Brazil*, [5]*Hospital de Clinicas de Porto Alegre - HCPA, Porto Algre, Brazil*, [6]*Hospital Moinhos de Vento, Porto Alegre, Brazil*, [7]*Federal University of Ceara, Fortaleza, Brazil*, [8]*Hospita Albert Einstein, Sao Paulo, Brazil*, [9]*Hospital Albert Einstein, Sao Paulo, Brazil*, [10]*Federal University of Parana - Bone Marrow Transplant, Curitiba, Brazil*, [11]*Uniritter, Porto Alegre, Brazil*, [12]*Federal University of Rio Grande do Sul, porto Alegre, Brazil*, [13]*Federal Unviersity of Rio Grande do Sul, Porto Alegre, Brazil*, [14]*Nationwide Childrens Hospital, Collumbus, OH, United States*

Background: Patients with relapsed, refractory, or CNS-positive AML respond poorly to chemotherapy. NK cells have anti-leukemic activity but are deficient in number and function in AML patients and are ablated by high-dose chemotherapy. Therefore, we initiated a Phase I study of adoptive transfer of haploidentical expanded NK cells to restore NK cell number and anti-leukemia function in patients with relapsed/refractory AML.

Methods: Haploidentical donors were selected after HLA and KIR typing. NK cells were expanded on feeder cells and cryopreserved for infusion at the assigned dose level, then thawed and infused thrice weekly for six doses after fludarabine, cytarabine, and G-CSF (FLAG). Patients were treated in 3 dose cohorts of 10^6, 5×10^6, and 10^7 NK cells/kg/infusion. Response was assessed at day 30.

Results: NK cell production was feasible for all subjects. 13 patients were treated (one treated twice), age 1-61y (median 22y), with primary refractory ($n = 5$) or relapsed ($n = 8$) AML. Patients had a median of five prior therapies, including nine with prior stem cell transplantation. Two patients had CNS, one bone and nerve root disease and one CNS probable mycetoma. Therapy was tolerated with manageable toxicity in such an ill population of patients. Median neutrophil and platelet recovery were at day 33 and 44, respectively. Complete response and overall response rate were 50% and 78.5%, respectively, including unexpected CNS responses that were associated with localized inflammation. Median OS and DFS after treatment were 271 and 90 days, respectively.

Conclusions: Repeated infusions of high doses of cryopreserved expanded NK cells are feasible and well-tolerated after high-dose chemotherapy and demonstrate encouraging systemic and CNS responses in high-risk AML.

Clinical Trial Registry: IRB/HCPA 00000921; CAI: 44444214.7.0000.5327 CinicalTrials.gov, NCT02809092.

Disclosure: DECIT/MS/SUS; FINEP/CNPq/MCTC and CAPES/ME - Brazilian Government.

Chronic leukaemia and other myeloproliferative disorders

O048.

Timing for Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) in Chronic Myelomonocytic Leukemia (CMML): A Joint Study from the International MDS/MPN Working Group and EBMT

Marie Robin[1], Liesbeth de Wreede[2], Eric Padron[3], Junfeng Wang[4], Sheree Hazelaar[5], Dietrich Beelen[6], Pierre Fenaux[7], Martin Bornhaeuser[8], Nicolaus Kroger[9], Aziz Nazha[10], Peter Dreger[11], Raajit K. Rampal[12], Jurgen Finke[13], Rami K Rampal[14], Victoria Potter[15], Sally Killick[16], Didier Blaise[17], Eric Solary[18], Angus Broom[19], Guillermo Garcia-Manero[20], Vittorio Rizzoli[21], Mrinal Patnaik[22], Francesco Onida[23], Ibrahim Yakoub-Agha[24], Raphael Itzykson[7]

[1]*Paris, France*, [2]*Leiden University Medical Center, Leiden, Netherlands*, [3]*H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, United States*, [4]*EBMT Statistical Unit, Leiden, Netherlands*, [5]*EBMT Data Office Leiden, Leiden, Netherlands*, [6]*University Hospital Essen, Essen, Germany*, [7]*Hopital Saint Louis, Paris, France*, [8]*Universitaetsklinikum Dresden, Dresden, Germany*, [9]*University Medical Center Hamburg-Eppendorf, Hamburg, Germany*, [10]*Cleveland Clinic, Avon Lake, OH, United States*, [11]*University Clinic Heidelberg, Heidelberg, Germany*, [12]*Memorial Sloan Kettering Cancer Center, New York, NY, United States*, [13]*University of Freiburg, Freiburg, Germany*, [14]*Moffitt Cancer Center, Tampa, FL, United States*, [15]*King's College Hospital NHS Foundation Trust, London, United Kingdom*, [16]*The Royal Bournemouth and Christchurch Hospitals NHS*

Foundation Trust, Bournemouth, United Kingdom, [17]*Institut Paoli Calmettes, Marseille, France*, [18]*INSERM U1170, Villejuif, France*, [19]*Western General Hospital, Edimburg, United Kingdom*, [20]*University of Texas, Houston, TX, United States*, [21]*CTMO of Hematology, Parma, Italy*, [22]*Mayo Clinic, Rochester, MN, United States*, [23]*IRCCS Ospedale Maggiore Policlinico Di Milano, Milano, Italy*, [24]*Université de Lille, Lille, France*

Background: Due to the absence of curative option in CMML patients and based on data available in MDS, HSCT is commonly proposed in the higher risk patients, given survival at 5 years between 20 and 40%. Through a large collaborative study, we address the question of added value and optimal timing for HSCT in CMML patients.

Methods: We retrospectively selected pts from 2 registries: International MDS/MPN Working Group (IWG cohort, Padron Blood Cancer J 2015) and EBMT with the following criteria: WHO-defined CMML, age ≤ 70y, ECOG 0-2, diagnosis after 2000, available CPSS at the time of diagnosis. A multi-variable Cox model was used to test transplantation as a time-dependent variable. For the multi-state model, the different states were considered in higher- (CPSS int-2 and high) and lower- risk (CPSS low/int-1) pts with 6, 12, 18 and 24 months landmark.

Results: 719 and 403 pts were identified in the IWG and EBMT registry. Median age was 64 (range 16-70) in IWG and 58 (19-70) years in EBMT cohort. Patients were male in 69% and 67% of IWG and EBMT cohorts. CPSS was low in 22% and 13%, int-1 in 31% and 31%, int-2 in 40% and 45% and high in 8% and 11% of the IWG and EBMT pts, respectively. Among the 719 pts from IWG, 102 received HSCT. The cumulative incidences of transformation into AML at 1 year were 7.3% and 18.2% in lower and higher risk patients, respectively. At the time of diagnosis the expected life time of higher risk patients was 25.2 months while it was 44.1 months in lower risk patients.

After adjustment for age, transformation into AML and CPSS, transplantation significantly decreased the risk of mortality (HR: 0.78, p-value < 0.001). The multi-state model showed that there was a gain of survival with transplantation in higher risk patients, transformed into AML or not transformed but the advantage was modest and all survivals were poor: ie, 5-year survival increased from 17 to 22% for transplanted vs. non-transplanted patients still alive at 12 months after diagnosis. The advantage was more pronounced when patients had transformed into AML (5-year survival from 5 to 15% if transplanted with the 12-month landmark). In lower risk patients, survival was not affected by transplantation (53% for both group transplanted or not within 6 months). When we performed a simulation in 60-year old patients, transplantation in untransformed lower risk patients was detrimental. For instance, lower-risk 60-year old alive at 12 months and who received transplantation within 12 months have a survival at 35% as compared to 50% at 5 years in those without transplantation. Of note, older patients kept the advantage of survival with transplantation if they were at higher risk.

Conclusions: For the first time, we could analyze the impact of transplantation over time on survival in CMML. In lower risk patients who remain untransformed within 24 months, survival with or without transplantation was similar, except for older patients where survival was decreased with transplantation. In higher risk patients, transplantation improved survival.

Disclosure: Robin: *Novartis Neovii:* Research Funding. **Padron:** *Incyte:* Research Funding; *Kura Oncology:* Research Funding; *Celgene:* Research Funding. **Beelen:** *Medac GmbH Wedel Germany:* Consultancy, Honoraria. **Fenaux:** *Celgene Corporation:* Honoraria, Research Funding; *Astex:* Honoraria, Research Funding; *Jazz:* Honoraria, Research Funding; *Aprea:* Research Funding. **Kroeger:** *Riemser:* Research Funding; *Novartis:* Honoraria, Research Funding; *Medac:* Honoraria; *DKMS:* Research Funding; *Neovii:* Honoraria, Research Funding; *Celgene:* Honoraria, Research Funding; *JAZZ:* Honoraria; *Sanofi-Aventis:* Honoraria. **Nazha:** *Tolero, Karyopharma:* Honoraria; *MEI:* Other: Data monitoring Committee; *Novartis:* Speakers Bureau; *Jazz Pharmacutical:* Research Funding; *Incyte:* Speakers Bureau; *Daiichi Sankyo:* Consultancy; *Abbvie:* Consultancy. **Rampal:** *Agios, Apexx, Blueprint Medicines, Celgene, Constellation, and Jazz:* Consultancy; *Constellation, Incyte, and Stemline Therapeutics:* Research Funding. **Finke:** *Riemser:* Honoraria, Other: research support, Speakers Bureau; *Neovii:* Honoraria, Other: research support, Speakers Bureau; *Medac:* Honoraria, Other: research support, Speakers Bureau. **Komrokji:** *Agios:* Consultancy; *DSI:* Consultancy; *pfizer:* Consultancy; *celgene:* Consultancy; *JAZZ:* Consultancy; *Novartis:* Speakers Bureau; *JAZZ:* Speakers Bureau; *Incyte:* Consultancy. **Killick:** *JAZZ:* Honoraria; *Celgene:* Honoraria; *NOVARTIS:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *ALEXION:* Honoraria. **Blaise:** *Molmed:* Consultancy, Honoraria; *Sanofi:* Honoraria; *Pierre Fabre medicaments:* Honoraria; *Jazz Pharmaceuticals:* Honoraria. **Garcia-Manero:** *Amphivena:* Consultancy, Research Funding; *Helsinn:* Research Funding; *Novartis:* Research Funding; *AbbVie:* Research Funding; *Celgene:* Consultancy, Research Funding; *Astex:* Consultancy, Research Funding; *Onconova:* Research Funding; *H3 Biomedicine:* Research Funding; *Merck:* Research Funding. **Patnaik:** *Stem Line Pharmaceuticals.:* Membership on an entity's Board of Directors or advisory committees.

O049.

The 10-years EBMT Landscape of Allogeneic Hematopoietic Cell Transplantation (Allohct) for Chronic Lymphocytic Leukemia

Olivier Tournilhac[1], Michel van Gelder[2], Peter Dreger[3], Martin Bornhäuser[4], Uwe Platzbecker[5], Christof Scheid[6], Dietrich Beelen[7], Pavel Jindra[8], Jan J. Cornelissen[9], Henrik Sengeloev[10], Stephanie Nguyen[11], Jiri Mayer[12], Matthias Stelljes[13], Marie-Sarah Dilhuydy[14], Laimonas Griskevicius[15], Antonin Vitek[16], Manos Nikolousis[17], Nicolaus Kröger[18], Andrzej Hellmann[19], Stella Santarone[20], Nienke Zinger[21], Patrick Hayden[22], Ibrahim Yakoub-Agha[23]

[1]CHU Estaing, Clermont-Ferrand University Hospital, Clermont-Ferrand, France, [2]University Hospital Maastricht, Maastricht, France, [3]University of Heidelberg, Heidelberg, Germany, [4]Universitaetsklinikum Dresden, Dresden, Germany, [5]Medical Clinic and Policinic 1, Leipzig, Germany, [6]University of Cologne, Cologne, Germany, [7]University Hospital, Essen, Germany, [8]Charles University Hospital, Pilsen, Czech Republic, [9]Erasmus MC Cancer Institute, Rotterdam, Netherlands, [10]Bone Marrow Transplant Unit L 4043, Rigshospitalet, Copenhagen, Denmark, [11]Universite Paris IV, Hospital la Pitié-Salpêtrière, Paris, France, [12]University Hospital Brno, Brno, Czech Republic, [13]University of Muenster, Muenster, Germany, [14]CHU Bordeaux, Bordeaux, France, [15]Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania, [16]Institute of Hematology and Blood Transfusion, Prague, Czech Republic, [17]Birmingham Heartlands Hospital, Birmingham, United Kingdom, [18]University Hospital Eppendorf, Hamburg, Germany, [19]Medical University of Gdansk, Gdansk, Poland, [20]Ospedale Civile, Pescara, Italy, [21]EBMT Data Office, Leiden, Netherlands, [22]Trinity College Dublin, St. James's Hospital, Dublin, Ireland, [23]CHU de Lille, LIRIC, INSERM U995, Université de Lille, Lille, France

Background: When chronic lymphoid leukemia (CLL) was managed with immunochemotherapy and alemtuzumab, allogeneic transplantation (alloHCT) was regularly considered as an option for high-risk patients, especially those with early relapse and/or impaired *TP53*. European Medicines Agency (EMA) approval of ibrutinib and idelalisib in mid-2014 followed by venetoclax end-2016 have deeply modified this therapeutic paradigm.

Methods: In this descriptive study (ELAC) of the CMWP, all cases of alloHCT for CLL were extracted from the database in order to evaluate this transition within countries participating in the EBMT.

Results: Between 2009 and 2018, 2856 transplants performed in 37 countries were reported to EBMT. At transplantation, the median age was 57 (19-76) years. Disease status was recorded as CR, PR/SD or PD in 22.5%, 63.2% and 13.9%, respectively. Conditioning regimens were myeloablative in 26% and reduced intensity in 74%.

Information of CLL treatment before alloHCT was available for 50% of the patients with 1, 2 and ≥3 lines in 33, 21 and 45% respectively and the following targeted therapy had been given: ibrutinib (18.1% ; $n = 254$), idelalisib (5.7% ; $n = 80$), venetoclax (4.3% ; $n = 60$). The median time interval between the initial systemic CLL treatment and alloHCT was 50 (0-357) months and 133 patients had received prior autologous HCT. Donors were HLA-identical sibling, unrelated or mismatched relatives in 33.4%, 61.8% and 4.1%, respectively.

The median follow-up of living patients post-transplant is 36.4 (0.3-123.5) months and the estimated overall survival is 47.4% and 32.6% at 3 and 5 years, respectively. (Fig. 1)

Overall the number of alloHCT decreased from a mean of 393 for the period 2009-2011, to 133 in 2017 and 94 in 2018.

Eight EBMT countries in which more than 100 alloHCT (in total during this period) were performed accounted for 2462 (86%) of the 2856 transplants. Within these 8 countries, there was a dramatic reduction in the number of alloHCT from a mean of 313 per year for the period 2009-2011 to 101 in 2017 and 75 in 2018 (Fig 2). The number of alloHCT as a proportion of the population of each country decreased from 1.1 (0.4-2.2)/M (10e6 inhabitants) for the period 2009-2011 to 0.4 (0.2 - 1.0)/M in 2017 and 0.2 (0.1-0.4)/M in 2018. There was some variation, the reduction being more gradual and from a smaller baseline in Italy, France and the United Kingdom.

Conclusions: Within a 10-year period, there was, unsurprisingly, a clear fall in the number of alloHCT recorded in the EBMT database. This decrease that began between 2011 and 2014 clearly followed the availability of ibrutinib and idelalisib. However, alloHCT continues to be performed in CLL patients despite the more recent availability of venetoclax, both within the eight aforementioned countries (in which the EMA regulates drug approval) ($n = 75$), and within other EBMT-affiliated countries ($n = 94$), knowing that the data collection of the last few years might not be exhaustive. Patients with double refractory CLL and/or who are intolerant of both BTK and BCL2 inhibitors represent a new challenge for cell therapy, including alloHCT and CAR-T.

Disclosure: None.

O050.

Determinants of Survival in Myelofibrosis Patients Undergoing Allogeneic Hematopoietic Cell Transplantation: A Study by the Chronic Malignancies Working Party of EBMT

Juan Carlos Hernández-Boluda[1], Arturo Pereira[2], Nicolaus Kröger[3], Dietrich Beelen[4], Marie Robin[5], Martin Bornhäuser[6], Emanuele Angelucci[7], Antonin Vitek[8], Igor Wolfgang Blau[9], Riitta Niittyvuopio[10], Jürgen Finke[11], Jan J Cornelissen[12], Jakob Passweg[13], Peter Dreger[14], Eefke Petersen[15], Lothar Kanz[16], Jaime Sanz[17], Tsila Zuckerman[18], Nienke Zinger[19], Simona Iacobelli[20], Patrick Hayden[21], Tomasz Czerw[22], Donal McLornan[23], Ibrahim Yakoub-Agha[24]

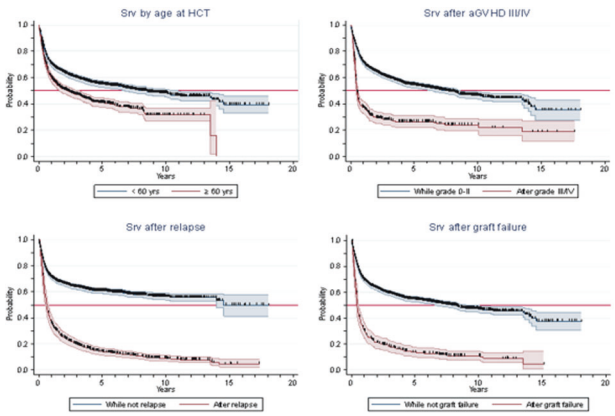
[1]Hospital Clínico Universitario Valencia, Valencia, Spain, [2]Hospital Clinic, Barcelona, Spain, [3]University Hospital Eppendorf, Hamburg, Germany, [4]University Hospital, Essen, Germany, [5]Hopital Saint Louis, Paris, France, [6]University Hospital, TU Dresden, Germany, [7]Ospedale San Martino, Genova, Italy, [8]Institute of Hematology and Blood Transfusion, Prague, Czech Republic, [9]Charité Universitaetsmedizin, Berlin, Germany, [10]HUCH Comprehensive Cancer Center, Helsinki, Finland, [11]Oncology and Stem Cell Transplantation, Freiburg, Germany, [12]Erasmus MC Cancer Institute, Rotterdam, Netherlands, [13]University Hospital, Basel, Switzerland, [14]University of Heidelberg, Heidelberg, Germany, [15]University Medical Center, Utrecht, Netherlands, [16]Universitaet Tuebingen, Tuebingen, Germany, [17]University Hospital La Fe, Valencia, Spain, [18]Rambam Medical Center, Haifa, Israel, [19]EBMT Data Office Leiden, Leiden, Netherlands, [20]University of Rome Tor Vergata, Rome, Italy, [21]Trinity College Dublin, Dublin, Ireland, [22]Maria Skłodowska-Curie Institute, Gliwice, Poland, [23]Guys' and St. Thomas' NHS Foundation Trust and University College London Hospitals, London, United Kingdom, [24]CHU de Lille, Lille, France

Background: A large multicenter retrospective study has been conducted to evaluate the main determinants of survival in transplanted patients with myelofibrosis (MF) and to describe the predictive factors for the main complications after allogeneic hematopoietic cell transplantation (allo-HCT).

Methods: This study by the European Society for Blood and Marrow Transplantation (EBMT) included 2916 MF patients who underwent first allo-HCT from an HLA-identical sibling or unrelated donor between January 2000 and December 2016. Primary endpoints were survival, non-relapse mortality (NRM), graft failure, disease progression/relapse, and acute and chronic graft-versus-host disease (GVHD). Period of first allo-HCT, patients and donor characteristics, disease risk profile, transplantation modalities, and the main post-transplant complications were taken into account for the analysis of factors predicting survival. Time-dependent variables were considered only after the first transplant and were analyzed by the time-span splitting method. Multivariate analyses of patient- or procedure-related factors predicting the post-transplant landmark events were done within the framework of competing risks by the method of Fine & Gray. To account for multiple comparisons, statistical significance was set at a p value < 0.01.

Results: After a median follow-up of 4.7 years (IQR: 4.4-5.0), 1381 patients (47%) had died. Projected median survival was 5.3 years (95% CI: 4.1-6.6). Factors independently associated with increased mortality were age ≥60 years and Karnofsky Performance Status <90% at transplant, and occurrence of graft failure, grade III-IV acute GVHD, and disease progression/relapse during follow-up. The divergent effects on NRM and relapse incidence of chronic GVHD resulted in a neutral influence on survival. Figure 1 shows the unadjusted survival curves for age 60 years or more, graft failure, grade III-IV acute GVHD, and disease relapse/progression. Graft failure increased in recipients of unrelated donors and decreased with myeloablative conditioning (MAC) and negative cytomegalovirus serostatus of both donor and recipient. Risk of grade III-IV acute GVHD was higher in recipients of unrelated donors and decreased with MAC. Risk of disease progression or relapse tended to be higher in patients with intermediate-2 and high risk DIPSS categories and to decrease in *CALR*-mutated patients. Acute and chronic GVHD reduced the subsequent risk of relapse.

Conclusions: We have characterized the prognostic significance of the main landmark events occurring after allo-HCT in MF patients and the predictive factors for these events. This information has potential implications for patient counseling and clinical decision-making.



[Figure 1. Unadjusted survival by risk factor after transplant in 2916 patients with myelofibrosis]

Disclosure: Nothing to declare.

O051.

Splenectomy Doesn't Preclude Subsequent Allogeneic Hematopoietic Cell Transplantation in Myelofibrosis Patients: A French Nationwide Study Using a Multistate Model

Jean-Baptiste Bossard[1,2], Jean-Baptiste Beuscart[1], Marie Robin[3], Mohamad Mohty[4], Fiorenza Barraco[5], Patrice Chevallier[6], Tony Marchand[7], Marie-Thérèse Rubio[8], Amandine Charbonnier[9], Didier Blaise[10], Jacques-Olivier Bay[11], Carmen Botella-Garcia[12], Gandhi Damaj[13], Sébastien Maury[14], Patrice Ceballos[15], Thomas Cluzeau[16], Jérôme Cornillon[17], Mathieu Meunier[18], Corentin Orvain[19], Alain Duhamel[1], Federico Garnier[20], Jean-Jacques Kiladjian[3], Ibrahim Yakoub-Agha[1]

[1]Université de Lille, Lille, France, [2]CHU Lille, Lille, France, [3]Hôpital Saint-Louis, Université Paris-Diderot, Paris, France [4]Saint-Antoine Hospital and University Pierre & Marie Curie, Paris, France, [5]Hospices Civils de Lyon, Pierre Bénite, Lyon, France, [6]CHU Hotel-Dieu, Nantes, France, [7]CHU Pontchaillou, Rennes, France, [8]Brabois Hospital, Nancy, France, [9]Amiens University Hospital, Amiens, France, [10]Institut Paoli Calmettes, Marseille, France, [11]Centre Hospitalier Universitaire de Clermont-Ferrand, Clermont-Ferrand, France, [12]University Hospital of Bordeaux, Bordeaux, France, [13]University Hospital, Caen, France, [14]Henri Mondor & Assistance Publique-Hospitaux de Paris, Universite Paris-Est Creteil, Creteil, France, [15]CHU Lapeyronie, Montpellier, France, [16]Archet Hospital, Nice, France, [17]Institut de Cancérologie Lucien Neuwirth, Saint-Priest-en-Jarez, France, [18]CHU Grenoble Alpes, Grenoble, France, [19]CHU Angers, Angers, France, [20]Agence de la Biomédecine, Saint-Denis, France

Background: Pretransplant splenectomy may improve allogeneic hematopoietic cell transplant (allo-HCT) outcomes but is associated with substantial morbidity and mortality that may delay or cancel a project of transplant. This study aims at determining whether pre-transplant splenectomy precludes subsequent allo-HCT, in myelofibrosis (MF) patients waiting for a transplant.

Methods: This study included all MF patients who were candidate to first allo-HCT from an unrelated donor in France, between January 1st, 2008 and January 1st, 2017, using the French registry of bone marrow transplantation (RFGM, *Registre France Greffe de Moelle*). With the Promise database, we identified transplanted patients, along with data regarding pretransplant splenectomy. For non-transplanted patients, local centers provided data from medical files. We excluded patients splenectomized before the initiation of unrelated donor search (ie, at registration).

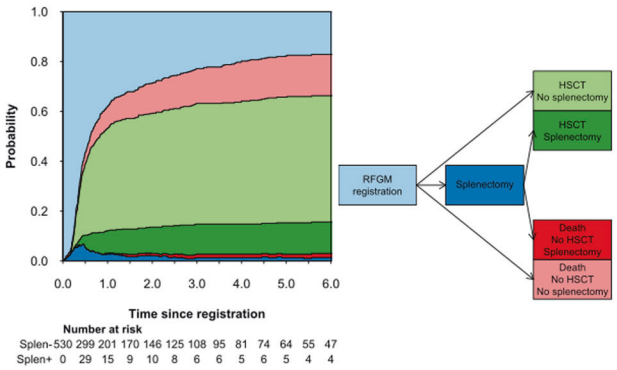
We applied a multi-state model including the four following states:

1. "RFGM registration", (ie, all patients at the time of initiation of unrelated donor search);
2. "Splenectomy", (ie, splenectomized patients);
3. "Death before allo-HCT"; and 4) "Allo-HCT".

All patients started in state

1) and could move to the intermediate state 2), or to one of the absorbing states 3) and 4). Similarly, patients could move from state 2) to state 3) or 4). We used Cox models with splenectomy as a time-varying variable and a clock-reset timescale to evaluate the association between splenectomy and subsequent HSCT or death.

Results: We recruited and analyzed 530 patients from 57 centers in France. Median age was 59 years old (interquartile range [IQR], 53 to 63 years old) and 310 (58.5%) were men. Median follow-up was 6 years. Eighty-one patients were splenectomized after registration, of whom 65 underwent subsequent allo-HCT and 9 died. Stacked probabilities of being in each state as a function of time are represented with the Aalen-Johansen estimator (Figure 1). At each timepoint, the distance between 2 adjacent curves represent the probability of being in the corresponding state. For instance; two years after registration on the RFGM, the estimated probabilities were: 28.6% for being alive, neither splenectomized nor transplanted; 2.1% for being alive, splenectomized and not transplanted; 45.7% for being transplanted without previous splenectomy; 12.1% for being dead without previous splenectomy; 10.6% for being splenectomized and transplanted; and 0.9% for being splenectomized and dead.



[Figure 1: Aalen-Johansen estimation of state occupancy probabilities.]

Splenectomized patients had a higher probability of being transplanted in the first 4 months after splenectomy, in

comparison with non-splenectomized patients (unadjusted HR [Hazard Ratio], 7.2; 95% CI, 5.1 to 10.3), but not afterwards (HR, 1.2; 95% CI, 0.7 to 2.0). We found no significant association between splenectomy and death without allo-HCT (unadjusted HR, 1.6; 95% CI, 0.8 to 3.1).

Conclusions: When indicated, splenectomy can be performed among MF patients without precluding subsequent allo-HCT. However, its impact on post-transplant outcomes must be clarified before recommending larger indications for it.

Disclosure: This work was funded by a grant from the *Agence Régionale de Santé Hauts-de-France* (*"Bourse année recherche"*) and by the patients' association ALTE-SMP.

Authors declare no conflict of interest.

Conditioning regimens

O052.

Population Pharmacokinetic Estimation of ATG Exposure Predicts Immune Reconstitution And Survival in Adults Undergoing Ex Vivo cd34-selected Allogeneic Hematopoietic Cell Transplantation

Michael Scordo[1,2], Christina Cho[1,2], Sean M. Devlin[1], Molly A. Maloy[1], Josel D. Ruiz[1], Valkal Bhatt[1], Melody Smith[1,2], Richard J. O'Reilly[1,2], Esperanza B. Papadopoulos[1,2], Ann A. Jakubowski[1,2], Roni Tamari[1,2], Miguel A. Perales[1,2], Sergio A. Giralt[1,2], Jaap Jan Boelens[1,2]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, United States, *[2]Weill Cornell Medical College, New York, NY, United States*,

Background: Empiric weight-based anti-thymocyte globulin (ATG) dosing in heavier patients prior to ex vivo CD34-selected allogeneic hematopoietic cell transplantation (allo-HCT) is associated with high non-relapse mortality (NRM) and poor survival (Scordo et al., BBMT 2019). We hypothesized that poorer outcomes observed with ATG overexposure derive from impaired immune reconstitution (IR). Using a population pharmacokinetic (PK) model to more precisely estimate ATG exposure, we evaluated the association of ATG overexposure with survival outcomes and IR.

Methods: We studied 415 consecutive adult patients who underwent first myeloablative ex vivo CD34-selected allo-HCT with ATG (Thymoglobulin) for antirejection prophylaxis between 2006 and 2017. We estimated pre-/post-HCT and total ATG area under the curve (AUC, in mg*d/L) using an established PK model (Admiraal et al., Lancet Hematol 2017). Using a penalized spline with a Cox regression model, we then evaluated the association between ATG exposure and 1) NRM and overall survival (OS) among all patients, and 2) CD4+ T cell IR, defined as CD4+ ≥ 50 cells/mcL by day 100, in a subgroup of 287 patients with adequate lymphocyte subset data.

Results: Among all patients, median follow-up was 3.9 years (range, 0.7-12). Median age was 55 (range, 19-73), 228 (55%) were male, 204 (49%) had AML, 105 (25%) MDS, 50 (12%) ALL, and 56 (14%) other hematologic malignancies. HCT-CI was 0 in 85 (20%), 1-2 in 146 (35%), and ≥ 3 in 184 (45%) patients. Donors were HLA matched related in 150 (36%), matched unrelated in 202 (49), and mismatched in 63 (15%). CMV serostatus was positive in 251 patients (60%). Conditioning regimens were chemotherapy based in 279 (67%) and TBI based in 136 (33%). All but 2 patients, who were inevaluable on account of early deaths, engrafted. All patients received 1-3 doses of ATG 2.5 mg/kg between days -4 and -1: 361 (87%) received 2 doses, 47 (11%) 3 doses, and 7 (2%) 1 dose. Median estimated pre-HCT, post-HCT, and total ATG AUC values were, respectively, 19 (range, 9-36), 48 (range, 17-101), and 66 (29-125).

Total ATG exposure, driven primarily by higher post-HCT ATG exposure, corresponded to significant differences in all-cause mortality and NRM. Among patients with an estimated post-HCT ATG AUC >60, 5-year OS was 33% (range, 19-47%), versus 62% (range, 57-67%) for those with AUC < 60, adjusted p< 0.001; and NRM was 52% (range, 37-66%) versus 22% (range, 17-26%), respectively, p< 0.001. Higher estimated post-HCT ATG exposure was also associated with a lower likelihood of achieving IR. Patients without IR by day +100, in turn, had 5-year NRM of 34%, compared with 8% in patients with successful IR, p< 0.001.

Conclusions: Population PK modeling confirms that post-HCT ATG overexposure in ex vivo CD34-selected allo-HCT leads to inferior OS driven by higher NRM, due at least partly to poorer CD4+ IR. These results suggest that optimization of ATG exposure using individualized PK dosing will augment early CD4+ IR and thereby improve survival.

Disclosure: Scordo, Michael: Consultancy - McKinsey & Company, Angiocrine Bioscience, Inc., Omeros Corporation; Research Funding - Angiocrine Bioscience, Inc.; Ad Hoc, Advisory Board - Kite - A Gilead Company.

Cho, Christina: Ad Hoc, Advisory Board - AlloVir

Devlin, Sean; Maloy, Molly; Ruiz, Josel: Nothing to declare

Bhatt, Valkal: Consultancy - Incyte

Smith, Melody: Nothing to declare

O'Reilly, Richard: Consultancy, Research Funding, Patents & Royalties - Atara Biotherapeutics

Papadopoulos, Esperanza; Jakubowski, Ann; Tamari, Roni: Nothing to declare

Perales, Miguel-Angel: Scientific Advisory Board - MolMed, NexImmune, Abbvie, Bellicum, Bristol-Myers Squibb, Incyte, Nektar Therapeutics, Novartis, Omeros, Takeda, Research Funding - Kite - A Gilead Company; Consultancy - Merck; DSMB - Servier, Medigene.

Giralt, Sergio: Consultancy and Research Funding - Amgen, Actinium, Celgene, Johnson & Johnson, Takeda; Research Funding - Miltenyi; Consultancy - Jazz Pharmaceuticals, Novartis, Kite - A Gilead Company, Spectrum Pharmaceuticals.

Boelens, Jaap-Jan: Consultancy - Takeda, Magenta, Bluerock, Avrobio, Omeros.

O053.

Flamsa-based Reduced Intensity Conditioning Versus Myeloablative Conditioning in Patients with Relapsed/refractory Acute Myeloid Leukemia with Active Disease at the Time of Transplantation: An Alwp/ebmt Analysis

Eduardo Rodríguez-Arboli[1], Myriam Labopin[2], Johanna Tischer[3], Arne Brecht[4], Arnold Ganser[5], Jürgen Finke[6], Igor Wolfgang Blau[7], Nicolaus Kröger[8], Peter Kalhs[9], Edouard Forcade[10], Donald Bunjes[11], Alexandros Spyridonidis[12], Bipin Savani[13], Arnon Nagler[14], Mohamad Mohty[15]

[1]Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla, University of Seville, Seville, Spain, [2]EBMT Paris Study Office, Saint Antoine Hospital, INSERM UMR 938, Sorbonne University, Paris, France, [3]University Hospital of Munich-Grosshadern, LMU, Munich, Germany, [4]Deutsche Klinik für Diagnostik, KMT Zentrum, Wiesbaden, Germany, [5]Hannover Medical School, Hannover, Germany, [6]University of Freiburg, Freiburg, Germany, [7]Charité Universitätsmedizin Berlin, Berlin, Germany, [8]University Hospital Eppendorf, Hamburg, Germany, [9]Medizinische Universität Wien, Vienna, Austria, [10]CHU Bordeaux, Hôpital Haut-Lévêque, Pessac, France, [11]Universitätsklinikum Ulm, Ulm, Germany, [12]University Hospital of Patras, Patras, Greece, [13]Vanderbilt University Medical Center, Nashville, TN, United States, [14]Chaim Sheba Medical Center, Tel HaShomer, Israel, [15]Hôpital Saint-Antoine, AP-HP, Sorbonne University, INSERM UMRs 938, Paris, France

Background: Allogeneic stem cell transplantation (alloSCT) remains a necessary requirement for long-term survival in patients with relapsed/refractory (R/R) acute myeloid leukemia (AML). A significant proportion of R/R AML patients undergo an alloSCT in the absence of disease response, and conditioning choice for this patient population is controversial. The use of myeloablative conditioning (MAC) in this setting has been limited by high non-relapse mortality (NRM), and sequential FLAMSA followed by reduced-intensity conditioning (RIC) has been proposed as an effective and safer alternative. As improvements in supportive care contribute to decreasing NRM rates after MAC, a reassessment of these two strategies is warranted.

Methods: This was a retrospective registry-based analysis performed by the ALWP of the EBMT. Eligibility criteria included age 18-50 years, primary refractory, first or second relapsed active AML, first alloSCT from a matched sibling donor (MSD) or an unrelated donor (UD) performed between 2005 and 2018, MAC with cyclophosphamide and total body irradiation (Cy/TBI) or busulfan/cyclophosphamide (Bu/Cy), or FLAMSA-RIC. The study endpoints were overall survival (OS), relapse incidence (RI), leukemia-free survival (LFS), non-relapse mortality (NRM), acute graft-versus-host disease (aGVHD), chronic graft-versus-host disease (cGVHD) and refined graft-versus-host disease, relapse-free survival (GRFS). Cox proportional hazards regression models (cause-specific for competing risk data) were constructed for all outcome measures.

Results: A total of 1018 patients were included. Median age was 39 (range 18-50) years. Two hundred fifty-eight patients received Bu/Cy, 314 Cy/TBI, 318 FLAMSA-TBI and 128 FLAMSA-chemotherapy without TBI (CT). Bu/Cy (53%) was the most common regimen among patients receiving FLAMSA-CT, followed by melphalan (17%) and Bu (14%). Patients in the MAC group were more likely to have received an alloSCT from a MSD (39% vs. 30% and 24% in the FLAMSA-TBI and FLAMSA-CT groups, $p< 0.01$), and less likely to have received ATG (32% vs. 87% and 84%, $p< 0.01$). There were no significant differences in the distributions of Karnofsky performance status, cytogenetic risk, secondary AML or disease status at transplantation. Median follow-up was 50.2 months.

In univariate analysis, 2-year RI (54% [95% CI: 50-57]), LFS (30% [95% CI: 27-33]) and GRFS (21% [95% CI: 18-24]) were not significantly different between cohorts. Lower 2-year NRM was observed in the FLAMSA-CT group (7% vs. 16% in Bu/Cy, 19% in Cy/TBI and 18% in FLAMSA-TBI; $p=0.04$), as well as increased 2-year OS (50% vs. 33% in Bu/Cy, 34% in Cy/TBI and 36% in FLAMSA-TBI; $p=0.03$). These results were maintained in the multivariate analysis (HR for NRM: 0.41, $p=0.01$; HR for OS: 0.67, $p=0.01$; Bu/Cy as reference). Conditioning regimen had no impact on grade II-IV aGVHD (35% [95% CI: 32-38]) or 2-year extensive cGVHD (12% [95% CI: 10-15]). Additionally, adverse cytogenetics and second relapse status were associated with an increase in RI and lower OS in the multivariate model.

Conclusions: MAC or FLAMSA-TBI resulted in similar outcomes among patients with R/R AML with active disease at the time time of alloSCT. FLAMSA-CT was associated with reduced NRM, leading to an OS benefit as compared with MAC and FLAMSA-TBI.

Disclosure: Nothing to declare.

O054.

Total Body Irradiation/Fludarabine Versus Thiotepa/busulfan/fludarabine for Adults with Acute Lymphoblastic Leukemia Treated with Haploidentical HCT. A Study by Acute Leukemia Working Party of the EBMT

Sebastian Giebel[1], Myriam Labopin[2,3], Emanuele Angelucci[4], Mutlu Arat[5], Mahmoud Aljurf[6], Simona Sica[7], Jiri Pavlu[8], Gerard Socié[9], Paolo Bernasconi[10], Luigi Rigacci[11], Johanna Tischer[12], Antonio Risitano[13], Montserrat Rovira[14], Riccardo Saccardi[15], Pietro Pioltelli[16], Gwendolyn Van Gorkom[17], Antonin Vitek[18], Zinaida Peric[19], Arnon Nagler[20], Mohamad Mohty[3]

[1]Maria Sklodowska-Curie Institute, Gliwice, Poland, [2]EBMT Paris Study Office, Saint Antoine Hospital, Paris, France, [3]Saint Antoine Hospital, INSERM UMR 938, Sorbonne University, Paris, France, [4]IRCCS Ospedale Policlinico San Martino, Genova, Italy, [5]Nightingale Sisli Hospital, Istanbul, Turkey, [6]King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, [7]Universita Cattolica S. Cuore, Rome, Italy, [8]Imperial College, Hammersmith Hospital, London, United Kingdom, [9]Hopital St. Louis, Paris, France, [10]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [11]Ospedale S. Camillo-Forlanini, Rome, Italy, [12]Klinikum Grosshadern, Munich, Germany, [13]University of Napoli, Napoli, Italy, [14]IDIBAPS, Hospital Clinic, Institut Josep Carreras, Barcelona, Spain, [15]Università degli Studi di Firenze, Firenze, Italy, [16]Ospedale San Gerardo, Universita Milano-Biocca, Monza, Italy, [17]University Hospital Maastricht, Maastricht, Netherlands, [18]Institute of Hematology and Blood Transfusion, Prague, Czech Republic, [19]University of Zagreb, Zagreb, Croatia, [20]Chaim Sheba Medical Center, Tel-Hashomer, Israel

Background: The use of hematopoietic cell transplantation from haploidentical donors (haplo-HCT) for adults with acute lymphoblastic leukemia (ALL) is increasing. While immunosuppression based on post-transplant administration of cyclophosphamide (PT-Cy) is preferable in this setting, the choice of optimal myeloblative conditioning remains unclear.

Methods: The goal of this study was to compare efficacy and safety of two most popular regimens: fludarabine + total body irradiation at the dose of 10 Gy or more (FluTBI) and thiotepa (2 days, total dose 10 mg/kg) + iv. busulfan (3 days, total dose 9.6 mg/kg) + fludarabine (TBF).

This was a retrospective analysis based on data from the EBMT registry, including haplo-HCT with PT-Cy performed between 2010- and 2018. Patients with both Ph(+) and Ph(-) ALL, in all disease stages (CR1, CR>1, advanced disease) were eligible.

Results: 117 patients treated with FluTBI and 119 individuals treated with TBF were included in the analysis. The characteristics of both groups were comparable except for older age of patients treated with TBF (median 36 years) than FluTBI (31 years, $p = 0.04$).

In a univariate analysis the incidence of non-relapse mortality (NRM) at 2 years was increased for TBF compared to FluTBI (31% vs. 19.5%, $p = 0.03$). In contrast, there was a tendency to reduced incidence of relapse (RI) after TBF (27% vs. 35%, $p = 0.11$). As a consequence no significant differences could be demonstrated for the rates of leukemia-free survival (LFS) (42% vs. 46%, $p = 0.56$), overall survival (53% vs. 54%, $p = 0.61$) as well as GVHD-free and relapse-free survival (GRFS) (33% vs. 35%, $p = 0.81$). The incidences of both acute and chronic GVDH were also comparable. Infections and GVHD were the most frequent causes of NRM with similar proportions in both groups.

In a multivariate model the use of FluTBI was associated with reduced risk of NRM (HR=0.49, $p = 0.03$) but a trend to increased risk of relapse (HR=1.81, $p = 0.054$). The effects became stronger when the analysis was restricted to patients transplanted in CR (NRM: HR=0.34, $p = 0.009$; RI: HR=2.59, $p = 0.01$). No association of the type of conditioning with LFS, OS, GRFS and GVHD could be found. Among other factors included in the analysis the risk of treatment failure (either NRM or relapse; inverse LFS) was influenced by increasing recipient age (per 10 years, HR=1.28, $p = 0.01$), disease stage (CR1 as reference; CR>1, HR=1.62, $p = 0.047$; advanced, HR=2, $p = 0.02$) and Karnofsky performance score (≥90, HR=0.61, $p = 0.04$).

Conclusions: The use of FluTBI and TBF as myeloablative conditioning regimens results in similar LFS after haploHSCT with PT-Cy. However, as the profile of treatment failures differ, the choice of conditioning should be personalized. FluTBI may be preferable for patients with high risk of NRM while TBF should be considered for individuals with high risk of relapse. Prospective, randomized studies are warranted to verify our findings.

Disclosure: Nothing to declare.

O055.

Busulfan-Cyclophosphamide Versus Cyclophosphamide-Busulfan as Conditioning Regimen before Allogeneic Hematopoietic Cell Transplantation: A Prospective Randomized Trial

Claire Seydoux[1], Michael Medinger[1], Sabine Gerull[1], Joerg Halter[1], Dominik Heim[1], Yves Chalandon[2], Stavroula Masouridi Levrat[2], Urs Schanz[3], Gayathri Nair[3], Patrick Simon[4], Jakob Robert Passweg[1], Nathan Cantoni[5]

[1]*University Hospital of Basel, Basel, Switzerland*, [2]*University Hospital of Geneva, University of Geneva, Geneva, Switzerland*, [3]*University Hospital of Zurich, Zurich, Switzerland*, [4]*Basel University, Basel, Switzerland*, [5]*Kantonsspital Aarau, Aarau, Switzerland*

Background: Busulfan and cyclophosphamide (BuCy) is a frequently used myeloablative conditioning regimen for allogeneic hematopoietic cell transplantation (allo-HCT). Theoretical considerations and pharmacological data indicate that prior application of busulfan may trigger liver toxicity of subsequent cyclophosphamide. Reversing the order of application to cyclophosphamide-busulfan (CyBu) might be preferable, hypothesis supported by animal data and retrospective studies. The aim of this randomized clinical trial is to test the impact of the order of application of Bu and Cy before allo-HCT.

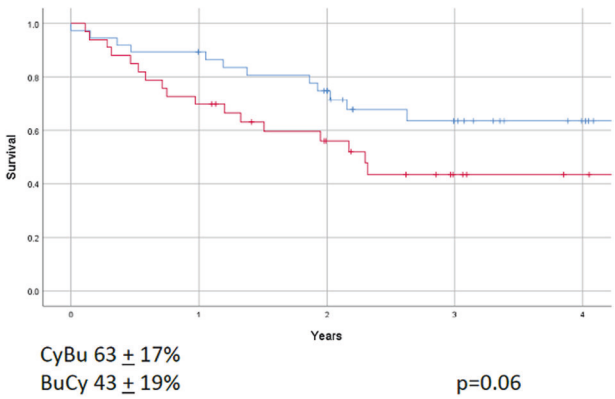
Methods: We performed a prospective multicenter (Basel, Geneva, Zurich) open label 1:1 randomized study exploring the order of drug application (BuCy versus CyBu). The primary endpoint was liver toxicity at day 30 after HCT. Additional endpoints were liver toxicity at day 100, incidence of veno-occlusive disease (VOD), relapse and overall survival at day 100. Survival analysis was by Kaplan-Meier estimator using the log-rank test and TRM and relapse by cumulative incidence function using Fine and Gray to test for differences. Inclusion goal was 72 patients to detect a difference of 35%.

Results: We analyzed 70 patients (2 screening failures) treated 2012 to 2017, with hematological malignancies (Table 1 for baseline characteristics), receiving HCT from HLA-matched siblings [34, 49%] or unrelated donors [36, 51%] after conditioning with BuCy or CyBu (33 vs 37 patients). Liver function measured as bilirubin, AST, ALT, GGT and AP were not different between groups before starting conditioning. In contrast, liver function was significantly different on day 30, with higher levels of AST (median 27 vs 22 IU/l, $p = 0.03$) and a frequency of VOD criteria ($\geq$1 of the following: hyperbilirubinemia, painful hepatomegaly or ascites) in 17 vs. 10 patients, ($p = 0.05$) in the BuCy vs. CyBu group. Overall survival at 4 years tended to be lower (43 $\pm$ 19% vs. 63 $\pm$ 17%; $p = 0.06$) and TRM to be higher (28 (15-52)% vs. 6 (2-22)%; $p = 0.049$), whereas relapse was similar (34 (21-55)% vs. 34 (22-55)%; $p = 0.79$) with BuCy compared to CyBu. Overt fatal VOD occurred in one patient in the BuCy group. Causes of death ($p = 0.32$), time to engraftment ($p = 0.21$) and acute graft-versus-host disease ($p = 0.40$) were similar in both groups.

Conclusions: This prospective RCT examined the order of busulfan and cyclophosphamide administration as part of myeloablative conditioning in allo-HCT patients and found some evidence of superiority of CyBu over BuCy. We show lower liver toxicity at day 30, lower TRM and a tendency of better (longterm) overall survival in patients receiving CyBu instead of BuCy.

	CyBu N = 37	BuCy N = 33	*p*-value
Age (median, range, yrs)	47 (21-62)	46 (20-65)	0.488
Male sex (*n*, %)	25 (68)	15 (46)	0.062
Disease : AML or ALL (*n*, %)	28 (76)	25 (76)	0.702
Disease : MDS/MPN or CML (*n*, %)	9 (24)	8 (24)	
Stage : CR1 or CP1 (*n*, %)	27 (73)	22 (67)	0.471
Stage : CR2 or untreated (*n*, %)	4 (11)	7 (21)	
Stage : no CR (*n*, %)	6 (16)	4 (12)	
GvHD Prophylaxis with ATG or T-depletion (*n*, %)	27 (73)	21 (64)	0.334
GvHD Prophylaxis with CyA or Tacrolimus +/- MTX or MMF (*n*, %)	10 (27)	12 (36)	

[Table 1. Patient baseline characteristics]



[Figure 1. Survival at 4 years]

Disclosure: Conflict of interest: None.
Fundings: Pierre Fabre SA

O056.

Rabbit Anti-Thymocyte Globulin (ATG) Exposure After EX VIVO T-Cell-Depleted Hematopoietic Cell Transplantation is Variable and Impacts Immune Reconstitution and Survival in Children and Young Adults

Madhavi Lakkaraja, Audrey Mauguen, Farid Boulad, Barbara Spitzer, Andromachi Scaradavou, Kevin Curran, Maria Cancio, Ichelle Roessel, Elizabeth Klein, Nancy Kernan, Richard O'Reilly, Susan Prockop, Jaap Jan Boelens

Memorial Sloan Kettering Cancer Center, New York, NY, United States

Background: Rabbit anti-thymocyte globulin (rATG) is used in allogeneic hematopoietic cell transplantation (HCT) to prevent graft versus host-disease (GvHD) and graft rejection. However, the level of rATG persisting in the post-HCT period is variable and its main toxicity is poor immune reconstitution. Poor immune reconstitution is associated with higher mortality: patients who reconstitute CD4+ early have lower non-relapse mortality (NRM) and higher overall survival (OS). Recently, a population pharmacokinetic pharmacodynamic rATG model identified optimal ATG exposure after HCT, in various T-replete HCT settings. However, no data is available in EX VIVO T-Cell Depleted (TCD) HCT. The goal of this study is to determine the optimal exposure of rATG in pediatric and young adult recipients of EX VIVO TCD HCT, allowing early CD4+ immune reconstitution (CD4+IR).

Methods: Pediatric and young adult patients receiving their first allogeneic EX VIVO TCD HCT at Memorial Sloan Kettering Cancer Center (2008 - 2018) were included. No restrictions were applied in terms of donor source, indication, conditioning, and age. Only patients receiving rATG (alone) or no ATG were included in analyses. CD4+IR was measured every 2-4 weeks. We estimated the exposure of rATG, beyond Day 0 as area under the curve (AUC) (mg*d/L) using an established pharmacokinetic (PK) model (Admiraal et al., Lancet Hematology 2017). Outcomes of interest were CD4+IR, defined as CD4+ levels above 50/uL at two consecutive measures within 100 days, OS, and NRM. We evaluated the association between rATG-exposures and CD4+IR using a smoothed exposure to define the optimal rATG exposure after HCT. Cox proportional hazard models, and multi-state competing risk models were used for analyses.

Results: 223 patients underwent a TCD HCT of whom 185 were included in the analysis because they received either rATG ($n = 164$) or no rATG ($n = 21$). 119 (64%) had malignant and 66 (36%) had non-malignant indications for HCT. Median age at transplant was 11 (0.2 - 44) years, 74 (40%) were females. In patients who received rATG, median rATG exposure after HCT was 34.4mg*d/L (range 0.6 -104) mg*d/L. A lower post-HCT AUC (optimum < 20mg*d/L) was associated with higher probability of CD4+IR ($p< 0.0001$); increased OS ($p = 0.006$); and lower NRM ($p = 0.005$). Time to CD4+IR varied depending on the ATG exposure ($p< 0.0001$). There was a significant difference in NRM according to the ATG exposure ($p = 0.04$), and in NRM according to the 100-day CD4+IR status ($p < 0.0001$). In multivariate analyses, patients with < 20mg*d/L post-HCT rATG exposure had a lower risk of NRM (HR 0.33, 95% CI 0.12, 0.92, $p = 0.005$) and higher OS (HR= 0.33, 95% CI 0.15, 0.73, $p = 0.002$). Other multivariate predictors for lower NRM were gender and CMV mismatching.

Conclusions: In patients who received an EX VIVO TCD graft, rATG exposure after stem cell infusion plays a crucial role in probability of CD4+IR and subsequent survival, mainly by impacting NRM. Individualizing ATG dosing to target a low post-HCT ATG exposure may improve early CD4+ reconstitution, decrease NRM, and improve overall survival.

Clinical Trial Registry: None.

Disclosure: Madhavi Lakkaraja, MD, MPH: None

Audrey Mauguen, PhD: None

Farid Boulad, MD: None

Barbara Spitzer, MD: None

Andromachi Scaradavou, MD: None

Kevin J. Curran, MD: Research funding: Novartis and Juno therapeutics, Consulting/Advisory Board: Novartis, Mesoblast

Maria I. Cancio, MD: None

Ichelle Roessel: None

Elizabeth Klein: None

Nancy A. Kernan, MD: Nancy A. Kernan, MD: Conflicts. None in relationship to abstract, Equity in Amgen, Merck, Johnson and Johnson, Pfizer.

Richard O'Reilly, MD: Received royalties following licensure of the EBV-specific T-cell bank by Atara Biotherapeutics and has subsequently received research support and consultant fees from Atara Biotherapeutics.

Susan Prockop, MD: Atara Biotherapeutics, Mesoblast - Other support for industry sponsored trials

Jaap Jan Boelens, MD, PhD:Consulting Takeda, Bluebird Bio, Omeros, Advanced clinical, Magenta, Bluerock.

O057.

A Retrospective Comparative Study of Beam vs Feam vs Team Conditioning Regimens in Lymphoma Patients Undergoing Autologous Stem Cell Transplant

Francesco Marchesi[1], Saveria Capria[2], Mariangela Pedata[3], Irene Terrenato[1], Laura Ballotta[2], Cira Riccardi[3], Elena Papa[1], Costantino Riemma[2], Silvia Trisolini[2], Maria Celentano[3], Felicetto Ferrara[3], Andrea Mengarelli[1], Alessandra Picardi[3]

[1]IRCCS Regina Elena National Cancer Institute, Rome, Italy, [2]University of Rome Sapienza, Rome, Italy, [3]AORN Cardarelli, Naples, Italy

Background: BEAM is the standard conditioning for lymphoma patients undergoing ASCT. However, in Italy, BCNU is often substituted by Fotemustine (FEAM) or Thiotepa (TEAM) due to difficult supplying. Our aim was to performing a retrospective comparative study of BEAM, FEAM and TEAM conditioning regimens in lymphoma patients undergoing ASCT.

Methods: From Jan-2007 to Jan-2017, 414 lymphoma patients undergoing ASCT in three Italian Institutions (Regina Elena National Cancer Institute - Rome; Sapienza University - Rome; Cardarelli Hospital - Naples) were reviewed. Selection for BEAM (200), FEAM (162) or TEAM (52) was based on BCNU availability. Median age was 47 years (15-69). ASCT was performed for aggressive B-NHL in 240 cases (58%), HL in 124 (30%), and T-NHL in the remaining 50 cases (12%) and after first line in 75 cases (18%), after first salvage treatment in 244 (59%) and in more advanced phase in the remaining 95 (23%). Pre-ASCT response status was CR in 61% (first CR 14%, ≥ second CR 47%), PR in 35% and refractory disease in 4% of cases. The three groups of patients were well-balanced for all analyzed parameters, expect for disease status at transplant due to an higher incidence of patients with uncontrolled disease (PR and refractory) in TEAM group (BEAM: 33%; FEAM: 38%; TEAM: 63%; P=0,001).

Results: Overall, we observed a significant higher incidence of day-100 post-transplant CR for BEAM group compared with both FEAM (CR: 87% vs 75%; P=0,005) and TEAM (CR: 87% vs 54%; P< 0,001). The 2y-PFS of BEAM and FEAM groups was significantly better than that of TEAM group (BEAM 76% vs FEAM 75% vs TEAM 52%; P=0,001), whereas no significant differences in terms of 2y-OS were reported (BEAM 87% vs FEAM 85% vs TEAM 83%; P=0,57). At multivariate analysis with Cox regression model, TEAM confirmed its inferiority in terms of PFS compared with BEAM [HR: 0,52 (95%CI: 0,32-0,85); P=0,009] but not with FEAM [HR: 0,71 (95% CI: 0,43-1,19); P=0,197]. In order to avoid the potential bias due to the higher incidence of patients with uncontrolled disease in TEAM group, we decided to perform a separate analysis on patients with uncontrolled disease at the transplant moment (PR and refractory: BEAM n = 67, FEAM n = 62, TEAM n = 33). Our results confirmed that TEAM regimen was associated to a significant worse 2y-PFS compared with BEAM (BEAM 68% vs TEAM 45%; P=0,008), but not with FEAM (FEAM 61% vs TEAM 45%; P=0,393). Finally, in our study a lower rate of grade 3-4 oral mucositis was reported in the TEAM group, whereas infectious complications, other non-hematologic toxicities and TRM were similar among the three groups of patients.

Conclusions: Despite the limitations due to the non-randomized nature of this study, in our experience TEAM regimen seems to be associated to a worse clinical outcome in terms of PFS but not OS both in overall patient population and in patients with pre-transplant uncontrolled disease. Further studies are warrant to confirm these results.

Clinical Trial Registry: NA

Disclosure: Nothing to declare.

O058.

Reduced Intensity Versus Myeloablative Conditioning Allogeneic Hematopoietic Cell Transplantation for Patients <60 with Acute Lymphoblastic Leukemia: A~ Multi-Center Canadian Experience

Ivan Pasic[1], Kristjan Paulson[2], Graham Dozois[1], Kirk R. Schultz[3], Rajat Kumar[1]

[1]Princess Margaret Cancer Centre, Toronto, Canada, [2]CancerCare Manitoba, Winnipeg, Canada, [3]University of British Columbia, Vancouver, Canada

Background: Allogeneic hematopoietic cell transplantation (HCT) is potentially curative in patients with high-risk acute lymphoblastic leukemia (ALL). However, the role of conditioning intensity to transplant outcomes remains unclear. Various groups have shown similar transplant outcomes using either myeloablative conditioning (MAC) or reduced intensity conditioning (RIC), but in most of these studies young patients received MAC while older and/or less fit patients received RIC. Until recently, at Princess Margaret Hospital Cancer Centre (PMCC), majority of transplants for ALL were performed using RIC, regardless of patient age and comorbidities. Therefore, we compared outcomes between a group of patients <60 who received RIC at PMCC with those of patients with similar

age and performance status who received MAC at other Canadian transplant centres.

Methods: This was a retrospective and multi-centre study involving PMCC and other Canadian centres reporting to Cell Therapy Transplant Canada (CTTC): the PMCC cohort consisted of 27 ALL patients who underwent HCT with RIC while the CTTC cohort included 226 ALL patients who received MAC. All patients received HCT between 2007 and 2018. Overall survival (OS) was calculated using Kaplan-Meier analysis and Cox proportional hazards regression. Cumulative incidence of relapse (CIR) and non-relapse mortality (NRM) were calculated using competing risk regression (Fine and Gray method).

Results: Patient demographics: males 139 (55%); median age 40y (range 18-59); median follow up 13 months (0.4-158). Median hematopoietic cell transplant comorbidity index (HCT-CI) and Karnofsky Performance Scale (KPS) scores were 2 (0-6) and 90% (60-100%), respectively. Most patients had Philadelphia chromosome (Ph)-negative B-cell ALL (52%) followed by Ph+ B-ALL (31%). Majority had a matched unrelated donor (MUD, 53%) followed by matched related donor (MRD, 45%). Peripheral blood stem cell (PBSC) grafts was used in 87% and T-cell depletion (TCD) was used in 14% of all cases.

PMCC and CTCC cohorts were well matched in terms of age (47 (22-59) vs 40 (18-59), $P=0.10$), gender (59% vs 54% male, $P=0.69$), follow-up time (12 (0.5-130) vs 14 (0.4-158) months, $P=0.35$), graft source (96% vs 85% PBSC, $P=0.49$), HCT-CI (2 (0-6) vs 2 (0-6), $P=0.12$) and KPS score (90% (70%-100%) vs 90% (60%-100%), $P=0.50$). Compared to CTTC cohort, PMCC cohort had more patients with Ph-positive B-cell ALL (48% vs 29%, $P=4.63 \times 10^{-3}$), fewer patents who received graft from a MRD (30% vs 47%, $P=1.02\times10^{-6}$) and more patients who received TCD (82% vs 5%, $P=1.60\times10^{-18}$).

At 2-y, the OS, CIR and TRM were 0.59 (95% CI 0.52-0.66), 0.19 (0.14-0.25) and 0.26 (0.20-0.32), respectively for the entire cohort. Compared to CTTC patients, PMCC patients had an inferior 2-y OS: 0.29 (0.11-0.29) vs 0.63 (0.56-0.70), hazard ratio (HR)=2.10 (1.23-3.55), $P=5.90\times10^{-3}$. Similarly, there was an increase in TRM and a trend toward increased risk of relapse at 2-y among those transplanted at PMCC: 0.41 (0.22-0.60) vs 0.24 (0.18-0.30), HR=2.00 (1.05-3.81), $P=0.04$ and 0.36 (0.17-0.56) versus 0.17 (0.12-0.22), HR=1.72 (0.82-3.62), $P=0.15$, respectively.

Conclusions: In fit patients <60 with ALL, the use of RIC with TCD is associated with inferior transplant outcomes compared to MAC with no TCD.

Clinical Trial Registry: N/A

Disclosure: Nothing to declare.

Experimental stem cell transplantation

O059.

Low-Dose Decitabine Improves Refractory Prolonged Isolated Thrombocytopenia After Hematopoietic Cell Transplantation: A Randomized Multicenter Clinical Trial

Jia Chen[1,2,3], Yaqiong Tang[1,2,3], Qifa Liu[4], Tiantian Chu[1,2,3], Jianying Liang[1,2,3], Xuefeng He[1,2,3], Feng Chen[1,2,3], Weiyang Li[1,2,3], Ting Yang[5,6], Xiao Ma[1,2,3], Xiaojin Wu[1,2,3], Shaoyan Hu[7], Xingyu Cao[8], Xiaohui Hu[1,2,3], Jiong Hu[9], Yi Fan[1,2,3], Yuejun Liu[1,2,3], Chengsen Cai[1,2,3], Meng Zhou[1,2,3], Changgeng Ruan[1,2,3], Yue Han[1,2,3], Depei Wu[1,2,3]

[1]The First Affiliated Hospital of Soochow University, Suzhou, China, [2]Key Laboratory of Thrombosis and Hemostasis of Ministry of Health, Suzhou, China, [3]Institute of Blood and Marrow Transplantation, Suzhou, China, [4]Nanfang Hospital, Southern Medical University, Guangzhou, China, [5]Fujian Institute of Hematology, Fuzhou, China, [6]Fujian Medical University, Union Hospital, Fuzhou, China, [7]Children's Hospital of Soochow University, Suzhou, China, [8]Hebei Yanda Lu Daopei Hospital, Langfang, China, [9]Rui Jin Hospital, Shanghai Jiao Tong University, Shanghai, China

Background: Refractory prolonged isolated thrombocytopenia (RPIT) is an intractable complication after allogeneic hematopoietic cell transplantation (HCT) which often leads to a poor prognosis. Existing treatment options result in limited response, and new approach for this setting is demanded. We have conducted a randomized trial to validate the efficacy and safety of low-dose decitabine in HCT-RPIT patients, and we have further explored the underlying mechanisms.

Methods: This prospective, open-label, three-arm clinical trial was conducted in 6 transplant centers between October 2015 to April 2019. Patients with platelet count $<30 \times 10^9$/L for more than 60 days post-HCT without identified causes, and had no response to conventional treatment were enrolled. Patients were randomly allocated to receive one of three interventions: decitabine 15 mg/m^2 daily intravenously for consecutive 3 days (day 1 to day 3), combined with recombinant human thrombopoietin (rhTPO) 15000 U daily subcutaneously beginning on day 4 and continuing until the response was achieved or the time of initial evaluation; Arm B: decitabine 15 mg/m^2 daily intravenously for consecutive 3 days alone; Arm C: conventional therapies with recommended options including rhTPO,

eltrombopag, immunoglobulin, rituximab, interleukin-11 and glucocorticoids, alone or in combination. The primary endpoint was an increased platelet count. Secondary endpoints included megakaryocyte counts 4 weeks after treatment and the survival during an additional follow-up of 24 weeks.

The protocol was approved by the institutional review board at each participating center. All the participants provided written informed consent. The study was registered at ClinicalTrials.gov (NCT02487563).

Results: A total of 97 patients meeting the inclusion criteria were enrolled into this study. These patients were randomly allocated into Arm A (N = 32), Arm B (N = 33) and Arm C (N = 32). Among the evaluable 91 patients, the response rates were 66.7% (20 patients), 73.3% (22 patients) and 19.4% (6 patients), respectively ($P < .001$). The response rate of Arm A and Arm B were not different ($P = .778$). The median duration of response for these responding patients was 25 (2-26) weeks, 24 (1-26) weeks and 25 (3-25) weeks in Arms A, B and C, respectively ($P = .423$).

At the end of 28 weeks after treatment, the patients' survival was 85.9% for Arm A, 83.9% for Arm B and 61.3% for Arm C (P = .066). With a median follow-up of 11 months, the estimated 1-year survival of either Arm A (64.4 ± 9.1%) or Arm B (73.4 ± 8.8%) was superior to Arm C (41.0 ± 9.8%) ($P = .025$). Decitabine treatment (Arm A + B) was associated with significantly longer 1-year survival (68.2 ± 6.4% versus 41.0 ± 9.8%%, P = .008).

Both megakaryocyte count ($P < .001$) and megakaryocyte polyploidy ($P = .002$) recovered in patients in Arms A + B compared to Arm C. Endothelial cells as well as cytokines relating to migration and endothelial cell damage were improved in patients responding to decitabine.

Conclusions: Decitabine effectively facilitated platelet recovery in HCT-RPIT patients, presumably by promoting the repair and reconstitution of megakaryocytes and marrow endothelial cells.

Clinical Trial Registry: NCT02487563

Disclosure: Nothing to declare.

Experimental transplantation

O060.

Successful and Safe Treatment of Intestinal Graft-Versus-Host Disease (GVHD) with Pooled-Donor Full Ecosystem Microbiota Biotherapeutics

Florent Malard[1], Faezeh Legrand[2], Jerome Cornillon[3], Amandine Le Bourgeois[4], Jean-Baptiste Mear[5], Deborah Desmier[6], Michael Loschi[7], Emilie Plantamura[8], Ronald Carter[8], Thomas Cluzeau[7], Natacha Maillard[6], Thierry Lamy de la Chapelle[5], Patrice Chevallier[4], Denis Guyotat[3], Didier Blaise[2], Mohamad Mohty[1]

[1]Hôpital Saint-Antoine, Paris, France, [2]Institut Paoli Calmettes, Marseille, France, [3]CHU St Etienne, Paris, France, [4]CHU de Nantes, Nantes, France, [5]CHU de Rennes, Rennes, France, [6]CHU de Poitiers, Poitiers, France, [7]CHU de Nice, Nice, France, [8]MaaT Pharma, Lyon, France

Background: Intestinal Graft-versus-Host Disease (GvHD), following allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT), comes with a high mortality rate and a reduced life-expectancy. In this context, failure to respond to steroid therapy is associated with an absence of further therapeutic options, and is an unmet medical need. With the aim of restoring microbiome functions, Fecal Microbiota Transfer (FMT) proved to be a promising treatment modality in this challenging clinical situation, with recent studies reporting favorable results in steroid refractory-acute GVHD (SR-aGvHD) patients. Here we report on the use of the next generation FMT product"MaaT013", a standardized, pooled-donor, high-richness microbiota biotherapeutic, used to treat 21 patients with intestinal-predominant aGvHD.

Methods: 11 allo-HSCT recipients with steroid-dependent or steroid-refractory gastrointestinal GvHD (classical aGVHD $n = 5$, late-onset aGVHD $n = 3$; aGvHD with overlap syndrome $n = 3$) were treated with the MaaT013 biotherapeutic as part of a compassionate use program. These patients had previously received and failed 1 to 5 lines (median 2) of GvHD systemic treatments. MaaT013 biotherapeutics were supplied as a pharmaceutical preparation to hospitals by the developer, "MaaT Pharma". Each patient received 1 to 3 doses (median: 3; total doses administered: 55) of MaaT013, in a 150 mL bag, by enema ($n = 20$) or nasogastric tube ($n = 1$). GvHD response was evaluated 7 days after each administration and 28 days after the first dose.

Prepared under Good Manufacturing Practices, MaaT013 biotherapeutics are characterized by a highly consistent richness of 455 +/− 3% Operational Taxonomic Units and an inverse Simpson index greater than 20. Batch release specifications are based on potency (viability), identity (diversity), and purity (microbiological safety testing and proportion of proinflammatory species), ensuring the desired consistency between batches.

Results: We observed an overall response rate of 82% (9/11) at day+28 after first dosing, including 5 Complete Responses (CR), 2 Very Good Partial Response (VGPR), and 2 Partial Responses (PR). Considering the best GI response achieved, all (11/11) patients experienced at least a PR, with 5 CRs, 4 VGPRs and 2 PRs. Among the 11 treated

patients, 7 were still alive at last follow-up (median 197 days; [range, 49-413]) Among the 5 patients with CR, all were still alive at last follow-up and were able to taper or stop steroids and immunosuppressants. Only one patient presented GI symptoms recurrence at 3 months. Of note, molecular relapse of hematologic malignancy was observed in another.

The safety of the MaaT013 microbiota biotherapeutic was satisfactory in all patients. One patient developed a possibly related sepsis one day after the third dosing. In this case, no pathogen was identified in blood cultures, and the patient recovered after a course of antibiotics.

Conclusions: We report for the first time the treatment of 11 patients with steroid-dependent or steroid-refractory intestinal aGvHD using a full ecosystem, standardized, pooled-donor, high-richness biotherapeutic. The overall response rate was 82% with the off-the-shelf MaaT013 product, shown to be safe and effective in these immunocompromised patients with severe conditions, warranting further exploration of the full ecosystem microbiota restoration approach.

Disclosure: FM reports lecture honoraria from Therakos/Mallinckrodt, Janssen, Keocyte, Sanofi, JAZZ pharmaceutical and Astellas, all outside the submitted work. EP and RC reports employment from Meat Pharma. MM reports grants and lecture honoraria from Janssen, Sanofi, and JAZZ pharmaceutical, lecture honoraria from Celgene, Amgen, BMS, Takeda, and Pfizer, grants from Roche, all outside the submitted work.

The other authors declare no competing financial interests.

Gene Therapy

O061.

Clinical Outcomes Following Autologous Hematopoietic Stem Cell Transplantation with Lentiglobin Gene Therapy in the Phase 3 Northstar-2 and Northstar-3 Studies for Transfusion-Dependent β-Thalassemia

Franco Locatelli[1], Janet L. Kwiatkowski[2], Alexis A. Thompson[3], Evangelia Yannaki[4], Andreas E. Kulozik[5], Martin G. Sauer[6], John B. Porter[7], Isabelle Thuret[8], Suradej Hongeng[9], Ashutosh Lal[10], Adrian J. Thrasher[11], Heidi Elliot[12], Ge Tao[12], Weijian Liu[12], Richard A. Colvin[12], Mark C. Walters[10]

[1]IRCCS Bambino Gesù Children's Hospital, Rome, Italy, [2]Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, United States, [3]Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University, Chicago, IL, United States, [4]George Papanikolaou Hospital, Thessaloniki, Greece, [5]University of Heidelberg, Heidelberg, Germany, [6]Medizinische Hochschule Hannover, Hannover, Germany, [7]University College London Hospitals, London, United Kingdom, [8]Hôpital de la Timone, Marseille, France, [9]Mahidol University, Ramathibodi Hospital, Bangkok, Thailand, [10]UCSF Benioff Children's Hospital, Oakland, CA, United States, [11]UCL Great Ormond Street Institute of Child Health, London, United Kingdom, [12]Bluebird Bio, Inc., Cambridge, MA, United States

Background: In a phase 1/2 study of LentiGlobin gene therapy for β-thalassemia (autologous CD34+ cells encoding $\beta^{A\text{-}T87Q}$-globin gene) 8/10 patients with transfusion-dependent β-thalassemia (TDT) and non-β^0/β^0 genotypes and 3/8 patients with β^0/β^0 genotypes achieved transfusion independence. With up to 5-year follow-up, integration was polyclonal and no oncogenesis was recorded. Herein, we present interim results of two phase 3 studies, Northstar-2 (NCT02906202; non-β^0/β^0 genotypes) and Northstar-3 (NCT03207009; β^0/β^0, $\beta^0/\beta^{+\ IVS\text{-}I\text{-}110}$ or $\beta^{+\ IVS\text{-}I\text{-}110}/\beta^{+\ IVS\text{-}I\text{-}110}$ genotypes).

Methods: CD34+ hematopoietic stem cells (HSCs) were collected via mobilization/apheresis and transduced with BB305 lentiviral vector using a refined manufacturing process compared to the phase 1/2 study. Patients were infused with transduced cells following pharmacokinetic-adjusted, single-agent busulfan myeloablation (target AUC: 3800-4500 [daily], 950-1125 [Q6H] μM*min). Statistics are presented as median (min-max).

Results: As of 12 June 2019 and 30 September 2019, 34 patients were treated in Northstar-2 and Northstar-3 with a follow-up of 11.6 (0.9-26.3) and 8.8 (2.5-20.0) months, respectively. Twenty-four patients were ≥12 years of age. Treatment characteristics are shown in Table 1.

Post-infusion non-hematologic grade ≥3 adverse events (AEs) in ≥3 patients in either study were stomatitis ($n = 17$), febrile neutropenia ($n = 14$), pyrexia ($n = 3$), epistaxis ($n = 3$), and liver veno-occlusive disease (VOD; $n = 3$). VOD prophylaxis was used in 82% (28/34) of patients (19, ursodiol; 8, ursodiol and defibrotide; 1, defibrotide). Drug product-related AEs were abdominal pain ($n = 3$), thrombocytopenia ($n = 3$), leukopenia ($n = 1$), neutropenia ($n = 1$), and pain in extremity ($n = 1$). All patients are alive and all samples showed a polyclonal vector integration profile.

In Northstar-2, 18/20 patients with >5 months follow-up have not received a transfusion in >3.5 months. The primary endpoint of transfusion independence (TI, weighted average Hb of ≥9 g/dL without RBC transfusions for ≥12 months) was achieved by 9/10 evaluable patients for an ongoing

duration of 15.2 (12.1-21.3) months. Weighted average Hb during TI was 12.2 (11.4-12.8) g/dL. HbA^{T87Q} levels were 8.7, 9.3, 9.4 and 8.8 g/dL at Months 6 ($n = 17$), 12 ($n = 11$), 18 ($n = 8$) and 24 ($n = 3$), respectively. Myeloid: erythroid ratios in patients who achieved TI were at 1:1.6-1.9-1 at Month 12 ($n = 9$) and 1:1.1 and 1:1.3 at Month 24 ($n = 2$) compared to 1:2.1-1:7.3 at baseline, indicating improved erythropoiesis.

In Northstar-3, 9/11 patients followed for >6 months have stopped transfusions for ≥3 months. At Months 6 and 12, total unsupported Hb was 10.2 (8.5-13.2) g/dL ($n = 10$) and 13.8 (10.3-14.0) g/dL ($n = 3$) while HbA^{T87Q} was 8.3 (0-12.0) g/dL ($n = 11$) and 11.1 (8.8-12.6) g/dL ($n = 3$), respectively. Two evaluable patients achieved transfusion independence.

Conclusions: Following treatment with LentiGlobin gene therapy for β-thalassemia in Northstar-2 and Northstar-3, 18/20 patients with non-β^0/β^0 genotypes and 9/11 patients with a β^0/β^0 genotype or an IVS-I-110 mutation with ≥6 months follow-up have stopped transfusions. In Northstar-2, 90% of patients achieved the primary endpoint of TI. The safety profile is consistent with single-agent busulfan myeloablation.

	Estimated average daily busulfan AUC (μM*min)	Neutrophil engraftment (days)	Platelet engraftment (days)	Hospitalization duration (days)
Northstar-2 ($N = 21$)	4428 (3709-8947)	23.0 (13.0-32.0)	46.0 (20.0-94.0)	44 (30-92)
Northstar-3 ($N = 13$)	4488 (3824-9087)	26 (14-38)	41 (21-64)	38 (29-68)

[Table 1: Treatment Characteristics (median [mix-max])]

Clinical Trial Registry: Northstar-2: NCT02906202; Northstar-3: NCT03207009

Disclosure: Franco Locatelli: Honoraria for Amgen, Bellicum, Miltenyi; Membership on Board of Directors/advisory committees for Amgen, Novartis, Bellicum; Consultancy for bluebird bio, Inc., Novartis. Janet Kwiatkowski: Consultancy for bluebird bio, Inc., Agios, Celgene, Imara; Research Funding for bluebird bio, Inc., Apopharma, Novartis, Terumo, Sangamo.

Alexis Thompson: Consultancy for bluebird bio, Inc., Celgene, Novartis; Research Funding for bluebird bio, Inc., Celgene, Novartis, Baxalta, Biomarin. Andreas Kulozik: Consultancy and Honoraria for bluebird bio, Inc., Novartis; Membership on Board of Directors/advisory committees for bluebird bio, Inc., Novartis. John Porter: Consultancy for Celgene, Agios, bluebird bio, Inc.; Honoraria for Celgene, Agios, bluebird bio, Inc., Protagonism, Vifor, La Jolla, Silence therapeutics. Isabelle Thuret: Investigator for bluebird bio, Inc., Novartis, Celgene, Apopharma. Ashutosh Lal: Research Funding for bluebird bio, Inc., Celgene, Insight Magnetics, La Jolla, Novartis, Protagonist, Terumo; Membership on Board of Directors/advisory committees for Celgene, Protagonist. Adrian Thrasher: Consultancy and Membership on Board of Directors/advisory committees for Orchard Therapeutics, Generation Bio, Rocket Pharmaceuticals; Equity Ownership for Orchard Therapeutics, Generation Bio. Other Membership for 4BIOCapital. Mark Walters: Consultancy for Editas, Trucode, AllCells, Inc. Heidi Elliot, Ge Tao, Weijian Liu, Richard Colvin: Employment/Equity Ownership for bluebird bio, Inc. Evangelia Yannaki, Martin Sauer, Suradej Hongeng: Nothing to declare.

O062.

Lentiviral Hematopoietic Stem and Progenitor Cell Gene Therapy (HSPC-GT) for Metachromatic Leukodystrophy (MLD): Clinical Outcomes from 33 Patients

Valeria Calbi[1,2], Francesca Fumagalli[1,2], Maria Sessa[1,3], Alberto Zambon[2], Cristina Baldoli[2], Federica Cugnata[4], Paola M. V. Rancoita[4], Serena Acquati[1], Daniela Redaelli[1], Fabiola De Mattia[1], Elena Fratini[2], Francesca Ferrua[1,2], Federica Barzaghi[1,2], Maria Pia Cicalese[1,2], Maddalena Migliavacca[1,2], Francesca Tucci[1,2], Vera Gallo[1,2], Francesca Ciotti[2], Maddalena Fraschini[2], Marina Sarzana[2], Paolo Silvani[2], Ivana Spiga[5], Marcella Facchini[1], Sara Locatelli[1], Gigliola Antonioli[1,2], Stefano Zancan[1], Andrea Calabria[1], Eugenio Montini[1], Giada Farinelli[1], Francesco Morena[6], Jesus Segovia[7], Laetitia C. Schwab[7], Gerald Downey[7], John Sharpe[7], Michela Gabaldo[1], Sabata Martino[6], Clelia Di Serio[4], Fabio Ciceri[2,4], Massimo Filippi[2,4], Maria Grazia Natali Sora[2], Maria Ester Bernardo[1,2], Luigi Naldini[1,4], Alessandra Biffi[8,9], Alessandro Aiuti[1,2,4]

[1]San Raffaele Telethon Institute for Gene Therapy, Milan, Italy, [2]IRCCS San Raffaele Scientific Institute, Milan, Italy, [3]ASST Papa Giovanni XXIII, Bergamo, Italy, [4]Vita-Salute San Raffaele University, Milan, Italy, [5]IRCCS San Raffaele Hospital, Milan, Italy, [6]University of Perugia, Perugia, Italy, [7]Orchard Therapeutics, London, United Kingdom, [8]Padua University and Hospital, Padua, Italy, [9]Dana Farber, Boston Children's Cancer and Blood Disorders Center, Boston, MA, United States

Background: Metachromatic leukodystrophy (MLD), a fatal demyelinating lysosomal storage disease resulting from arylsulfatase A (ARSA) deficiency, currently has no

effective treatment. We present safety and efficacy results in 33 early-onset patients (18 late infantile [LI]; 15 early juvenile [EJ]) treated with an experimental hematopoietic stem and progenitor cell (HSPC)-based gene therapy ("OTL-200"), with follow-up from 1 month to 7.5 years (median: 2.99 years, range 0.09 to 7.51).

Methods: Twenty-nine patients were treated with a fresh formulation of OTL-200 ("OTL-200-f"), and four were treated with a cryopreserved formulation ("OTL-200-c"). Autologous $CD34^+$ cells were transduced ex vivo with a lentiviral vector encoding for the functional human ARSA gene. Following busulfan conditioning, the drug product was infused intravenously. Key endpoints included reconstitution of ARSA activity, safety and tolerability of OTL-200, and effects on gross motor function and cognitive development, compared to a natural history (NH) cohort.

Results: Of 33 patients treated, 30 are alive (2 died from disease progression, 1 from cerebral stroke). There was no treatment-related mortality, no malignancies, no abnormal clonal expansion, and no evidence of replication-competent lentiviruses. All patients achieved hematological recovery and showed stable engraftment of gene-corrected cells. Restoration of ARSA activity was observed in the hematopoietic system and cerebrospinal fluid. Preliminary data from patients treated with the cryopreserved formulation show engraftment and ARSA activity comparable to those from patients treated with the fresh formulation. The majority of pre-symptomatic patients displayed long-term stabilization of motor function, many within normal range. Severe motor impairment-free survival was significantly longer in OTL-200-f treated patients versus a NH cohort (LI, $p < 0.001$; EJ $p = 0.016$) and most treated patients showed normal cognitive development.

Conclusions: Data from 33 early-onset MLD patients with ≤7.5 years follow-up show OTL-200 is safe, well tolerated, and effective in modifying the disease course of early-onset MLD patients.

Clinical Trial Registry: Trial 1, OTL-200-f: Gene Therapy for Metachromatic Leukodystrophy (MLD). NCT01560182, https://clinicaltrials.gov/ct2/show/NCT01560182; EudraCT # 2009-017349-77.

Trial 2: OTL-200-c: A Safety and Efficacy Study of Cryopreserved OTL-200 for Treatment of Metachromatic Leukodystrophy (MLD); NCT03392987, https://clinicaltrials.gov/ct2/show/NCT03392987.

Disclosure: Francesca, Fumagalli; Valeria, Calbi; Maria, Sessa; Alberto, Zambon; Cristina, Baldoli; Federica, Cugnata; Paola, Rancoita; Serena, Acquati; Daniela, Redaelli; Francesca, Ferrua; Federica, Barzaghi; MariaPia, Cicalese; Maddalena, Migliavacca; Francesca, Tucci; Vera, Gallo; Francesca, Ciotti; Maddalena, Fraschini; Marina, Sarzana; Marcella, Facchini; Sara, Locatelli; Gigliola, Antonioli; Stefano, Zancan; Sabata, Martino; Clelia, Di Serio; Eugenio, Montini; MariaGrazia, Natali-Sora; MariaEster, Bernardo, and Luigi, Naldini report participation in the clinical trial sponsored by Orchard Therapeutics (OTL) and assisting in the design of and/or participating in clinical studies using product manufactured by OTL and did not receive any financial support from OTL.

Luigi, Naldini also reports holding a patent for a product referred to in the presentation or marketed by OTL or in receipt of royalties.

Alessandra, Biffi reports: scientific advisory board member, OTL; Founder, board of directors' member, scientific advisor, Altheia Science.

Alessandro, Aiuti reports current or recent participation in clinical trials sponsored by OTL.

Paolo, Silvani; Ivana, Spiga; Andrea, Calabria; Giada, Farinelli; Francesco, Morena; Michela, Gabaldo; Fabiola, De Mattia, and Fabio, Ciceri have nothing to declare.

Laetitia, Schwab; Gerald, Downey; John, Sharpe; and Jesus, Segovia are employees and hold stock in OTL (trial sponsor).

Massimo, Filippi is Editor-in-Chief of the Journal of Neurology; received compensation for consulting services and/or speaking activities from Bayer, Biogen Idec, Merck-Serono, Novartis, Roche, Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Teva Pharmaceutical Industries, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and Fondazione Italiana di Ricerca per la SLA.

O063.

A Single Dose of Short Half-Life CD117 Antibody Drug Conjugate Enables Hematopoietic Stem Cell Based Gene Therapy in Nonhuman Primates

Anthony Boitano[1], John Tisdale[2], Naoya Uchida[2], Robert Donahue[2], Bradley Pearse[1], Sean McDonough[1], Jennifer Proctor[1], Allen Krouse[2], Nathaniel Linde[2], Aylin Bonifacino[2], Rajiv Panwar[1], Ganapathy Sarma[1], Lena Kien[1], Kellie Latimer[1], Junia Dushime[1], Sharon Hyzy[1], Melissa Brooks[1], Rahul Palchaudhuri[1], Qing Li[1], Pranoti Sawant[1], Charlotte McDonagh[1], Michael Cooke[1]

[1]Magenta Therapeutics, Cambridge, MA, United States, [2]National Institutes of Health, Bethesda, MD, United States

Background: Autologous hematopoietic stem cell transplantation (Auto-HSCT) with gene-modification represents a potential cure for multiple genetic diseases, but its broad

curative potential, is limited because of morbidity/mortality from cytotoxic chemotherapy-based conditioning. To overcome these limitations, we developed antibody drug conjugates (ADC) targeting CD117 (C-KIT) to specifically deplete the hematopoietic stem and progenitor cells (HSPC). To validate CD117 ADC-mediated depletion prior to HSCT preclinically, we developed an optimized non-human primate (NHP) fast half-life anti-CD117 ADC and evaluated it in an auto-gene modified HSCT in a rhesus model.

Methods: The CD117-ADC has potent depletion of human and NHP CD34+ cells in vitro. Humanized NSG mice treated with a single dose had full depletion of human HSPCs in the bone marrow, while maintaining peripheral immune cells. In rhesus, a single administration achieved >99% HSPC depletion in bone marrow and was comparable to HSPC depletion observed following targeted busulfan conditioning (6 mg/kg/day x4) that is known to be myeloablative in the clinic. There was no effect of the ADC on the peripheral and bone marrow lymphocytes and the ADC was well tolerated compared to busulfan where multiple severe adverse events were seen. To facilitate use in HSCT, the CD117-ADC was engineered to have a fast clearance and the half-life was <10 h in NHP.

Results: We next explored whether the tool CD117-ADC could enable auto gene modified HSCT in the rhesus model. Two rhesus NHP were mobilized with GCSF and plerixafor. The selected CD34+ cells were transduced with β-globin encoded lentivirus and cryopreserved. The tool CD117-ADC was dosed on day -6 and the CD34+ cells were infused on day 0. Bone marrow aspirates analyzed on the day of infusion (day 0) demonstrated >99% depletion of the HSPCs and maintenance of the bone marrow lymphocytes. The primates engrafted neutrophils (day 8 and 10) and platelets (day 10 and 11), while peripheral lymphocytes were maintained throughout the transplant. The gene marking in the granulocytes is stable for >100 days and comparable to busulfan conditioned animals previously reported (Tisdale, Molecular Therapy 2019). Longer follow up and data from additional animals will be presented.

Conclusions: In summary, we have developed a tool fast half-life CD117 ADC that shows potent activity on NHP CD34+ cells, achieved >99% HSPC depletion in vivo, has a favorable safety profile compared to busulfan, spares the immune system and is cleared rapidly as designed. In a rhesus model of auto-gene modified HSCT, a single dose of the ADC enabled engraftment of gene modified HSCs. These proof of concept studies validate the use of CD117-ADC for targeted HSPC depletion prior to transplant and support its use as a new conditioning agent for auto-gene modified HSCT. This targeted approach for safer conditioning could improve the risk benefit profile for patients undergoing HSCT and enable more patients to benefit from these potentially curative therapies.

Disclosure: John Tisdale, Naoya Uchida, Robert Donahue, Allen Krouse, Nathaniel Linde, Aylin Bonifacio are collaborators of Magenta.

All other authors are employees and hold equity in Magenta Therapeutics.

O064.

Lenti-D Hematopoietic Stem Cell Gene Therapy Stabilizes Neurologic Function in Boys with Cerebral Adrenoleukodystrophy

Jörn-Sven Kühl[1], Florian Eichler[2], Christine Duncan[3], Paul J. Orchard[4], Satiro De Oliveira[5], Adrian J. Thrasher[6], Troy Lund[4], Caroline Sevin[7], Paul Gissen[6], Hernan Amartino[8], Nicholas Smith[9], Esther Shamir[10], Wai Chin[10], Elizabeth McNeil[10], Patrick Aubourg[11], David A. Williams[12]

[1]University Clinic Leipzig, Leipzig, Germany, [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [3]Boston Children's Hospital, Dana-Farber Cancer Institute, Boston, MA, United States, [4]University of Minnesota Masonic Children's Hospital, Minneapolis, MN, United States, [5]University of California Los Angeles, Los Angeles, CA, United States, [6]University College London Great Ormond Street Hospital, Institute of Child Health, Great Ormond Street Hospital NHS Trust, London, United Kingdom, [7]Hôpital Universitaire, Hôpital Bicêtre, Hôpitaux Universitaires Paris Sud, Paris, France, [8]Medeos, Buenos Aires, Argentina, [9]Women's and Children's Hospital, Adelaide, Australia, [10]Bluebird Bio, Inc., Cambridge, MA, United States, [11]INSERM, Hôpital Bicêtre, Paris, France, [12]Dana-Farber and Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Harvard Stem Cell Institute, Boston, MA, United States

Background: Cerebral adrenoleukodystrophy (CALD) is a rare metabolic disorder in which rapid and progressive inflammatory cerebral demyelination leads to irreversible loss of neurologic function and death. Early diagnosis and treatment are key to ensure optimal long-term outcomes. Lenti-D Drug Product (DP) is an investigational gene therapy for the treatment of CALD.

Methods: Boys with CALD (≤17 years) enrolled in ALD-102, an open-label phase 2/3 study of the safety and efficacy of Lenti-D DP, underwent full myeloablation with busulfan

and cyclophosphamide followed by infusion of autologous CD34+ cells transduced with Lenti-D lentiviral vector. The primary efficacy endpoint of this study is the proportion of patients who are alive and free of major functional disabilities (MFD) at Month 24. The primary safety endpoint is the proportion of patients who experience acute (≥Grade 2) or chronic graft-versus-host disease (GVHD) by Month 24. Additional assessments include engraftment failure, and changes in neurologic function score and Loes score.

Results: ALD-102 has completed enrollment and 32 boys have received Lenti-D DP as of April 2019. The median DP cell dose was 11.4 (min - max, 5.0 - 20.1) $x10^6$ CD34 cells/kg; median DP vector copy number was 1.2 (min - max, 0.5 - 2.7) copies/diploid genome. Median day of neutrophil and platelet engraftment was 13.0 days (min - max, 11.0 - 41.0) and 32.0 days (min - max, 16.0 - 60.0), respectively. Median follow-up time is 21.2 months (min - max, 0.0 - 60.2). Fifteen patients have completed 24 months of follow-up in ALD-102 and continue to be free of MFDs through their last follow-up in a long-term extension study. Fourteen patients remain in ALD-102, with the longest follow-up among these patients at 20.4 months. Two patients were withdrawn and referred for allo-HSCT before their Month 24 visit. Another patient experienced early and rapid disease progression while on study that resulted in multiple MFDs, and the patient subsequently died. All other Lenti-D DP-treated patients showed stabilization of neurologic function score at their last follow-up (stable NFS was defined as NFS ≤4 without a change of >3 from baseline). All patients engrafted and there have been no reports of GVHD or transplant-related mortality. Recorded adverse events are generally consistent with myeloablative conditioning. There is no evidence of replication competent lentivirus or insertional oncogenesis.

Conclusions: Lenti-D DP appears to stabilize cerebral disease progression and shows favorable safety with the longest follow-up at 60.2 months. Additional follow-up is ongoing to assess durability of treatment and long-term safety.

Disclosure: Elizabeth McNeil, Esther Shamir, and Wai Chin are employees of bluebird bio. Florian Eichler has received consulting fees from Ionis Pharmaceuticals and SwanBio Therapeutics and financial support from bluebird bio and Minoryx Therapeutics to conduct clinical trials. Christine Duncan, Caroline Sevin, and Jörn-Sven Kühl have received consulting fees from bluebird bio. Paul J. Orchard, Troy Lund, and Patrick Aubourg have received grant support from bluebird bio. Satiro De Oliveira, Paul Gissen, and Hernan Amartino have nothing to disclose. Adrian J, Thrasher has received consulting fees from Orchard Therapeutics and Autolus Ltd. Nicholas Smith has received clinical trial funding from bluebird bio. David A. Williams has received research funding from bluebird bio and is an inventor on intellectual property licensed to bluebird bio.

O065.

Safety of Autologous Hematopoietic Stem Cell Transplantation with Gene Addition Therapy for Transfusion-Dependent β-Thalassemia, Sickle Cell Disease, and Cerebral Adrenoleukodystrophy

Evangelia Yannaki[1], Franco Locatelli[2], Adrian J. Thrasher[3], John F. Tisdale[4], Paul J. Orchard[5], Christine N. Duncan[6], Jörn-Sven Kühl[7], Satiro De Oliveira[8], Martin G. Sauer[9], Andreas E. Kulozik[10], Suradej Hongeng[11], Markus Y. Mapara[12], Lakshmanan Krishnamurti[13], Olivier Hermine[14], Stephane Blanche[15], Patrick Aubourg[16], Nicholas Smith[17], Weiliang Shi[18], Richard A. Colvin[18], Elizabeth McNeil[18], Jean-Antoine Ribeil[18], Marina Cavazzana[19], Mark C. Walters[20], David A. Williams[21]

[1]George Papanikolaou Hospital, Thessaloniki, Greece, *[2]IRCCS Bambino Gesù Children's Hospital, Rome, Italy*, *[3]UCL Great Ormond Street Institute of Child Health, London, United Kingdom*, *[4]National Institutes of Health, Bethesda, MD, United States*, *[5]University of Minnesota Masonic Children's Hospital, Minneapolis, MN, United States*, *[6]Boston Children's Hospital and Dana-Farber Cancer Institute, Boston, MA, United States*, *[7]University Clinic Leipzig, Leipzig, Germany*, *[8]University of California, Los Angeles, Los Angeles, CA, United States*, *[9]Medizinische Hochschule Hannover, Hannover, Germany*, *[10]University of Heidelberg, Heidelberg, Germany*, *[11]Mahidol University, Ramathibodi Hospital, Bangkok, Thailand*, *[12]Columbia University College of Physicians and Surgeons, New York, NY, United States*, *[13]Emory School of Medicine, Atlanta, GA, United States*, *[14]Necker Children's Hospital, Assistance Publique-Hôpitaux, Paris, France*, *[15]Hôpital Necker-Enfants Malades Assistance Publique-Hôpitaux de Paris and Paris University, Paris, France*, *[16]INSERM, Hôpital Bicêtre, Paris, France*, *[17]Women's and Children's Hospital, Adelaide, Australia*, *[18]bluebird bio, Inc., Cambridge, MA, United States*, *[19]Necker Children's Hospital, Assistance Publique-Hôpitaux, INSERM, Université Paris Descartes, Sorbonne Paris Cité, Paris, France*, *[20]UCSF Benioff Children's Hospital, Oakland, CA, United States*, *[21]Dana-Farber and Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Harvard Stem Cell Institute, Boston, MA, United States*

Background: Allogeneic hematopoietic stem cell (HSC) transplantation (allo-HSCT) is a treatment option for several monogenic inherited diseases; however, its use is limited by the need for a matched donor and risk of immunological complications. Ex vivo HSC gene addition therapy using lentiviral vectors (LVV) does not have these limitations and is being evaluated in patients with transfusion-dependent β-thalassemia (TDT) using LentiGlobin for TDT in HGB-204, -205, -207, and -212, sickle cell disease (SCD) using LentiGlobin for SCD in HGB-205 and -206, and cerebral adrenoleukodystrophy (CALD) using Lenti-D in ALD-102 trials. Safety outcomes following autologous gene modified HSCT in these ongoing studies are summarized.

Methods: HSCs are collected using disease-appropriate procedures and CD34+ cells are transduced with LVV encoding disease-specific therapeutic transgenes. After myeloablation, patients are infused with LVV-transduced CD34+ HSCs. Patients are followed for two years and offered participation in long-term follow-up studies (LTF-303 [NCT02633943]; LTF-304 [NCT02698579]).

Results: Across all 6 studies, 110 patients have been treated as of last follow-up (Table 1). Follow-up ranges from <1 to 60.6 months and 47 patients have >2 years follow-up. No patient experienced primary or secondary graft rejection. One patient with CALD experienced disease progression and died 22 months after drug product (DP) infusion of disease complications. Two additional patients with CALD withdrew from the study after infusion and were referred for allo-HSCT. All other patients remain alive.

The majority of adverse events (AE) attributed to DP were grade 1/2 (Table 1). Most (107/110) patients had ≥1 grade 3 or 4 AE attributed to conditioning; most common AEs were cytopenia, febrile neutropenia, and stomatitis. Myelodysplastic syndrome was reported in one patient with SCD; after investigation for LVV insertion in malignant cells, the AE was assessed as not related to LentiGlobin insertion or transgene expression. There was no clinically relevant clonal dominance or LVV-mediated replication competent lentivirus detected and reasonably, no GVHD.

Conclusions: Data from 110 patients with TDT, CALD, or SCD followed for up to 5 years supports that the safety profile of HSC gene therapy does not carry the risks of graft rejection and long-term immunosuppression associated allo-HSCT. Additionally, there were no AEs related to vector integration. While safety beyond 5-years is still being established, these data suggest that HSC gene therapy may be a suitable therapy for patients with TDT, SCD, and CALD, particularly in those who are lacking a suitable donor or at an increased risk of complications from allo-HSCT.

	Neutrophil engraftment, days, median (min - max)	Platelet engraftment, days, median (min - max)	Drug product-related adverse events, Grade 1/2, (n)	Drug product-related adverse events, Grade 3/4, (n)	Follow-up, months, median (min - max)
TDT N=53	**22** (13-38)*	**41** (19-191)†	Abdominal pain (5) Dysplasia (1) Dyspnea (1) Hot flush (1) Leukopenia (1) Non-cardiac chest pain (1) Pain in extremity (1) Thrombocytopenia (1)	Thrombocytopenia§ (1)	**15.7** (0.5-60.6)
CALD N=32	**13** (11-41)‡	**32** (16-60)‡	Vomiting (2)	Viral cystitis§ (1)	**21.2** (0.0-60.2)
SCD N=25	**20** (15-38)^	**40.5** (19-136)^	Hot flush (1)	None	**15.2** (1.0-52.5)

Datacuts: HGB-204 (NCT01745120), HGB-207 (NCT02906202): December 2018; HGB-212 (NCT03207009): April 2019; HGB-205 (NCT02151526): June 2019; HGB-206 (NCT02140554): March 2019; ALD-102 (NCT01896102): April 2019. *$n = 51$; †$n = 45$; ‡$n = 31$; ^$n = 24$; §Serious.

[Treatment characteristics and drug product-related adverse events.]

Clinical Trial Registry: HGB-204 (NCT01745120); HGB-207 (NCT02906202); HGB-212 (NCT03207009); HGB-205 (NCT02151526); HGB-206 (NCT02140554); ALD-102 (NCT01896102); LTF-303 (NCT02633943); LTF-304 (NCT02698579)

Disclosure: Franco Locatelli: Honoraria for Amgen, Bellicum, Miltenyi; Membership on Board of Directors/advisory committees for Amgen, Novartis, Bellicum; Consultancy for bluebird bio, Inc., Novartis. Adrian Thrasher: Consultancy and Membership on Board of Directors/advisory committees for Orchard Therapeutics, Generation Bio, Rocket Pharmaceuticals; Equity Ownership for Orchard Therapeutics, Generation Bio. Other Membership for 4BIOCapital. Paul Orchard: Received grants from bluebird bio, Inc. Christine Duncan: Consulting fees for bluebird bio, Inc. Andreas Kulozik: Consultancy and Honoraria for bluebird bio, Inc., Novartis; Membership on Board of Directors/advisory committees for bluebird bio, Inc., Novartis. Olivier Hermine: Consultancy, Stock or other Equity Ownership, Research funding, Honoraria for AB Science; Research funding for Celgene, Novartis. Patrick Aubourg: Received grants from bluebird bio, Inc. Nicholas Smith: Clinical trial funding from bluebird bio, Inc. Weiliang Shi, Richard A. Colvin, Elizabeth McNeil, Jean-Antoine Ribeil: Employment and Equity Ownership for bluebird bio, Inc. Mark Walters: Consultancy for Editas, Trucode. AllCells, Inc. David Williams: research funding from bluebird bio, Inc.; has licensed intellectual property relevant to sickle cell disease to bluebird bio, Inc. Evangelia Yannaki, John Tisdale, Jörn-Sven Kuhl, Satiro De Oliveira, Martin G. Sauer, Suradej Hongeng, Markus Y. Mapara, Lakshmanan Krishnamurti, Stephane Blanche, Marina Cavazzana: nothing to disclose.

O066.

Lentiviral Haematopoietic Stem Cell Therapy in Patients With Wiskott Aldrich Syndrome (WAS): London Experience

Reem Elfeky[1,2], Christine Rivat[2], Katie Snell[1,2], Jinhua Xu-Bayford[1], Kimberly Gilmour[1], Stuart Adams[1], Emma Morris[2], Gerialdine Honnet[3], Anne Galy[3], Claire Booth[1,2], Adrian J Thrasher[2]

[1]Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom, [2]Institute of Child Health, University College London, London, United Kingdom, [3]Genethon, Evry, France

Background: Lentiviral vector-mediated haemopoietic stem cell (HSC) gene therapy is a potentially curative treatment that represents an alternative to allogeneic HSC transplantation for patients with WAS. Here, we report safety and efficacy data on the use of a self-inactivating vector (LV-w1.6 WASp) lentiviral vector-derived gene therapy for WAS patients for whom an HLA-matched donor was unavailable.

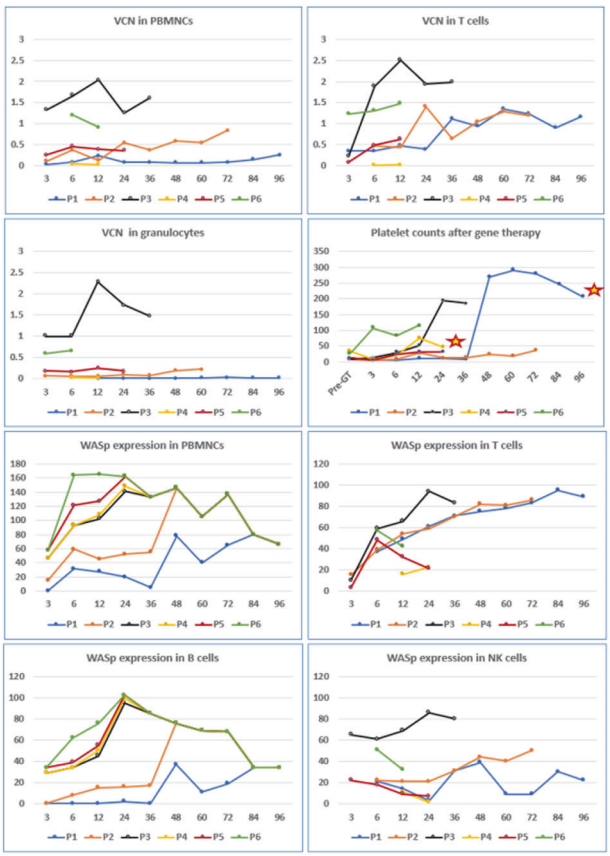
Methods: Between March 2011 and March 2018, gene -corrected autologous HSCs were infused in 6 children (range: 0.8-11 years) and a 30 year old previously reported adult patient (Morris EC et al, 2017) with severe WAS (WAS scores 3-5) after Busulphan/Fludarabine based conditioning. Median infused CD34 stem cell dose and vector copy number (VCN) among children were 5.8x10*6/Kg (range: 1.12-34.5), and 1.9 (0.71-3.8); respectively.

Results: The splenectomised adult patient died 4 years post-gene therapy from pneumococcal sepsis, having stopped prophylaxis. This report discusses outcome across paediatric patients.

All patients were alive at a median follow-up of 34.2 months (range: 18-96m). 5 out of 6 had neutrophil recovery at a median of 25 days post-gene therapy. P4 failed to achieve neutrophil recovery and was infused a back-up harvest at D+39. P4 had failed to engraft after a cord transplant and had failed to mobilise twice pre-gene therapy.

Patients with eczema demonstrated resolution at a median of 15.3 months post gene therapy (range: 5.7-18.6m) with a noticeable drop in IgE levels. None of the patients had viral reactivation at 100 days post gene therapy. Moreover, P3 who had active CMV viraemia at the time of infusion was able to clear the virus by D+55. Late infections requiring hospital admission was recorded in 2 patients; P5 for influenza and P1 (splenectomized) developed pneumococcal pneumonia at 6 months and then 8 years post-gene therapy. Three patients developed autoimmunity at a median of 19.5 months post-gene therapy (range: 2-34 months); 2 of them had pre-existing autoimmune disease. One patient; P3 remains on a tapering dose of immunosuppression at last follow-up, for management of late onset nephrotic syndrome at 19.7 months post-gene therapy. Two patients were splenectomised; P1 post-gene therapy and P4 pre-gene therapy for thrombocytopenia. None of the patients had bleeding episodes after gene therapy. Multilineage engraftment in peripheral blood of gene-corrected cells was sustained to the latest time point analysed and was associated with WAS protein (WASp) expression by flowcytometry as shown in figure 1. T cells exhibited the highest level of gene marking and WASp expression at 12 months post-gene therapy. Median time to CD3 counts>1000 cells/ul, CD4>300 cells /ul and CD19 cells>200 cells was 6.7m, 7.9m and 6.7m ; respectively. Four patients discontinued immunoglobulin replacement with adequate vaccine responses at a median of 15.7 months post gene therapy. Integration site analysis was carried out for 3 of 6 patients and showed no evidence of sustained clonal dominance at sites linked to proto-oncogenes.

Conclusions: Data from this study demonstrates robust immune recovery with reduction in infections and eczema together with a sustainable but often modest increase in platelet count after gene therapy for WAS.



[Multilineage engraftment, WASp expression, sustained platelet levels; star denotes splenctomised cases]

Clinical Trial Registry: NCT01347242 https://clinicaltrials.gov/ct2/results?cond=&term=NCT01347242&cntry=&state=&city=&dist=

Disclosure: Claire Booth:Hoc consultancy for SOBI, Novimmune and Rocket and have done educationalWork sponsored by GSK and Novimmune.

Adrian J Thrasher: consultant and co-founder in Orchard Therapeutics, consultant for Rockets Pharmaceuticals, Generation bio, Bluebirdbio, Sarepta, Sana and 4 Bio Capital partners.

Other co-authors have no conflict of interest to declare.

O067.

Lentiglobin for Sickle Cell Disease (SCD) Gene Therapy (GT): Updated Results in Group C Patients from the Phase 1/2 HGB-206 Study

Markus Y. Mapara[1], John F. Tisdale[2], Julie Kanter[3], Janet L. Kwiatkowski[4], Lakshmanan Krishnamurti[5], Manfred Schmidt[6], Alexandra L. Miller[7], Francis J. Pierciey Jr.[7], Melissa Bonner[7], Wenmei Huang[7], Jean-Antoine Ribeil[7], Alexis A. Thompson[8], Mark C Walters[9]

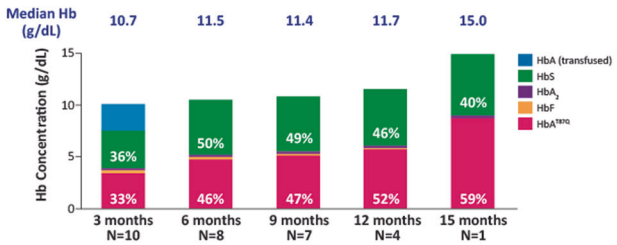
[1]Columbia University College of Physicians and Surgeons, New York, NY, United States, [2]National Institutes of Health, Bethesda, MD, United States, [3]University of Alabama at Birmingham, Birmingham, Birmingham, AL, United States, [4]University of Pennsylvania, Philadelphia, PA, United States, [5]Emory School of Medicine, Atlanta, GA, United States, [6]GeneWerk GmbH, Heidelberg, Germany, [7]Bluebird Bio, Inc., Cambridge, MA, United States, [8]Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University, Chicago, IL, United States, [9]UCSF Benioff Children's Hospital, Oakland, CA, United States

Background: LentiGlobin for SCD GT contains autologous CD34+ hematopoietic stems cells (HSCs) encoding β-globin with the anti-sickling T87Q mutation ($\beta^{A\text{-}T87Q}$) and is being evaluated in the ongoing Phase 1/2 HGB-206 Study (NCT02140554) in patients with SCD. Levels of GT-derived hemoglobin (HbA^{T87Q}) in 7 initial patients (Group A) were suboptimal but were maintained for ≥ 30 months of follow-up post-treatment, suggesting durable transgene expression. To increase HbA^{T87Q} production, protocol and manufacturing changes were made (Group B; N=2). In addition, HSC collection by plerixafor mobilization and apheresis was instituted in Group C.

Methods: Adults with severe SCD (including recurrent vaso-occlusive crisis [VOC] and acute chest syndrome [ACS]) were enrolled. CD34+ HSCs were harvested by apheresis following plerixafor mobilization and transduced with BB305 lentiviral vector (LVV). Patients received myeloablative busulfan conditioning, were infused with LentiGlobin drug product (DP) and monitored for adverse events (AEs), Hb fractions, and other parameters. LVV presence in transduced cells (%LVV+) was measured by qPCR of individual colonies from colony-forming unit assays from pre-infusion DP) and post-infusion from CD34+ bone marrow (BM) HSCs and peripheral blood mononuclear cells (PBMCs). Data are shown as median (min-max).

Results: As of 7 March 2019, 13 Group C patients received DP, with follow-up of 9.0 (1.0-15.2) months. All but 1 patient had neutrophil and platelet engraftment as of the data cut date. Median HbS was ≤50% of total Hb in those with ≥6 months follow-up ($n = 8$; Figure 1). Total unsupported Hb at last visit in patients with ≥6 months of follow-up was 11.5 (10.2-15.0) g/dL, with HbA^{T87Q} levels of 5.3 (4.5-8.8) g/dL. Six of these 8 patients had a history of VOCs or ACS; the annualized VOC+ACS rate decreased from 5.3 (3-14) pre-treatment to 0 (0-2) post-treatment. A decrease in hemolysis markers was also seen post-DP. Most common non-hematologic Grade ≥ 3 AEs were febrile neutropenia ($n = 10$) and stomatitis ($n = 7$). Serious AEs occurred in 6 patients; the most frequent were nausea and vomiting. To date, there have been no cases of DP-related AEs, graft failure, vector-mediated replication competent lentivirus, or clonal dominance. The %LVV+ colonies from PBMCs at 9 months and BM at 12 months post-DP infusion ($n = 5$) were 79.2 (67.0-88.4) % and 81.5 (60.6-88.1) %, respectively, indicating stable engraftment of transduced cells from DP (%LVV+ was 80 [71-88] %).

Conclusions: Patients in HGB-206 Group C show stable LentiGlobin engraftment, with median total Hb >10 g/dL and median HbS ≤50% of total Hb in those with ≥6 months follow-up. The decrease in SCD-related complications and hemolysis in this cohort demonstrate a strong therapeutic benefit of LentiGlobin in patients with SCD.



[Figure 1. Median Total Hb and Hb fractions at various follow-up time points in HGB-206 Group C]

Disclosure: Julie Kanter: Consultant for Novartis, Imara, Sangamo, Modus, Guidepoint Global, GLG, Cowen, Jeffries, bluebird bio, Inc.; Honoraria from Medscape, Rockpointe, Peerview, Novartis; and Membership on an entity's Board of Directors or advisory committees for SCDAA, NHLBI. Janet Kwiatkowski: Consultant for bluebird bio, Inc., Agios, Celgene, Imara; Research Funding for bluebird bio, Inc., Apopharma, Novartis, Terumo, Sangamo. Manfred Schmidt: Employment for German Cancer Research Center; Equity ownership for GeneWerk GmbH. Alexandra Miller, Francis Pierciey Jr., Melissa Bonner, Wenmei Huang, Jean-Antoine Ribeil have Ownership Interest and Salary for bluebird bio, Inc. Alexis Thompson: Consultancy for bluebird bio, Inc., Celgene, Novartis; Research funding for bluebird bio, Inc., Celgene, Novartis, Baxalta, Biomarin. Mark Walters: Consultancy for Editas, Trucode. AllCells, Inc. Markus Y. Mapara, John F. Tisdale, Lakshmanan Krishnamurti have nothing to disclose.

Graft-versus-host disease – clinical

O068.

KD025 for Patients with Chronic Graft-Versus-Host Disease (CGVHD) - Long-Term Follow-up of a Phase 2A Study (KD025-208)

Aleksandr Lazaryan[1], Amandeep Salhotra[2], Carlos Bachier[3], Behyar Zoghi[4], Daniel Weisdorf[5], James Essell[6], Laurie Green[7], Olivier Schueller[7], Zhongming Yang[7], David Eiznhamer[7], Sanjay K Aggarwal[7], Bruce R Blazar[8], Stephanie J Lee[9], Madan Jagasia[10]

[1]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, United States, [2]City of Hope Medical Center, Duarte, CA, United States, [3]Sarah Cannon Research Institute, LLC (SCRI), Nashville, TN, United States, [4]Texas Transplant Institute, Methodist Hospital, San Antonio, TX, United States, [5]University of Minnesota, Minneapolis, MN, United States, [6]Oncology and Hematology Care, Cincinnati, OH, United States, [7]Kadmon Corporation, LLC, New York, NY, United States, [8]University of Minnesota, Minneapolis, MN, United States, [9]Fred Hutchinson Cancer Research Center, Seattle, WA, United States, [10]Vanderbilt University Medical Center, Nashville, TN, United States

Background: cGVHD exhibits both autoimmune and fibrotic features across multiple organ systems. KD025 is an orally available Rho-associated coiled-coil kinase 2 (ROCK2) selective inhibitor.

Methods: KD025-208 enrolled 3 cohorts (C) (C1: 200 mg QD, C2: 200 mg BID, and C3: 400 mg QD) of cGVHD patients (pts) after 1-3 prior lines of therapy. Treatment was until progression or toxicity. Primary endpoint is overall response rate (ORR) per 2014 NIH response criteria. Additional endpoints include duration of response (DOR), corticosteroid (CS) dose reductions, failure free survival (FFS) and Lee Symptom Scale (LSS) score.

Results: 17, 16, and 21 pts were enrolled in C1, C2, and C3. As of 30Jun19, median duration of follow up was 30, 26 and 19 months (mos) respectively. Median age was 52 yrs, median time from cGVHD diagnosis was 20 mos, and median prior lines of therapy was 2. The median duration of treatment was 9, 8, and 9 mos, respectively. 11 pts remained on KD025. Reasons for discontinuation included cGVHD progression (20), voluntary withdrawal (7), relapse of underlying disease (6), investigator decision (5), AE (3), and death (2).

ORR [95% CI] was 65% [38, 86] in C1, 69% [41, 89] in C2, and 62% [38, 82] in C3, 65% [51, 77] across all 3 cohorts. Responses were achieved across key subgroups with ORRs of 66% (23/35) in pts with ≥2 prior lines of therapy, 70% (19/27) in pts with ≥4 organs involved, 60% (25/42) in pts with severe cGVHD, and 63% (22/35) in pts refractory to their previous line. CRs were observed in all affected organs except lung; PRs were observed in lung.

While responses were often achieved within 8 wks, 4/35 responses occurred after 24 wks.

Responses were durable with a Kaplan-Meier (K-M) median DOR of 35 wks across all cohorts. 51% of responders sustained a response for ≥20 wks. FFS at 6, 12, 18 and 24 mos was 76%, 47%, 37% and 32%, respectively.

Baseline median CS dose was 0.2 mg/kg/day (prednisone eq). During treatment, median CS dose was reduced by 50%. 19% of pts discontinued CS completely.

35% of pts reported a clinically meaningful improvement (≥7-point reduction on consecutive visits) in LSS score.

AEs were consistent with those expected in cGVHD pts receiving CS. Common AEs were URI 46%, diarrhea 33%, increased LFTs 33%, nausea 33%, fatigue 32%, dyspnea 30%, and peripheral edema 24%. 56% had a Grade ≥3 AE, the most common was dyspnea 15% and lung infection/pneumonia 15%. <10% pts experienced Grade 3 anemia, neutropenia, or thrombocytopenia. Three pts discontinued KD025 due to possibly related AEs (C1: diarrhea, headache; C3: fatigue). No apparent increased risk of infection was observed. 3 pts died on study (C3: relapse of leukemia; lung infection; cardiac arrest), all considered unrelated to KD025.

Conclusions: Durable and clinically meaningful responses have been seen across all 3 cohorts. KD025 was well tolerated, allowing pts to remain on treatment and realize benefits of sustained therapy.

Clinical Trial Registry: NCT02841995
http://clinicaltrials.gov/ct@/show/NCT02841995

Disclosure: Lazaryan, Aleksandr (Kadmon); Salhotra, Amandeep (Celgene, Kadmon); Weisdorf, Daniel (Fate, Incyte, Pharmacyclics); Green, Laurie (Kadmon); Schueller, Olivier (Kadmon); Yang, Zhongming (Kadmon); Eiznhamer, David (Kadmon); Aggarwal, Sanjay K (Kadmon); Blazar, Bruce R (Abbvie, Alpine, Blue Rock, Children's Cancer Research, Fate, Five Prime, Kid's First, Kadmon, Leukemia/Lymphoma, Magenta, Regeneron, RXi, Tmunity); Lee, Stephanie J (Amgen, Astra Zeneca, Incyte, Kadmon, Millenium, Novartis, Pfizer, Syndax).

O069.

A Phase 2 Study of F-652, a Novel Tissue-Targeted Recombinant Human Interleukin-22 (IL-22) Dimer, for Treatment of Newly Diagnosed Acute Lower GI GVHD

Doris Ponce[1,2], Amin Alousi[3], Ryotaro Nakamura[4], Karamjeet Sandhu[4], Juliet Barker[1,2], Jinru Shia[1], Xiaoqiang Yan[5], William Daley[5], Gillian Moore[1], Samira Fatmi[1], Cristina Soto[1], Antonio Gomes[1], John Slingerland[1], Paul Giardina[1], Jonathan Peled[1,2], Marcel van den Brink[1,2], Alan Hanash[1,2]

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

[2]Weill Cornell Medical College, New York, NY, United States, *[3]University of Texas MD Anderson Cancer Center, Houston, TX, United States*, *[4]City of Hope National Medical Center, Duarte, CA, United States*, *[5]Generon (Shanghai) Corporation, Shanghai, China*

Background: IL-22 has been shown to support intestinal mucosa after damage through multiple mechanisms, including direct signaling to the intestinal epithelium that promotes its survival and regeneration as well by inducing epithelial production of innate antimicrobial molecules such as REG3. In murine models, aGVHD resulted in elimination of host-derived IL-22-producing cells, IL-22 deficiency increased GVHD mortality and GI pathology, and early initiation of treatment with IL-22 reduced GI pathology and improved survival. We thus tested if the addition of IL-22 to corticosteroids could promote healing of GI tract injury and improve treatment response in patients with lower GI aGVHD.

Methods: We conducted a 27-pts, single-cohort, multicenter prospective phase 2 study between 05/16 and 05/19. Eligible pts were $\geq$18 years-old and had new onset biopsy-proven lower GI aGVHD. Patients were treated with 4 weekly doses of F-652, a recombinant human IL-22 dimer/Fc fusion molecule at a dose of 45 μg/kg in combination with standard corticosteroid treatment. Primary endpoints included PK, safety, and day 28 lower GI aGVHD response. Additional endpoints included day 56 treatment response, evaluation of changes in gut microbiota by 16S sequencing, and plasma GVHD biomarkers. The study was powered to distinguish between an unpromising response rate of 35% and a promising response rate of 60%.

Results: The 27 patients (median age 55 yrs, mostly PBSC recipients) had predominantly stage 2-4 lower GI GVHD. All pts had detectable F-652 levels and measurement of CRP levels in a subset of patients confirmed in vivo biologic activity. Overall, 19/27 achieved a day 28 response (70%, 90%CI: 56-79, Fig. 1A). Response to treatment based on Ann Arbor Risk, evaluable in 20 pts, was 7/12 (58%) with high, 3/4 (75%) with intermediate, and 4/4 (100%) with low risk biomarkers (Fig. 1B). At day 56, 16 pts remained treatment responders (59%, 90%CI: 45-69). Three pts had repeat GI biopsy after treatment and demonstrated improvement in GI epithelial injury (Fig. 2). Additionally, in a subset of 17 pts with evaluable stool samples, microbial diversity and the relative abundance of commensal Blautia were higher in pts with a clinical response to F-652 ($p = 0.082$ and 0.048, respectively, Fig 3A-B). Principal component analysis (PCA) demonstrated that baseline microbiota composition was similar among pts ($n = 19$ pts) whereas the global microbiota composition was significantly different between responders and non-responders ($n = 17$ pts, $p = 0.01$, Fig 3C-D). Serious TEAEs were observed in 11 pts (40%) including enterocolitis ($n = 1$), pyrexia ($n = 1$), infection (2 sepsis, 1 device-related, 1 pneumonia, 1 sinusitis), musculoskeletal ($n = 2$), and respiratory ($n = 1$).

Conclusions: IL-22 in combination with corticosteroids was well tolerated and the 70% lower GI aGVHD response rate met the primary efficacy endpoint. These findings support further development of this approach and provide a proof-of-concept for combining standard immunosuppression with tissue-supportive strategies to enhance recovery of damaged mucosa, promote microbial health, and improve GVHD treatment response. Furthermore, our findings suggest that monitoring of the intestinal microbiome could function as a biomarker of treatment response in GI aGVHD.

Clinical Trial Registry: NCT02406651

Disclosure: Doris M Ponce: Grant support.

Xiaoqiang Yan, William L Daley: Work for Generon Corporation.

Marcel R. M. van den Brink: IL-22 patent.

Alan M. Hanash: IL-22 patent, grant support.

Nothing to declare: Amin M. Alousi; Ryotaro Nakamura; Karamjeet S. Sandhu; Juliet N. Barker; Jinru Shia; Gillian Moore; Samira Fatmi; Cristina Soto; Antonio Gomes; John Slingerland; Paul Giardina; Jonathan U. Peled.

O070.

The Magic Biomarker Algorithm Predicts Outcomes for Children with Acute Graft Versus Host Disease

Muna Qayed[1,2], Urvi Kapoor[3], Scott Gillespie[1], Courtney McCracken[1], Ghada Abusin[4], Paibel Aguayo-Hiraldo[5], Francis Ayuk[6], Mina Aziz[3], Hannah Choe[7], Stephan Grupp[8], Elizabeth Hexner[9], Ernst Holler[10], Steven Kowalyk[3], Hannah Major-Monfried[3], Pietro Merli[11], George Morales[3], Ryotaro Nakamura[12], Umut Ozbek[3], Michael Pulsipher[5], Wolf Rösler[13], Tal Schechter[14], Jay Shah[3], Hrishikesh Srinagesh[3], Matthias Wölfl[15], Kitsada Wudhikarn[16], Rachel Young[3], James Ferrara[3], Carrie Kitko[17], John Levine[3]

[1]Emory University, Atlanta, GA, United States, [2]Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Atlanta, GA, United States, [3]Icahn School of Medicine at Mount Sinai, New York, NY, United States, [4]University of Michigan, Ann Arbor, MI, United States, [5]Children's Hospital Los Angeles, Los Angeles, CA, United States, [6]University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [7]Ohio State University Wexner Medical Center, Columbus, OH, United States, [8]Children's Hospital of Philadelphia, Philadelphia, PA, United States, [9]Hospital of the University of Pennsylvania, Philadelphia, PA, United States, [10]University of Regensburg, Regensburg, Germany, [11]Ospedale Bambino Gesu', Rome, Italy, [12]City of Hope National Medical Center, Duarte, CA, United States, [13]Med. Klinik III / Poliklinik, Universitätsklinik Erlangen, Erlangen, Germany, [14]Hospital for Sick Children, Toronto, Canada, [15]University of Würzburg, Wurzburg, Germany, [16]Chulalongkorn University, Bangkok, Thailand, [17]Vanderbilt University, Nashville, TN, United States

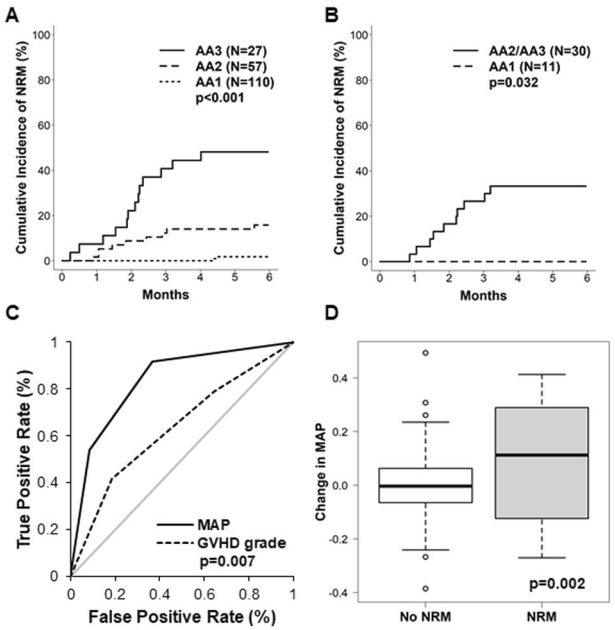
Background: Acute graft versus host disease (aGVHD) remains the major cause of non-relapse mortality (NRM) following allogeneic hematopoietic cell transplantation. Clinical severity at aGVHD onset is a modest predictor of NRM. Treatment response on day 28 is the standard surrogate for long-term outcomes in clinical trials despite limited accuracy. The Mount Sinai Acute GVHD International Consortium (MAGIC) algorithm combines two biomarkers ST2 and REG3α to generate an individual patient's estimated probability of 6-month NRM (MAGIC algorithm probability, MAP), and stratifies adults into NRM risk groups. We hypothesized that the MAP would be both a prognostic and response biomarker in children treated for aGVHD.

Methods: We tested the algorithm in 194 pediatric patients (≤21y) with aGVHD who were transplanted at 16 MAGIC centers between 2005 and 2018 and had serum samples collected at initiation of systemic steroid treatment. We applied the published MAP thresholds to categorize patients into 3 risk groups at start of treatment (Ann Arbor (AA) 1, < 0.141; AA2, 0.141-0.290; and AA3, >0.290), and at d28 for patients with samples ($n = 148$). We compared clinical measures to MAPs for 6-month NRM prediction at d0 and 28 of treatment.

Results: Median age was 12y (range 0.3-21). On d0 of treatment, aGVHD was grade I (34%), grade II (45%), or grade III-IV (21%). MAP thresholds categorized patients as AA1 (57%), AA2 (29%), or AA3 (14%). We compared clinical severity to MAP as predictors of NRM at d0 of treatment. Patients with grade I and II aGVHD had the same NRM, which was significantly less than the NRM for patients with grade III-IV aGVHD (9% vs 24%, $p = 0.008$). The MAP stratified these same patients into 3 distinct groups with significantly different NRM, AA1 (2%), AA2 (16%) and AA3 (48%) (Figure 1A). An analysis restricted to children <12y yielded similar results. The MAP also stratified patients into low (AA1) and high risk (AA2/3) risk groups within each Glucksberg grade (I, II, III/IV) at start of treatment. For example, 27% of patients who presented with grade III/IV GVHD were AA1 and experienced 0% NRM (Figure 1B). The area under the curve (AUC) for NRM was significantly better for the MAP than clinical severity (0.84 vs 0.63, $p = 0.007$) (Fig. 1C). We evaluated both overall response and MAP at d28 as predictors for NRM with MAPs >0.290 considered high. Patients who did not respond to treatment ($n = 45$) had significantly more NRM than patients who responded ($n = 103$); 31% vs 6%, p< 0.001. The MAP on d28 stratified both non-responders for NRM (low MAP, 7% vs high, 75%; p< 0.001) and responders (low MAP, 3% vs high, 23%; $p = 0.026$). Change in MAP from d0 to d28 also predicted outcomes. Patients who experienced NRM were more likely to have an increase, while patients who survived were more likely to have no change or decrease in MAP ($p = 0.002$) (Fig. 1D).

Conclusions: We have validated the MAP as both a prognostic and a response biomarker in children with

aGVHD and shown that it is a better predictor of long term outcomes than clinical severity.



[1A.NRM by AA score B.NRM for GIII/IV aGVHD C. ROC curves for prediction of NRM D.NRM by change in MAP]

Disclosure: Disclosure: MQ: Consultancy, Bristol-Myers Squibb, Novartis. SG: Consultancy, Novartis, Jazz, Adaptimmune, Curegenetics. Research funding, Servier, Kite. EH: Research funding, Novartis, Blueprint Medicine, Samu. PM: Honoraria, Amgen, Neovii. RN: Research funding, Helocyte, Miyarisan. MP: Consultancy, Novartis, Adaptive, CSL Behring. Research funding: Miltenyi, Adaptive. Speaker's Bureau, Novartis. JF: Consultancy, Incyte, Mallinckrodt, Enlivex, Xenikos, CSL Behring. Research funding, Kamada. CK: Honoraria, Novartis, Mallinckrodt. JL: Consultancy, Novartis, Incyte, Bluebird Bio. Research funding, Incyte, Kamada. UO, JF and JL are co-inventors on a GVHD biomarker patent and receive royalties from Viracor.

O071.

A Novel Treatment in Chronic Ocular Graft-Vs-Host Disease (OGVHD): A Phase II Clinic Trial with Transdermal Progesterone

Zhonghui Katie Luo[1], Edgar Domenech-Estarellas[2], Amy Han[3], Robert Soiffer[3], Vincent Ho[3]

[1]Harvard Medical School, Massachusetts Eye and Ear, Boston, MA, United States, [2]Ponce Health Sciences University, Ponce, Puerto Rico, [3]Harvard Medical School, Dana Farber Cancer Center, Boston, MA, United States

Background: Chronic GvHD affects more than half of the patients after allogeneic hematopoietic cell transplant (allo-HCT), and a majority of them suffer from ocular GvHD that can lead to excruciating pain and permanent vision loss in severe cases. There is no FDA-approved treatment to date as the current options are limited and mostly ineffective. Forehead application of 1% progesterone gel (Pro-ocular^{TM}) increases resistance to painful corneal stimuli in animal studies, as well as improves tear film in human volunteer studies. While the precise mechanism of action is unclear, a cranial nerve V1 mediated neuro-pathway has been implicated.

Methods: The prospective, randomized, placebo-controlled, double-masked phase II clinical trial of adult patients with chronic oGvHD who underwent allo-HCT at Dana-Farber/Brigham and Women's Hospital was sponsored by Glia LLC. All subjects had moderate to severe eye symptoms, were free of other major ocular comorbidities, and remained on previous ocular treatments and systemic immune suppression through the trial. Subjects were randomized in a 2:1 treatment to placebo fashion. The trial drug or placebo was self-applied to the forehead in the home settings twice a day for a total of 10 weeks. All subjects kept daily diaries to document their medication use and symptoms, and were evaluated in the clinic at baseline, 2 weeks, 6 weeks and 10 weeks. The endpoints of the study were patient reported ocular symptoms and physician recorded ocular signs such as ocular surface staining and tear film. Safety assessments included blood tests of hematology, chemistry and endocrine panels.

Results: 32 out of the 33 enrolled patients completed the trial with 21 in the active arm and 11 in the placebo arm. Only 1 patient was lost to follow up. Treatment was well tolerated and compliance was high. There was no severe adverse event in the active arm. There was much more reduction of total cornea fluorescein staining in the active arm at 2 weeks (-2.54 vs. -0.24, $p = 0.014$), 6 weeks (-3.29 vs. -1.35, $p = 0.039$) and 10 weeks (-3.95 vs -1.42, $p = 0.008$). The Symptom Assessment Questionnaire iN Dry Eye (SANDE) quantifies ocular symptoms on a visual analog scale filled by the patients. Strikingly, the reduction of global score was significantly superior in the active arm at 6 weeks (-26.35 vs. -5.64, $p = 0.004$) and 10 weeks (-25.87 vs -1.04, $p = 0.0006$). Patients specifically reported improvement in light sensitivity, airflow sensitivity, and eye pain among other parameters that improved their quality of life. The systemic progesterone level in the active arm did not change significantly within the 10 weeks. All subjects in the placebo arm received crossover active treatment for 6 weeks. 31 out of

the 32 total patients chose to continue with the active treatment in the ongoing long term open label phase.

Conclusions: Forehead application of 1% progesterone gel significantly improved ocular symptoms and signs in just 10 weeks. It appears to be a safe and effective novel treatment for chronic oGvHD. A larger randomized phase III trial to confirm the results is planned.

Clinical Trial Registry:

ClinicalTrials.gov Identifier: NCT03990051

https://clinicaltrials.gov/ct2/show/NCT03990051?cond=ocular+graft+vs+host+disease&draw=2&rank=6

Disclosure: Nothing to declare.

O072.

Effect of Single or Double Mismatches at Each HLA Locus on the Outcomes After Single Cord Blood Transplantation: The JSHCT HLA WG Study

Junya Kanda[1], Shigeki Hirabayashi[1], Hisayuki Yokoyama[2], Takakazu Kawase[3], Hidenori Tanaka[4], Naoyuki Uchida[5], Satoshi Takahashi[6], Makoto Onizuka[7], Masatsugu Tanaka[8], Yasuhiro Sugio[9], Tetsuya Eto[10], Takafumi Kimura[11], Tatsuo Ichinohe[3], Yoshiko Atsuta[12,13], Satoko Morishima[14]

[1]Kyoto University, Kyoto, Japan, [2]Tohoku University, Sendai, Japan, [3]Hiroshima University, Hiroshima, Japan, [4]HLA Foundation Laboratory, Kyoto, Japan, [5]Toranomon Hospital, Tokyo, Japan, [6]University of Tokyo, Tokyo, Japan, [7]Tokai University, Isehara, Japan, [8]Kanagawa Cancer Center, Kanagawa, Kanagawa, Japan, [9]Kitakyushu Municipal Medical Center, Kitakyushu, Japan, [10]Hamanomachi Hospital, Fukuoka, Japan, [11]Japanese Red Cross Kinki Block Blood Center, Tokyo, Japan, [12]Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya, Japan, [13]Nagoya University, Nagoya, Japan, [14]University of the Ryukyus, Okinawa, Japan

Background: Effect of single or multiple mismatches at each HLA locus on outcomes after cord blood transplantation (CBT) remains unclear. Therefore, we analyzed the effects of single or multiple HLA-locus mismatches on the outcomes after single CBT using a Japanese registry data from the Japan Society for Hematopoietic Cell Transplantation (JSHCT).

Methods: Patients with acute myelogenous leukemia, acute lymphoblastic leukemia, and myelodysplastic syndromes aged >=16 years who underwent their first CBT between 2003 and 2017 (n = 4,074) were included. The effect of the number of HLA-locus mismatches (0, 1, and 2, for the HLA-A, -B, -C, and -DRB1 loci) on the outcome was analyzed after adjusting for other significant variables.

Results: The patients' median age was 54 years. Median total nucleated and CD34 cell doses were 2.6 × 10^7/kg (range, 0.8-8.1x10^7/kg) and 0.8 × 10^5/kg (range, 0.1-14.0x10^5/kg), respectively. The number of CBTs with single and double mismatches at each HLA locus were as follows: 2,099 (52%) and 292 (7%) for the HLA-A locus; 2,699 (66%) and 341 (8%) for the HLA-B locus; 2,555 (63%) and 609 (15%) for the HLA-C locus; and 2,593 (64%) and 571 (14%) for the HLA-DRB1 locus, respectively. The median number of allele mismatches was 3 (range, 0-8).

Single and double HLA-DRB1 mismatches were associated with higher risks of grade II-IV acute graft-versus-host disease (GVHD, single: HR 1.29, P < 0.001, double: HR 1.49, P < 0.001; trend-P: P < 0.001). Other locus mismatches were not associated with this risk. Single and double mismatches at the HLA-DRB1 locus and a single mismatch at the HLA-A and HLA-B loci were also associated with grade III-IV acute GVHD. Single and double HLA-B mismatches and double HLA-DRB1 mismatches were associated with a higher risk of non-relapse mortality. In contrast, double mismatches at the HLA-A and -DRB1 loci and a single mismatch at the HLA-B locus were associated with a lower risk of relapse. There was no impact of HLA locus mismatches on overall survival.

Conclusions: HLA-DRB1 double mismatch was associated with higher risks of grade II-IV and III-IV acute GVHD and non-relapse mortality but with lower risks of relapse. Not only locus mismatch but also the number of mismatches at the DRB1 locus may be considered in cord blood unit selection.

Disclosure: Nothing to declare.

O073.

Interim Analysis of KD025-213: A Phase 2, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 in Subjects with CGVHD (the Rockstar Study)

Madan Jagasia[1], Stephanie J Lee[2], Zachariah DeFilipp[3], Amandeep Salhotra[4], Rohtesh Mehta[5], Trent Wang[6], Wanxing Chai-ho[7], Mukta Arora[8], Iskra Pusic[9], Ayman Saad[10], Sunil Abhyankar[11], Carlos Bachier[12], John Galvin[13], Annie Im[14], Amelia Langston[15], Nirav Shah[16], Mark Juckett[17], Jane Liesveld[18], Aaron Logan[19], Levanto Schachter[20], Asif Alavi[21], Dianna Howard[22], Laurie Green[23], Olivier Schueller[23], Zhongming Yang[23], David Eiznhamer[23], Sanjay K Aggarwal[23], Bruce R Blazar[24], Steven Pavletic[25], Corey Cutler[26]

[1]Vanderbilt University Medical Center, Nashville, TN, United States, [2]Fred Hutchinson Cancer Research Center,

Seattle, WA, United States, [3]*Massachusetts General Hospital, Boston, MA, United States*, [4]*City of Hope Medical Center, Duarte, CA, United States*, [5]*MD Anderson Cancer Center, Houston, TX, United States*, [6]*University of Miami, Miami, FL, United States*, [7]*University of California, Los Angeles, Los Angeles, CA, United States*, [8]*University of Minnesota, Minneapolis, MN, United States*, [9]*Washington University, St. Louis, MO, United States*, [10]*The Ohio State University (OSU), Columbus, OH, United States*, [11]*University of Kansas Cancer Center, Fairway, KS, United States*, [12]*Sarah Cannon Research Institute, LLC (SCRI), Nashville, TN, United States*, [13]*University of Illinois at Chicago, Chicago, IL, United States*, [14]*University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA, United States*, [15]*Emory University, Atlanta, GA, United States*, [16]*Froedtert Hospital and the Medical College of Wisconsin, Milwaukee, WI, United States*, [17]*University of Wisconsin, Madison, WI, United States*, [18]*University of Rochester, Rochester, NY, United States*, [19]*University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, United States*, [20]*Oregon Health & Science University (OHSU), Portland, OR, United States*, [21]*Barbara Ann Karmanos Cancer Institute, Detroit, MI, United States*, [22]*Wake Forest Baptist Medical Center, Wake Forest University, Winston-Salem, NC, United States*, [23]*Kadmon Corporation, LLC, New York, NY, United States*, [24]*University of Minnesota, Minneapolis, MN, United States*, [25]*National Cancer Institute, Bethesda, MD, United States*, [26]*Dana-Farber Cancer Institute, Boston, MA, United States*

Background: KD025 is an orally available Rho-associated coiled-coil kinase 2 (ROCK2) selective inhibitor that decreases pro-inflammatory Stat3 and increases Stat5 favoring regulatory T cells. Previous data (KD025-208, NCT02841995) supported efficacy and tolerability in cGVHD after 1-3 prior lines of systemic therapy (LOT).

Methods: We randomly assigned cGVHD patients (pts) after 2-5 prior LOT to KD025 200mg QD (n = 66), or KD025 200mg BID (n = 66), across 28 sites, stratified according to cGVHD severity and prior ibrutinib. The primary endpoint was the overall response rate (ORR) per 2014 NIH response criteria, assessed by investigators. Additional endpoints include Duration of Response, Lee Symptom Scale (LSS) score, corticosteroid reductions, FFS and OS. Treatment was until clinically significant progression or unacceptable toxicity. A pre-specified interim analysis (IA) occurred 2 months after the last pt was enrolled, with the primary analysis to occur 6 months after the last pt was enrolled.

Results: At this IA, median (range) duration of follow up was 5 (2, 12) months. Baseline characteristics are shown in the table below.

	KD025 QD (n = 66)	KD025 BID (n = 66)	Overall (n = 132)
Median age [yrs (range)]	53 (21-77)	57 (21-77)	56 (21-77)
Male	64%	50%	57%
Median prior LOT	3	4	4
Median time from cGVHD Dx (mos)	25	30	28
Severe cGVHD [n (%)]	45 (68%)	42 (64%)	87 (66%)
Prior Ibrutinib [n (%)]	23 (35%)	22 (33%)	45 (34%)
≥4 Organs Involved [n (%)]	34 (52%)	35 (53%)	69 (52%)
Median prednisone dose (mg/kg/day)	0.2	0.2	0.2
Refractory to prior line	81% (42/52)	65% (32/49)	73% (74/101)

[Baseline Characteristics]

The ORR [95% CI] was 64% [51, 75] with KD025 QD and 67% [54, 78] with KD025 BID. Three pts achieved a complete response. Responses were consistent across key subgroups as shown in the figure.

KD025 has been generally well tolerated, and AEs have been consistent with those expected in this population. 67% and 65% of the pts remained on study treatment in the QD and BID arms respectively. AEs (QD, BID) in >15% pts were fatigue (30%, 18%), diarrhea (24%, 18%), nausea (23%, 20%), liver related investigations (SMQB) (20%, 23%), edema (24%, 15%), cough (18, 14%) dyspnea (20%, 12%). SAEs in >2% were pneumonia (3%, 3%), nausea (3%, 2%), pyrexia (5%, 0) and vomiting (3%, 2%). 5 deaths occurred on study. 4 were considered unrelated to KD025 (QD: hemothorax post lung biopsy, aspiration pneumonia, AML relapse; BID: cardiac arrest) and 1 subject (QD) with severe nausea, diarrhea and vomiting leading to multiple organ dysfunction syndrome.

Conclusions: Clinically meaningful ORR has been achieved in this population of cGVHD pts with QD and BID dosing, consistent with previous observations. ORR was consistent across key subgroups. KD025 has been generally well tolerated. This study is ongoing; additional data will be available for presentation.

Clinical Trial Registry: NCT03640481 http://clinicaltrials.gov/ct@/show/NCT03640481.

Disclosure: Lee, Stephanie J (Amgen, Astra Zeneca, Incyte, Kadmon, Millenium, Novartis, Pfizer, Syndax); DeFilipp, Zachariah (Incyte); Salhotra, Amandeep

(Celgene, Kadmon); Abhyankar, Sunil (Incyte, Therakos); Langston, Amelia(Incyte, Jazz, Kadmon); Logan, Aaron (Abbvie, Agios, Amgen, Astellas, Incyte, Jazz, Kadmon, Kite, Marker, Novartis, Pharmacyclics); Green, Laurie (Kadmon); Schueller, Olivier (Kadmon); Yang, Zhongming (Kadmon); Eiznhamer, David (Kadmon); Aggarwal, Sanjay K (Kadmon); Blazar, Bruce R (Abbvie, Alpine, Blue Rock, Children's Cancer Research, Fate, Five Prime, Kid's First, Kadmon, Leukemia/Lymphoma, Magenta, Regeneron, RXi, Tmunity); Cutler, Corey (Kadmon).

O074.

Anti-T-Lymphocyte Globulin (ATLG) and Rituximab for Immunomodulation of Graft-Versus-Host Disease and Graft Failure in Patients with Non-Malignant Disorders: Results of a Multicentre, Randomized, Open-Label Study

Mattia Algeri[1], Stefania Galimberti[2], Maria Ester Bernardo[3], Attilio Rovelli[4], Marco Zecca[5], Giorgio La Nasa[6], Sarah Marktel[3], Pietro Merli[1], Alice Bertaina[7], Daria Pagliara[1], Emilia Boccieri[1], Francesca Del Bufalo[1], Stefania Gaspari[1], Annalisa Ruggeri[1], Giulia Capitoli[2], Maria Grazia Valsecchi[2], Franco Locatelli[1,8]

[1]*IRCCS Bambino Gesù Children's Hospital, Rome, Italy*, [2]*University of Milan-Bicocca, Monza, Italy*, [3]*IRCCS San Raffaele Scientific Institute, Milan, Italy*, [4]*San Gerardo Hospital, Fondazione MBBM, Monza, Italy*, [5]*Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*, [6]*A. O Brotzu, P.O. R. Binaghi, Cagliari, Italy*, [7]*Stanford University, Palo Alto, CA, United States*, [8]*University of Rome Sapienza, Rome, Italy*

Background: Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is increasingly used to treat many non-malignant disorders. However, the optimal strategy for graft-versus-host disease (GvHD) prevention remains a matter of debate. In particular, the use of ATLG for preventing immune-mediated complications in patients transplanted from a matched-related donor (MRD) is still controversial. In the matched unrelated donor (MUD) setting, there is retrospective evidence that rituximab used as prophylaxis of EBV viremia may protect from acute GvHD (aGvHD) development, but the clinical benefit of pre-transplant rituximab has never been prospectively assessed.

Methods: We conducted a multicentre, randomized, open-label, trial (NCT01810926) in 5 Italian centres enrolling patients with non-malignant disorders transplanted from either a MRD or a MUD, selected using high-resolution typing for HLA-class I/II loci and stringent HLA-compatibility criteria ($\geq$9/10). All patients received the same myeloablative regimen including Treosulfan/Thiotepa/Fludarabine and were randomized (1:1) to receive either standard or intensified GvHD prophylaxis. Cyclosporine-A +short-term methotrexate was the standard GvHD prophylaxis in MRD HSCT recipients. In the experimental arm, patients were additionally given ATLG (Grafalon®, Neovii, 5 mg/kg/day on day -4,-3, and -2). In patients transplanted from a MUD, standard GvHD prophylaxis included Cyclosporine-A+short-term methotrexate and ATLG (10 mg/kg on day -4,-3 and-2). In the experimental arm, patients were additionally given rituximab 200 mg/sq on day -1 (Mabthera®, Roche).

For patients given MRD HSCT, the primary end-point was the probability of survival (SUR) free from: a) primary and secondary graft failure (GF), b) grade II-IV aGvHD, c) chronic GvHD (cGvHD), d) death, whichever occurred first. For patients transplanted from a MUD, the primary end-point was SUR probability free from: a) grade II-IV aGvHD, b) EBV viremia, whichever occurred first.

Results: Between August 2011 and February 2018, 126 patients were enrolled. Patient/disease characteristics are shown in Table 1. Median follow-up was 3.6 years.

Among the 51 MRD-HSCT recipients, 25 were randomly assigned to the ATLG group and 26 to the NO-ATLG group. No death and no cases of grade II-IV aGvHD were observed in either of the two arms. Two GF occurred in each of the two arms, while 1 and 2 cases of cGvHD occurred in the ATLG and NO-ATLG groups, respectively. Consequently, there was no statistically significant difference in the 3-year estimate of SUR without events (±SE) [86.9% ± 7.1% vs. 83.8% ± 7.5%, respectively ($p = 0.75$)].

In the MUD population, 38 patients were allocated to the rituximab group and 37 to the NO-rituximab group. Although no statistically significant difference in OS ($p = 0.21$) was observed between the two arms (3-years estimates: 94.1% ± 4.1% for rituximab, 85.7% ± 5.9% for No-rituximab), patients receiving rituximab had a better probability of SUR without events (73.0% ± 7.3% vs 26.5% ± 7.3%, respectively; $p = 0.0002$), entirely due to lower incidence of EBV viremia.

Conclusions: In patients with non-malignant disorders given MRD-HSCT, the addition of ATLG does not confer any advantage in the prevention of both aGvHD and cGvHD, as well as of GF.

In MUD-HSCT recipients, the administration of a fixed dose of pre-transplant rituximab does not affect the risk of aGvHD and transplant-related mortality, while it significantly reduces the incidence of EBV-viremia episodes, without affecting B-cell recovery.

Clinical Trial Registry: ClinicalTrials.gov Identifier: NCT01810926

https://clinicaltrials.gov/ct2/show/NCT01810926

EudraCT Number: 2011-004730-34

https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-004730-34/IT

Disclosure: Mattia Algeri: Consultancy and Honoraria: Bluebird bio, Atara Biotherapeutics. Honoraria: Miltenyi. Pietro Merli: Honoraria: Novartis, Amgen. Consultancy: Sobi, Bellicum.

Franco Locatelli: Consultancy and Membership on an entity's Board of Directors or advisory committees: Amgen, Bellicum, Novartis. Consultancy: Bluebird bio. Honoraria: Miltenyi.

Other authors: nothing to declare.

O075.

Experience Using Dual T-Cell Depletion with ATG and PTCY For GVHD Prophylaxis in RIC Allohct Using in 10/10 Matched Related and Unrelated Donors

Maria Queralt Salas[1], Eshetu G Atenafu[2], Arjun Datt Law[1], Wilson Lam[1], Zeyad Al-Shaibani[1], Ivan Pasic[1], Fotios V Michelis[1], Dennis (Dong Hwan) Kim[1], Armin Gerbitz[1], Jeffrey Howard Lipton[1], Jonas Mattsson[1], Rajat Kumar[1], Auro Viswabandya[1]

[1]Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada, [2]Princess Margaret Cancer Centre, Toronto, Canada

Background: Dual T-cell depletion with ATG (Thymoglobulin; total dose: 4.5mg/kg) and PTCy, combined with cyclosporine (ATG-PTCY-CsA) in peripheral blood RIC alloHCT provides good control of clinically relevant GVHD. The use of this combination was stablished at our Centre on October 2015. However, infectious complications were the main consequence of the degree of immunosuppression provided by this approach.

With the aim reduce transplant related complications by preserving the GVHD prophylactic effect provided by this combination, the total dose of ATG was lowered to 2mg/kg in May 2018. We aim to share the largest single center experience using this novel GVHD combination in RIC alloHCT using 10/10 MRD and 10/10 MUD, and to explore the efficacy of this approach after decreasing the ATG dose.

Methods: Two hundred-fifty adults were included: 175 (70%) patients received 4.5mg/kg of ATG (given on day -3,-2,-1), and 75 (30%) patients received 2mg/kg (given on day -3,-2). Seventy-seven (31.8%) patients received grafts from MRD and 275 (69.2%) from MUD.

Data was collected retrospectively and updated on October 2019. Risk factors for OS, RFS, NRM and GRFS were analyzed using univariate and multivariate Grey's and Cox Regression Models. Variables found to be significant in the univariate analysis were included in the multivariate analysis.

Results: Baseline characteristics and main results are shown in the Figure 1. The reduction of the ATG dose did not have a significant impact on the cumulative incidence of grade II-IV and grade III-IV aGVHD, and moderate/severe cGVHD. The cumulative incidence of clinically relevant GVHD was comparable between both donor types ($P > 0.05$).

Proportions of CMV and EBV reactivation were comparable among both cohorts. Four recipients had CMV disease, and all received 4.5mg/kg of ATG. Seventeen (6.8%) patients had PTLD, and one received a total ATG dose of 2mg/kg. The proportion of patients with other viral infections was lower in the cohort who received 2mg/kg of ATG ($P = 0.002$).

With a median follow-up of 13.9 months, 79 (31.6%) patients died and 59 (23.6%) relapsed. Main causes of death were infection (15%) and relapse (14%).

The multivariable analysis confirmed that there was a non-significant trend to lower NRM in patients who received 2mg/kg of ATG, and the reduction of the ATG dose did not have a significant impact on OS, RFS GRFS. Donor type did not have a significant impact on OS and NRM. However, to receive grafts from 10/10 MUD grafts had a protective effect on RFS and GRFS.

Conclusions: RIC alloHCT combined with ATG-PTCy-CSA is a safe protocol for adults undergoing Allogeneic Stem cell transplantation and effectively controls Graft Versus Host Disease.

Dual T-cell depletion with ATG and PTCy provides an impressive control of GVHD with acceptable relapse rates using PB stem cell grafts.

The reduction of the dose of ATG to 2mg/kg has decreased NRM providing comparable control of acute GVHD Longer follow-up is needed to confirm the efficacy of the refined protocol in controlling chronic GVHD.

Clinical Trial Registry: No applicable

Disclosure: Nothing to declare.

O076.

Machine Learning Applied to the Grading of Acute Graft-Versus-Host Disease Improves Survival Estimation After Allogeneic Hematopoietic Cell Transplantation

Amin Turki, Evren Bayraktar, Saskia Leserer, Ji-Hee Yi, Rashit Bogdanov, Dietrich Beelen

Universitätsklinikum Essen, Essen, Germany

Background: Acute graft-versus-host disease (aGVHD) remains a major cause of morbidity and mortality after

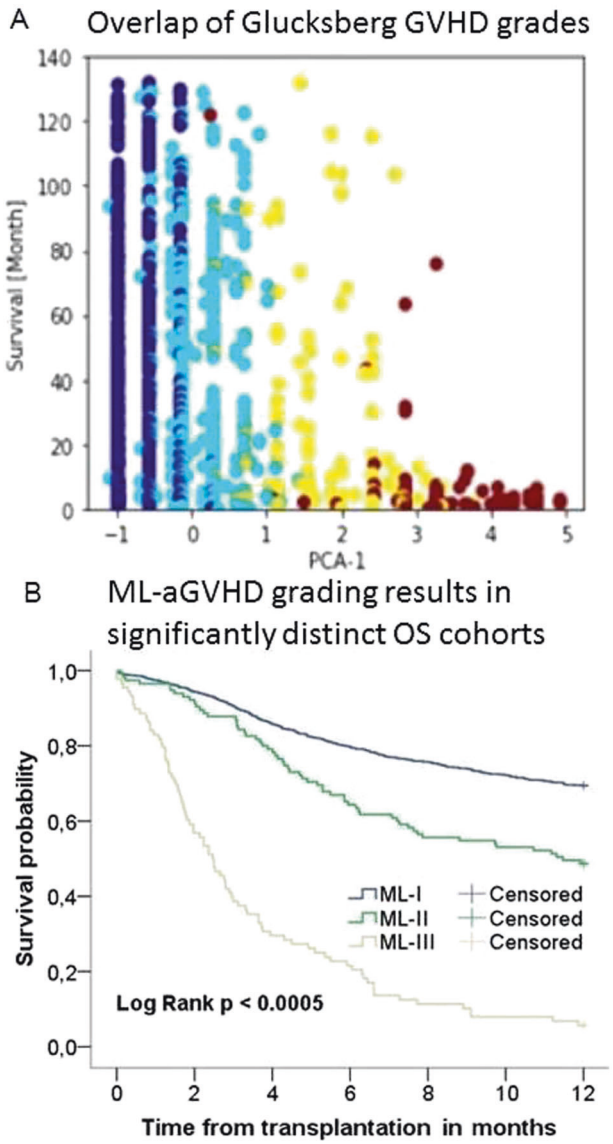
allogeneic hematopoietic cell transplantation (HCT). Since the first GVHD grading score by Glucksberg in 1974, several studies have tried to further improve aGVHD severity indexing (SI). While aGVHD grade IV clearly associates with reduced overall survival (OS), patients with high non-relapse mortality (NRM) are found across all aGVHD grades. We therefore hypothesized that a data-driven grading approach might significantly improve clinical GVHD grading.

Methods: We analyzed the modified Glucksberg scoring system in 1345 consecutive adult patients with aGVHD after HCT from a single center between 2008 and 2018 and compared it to a ML model, based on aGVHD organ involvement staging, transplant- and OS data. We constructed a 3D discrete space (*V*), of which axes corresponded to the aGVHD stage of the corresponding organ (skin, liver, intestine). By using dimensionality reduction from a multidimensional space (3 dimensions, each for the corresponding aGVHD organ stage: skin, liver and intestine) into a single dimension the patients' data had a variation of 63% on the first principle component (PCA1) axis. PCA1 was adopted as the new space (*V**). This index was transformed into a ML-aGVHD score and ML-aGVHD grading. Analysis was performed using Anaconda's Jupyter Notebook 5.0.0 for python version 3.3 (https://www.anaconda.com) and related libraries (scikit-learn and scipy), Matlab (MATLAB and Statistics Toolbox Release 2016a). The performance of the ML-aGVHD and Glucksberg grading systems were compared with Cox regression analysis in SPSS.

Results: The ML-aGVHD analysis revealed a significant intergrade OS variability and overlap for Glucksberg aGVHD graded patients (Fig. 1a). The Glucksberg grading had a tendency towards overfitting. OS (Fig. 1b) and NRM of the developed ML-aGVHD grading model significantly distinguished patients of a given score. Our data revealed 12 ML-aGVHD scores and 3 significantly distinct ML risk cohorts (ML-II hazard ratio (HR) 1.93, 95% confidence interval (CI), 1.4-2.54 and ML-III HR 7.89, 95%CI, 6.17-10.08; $p < 0.0005$). We confronted these results with the conventional Glucksberg grading and observed no significant difference in OS for patients with Glucksberg grade I and grade II aGVHD ($p = 0.977$).

Using Logit analysis ML-aGVHD grading allowed maximum survival estimations for patients of each ML-aGVHD score and specifically adopted to different time-points after transplantation (i.e. after 6-, 12- or 24 months) to allow individualized survival estimation within each of the 12 scores. For patients with a ML-aGVHD score of 1 to 4 (cohort ML-I), the most probable survival period was >24 months. For patients with ML-aGVHD scores of 5 to 8 (cohort ML-II), long-term survival (>24 months) probability decreased from 0.4 for ML-aGVHD score 5 to 0.2 for ML-aGVHD score 8. For patients with a ML-aGVHD scores of 9 to 12 (cohort ML-III), the most probable survival period was 6 months.

Conclusions: Machine Learning applied to aGVHD grading allowed refined aGVHD grading and improved association with OS and NRM in all severity cohorts. Improved aGVHD grading is warranted for distinct cohort definitions in clinical trials.



[Fig.1A) PCA1 reveals overlap in Glucksberg GVHD grading B) Kaplan-Meier analysis of ML-aGVHD grading]

Clinical Trial Registry: Not applicable.

Disclosure: ATT consultancy: Jazz Pharmaceuticals, CSL Behring, MSD. Travel subsidies: Neovii Biotech, all outside the submitted work. RB: travel subsidies Neovii, DWB received travel subsidies from Medac, all outside the submitted work. The other authors declare no competing financial interests within the submitted work.

O077.

Single-Cell Molecular Analysis Defines Characterization of Specific T Cell Subsets Correlate with Human Chronic GVHD and Bronchiolitis Obliterans

Haowen Xiao[1], Yang Gao[1], Yi Luo[2], Hongyu Shi[3], Weiwei Yin[4], Xun Zeng[4], He Huang[2]

[1]Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China, [2]The First Affiliated Hospital, Zhejiang University, Hangzhou, China, [3]Zhejiang PuLuoTing Health Tech Co. LTD, Hangzhou, China, [4]Zhejiang University, Hangzhou, China

Background: Despite advances that have improved survival after allogeneic hematopoietic stem cell transplantation (allo-HSCT), chronic graft-versus-host disease (cGVHD) remains a leading cause of late morbidity and mortality after transplant. Although rare with an estimated incidence of ~ 6% in allo-HSCT patients, bronchiolitis obliterans syndrome (BOS), the manifestation of cGVHD in the lungs, is associated with high morbidity and mortality with a 5-year survival of only 13%. However, to date, the exact mechanism of cGVHD and BOS remains unknown.

Methods: From November 2017 to May 2019, peripheral blood samples were obtained from 31 individual patients who underwent T-cell replete haploidentical allo-HSCT and survived ≥ 6 months post-HSCT at our center, in which 12 patients were without cGVHD, 7 patients experienced moderate cGVHD and 12 patients experienced severe cGVHD. The involved organs in patients with cGVHD are skin ($n = 10$), lung ($n = 6$), skin and lung ($n = 3$). According to those patients with cGVHD, peripheral blood samples were all obtained at *de novo* of cGVHD. We used single cell-based mass cytometry analysis to systematically profile immune cell populations in patients with varying grades of cGVHD. In parallel, each sample was flow-sorted into targeted immune cells for RNA sequencing analysis, respectively.

Results: We used 42 antibody panels in mass cytometry analysis, including the T cell panel designed to identify different populations of naive, memory, effector, regulatory, and exhausted T cells as well as markers for the identification of B cells, natural killer cells, plasma cells, granulocytes, and myeloid cells. In 4 million measured cells, we identified 41 immune cell phenotypes, in which there were 19 T cell phenotypes, 6 B cell phenotypes, 4 monocyte phenotypes, 4 granulocyte phenotypes, 2 NK and 2 NKT phenotypes, 2 dentritic cell (DC) phenotypes and 2 myeloid-derived suppressor cell (MDSC) phenotypes. To generate a comprehensive view of the immune ecosystem of cGVHD, we generated two-dimensional maps of the data using the dimensionality reduction algorithm t-SNE. This analysis showed a strong overlap between cGVHD of moderate and severe grades, but seperation from patients without cGVHD. There is also distinct multidimensional depiction of immune cellular subsets according to cGVHD-involved organs (skin or lung). More importantly, we isolated 3 subpopulations across T cells, a subset of CD4+ T cell and 2 subsets of CD8+ T cells, which were associated with the pathophysiologic mechanisms of BOS. Further targeted-cell RNA sequencing results revealed that the subset of CD4+ T cells with activated MAPK signaling, high expressions of IL1RAP and HLA-II protein complex may be BOS-inducing cells. The features implicated the subsets of CD8+ T cells, which may confer protective effect against BOS, were high expressions of CTLA-4 and IL-10.

Conclusions: This study revealed potential biomarkers and targets for immunotherapy of human cGVHD and BOS by single-cell molecular analytical methods.

Clinical Trial Registry: No.

Disclosure: Nothing to declare.

O078.

A Phase II Trial Evaluating the Use of the Histone Deacetylase Inhibitor Panobinostat for Graft-Versus-Host Disease (GVHD) Prevention

Lia Perez[1], Hugo Fernandez[1], Mohamed Khargan-Dabaja[2], Farhad Khimani[1], Brian Betts[3], Asmita Mishra[1], Ernesto Ayala[2], Fred Locke[1], Leonel Ochoa[1], Michael Nieder[1], Joseph Pidala[1], John Powers[1], Eva Sahakian[1], Claudio Anasetti[1]

[1]Moffitt Cancer Center, Tampa, FL, United States, [2]Mayo Clinic, Jacksonvile, FL, United States, [3]University of Minnesota, Minneapolis, MN, United States

Background: Histone deacetylase inhibitors have shown promising results for acute graft-versus-host disease (aGVHD), MDS maintenance and DLI epigenetic treatment after allogenic transplant (HCT) (Choi, Lancet Oncology,

2014; Bug, Leukemia, 2017; Cornelissen, EHA 2018). We demonstrated that panobinostat is tolerable to treat steroid refractory-aGVHD (Perez et al, BMT 2018). Herein, we build on our prior experience by adding panobinostat to tacrolimus and sirolimus for GVHD prevention (Pidala, Haematologica, 2012 and 2015) to abolish aGVHD while sparing the graft-versus-leukemia.

Methods: This is a phase II Simon's design; the null hypothesis will be rejected if the number of patients with grade II-IV aGVHD is 12 or less among 38 evaluable patients. Panobinostat at 5 mg orally 3 times/week was initiated on day −5 or −6 and continued for 26 weeks. Tacrolimus was given starting on day −3, with taper recommended from day +50, and sirolimus was started on day -1 with taper recommended from day +365.

Results: We enrolled 40 patients and 2 replaced (S0S $n = 1$; consent withdrawal $n = 1$) with 38 evaluable patients for a-GVHD. Indication for HCT included AML (17), ALL (4), MDS (8), MPN (4), and CML, CMML, PTCL, BPCDN and chronic neutropenia (1 each). Median patient age was 58 years (range, 19-72 years). HCT was performed with either HLA-8/8 matched unrelated-donor ($n = 28$) or related-donor ($n = 10$). The conditioning regimen was FLU/BU AUC 5300 (18 patients), FLU/BU AUC 3500 (1 patient), or fludarabine/melphalan 140 mg/m^2 (19 patients). All participants received mobilized PBSC. Panobinostat treatment was completed for 26 weeks in 23 patients and stopped early because of GVHD ($n = 5$, Day+35-141), adverse events ($n = 5$, DAY+ 7-65; rash $n = 3$, renal failure $n = 1$, dysesthesia $n = 1$), relapse ($n = 2$, Day+ 164-120), or consent withdrawal ($n = 2$, day 87-97).

Engraftment occurred in all patients at a median of 15 days (range, 12-21 days) for ANC over 500/μL and median of 16 days (range, 9-31 days) for platelets over 20,000/μL. Sinusoidal obstruction syndrome (SOS) occurred in 1 patient. Among 38 evaluable patients, a-GVHD grade II occurred in 6 patients, grade III in 1 patient, and grade IV in none, thus grades II-IV occurred in 7 (18%) of patients and the study met the primary endpoint. Three patients with a-GVHD grade II responded to prednisone at 1MG/KG prednisone, 1 to prednisone and ruxolitinib that had been discontinued before transplant and 3 did not require steroids. C-GVHD was mild in 10, moderate in 2, and severe in no patients. One patient with SOS died of non-relapse mortality. 7 (18%) patients relapsed at 4-8 months after transplant: 4 had AML (FLT3+ (3), DNMT3A/IDH1 mutations (1)), 1 had ALL, 1 had MPN and 1 had MDS with complex cytogenetics. At one year, OS was 87% [95% C.I. 0.77-0.98] and relapse-free survival was 77% [95% C.I. 0.64-0.91].

Conclusions: The combination of tacrolimus-sirolimus-panobinostat seems to be an effective strategy to reduce aGVHD in unrelated-donor or related-donor transplant with a 18% incidence of aGVHD compared with 43% reported with tacrolimus-sirolimus in our previous study. Correlative studies compared to control patients will be presented at the meeting.

Clinical Trial Registry: NCT02588339 https://clinicaltrials.gov/ct2/show/NCT02588339?term=panobinostat+and+GVHD&draw=1&rank=1

Disclosure: Nothing to declare.

O079.

Reduced Calcium Signaling is Associated with GVHD: Results from Preclinical Allosct Models and from a Prospective Multicenter Study

Katarina Riesner[1], Steffen Cordes[2], Martina Kalupa[1], Constanze Schwarz[1], Yu Shi[1], Sarah Mertlitz[1], Christophe Peczynski[3,4], Steffie van der Werf[5], Zinaida Peric[4,6], Christian Koenecke[4,7], Helene Schoemans[4,8], Rafael F. Duarte[4,9], Grzegorz W. Basak[4,10], Olaf Penack[1,4]

[1]Charité Universitätsmedizin Berlin, Berlin, Germany, [2]Max Delbrück Center for Molecular Medicine, Berlin, Germany, [3]EBMT Statistical Unit, Paris, France, [4]EBMT Transplant Complications Working Party, Paris, France, [5]EBMT Data Office Leiden, Leiden, Netherlands, [6]University Hospital Center Rebro, Zagreb, Croatia, [7]Hannover Medical School, Hannover, Germany, [8]UZ Leuven, Leuven, Netherlands, [9]Hospital Universitario Puerta de Hierro, Madrid, Spain, [10]Medical University of Warsaw, Warsaw, Poland

Background: Calcium (Ca^{2+}) is relevant for "danger-associated molecular pattern" (DAMP) signaling. Extracellular Ca^{2+} activates the multi-protein complex of the NLPR3 inflammasome via the calcium sensing receptor and the G-protein coupled receptor 6a (*GPRC6a*). Current literature demonstrated the involvement of calcium signaling in the regulation of various immune functions, including the allo-activation of T lymphocytes by antigen presenting cells. The role of calcium signalling during GVHD is unknown. We performed experiments in preclinical GVHD models and we performed a prospective non-interventional clinical study following the hypothesis that calcium signalling is involved in the pathophysiology of GVHD.

Methods: Murine models: We performed alloSCTs in the BALB/c→C57BL/6 model after 1200 cGy radiation

conditioning using mice deficient for *GPR-C6a* (C57BL/6 background) as alloSCT recipients. The severity of GVHD was monitored by daily clinical scoring and by histopathological analysis of tissue sections. *GPR-C6a* expression during GVHD was assessed by Real Time qPCR. In vivo T cell proliferation was performed with CFSE-labeled BALB/c CD3+ T cells in irradiated C57BL/6 *GPR-C6a* deficient mice. T cell proliferation after 96 hours and phenotype of inflammatory cells was analyzed by flow cytometry.

Human data: To investigate the association of Ca^{2+} serum levels before start of conditioning with allo-HSCT outcome, the EBMT Transplant Complication Working Party performed a prospective, non-interventional study including 360 patients from 17 centers in 10 countries (61 % male, 39 % female, Median age 53.28 years [17.12-71.29]) from 6/2014 until 3/2018. Patients with acute leukemia, lymphoma or myelodysplastic syndrome receiving a first matched sibling alloSCT from peripheral blood, regardless of conditioning were included. Outcomes between patients with high (> median 2.2mmol/l) and low (< =2.2mmol/l) Ca^{2+} serum levels before alloSCT were compared with univariate- and multivariate analysis using a cause-specific Cox model.

Results: In experimental models, we found significantly decreased *GPR-C6a* expression in the colon of alloSCT recipients, suggesting defects in calcium induced signaling during acute GVHD. In line, *GPR-C6a* deficient alloSCT recipients had significantly higher clinical and histopathological GVHD scores leading to increased mortality. As underlying mechanism, we found increased antigen presentation potential in *GPR-C6a* deficient alloSCT recipients demonstrated by higher proliferation rates of allogeneic wild type T lymphocytes as compared with wild type alloSCT recipients.

Underlining the clinical significance of these preclinical findings, we found a lower incidence of acute GVHD grades II-IV (HR=0.43 CI=0.26-0.69, $p = 0.0006$) and severe acute GVHD grades III-IV (HR=0.30 CI=0.14-0.63, $p = 0.002$) in patients with high Ca^{2+} serum levels before alloSCT as compared to patients with low Ca^{2+} serum levels. We observed no differences in incidence of chronic GVHD between the two cohorts, however extensive cGVHD was significantly decreased in patients with high Ca^{2+} serum levels (HR=0.50 CI=0.26-0.96, $p = 0.04$). This translated in a lower (but not significant) non-relapse-mortality of patients (HR=0.57 CI=0.32-1.002, $p = 0.06$) with Ca^{2+} serum levels above median vs below median.

Conclusions: Our pre-clinical and clinical results demonstrate a previously unrecognized role for calcium signaling in the pathophysiology of GVHD.

Clinical Trial Registry: not applicable.

Disclosure: Nothing to declare.

Graft-versus-host disease – preclinical and animal models

O080.

Dietary Stearic Acid Leads to a Severe AGVHD by Modulating the GUT Microbiota and Glucose Metabolism

Bingyu Yang[1,2,3], Shoubao Ma[1,2,3], Yan Yu[1,2,3], Xiaojin Wu[1,2,3], Depei Wu[1,2,3]

[1]Soochow University, Suzhou, China, [2] The First Affiliated Hospital of Soochow University, Suzhou, China, [3]Institute of Blood and Marrow Transplantation, Medical College of Soochow University, Suzhou, China

Background: Acute graft-versus-host disease (aGVHD) is a major clinic issue that need to be addressed urgently in hematopoietic stem cell transplantation (HSCT). By using the gas chromatography-mass spectrometry-based metabonomic approach, we previously identified that serum stearic acid/palmitic acid ratio on day 7 was an excellent biomarker to predict aGVHD after allo-HSCT, suggesting an important role of saturated fatty acid intake in the pathogenesis of aGVHD. However, the mechanism remains unknown.

Methods: We investigated the dynamic changes and the underlying regulatory mechanism of stearic acid in aGVHD in both humans and mice. Serum metabolic features and intestinal microbiota composition were assessed.

Results: In mouse aGVHD model, we found that high stearic acid diet (HSAD), but not palmitic acid diet, significantly aggravated aGVHD, and its promoting role was mediated by gut microbiota. 16S rRNA sequencing identified *Akkermansia* muc*iniphila (Akk)* was obviously increased in HSAD recipient. Add back *Akk* in WT mice ameliorated aGVHD-related mortality. In addition, HSAD recipients of IFN-$\gamma^{-/-}$ allografts or ROR$\gamma t^{-/-}$ allografts had improved survival compared with recipients of WT allografts, indicating that Th1 and Th17 cells were involved in HSAD induced aGVHD. Furthermore, serum metabolic analysis demonstrated that the increased *Akk* was coincided with abnormalities in glucose homeostasis. Meanwhile, if glucose utilization was limited in vivo as a consequence of therapy with the glycolytic inhibitor 2-deoxy-glucose (2DG), HSAD recipients had improved survival compared with PBS controls. We elucidated that exposure to high stearic acid causes gut dysbiosis and may subsequently contribute to the development of proinflammatory Th1 and Th17 cells and abnormalities in glucose metabolism, thereby exacerbating aGVHD.

Conclusions: We have thus revealed a previously unrecognized mechanism of high stearic acid intake in the

pathogenesis of aGVHD. Our findings hold promise of therapeutic targeting of the gut microbiota and glucose metabolism as treatment for aGVHD.

Disclosure: Nothing to declare.

O081.

Granulocyte Colony-Stimulating Factor-Primed Donor T Cells Attenuate Murine Acute GVHD Through Regulating T Cell Differentiation in Target Organs

Yang Zhou[1], Ying-Jun Chang[1], Le-Qing Cao[1], Yu Wang[1], Lan-Ping Xu[1], Xiao-Hui Zhang[1], Kai-Yan Liu[1], Xiao-Jun Huang[1,2]

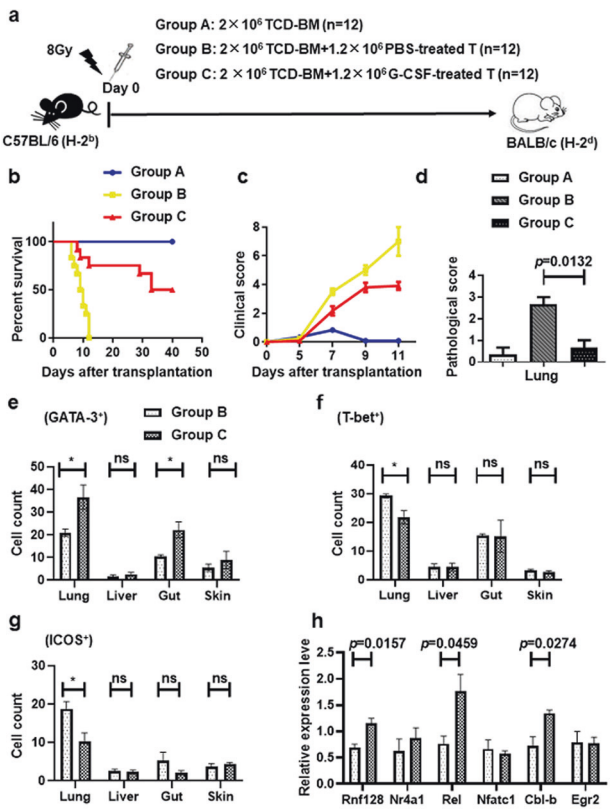
[1]Peking University People's Hospital, Peking University Institute of Hematology, National Clinical Research Center for Hematologic Disease, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Peking University, Beijing, China, Beijing, China, [2]Peking-Tsinghua Center for Life Sciences, Academy for Advanced Interdisciplinary Studies, Peking University, Beijing, China, Beijing, China

Background: The roles of treating healthy donors with granulocyte colony-stimulating factor (G-CSF) played in alleviation of acute graft-versus-host disease (GVHD) after allogeneic stem cell transplantation (allo-SCT) have been demonstrated. However, the mechanisms of which remain to be elucidated.

Methods: For establishing GVHD mouse model, lethally irradiated BALB/c recipient mice were transplanted with T cell-depleted bone marrow (TCD-BM) (Group A), or TCD-BM plus purified spleen T cells from PBS (Group B)- or G-CSF (Group C)- treated B6 donor mice (Fig. 1a). Survival rates, clinical and pathological GVHD score and histological examination were performed. Subsets and surface costimulatory molecules of T cells from donor spleen and recipient GVHD target organs (gut, skin, liver, lung) were analyzed. Besides, the expression of genes related to tolerance was detected in T cells from recipient mice by qRT-PCR.

Results: (1) G-CSF-treated donor T cells attenuated murine aGVHD by indicating prolonged survival, ameliorated weight loss, decreased clinical score (Fig. 1b, c). We found a significant lower pathological score in lung of group C recipients compared with group B recipients (Fig. 1d), the same trend was also observed in gut, liver and skin (Data not shown). (2) The expression of transcription factors GATA3, T-bet, and RORγt in $CD4^+$ T cells was determined by flow cytometry, we found an induction of T helper 2 (Th2) differentiation in both donor and recipient spleens. Same result was also detected in GVHD target organs by immunohistochemical staining, the mean number of GATA-3-expressing cells per visual field in group C recipient lung ($n = 3$ *vs.* 3, 36.7 *vs.* 21, P=0.0482) and gut ($n = 3$ *vs.* 3, 22.2 *vs.* 10.4, P=0.0307) was significantly higher compared with that of group B recipients, while T-bet-expressing ($n = 3$ *vs.* 3, 21.8 *vs.* 29.2, P=0.0373) and RORγt-expressing cells ($n = 3$ *vs.* 3, 5.1 *vs.* 8.2, P=0.0392) were much lower (Fig. 1e, f). The expression of Foxp3 didn't increase in neither donor nor recipient spleens, but GVHD organ (the mean number of Foxp3-expressing cells per visual field in group C recipient lung 13.4, *vs.* group B recipient 8.1, P=0.0444). (3) We found G-CSF reduced inducible co-stimulator (ICOS) expression in both donor and recipient spleen $CD4^+$T cells, also the GVHD target organ (Fig. 1g). (4) We detected an up-regulation of tolerance-related genes in $CD4^+$T cells from group C recipient spleen, including Rnf128, Cbl-b and Rel (Fig. 1h).

Conclusions: Our results suggest G-CSF-treated donor T cells could attenuate murine aGVHD through regulating the differentiation of T cells, reducing ICOS in $CD4^+$ T cells and enhancing expression of tolerance-related genes, not only in donor and recipient spleen, but also in the GVHD target organs. These data provide a novel insight into the immune regulatory effects of G-CSF on acute GVHD after allo-SCT.



[Fig.1]

Disclosure: Nothing to declare

O082.

Mtor Regulate Generation and Function of PMN-MDSCS and Play Protection Role in Acute Graft-Versus-Host Disease

Xiaoqing Li[1,2], Lin Xu[1,2], Yamin Tan[1,2], He Huang[1,2], Yu Lin[1,2]

[1]The First Affiliated Hospital, Zhejiang University, Hangzhou, China, [2]Institute of Hematology, Zhejiang University, Hangzhou, China

Background: Myeloid-derived suppressor cells (MDSCs) represent a population of heterogeneous myeloid cells that are characterized by a remarkable ability to suppress the activity of T cells and NK cells. MDSCs includes two major subsets: polymorphonuclear MDSCs(PMN-MDSCs) and monocytic MDSCs (M-MDSCs). MDSCs have been proven to play positive role in protecting acute graft-versus-host disease(aGVHD). We aim to find effective methods to regulate the generation and function of MDSCs and explore its role in aGVHD.

Methods: $mTOR^{KO}$ MDSCs were obtained from bone marrow of $mTOR^{fl/fl}$, Lysm-cre mice. MDSCs were cocultured with activated $CD3^+$ T cells to evaluate the suppressive function. Immunosuppressive factors were assessed by qPCR and Western blot. Short hairpin (sh) RNA was used to downregulate STAT3. aGVHD models were built. $mTOR^{fl/fl}$ PMN-MDSCs and $mTOR^{KO}$ PMN-MDSCs were co-injected with the allogeneic transplant on Day 0.

Results: The proportion of PMN-MDSCs and M-MDSCs in bone marrow was comparable in $mTOR^{fl/fl}$ and $mTOR^{fl/fl}$, Lysm-cre mice. mTOR depletion did not affect the apoptosis and cell cycle of MDSCs. But the expression of cKit and CXCR4 were higher in $mTOR^{KO}$ PMN-MDSCs, which revealed that $mTOR^{KO}$ cells obtained the characteristic of precursor myeloid cells. The function assay showed that $mTOR^{KO}$ PMN-MDSCs expressed strong immunosuppressive ability compared with $mTOR^{fl/fl}$ cells. Results of qPCR and Western blot revealed that Arg1 and iNOS2 had significantly up-regulated expression in $mTOR^{KO}$ PMN-MDSCs. L-NMMA, an inhibitor of iNOS, and nor-NOHA, an inhibitor of Arg1, were applied to the functional in vitro assay. Both L-NMMA and nor-NOHA reduced the immunosuppressive activity efficiently. We next investigated the potential mechanisms underlying mTOR regulation. RNA-seq revealed that STAT pathway enriched in $mTOR^{KO}$ PMN-MDSCs and one of the most significant changes was associated with STAT3. This was confirmed by qPCR and Western Blot. Both STAT3 inhibitor, Stattic and knockdown STAT3 with shRNA can significantly reduce the suppressive ability of $mTOR^{KO}$ PMN-MDSCs, thereby implicating that mTOR regulate the suppressive function of PMN-MDSCs through STAT3 pathway.

Next, we explored the therapeutic capacity of $mTOR^{KO}$ PMN-MDSCs in the models of aGVHD. Reduced mortality and lower aGVHD scores were observed in $mTOR^{KO}$ PMN-MDSCs infusion group. Although we found that the transfused PMN-MDSCs persisted no more than 10 days in both two co-injection groups. Th1/Th2 proportion in peripheral blood and spleen were lower in $mTOR^{KO}$ PMN-MDSC infusion group, while Treg was upregulated at day 7. Also, the serum proinflammatory cytokines, including IL-1β, IL-2, IL-6, IFN-γ were reduced in $mTOR^{KO}$ PMN-MDSC infusion group. At day 14 and day 28, the absoluted number of donor-derived PMN-MDSCs remarkably increased in bone marrow, spleen and liver of $mTOR^{KO}$ PMN-MDSCs infused models. The immunosuppressive ability of PMN-MDSCs from $mTOR^{KO}$ PMN-MDSCs infusion group were much more robust than aGVHD group and $mTOR^{fl/fl}$ PMN-MDSCs infusion group at day 28.

Conclusions: mTOR is an effective intrinsic regulation factor for the differentiation and immunosuppressive function of PMN-MDSCs. $mTOR^{KO}$ PMN-MDSCs transfusion can play a protective role to alleviate the cytokine storm at the initial stage and promote the quantity and function recovery of donor-derived PMN-MDSCs in aGVHD.

Disclosure: Nothing to declare.

O083.

Full Regulatory T Cell Reconstitution Before T Cell Transfer Prevents Graft-Versus-Host Disease by Suppressing Costimulation and T Cell Activation in a Haploidentical Model

Barbara Fazekas de St Groth, Holly Bolton, Aster Pijning

University of Sydney, Sydney, Australia

Background: We have shown that graft-versus-host disease in a haploidentical model can be prevented by full regulatory T cell reconstitution before T cell transfer (Bolton et al, (2015) J Clin Invest 125:3627). Here we investigated the underlying mechanism.

Methods: Haploidentical bone marrow transplants were performed in B10.BR⇒[C57BL/6xB10.BR] and B10.BR⇒[B10.SxB10.BR] models. All irradiated hosts (600 Rad × 2) were transplanted on day 1 with 5 × 10^6 T-cell depleted B10.BR bone marrow cells and received 2.5x10^6 regulatory T cell-depleted B10.BR CD4 T cells on day 8. Three experimental groups were included in each experiment: Regulatory T cell

reconstituted mice received 2.5x10^6 bead-selected B10.BR regulatory T cells on day 1 and second-daily IL-2/anti-IL-2 antibody complexes to support regulatory T cell reconstitution. Co-transferred mice received 2.5x10^6 bead-selected B10.BR regulatory T cells on day 8. The graft-versus-host disease control group received no regulatory T cells.

CFSE-labelled regulatory T cell-depleted B10.BR CD4 T cells provided a readout of T cell proliferation in the B10.BR⇒[C57BL/6xB10.BR] model. To unequivocally identify alloreactive T cell proliferation, a small number of CFSE-labelled IAs-reactive monoclonal 5C.C7 T cell receptor transgenic T cells on a B10.BR RAG-/- background (containing no regulatory T cells) were included with the regulatory T cell-depleted B10.BR CD4 T cells in the B10.BR⇒[B10.SxB10.BR] model. Cells were harvested at days 4 and 7 and proliferation and differentiation were detected using flow cytometry. Intracellular cytokine production was determined after in vitro restimulation. Small bowel cells were isolated on day 10-11 and differentiation state and cytokine production were determined by flow cytometry.

Results: Regulatory T cell reconstitution profoundly suppressed activation, proliferation, differentiation and cytokine production by alloreactive CD4 T cells. Entry into sites of graft versus host disease, such as small bowel, was markedly reduced, consistent with the absence of pathology and weight loss. However cytokine production by those cells that did reach the small bowel was not distinguishable from that in controls, indicating that the suppression of clinically apparent graft-versus-host disease is due to the decrease in the number of infiltrating cells, not a change in their phenotype.

Conclusions: These data indicate that normalising expression of CD80/86 in a haploidentical bone marrow transplant model has a profound effect on the activation, proliferation and differentiation of allogeneic T cells and is sufficient to prevent acute graft-versus-host disease. The major mechanism is a reduction in the number of effector cells entering the tissues. The level of CD80/86 at the time of initial T cell activation is crucial, and requires prior regulatory T cell reconstitution, while co-transfer of regulatory T cells and alloreactive T cells is less effective in reducing the alloreactive T cell response.

Disclosure: Nothing to declare.

O084.

Targeting of Chemokine Receptor 7 Prevents Acute Graft-Versus-Host Disease

Cecilia Muñoz[1,2], Carlos Cuesta-Mateos[1,3], Itxaso Portero-Sainz[1], Valle Gómez García de Soria[1], Marina García-Peydró[2,4], Juan Alcain[2,4], Patricia Fuentes[2,4], Raquel Juárez[3], Yaiza Pérez-García[1], Tamara Mateu-Albero[1], Paula Díaz-Fernández[1], Lorena Vega-Piris[1], Ana Marcos-Jiménez[1], Laura Cardeñoso[1], María Luisa Toribio[2,4]

[1]*Instituto de Investigación Sanitaria Princesa, Madrid, Spain*, [2]*Universidad Autónoma de Madrid, Madrid, Spain*, [3]*Immunological and Medicinal Products, S.L., Madrid, Spain*, [4]*Centro de Biología Molecular Severo Ochoa (CBM-SO), Madrid, Spain*

Background: Graft-versus-host disease (GVHD) is the main complication after HSCT. We previously unveiled a correlation between proportions of C-C motif chemokine receptor 7 $(CCR7)^+$ T-cells in the apheresis and the risk of developing GVHD.

Methods: We evaluated in vivo whether the treatment with an anti-human CCR7 monoclonal antibody (mAb) was a suitable strategy to prevent or treat GVHD in pre-clinical xenogeneic models of acute GVHD by engrafting human peripheral blood mononuclear cells (hPBMC). The anti-CCR7 mAb or an isotype control (IC) were dosed at ~10 mg/kg and given every 3 days until a total of 5 doses.

Results: The xeno-reactivity peak was detected in the peripheral blood (PB) of mice by day +5, mirroring the allogenic T-cell activation in patients. This kinetics prompted us to challenge the antibody in three models: before the peak ("preventive model"), during the peak ("cyclophosphamide-like model") and after the peak ("therapeutic model") could be detected in PB. In the preventive model, the antibodies were administered two hours before hPBMC inoculation. All animals treated with the anti-CCR7 mAb remained alive at the time when the last mouse treated with the IC had to be euthanized. The active-drug group was sacrificed on day 30, once the median OS exceeded double OS in the IC group which is considered as a *bona-fide* disease-free period. Tissue analyses from the anti-CCR7 group of mice revealed practically undetectable proportion of T-cells in PB, bone marrow (BM) and spleen, unlike the IC mice. In the "cyclophosphamide-like" model we started treating animals on day +5, once weight loss and human $CD3^+$ cells were detected in mice PB. Anti-CCR7 mAb resolved xeno-reactivity peak whereas T-cells expanded in PB from animals treated with an IC. Again, all control recipient mice where sacrificed due to clinical signs whereas anti-CCR7 group showed no signs of disease. Accordingly, tissues showed a reduced number of T-cells in the anti-CCR7 mAb group compared to a significantly higher proportion of infiltration in PB, BM, and spleen from control animals. In the therapeutic model the treatment was initiated on days +3, +7, or +10. The best results were

seen in the group treated on day +3. These animals gained weight and survived until the experiment was purposely terminated. Compared to IC, the anti-CCR7 mAb extended survival when administered for the first time on days +7 and +10.

Regarding the mechanisms of action, the selected anti-CCR7 mAb neutralized in vitro migration of naïve and central memory T-cells towards CCR7 ligands and depleted target $CCR7^{positive}$ subsets through complement activation. Both mechanisms of action spared $CCR7^{negative}$ subsets, including effector and effector memory T-cells which may mediate graft versus leukemia effect and immunity against infections. Accordingly, a multivariate logistic regression analysis confirmed that the numbers of donor T-cells $CCR7^{positive}$ cells in the graft was not a risk factor for cytomegalovirus reactivation or the recurrence of the underlying disease.

Conclusions: These findings provide a promising new strategy to prevent and treat acute GVHD, a condition where new specific, safety and effective treatment is needed.

Disclosure: Carlos Cuesta-Mateos declares that he is an employee of Immunological and Medical Products (IMMED S.L.), Madrid, Spain. Cecilia Muñoz-Calleja is a consultant of IMMED S.L., has a granted patent for the use of therapeutic antibodies targeting CCR7 in cancer and has received research funds from IMMED.S.L.

Haematopoietic stem cells

O085.

Haploidentical Donor Beats Matched Sibling Donor for Pre-Transplantation MRD Positive all: A Phase 3 Biologically Randomized Study

YingJun Chang[1], Yu Wang[1], Lan-Ping Xu[1,2], Xiao-Hui Zhang[1], Huan Chen[1], Yu-Hong Chen[1], Feng-Rong Wang[1], Wei Han[1], Yu-Qian Sun[1], Chen-Han Yan[1,2], Fei-Fei Tang[1], Xiao-Dong Mo[1,2], Yan-Rong Liu[1], Kai-Yan Liu[1], Xiao-Jun Huang[1,2,3]

[1]Peking University People's Hospital, Peking University Institute of Hematology, National Clinical Research Center for Hematologic Disease, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Beijing, China, [2]Research Unit of Key Technique for Diagnosis and Treatments of Hematologic Malignancies, Chinese Academy of Medical Sciences, Beijing, China, [3]Peking-Tsinghua Center for Life Sciences, Beijing, China

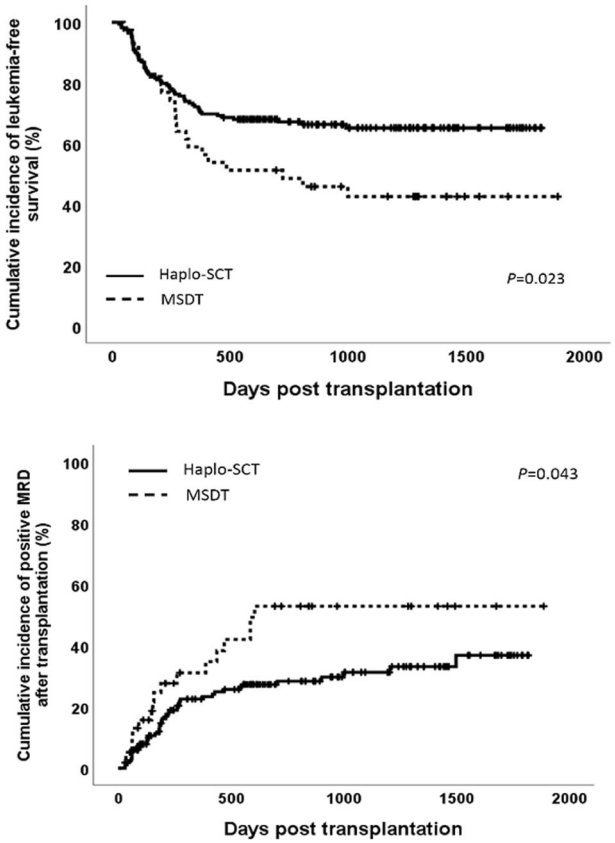
Background: Previous reports suggest a benefit associated with haploidentical donor transplantation (HIDT) compared to matched sibling donor transplantation (MSDT) in certain contexts, and the choice of optimal candidates warrants further investigation.

Methods: We designed a prospective biologically randomized study to evaluate donor options between acute lymphoblastic leukemia (ALL) patients positive for measurable residual disease (MRD) pre-transplantation who underwent HIDT (n = 169) or MSDT (n = 39). Patients were treated with a myeloablative conditioning regimen according to a previous study by our group (*Clin Cancer Res*. 2016;22 (14):3467-3476). Eight-color multiparameter flow cytometry (MFC) was performed in all patients as a routine clinical test on bone marrow aspirate samples that were obtained as part of the baseline assessment before SCT, as well as approximately 30 to 180 days after transplantation. The primary study end-point was leukemia-free survival (LFS). Secondary end-points were the engraftment rate, the incidence of acute graft-versus-host disease (GVHD) grades II-IV and chronic GVHD, and the cumulative incidence of MRD after transplantation, relapse, non-relapse mortality, and overall survival (OS).

Results: The 100-day cumulative incidence of platelet engraftment in the HIDT group was significantly higher in the MSDT group (95%, 95% CI, 92%-98% vs. 100%, $P<$ 0.001). The 100-day cumulative incidence of acute GVHD grades II-IV in the HIDT group was similar to that of the MSDT group (21%, 95% CI, 17%-27% vs. 23%, 95% CI, 10%-36%; P=0.884). In addition, the 3-year cumulative incidence of chronic GVHD was comparable between the HIDT and MSDT groups (44%, 95% CI, 36%-52% vs. 48%, 95% CI, 31%-65%; P=0.850). The cumulative incidence of MRD post-transplantation was 26% (95% CI, 19%-33%) and 44% (95% CI, 28%-60%) for HIDT and MSDT, respectively (P=0.043). Compared to the HIDT cohort, the MSDT cohort had a higher 3-year cumulative incidence of relapse (CIR; 47%, 95% CI, 31%-63% *vs*. 23%, 95% CI, 17%-29%; P=0.006) and lower 3-year probability of LFS (43%, 95% CI, 27%-59% *vs*. 65%, 95% CI, 58%-72%; P=0.023) and OS (46%, 95% CI, 30%-62% *vs*. 68%, 95% CI, 61%-75%; P=0.039), without a difference in non-relapse-mortality (10%, 95% CI, 1%-19% *vs*. 11%, 95% CI, 6%-16%; P=0.845). Multivariate analysis showed that HIDT is associated with a low CIR (HR=0.364; 95% CI, 0.202-0.655; P=0.001) and better LFS (HR=0.414; 95% CI, 0.246-0.695; P=0.001) and OS (HR=0.380; 95% CI, 0.220-0.656; P=0.001).

Conclusions: In conclusion, HIDT is better than MSDT in view of favorable anti-leukemia activity for patients with pre-transplantation MRD positive ALL. The current study paves the way to determine that haploidentical donors are

the preferred choice regardless of available matched sibling donors in a subgroup population.



[Figure]

Clinical Trial Registry: NCT02185261
http://apps.who.int/trialsearch/Default.aspx
Disclosure: Nothing to declare.

O086.

Results of Hematopoietic Stem Cells Transplantation from Matched Related Donor with TCRαβ+/CD19 +-Depletion and a Fixed Dose Memory T Cell (CD45RA-Depleted) Add-Back

Anna Bogoyavlenskaya, Larisa Shelikhova, Maria Ilushina, Dmitriy Balashov, Anna Livshits, Sergey Blagov, Maria Dunaykina, Rimma Khismatullina, Svetlana Kozlovskaya, Elvira Sultanova, Elena Kurnikova, Yakov Muzalevsky, Alexey Kazachenok, Natalya Miakova, Dmitriy Litvinov, Galina Novichkova, Alexei Maschan, Michael Maschan

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

Background: Despite overall high success rate of HSCT from matched family donors, relapse, graft-versus-host disease (GvHD) and graft failure remain problematic and may cause failure in up to 30% of MFD transplantations. αβ T cell depletion is designed to prevent the development of clinically significant GVHD, achieve a high level of engraftment and rapid immune reconstruction. We have used a fixed dose of $1x10^6$/kg CD45RA-depleted mononuclear cells (memory DLI) on day 0 in order to improve immune reconstitution.

Methods: A total of 30 children (19 - acute leukemia, 11 - non-malignant diseases, 10 female, 21 male, median age 10.5 y) underwent allo-HSCT from matched related donor between 01.09.2014 and 01.04.2019.

Patients with primary immune deficiency received fludarabine, ATG and either busulfan ($n = 3$) or treosulfan ($n = 3$). Patients with severe aplastic anemia (n-4) received cyclophosphamide/fludarabine/ATG. A patient with thalassemia (n-1) - treosulfan, thiotepa, fludarabine, ATG. As serotherapy rATG (n-10) or hATG (n-1) were used. Rituximab was used in all pts. For GVHD prophylaxis an abbreviated calcineurin-based regimen was used. Among patients with acute leukemia conditioning regimen included: fludarabine (n-19), thiotepa (n-19), and either treosulfan (n-11) or TBI (12 Gy) (n-8). As GVHD prophylaxis we used bortezomib (n-16), rituximab (n-19) and abatacept (n-19). aβ T cell depletion with CliniMACS was used in all cases. The median dose of CD34+ cells was 12.5×10^6/kg, aβ T cells - 21.5×10^3/kg. Median time of follow-up for survivors was 2.3 years (range, 0.3 - 4.5). All patients on day 0 received 1×10^6/kg doses of CD45RO T cells.

Results: Primary engraftment was achieved in all evaluable pts (100%) with full donor chimerism, the median time to neutrophil and platelet recovery was 12 and 14 days. 2-year TRM in whole group was 0% (95%CI:0-25). Death occurred in patients with AL in two cases as a result of relapse and further progression. CI of relapse in pts with AL was 32% (95%CI:16-66). CI aGVHD (stage ≥ 2) was 10% (95%t: 3-30) for malignant vs. 0 % (95% CI) for non-malignant diseases. CI cGVHD in whole groups was 7% (95% CI: 2-26,5). For all pts 2-year pEFS (relapse=death) was 80% (95%C:66-94), pOS - 97% (95%CI:85-100). Signs of graft failure among patients with non-malignant disorders were not recorded in any of the cases.

Conclusions: We confirm that the depletion of αβ T cells from related graft in combination with intensive conditioning regimen and additional infusion 1×10^6/kg CD45RO T cells on day 0 provides is associated with high rate of engraftment, very low risk of GVHD, absent TRM, and promising long-term survival in a cohord of children with malignant and non-malignant HSCT indications.

Disclosure: Nothing to declare.

Haemoglobinopathy and inborn errors

O087.

Succesful HLA-Mismatched HSCT in Paediatric Patients with Hemoglobinopathies Using ATG Serotherapy and Posttransplant Cyclophosphamide

Lisa V. E. Oostenbrink, Alexander B. Mohseny, Emma S. Pool, Els C. M. Jol-van der Zijde, Anja M. Jansen-Hoogendijk, Carly Vervat, Astrid G. S. van Halteren, Robbert G. M. Bredius, Frans J.W. Smiers, Maarten J. D. van Tol, Marco W. Schilham, Arjan C. Lankester

Leiden University Medical Center, Leiden, Netherlands

Background: HSCT is a curative treatment for thalassemia and sickle cell disease (SCD). However, HSCT procedures are restrained by limited availability of HLA-matched donors. The use of HLA-mismatched (un)related donors may overcome this limitation. Nonetheless, the use of such alternative donors is historically associated with a higher incidence of transplant-related complications and mortality. Recently, posttransplant cyclophosphamide (PT-CY) has emerged as a promising approach to limit the risk of GvHD in this setting. In this study, we compared outcome in HLA-mismatched (un)related HSCT using the PT-CY approach with regular HLA-identical or HLA-matched HSCT without PT-CY in a cohort of paediatric hemoglobinopathy patients.

Methods: Thirty-seven children ($n = 23$ HLA-identical or 10/10-matched unrelated donors, no PT-CY group; $n = 14$ HLA-mismatched (un)related donors, PT-CY group), who received a non-depleted BM graft for the treatment of SCD ($n = 22$) or thalassemia ($n = 15$) between November 2012 and November 2019 were included. All patients received treosulfan/fludarabine myeloablative conditioning regimens, to improve graft rejection rate in 22 no PT-CY and 8 PT-CY patients thiotepa was added. ATG-Thymoglobulin® was administered at a total dose of 6-10mg/kg. GvHD prophylaxis included ciclosporin and methotrexate for the no PT-CY group, while patients in the PT-CY group received 50mg/kg/day CY on days +3 and +4, and ciclosporin and mycophenolate mofetil starting at day +5. Serum samples (pre-conditioning, day 0; +1; +2; +3; +4 and +6 weeks and +2 and +3 months post-HSCT) were analysed by quantitative flowcytometry on HUT78 cells to determine the level of active ATG. Lymphocyte subsets were measured by flowcytometry until +12 months after transplantation.

Results: Neutrophil engraftment occurred in 100% *vs*. 90% at median day +22 (no PT-CY) and day +27 (PT-CY) ($p = 0.003$). Likewise, T-cell recovery was significantly delayed in the PT-CY group (203 *vs*. 21 cells/μL, $p = 0.013$, 3 weeks post-HSCT) though no difference in the day post-HSCT when active ATG fell below the lympholytic level of 1 AU/mL was seen between both groups (no PT-CY median day 0, PT-CY median day -1, $p = 0.14$). Graft failure within 1 year post-HSCT occurred in 2 no PT-CY patients and 3 PT-CY patients ($p = 0.27$). The incidence of aGvHD and cGvHD was not significantly higher in the PT-CY group compared to the no PT-CY group ($p = 0.61$ and $p = 0.64$ respectively, see graph). Extensive aGvHD (grade III-IV) only occurred in the no PT-CY group. The incidence of CMV reactivation was higher in the PT-CY group (55% *vs*. 20%). OS and EFS (events: death, extensive cGvHD, non-engraftment, rejection) were similar in both groups (OS no PT-CY 96% *vs*. PT-CY 100%; EFS no PT-CY 76% *vs*. PT-CY 79%, $p = 0.96$, see graph).

Conclusions: Our data show that in the setting of treosulfan-based myeloablative HSCT the use of mismatched donors plus PT-CY results in similar OS and EFS as obtained with matched donor HSCT without PT-CY in children with hemoglobinopathies. Delayed neutrophil and early T-cell recovery in the PT-CY group did not negatively impact outcome. Therefore, in the absence of a matched donor, a mismatched donor using the platform of treosulfan-based myeloablative conditioning, ATG and PT-CY may be considered an equally safe and effective treatment option.

Disclosure: The work described in this study is funded in part by Neovii Biotech (Rapperswil, Switzerland).

O088.

Outcomes of Allogeneic Hematopoietic Stem Cell Transplant in Patients with Cerebral Adrenoleukodystrophy Vary by Donor Cell Source, Conditioning Regimen, and Stage of Cerebral Disease Status

Jaap Jan Boelens[1], Robert Chiesa[2], Christine Duncan[3], Simon Jones[4], Neena Kapoor[5], Jörn-Sven Kühl[6], Caroline Lindemans[7], Vinod K. Prasad[8], Caroline Sevin[9], Esther Shamir[10], Wai Chin[10], Elizabeth McNeil[10], Paul J. Orchard[11]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, United States, [2]Great Ormond Street Hospital for Children, London, United Kingdom, [3]Boston Children's Hospital and Dana-Farber Cancer Institute, Boston, MA, United States, [4]Manchester University NHS Foundation Trust, Manchester, United Kingdom, [5]Children's Hospital Los Angeles, Los Angeles, CA, United States, [6]University Clinic Leipzig, Leipzig, Germany, [7]Princess Maxima Center and UMC Utrecht, Utrecht, Netherlands, [8]Duke Children's Hospital and Health Center, Durham, NC, United States, [9]Hôpital

Universitaire Hôpital Bicêtre-Hôpitaux Universitaires Paris Sud, Paris, France, [10]*Bluebird Bio, Inc., Cambridge, MA, United States*, [11]*University of Minnesota Masonic Children's Hospital, Minneapolis, MN, United States*

Background: Cerebral adrenoleukodystrophy (CALD) is characterized by inflammatory demyelination leading to progressive loss of neurologic function and death. Early treatment of CALD with allogeneic hematopoietic stem cell transplantation (allo-HSCT) has a beneficial effect on clinical indices of disease and long-term survival but is associated with immunologic risks. We aim to understand how outcomes of allo-HSCT differ by disease stage, donor cell source, and conditioning regimen.

Methods: ALD-103 is an observational study designed to evaluate outcomes in patients with CALD ≤17 years old who received allo-HSCT. Retrospective data (patients receiving transplants January 2013 or later) are collected, and/or patients are followed prospectively for 4 years after their last allo-HSCT. Assessments include survival free of major functional disabilities (MFD-free), and neurologic and safety evaluations.

Results: As of February 2019, 47 boys were enrolled in ALD-103. Efficacy was analyzed for advanced (Loes >9 or Neurologic Function Score [NFS] >1; $n = 10$) and two early disease cohorts (ED1, Loes ≤4 and NFS ≤1 [$n = 21$]; ED2, Loes >4-9, and NFS ≤1 [$n = 9$]). Safety was analyzed by donor source and conditioning regimen. There was no statistical difference in survival and neurologic findings between the ED cohorts. Patients with advanced CALD had the worst outcomes. At 24 months, overall and MFD-free survival were 90.5% (95% CI 67.0, 97.5) and 78.9% (53.2, 91.5) for ED1, 85.7% (33.4, 97.9) and 70.0% (22.5, 91.8) for ED2, and 52.5% (16.8, 79.3) and 35.0% (8.5, 64.0) for advanced CALD, respectively. Most patients in both ED cohorts, and fewer of those with advanced CALD, had stable Loes scores and NFS through last follow up. Of patients with baseline gadolinium enhancement (GdE+) and follow-up data, 9/9 in ED1, 4/5 in ED2, and 2/4 in the advanced disease cohort had resolution of GdE+ throughout follow-up. Acute (Grade ≥2) and chronic graft-versus-host disease (GVHD) occurred in 23.5% (8/34) and 27.6% (8/29) of patients, respectively. One-year transplant-related mortality was 12.1% (4/33), and 21.6% (8/37) of patients had engraftment failure. There were no substantial observed differences in most transplant-related outcomes by donor cell source. However it is observed that more patients who received umbilical cord (UC) cells from an unrelated donor had engraftment failure (38.9%, 7/18) compared to patients who received bone marrow (BM) or UC cells from a matched sibling donor (MSD), or BM cells from an unrelated donor (0% for both [0/8]; $p = 0.062$). Importantly, while transplants performed using cells from a MSD are considered safe, they resulted in chronic GVHD in 28.6% (2/7) of patients. Trade-offs in transplant-related risks with myeloablative conditioning were noted. Compared to busulfan/fludarabine (Bu/Flu), the use of busulfan/cyclophosphamide increased the risk of acute and chronic GVHD (6.3% [1/16] vs. 42.9% [6/14] [$p = 0.0309$] and 13.3% [p=2/15] vs. 54.5% [6/11] [$p = 0.0384$], respectively), while myeloablative conditioning with Bu/Flu resulted in higher rates of engraftment failure (28.6% [6/21] vs. 0% [0/11], $p = 0.0711$).

Conclusions: These data suggest that treatment in early CALD provides better efficacy outcomes irrespective of the stage of early disease, although neuropsychological outcome data are not yet available. Transplant-related risks highlight an unmet need for improved safety outcomes.

Disclosure: Jaap Jan Boelens, Robert Chiesa, Jörn-Sven Kühl and Christine Duncan have received consulting fees from bluebird bio. Esther Sharmir, Wai Chin, and Elizabeth McNeil are employees of bluebird bio. Paul J. Orchard has received grants from bluebird bio. Simon A. Jones, Neena Kapoor, Caroline Lindemans and Vinod K. Prasad have nothing to disclose.

O089.

The Role of HLA Matching In Unrelated Donor Hematopoietic Stem Cell Transplantation for Sickle Cell Disease in Europe

Eliane Gluckman[1,2], Josu De la Fuente[3], Barbara Cappelli[1,2], Graziana M. Scigliuolo[1,2], Fernanda Volt[1,2], Karina Tozatto Maio[1,2,4], Vanderson Rocha[2,5], Tommaso Mina[6], Farah O'Boyle[3], Frans Smiers[7], Claudia Bettoni Da Cunha-Riehm[8], Elisabetta Calore[9], Sonia Bonanomi[10], Stelios Graphakos[11], Anna Paisiou[11], Michael H. Albert[12], Annalisa Ruggeri[1,2,13], Marco Zecca[6], Arjan C. Lankester[7], Selim Corbacioglu[14]

[1]Monacord Centre Scientifique, Monaco, Monaco, *[2]Eurocord, Hopital Saint-Louis,, Paris, France*, *[3]St. Mary's Hospital, London, United Kingdom*, *[4]Universidade de Sao Paulo, Ribeirao Preto, Brazil*, *[5]Hospital Sirio Libanes, São Paulo, Brazil*, *[6]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*, *[7]Leiden University Medical Center, Leiden, Netherlands*, *[8]Medical School Hannover, Hannover, Germany*, *[9]Azienda Ospedaliera-University of Padova, Padova, Italy*, *[10]University of Milano-Bicocca, MBBM Fundation c/o San Gerardo Hospital, Monza, Italy*, *[11]Aghia Sophia Children's Hospital, Thivon and Papadiamantopoulou, Athens, Greece*, *[12]Dr. von Haunersches University Children's Hospital, Munich, Germany*, *[13]IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy*, *[14]University of Regensburg, Regensburg, Germany*

Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is, to date, the only curative treatment for sickle cell disease (SCD). Because a human leukocyte antigen (HLA) matched sibling donor is not always available, alternative stem cell sources such as unrelated or haploidentical related donors have been explored. The likelihood of finding an unrelated matched donor varies among ethnic groups, with the lowest probability among individuals of African descent. To date, few series of SCD patients transplanted with an unrelated donor (UD) have been reported, but the high rates of rejection and chronic graft versus host disease (cGvHD) have limited its widespread application.

Methods: We report the results of a European, retrospective, registry (EBMT, MONACORD) based, survey on 71 unrelated donor allogeneic hematopoietic stem cell transplantations (HSCT) for patients with SCD in 23 EBMT centers between 2005 and 2017. Primary endpoint was 3-years overall survival (OS); secondary endpoints were 3-years graft versus host-free, relapse-free survival (GFRS - considering death, graft failure, grade III-IV acute GvHD and extensive cGVHD as events), engraftment, acute and chronic GvHD.

Results: Median follow-up was 38 months. Median age at HSCT was 9.3 years (range 2-43). Most patients were HbSS (79%) and had positive CMV serology (79%). Graft type was bone marrow in 79% and peripheral blood stem cells in 21%. Recipient-donor HLA match at high resolution typing was 10/10 in 31, 9/10 in 20 and 8/10 in 4 patients.

The most frequent conditioning regimens were fludarabine-thiotepa-treosulfan (FLU-THIO-TREO (64%) and busulfan-cyclophosphamide (12%). GvHD prophylaxis was cyclosporine plus methotrexate in 60%. Most patients (98%) had a Karnofsky performance score of more than 80% before transplantation.

Cumulative incidence (CI) of neutrophil engraftment at 60 days was 92%; platelet engraftment at 180 days was 90%. Eleven patients experienced graft failure (6 primary and 5 secondary). CI of grade II-IV acute GvHD (graft-versus-host disease) was 23%; 3-year CI chronic GvHD was 23%. Three-year OS and 3-year GFRS were 88±4% and 75 ± 6%, respectively. HLA matching was a significant risk factor for both OS and GFRS: 3-year OS was 96 ± 4% in the 10/10 group and 75 ± 10% in the 9-8/10 (p 0.042) and GFRS was 69 ± 9% vs 50 ± 12% (p 0.114), respectively. Three-year OS (95 ± 4 % vs 76 ± 10%, p= 0.025) and GFRS (66 ± 7% vs 53 ± 11%, p= 0.339) were higher in patients treated with a FLU-THIO-TREO conditioning regimen compared to those treated with other regimens.

Conclusions: Unrelated HSCT is a valid option for SCD patients who lack an HLA-identical sibling donor. Using a 10/10 HLA-matched unrelated donor yields better OS and GFRS in comparison to mismatched donors. Also, the use of FLU-THIO-TREO as conditioning regimen is associated with better survival. When a matched unrelated donor is not available, using a haplo-identical relative or an unrelated cord blood as donor source could be evaluated.

Disclosure: Nothing to declare

O090.

Outcome of Non Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation in Adult Patients with Severe Sickle Cell Disease; A 100 Patient Experience From Saudi Arabia

MOHSEN ALZAHRANI[1,2,3], Bader Alahmari[1,2,4], Ahmed Alaskar[1,2,4], Ayman Hejazi[1,2,4], Abdulrahman Alghamdi[1,2,4], Gamal Gmati[1,2,4], Khadega Abuelgasim[1,2,4], Hend Salama[1,2,4], Mohammed Bakkar[5], Walid Almashaqbeh[1,2], Heba Alshobaki[1], Maybelle Balili[1], Mohammed Quarshi[1], Mazin Ahmed[1], Moussab Damlaj[1,2,4]

[1]King Abdulaziz Medical City, Riyadh, Saudi Arabia, [2]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, [3]Saudi Society of Blood & Marrow Transplantation SSBMT, Riyadh, Saudi Arabia, [4]King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia, [5]Prince Mohammed Bin Nasser Hospital, Jazan, Saudi Arabia

Background: Allogeneic HSCT for adult patients with sickle cell disease (SCD) is potentially curative but not commonly utilized therapy due to complications such as graft failure (GF) and organ toxicity. At our center, we adopted a non-myeloablative (NMA) conditioning regimen in adult patients with severe SCD. Herein, we are reporting our outcome data of up to 5-years post HSCT.

Methods: Following IRB approval, adult patients whom underwent HSCT from 2015 to 2019 for severe SCD were included. Donors with sickle cell trait (SCT) were eligible. Severe SCD was defined as; the presence of recurrent vaso-occlusive crisis (VOC) or end organ damage. Conditioning regimen consisted of alemtuzumab (1 mg/kg divided over 5 days on days -7 to -3) and 300 cGy TBI on day -2. Peripherally mobilized stem cells targeting $10x10^6$/kg of CD34 cells were used. For GVHD prophylaxis sirolimus was used starting from day -1. EFS was defined as time to graft failure or death from any cause.

Results: A. Baseline Characteristics: A total of 100 patients were included with a median (range) age of 28 years (14-42), 58% of patients were males. Baseline median hemoglobin and hemoglobin S (HbS) was 95 g/L

(6.4-12.1) and 72.9% (26.4-97), respectively. The common indications for HSCT were (overlapping); recurrent VOC in 93%, ACS in 36%, stroke in 26%, and avascular necrosis in 25%. Nine patients had Moyamoya disease, 13 had severe sickling hepatopathy and one patient was hemodialysis dependent. Forty-five and 18 patients had two and three indications for HSCT, respectively. A total of 55 donors were SC trait and underwent G-CSF mobilization without major adverse events. The remaining characteristics are found in table 1.

B. Transplant Characteristics and Post HSCT **Outcome:** Median infused CD34x10^6/kg was 11.6 (6.4-23.9) and 98 patients had successful engraftment. A total of 10 patients experienced GF; 2 as primary and 8 as secondary with a median time of 129 days (40-583). Outcome post GF was as follows; recurrence of SCD in 4, aplastic bone marrow in 5 of whom 4 underwent a second allogeneic HSCT with Flu-Cy-ATG platform while the remaining patient experienced HLH post Parvo virus infection. 2 patients died due to primary and secondary GF. Acute skin GVHD (grade I to II) occurred in 3 cases and 2 cases developed autoimmune haemolytic anemia. A total of 35 patients successfully discontinued sirolimus, and subsequently there were a total of 3 successful pregnancies in 3 patients. Median follow up for the cohort is 300 (2-1502) days. Estimated 2-year EFS and overall survival (OS) is 85.1% (0.73-0.92) and 97.7% (0.91-0.99). There was no difference in outcome (GF or OS) between patients receiving graft from normal vs. SC trait. Post HSCT Hb and chimerism results are shown in table 2.

Conclusions: Herein, we present a large real-life experience demonstrating feasibility and favorable outcome of NMA HSCT in adult patients with severe SCD including patients with significant organ dysfunction. Successful pregnancies and long term discontinuation of immune suppression was possible. Longer follow up is warranted to ascertain stability of graft function over time.

Disclosure: The authors declare they have no relevant conflicts of interest.

O091.

Donor Characteristics Predict The Success of Allogeneic Haematopoietic Stem Cell Transplantation in Thalassaemia Major: A Single Centre Analysis of 250 Patients

Revathi Raj[1], Ramya Uppuluri[1], Venkateswaran vellaichamy[1], Nikila Ravichandran[1], Kesavan Iyer[1], David Dennison[2], Abdulhakim Alrawas[2]

[1]Apollo Speciality Hospital, Chennai, India, [2]Sultan Qaboos University Hospital, Muscat, Oman

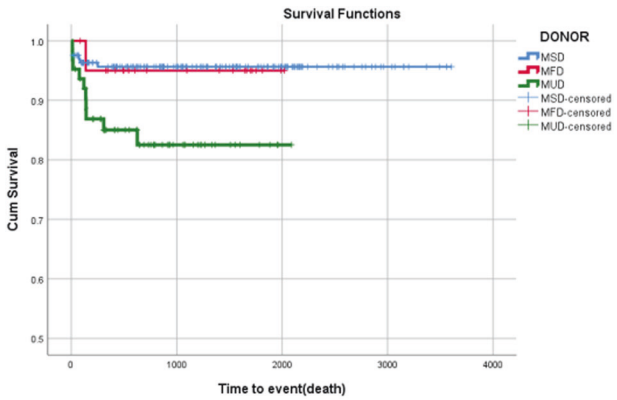
Background: The outcome of haematopoietic stem cell transplantation (HSCT) in thalassaemia major has been linked to comorbidity in the recipient and published risk groups like Lucarelli and Vellore high-risk help modify HSCT algorithms. However, scant data is available on the impact of donor characteristics such as matched family versus alternate donor, the age, ABO compatibility and the sex of the donor on the overall survival, disease-free survival, graft versus host disease and graft rejection rates. We present data on the impact of donor characteristics in a cohort of patients transplanted for thalassaemia major.

Methods: Data on 250 patients between the ages of 7 months to 19 years who underwent HSCT from 2009 to 2019 for thalassaemia major was analysed retrospectively. All patients were transplanted using fludarabine, thiotepa, and treosulfan protocol (n = 187) with additional horse anti-thymocyte globulin for the alternate donor group (n = 63). Follow up was performed in 42 patients at Muscat. The impact of donor characteristics such as sex mismatch and ABO compatibility was analysed with respect to graft rejection, graft versus host disease, and thalassaemia free survival.

Results: The median survival time was 3341 days, with 57% male and 43% female patients. Sex mismatch was present in 44% of the cohort. The graft rejection rate was 3.7% and all these patients had a sex mismatched HSCT (Fisher's exact test 0.001). The donor age did not have an impact on the outcome. ABO incompatibility, both minor and major, did not impact survival, rejection, or graft versus host disease. Chronic graft versus host disease was high in matched unrelated donor (55.1 %) versus family donor (30.6%). Mortality was higher in the unrelated donor cohort at 15% when compared to matched sibling donor at 5% ($p = 0.009$). The thalassaemia free survival calculated using Log Rank test was superior in matched family donor at 3451 days versus matched unrelated at 1755 days ($p = 0.008$). The time to significant events like death, rejection, and graft versus host disease was less than 120 days ($p = 0.0001$).

Conclusions: This study has the largest cohort of children transplanted for thalassaemia major using a uniform conditioning protocol that has enabled us to analyze the impact of donor characteristics on the outcome. Thalassaemia free survival is excellent at over 90%. The most significant results were that donor-recipient sex mismatch resulted in a higher graft rejection rate and unrelated donor HSCT in a higher rate of initial mortality and chronic graft versus host disease. We recommend two weekly chimerism analysis until day 120 in sex mismatched HSCT. Early withdrawal of immunosuppression and donor lymphocyte infusion in the case of mixed chimerism with help prevent graft rejection. In matched unrelated donors, we recommend

more aggressive sepsis prevention and early introduction of novel agents like ruxolinitib for graft versus host disease and slow taper of immunosuppression after 18 months to reduce chronic graft versus host disease. Incorporation of these post HSCT intervention algorithm based on donor characteristics will help improve outcomes.



[SURVIVAL- MFD VERSUS MUD]

Disclosure: NIL

O092.

Long-Term Neurodevelopmental Outcomes of Hematopoietic Stem Cell Transplantation for late-Infantile Krabbe Disease

Maria Escolar[1,2], Isabel Yoon[2], Nicholas Bascou[1,2], Michele Poe[1,2]

[1]University of Pittsburgh, Pittsburgh, PA, United States, [2]UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, United States

Background: Krabbe disease is a rare neurodegenerative disorder caused by a deficiency in the lysosomal enzyme galactocerebrosidase, resulting in demyelination. It is divided into 4 subtypes (early-infantile, late-infantile, juvenile, and adult) based on age of symptom onset. Currently, the only effective treatment for Krabbe disease is hematopoietic stem cell transplantation (HSCT). Previous studies have shown the efficacy of HSCT for improving lifespan and functional abilities in early-infantile patients who underwent transplantation before the onset of overt symptoms. However, there is a lack of studies that evaluate the efficacy of HSCT for late-infantile patients.

Methods: In this prospective longitudinal study, patients were evaluated by a multidisciplinary team of neurodevelopmental pediatricians, speech pathologists, audiologists, physical therapists, and psychometricians. All evaluations were conducted at a single site and followed a standardized protocol designed for long-term neurodevelopmental assessment.

Results: Nineteen late-infantile patients underwent HSCT (15 boys, 4 girls). Five were asymptomatic and 14 were symptomatic at the time of transplantation. Sixteen were evaluated longitudinally (median follow-up 4.75 years, range 0.42-8.83), as one died and two were lost to follow-up. All asymptomatic children have normal cognitive function, 3 symptomatic have near-normal, and the remaining plateaued below 2 years of age. Gross motor is most affected with 3 asymptomatic children developing normally and 2 plateauing at 3 and 1.5 years of age. All symptomatic children plateaued or regressed around 6 months of age. Fine motor followed a similar trend. Language was least affected with 7 children developing normally for receptive language and 8 for expressive language. For both, the remaining symptomatic children plateaued or regressed.

Conclusions: HSCT improves the lifespan and functional abilities of late-infantile Krabbe patients compared to the natural history. Children who underwent HSCT while asymptomatic experienced normal development in all domains but may plateau in motor skills at 3 years of age or below.

Disclosure: Nothing to declare.

Immunodeficiency diseases and macrophages

O093.

Impact of Different EX VIVO T-Cell Depletion Strategies on Outcomes Following Hematopoietic Cell Transplantation for Children with Primary Immunodeficiency

Su Han Lum[1], Ali Sobh[1], Peter McNaughton[1], Helen Watson[1], Zohreh Nademi[1], Stephen Owens[1], Eleri Willliams[1], Marieke Emonts[1,2], Terry Flood[1], Sophie Hambleton[1,2], Mario Abinun[1,2], Andrew Cant[1], Andrew Gennery[1,2], Mary Slatter[1,2]

[1]Great North Children's Hospital, Newcastle upon Tyne, United Kingdom, [2]Newcastle University, Newcastle upon Tyne, United Kingdom

Background: Our centre performed the first ex-vivo T-lymphocyte depleted (TCD) haploidentical allograft in 1987 in a child with PID. Different TCD methods have been used including CAMPATH-1M TCD marrow (n = 34), CD34+ selected marrow (CD34-S, n = 34), CD3/CD19 TCD PBSC (n = 7), and CD3-TCRab/CD19 TCD

PBSC (ab-TCD, $n = 30$)). This study aimed to examine transplant outcomes according to different methods in children with PID.

Methods: Between January 1987 and March 2019, 105 PID patients underwent first TCD allograft and were included in the study. Thirteen patients who received gene-modified add-back T cells were excluded. The main outcomes of interest were OS, EFS and graft failure. An event was defined as death, graft failure or second procedures for slipping chimerism. Other endpoints were neutrophil engraftment, GvHD, immune reconstitution and donor chimerism. Log-rank test was used to compare OS and EFS according to TCD methods. Cumulative incidences (CI) graft failure was calculated using a competing risk analysis, considering death as a competing event. Multilevel mixed effects modelling was performed for the longitudinal analysis of immune reconstitution and CAMPATH-1M was used as a reference group.

Results: Median age at transplant was 0.65 years (range 0.1 to 18.1 years). Donors were haploidentical donor ($n = 88$, 83%), MUD/MFD ($n = 9$, 9%) and MMFD/MMUD ($n = 8$, 8%). 94% received conditioning. Thirteen (12%) patients had aGvHD, of whom 3 had grade III-IV. None had cGvHD. The cause of death changed from predominantly infection (18/25, 72%) in CAMPATH-IM and CD34-S to non-infectious causes in all 6 deaths in CD3/CD19 and ab-TCD. Analysis by TCD methods revealed a 5-year OS of 58% (95% CI, 40-73%) for CAMPATH-1M, 68% (49-81%) for CD34-S, 69% (22-91%) for CD3/CD19 TCD and 83% (61-93%) for (ab-TCD (p=0.24). Age was a significant predictor of OS for non-SCID PID (p=0.02). The corresponding EFS was 46% (29-62%) for CAMPATH-1M, 47% (30-62%) for CD34-S, 69% (95% CI, 22-91%) for CD3/CD19 TCD and 83% (61-93%) for ab-TCD (p=0.04) (Fig 1B) The CI of graft failure reduced significantly, from 29% (14-61%) for CAMPATH-1M, to 19% (95%CI, 8-45%) for CD34-S, 17% (2-18%) for CD3/CD19 TCD and none had graft failure in ab-TCD (p=0.002). CD4+ lymphocytes were significantly higher in CD34-S at months 4 (p=0.02), 5 (p=0.01), and 6 (p=0.006) post-HCT and at month 4 (p=0.04) post-HCT in ab-TCD when compared to CAMPATH-1M (Fig 1D). The median donor myeloid chimerism at last follow-up was higher in newer TCD; 100% (range, 0-100%) for ab-TCD, 93% (0-100%) for CD3/CD 19 depletion, 6% (0 -49%) for CD34-S, 20% (0-100%) for CAMPATH-1M (p< 0.001). There was no significant difference in donor T-lymphocyte chimerism between TCD.

Conclusions: Outcomes after CD3+TCR 흰흰/CD19+ depletion are superior to previously used TCD methods. In an experienced centre it is a safe alternative procedure and enables a wide spectrum of PID to be transplanted. The result has led to evolution of donor hierarchy in our centre. Haploid is preferred to MUD in SCID without MFD while Haploid is preferred to MMUD in non-SCID PID without MUD/MFD.

Clinical Trial Registry: None

Disclosure: Nothing to disclosure.

O094.

Outcomes and Immune Reconstitution After T-Cell Replete Haploidentical Stem Cell Transplantation With Post-Transplantation Cyclophosphamide (PTCY) for Pediatric Patients with Primary Immunodeficiencies

Juliana Folloni Fernandes[1,2,3], Samantha Nichele[4,5], Leonardo Javier Arcuri[1], Lisandro Ribeiro[4,5], Gabriele Zamperlini Netto[1], Gisele Loth[4], Ana Luiza Melo Rodrigues[6], Cilmara Kuwahara[6], Adriana Koliski[4], Julia Lopes Garcia[1,2], Liane Esteves Daudt[7], Adriana Seber[8], Alessandra Araujo Gomes[2,3,9], Nelson Hamerschlak[1], Carmem Bonfim[4,5,6]

[1]Hospital Israelita Albert Einstein, Sao Paulo, Brazil, [2]Hospital das Clínicas da Universidade de São Paulo, Sao Paulo, Brazil, [3]Hospital 9 de Julho, Sao Paulo, Brazil, [4]Hospital de Clinicas da Universidade Federal do Paraná, Curitiba, Brazil, [5]Hospital Nossa Senhora das Graças, Curitiba, Brazil, [6]Hospital Infantil Pequeno Príncipe, Curitiba, Brazil, [7]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, [8]Hospital Samaritano, Sao Paulo, Brazil, [9]Hospital Sirio Libanes, Sao Paulo, Brazil

Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative treatment for several primary immunodeficiency diseases (PID). In the absence of a matched sibling or a well matched unrelated donor, the use of an haploidentical family donor can be considered. The use of T-cell replete haploidentical HSCT with PTCy in children with PID has been described in only a few case-series.

Methods: Retrospective study reporting the outcomes of patients who underwent haploidentical HSCT with PTCy for PID in Brazil. Study performed on behalf of the Brazilian Society of Bone Marrow Transplantation - pediatric study group.

Results: From July 2012 to May 2019, 73 patients underwent haploidentical HSCT with PTCy for PID in 9 Brazilian centers. Fifty-five patients received first allogeneic transplants, and 18 were rescued after graft failure of a previous transplant. Median age was 1.6 years (2 months to 19 years). Most patients were male ($n = 54$) and had active infection at the time of transplant ($n = 50$). Diagnoses were:

severe combined immunodeficiency ($n = 34$), Wiskott-Aldrich Syndrome ($n = 14$), chronic granulomatous disease ($n = 10$) and other PID ($n = 15$). Donors were father ($N = 46$), mother ($N = 24$), or siblings ($N = 3$); and cell source was predominantly bone marrow (94% of patients). Conditioning regimen was non-myeloablative (fludarabine 150mg/m2 + cyclophosphamide 29mg/Kg + TBI 200cGy) in 35 patients; and myeloblative in 38 patients (most part receiving: bussulfan + fludarabine 160mg/m2 + ATG 4-7,5 mg/Kg or alemtuzumab 0,5-1mg/Kg). GVHD prophylaxis was PT-Cy, CsA or Tacrolimus and MMF. The median follow-up of surviving patients was 24 months. Four patients died before 28 days and were not evaluable for engraftment. Sixty-one patients engrafted in a median of 15 days. The 100-day incidence of acute GVHD grades II-IV was 33% and grades III-IV, 14%. The incidence of Chronic GVHD at 1 year was 16%. Twenty-two patients died, most of them due to infection ($n = 15$). The two-year overall survival was 66%. Patients transplanted for WAS or SCID had a better OS compared to those transplanted for CGD ($p = 0,02$). The majority of patients reached 200/mL CD4+ and 1000/mL CD3+ cell counts between 3 and 6 months. In an univariate analysis, having total lymphocyte counts above 250 cells/mL at 30 days after HSCT was associated to a better OS ($p = 0.01$).

Conclusions: In conclusion, 66% of Brazilian children with severe PID and no matched donor could be cured with haploidentical HSCT with PTCy. Early lymphocyte recovery was associated with a better OS. The high proportion of patients in our cohort transplanted with an active infection (70%) may have had a major impact in our results.

Disclosure: Nothing to declare

O095.

Hematopoietic Stem Cell Transplantation for Inborn Errors of Immunity in Japan: Overview of a Nationwide Retrospective Analysis

Satoshi Miyamoto[1,2], Masakatsu Yanagimachi[1,2], Katsutsugu Umeda[2,3], Akihiro Iguchi[2,4], Yoji Sasahara[2,5], Hidetoshi Takada[2,6], Masafumi Yamada[4], Masataka Ishimura[7], Takashi Koike[8], Masahiro Yasui[9], Yoshiyuki Takahashi[10], Hiroshi Kawaguchi[11], Michiko Kajiwara[1], Masami Inoue[9], Koji Kato[12], Yoshiko Hashii[13], Yoshiko Atsuta[14], Hiromasa Yabe[2,8], Kohsuke Imai[1,2], Tomohiro Morio[1,2]

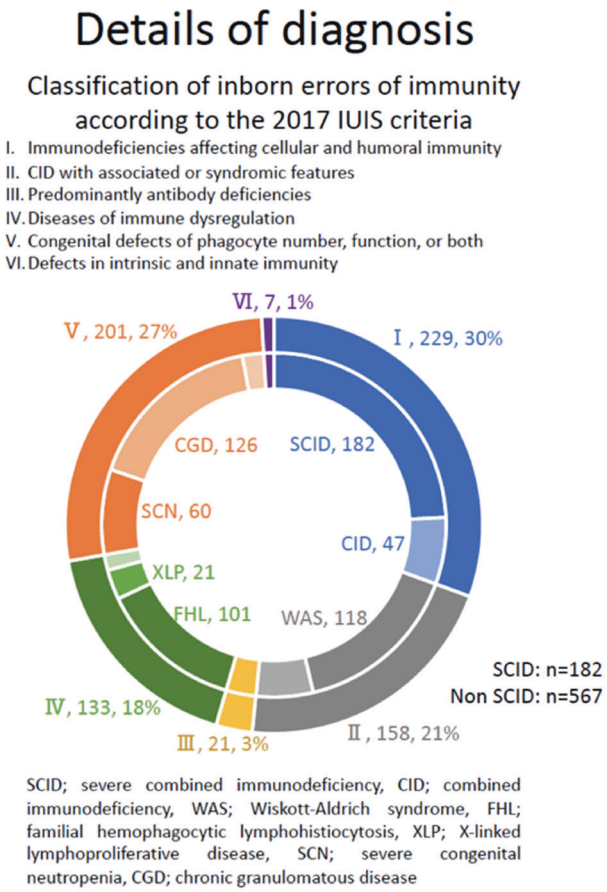
[1]Tokyo Medical and Dental University, Tokyo, Japan, [2]Hereditary Disorder Working Group of the Japan Society for Hematopoietic Cell Transplantation, Nagoya, Japan, [3]Kyoto University Hospital, Kyoto, Japan, [4]Hokkaido University Hospital, Sapporo, Japan, [5]Tohoku University Hospital, Sendai, Japan, [6]University of Tsukuba Hospital, Tsukuba, Japan, [7]Kyushu University Hospital, Fukuoka, Japan, [8]Tokai University Hospital, Isehara, Japan, [9]Osaka Women's and Children's Hospital, Izumi, Japan, [10]Nagoya University, Nagoya, Japan, [11]Hiroshima University Hospital, Hiroshima, Japan, [12]Central Japan Cord Blood Bank, Seto, Japan, [13]Osaka University, Suita, Japan, [14]Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya, Japan

Background: Hematopoietic stem cell transplantation (HSCT) is a curative therapy for most patients with inborn errors of immunity (IEI), but no comprehensive study has been performed in Japan.

Methods: We retrospectively analyzed 749 patients with IEI, who underwent their first allogenic HSCT in Japan between 1974 and 2016 by using the Japanese database Transplant Registry Unified Management Program (TRUMP).

Results: Details of diagnosis according to IUIS2017 classification are shown in the figure: 182 (24%) patients with severe combined immunodeficiency (SCID) and 567 (76%) patients with non-SCID were eligible for analysis. 596 (80%) male patients and 153 (20%) female patients received transplants at a median age of 2 years. 280 (37%) patients received transplants from related donors (RDs) and 164 (22%) from phenotypically matched RDs. 469 (63%) cases were from unrelated donors and 238 (32%) were from umbilical cord blood (UCB) donors. Death occurred in 204 (27%) patients, among which the most frequent reason was infection (71 cases; 35%). Re-HSCT was performed in 78 (14%) cases at a median interval of 162 days (ranged between 20 and 3574 days) from the first HSCT. As a whole, overall survival (OS) rate after HSCT was 59% and retransplantation-free survival was 49% over a 25-year period. 10-year OS rate improved significantly according to HSCT date, 75% for 2000-2016 vs 59% for 1974-1999 ($p < 0.001$), whereas the subgroup analysis revealed that refinement in OS rate of the patients with non-SCID did not show statistical significance (76% for 2000-2016 vs 66% for 1985-1999; $p = 0.08$). The patients with non-SCID had significantly better 10-year OS rate than SCID (74% vs 60% respectively; $p < 0.001$). Among the patients with non-SCID, the patients with Wiskott-Aldrich syndrome, phagocytic cell disorders, and combined immune deficiency had equivalent 10-year OS rate (82%, 80% and 74% respectively). However, the patients with hemophagocytic syndromes had a worse outcome (65%; $p < 0.05$). In terms of donor source, HSCT from matched RD seemed to have the best outcome (82%

for 10-year OS rate), and HSCT from mismatched RD was the worst (44% for 10-year OS rate). UCBT showed inferior 10-year OS rate to BMT in non-SCID (68% for UCBT and 78% for BMT; $p = 0.007$), whereas such tendency was not observed in SCID (70% for UCBT and 53% for BMT; $p = 0.37$). Multivariate analysis of the patients who received transplants after 2005 revealed that performance status 2-4 was an independent risk factor for survival in both SCID and non-SCID. Furthermore, UCB donors and mismatched RD were also associated with worse retransplantation-free survival in the patients with non-SCID.



[Details of diagnosis]

Conclusions: This is the largest nationwide study of HSCT for IEI in Japan. UCBT seemed to be disadvantageous for the patients with non-SCID. Novel treatments should be explored especially for the patients without appropriate donors to overcome HLA barriers, including GVHD prophylaxis using post-transplant cyclophosphamide or alemutuzumab, HSCT with ex vivo T/B cell depletion or gene therapy. Obviously, optimization of strategies of HSCT for each IEI is very important as well.

Disclosure: Nothing to declare.

O096.

Hematopoietic Stem Cell Transplantation with TCRαβ/CD19 Graft Depletion Among Children with Primary Hemophagocytic Lymphohistiocytosis: High Survival with Low Rate of GVHD

Aishat Kantulaeva, Elena Gutovskaya, Alexandra Laberko, Yulia Skvortsova, Larisa Shelikhova, Julia Starichkova, Dmitry Pershin, Elena Kurnikova, Yakov Muzalevskii, Aleksey Kazachenok, Galina Novichkova, Aleksey Maschan, Dmitry Balashov, Michael Maschan

Dmitry Rogachev National Medical Research Center Of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation

Background: Allogeneic HSCT is the only curative option for patients with hemophagocytic lymphohistiocytosis (HLH). Selective αβ T cell depletion is a viable approach to reduce the morbidity of HSCT by prevention of GVHD. We report the outcomes of HSCT with TCRαβ/CD19 graft depletion in 36 children with HLH.

Methods: From 2012 to 2019 36 patients with various forms of genetic HLH (familial HLH ($n = 20$), X-linked lymphoproliferative disease (XLP) type 1($n = 4$), XLP type 2 ($n = 9$), Griscelli syndrome($n = 1$), Chediak-Higashi syndrome ($n = 2$)) received HSCT with TCRαβ/CD19 graft depletion. The median age at HSCT was 2.8 years (range 0.5-17.5). Twenty-three patients received HSCT from matched unrelated donor (MUD), 3 - from matched related donor (MRD), 10 - from haploidentical family donors (haplo-HSCT). The conditioning regimens (CR) were based either on treosulfan (treo) at 36-42g/m^{2}in 9 patients, or on two alkylating agents: treo 36-42g/m2 with either melphalan 140mg/m^2($n = 9$) or thiotepa at 10mg/kg ($n = 18$), all 36 patients received fludarabine 150 mg/m^2. All patients received serotherapy: rabbit ATG (thymoglobulin) at 5mg/kg among 34 patients, horse ATG at 90mg/kg in 1 pt and anti-CD52 monoclonal antibodies at 1mg/kg in 1 pt. Thirty-two patients received rituximab at 100mg/m^{2}on day -1. Among 27 patients calcineurin-based post-HSCT GVHD prophylaxis was used. Seven patients received no post-HSCT immunosuppression and 2 pts - alternative regimens. Median follow up in survivors was 3.3 years (range 0.1-6.8 years).

Results: Engraftment was registered among 33 patients, the cumulative incidence of 1°/2° graft failure (GF) among all patients was 0.11 (95% CI 0.04-0.29); 0.33 (95%CI 0.12-0.83) after haplo-HSCT, 0.05 (95%CI 0.01-0.31) after MUD, and 0 after MRD-HSCT p = 0.06. The incidence of GF in two alkylating agents group was 0.08 (95%CI 0.02-0.29) vs 0.25 (95%CI 0.08-0.83) in one alkylating agent group, p = 0.23. The rates of viral infections were: CMV 0.27 (95% CI 0.15- 0.47), HHV-IV 0.06 (95% CI 0.02 -

0.22), EBV 0.06 (95% CI 0.02-0.25). The incidence of acute GVHD grade I-II 0.28 (95% CI 0.16-0.47) - predominantly skin involvement, moreover, grade II aGVHD observed in only 2 patients (6%); There was no acute GVHD grade III-IV and only 2 patients experienced limited chronic GVHD. The usage of GVHD prophylaxis did not influence GVHD-incidence. None of the engrafted patients developed HLH reactivation after HSCT. Overall survival (OS) in a cohort of 36 patients was 0.91 (95%CI 0.82-1). Severe infections*(Ps.auerogenosa, Kl.pneumoniae, P. jirovecii)* were the main cause of transplant-related mortality in all 3 deaths. OS after haplo-HSCT was 0.79 (95%CI 0.52-1), after MUD achieved 0.96 (95%CI 0.87-1) and no patients died after MRD-HSCT, $p = 0.33$. OS in two alkylating agents group was 0.92 (95%CI 0.82-1), similar to one alkylating agent group - 0.89 (95%CI 0.68-1) $p = 0.75$.

Conclusions: Allogeneic HSCT with TCRαβ/CD19 depletion is associated with high engraftment, low rate of GVHD and high survival among patients with various forms of inherited HLH, grafted from all types of donors. Graft failure remains an issue among XLP type 2 patients, transplanted from haploidentical donors.

Disclosure: Nothing to declare.

O097.

National Health Service England (NHSE) Program for Selection of Adult Primary Immunodeficiency Patients For Allogeneic Haematopoietic Stem Cell Transplantation

Emma Morris[1,2], Venetia Bigley[3], Siobhan O Burns[2], Smita Patel[4], David Lowe[2], Arian Laurence[1,2], Suzanne Elcombe[3], Helen Baxendale[5], Benjamin Uttenthal[6], Aarnoud Huissoon[7], Ravishankar Sargur[8], Patrick Yong[9], Sarah Grace[1], Mari Campbell[2], Benjamin Carpenter[1], Rachael Hough[1], John Snowden[8], Matthew Collin[3], Ronjon Chakraverty[1,2]

[1]University College London Hospitals NHS Foundation Trust, London, United Kingdom, [2]Royal Free London Hospitals NHS Trust, London, United Kingdom, [3]Newcastle Upon Tyne NHS Foundation trust, Newcastle, United Kingdom, [4]Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom, [5]Royal Papworth Hospitals NHS Foundation Trust, Papworth, United Kingdom, [6]Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom, [7]University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom, [8]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom, [9]Frimley Health NHS Foundation Trust, Frimley, United Kingdom

Background: Optimizing patient benefit from allogeneic haematopoietic stem cell transplantation (Allo-HSCT) in rare diseases such as the primary immunodeficiencies (PID) requires careful patient selection and thorough consideration of non-transplant therapeutic options. Despite more PID patients surviving into adulthood, there remains little published natural history data.

Prior to January 2018, routine funding within the NHS of Allo-HSCT for PID patients was only available for those< 18 yrs, reflecting national and EBMT transplant indication recommendations. Following publication of equivalent Allo-HSCT outcomes for adult patients compared to children[1,2], NHS England updated its national commissioning policy allowing access to Allo-HSCT for PID patients either presenting for the first time in adulthood, or with refractory autoimmunity/autoinflammation, PID-associated malignancy, incipient end organ failure or life-threatening infections[3].

Methods: We have established a national expert multidisciplinary panel to discuss all patients aged 18 years or above, referred for Allo-HSCT with an underlying diagnosis of PID. The NHSE-based panel is available to support clinicians elsewhere, including devolved UK nations and inEurope. The panel is drawn from major PID centres and it includes: 2 immunologists (independent centres) with expertise managing PID; 2 transplant haematologists (independent centres); a TYA transplant haematologist; an infectious disease expert; a hospital pharmacist; a clinical psychologist; a clinical nurse specialist (immunology or Allo-HSCT); and invited experts as indicated (e.g. radiology, cardiology, respiratory, hepatology, renal). MDT outcomes are recorded in the patient medical records. Cases are presented by the referring specialist. Documentation includes (i) appropriateness of transplant (acceptable indication), (ii) whether transplant predicted to be curative, (iii) response to conservative management (iv) other treatment options (iv) donor selection, (v) conditioning regimen, (vi) additional patient-specific pre-transplant investigations and optimization where required, (vii) post-transplant management, and (viii) transplant centre selection.

Results: Between February 2018 and December 2019 we held 20 MDT panel meetings and discussed a total of 39 UK and 5 overseas patients. The median age of patients was 32 years (range: 18-64), and the PID diagnoses included X-CGD (6), LoCID (5), HLH (5), Complex CVID (4), XIAP Defic (4), Undefined CID (3), DOCK8 Defic (2), Rag2-/- (2), STAT3/Hyper IgE (2), CTLA4 Defic (2), CHH (1), CD40L Defic (1), CARD 9 Defic (1), Undefined CAEBV (1), APDS2 (1), ADA2 Defic (1), AR-CGD (1), BACH2 deletion (1), and CID/Hyper IgM (1). Of the 39 patients discussed, Allo-HSCT was considered appropriate and timely in 34 cases, not appropriate in 8 cases, and for further discussion in 2. Of the 34 patients for whom

Allo-HSCT was recommended, 16 have been transplanted, 2 have deferred for social reasons, 9 are scheduled for Allo-HSCT in 2020. A donor search is in progress for 2, one is deteriorating waiting for transplant and one died pre-transplant of acute hepatic failure. Transplant status of 3 others is unknown. Of those transplanted, 15 are alive.

Conclusions: In the UK, systematic multidisciplinary panel discussion of adult PID patients referred for Allo-HSCT is both mandatory and linked to transplant funding. This has generated a robust mechanism for sharing experience in rare transplant indications, building effective networks and optimizing transplant outcomes.

Disclosure: Nothing to declare.

O098.

Outcome After Haematopoietic Cell Transplantation in Adolescents and Young Adults with Primary Immunodeficiency

Su Han Lum[1], Venetia Bigley[2], Daniel Drozdov[1], Zohreh Nademi[1,2], Terry Flood[1], Mario Abinun[1,2], Andrew Cant[1], Sophie Hambleton[1,2], Mary Slatter[1,2], Andrew Gennery[1,2]

[1]Great North Children's Hospital, Newcastle upon Tyne, United Kingdom, [2]Newcastle University, Newcastle upon Tyne, United Kingdom

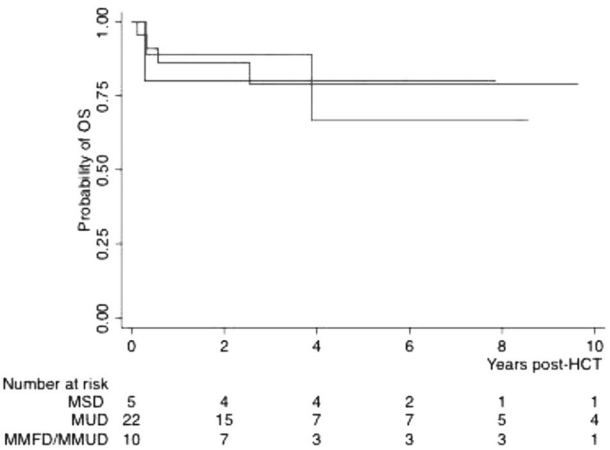
Background: Haematopoietic cell transplantation (HCT) is the standard of care children with severe or complex primary immunodeficiency (PID). Most reported outcomes have focussed on younger children. HCT in adolescents and adults has historically been associated with a higher TRM and lower OS with few reported outcomes for PID in this age group.

Methods: We report the outcome of 41 consecutive adolescents (≥15 years) and adults who underwent first HCT for PID at our centre between 1999-2019. Outcomes of interest were overall survival (OS), event-free survival (events defined as death, graft failure or second procedure), toxicity, long-term disease outcome and graft function. Log-rank test was used to analyse predictors of OS. Variables included for predictor analysis were year of transplant (< 2010 vs >2010), age at transplant (≤17 years vs >17 years), donor (MFD vs MUD vs MMUD/MMFD) and conditioning (MAC vs RTC vs RIC).

Results: The median age at HCT was 17.1 (range 15.1-41.2). Indications for HCT were CGD, ($n = 10$), CTLA4 ($n = 5$), GATA2 ($n = 3$), IPEX ($n = 2$), PI3 kinase deficiency ($n = 2$), chronic active EBV disease (CAEBV, $n = 2$), CARMIL2 ($n = 1$), SLE ($n = 2$), complex autoimmune disease ($n = 2$), CTPS1 ($n = 1$), DOCK8 deficiency ($n = 1$), C1q deficiency ($n = 1$), ALPS/NHL ($n = 1$), IRF8 ($n = 2$) here (MS with paeds and sib NS with us), SIFD ($n = 1$), STAT3 gain-of-function ($n = 1$), STAT3 loss-of-function ($n = 1$), WAS/NHL ($n = 1$), Kostman syndrome ($n = 1$) and undefined CID ($n = 2$). Stem cell donors were MFD ($n = 8$), MUD ($n = 22$), mismatched FD/UD ($n = 9$) and haplo ($n = 2$). Stem cell source was marrow ($n = 13$), unmanipulated PBSC ($n = 27$) and TCR ab/CD19 depleted PBSC ($n = 1$). Conditioning regimens were BuCy MAC in 4 patients, reduced toxicity myeloablative conditioning (RTC) in 14 patients (9 Flu-Treosulfan; 6 Flu-Treosulfan-Thiotepa) and reduced intensity conditioning (RIC) in 23 patients (14 Flu-Melphalan; 3 FluCyTBI2Gy with post-grafting cyclophosphamide; 3 BuFlu; 2 FluCy; FLAMSA TBI).

The 5-year OS for the entire cohort was 71% (95% CI, 52-84%), and by donor was 63% (23-86%) for MFD ($n = 8$), 79% (52-91%) for MUD ($n = 22$) and 61% (17-87%) for MMUD/MMFD ($n = 11$) (p=0.71). OS after 2010 was 75% (39-91%) compared to 63% (35-81%) before 2010 (p=0.17). Analysis by age at transplant indicated OS was 75% (45-90%) for patients £ 17 years of age and 68% (42-85%) for >17 years of age (p=0.69). Conditioning had no association with OS (MAC 80% vs RTC 65% vs RIC 69%, p=0.75). The 5-year EFS for the entire cohort was 68% (95% CI 51-81%). Four had second procedures. Of 10 total deaths, 8 were due TRM (3 GvHD; 3 multi-organ failure; 2 infection) and 2 were due to non-TRM (1 diabetic coma; 1 insulin overdose). Twelve (30%) had grade II-IV aGvHD and four (10%) had grade III-IV GvHD. Five (12%) had cGvHD (3 limited; 2 extensive The median age at last follow-up was 25.0 years (range, 16.3 to 44.1) with a median duration of follow-up 3.87 years (0.6 to 14.2). Twenty-six (83%) had myeloid donor chimerism >80% (median, 100%; range, 16-100%). Median T-lymphocyte chimerism was 95% (range, 30-100%)

Conclusions: HCT should be considered a treatment option in carefully selected adolescents and adults with PID.



[Figure 1: OS according to donor type]

Clinical Trial Registry: Not applicable.

Disclosure: Nothing to declare.

O099.

Very Long-Term Follow Up of 83 Adults WHO Underwent Allogeneic HSCT in Childhood for Primary Immunodeficiency (PID): A Single Centre Experience

James Day[1], Rupert Goodman[2], Bethany Nicholson[2], Austen Worth[1,3], Paul Veys[3], Ronjon Chakraverty[1,2,4], Benjamin Carpenter[4], Rachael Hough[4], Mari Campbell[2], Penny Titman[3], Deborah Ridout[5], Kit Sandford[2], Siobhan O Burns[1,2], Emma Morris[1,4,6]

[1]*University College London, London, United Kingdom*, [2]*Royal Free London Hospitals NHS Trust, London, United Kingdom*, [3]*Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom*, [4]*University College London Hospitals NHS Foundation Trust, London, United Kingdom*, [5]*UCL Great Ormond Street Institute of Child Health, London, United Kingdom*, [6]*Royal Free London Hospitals NHS Foundation Trust, London, United Kingdom*

Background: Allogeneic haematopoietic stem cell transplant (Allo-HSCT) remains the treatment of choice for most patients with severe primary immunodeficiency (PID), where an appropriate donor is available. While offering a chance of a cure, risks include acute and chronic graft vs host disease (GVHD), engraftment failure, poor immune reconstitution with ongoing susceptibility to infection or autoimmunity, infertility and other late effects. Factors influencing early outcome post Allo-HSCT include underlying diagnosis, age at transplant, conditioning regimen, donor type and HLA disparity. There is very little published medical outcome data on large cohorts of patients with greater than 15 years follow up post Allo-HSCT. Longer term follow-up data is important for providing accurate information to young transplant recipients and their families.

Methods: Immune reconstitution, chimerism, GVHD, infections and systemic sequelae were documented in 83 adult patients who survived 5 years or more following Allo-HSCT, where transplant was performed in childhood.

Results: *Patient demographics:* 83 of 153 surviving patients consented to participate in the study. The mean age at last follow up was 26 years (range: 17-37 years), with a mean post-transplant follow-up duration of 18.3 years (range: 5.6-37 years). Mean age at transplant was 5 years (range: 0-17.7 years) and 57 patients were male (69%) and 26 female (31%). Underlying diagnoses were categorised into groups including: severe combined immunodeficiency (SCID) ($n = 29$), combined immunodeficiency (CID) ($n = 27$), phagocyte disorders ($n = 11$), cartilage-hair hypoplasia (CHH) ($n = 3$), activated PI3K delta syndrome (APDS) ($n = 1$), X-linked lymphoproliferative disease (XLP) ($n = 3$), adenosine deaminase deficiency (ADA SCID) ($n = 6$), Chediak Higashi ($n = 2$) and purine nucleoside phosphorylase deficiency (PNP SCID) ($n = 1$).

Transplant characteristics: 36 patients had matched unrelated donors (MUD), 31 patients had matched related donors (MRD), 10 patients had haploidentical donors (Haplo) and 6 patients had mismatched unrelated donors (MMUD). Most patients ($n = 67$) received conditioning chemotherapy (81%) prior to stem cell infusion. A total of 7 patients (8%) required a second transplant.

Immune reconstitution: 73 (88%) patients had normal B cell reconstitution and 71 (86%) had normal T cell reconstitution. 65 (78%) patients had normal immunoglobulin levels with just 10 (12%) requiring ongoing immunoglobulin replacement therapy.

Chimerism: Of 79 patients with chimerism data, 40 (51%) had durable multi-lineage engraftment with >95% donor chimerism at last follow-up.

GVHD: A total of 22 patients (27%) had developed GVHD post-transplant, with ongoing chronic GvHD in 10 (12%).

Infections: The number of patients with 3 or more infections in the past year was 13 (16%), with 15 (18%) patients requiring antibiotic treatment and 4 (5%) being hospitalised for infection.

Conclusions: This study provides accurate insight in to very long-term outcomes for patients following paediatric Allo-HSCT for PID. The burden of ongoing GVHD was low and mild in severity. The majority of our patients achieved excellent, durable immune reconstitution with infrequent late, severe infections. We will present further analysis of this cohort of patients including growth, hearing, visual, dental, gastroenterological, dermatological, endocrine and fertility complications. We will use this data to identify patient groups most at risk of complications, allowing more effective monitoring and improvement in health outcomes.

Disclosure: Nothing to declare.

Infectious complications

O100.

Pneumocystis Pneumonia After Allogeneic HCT: A Case-Control Study On Risk Factors, Timing, and PCR use, from the IDWP of EBMT

Christine Robin[1,2], Catherine Cordonnier[3], Gloria Tridello[4], Nina Knelange[5], Alienor Xhaard[6], Sylvain

Chantepie[7], Aline Tanguy-Schmidt[8,9], Harry Schouten[10], Moshe Yesherun[11], Rocha Vanderson[12], Ibrahim Yakoub-Agha[13,14], Nicolaus Kröger[15], Marie-Pierre Ledoux[16], Jakob Dalgaard[17], Anne Thiebaut[18,19], Stefano Giardino[20], Elisabetta Calore[21], Tsila Zuckerman[22], Andreas Groll[23], Ludek Raida[24], Simona Avcin[25], Marta Gonzalez Vicente[26], Ain Kaare[27], Joanna Drozd-Sokolowska[28], Pascal Turlure[29], Stephane Bretagne[30,31], Malgorzata Mikulska[32,33], Simone Cesaro[34], Jan Styczynski[35]

[1]Assistance Publique-Hopitaux de Paris (APHP), Henri Mondor University Hospital, CRETEIL, France, [2]UPEC, CRETEIL, France, [3]Assistance Publique-Hopitaux de Paris (APHP), Henri Mondor University Hospital, Creteil, France, [4]Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy, [5]EBMT Data Office, Leiden, New Caledonia, [6]APHP, Saint-Louis Hospital, Université Paris Diderot, Paris, France, [7]Caen University Hospital, Caen, France, [8]Angers University Hospital, Angers, France, [9]CRCINA, UMR Inserm 1232, FHU GOAL, Angers, France, [10]University Hospital Maastricht, Maastricht, Netherlands, [11]Beilinson Hospital, Petach Tikva, Israel, [12]Hospital Sirio-Libanes, Sao-Paulo, Brazil, [13]Lille University Hospital, Lille, France, [14]LIRIC, INSERM U995, University of Lille, Lille, France, [15]University Hospital Eppendorf, Hamburg, Germany, [16]New Civil Hospital, Strasbourg, France, [17]Oslo University Hospital, Rikshospitalet, Oslo, Norway, [18]Grenoble Alpes University Hospital, Grenoble, France, [19]Grenoble Alpes University, Grenoble, France, [20]Istituto Giannina Gaslini, Genova, Italy, [21]Azienda Ospedaliera-Università di Padova, Padova, Italy, [22]Rambam Medical Center, Haifa, Israel, [23]University Children's Hospital, Munster, Germany, [24]Department of Haemato-oncology, University Hospital Olomouc, Olomouc, Czech Republic, [25]University Medical Center, Ljubljana, Slovenia, [26]Hospital Niño Jesus, Stem cell transplant unit, Madrid, Spain, [27]Tartu University Hospital, Tartu, Estonia, [28]Medical University of Warsaw, Warsaw, Poland, [29]Limoges University Hospital, Limoges, France, [30]APHP, Saint-Louis University Hospital, Paris, France, [31]CNRMA, Pasteur Institute, Paris, France, [32]University of Genoa (DISSAL), Genova, Italy, [33]IRCCS Ospedale Policlinico San Martino, Genova, Italy, [34]Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy, [35]University Hospital, Collegium Medicum UMK, Bydgoszcz, Poland

Background: *Pneumocystis jirovecii* pneumonia (PCP) has a high mortality after allo-HCT. Due to an increasing use of PCR in most European laboratories, we investigated whether the change in diagnostic methods could have modified the features and outcomes of PCP after allo-HCT. The main objectives of this study were to explore the diagnostic methods used for PCP in the EBMT centers and to identify pre- and post-transplant factors associated with the development of PCP after allo-HCT.

Methods: This is a multicenter, nested case-control study. Patients who had received an allo-HCT during the previous 24 months and had a BAL fluid positive for *P. jirovecii* (qPCR, immunofluorescence (IF) or microscopy) during the study period (May 1 2016-Jan. 31 2019) were included. Two controls per patient were matched for center, date of allo-HCT and underlying disease. Qualitative and quantitative variables were described with proportion and median respectively. Univariate and multivariate analysis were performed using logistic regression.

Results: One hundred and fifty-six patients were included: 52 cases and 104 controls. The median age was 55 years. Most patients were transplanted for AML (30%), with PBSC as the cell source (71%) and a reduced intensity conditioning (54 %). Post-transplantation relapse occurred in 10%.

Microscopy in BAL was performed in 42/52 cases and was positive in 18/42 cases (12 IF and 6 methenamin silver). PCR was performed and positive in 42/52 cases. Thirty-two patients were diagnosed only by PCR. Beta-D-glucan test was performed in serum for 11 patients and was positive in 7 with a median titer of 213 pg/mL.

Clinical presentation of PCP included fever (41/52) and dyspnea (41/52). Complications of PCP were severe sepsis (8/52), septic shock (6/41), ICU transfer (25/50), and requirement of a non-invasive (24/52) or mechanical (19/51) ventilation. Median worst PaO_2 was 55 mmHg, median SpO_2 90% and O_2 therapy was required for 40/51 patients. PCP occurred at a median of 11.5 months (range: 0.1-31) after allo-HCT. More than a half of the cases (30/51) were under PCP prophylaxis at the time of PCP diagnosis: TMP-SMX (19/30) or other prophylaxis (11/30) (data on compliance not collected). Fifty out of the 52 patients (94%) received a treatment directed against PCP. Mortality rates were 25% at day 30 and 37% at day 90.

In univariate analysis, stem cell source other than PBSC (OR 2.56 (1.04-6.28), $p = 0.04$), relapse (OR 3.60 (1.21-10.74), p= 0.02) and increased neutrophil count (OR 1.17 (1.04-1.33), p= 0.02) were associated with a higher risk of PCP. CD_4 count (OR 0.99 (0.99-1.00), p= 0.06) was not associated with PCP occurrence. In multivariate analysis, stem cell source other than PBSC (OR 3.07 (1.04-9.05), $p = 0.04$), relapse (8.88 (2.16-36.49), $p = 0.003$) and increased neutrophil count (OR 1.24 (1.06-1.44), $p = 0.006$) remained associated with a higher risk of PCP.

Conclusions: In the age of more sensitive diagnostic methods, PCP remains a life-threatening infection after allo-HCT and justifies a high level of vigilance about prophylaxis, and prophylaxis compliance. Factors associated with

development of PCP were stem cell source, relapse and increased neutrophil count.

Disclosure: nothing to declare

O101.

Upper and/or Lower Respiratory Tract Infection Caused by Human Coronavirus After Allogeneic Stem Cell Transplantation

Jose Luis Piñana[1], Gloria Tridello[2], Anne Kozjin[3], Aliénor Xhaard[4], Jakob Passweg[5], Nicola Polverelli[6], Inmaculada Heras[7], Ariadna Perez[8], Jaime Sanz[9], Dagmar Berghuis[10], Lourdes Vázquez[11], María Suárez-Lledó[12], Maija Itäla-Remes[13], Mutlu Arat[14], Isabel Iturrate Basarán[15], Musa Karakukcu[16], Mohsen Al Zahrani[17], Goda Choi[18], Marián Angeles Cuesta Casas[19], Montserrat Batlle Massana[20], Amato Viviana[21], Nicole Blijlevens[22], Arnold Ganser[23], Duygu Uckan-Cetinkaya[24], Hélène Labussière-Wallet[25], Peter J. Shaw[26], Zeynep Arzu Yegin[27], Marta González-Vicent[28], Vanderson Rocha[29], Alina Ferster[30], Nina Knelange[3], David Navarro[31], Malgorzata Mikulska[32], Rafael de la Camara[15], Jan Styczynski[33]

[1]Hospital Universitario y Politécnico La Fe, Valencia, Spain, [2]Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy, [3]EBMT Data Office Leiden, Leiden, Netherlands, [4]Hôpital Saint-Louis, Université Paris-Diderot, Paris, France, [5]University Hospital Basel, Basel, Switzerland, [6]University of Brescia, ASST Spedali Civili di Brescia, Brescia, Italy, [7]Hospital Morales Meseguer, Murcia, Spain, [8]Hospital Clínico Universitario de Valencia, Valencia, Spain, [9]Hospital Universitario y Politécnico La Fe, Valencia, Spain, [10]Willem Alexander Children's Hospital, Leiden University Medical Center, Leiden, Netherlands, [11]Hospital Universitario de Salamanca, Salamanca, Spain, [12]Hospital Clinic, Barcelona, Spain, [13]Turku University Hospital, Turku, Finland, [14]Sisli Florence Nightingale Hospital, Istanbul, Turkey, [15]Hospital de la Princesa, Madrid, Spain, [16]Erciyes University, Kayseri, Turkey, [17]King Abdulaziz Medical City-Riyadh, Riyadh, Saudi Arabia, [18]University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [19]Hospital Regional de Málaga, Malaga, Spain, [20]ICO-Hospital Germans Trias i Pujol, Barcelona, Spain, [21]Universita Cattolica S. Cuore, Roma, Italy, [22]Radboud university Medical Center, Nijmegen, Netherlands, [23]Hannover Medical School, Hannover, Germany, [24]Hacettepe University Children's Hospital, Ankara, Turkey, [25]Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Lyon, France, [26]The Children's Hospital at Westmead, Sydney, Australia, [27]Gazi University, Ankara, Turkey, [28]Niño Jesus Children's Hospital, Madrid, Spain, [29]Hospital Sirio-Libanes, São Paulo, Brazil, [30]Children's University Hospital Queen Fabiola, Université Libre de Bruxelles, Brussels, Belgium, [31]Hospital Clinico Universitario de Valencia, Valencia, Spain, [32]University of Genoa (DISSAL), IRCCS Ospedale Policlinico San Martino, Genova, Italy, [33]Collegium Medicum UMK, University Hospital, Bydgoszcz, Poland

Background: Human coronavirus (HCoV) including HCoV-NL63, HCoV-229E, HCoV-OC43 and HCoV-HKU1 are globally circulated in the human population and contribute to approximately one-third of common cold infections. Compared to other respiratory viruses, little is known about the clinical impact of HCoV subtype and risk factors of progression and mortality after allogeneic stem cell transplantation (allo-HSCT).

Methods: This was a retrospective cohort collaborative Spanish transplant group (GETH) and EBMT infectious disease working party (IDWP) multicentre study, which included all allo-HSCT recipients (adults and paediatrics) who developed upper (URTD) and/or lower respiratory tract disease (LRTD) caused by HCoV (excluding MERS and SARS HCoV) diagnosed by multiplex PCR panels. The inclusion criteria were consecutive HCoV respiratory infections diagnosed from the start of conditioning until the last follow-up during a period comprising from January 2012 to January 2019. Specific information, regarding respiratory symptoms, clinical and laboratory variables for immunodeficiency scoring index (ISI) computation, as well as hospital admission, intensive care unit (ICU) admission, was obtained for the study purpose.

Results: We included 402 allo-HSCT recipients who developed 449 U/LRTD HCoV episodes, reported from 28 EBMT transplant centres in 13 countries around the world (Europe, Asia, Australia and South America). Clinical and transplant characteristics are detailed in Table 1. The series comprised a high-risk cohort, since 57% of the recipients were allografted from alternative donors [adult unrelated donor, cord blood units or haplo-identical family donors]. HCoV episodes were diagnosed at a median of 222 days after allo-HSCT (range, day -12 to + 20.7 years). Most of recipients had URTD ($n = 328$, 73%) whereas 121 (27%) had LRTD involvement. The most common HCoV subtype reported was OC43 ($n = 170$, 38%) followed by 229E ($n = 97$, 22%), NL63 ($n = 62$, 14%) and KHU1 ($n = 53$, 12%). There were 75 episodes (17%) of non-subtypable HCoV. Compared to URTD, recipients who developed HCoV LRTD had significantly higher proportion of lymphopenia (<0.5 x10^9/L), active GVHD, steroid therapy and high-risk ISI score at the time of HCoV ($p \leq 0.05$ for all comparisons). The HCoV LRTD episodes were more frequently accompanied by fever (27% vs 56%), bacterial co-infections (5% vs 29%), fungal co-infection (2% vs

28%), hospitalization (9% vs 44%) and ICU admission (0.3% vs 10%), ($p \leq 0.01$ for all comparisons). Overall, there were 31 death at day +90 (7%) out of 449 HCoV episodes. Among allo-HSCT recipients with LRTD, day +90 overall survival (OS) after HCoV detection was not significantly different between HCoV subtypes [100% in HCoV-NL63, 94% in HCoV-229E, 92% in HCoV-KHU1 and 89% in HCoV-OC43 ($p = 0.6$)] although non-subtypable HCoV showed lower OS ($p = 0.0003$). Preliminary univariate analysis for day +90 mortality showed the prognostic value of high-risk ISI.

Conclusions: HCoV after allo-HSCT could progress to LRTD, leading to hospitalization and ICU admission in a significant proportion of cases. Our study suggests that mortality in recipients with LRTD did not vary according to the HCoV subtypes except for non-subtypable HCoV. We provide evidence of the ISI prognostic value in HCoV mortality after allo-HSCT.

Disclosure: nothing to disclose.

O102.

Successful Treatment of Progressive Multifocal Leukoencephalopathy with JCV-Targeted T-Cell Therapy

Sabrina Basso[1], Enrico Marchioni[2], Luca Stoppini[1], Jessica Bagnarino[1], Francesca Compagno[1], Alessandra Maiello[1], Gloria Acquafredda[1], Arianna Panigari[1], Fausto Baldanti[1], Cesare Perotti[1], Maura Faraci[3], Mario Luppi[4,5], Marco Zecca[1], Patrizia Comoli[1]

[1]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [2]IRCCS Mondino Foundation, Pavia, Italy, [3]Istituto G. Gaslini, Genova, Italy, [4]Azienda Ospedaliera Universitaria di Modena, Modena, Italy, [5]University of Modena and Reggio Emilia, Modena, Italy

Background: Progressive multifocal leukoencephalopathy (PML) is a rare progressive demyelinating disease developing in immunocompromised hosts as the result of JC polyomavirus (JCPyV) reactivation. Therapeutic options in PML are limited, as no antiviral agent has, so far, proved effective in controlling the disease. Immune reconstitution may lead to resolution of PML, and this has been the basis for the recent reports of successful treatment with checkpoint inhibitors (CI). However, the use of CI requires the presence of functional T cells, and may lead to GVHD/rejection exacerbation in transplant recipients. Transfer of JCPyV-specific T cells could restore virus-specific cellular immunity and control PML.

Methods: The efficacy and safety of T cell therapy in a series of seven PML patients with a condition of immune suppression due to hematologic neoplasia treatment or primary immunodeficiency is reported. JCPyV-specific T cells were obtained from healthy donors and patients with PML, by a validated GMP method based on lymphocyte stimulation with 15-mer peptide pools derived from the JCV Viral Capsid (VP) 1 and Large T (LT) proteins. The advanced therapy medicinal products (ATMPs) exerted JCPyV-specific IFNγ-production, measured by ELISPOT assay.

Results: We employed autologous or donor JCPyV-specific ATMPs to treat 7 patients with PML, developed after chemoimmunotherapy for hematologic cancer, HSCT or a diagnosis of common variable immune deficiency. The patients had progressive disease, and were moderately to severely disabled (modified Rankin Score, mRS 3-4) when T cell therapy was started. They received 1-6 escalating infusions of autologous ($n = 3$), HSCT donor ($n = 1$) or haplo third-party family donor ($n = 3$) derived JCPyV-specific T cells (from 0.1 to 0.5×10^6 cells/kg bw per dose, 15 days apart, according to ATMP origin and clinical setting). No adverse event attributable to ATMP infusion was recorded, and no sign of immune reconstitution inflammatory syndrome (IRIS) was observed. Two patients died due to disease progression ($n = 1$) or to a different viral infection while recovering from PML ($n = 1$). The other 5 patients are long-term survivors, with 1 remaining severely disabled and the other 4 gradually improving until achieving a favorable functional outcome, with mild (or no) residual deficits at a median follow-up of 37 months. Reduction of PML lesions and evolution to cortical atrophy on MRI imaging was observed in all 5 surviving patients.

Conclusions: T cell therapy with JCV-specific ATMP is an attractive and promising option that may restore virus-specific cellular immunity and cure immune deficient patients with PML.

Clinical Trial Registry: not applicable.

Disclosure: Nothing to declare.

O103.

Efficacy, Safety and Feasibility of Treatment of Chronic HCV Infection with Directly Acting Agents (DAAS) in HCT Recipients - EBMT Infectious Diseases Working Party Study

Malgorzata Mikulska[1], Gloria Tridello[2], Nina Knelange[3], Stella Santarone[4], Paolo Di Bartolomeo[4], Rafael de la Camara[5], Clara Cuéllar[5], Andrea Velardi[6], Katia Perruccio[6], Per Ljungman[7], Stephan Mielke[7], Jan Zaucha[8], Agnieszka Piekarska[8], Grzegorz Basak[9,10], Ewa Karakulska-Prystupiuk[9,10], Emanuele Angelucci[11], Fabio Ciceri[12], Maria Teresa Lupo Stanghellini[12], Loic Fouillard[13], Irene Garcia[14], Maria Cristina Menconi[15],

Igor Wolfgang Blau[16], Luca Nassi[17], Laura Ambra Nicolini[18], Simone Cesaro[2], Jan Styczynski[19]

[1]Division of Infectious Diseases, University of Genoa (DISSAL) and IRCCS Ospedale Policlinico San Martino, Genoa, Italy, [2]Paediatric Haematology Oncology, Verona, Italy, [3]EBMT Data Office, Leiden, Netherlands, [4]Ospedale Civile, Pescara, Italy, [5]Hospital de la Princesa, Madrid, Spain, [6]Sezione di Ematologia, Perugia, Italy, [7]Karolinska University Hospital, Stockholm, Sweden, [8]Medical University of Gdansk, Gdansk, Poland, [9]Central Clinical Hospital, Warszawa, Poland, [10]Medical University of Warsaw, Warsaw, Poland, [11]IRCCS Ospedale Policlinico San Martino, Genova, Italy, [12]San Raffaele Scientific Institute IRCCS, Milano, Italy, [13]Grand Hôpital de l`Est Francilien (GHEF), Meaux, France, [14]Jose Carreras Leukemia Research Institute, Hospital Santa Creu i Sant Pau, Barcelona, Spain, [15]Azienda Ospedaliera Universitaria Pisa, Pisa, Italy, [16]Campus Virchow Klinikum CVK, Berlin, Germany, [17]Universita del Piemonte Orientale, Azienda Ospedaliero-Universitaria Maggiore della Carita, Novara, Italy, [18]IRCCS Ospedale Policlinico San Martino, Genova, Italy, [19]University Hospital, Collegium Medicum UMK, Bydgoszcz, Poland

Background: Limited data are available on the feasibility, efficacy and tolerability of HCV treatment with directly acting agents (DAAs) in hematopoietic cell transplant (HCT) recipients. The aim of this study was to report the characteristics and HCV treatment practices and outcome in HCT recipients.

Methods: All EBMT centres were invited to participate in this prospective observational Infectious Diseases Working Party (IDWP) study. The inclusion criteria were HCV-RNA positivity or ongoing HCV treatment in all HCT recipients cared for during the study period.

Results: Between 12/2015 and 07/2018, 46 patients were included: 54% male (n = 25); median age of 38 years (range, 8-75; 5 were ≤16); acute leukaemia (39%, n=18), lymphoma (17%, n=8), haemoglobinopathies (15%, n=7). They received allogeneic HCT in 85% of cases (n = 39), mainly from HLA-identical sibling (46%, n=21), followed by unrelated donor (24%, n=11) and mismatched related (15%, n=7). Most of them were off immunosuppressive treatment (76%, n=35).

HCV genotypes 1, 2, 3 and 4 were detected in the 23 (50%), 10 (22%), 7 (15%) and 5 (11%) of cases, respectively. Four patients (11%) had cirrhosis (i.e. liver stiffness higher than 12.5 or Metavir F4 at liver biopsy). One patient was HBsAg positive, and 11 (24%) had a resolved HBV infection.

Overall, 36 (78%) patients received DAAs at a median time of 7.7 years (range 0.6-35.5) after HCT. Most of them did not receive concomitant immunosuppressive treatment (81%, n=29). Ribavirin was added to DAAs in 6 cases. Sofosbuvir-based treatment was given to 23 patients (64%), in association with ledipasvir in 13, ledipasvir/ribarivin in 2, velpatasvir in 3, daclatasvir in 2, ribavirin in 2, and simeprevir in 1. The remaining patients received dasabuvir/ombitasvir/paritaprevir/ritonavir in 6, elbasvir/grazoprevir in 3, glecaprevir/pibrentasvir in 2, ombitasvir/paritaprevir/ritonavir/ribavirin in 1, and daclatasvir/ribavirin in 1.

Among 5 paediatric patients, two were not treated (age 9 and 12) because no DDAs were approved for this age, while 3 were treated (age 7, 13 and 15) with sofosbuvir/ribavirin in 2 and sofosbuvir/ledipasvir in 1, with sustained virological response (SVR) and haematological side effects.

All but two patients completed the planned treatment course: 8 weeks in 2 (6%), 12 weeks in 31 (86%) and 24 weeks in 3 (8%). One patient with active lymphoma died of chemotherapy-associated infectious complications other than HCV and one was still on treatment at the time of data analysis. Of 34 patients who completed DAAs treatment, 32 (94%) experienced SVR, while 2 developed a relapse or reinfection (6%).

Grade 1-3 side effects possibly related to DAAs were reported in 5 patients (14%), of whom 3 received ribavirin-including (2 anemia, 1 hypergammaglobulinemia, loss of appetite, hypoesthesia) and 2 ribavirin-free regimen (1 pancytopenia during concomitant CMV reactivation, 1 insomnia). Treatment with ribavirin-containing regimens was associated with higher risk of side effects (p = 0.02). Two patients received azoles for fungal infection treatment/prophylaxis without experiencing drug-drug interactions.

Conclusions: DAAs treatment was effective, safe and feasible in this cohort of mainly allogeneic HCT recipients with mild-to-moderate liver damage. Side effects were usually haematological and more frequent in case of ribavirin-containing regimens.

Disclosure: Nothing to declare.

O104.

Tuberculosis After Hematopoietic Stem Cell Transplantation: Retrospective Study of Infectious Diseases Working Party EBMT

Joanna Drozd-Sokołowska[1], Gloria Tridello[2], Anne E. Kozijn[3], Musa Karakukcu[4], Nour Ben Abdeljelil[5], Nicolaus Kröger[6], Jakob Passweg[7], Mahmoud Aljurf[8], Anca Colita[9], Didem Atay[10], Alina Tanase[11], Lourdes Vázquez[12], Agnieszka Piekarska[13], Maura Faraci[14], Tugrul Elverdi[15], Kristina Carlson[16], Grant McQuaker[17], John A. Snowden[18], Hélène Labussière-Wallet[19],

Katharine Patrick[20], Pavel Jindra[21], Mohsen Al Zahrani[22], Zahit Bolaman[23], Anna Waszczuk-Gajda[1], Herrad Baurmann[24], Gergely Kriván[25], Annoek E.C. Broers[26], Ola Blennow[27], Grzegorz W. Basak[1], Nina Knelange[3], Diana Averbuch[28], Lidia Gil[29], Malgorzata Mikulska[30], Jan Styczynski[31]

[1]Medical University of Warsaw, Warsaw, Poland, *[2]Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy*, *[3]EBMT Data Office Leiden, Leiden, Netherlands*, *[4]Erciyes University, King Abdulaziz Medical City, Kayseri, Turkey*, *[5]Centre National de Greffe de Moelle Osseuse, Tunis, Tunisia*, *[6]University Hospital Eppendorf, Hamburg, Germany*, *[7]University Hospital, Basel, Switzerland*, *[8]King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia*, *[9]Carol Davila University of Medicine and Pharmacy, Fundeni Clinical Institute, Bucharest, Romania*, *[10]Acibadem University Altunizade Hospital, Istanbul, Turkey*, *[11]Fundeni Clinical Institute, Bucharest, Romania*, *[12]Hospital Universitario de Salamanca, Salamanca, Spain*, *[13]Medical University of Gdansk, Gdansk, Poland*, *[14]IRCSS Istituto G. Gaslini, Genoa, Italy*, *[15]Istanbul University-Cerrahpasa, Istanbul, Turkey*, *[16]University Hospital, Uppsala, Sweden*, *[17]Queen Elizabeth University Hospital, Glasgow, United Kingdom*, *[18]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom*, *[19]Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Lyon, France*, *[20]Sheffield Childrens NHS Foundation Trust, Sheffield, United Kingdom*, *[21]Charles University Hospital, Pilsen, Czech Republic*, *[22]King Abdulaziz Medical City, Riyadh, Saudi Arabia*, *[23]Adnan Menderes University, Aydin, Turkey*, *[24]HELIOS Klinikum Berlin-Buch, Berlin, Germany*, *[25]Central Hospital of Southern Pest, Budapest, Hungary*, *[26]Erasmus MC Cancer Institute, Rotterdam, Netherlands*, *[27]Karolinska Institute, Stockholm, Sweden*, *[28]Hadassah Medical Center, Jerusalem, Israel*, *[29]Poznan University of Medical Sciences, Poznan, Poland*, *[30]University of Genoa (DISSAL), IRCCS Ospedale Policlinico San Martino, Genoa, Italy*, *[31]Collegium Medicum UMK, University Hospital, Bydgoszcz, Poland*

Background: Tuberculosis (TBC) is an infectious disease caused by *Mycobacterium tuberculosis*. Data on TBC after hematopoietic stem cell transplantation (HSCT) are scarce and inconsistent. Therefore, we launched a retrospective study to elucidate the issues of clinical course and outcome of tuberculosis after HSCT.

Methods: All EBMT centers were invited to participate in this retrospective study. The primary end-point was the outcome of TBC after HSCT, the secondary end-points: incidence of drug-resistant TBC, clinical presentation and identification of factors prognostic for survival.

Results: Forty-seven patients transplanted 2000-2019 were included, 68% males, median age at HSCT 30 years (0-66). The underlying diagnoses were acute leukemias (38%), lymphomas (15%), myelodysplastic or myeloproliferative neoplasms (17%), bone marrow failure (9%), inherited disorders (15%), plasma cell disorders (4%) and chronic leukemia (2%). 89.4% received allo-HSCT, 10.6% auto-HSCT. Total number of HSCTs in participating centers was: 18858 alloHSCT, 16974 autoHSCT. The intensity of conditioning was myeloablative in 63%. TBI was used in 21%. The donor was HLA-identical sibling in 29.8%, matched unrelated in 42.6%, haploidentical in 17%. The source of stem cells was peripheral blood in 76%. T-cell depletion was used in 44%, ATG in 36%. No patient had pre-HSCT TBC. Screening for TBC pre-HSCT was positive in 2 out of 12 patients tested. 6% patients received prophylaxis for latent TBC before HSCT, 9% after HSCT. Median time from HSCT to TBC diagnosis reached 135 days (16-3225); median time from onset of symptoms to diagnosis 15.5 days (0-347). 75% patients were either in complete or partial remission. 66% were receiving immunosuppression; 4% were suffering from acute, 4% from chronic GvHD. The leading clinical symptoms of TBC were fever (63%), cough (35%), lymph node enlargement (22%), weight loss (22%), asthenia (22%). 38% patients had extrapulmonary TBC, mostly affecting lymph nodes (17%). Culture was positive in 74% patients, PCR 68%, Ziehl-Neelsen staining 55%, histopathology 49%. The diagnosis was made based on clinical symptoms and radiological findings in 26% patients.

Drug susceptibility was tested in 43% patients; no drug-resistant *M. tuberculosis* was detected. 23% received initially 3 drugs, 51% 4 drugs. 51% continued with 2 drugs.

The total duration of treatment was median 8 months (1-18); 6 months (1-12) for pulmonary, 12 months (4-18) for extrapulmonary TBC. 4% patients did not receive treatment and died shortly after the diagnosis. The effect of treatment as assessed by the investigator was: cured (38%), treatment completed (19%), treatment success (15%), treatment failed (6%), lost to follow-up (2%), not evaluated (6%), died (6%). The 6-month and 1-year overall survival calculated from the time of TBC diagnosis were 84.4% and 76.8% respectively. TBC did contribute to death in 8 patients. No prognostic risk factors for survival were found in Cox model.

Conclusions: TBC is still a problem in HSCT patients. It can develop anytime from HSCT, although most frequently during the early post-transplant period. TBC manifests frequently as extrapulmonary disease and contributes to death in a significant proportion of patients, mostly failing treatment. Drug-resistance appears not to be a problem within participating EBMT centers.

Clinical Trial Registry: not applicable.

Disclosure: The authors declare no competing conflicts of interest.

O105.

Faecal Microbiota Transplant (FMT) Can Reduce The High NRM Associated with Multi-Drug Resistant Organism (MDRO) Colonisation Prior to Allogeneic HCT

Andrew J. Innes[1,2], Rohma Ghani[1], Benjamin H. Mullish[1], Richard Szydlo[1], Eimear Brannigan[2], Renuka Palanicawandar[2], Eduardo Olavarria[2], Jane F. Apperley[1,2], Mark R. Thursz[1], Horace R. T. Williams[1], Julian R. Marchesi[1], Frances Davies[2], Jiri Pavlu[2]

[1]Imperial College London, London, United Kingdom, *[2]Imperial College Healthcare NHS Trust, London, United Kingdom*

Background: Multi-drug resistant organisms (MDRO) are a global threat to public health, and their emergence within allogeneic haematopoetic stem cell transplant (allo-HCT) recipients has the potential to significantly impact upon transplant outcome. Bloodstream infections caused by MDRO are difficult to treat, often because there is a delay in identifying the resistance pattern of the causative organism, which leads to delays in delivery of appropriate antibiotics. This problem is confounded by the propensity of MDRO to acquire new resistance mechanisms, rendering them even more difficult to treat, and in some cases, resistant to all therapies. Faecal microbiota transplant (FMT) is an effective therapy in patients with recurrent *Clostridioides difficile* infections, and it has been shown to offer promise as a biological approach to suppress MDRO in colonised patients prior to allo-HCT.

Methods: Since 2015, within our institution we have routinely screened allo-HCT recipients for MDRO by rectal swab prior to admission for transplantation, as well as during the course of their admission. Since 2016, we have routinely offered FMT to patients identified with MDRO colonisation prior to HCT. In order to assess the impact of MDRO colonisation on outcome of allo-HCT, we retrospectively compared non-relapse mortality in patients with MDRO colonisation and MDRO colonisation treated with FMT to respective control cohorts (2:1 matching). Matched control cohorts were used to ensure the analysis was not bias by differences in the baseline characteristics between those receiving FMT and those not. Control cohorts were matched for disease type (AML, CML, ALL or lymphoma), disease stage, transplant intensity (myeloablative or reduced intensity), donor type (matched sibling, matched unrelated donor and haplo-identical related donor) and age. Probabilities of NRM were calculated using the Kaplan-Meier method, and groups compared using the log-rank test.

Results: Since 2016, a total of 18 patients screened positive for MDRO either prior to, or in the immediate course of an allo-HCT (up to day +35). The organisms identified were *Klebsiella pneumoniae* ($n = 4$), *E. coli* ($n = 4$), *Enterobacter cloacae* ($n = 3$), *Citrobacter freundii* ($n = 3$), *Klebsiella oxytoca* ($n = 2$), and others ($n = 2$); mechanisms of resistance were OXA-48 ($n = 8$), IMP1 ($n = 3$), GES-5 ($n = 2$), NDM ($n = 2$), VIM ($n = 2$) and others ($n = 2$). Of the 18 patients who screened positive for MDRO, 8 received FMT prior to HCT. FMT was well tolerated, with no serious adverse events. Patients colonised with MDRO had a significantly worse non-relapse mortality than matched controls (day 100 NRM 30% vs 6%, 1-year NRM 56% vs 6%, $p = 0.004$). In contrast, patients who were MDRO colonised, but received an FMT prior to HCT, had similar NRM to controls (100 day and 1-year NRM 18% vs 29%, $p = 0.367$), suggesting that FMT can negate the high NRM associated with MRDO colonisation in the setting of allo-HCT.

Conclusions: Identification of modifiable risk factors for NRM are critical to improving the outcome for patients with haematological malignancies. These data demonstrate a high mortality associated with MDRO colonisation in the setting of allo-HCT, and moreover they show that this risk can be mitigated with the used of FMT prior to allo-HCT.

Disclosure: Nothing to declare.

O106.

Epidemiology, Risk Factors and Outcomes of CMV Infection in Adults Undergoing Allogeneic Hematopoietic Cell Transplant (HCT): A Single Institutional Cohort Study

Joyce Johnsrud[1], Isabelle Nguyen[1], Walter Domingo[1], Amitkumar Raval[2], Yuexin Tang[2], Janice (Wes) Brown[1]

[1]Stanford University Medical Center, Palo Alto, CA, United States, *[2]Merck & Co., Inc., Kenilworth, NJ, United States*

Background: Despite significant advances in management including preemptive therapy (PET), CMV remains the most common infection in HCT patients. We studied evolving risks for and impact of CMV over the past decade at a single, large transplant center.

Methods: From a retrospective cohort of 1,283 seropositive adults who underwent HCT at Stanford University from

January 2009 to May 2019, we analyzed 1,107 adults after the exclusion of patients on letermovir ($N = 78$), who received a second HCT ($N = 78$), or were not screened ($N = 8$). From 2009-2012, high risk patients received ganciclovir prophylaxis (PPX). From 2015-2017 umbilical cord blood (UCB) recipients received valacyclovir 2000 mg thrice daily. Plasma CMV PCR was performed weekly through D+100 post-HCT. PET was instituted if viral load (VL) reached a threshold of 400 copies/ml (2009-2012) or 400 IU/ml (2013-2019). An episode of CMV reactivation was defined as detectable DNAemia without interruption for >2 weeks. CMV disease was defined consistent with published criteria and clinician impression. Bivariate analyses were performed to examine the differences between those with versus without CMV reactivation and/or PET.

Results: 550/1,107 patients received PET and/or CMV disease treatment (TX). Of 1,065 HCT recipients who were managed using the preemptive approach, 768 (72.1%) developed CMV DNAemia; 210 (19.7%) had low-grade DNAemia (<135 IU/ml or <150 copies/ml) [86% resolved spontaneously and only 2.4% had contemporaneous CMV disease]; and 95 (8.9%) developed CMV disease. Despite higher frequency of detectable low-level DNAemia and high-risk transplants, CMV disease has decreased over the last decade. Highest risk groups for reactivation were recipients of ATG (74.3%), myeloablative regimens (72.8%) and haploidentical transplants (72.7%); 56.3% of UCB had DNAemia. Recipients of haplo grafts were statistically more likely than UCB to have VL >= 400 (57.6% vs 29.2%) or to receive PET (95.8% vs 70.3%). Median overall antiviral exposure through D+100 was 30 days (range 0-100); ganciclovir (54%) was the most common initial agent used [median exposure 24 days (range 1-92)] vs 39% valganciclovir [median 25d (1-93d)] vs 7% foscarnet [median 10d (0-53d)]. Valganciclovir exposure was longer in the ATG [median 27d (range 1-93)] vs non-ATG group [median 21d (3-82)]. CMV reactivation was associated with significantly greater median number of hospitalizations (2 vs 1), a trend toward greater inpatient LOS (29d vs 26d), and greater number of outpatient treatment center days [median 28d (0-153) vs 25 days (0-80)] compared to those without CMV reactivation. In univariate analysis, there were no differences in the incidence of acute graft-vs-host disease (GVHD) or grades of acute GVHD as well as overall survival (88.6% vs 88.2%) between those treated with PET and those without CMV reactivation.

Conclusions: Despite effective preemptive therapy strategies, CMV infection remains a significant and common complication of HCT and to have a measurable impact on patients and healthcare system.

Disclosure: Abstract in part has been previously submitted to TCT 2020.

Joyce Johnsrud- Research fellow, Partial salary for research funded by Merck & Co., Inc.

Isabelle Nguyen- Research associate, Partial salary for research funded by Merck & Co., Inc.

Walter Domingo- Nothing to declare

Yuexin Tang- Employed by Merck & Co., Inc.

Amit Raval- Empolyed by Merck & Co., Inc.

Janice (Wes) Brown- PI on clinical trials and research funding from Merck & Co., Inc.;Consultant and PI on clinical trials for Chimerix; Consultant for Cidara; Consultant for Cellerant Therapeutics.

O107.

Use of Letermovir in Off-Label Indications: Infectious Diseases Working Party EBMT Retrospective Study

Jan Styczynski[1], Gloria Tridello[2], Nina Knelange[3], Alienor Xhaard[4], Gerard Socie[4], Jakob Passweg[5], Stephan Mielke[6], Mervi Taskinen[7], Nicole Blijlevens[8], M Aranzazu Bermudez Rodriguez[9], Carlos Solano[10], Emmanouil Nikolousis[11], Alessandra Biffi[12], Andreas Groll[13], Christian Junghanss[14], Panagiotis Tsirigotis[15], Bruno Lioure[16], Pavel Jindra[17], Ernst Holler[18], Federica Galaverna[19], Franca Fagioli[20], Rafael de la Camara[21], Malgorzata Mikulska[22], Per Ljungman[6]

[1]Collegium Medicum UMK, University Hospital, Bydgoszcz, Poland, *[2]Azienda Ospedaliera Universitaria Integrata, Verona, Italy*, *[3]EBMT IDWP Office, Leiden, Netherlands*, *[4]Hopital St. Louis, Paris, France*, *[5]University Hospital, Basel, Switzerland*, *[6]Karolinska University Hospital, Stockholm, Sweden*, *[7]Helsinki University Hospital, Helsinki, Finland*, *[8]Nijmegen University Medical Centre, Nijmegen, Netherlands*, *[9]Hospital Universitario Marqués de Valdecilla, Santander, Spain*, *[10]Hospital Clínico de Valencia, Valencia, Spain*, *[11]Birmingham Heartlands Hospital, Birmingham, United Kingdom*, *[12]University Hospital of Padova, Padova, Italy*, *[13]Universitaetsklinikum Muenster, Munster, Germany*, *[14]Universitaet Rostock, Rostock, Germany*, *[15]Attikon University General Hospital, Athens, Greece*, *[16]Techniciens d`Etude Clinique Suivi de Patients Greffes, Strasbourg, France*, *[17]Charles University Hospital, Pilsen, Czech Republic*, *[18]University Regensburg, Regensburg, Germany*, *[19]IRRCS Ospedale Pediatrico Bambino Gesù, Sapienza University of Rome, Rome, Italy*, *[20]Onco-Ematologia Pediatrica, Torino, Italy*, *[21]Hospital de la Princesa, Madrid, Spain*, *[22]University of Genoa, IRCCS Ospedale Policlinico San Martino, Genova, Italy*

Background: Letermovir (LMV) is licensed for prophylaxis of CMV infection in adult CMV-seropositive patients. Due to its favorable safety profile, LMV brings potential for use in other clinical situations, outside the approved indication. The objective of the study was the analysis of the efficacy and safety of the use of LMV in off-label indications.

Methods: A questionnaire regarding retrospective data on the off-label use of LMV was sent to all EBMT centers in September'2019. The inclusion period was 11/2017-08/2019.

Results: A total number of 50 patients was reported including 43 adults and 7 children. LMV was administered for: secondary prophylaxis (35 adults, 4 children), primary prophylaxis in CMV-seronegative recipient (3 adults, 2 children), preemptive treatment (1 adult), and therapy of CMV disease (4 adults, 1 child).

LMV was administered: p.o. ($n = 45$), i.v. ($n = 1$), both ($n = 4$); CsA was concomitantly used in 23 pts. The median dose of LMV was 480 mg (range: 120-480) p.o. and 240 mg (range: 240-480) i.v. Nine patients received 2 courses of LMV, including 1 who received 3 courses. The median time between the first and the second course was 63 days (range: 10-160).

For the first course, LMV was used for a median number of 103 days (range: 9-409) starting from median day +116 (range: 1-801) to median day +226 (range: 18-942). LMV was stopped in 42 pts after first course due to: completed therapy ($n = 24$, including 3 with toxicity), toxicity (5 pts), CMV resistance/reactivation ($n = 2$), primary disease progression ($n = 3$), use of other treatment ($n = 3$; CMVIG, or other antivirals due to HSV/VZV), death of patient ($n = 3$), lack of drug ($n = 1$), no information ($n = 1$).

For the second course, LMV was used for a median number of 48 days (range: 3-307), starting from median day +300 (range: 31-379) to median day +388 (range: 41-619). LMV was stopped in 9 pts after second course due to: completed therapy ($n = 3$), CMV resistance/reactivation ($n = 3$), death of patient ($n = 2$), conditioning before second transplant ($n = 1$).

In 6/41 patients for whom data are available, CMV reactivation/disease was diagnosed. At the end of the study, 3 pts were on pre-emptive treatment and 2 on therapy of CMV disease with other antiviral drugs. Treatment with LMV resulted in 93.1% (95%CI=75.1-98.2) probability of 60-day survival without CMV infection during secondary prophylaxis and 80.0% (95%CI=20.4-96.9) during therapy of CMV infection/disease, while 120-day survival without CMV infection was 78.8% (95%CI=58.7-89.9; 11/30 events) and 26.7% (95%CI=1.0-68.6; 4/5 events) with persistent CMV infection, respectively.

Overall 4/7 children are alive without CMV reactivation/disease, 2 died after CMV reactivation, 1 died during the second course of LMV, LMV ongoing in 1 patient, alive without CMV reactivation/disease, LMV stopped 3/6 (50%). Adverse events were reported in 13/50 (26%) of patients: nausea/vomiting ($n = 11$, including severe diarrhea in 1), liver ($n = 1$) and renal ($n = 1$) toxicity. In 2 children LMV was stopped due to poor tolerance (nausea/vomiting: 2/7).

Conclusions: The efficacy of the use of LMV as secondary prophylaxis was high. The preliminary experience with the use of LMV for treatment of patients with refractory/resistant CMV infection/disease showed good short-term effect.

Disclosure: First and Last author received lecture fees from MSD. All other authors have nothing to disclose with respect to this study; they participated in the collection and analysis of data.

Lymphoma

O108.

Long Term Survival After 2 Years Event Free Survival in Relapsed DLBCL After Autologous Transplantation in the Two Randomized Trials LY.12 and Coral

Sarit assouline[1], Shen Li[2], Christian gisselbrecht[3], Patrick Fogarty[4], Annette Hay[5], Eric van den Neste[6], Lois E. Shepherd[5], Norbert Schmitz[7], Armand Armand[8], Sue Robinson[9], Matthew Seftel[10], Caterina Stelitano[11], Marina Djurfeldt[5], Ralph Meyer[12], Bingshu Chen[5], Michael Crump[8]

[1]Lady Davis Institute, McGill University,, Montreal,, Canada, [2]Lady Davis Institute, Jewish General Hospital, McGill University, Montreal,, Canada, [3]Hopital Saint Louis, Paris, France, [4]Lysarc, Hospital Lyon Sud, Pierre Benite, France, [5]Canadian Cancer Trials Group, Queens University, Kingston, Canada, [6]Cliniques Universitaires UCL Saint-Luc, Brussels, Belgium, [7]University Hospital Münster,, Münster, Germany, [8]Princess Margaret Hospital,, Toronto, Canada, [9]Queen Elizabeth II Health Sciences Centre, Halifax, Canada, [10]Max Rady College of Medicine, Winnipeg, Canada, [11]Azienda Ospedaliera Bianchi Melacrino Morelli, Reggio Calabria, Italy, [12]Juravinski Cancer Center, Hamilton, Canada

Background: In diffuse large B cell lymphoma, surviving disease free for 2 years after immunochemotherapy is associated with a high likelihood long term survival.

Our study aimed to examine the conditional survival and standardized mortality ratio (SMR) among patients with relapsed *de novo* diffuse large B cell (DLBCL) successfully undergoing an autologous stem cell transplant (ASCT) after first relapse.

Methods: A total of 478 patients with *de novo* DLBCL, relapsed after one treatment regimen from CORAL (Gisselbrecht et al, JCO 2012) and LY.12 (Crump et al, JCO 2013) were included in this analysis. These studies tested two salvage regimens against R-DHAP pre-ASCT, and maintenance rituximab post-ASCT. Patients were followed prospectively after ASCT for a median of 5.3 and 8.2 years, respectively. Individual patient data were analysed for event free survival (EFS) and overall survival (OS). As well, standardized mortality ratios (SMR) were estimated using French and Canadian lifetables.

Results: The number of patients alive and event free (EFS) 2 years after ASCT was 55.6% for patients treated in CORAL, 54.8% for LY.12, and 55.2% for the entire cohort. At 5 years, 33.5% and 39.4% are alive without event for CORAL and LY.12, respectively. Patients who achieve EFS24 have an overall survival of 82.3% for CORAL and 85.8 % for LY.12 at 5 years. Compared with the age and sex matched population, the standardized mortality ratio (SMR) was significantly higher until 5 years after ASCT, when there is no longer a statistically significant difference, SMR is 4.5 (95% CI 0.9-13.3) for CORAL and 2.3 (95% CI 0.8-5.0) for LY.12. Causes of death are dominated by ongoing lymphoma relapse.

Conclusions: Patients undergoing ASCT for relapsed DLBCL who achieve EFS24 have a very good long-term survival rate but continue to have a higher rate of death than the general population at least until they have survived disease free for 5 years. These observations can help to determine endpoints for clinical trials of new agents and approaches in this population, and in discussing outcomes with patients referred for ASCT.

Disclosure: Nothing to declare.

O109.

Exploratory Analysis of Brentuximab Vedotin Plus CHP (A+CHP) as Frontline Treatment for Patients with CD30-Expressing PERIPHERAL T-Cell Lymphomas (Echelon-2): Impact of Consolidative Stem Cell Transplant

Marek Trněný[1], Kerry J. Savage[2], Steven M. Horwitz[3], Ranjana Advani[4], Jacob H. Christensen[5], Eva Domingo-Domenech[6], Giuseppe Rossi[7], Franck Morschhauser[8], Onder Alpdogan[9], Cheolwon Suh[10], Kensei Tobinai[11], Andrei R. Shustov[12], Sam Yuen[13], Pier Luigi Zinzani[14], Lorenz Trümper[15], Timothy Illidge[16], Owen O'Connor[17], Barbara Pro[18], Meredith Little[19], Veronica Bunn[19], Keenan Fenton[20], Thomas Manley[20], Swaminathan P. Iyer[21]

[1]Charles University, General Hospital, Prague, Czech Republic, [2]BC Cancer Agency, University of British Columbia, Vancouver, Canada, [3]Memorial Hospital, New York, NY, United States, [4]Stanford Cancer Institute, Stanford, CA, United States, [5]Odense University Hospital, Odense, Denmark, [6]Institut Català d'Oncologia, Hospital Duran i Reynals Barcelona, Spain, [7]ASST Spedali Civili di Brescia, Brescia, Italy, [8]CHU Lille, Lille, France, [9]Thomas Jefferson University, Philadelphia, PA, United States, [10]Asan Medical Center, Songpa-gu, Korea, Republic of, [11]National Cancer Center Hospital, Tokyo, Japan, [12]Seattle Cancer Care Alliance & Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, United States, [13]Calvary Mater Newcastle, Waratah, Australia, [14]University of Bologna, Bologna, Italy, [15]Universitätsmedizin Göttingen, Göttingen, Germany, [16]University of Manchester, The Christie NHS Foundation Trust, Manchester, United Kingdom, [17]Columbia University Medical Center, New York, NY, United States, [18]Thomas Jefferson University, Philadelphia, PA, United States, [19]Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda, Cambridge, MA, United States, [20]Seattle Genetics, Bothell, WA, United States, [21]The University of Texas, MD Anderson Cancer Center, Houston, TX, United States

Background: ECHELON-2 (NCT01777152) demonstrated significantly longer progression-free survival (PFS) and overall survival with brentuximab vedotin plus cyclophosphamide, doxorubicin and prednisone (A+CHP) versus cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) as frontline treatment for patients with sALCL or other CD30-expressing PTCL. Patients could have received consolidative stem cell transplant (SCT) after treatment at the discretion of the treating investigator. Only 22% (50/226) of all patients treated with A+CHP underwent SCT. We present outcomes from an exploratory analysis of patients in complete remission (CR) following A+CHP who received an SCT and those who did not.

Methods: CR rate was defined at the end of treatment (EOT) by independent review per the Revised Response Criteria for Malignant Lymphoma. ALK+ sALCL patients were excluded. Consolidative transplant was not considered a PFS event. Univariate analysis of SCT versus no SCT and

multivariate analyses adjusting for region and age were performed.

Results: 67% (76/113) of A+CHP-treated patients with ALK- sALCL were in CR at EOT; 36% (27/76) of them received SCT. Patients who underwent SCT were younger than those without (median age [range]: 50 years [18-68] versus 59 [20-85] years). Median PFS for patients with SCT was not reached (95% CI: 36.57, not estimable [NE]) versus 55.66 months (95% CI: 23.72, 55.66) for patients without SCT. 59% (38/64) of A+CHP-treated patients with non-sALCL were in CR at EOT; 29% (11/38) of them received SCT. Patients who underwent SCT were younger than those without (median age [range] 57 years [35-73] versus 66 years [49-77]). Median PFS for patients who did and did not receive SCT was not reached (95% CI: 20.70, NE) versus 33.22 months (95% CI: 8.08, NE), respectively.

Before treatment, the intent to transplant in Asian countries among ALK- sALCL and non-ALCL patients was less frequent compared to non-Asian countries (13% and 29% versus 49% and 57%, respectively). SCT use was also less frequent in Asia (13% and 12%) versus non-Asian countries (32% and 23%). Standard PFS and multivariate proportional hazards regression analyses favoured SCT use in PTCL patients in CR after A+CHP (Table).

	ALK- sALCL (n = 76)		Non-sALCL (n = 38)		Combined (N = 114)	
	SCT (n = 27)	No SCT (n = 49)	SCT (n = 11)	No SCT (n = 27)	SCT* (n = 38)	No SCT (n = 76)
Estimated PFS at 3 years, % (95% CI)	80.4 (59.1, 91.4)	56.9 (40.6, 70.3)	70.1 (32.3, 89.5)	46.7 (26.7, 64.4)	76.1 (56.9, 87.6)	53.3 (40.7, 64.3)
Univariate HR (95% CI)	0.49 (0.19, 1.27)	0.36 (0.10, 1.26)	0.38 (0.18, 0.82)			
Multivariate HR (95% CI) adjusted for:						
Age†	0.54 (0.20, 1.45)	0.32 (0.09, 1.15)	0.39 (0.18, 0.86)			
Region‡	0.47 (0.18, 1.22)	0.37 (0.10, 1.33)	0.38 (0.18, 0.82)			
Age† + Region‡	0.52 (0.19, 1.41)	0.32 (0.09, 1.19)	0.39 (0.18, 0.86)			
Median follow-up, months (95% CI)	29.9 (24.2, 36.1)	41.6 (29.8, 42.0)	49.8 (21.2, 54.0)	42.6 (29.5, 53.9)	35.9 (24.5, 41.9)	41.6 (33.2, 42.1)

This research was originally published in Blood. Savage KJ et al. An Exploratory Analysis of Brentuximab Vedotin Plus CHP (A+CHP) in the Frontline Treatment of Patients with CD30+ Peripheral T-Cell Lymphomas (ECHELON-2): Impact of Consolidative Stem Cell Transplant. Blood. 2019;134(Supplement 1):p464. © The American Society of Hematology. Table presents HR of PFS for patients who achieved CR on A+CHP, SCT versus no SCT; HR<1 favours SCT; all HRs were stratified for baseline IPI score (0-1; 2-3; 4-5). PFS was measured from randomisation to progressive disease, death, or receipt of subsequent systemic chemotherapy to treat residual or progressive PTCL as determined by the investigator, whichever came first. Consolidative SCT was not considered an event. * Includes 2 allogeneic SCTs. † <65; ≥65 years. ‡ Non-Asia (rest of world); Asia (Taiwan, Japan, and South Korea). ¶ Median follow-up is calculated for PFS using the Kaplan-Meier method of switching the PFS event and censored status.

[Table]

Conclusions: Numerical PFS estimates favour SCT use in PTCL patients in CR after A+CHP. However, sample sizes are small and unknown confounders may impact this posthoc analysis. SCT use was infrequent in Asia, suggesting regional practice differences. The overall impact of consolidative SCT remains unconfirmed, including in patients treated with A+CHP. Further studies are needed to establish its role in this setting.

Clinical Trial Registry: NCT01777152
https://clinicaltrials.gov/ct2/show/NCT01777152

Disclosure: Study funded by Seattle Genetics, Inc. and Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. This research was funded in part through the National Institutes of Health/National Cancer Institute Cancer Center Support Grant P30 CA008748.

O110.

Brentuximab Vedotin for Relapse After Autologous Stem Cell Transplant in Patients With Hodgkin Lymphoma. A Study of the LWP-EBMT

Nikesh Chavda[1], Stephen Robinson[1], Ariane Boumendil[2], Irma Khvedelidze[2], Hervé Finel[2], Saad Akhtar[3], Muhammad Shahzad Rauf[3], Nadira Durakovic[4], Radovan Vrhovac[4], Maurizio Musso[5], Pauline Brice[6], Mutlu Arat[7], Didier Blaise[8], Matthew Collin[9], Joanna Romejko-Jarosinska[10], Aspasia Stamatoullas[11], Zubeyde Nur Ozkurt[12], Tadeusz Robak[13], Björn Wahlin[14], Keith M O Wilson[15], Eleonora Alma[16], Rocco Pastano[17], Luca Castagna[18], Ali Bazarbachi[19], Hervé Ghesquieres[20], Andrei Colita[21], Silvia Montoto[22]

[1]University Hospitals Bristol NHS Trust, Bristol, United Kingdom, [2]The European Society for Blood and Marrow Transplantation, Paris, France, [3]King Faisal Specialist Hospital, Riyadh, Saudi Arabia, [4]University Hospital Center Rebro, Zagreb, Croatia, [5]Ospedale La Maddalena, Palermo, Italy, [6]Hopital St. Louis, Paris, France, [7]Florence Nightingale Sisli Hospital, Istanbul, Turkey, [8]Institut Paoli Calmettes, Marseille, France, [9]Freeman Hospital, Newcastle, United Kingdom, [10]Maria Sklodowska-Curie Institute, Warsaw, Poland, [11]Centre Henri Becquerel, Rouen, France, [12]Gazi University, Çankaya, Turkey, [13]Copernicus Memorial Hospital, Lodz, Poland,

[14]Karolinska University Hospital, Stockholm, Sweden, [15]University Hospital Of Wales, Cardiff, United Kingdom, [16]Universita Cattolica S. Cuore, Rome, Italy, [17]European Institute of Oncology, Milan, Italy, [18]Humanitas Clinical Institute, Milan, Italy, [19]American University of Beirut Medical Center, Beirut, Lebanon, [20]Hospices Civils de Lyon, Lyon, France, [21]Coltea Clinical Hospital, Bucharest, Romania, [22]Queen Mary University of London, London, United Kingdom

Background: Patients with Hodgkin Lymphoma (HL) who relapse/progress after primary therapy can be successfully treated with salvage chemotherapy and consolidation with an autologous stem cell transplant (ASCT). However, around half will eventually relapse after the ASCT, requiring further therapy. Brentuximab Vedotin (BV) has been shown to induce complete remission (CR) in around one third of cases in a pivotal phase II trial (SG035-00303), with 12% achieving long-term disease-free survival only with monotherapy. The objective of the current study was to assess the efficacy of this treatment outside the setting of a clinical trial.

Methods: We analysed data from 101 patients (median age at ASCT 34 years, 60%, male) who received BV as their first therapy after relapsing post ASCT from 2012 onwards and were included in the EBMT registry.

Results: The median time from diagnosis to ASCT was 20.5 months, with 62% of patients in CR before ASCT. BEAM was the most common conditioning regimen employed (72%). The median time from ASCT to relapse was 10.1 months (interquartile range (IQR): 6.1-25.1). The median time on BV was 3.4 months and resulted in an overall response rate (ORR) of 59% with CR in 37% of patients. Disease progression (37%) was the main cause for BV discontinuation, with 5% stopping due to toxicity (PN being the most common). One fifth of patients completed the full 16 cycles of BV therapy. 58% of patients required further therapy after BV, with the most common agents (24%) being check point inhibitors (CPIs). Overall 63% of patients underwent a second stem cell transplant at a median of 7 months after starting BV. The majority (92%) were allogeneic (alloSCT) and 83% of these had reduced intensity conditioning (RIC). Mismatched relatives were the most common donors used (42%). Acute graft vs host disease (GvHD) was diagnosed in 45% of the patients (grade II-IV, 26%). Chronic GvHD was also seen in 45% of allografted patients with 25% being extensive. At last follow up 62% of all patients treated with BV (63/101) were still alive, with 68% of these continuing to be in CR. Of the patients who had died, 47% were due to disease progression/relapse and 42% from transplant related causes. Overall 11% of all patients (11/101) continued to be responding to BV monotherapy alone (10% CR, 1% PR) at a median time from response to last follow-up of 30 months.

Conclusions: BV is a well tolerated therapy leading to a CR in a third of patients. However, more than half needed subsequent therapy, with CPIs being the most popular agents. Almost two thirds of patients underwent a second transplant, which were predominantly RIC alloSCTs. A minority of patients seemingly continue to have long term PFS with BV monotherapy alone, which is in keeping with what was reported from the pivotal trial.

Disclosure: Nothing to declare.

O111.

Allogeneic Stem Cell Transplantation as A Curative Option in Relapse/refractory Diffuse Large B Cell Lymphoma: Spanish Multicenter Geth/geltamo Study

Leyre Bento[1], Antonio Gutiérrez[1], Silvana Novelli[2], Juan Montoro[3], José Luis Piñana[3], Lucía López-Corral[4], Mónica Cabrero[4], Gonzalo Gutiérrez-García[5], Marcela Ortiz-Moscovich[5], Mariana Bastos[6], Nieves Dorado[6], Ariadna Pérez[7], Rafael Hernani[7], Christelle Ferrà[8], Isabel Sánchez-Ortega[9], Irene García-Cadenas[2], Pilar Herrera[10], Nancy Rodríguez[11], Guillermo Rodríguez[11], Carmen Martín[12], Lucrecia Yáñez[13], Joud Zanabili[14], María Rosario Varela[15], Teresa Zudaire[16], Oriana López Godino[17], Inmaculada Heras[17], Ignacio Español[18], Carmen Martínez[5], Rocío Parody[9], José Antonio Pérez-Simón[11], Carlos Solano[7], Antonia Sampol[1], Jordi Sierra[2], Dolores Caballero[4]

[1]Son Espases University Hospital, IdISBa, Palma de Mallorca, Spain, [2]Hospital Sant Creu i Sant Pau, Barcelona, Spain, [3]Hospital La Fe, Valencia, Spain, [4]Hospital Universitario de Salamanca, Salamanca, Spain, [5]Hospital Clínic, University of Barcelona, IDIBSAPS, Barcelona, Spain, [6]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [7]Hospital Clínico de Valencia, Valencia, Spain, [8]ICO-IJC-Hospital Germans Trias i Pujol, Badalona, Spain, [9]Institut Català d'Oncologia (ICO)-Hospitalet, IDIBELL, Barcelona, Spain, [10]Hospital Ramón y Cajal, Madrid, Spain, [11]Hospital Virgen del Rocío, Sevilla, Spain, [12]Hospital Reina Sofía, Córdoba, Spain, [13]Hospital Valdecilla, Santander, Spain, [14]Hospital Central Asturias, Asturias, Spain, [15]Complejo Hospitalario Juan Canalejo, Coruña, Spain, [16]Complejo Hospitalario Navarra, Pamplona, Spain, [17]Hospital Morales Meseguer, Murcia, Spain, [18]Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain

Background: Diffuse large B cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma. Although it is a curable disease, up to 30-40% of DLBCL patients will experience relapse/progression (R/R). For those patients relapsing or not candidates to autologous (auto) hematopoietic stem cell transplantation (HSCT), allogeneic (allo)-HSCT may be a curative option although its efficacy could be limited by non-relapse mortality (NRM). Recent approval of CART therapy for patients with R/R DLBCL after at least two lines of therapy has established a possible curative option for these patients. Our objective was to analyze long term follow up in patients receiving allo-HSCT and try to define the optimal role of allo-HSCT in R/R DLBCL in the CAR-T era.

Methods: We performed a retrospective multicenter study including patients from centers of GETH/GELTAMO with R/R DLBCL who underwent allo-HSCT from March 1995 to November 2018. The primary endpoint was PFS, OS, NRM and cumulative incidence (CI) of graft versus host disease (GVHD).

Results: One-hundred and forty-four patients [41% male, median age 47 years (14-75)] fulfilled the inclusion criteria. Ninety-one percent of the patients were diagnosed with DLBCL NOS subtype, 7% double hit/double expressor and 2% mediastinal/plasmablastic lymphoma. Seventy-five percent had received a previous auto-HSCT and the median number of lines pre-allo-HSCT were 3 (1-9). Disease status at allo-SCT was complete response (CR) in 58%, partial response (PR) in 29% and active disease in 13%. The allo-HSCT characteristics are summarized in Table 1. The CR rate at day +100 was 62%. After a median follow-up of 47 months (5-207), 40% of the patients are alive and 91% of them are free of disease. One and 4-year-PFS were 50% and 36% and 1 and 4y-OS 56% and 38%, respectively. Overall NRM rate was 38% and 23% at day 100. The main causes of death were HSCT-related in 61% (32% infections and 24% GVHD) and disease progression in 34%. CI of grade III-IV acute GVHD at day 100 was 12% and moderate/extensive chronic GVHD at 4 years 11%. PFS and OS were influenced by disease status at HSCT, HCT-CI pre-HSCT, patient and donor age ($p< 0.01$). NRM was influenced by HCT-CI, time interval from diagnosis to allo-HSCT, previous auto-HSCT and donor age ($p< 0.01$). In the multivariate analysis HCT-CI ≥2 and donor age >43 years were the only independent variables for both PFS (HR 2.7, $p = 0.002$ and HR 2.7, $p = 0.004$) and OS (HR 3.1, $p = 0.001$ and HR 2.8, $p = 0.006$), respectively; NRM was significantly modified by HCT-CI ≥2 (HR 5.3, $p = 0.003$) and previous auto-HSCT (HR 4.4, $p = 0.04$).

Conclusions: Our data confirmed that allo-HSCT could be a curative option for patients with R/R DLBCL that are able to reach the procedure, although toxicity is high. Results are better for patients with HCT-CI 0-1 and chemosensitive disease receiving the transplant from a young donor. For the future, the role of allo-HSCT in the CART era has to be redefined and perhaps only patients who achieved CR as well as those failing after CAR-T could be considered as candidates for allo-HSCT.

Disclosure: Nothing to declare.

O112.

ADAM17 Inhibitor INCB7839 with Rituximab as Consolidation After Autologous HCT for Diffuse Large B Cell Lymphoma: A Novel Relapse Prevention Strategy

Veronika Bachanova, Bhaskar Kolla, Qing Cao, Daniel Weisdorf, Armin Rashidi, Erica Warlick, Najla El Jurdi, Rose Wangen, Mukta Arora, Claudio Brunstein, Jeffrey Miller

University of Minnesota, Minneapolis, MN, United States

Background: High-dose chemotherapy followed by autologous HCT (AHCT) is an effective strategy for chemosensitive recurrence of DLBCL. Yet, disease relapse is common (~30-40%), particularly early. NK cells are the first lymphocytes to recover after AHCT. We hypothesize that immune based consolidation can eliminate BEAM-resistant tumor cells. Several receptors and ligands important in NK cell killing are targets of ADAM17 proteinase. Enzymatic shedding of CD16, MICA, and MICB impairs NK cell mediated rituximab cytotoxicity. We report a novel strategy combining the ADAM17 inhibitor and rituximab to prevent DLBCL recurrence.

Methods: This is a Phase I/II single center dose escalation study of a small molecule ADAM17 inhibitor INCB7839 in combination with rituximab as a consolidation after AHCT for DLBCL. The aims were to establish a MTD of INCB7839, obtain the safety profile and estimate 1-year progression free survival (PFS). INCB7839 was administered orally at 3 dose levels (100mg, 200mg, and 300mg) twice a day starting between days 28-60 post AHCT for 3 months. Rituximab (375mg/m2) IV started with 1st INCB7839 dose and every 6 weeks × 3 infusions. Consecutive patients who recovered from AHCT and in remission at day 28 were enrolled.

Results: We enrolled 30 patients; 57% were males. The median age was 60 yrs (range 25-76), most patients were in CR1 or CR2 (23% and 54%), 7 patients were in PR (23%) at the time of AHCT. High risk features such as stage IV (57%), double/triple hit biology (26%), non-GCB cell of

origin subtype (40%), KPS < 80% (13%) were common. All patients received BEAM conditioning followed by a median of 5.2 x10^6 $CD34^+$ cells/kg. Only 1 patient received XRT post AHCT. The median follow-up was 32 months and range of 12 to 57 months.

The were no dose limiting toxicities and 300mg BID was declared the MTD. Dose escalation phase Grade 1-2 adverse events (AE) included leukopenia ($n = 19$), neutropenia ($n = 12$), thrombocytopenia ($n = 13$), anorexia ($n = 11$), nausea ($n = 13$) and jaw pain ($n = 8$). Grade 3-4 events were related to cytopenia ($n = 5$). Serious AE included: incidental thrombus ($n = 1$), full body pain ($n = 1$) and ovarian Ca ($n = 1$). Most AE were dose-dependent. In the expansion phase, 20 additional grade 3 AEs were observed, including cytopenia, anorexia, GI toxicity and headaches. Eleven subjects experienced persistent grade 2-3 AEs which were mitigated by INCB7839 dose reduction to 100-200mg BID and 9 unable to complete the therapy due to AE.

In intention to treat analysis, 1-yr PFS was 90% (95%CI 72-97) and OS was 97% (95%CI 79-100%); three patients experienced recurrence and one died due to progressive disease. Four more patients relapsed at 2nd year with 2-year PFS 75% (95%CI 54-97%). Plasma levels of soluble proteins, which are targets of ADAM17, such as sCD16, sMICA, sMICB demonstrated pharmacodynamic evidence of ADAM17 inhibitor activity in vivo.

Conclusions: The combination of the INCB7839 with Rituximab used in consolidation therapy for DLBCL post AHCT is feasible but lower than MTD dose is better tolerated long-term. The short-term clinical efficacy suggest improvement in disease control.

Clinical Trial Registry: ClinicalTrials.gov Identifier: NCT02141451

Disclosure: The trial was sponsored by Incyte and BMS.

Additionl funding was recieved from Randy Shavers Oncology Community Fund and Masonic Center Pilot Award.

COI: Veronika Bachanova: received funding from Incyte and BMS

O113.

Haploidentical Stem Cell Transplantation with Post-Transplant Cyclophosphamide in Patients with Non-Hodgkin Lymphoma: The Spanish Experience

Nieves Dorado[1,2], Gillen Oarbeascoa[1,2], Mariana Bastos[1,2], Carlos Solano[3], Isabel Sanchez Ortega[4], Lucia Lopez Corral[5], Christelle Ferra[6], Inmaculada Heras[7], Maria Jesus Cascon[8], Arancha Bermudez[9], Jaime Sanz[10], Ana Alarcon[11], Antonia Sampol[12], Jose Antonio Perez Simon[13], Carmen Martin[14], Santiago Jimbra[15], Pilar Herrera[16], Karem Humala[17], Victor Noriega[18], Jose Luis Diez-Martin[1,2,19], Mi Kwon[1,2]

[1]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [2]Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain, [3]Hospital Clinico Universitario de Valencia, Valencia, Spain, [4]ICO-Hospital Duran i Reynals, Barcelona, Spain, [5]Hospital Universitario de Salamanca, Salamanca, Spain, [6]ICO-Hospital Germans Trias i Pujol, Badalona, Spain, [7]Hospital General Universitario Morales Meseguer, Murcia, Spain, [8]Hospital Universitario Carlos Haya, Malaga, Spain, [9]Hospital Universitario Marques de Valdecilla, Santander, Spain, [10]Hospital Universitari i Politècnic La Fe, Valencia, Spain, [11]Hospital Universitario Puerta de Hierro, Madrid, Spain, [12]Hospital Universitario Son Espases, Palma de Mallorca, Spain, [13]Hospital Universitario Virgen del Rocío, Sevilla, Spain, [14]Hospital Universitario Reina Sofia, Cordoba, Spain, [15]Hospital Universitario de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria, Spain, [16]Hospital universitario Ramón y Cajal, Madrid, Spain, [17]Hospital Universitario La Paz, Madrid, Spain, [18]Complejo Hospitalario Universitario A Coruña, A Coruña, Spain, [19]Universidad Complutense de Madrid, Madrid, Spain

Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative option for patients with relapsed or refractory non-Hodgkin Lymphoma (NHL). However, experience with Haploidentical HSCT (HaploSCT) with post-transplant cyclophosphamide (PTCy) is scarce in this indication.

Methods: We retrospectively analyzed outcomes of 86 patients who received a HaploSCT with PTCy from 2012 to 2018 and reported in the GETH registry (Grupo Español de Trasplante Hematopoyético y Terapia Celular). Median follow-up was 21 months (range, 12-45).

Results: Median age of patients was 52, 74% were male. 29 patients were diagnosed from T cell lymphomas, and 20 from DLBCL. Most patients proceeded to transplant in an overall response (85%), with 49% in CR (33 confirmed by PET-CT). Up to 62% of patients had received a previous transplant, from which 6% was an allogeneic transplant.

Source of stem cells was mostly peripheral blood (87%), and reduced intensity conditioning was the preferred regimen (87%). GVHD prophylaxis consisted in cyclophosphamide 50 mg/kg/d on days +3 and +4, and MMF and a calcineurin inhibitor from day +5.

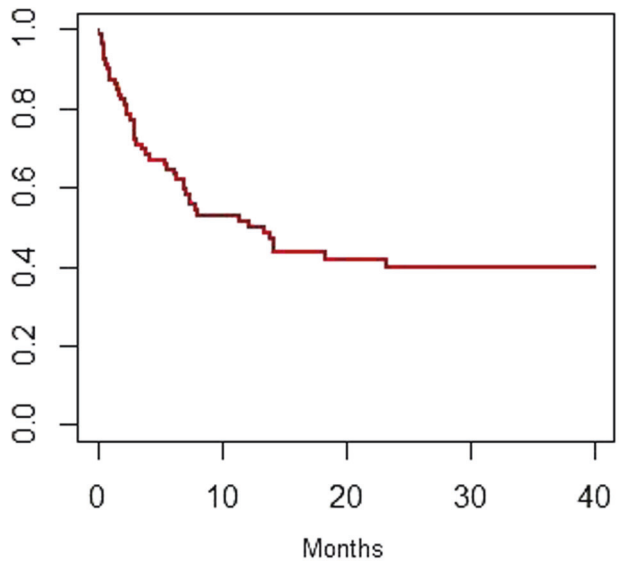
Donors were 46% siblings ($n = 40$), 40% offsprings ($n = 34$), and 17% parents ($n = 11$). Median time for neutrophil and platelet engraftment was 18 (16-21) and 29 (21-42) days, respectively.

The 2-year overall survival (OS) and event free survival (EFS) was 47% and 41%, respectively. Indolent and T cell

lymphomas showed better 2-year OS (61% and 50% vs 37%, respectively) compared to aggressive lymphomas, although not statistically significant ($p = 0.2$). Patients with aggressive B or T-cell lymphomas tended to show higher 2-year relapse rates (26% and 24%) compared to indolent lymphomas (13%, $p = 0.5$). Patients with an overall response (ORR) pretransplant (partial or complete) showed a significantly lower 2-year cumulative incidence of relapse (18% vs 60% respectively, $p = 0.008$,), and a trend towards a better 2-year EFS (ORR patients 43% vs no-ORR 22%, $p = 0.2$). NRM at 2 years was 33%. Cumulative incidence of acute GVHD grade II-IV was 46% at day +180, with 10% developing grade III-IV. Chronic GVHD rate was 20% at 5 years, and 5% for extensive chronic GVHD.

Among the 20 patients who received HaploSCT for relapsed DLBCL, 3 patients (15%) had progressive disease at the time of transplant. The cumulative incidence of relapse in these patients at 2 years was 59%, with 25% NRM. EFS at 2 years was 16%.

Conclusions: In our experience, HaploSCT with PTCy is a valid option for patients with relapsed or refractory non-Hodgkin Lymphoma, providing acceptable outcomes, especially among those with indolent and T cell lymphomas. Outcome of patients with aggressive B cell lymphomas, particularly DLBCL, remains poor even after achieving response, therefore new treatment options (i.e. CART cells) may have a significant role in these particular patients.



[Tables 1 and 2 show patients' characteristics. Fig 1 shows event-free-survival.]

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

Minimal residual disease, tolerance, chimerism and immune reconstitution

O114.

T Cell Chimerism After HCT Does Not Predict for Graft Loss in Non-Malignant Diseases, and is a Failure of Myelosuppression Rather Graft Rejection

Rubiya Nadaf, Michelle Carr, Helena Lee, Denise Bonney, Helen Campbell, Hemalatha Doss, Robert Wynn

Royal Manchester Children's Hospital, Manchester, United Kingdom

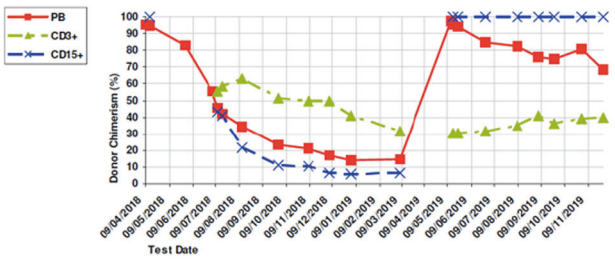
Background: Mixed whole blood chimerism following Hematopoietic Stem cell transplant (HCT) transplant for non-malignant disease (NMD) in children. Mixed chimerism is sufficient in most such disease to correct the underlying illness, and chimerism after transplant is useful in the assessment of graft loss and relapse. In general, myeloid chimerism indicates donor stem cell engraftment and loss of myeloid chimerism might indicate the need to re-transplant. The management of mixed chimerism is not standardised, but includes T-cell suppression, modulation or donor lymphocyte infusion (DLI). We evaluated post-HSCT, lineage specific (CD3/CD15) peripheral blood leucocyte chimerism data to characterize patterns and assess prognostic significance of these patterns with respect to graft outcome following HCT for NMD.

Methods: We reviewed 132 patients aged 1-16 years, treated with allogenic HSCT for non-malignant diseases at Royal Manchester Children's Hospital since September 2014. Chimerism monitoring was monthly and was of whole blood unless mixed when T-cell and myloid chimerism was additionally performed. All patients received serotherapy, usually with Alemtuzumab, but with ATG when a cord was performed. Graft failure was defined as less than 20% myeloid chimerism and recurrence of original disease.

Results: Mixed chimerism is common in this population. Our study of 132 patients on engraftment as determined by STR analysis, showed that 6% subsequently lost the graft and were re-transplanted, at a median of 12 months after transplant. All re-transplanted patients retained adequate donor cell engraftment, and were usually performed with the same donor. 37% were always fully donor after transplant and 63% had mixed chimerism. The median T cell chimerism in graft rejected subjects and in subjects with mixed chimerism with preserved graft was 62.7% and 43.2% respectively at matched time points, and no clear relationship was seen between T-cell donor chimerism and graft outcome. Significantly mixed T-cell chimerism

(<50% donor) was associated with reduced intensity conditioning, and with virus infection (expansion of autologous, virus-specific T-cells), and inversely with acute GVHD. There was no difference in the median times post-transplant at which immune suppression (IS) was withdrawn. No grade III-IV GvHD was seen and no extensive chronic GVHD was seen.

Conclusions: We have previously demonstrated reduction of late graft relapse with autologous reconstitution of host cells after optimisation of busulfan-based, myeloablative conditioning in IEM (Aldenhoven, BBMT, 2015). Here we demonstrate no relationship between T-cell chimerism and graft outcomes in non-malignant diseases, that second transplant can be effectively performed using the same donor, and that withdrawal of IS is permissible even where there is significant mixed T-cell chimerism. These data suggest that mixed myeloid chimerism and graft loss is related to conditioning and stem cell engraftment and is not immunologically mediated.



[Graph 1: This graph depicts that graft loss despite good donor T cell chimerism in a patient with si]

Disclosure: Nothing to declare.

O115.

Faster Engraftment and Reconstitution of Innate-Immunity After Anti-T -lymphocyte Globuline (ATLG) than Post-Transplant-Cyclophosphamide (PTCY) as GVHD Prophylaxis After Myeloablative Conditioning (MAC) Peripheral-Blood-Stem-Cell (PBSC) Allogeneic-Transplantation (ALLO-SCT)

Radwan Massoud, Martina Güllstorf, Christine Wolschke, Max Christopeit, Boris Fehse, Petra Freiberger, Francis Ayuk, Nicolaus Kröger

University Medical Center, Hamburg, Germany

Background: PTCY and ATLG are widely used strategies for GVHD prevention in allo-SCT. However, data comparing immune-reconstitution (IR) between the two is scarce.

We compared the dynamics of IR post-allo-SCT between ATLG and PTCY.

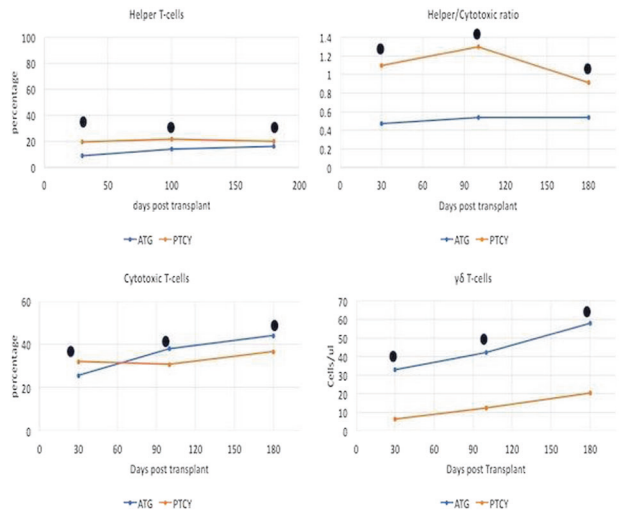
Methods: This retrospective study was conducted at University-Medical-Center-Hamburg-Eppendorf between the years 2005-2019 and included 599 patients who underwent allo-SCT from MRD ($n = 105$), MUD ($n = 360$), MMRD ($n = 17$) and MMUD ($n = 117$). 476 patients received ATLG (34% 30mg/kg, 66% 60mg/kg) between days -4 to -1 and 123 patients received 50mg/kg/day-PTCY on days+3+4 combined with Calcineurin-inhibitor and mycophenolate mofetil for mismatched-donors. To render groups comparable, we included only patients that received PBSC-MAC-allo-SCT. All patients were transplanted for hematological-malignancies, with AML and ALL as the most common diseases in the ATLG group and PTCY group respectively. Blood-samples were collected on days +30, +100 and +180 and analyzed by multiparametric-flow-cytometry for the following cells: T-Lymphocytes (CD3+), activated-T-Lymphocytes (CD3+HLADR+), T-helper (CD3+/CD4+), T-Cytotoxic (CD3+/CD8+), B-Lymphocytes (CD19+), B-Lymphocytes subpopulations (CD19+CD5+CD1d+)(CD19+CD27+), Naïve-B-cells (CD19+CD27-CD10+), NK-cells (CD56+CD3-), NKT-cells (CD56+CD3+), naïve-T-helper (CD4+CD45RA+), Memory-T-helper (CD4+CD45R0+), naïve-T-cytotoxic (CD8+CD45RA+), memory-T-cytotoxic (CD8+CD45R0+), γδT-cells (γδTCR+, CD3+), regulatory-T-cells (CD4+CD25+CD127+).

Results: We observed a more rapid neutrophil engraftment in the ATLG group (median days 12 (range,8-36) vs median days 16 (range,12-27) p< 0.001). ATLG was associated with significantly higher percentage of total-T-cytotoxic at days30 and 100 and a higher percentage and count at day100. When comparing T-cytotoxic-subpopulations, ATLG had a higher percentage and count of naïve-T-cytotoxic-cells at day 30 and 100 and only a higher percentage at day180 and a higher naïve-to-memory ratio at day 30. The helper/cytotoxic T-cell ratio did not return to normal in either of the two groups, however the helper/suppressor ratio was significantly higher in all evaluations in the PTCY group and the absolute number of naïve helper-T-cells and percentage of total helper-T-cells and all helper T-cell subpopulations excluding regulatory T-cells were constantly higher in the PTCY group. In addition, we observed a higher naïve/memory helper-T-cell ratio at days 30 and 100 in the PTCY group. In the ATLG group, γδT-cells had a significantly higher percentage and count in at all evaluations, while NKT-cells had a significantly higher percentage and count at days 30,100 and only a higher percentage at day 180. When comparing NK-cells the ATLG group had a significantly higher percentage and count at day 30.

In the PTCY-group we observed a higher overall incidence of infection at day 30 and at days 30-100

(Day30 77% vs 64%, $p = 0.06$; Day60-100 54% vs 36%, p< 0.001); and a higher CMV reactivation at day 30 (35% vs 34%, $p = 0.013$). Moreover, we observed a higher proportion of bacterial and viral infections in the PTCY group ($p = 0.034$). We observed no significance difference in incidence of Grade II-IV aGVHD and chronic GVHD overall survival and progression free survival. All our findings were confirmed by donor subgroup analysis.

Conclusions: Strong differences exist in terms of IR when comparing ATLG to PTCY in MAC-PBSC-allo-SCT, which led to a higher rate of infections after PTCY. A faster cytotoxic-T-cell, NK-cells, NKT-cells and γδT-cell recovery, while a better helper-T-cell-recovery is the hallmark of PTCY.



[IR ATLG vs PTCY. Black circles indicate P<0.05]

Clinical Trial Registry: not applicable
Disclosure: nothing to disclose

O116.

CMV Seropositivity Drives T Cell Reconstitution After CD34-Selected Allogeneic HCT Despite Reduction of Viremia with Letermovir

Christina Cho[1,2], Jessica Lavery[1], Josel Ruiz[1], Molly Maloy[1], Peter Maslak[1,2], Sergio A. Giralt[1,2], Richard J. O'Reilly[1,2], Marcel R.M. van den Brink[1,2], Miguel-Angel Perales[1,2]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, United States, [2]Weill Cornell Medical College, New York, NY, United States

Background: CD34-selected HCT has historically been associated with rates of CMV viremia of 60-80%. We have previously shown that CMV reactivation after CD34-selected HCT is associated with more rapid peripheral T-cell expansion. With the introduction of letermovir for CMV prevention, however, it is unknown how CMV informs T-cell recovery kinetics. We therefore evaluated T-cell reconstitution in recipients of CD34-selected HCT before and after the advent of letermovir prophylaxis.

Methods: This single-center analysis included adult recipients of CD34-selected HCT from 4/2012 through 3/2019. Following FDA approval of letermovir in 11/2017, CMV-seropositive patients received letermovir beginning day +7 post-HCT. We excluded T-cell data after DLI, stem cell boost, targeted CTLs, or 2nd HCT. Hierarchical models with a random intercept for each patient and fixed effect for time post-transplant modeled univariable associations between log lab values and patient characteristics of interest. We estimated Loess smoothed curves to evaluate trends in cell populations over time.

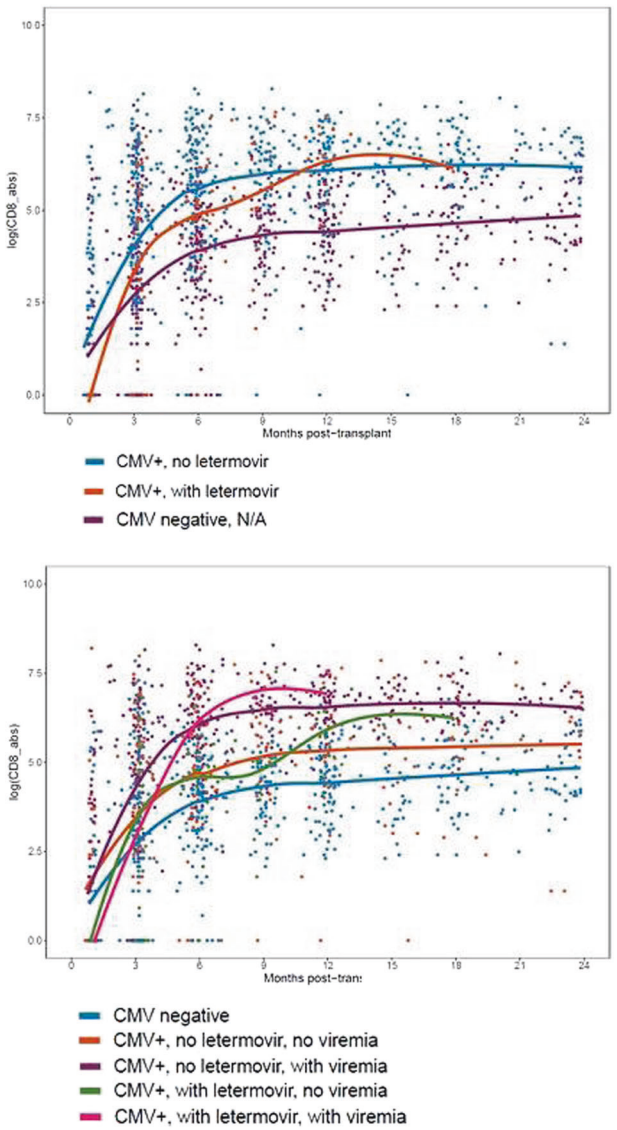
Results: Of 335 patients studied, 168(50%) were CMV seropositive and did not receive letermovir, 33(10%) were seropositive and received letermovir, and 134(40%) were seronegative. Among CMV+ patients with evaluable PCR data who did not receive letermovir, 114/167(68%) developed viremia; in those who received letermovir, 4/32(12.5%) developed viremia while receiving prophylaxis. Another 4 patients reactivated CMV after letermovir discontinuation; we excluded these from T-cell reconstitution analyses.

Compared with a reference group of CMV+ patients who did not receive letermovir, CD3+ recovery was slower in CMV- patients (univariable estimate[95% CI]: -0.59[-0.93,-0.26]) but not significantly different in CMV+ patients receiving letermovir (0.31[-0.25,0.88]; p< 0.001 for overall association; figure). CD8 recovery was also similar in CMV + patients regardless of letermovir exposure but slower in CMV- patients (table; figure). Compared with CMV- patients, CD8 recovery was faster in all CMV+ patients regardless of viremia, though pace of recovery appeared slower in the absence of viral reactivation (table; figure). Observed differences in CD4 recovery were less significant (CMV+/letermovir: Reference; CMV+/with letermovir: 0.49[0,0.98]; CMV-: -0.21[-0.50,0.08]; $p = 0.02$).

Conclusions: Despite reduction of CMV viremia with letermovir prophylaxis, CMV seropositivity alone correlated with more rapid T-cell recovery, particularly CD8+ expansion, after CD34-selected HCT. To our knowledge, these are the first data to indicate that prior CMV exposure exerts effects on T-cell reconstitution independent of quantifiable viremia. Further investigation into the mechanisms underlying these findings will shed greater light on the complexity of the interaction between CMV and host T-cell response and, perhaps, inform the development of future adoptive cell therapy approaches.

CMV STATUS AND VIREMIA / LETERMOVIR EXPOSURE	n	UNIVARIABLE ESTIMATE (95% CI)	p
CMV+ / No letermovir	168	Reference	<0.001
CMV+ / With letermovir	33	-0.06(-0.65,0.52)	
CMV-	134	-1.07(-1.42,-0.72)	
---	---	---	---
CMV-	134	Reference	<0.001
CMV+ / No letermovir / No viremia	53	0.58(0.10,1.06)	
CMV+ / No letermovir / With viremia	114	1.29(0.91,1.67)	
CMV+ / With letermovir / No viremia	24	0.76(0.09,1.43)	
CMV+ / With letermovir / With viremia	4	1.56(0.02,3.10)	

[Univariable Estimates of CD8+ T-Cell Reconstitution Based on CMV Serostatus/Viremia and Letermovir Exposure]



[Loess Curves Illustrating CD8+ T-Cell Recovery by CMV Serostatus/Viremia and Letermovir Exposure]

Clinical Trial Registry: Not applicable.

Disclosure: Cho, Christina: Allovir(consultancy).

Giralt, Sergio: Spectrum Pharmaceuticals(consultancy); Novartis(consultancy); Actinium(consultancy/research funding); Johnson & Johnson(consultancy/research funding); Celgene(consultancy/research funding); Kite(consultancy); Jazz Pharmaceuticals(consultancy); Amgen(consultancy/research funding); Miltenyi(research funding); Takeda(consultancy/research funding).

van den Brink, Marcel: Flagship Ventures(consultancy/honoraria); Novartis(consultancy/honoraria); Evelo(consultancy/honoraria); Jazz Pharmaceuticals(consultancy/honoraria); Therakos(consultancy/honoraria); Amgen (consultancy/honoraria); Merck(consultancy/honoraria); Acute Leukemia Forum (consultancy/honoraria); Magenta/DKMS Medical Council(membership on board of directors or advisory committees); Juno Therapeutics(licensing); Seres Therapeutics(consultancy/honoraria/membership on board of directors or advisory committees/research funding).

O'Reilly, Richard: Atara Biotherapeutics(consultancy/patents & royalties/research funding).

Perales, Miguel-Angel: Bristol-Meyers Squibb(honoraria/membership on board of directors or advisory committees); Incyte(honoraria/membership on board of directors or advisory committees/research funding); Nektar Therapeutics(honoraria/membership on board of directors or advisory committees); Novartis(honoraria/membership on board of directors or advisory committees); Omeros(honoraria/membership on board of directors or advisory committees); Bellicum(honoraria/membership on board of directors or advisory committees); Abbvie(honoraria/membership on board of directors or advisory committees); NexImmune (membership on board of directors or advisory committees); MolMed(membership on board of directors or advisory committees); Merck(consultancy/honoraria); Medigene (membership on board of directors or advisory committees); Servier(membership on board of directors or advisory committees); Takeda(honoraria/membership on board of directors or advisory committees); Kite/Gilead(research funding); Miltenyi(research funding).

The remaining authors have nothing to declare.

O117.

Comparing Outcomes of Patients Having Mixed T Chimerism and Unrelated Donor Allografts for Acute Leukaemia/MDS to Patients with Complete Chimerism - Single Centre Retrospective Study

Vipul Sheth[1], Victoria Potter[2], Donal McLornan[3], Hugues Delavallade[4], Shreyans Gandhi[4], Austin Kulasekararaj[4],

Francesco Dazzi[4], Judith Marsh[4], Ghulam Mufti[4], Antonio Pagliuca[4], Kavita Raj[3]

[1]Fred Hutchinson Cancer Research Center, Seattle, WA, United States, [2]Kings College Hospital, London, United Kingdom, [3]Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom, [4]Kings College Hospital NHS Foundation Trust, London, United Kingdom

Background: T-cell depletion, especially alemtuzumab, reduces the risk of graft-versus-host disease (GVHD) following allogeneic hematopoietic stem cell transplantation (HSCT) using unrelated donor peripheral stem cell graft (PBSC-matched/mismatched), but has been associated with an increased frequency of mixed t cell chimerism (MC) and subsequent relapse. In adult patients receiving alemtuzumab and having MC (T cell), early pre-emptive donor lymphocyte infusion (pDLI) has been safe and effective in reducing relapses (facilitating donor chimerism), without increasing risk of GVHD. Among responders in paediatric cohort having lineage specific MC(CD34/33), pDLI could achieve outcomes nearly similar to patients having complete chimerism (CC). However, many patients having MC actually fail to receive timely pDLI, and their outcomes remain particularly dismal, which is not considered. Thus, we compared long term outcomes of patients with T cell MC (including patients not receiving pDLI) to patients having complete chimerism CC.

Methods: One-hundred fifteen adult patients with CD3 MC after day 60, in patients undergoing HSCT for acute leukaemia/myelodysplastic syndrome(MDS) from an unrelated donor(UD), using alemtuzumab and predominantly PBSC grafts, between 2007-2016, were compared with 185 patients having CC. CD15 chimerism was >98%. In patients with MC intention was to start incremental pDLI (by day 100) after rapid withdrawal of immunosuppressants (chimerism < 50%).

Results: Both groups were comparable for age, mismatches, graft source, and disease risk. MC group had more patients receiving reduced intensity (RIC) regimen (62% vs 52% in CC, $p = 0.15$). The median follow-up was 33 (0.6-150 months). Sixty-five (56%) patients received pDLI. The median dose of pDLI was 1 x10^6/kg and median time to pDLI was 5 months from transplantation. Out of 65 patients, 43 patients (67%) had a response (RR) (36/43 achieving CC) and 22 (33%) patients had no response (NR). Fifty patients (44%) did not receive any pDLI (ND). pDLI was well tolerated with no difference in GVHD ($p = 0.65$), infections ($p = 0.37$) or NRM ($P = 0.37$) between pDLI and ND. Overall survival (OS) was significantly better in MC group as compared to CC (52.4% vs 42%, $p = 0.02$), mainly due to reduction in non- relapse mortality NRM (14% vs 26%, $p = 0.004$) and all grade acute and chronic GVHD (38% vs 68%, $p = 0.0009$, and 37% vs 51%, $p = 0.025$). Relapses and disease-free survival were comparable (32% vs 38%, $p = 0.99$ and 38.5% vs 45%, $p = 0.12$, for CC and MC, respectively). After multivariate analysis, MC still had significantly better OS ($p = 0.01$, HR-1.53, CI-1.0-2.2) and NRM ($p = 0.007$, HR-2.44, CI-1.3-5.2, ref MC). Within MC group, response to pDLI was the only significant factor predicting OS, DFS and relapses with NR and ND having unfavourable outcomes as compared to RR ($p = 0.0001$, HR=5.45, and $p = 0.001$, HR-5.95, respectively).

Conclusions: In this large single centre study, we have shown that T cell MC in patients undergoing UD allografts with alemtuzumab is no longer an adverse prognostic factor, with timely initiation of pre-emptive DLI, and their OS is in fact better than CC, mainly due to reduction in NRM. This strategy is safe and well tolerated. Response to DLI is the main independent predictor of overall outcomes in patients with MC.

Clinical Trial Registry: Not applicable.

Disclosure: No conflicts of interest to declare.

Multiple myeloma

O118.

Daratumumab Plus Bortezomib, Thalidomide, and Dexamethasone (D-VTD) in Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM): Subgroup Analysis of High-Risk Patients in Cassiopeia

Pieter Sonneveld[1], Michel Attal[2], Aurore Perrot[3], Cyrille Hulin[4], Denis Caillot[5], Thierry Facon[6], Xavier Leleu[7], Karim Belhadj[8], Lionel Karlin[9], Lotfi Benboubker[10], Mark-David Levin[11], Monique C. Minnema[12], Matthijs Westerman[13], Michel Delforge[14], Sonja Zweegman[15], Lixia Pei[16], Carla de Boer[17], Veronique Vanquickelberghe[18], Tobias Kampfenkel[17], Philippe Moreau[19]

[1]Erasmus MC Cancer Institute, Rotterdam, Netherlands, [2]Institut Universitaire du Cancer de Toulouse-Oncopole, Toulouse, France, [3]University Hospital Antwerp, Vandoeuvre-lès-Nancy, France, [4]Hospital Haut Leveque, University Hospital Bordeaux, France, [5]CHU Dijon, Hôpital Du Bocage, Dijon, France, [6]University of Lille, CHU Lille, Lille, France, [7]CHU Poitiers - Hôpital la Milétrie, Poitiers, France, [8]Hopital Henri Mondor, Creteil, France, [9]Centre Hospitalier Lyon-Sud Hematologie (HCL), Pierre - Benite Cedex, France, [10]CHU de Tours, Hôpital de Bretonneau, Tours, France, [11]Albert Schweitzer Hospital, Dordrecht, Netherlands, [12]UMC Utrecht Cancer Center, Utrecht,

Netherlands, [13]*Northwest Clinics, Alkmaar, Netherlands*, [14]*Universitaire Ziekenhuizen Leuven, Leuven, Belgium*, [15]*Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Netherlands*, [16]*Janssen Research & Development, LLC, Raritan, NJ, United States*, [17]*Janssen Research & Development, LLC, Leiden, Netherlands*, [18]*Janssen Research & Development, Beerse, Belgium*, [19]*University Hospital Hôtel-Dieu, Nantes, France*

Background: High-risk cytogenetic abnormalities and International Staging System (ISS) disease stage III confer poor outcomes in multiple myeloma (MM). In the phase 3 CASSIOPEIA study, at median follow-up of 18.8 months, D-VTd significantly reduced risk of progression/death by 53% and improved rates of stringent complete response (sCR), CR or better (≥CR), and minimal residual disease (MRD) negativity versus bortezomib/thalidomide/dexamethasone (VTd) in transplant-eligible newly diagnosed MM (NDMM) patients. We present a subgroup analysis of high-risk patients in CASSIOPEIA based on cytogenetic risk and ISS stage.

Methods: Transplant-eligible NDMM patients were stratified by site affiliation (Intergroupe Francophone du Myélome or Hemato-Oncologie voor Volwassenen Nederland), ISS stage (I, II, III), and cytogenetic risk status. High-risk cytogenetic patients had del17p (≥50% abnormal cells) and/or t(4;14) (≥30% abnormal cells) by centrally assessed fluorescent in situ hybridization. Patients were randomized 1:1 to 4 pretransplant induction and 2 posttransplant consolidation cycles with D-VTd or VTd. Primary endpoint was sCR post consolidation (Day 100 post autologous stem cell transplant), per International Myeloma Working Group (IMWG) criteria. Additional endpoints were rates of MRD negativity (multiparametric flow cytometry; 10^{-5}), ≥CR, and progression-free survival (PFS).

Results: Of 1085 patients randomized to D-VTd (n = 543) or VTd (n = 542), 15.5% had a high-risk cytogenetic abnormality. The proportions of patients with ISS stage I, II, and III were 39.8%, 45.0%, and 15.2%, respectively. A greater proportion of patients was classified as stage II in the D-VTd than the VTd group (47.0% vs 43.0%); the proportion classified as stage III was similar in both groups (15.5% vs 14.9%). Postconsolidation sCR rates were significantly higher with D-VTd versus VTd (28.9% vs 20.3%; odds ratio [OR] 1.60; 95% CI 1.21−2.12; P=0.0010). Prespecified subgroup analyses of sCR showed consistent treatment effect of D-VTd over VTd except in high-risk cytogenetic (OR 0.83; 95% CI 0.42−1.66) and ISS stage III (OR 1.07; 95% CI 0.54−2.12) patients. However, the proportion of patients with ≥CR favored D-VTd versus VTd (high-risk cytogenetic, 36.6% vs 32.6%; OR 1.11; 95% CI 0.58−2.10; and ISS stage III, 44.0% vs 33.3%; OR 1.54; 95% CI 0.83−2.88). A greater proportion of D-VTd versus VTd patients were MRD negative (63.7% vs 43.5%; OR 2.27; 95% CI 1.78−2.90; P< 0.0001), including in high-risk cytogenetic (59.8% vs 44.2%; OR 1.88; 95% CI 1.02−3.46) and ISS stage III (64.3% vs 45.7%; OR 2.14; 95% CI 1.15−4.00) subgroups. At median follow-up of 18.8 months, D-VTd reduced the risk of progression/death versus VTd (hazard ratio [HR] 0.47; 95% CI 0.33−0.67; P< 0.0001), including in high-risk cytogenetic (HR 0.67; 95% CI 0.35−1.30) and ISS stage III (HR 0.66; 95% CI 0.32−1.39) subgroups.

Conclusions: Prespecified subgroup analyses of sCR (using strict IMWG criteria) demonstrated consistent treatment benefit of D-VTd over VTd, except in patients with high-risk cytogenetic abnormalities and ISS stage III disease. Importantly, D-VTd resulted in a benefit in terms of ≥CR, MRD negativity, and PFS in these high-risk patient subgroups. The clinical benefit of these deeper responses will be evaluated with additional follow-up and in Part 2 of the study.

Clinical Trial Registry: NCT02541383

Disclosure: Sonneveld: *Amgen, Celgene, Janssen, Karyopharm, Takeda:* Honoraria, Research Funding; *Bristol-Myers Squibb:* Honoraria; *SkylineDx:* Research Funding. **Attal:** *Celgene, Takeda:* Consultancy, Other: Travel Fees, Lecture Fees, Research Funding. **Perrot:** *Amgen, Sanofi, Takeda:* Honoraria; *Celgene, Janssen:* Honoraria, Membership on an Entity's Board of Directors or Advisory Committees; **Hulin:** *Celgene:* Consultancy, Honoraria; *Janssen, AbbVie, Celgene, Amgen:* Honoraria. **Caillot:** Nothing to disclose. **Facon:** *Amgen, Karyopharm, Oncopeptides, Roche, Sanofi:* Membership on an Entity's Board of Directors or Advisory Committees; *Celgene, Janssen, Takeda:* Membership on an Entity's Board of Directors or Advisory Committees, Speakers Bureau. **Leleu:** *AbbVie, Amgen, Bristol-Myers Squibb, CARsgen, Celgene, GSK, Incyte, Janssen, Karyopharm, Merck, Novartis, Oncopeptide, Sanofi, Takeda:* Honoraria. **Belhadj:** *Celgene: Amgen, Celgene, Janssen, Takeda*: Personal Fees; *Janssen*: Outside the Submitted Work. **Karlin:** *Amgen, Janssen:* Honoraria, Membership on an Entity's Board of Directors or Advisory Committees, Other: Travel Support; *Celgene, Takeda:* Honoraria, Membership on an Entity's Board of Directors or Advisory Committees. **Benboubker:** Nothing to disclose. **Levin:** *AbbVie, Amgen, Janssen, Roche, Takeda:* Membership on an Entity's Board of Directors or Advisory Committees, Other: Educational Grant. **Minnema:** *Amgen, Celgene, Kastritis, Genesis, Gilead, Janssen Cilag, Pfizer, Prothena, Servier, Takeda, Vos:* Honoraria; *Amgen, Celgene Corporation, Janssen:* Research Funding. **Westerman:** Nothing to disclose. **Delforge:** *Adaptive Biotech, Bristol-Myers Squibb, Takeda:* Consultancy, Honoraria; *Amgen, Celgene, Janssen, GSK, Takeda:* Honoraria. *Amgen:* Consultancy, Research Funding; *Celgene*

Corporation, Janssen, Sanofi: Consultancy, Honoraria, Research Funding; *Karyopharm:* Other: IRC Data Review; *Weisel, Juno:* Consultancy. **Zweegman:** *Celgene, Janssen Pharmaceuticals, Takeda:* Membership on an Entity's Board of Directors or Advisory Committees, Research Funding. **Pei:** Employee of Janssen. **De Boer:** Employee of Janssen. **Vanquickelberghe:** Employee of Janssen. **Kampfenkel:** Employee of Janssen. **Moreau:** *AbbVie, Amgen, Celgene, Janssen, Takeda:* Consultancy, Honoraria.

O119.

Evaluation of Prognostic Value of Positron Emission Tomography-Computed Tomography (PET/CT) in Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM) Phase 3 Cassiopeia Study Patients: Cassiopet Study Results

Philippe Moreau[1], Sonja Zweegman[2], Aurore Perrot[3], Cyrille Hulin[4], Denis Caillot[5], Thierry Facon[6], Xavier Leleu[7], Karim Belhadj[8], Lionel Karlin[9], Lotfi Benboubker[10], Mark-David Levin[11], Monique C Minnema[12], Bastien Jamet[13], Caroline Bodet-Milin[13,14], Pieter Sonneveld[15], Jérôme Lambert[16], Lixia Pei[17], Carla de Boer[18], Jessica Vermeulen[18], Tobias Kempfenkel[18], Francoise Kraeber-Bodere[13,14]

[1]University Hospital Hôtel-Dieu, Nantes, France, [2]Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Netherlands, [3]University Hospital, Vandoeuvre Les Nancy, Nancy, France, [4]Hôpital Haut Lévêque, University Hospital Bordeaux, Pessac, France, [5]CHU Dijon, Hôpital Du Bocage, Dijon, France, [6]University of Lille, CHU Lille, Lille, France, [7]CHU Poitiers, Hôpital la Milétrie, Poitiers, France, [8]Hôpital Henri Mondor, Creteil, France, [9]Centre Hospitalier Lyon-Sud Hématologie (HCL), Pierre-Bénite, France, [10]CHU de Tours, Hôpital de Bretonneau, Tours, France, [11]Albert Schweitzer Ziekenhuis, Dordrecht, Netherlands, [12]University Medical Center Utrecht, Utrecht, Netherlands, [13]Service de Médecine Nucléaire, Hôtel-Dieu, CHU de Nantes, Nantes, France, [14]CRCINA, INSERM, CNRS, Université d'Angers, Université de Nantes, Nantes, France, [15]Erasmus MC Cancer Institute, Rotterdam, Netherlands, [16]Hôpital Saint Louis, Paris, France, [17]Janssen Research & Development, LLC, Raritan, NJ, United States, [18]Janssen Research & Development, LLC, Leiden, Netherlands

Background: 18F-fluorodeoxyglucose positron emission tomography–computed tomography (PET/CT) is a reliable technique for multiple myeloma (MM) staging/monitoring with prognostic value for progression-free survival (PFS). In CASSIOPEIA, bortezomib/thalidomide/dexamethasone (VTd) plus daratumumab (D-VTd) reduced the risk of disease progression/death and improved stringent complete response, complete response (CR) or better, and minimal residual disease (MRD)-negativity rates versus VTd in transplant-eligible newly diagnosed MM (NDMM) patients. Although MRD negativity is associated with improved outcomes, relapse may occur in MRD-negative patients, possibly due to focal bone disease. A 2009 Intergroupe Francophone du Myélome trial demonstrated better PFS in patients who were double negative (ie, lacking residual disease assessed by MRD [multiparametric flow cytometry {MFC}] and PET/CT) versus patients who were not. Here, we report the results of the CASSIOPET companion study of CASSIOPEIA, which evaluated the prognostic value of PET/CT at diagnosis, postconsolidation PET-complete response (PET-CR) rates of D-VTd versus VTd, and PET-CR/MRD-negativity concordance.

Methods: In CASSIOPEIA, 1085 transplant-eligible NDMM patients were randomized 1:1 to 4 pretransplant induction and 2 posttransplant consolidation cycles with D-VTd or VTd. MRD evaluations using 8-color MFC on bone marrow (BM) aspirates were correlated with imaging data for the CASSIOPET PET/MRD endpoint. The primary objective was to compare PFS of patients who are double negative with those who are not, to be evaluated upon mature PFS data availability. This analysis evaluates prognostic value of PET/CT at diagnosis (PFS), postconsolidation double-negativity rates (MRD, PET), and concordance between MRD (MFC) and PET-CR negativity. Patients who were randomized but not treated were excluded ($n = 2$). PET/CT scans were performed at baseline (before first dose) and post consolidation (Day 100 post transplant). The 5-point Deauville scores were applied to BM, focal lesions (FL), extramedullary disease (EMD), and paramedullary disease (PMD). For each PET dataset, localization of most intense fluorodeoxyglucose uptake was identified and maximum standardized uptake value (SUVmax) was calculated. CR was defined as lesion uptake < mediastinum blood pool (MBP); unconfirmed CR (uCR) as lesion uptake between MBP and liver. Images were interpreted by independent, blinded nuclear medicine physicians.

Results: 268 patients (D-VTd, 137; VTd, 131) had assessable baseline PET; of these, 20.1% were PET negative and 79.9% were PET positive. Additionally, 67.2% had FLs (91.7% with uptake>liver), with median SUVmax of 6.115, and 22.0% had diffuse BM infiltration with median SUVmax of 3.195. PET/CT revealed PMD in 17.5% (SUVmax=7.110) and EMD in 7.8% (SUVmax=6.850). Of patients with postconsolidation PET measurements ($n = 184$), the proportions who achieved CR, uCR, partial response, and stable disease were 64.1%,

25.5%, 9.2%, and 1.1%, respectively. PFS rates were higher in PET-negative than PET-positive patients at 12 months (100% vs 92.5%) and 18 months (100% vs 87.5%). In an assessment of postconsolidation concordance of PET-CR and MRD, 102 patients were double negative. Postconsolidation double-negativity rates were 47.5% (VTd) and 66.7% (D-VTd) (odds ratio [OR] 2.21; 95% CI 1.20−4.07; P=0.0105).

Conclusions: In CASSIOPET, baseline PET/CT findings revealed prognostic value. Post consolidation, more D-VTd patients than VTd patients were double negative. With more mature data, PET-CR/MRD-negativity concordance may provide insight as a predictive surrogate for patient outcomes.

Clinical Trial Registry: NCT02541383.

Disclosure: STUDY SUPPORT: Janssen

Moreau: *AbbVie*, *Amgen*; *Celgene*, *Janssen, Takeda:* Consultancy, Honoraria. **Zweegman**: *Celgene*, *Janssen Pharmaceuticals*, *Takeda:* Membership on an Entity's Board of Directors or Advisory Committees, Research Funding. **Perrot:** Nothing to disclose. **Hulin**: Nothing to disclose. **Caillot**: Nothing to disclose. **Facon**: *Amgen, Karyopharm, Oncopeptides, Roche, Sanofi:* Membership on an Entity's Board of Directors or Advisory Committees; *Celgene*; *Janssen, Takeda:* Membership on an Entity's Board of Directors or Advisory Committees, Speakers Bureau. **Leleu**: Nothing to disclose. **Belhadj**: Nothing to disclose. **Karlin**: Nothing to disclose. **Benboubker:** Nothing to disclose. **Levin:** Nothing to disclose. **Minnema:** Nothing to disclose. **Jamet:** Nothing to disclose. **Bodet-Milin**: Nothing to disclose. **Sonneveld:** *Amgen, Celgene, Janssen, Karyopharm, Takeda:* Honoraria, Research Funding; *Bristol-Myers Squibb:* Honoraria; *SkylineDx:* Research Funding. **Lambert:** Nothing to disclose. **Pei:** Employee of Janssen. **Boer:** Employee of Janssen. **Vermeulen:** Employee of Janssen. **Kampfenkel:** Employee of Janssen. **Kraeber-Bodere:** Nothing to disclose.

O120.

Depth of Response to Daratumumab, Lenalidomide, Bortezomib, and Dexamethasone Improves Over Time in Patients with Transplant-Eligible Newly Diagnosed Multiple Myeloma: Griffin Study Update

Peter M. Voorhees[1], Jonathan L. Kaufman[2], Jacob Laubach[3], Douglas W. Sborov[4], Brandi Reeves[5], Cesar Rodriguez[6], Ajai Chari[7], Rebecca Silbermann[8], Luciano J. Costa[9], Larry D. Anderson, Jr.[10], Nitya Nathwani[11], Nina Shah[12], Yvonne A. Efebera[13], Caitlin Costello[14], Andrzej Jakubowiak[15], Tanya M. Wildes[16], Robert Z. Orlowski[17], Kenneth H. Shain[18], Andrew J. Cowan[19], Sean Murphy[20], Yana Lutska[20], Huiling Pei[21], Jon Ukropec[22], Jessica Vermeulen[23], Carla de Boer[23], Daniela Hoehn[20], Thomas S Lin[20], Paul G. Richardson[3]

[1]Levine Cancer Institute, Atrium Health, Charlotte, NC, United States, *[2]Emory University, Atlanta, GA, United States*, *[3]Dana-Farber Cancer Institute, Boston, MA, United States*, *[4]University of Utah, Salt Lake City, UT, United States*, *[5]University of North Carolina Chapel Hill, Chapel Hill, NC, United States*, *[6]Wake Forest University, Winston-Salem, NC, United States*, *[7]Mount Sinai School of Medicine, New York, NY, United States*, *[8]Oregon Health & Science University, Portland, OR, United States*, *[9]University of Alabama at Birmingham, Birmingham, AL, United States*, *[10]UT Southwestern Medical Center, Dallas, TX, United States*, *[11]City of Hope Comprehensive Cancer Center, Duarte, CA, United States*, *[12]University of California San Francisco, San Francisco, CA, United States*, *[13]Ohio State University Comprehensive Cancer Center, Columbus, OH, United States*, *[14]University of California San Diego, La Jolla, CA, United States*, *[15]University of Chicago Medical Center, Chicago, IL, United States*, *[16]Washington University School of Medicine, St. Louis, MO, United States*, *[17]University of Texas M.D. Anderson Cancer Center, Houston, TX, United States*, *[18]H. Lee Moffitt Cancer Center, Tampa, FL, United States*, *[19]University of Washington, Seattle, WA, United States*, *[20]Janssen Scientific Affairs, LLC, Horsham, PA, United States*, *[21]Janssen Research & Development, LLC, Titusville, NJ, United States*, *[22]Janssen Global Medical Affairs, Horsham, PA, United States*, *[23]Janssen Research & Development, LLC, Leiden, Netherlands*

Background: Daratumumab (DARA), a human monoclonal antibody targeting CD38, is approved as monotherapy and in combination with standard-of-care (SoC) regimens for multiple myeloma (MM). In randomized studies, DARA-based regimens significantly improved response rates and depth of response, including minimal residual disease (MRD) negativity and progression-free survival, in newly diagnosed MM (NDMM) and relapsed/refractory MM patients. Lenalidomide, bortezomib, and dexamethasone (RVd) followed by high-dose therapy (HDT), autologous stem cell transplant (ASCT), and consolidation is an SoC regimen for US NDMM patients. This phase 2, randomized study (GRIFFIN; NCT02874742) evaluated DARA plus RVd (D-RVd) versus RVd in ASCT-eligible NDMM.

Methods: Patients were randomized 1:1 to RVd ± DARA and stratified by International Staging System (ISS) stage and creatinine clearance. Patients received 4 induction cycles, HDT, ASCT, 2 consolidation cycles, and maintenance with R ± DARA for 24 months. During induction

and consolidation (Cycles 1-6), patients received R 25 mg PO (Days 1-14); V 1.3 mg/m^2 SC (Days 1, 4, 8, 11); and d 40 mg QW every 21 days. DARA 16 mg/kg IV was given on Days 1, 8, and 15 (Cycles 1-4) and Day 1 (Cycles 5-6). During maintenance (Cycles 7-32), patients received R 10 mg (15 mg in Cycles 10+ if tolerated) on Days 1-21 every 28 days±DARA 16 mg/kg IV Q8W (or Q4W per patient decision after Amendment 2). Primary endpoint was stringent complete response (sCR) rate per International Myeloma Working Group (IMWG) by the end of consolidation. MRD (10^{-5} per IMWG criteria) was assessed by next-generation sequencing (clonoSEQ; Adaptive Biotechnologies).

Results: 207 patients (D-RVd, n=104; RVd, n=103) were randomized; baseline characteristics were well balanced. Median age was 60 years; 30 (14%) patients had high cytogenetic risk defined by fluorescence in situ hybridization for del(17p), t(4;14), or t(14;16). D-RVd improved the sCR rate by the end of consolidation (42.4% vs 32.0%; odds ratio 1.57; 95% CI 0.87-2.82; 1-sided P=0.068) at the preset 1-sided alpha of 0.1. Responses deepened over time; sCR rates after a median follow-up of 22.1 months were 62.6% vs 45.4%, respectively. MRD negativity was obtained by 51.0% versus 20.4% of patients, including 47.1% and 18.4% of patients who achieved ≥CR, respectively. Median stem cell yield and median time to platelet and neutrophil engraftment were similar for D-RVd and RVd. Grade 3/4 treatment emergent AEs (≥10%) with D-RVd versus RVd included neutropenia (41% vs 22%), lymphopenia (23% vs 22%), thrombocytopenia (16% vs 9%), and leukopenia (16% vs 7%). There was no difference in grade 3/4 infection rates between arms. Infusion-related reactions, primarily grade 1-2, occurred in 42% of DARA-treated patients.

Conclusions: Addition of DARA to RVd significantly improved response rates and depth of response, including sCR and MRD negativity; continued use of DARA improved depth of response. The overall safety profile of D-RVd is consistent with previous reports of DARA plus SoC. Stem cell mobilization and ASCT are feasible with D-RVd, without a significant effect on hematopoietic reconstitution. The study is ongoing, with patients continuing maintenance therapy.

Clinical Trial Registry: NCT02874742.

Disclosure: STUDY SUPPORT: Janssen.

Voorhees: *Adaptive Biotechnologies, Amgen*, *BMS*, *Celgene, Janssen*, *GSK*, *Novartis, Oncopeptides, Takeda*, *TeneBio*. **Kaufman**: *Amgen*, *BMS, Celgene, Janssen, Sanofi/Genzyme, Takeda, Tecnopharma, Incyte, Karyopharm, TG Therapeutics*. **Laubach**: None. **Sborov**: *Amgen, Janssen, Celgene*. **Reeves:** *Incyte, Seattle Genetics, Takeda*, *Celgene*. **Rodriguez:** *Amgen, Takeda*. **Chari:** *Amgen, Celgene, Janssen, Novartis, BMS*, *Pharmacyclics*. **Silbermann**: *Janssen, Sanofi*. **Costa:** *Abbvie*, *Amgen, Celgene, GSK*, *Fujimoto, Janssen*, *Karyopharm*, *Sanofi*. **Anderson:** *Amgen, Janssen, Takeda, Celgene*. **Nathwani:** None. **Shah:** *Amgen, BMS, Celgene, Janssen, bluebird bio, Sutro Biopharma, Poseida*, *Indapta, Genentech, Seattle Genetics, Oncopeptides, Karoypharm, Surface Oncology, Precision biosciences, GSK, Nektar, Amgen, Sanofi*, *Kite, Nkarta, Teneobio*. **Efebera:** *Akcea*, *Janssen, Takeda*. **Costello:** *Celgene, Janssen, Takeda*. **Jakubowiak:** *Abbvie, Amgen, BMS, Celgene, GSK, Janssen, KaryoPharm, Millennium, Sanofi, SkyLineDX, Takeda, Juno, Adaptive*. **Wildes:** *Carevive Systems, Janssen, Seattle Genetics*. **Orlowski:** *Amgen*, *BioTheryX, Spectrum Pharma, Celgene, Janssen, Kita Pharma, Sanofi-Aventis, Ionis Pharmaceuticals, Legend Biotech, Molecular Partners, Servier*, *Takeda*. **Shain:** *AbbVie, Adaptive*, *Amgen, BMS, Celgene, Janssen, Sanofi*. **Cowan:** *Celgene*, *Janssen*, *Abbvie, Juno*, *Cellectar, Sanofi*. **Murphy, Lutska, Pei, Ukropec, de Boer, Hoehn, Lin**: *Janssen*.

O121.

How to Assess Risk of Progression in Multiple Myeloma Patients Achieving Complete Remission After Autologous Transplant: Sub Analysis from the GEM2012MENOS65 Phase III Clinical Trial

Ana Jimenez Ubieto[1], Bruno Paiva[2], Joaquín Martinez López[1], María Teresa Cedena[1], Noemi Puig[3], Albert Oriol[4], María Jesús Blanchard[5], Rafael Martinez[6], Rafael Rios[7], Jesus Martin[8], Anna Sureda[9], Miguel Teodoro Hernández[10], Javier de la Rubia[11], José Gonzalez Medina[1], Rafael Alonso Fernandez[1], Isabel Krsnik[12], Luis Palomera[13], José María Moraleda[14], Joan Bargay[15], Norma Gutierrez[3], Paula Otero[2], María Victoria Mateos[3], Laura Rosiñol[16], Jesus San Miguel[2], Joan Bladé[16], Juan José Lahuerta[1]

[1]Hospital 12 de Octubre, Madrid, Spain, *[2]Clínica Universidad de Navarra, Pamplona, Spain*, *[3]Hospital Universitario de Salamanca-IBSAL, Salamanca, Spain*, *[4]Hospital Germans i Trials, Barcelona, Spain*, *[5]Hospital Ramon y Caja, Madrid, Spain*, *[6]Hospital Universitario Clinico San Carlos, Madrid, Spain*, *[7]Hospital Universitario Virgen de las Nieves de Granada, Granada, Spain*, *[8]Hospital Universitario Virgen del Rocío, Sevilla, Spain*, *[9]Institut Catala d' 'Oncologia-l'Hospitalel, l'Hospitalel, Spain*, *[10]Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain*, *[11]Hospital Dr Peset, Valencia,, Valencia, Spain*, *[12]Hospital Puerta de Hierro Majadahonda, Madrid, Spain*, *[13]Hospital Clinico de Zaragoza, Zaragoza, Spain*,

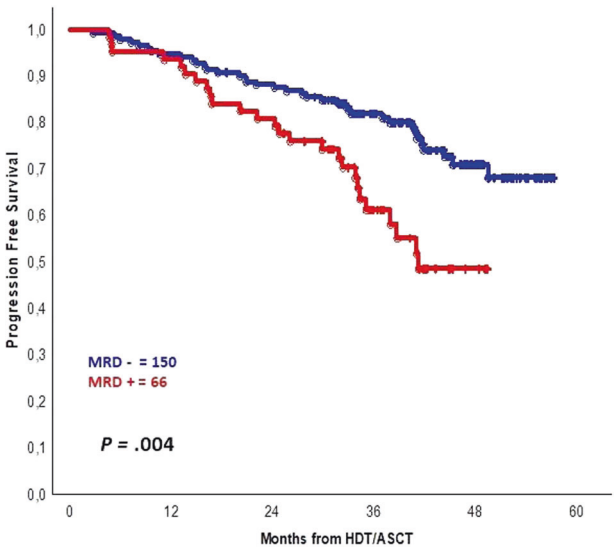
[14]*Hospita Virgen de la Arriaxaca, El Palmar, Spain*, [15]*Hospital Son Llatzer, Palma, Spain*, [16]*Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi I Sunyer, Barcelona, Spain*

Background: Recent studies with optimized induction followed by high-dose therapy (HDT) and ASCT are showing CR rates above 50%. Despite achieving the treatment endpoint, many CR patients relapse early-on and therefore, practical guidelines are needed to predict unsustained CR. These patients have been traditionally associated with dismal survival, but there are no confirmatory studies in the context of modern therapy. Thus, our aim was to define practical guidelines for prospective identification of patients at risk of unsustained CR after VRD induction, HDT/ASCT and VRD consolidation.

Methods: This analysis was performed in 238 patients enrolled in the phase 3 PETHEMA/GEM2012MENOS65 trial, who were in CR after HDT/ASCT and/or consolidation. Briefly, patients received six induction cycles of bortezomib, lenalidomide and dexamethasone (VRD), ASCT conditioned with Bu-Mel or Mel-200 HDT, and two consolidation cycles of VRD. Afterwards, patients were enrolled in the PETHEMA/GEM2014MAIN clinical trial that randomized maintenance with RD or RD plus ixazomib for two years, after which patients continued with RD for three additional years if minimal residual disease (MRD) positive, or stopped therapy if MRD negative. MRD was evaluated using next-generation flow cytometry (median limit of detection: 3×10^{-6}). Median follow-up of the series: 53 months. Unsustained CR was defined as disease progression < 12 months after HDT/ASCT.

Results: The median percentage of plasma cells (PCs) by morphology was 1% (range, 0-5) in the 238 patients in CR after HDT/ASCT. PC enumeration by morphology had no prognostic value. In fact, only 1/239 (0.4%) patients was not confirmed to be in CR due to >5% PCs, highlighting the limited value of cytological response assessment in transplant-eligible MM patients. Similarly, patients with an abnormal serum free light chain (sFLC) ratio (29% of those in CR) had identical progression-free survival (PFS) than cases with normal sFLC ratio (3 years-PFS rates of 78% vs 77%; P=.7). Thus, the stringent CR response criterion had limited value to identify patients in CR with different outcome. By contrast, persistent MRD positivity (31% of those in CR) resulted in significantly inferior PFS as compared to cases with undetectable MRD (3 years rates of 60% vs 83%; P=.001). Afterwards, we investigated which baseline and response assessments were useful to predict unsustained CR. Noteworthy, 14/238 (6%) patients had unsustained CR despite maintenance therapy and showed dismal survival (median PFS and OS of 6 and 9 months from ASCT). When compared to those with sustained CR, patients with unsustained CR were characterized by persistent MRD after consolidation (21% vs 78% ; P< .00001) and later CR achievement (ie. after HDT/ASCT: 50% vs 80%; P=.008).

Conclusions: This is the first study evaluating which baseline and response assessments are useful to risk-stratify patients in CR after HDT/ASCT in the context of modern therapy. Our results unveil that morphologic and sFLC measurements are useless in patients with negative immunofixation, and that only MRD assessment together with response kinetics are useful to prospectively identify patients at risk of unsustained CR. We also confirmed that this remains a high-risk population despite modern induction, consolidation and maintenance therapy.



[Progression Free survival from HDT/ASC according to the MRD status post-HDT/ASCT]

Clinical Trial Registry: NCT01916252.

Bortezomib (Velcade®), Lenalidomide (Revlimid®) and IV Busulfan (Busilvex®) in Patients Under 65 Years Old (GEM2012MENOS65).

Disclosure: Conflict-of-interest disclosure: J.-J.L. received honoraria for lectures from and participated in advisory boards for Janssen-Cilag, Celgene, Takeda, and Amgen. B.P. received honoraria from, served in a consulting or advisory role for, and received travel, accommodation, and expenses from Janssen and Celgene, and received research funding for his institution from Celgene. J.M.-L. served in a consulting or advisory role for, served on a Speakers' Bureau for, and received research funding for his institution from Novartis, Janssen-Cilag, Celgene, and Bristol-Myers Squibb. N.P. received honoraria from Janssen-Cilag, Takeda, and Amgen, and served in a consulting or advisory role and received travel,

accommodations, and expenses from Janssen-Cilag. A.O. served in a consulting or advisory role for Amgen and Janssen-Cilag. L.P. received honoraria from and served in a consulting or advisory role for Janssen-Cilag and Celgene. M.-V.M. received honoraria from and served on a Speakers' Bureau for Janssen-Cilag and Celgene. L.R. received honoraria from Janssen-Cilag and Celgene. J.F.S.M. served as a consultant for Bristol-Myers Squibb, Janssen-Cilag, Celgene, Merck, Takeda, Novartis, Amgen, Sanofi, and Roche. J. Blade received honoraria for lectures and advisory boards from Janssen-Cilag, Celgene, Amgen, and Takeda. The remaining authors declare no competing financial interests.

O122.

Outcomes of Anti-BCMA CAR T Cell Therapy for Relapsed/refractory Multiple Myeloma: A Meta-Analysis

Nico Gagelmann[1], Francis Ayuk[1], Djordje Atanackovic[2], Nicolaus Kröger[1]

[1]University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [2]University of Utah, Salt Lake City, UT, United States

Background: Cellular immunotherapies represent a promising strategy for relapsed/refractory multiple myeloma (RRMM). We aimed to summarize the current body of evidence on the role of anti-BCMA CAR T cell therapy for RRMM.

Methods: We performed a systematic literature review using publically available databases as well as archived meeting abstracts. To minimize product heterogeneity, studies on CARs using multiple targets were excluded. Pooled event rates and 95% confidence intervals were calculated using the inverse variance method within a random-effects framework. Efficacy outcomes were overall response rate (ORR), complete response (CR), and minimal residual disease (MRD). Relapse, progression-free survival (PFS), and overall survival (OS) were only pooled from fully published studies. Safety outcomes were cytokine release syndrome (CRS), neurotoxicity, and cytopenia.

Results: Twenty studies (10 from USA/Europe, 10 from China) comprising a total of 447 patients with heavily pretreated RRMM were included. Median line of prior therapy differed according to country (8 in USA/Europe vs. 5 in China). Prior autologous stem cell transplantation was received by 90% of patients. Extramedullary disease (EMD) was present in 35% of patients at time of CAR T infusion. The median age of patients was 60 years and median follow-up duration ranged from 1.1 to 12.6 months. Most studies used 4-1BB as an activation-induced T-cell costimulatory molecule. Most studies used fludarabine and cyclophosphamide for lymphodepletion while 1 study used busulfan and cyclophosphamide and 1 study used cyclophosphamide only. Most studies used the former Lee criteria for CRS grading.

Anti-BCMA CAR T cell therapy resulted in a pooled ORR of 84% (78-89%). Pooled CR in evaluable patients was 36% (24-50%) and median duration of response was 11 months. Higher dose levels of infused CAR^+ cells were associated with higher ORR resulting in a pooled proportion of 92% (82-98%). Pooled CR was 43% (32-53%) and pooled MRD negativity was 83% (67-92%), while measurement and cutoffs of MRD significantly differed in studies.

The presence of high-risk cytogenetics appeared to be associated with lower ORR resulting in a pooled proportion of 68% (50-81%). Presence of EMD at time of infusion was associated with similar response rates compared with RRMM patients without EMD, resulting in a pooled proportion of 78% (47-93%).

Pooled relapse rate of all responders was 45% (27-64%). MRD negativity did not seem to affect outcome. Median PFS was 10 months and pooled OS rate was 84% (60-95%) at last follow-up (median, 11 months).

In terms of safety, pooled CRS of any grade was 73% (57-84%). Notably, pooled CRS grades 3-4 and neurotoxicity were 15% (9-23%) and 17% (10-27%). Peak CAR T cell expansion appeared to be more likely in the setting of more severe CRS in 3 studies. Most hematologic toxic effects grade >2 were neutropenia (75%), leukopenia (70%), and thrombocytopenia (60%).

Conclusions: Anti-BCMA CAR T cell therapy showed high response rates and manageable toxicity across early-phase studies. However, almost half of the patients achieving a response eventually relapsed. Notably, present extramedullary disease at time of CAR T infusion was not associated with worse outcome. Larger studies with longer follow-up are needed.

Disclosure: Nothing to declare.

O123.

25 Years of Autologous Transplantation for Myeloma in Ebmt Centres - Changing Practice Patterns

Patrick J. Hayden[1], Dirk-Jan Eikema[2], Linda Koster[3], Hartmut Goldschmidt[4], Didier Blaise[5], Michael Potter[6], Cyrille Touzeau[7], Anne Huynh[8], Jenny Byrne[9], Cyrille Hulin[10], Neil K. Rabin[11], Reuben Benjamin[12], Jan J. Cornelissen[13], Hareth Nahi[14], Gordon Cook[15], John G. Gribben[16], Ellen Meijer[17], Péter Reményi[18], Jiri Mayer[19],

Panagiotis Tsirigotis[20], Paolo Bernardeschi[21], Meral Beksac[22], Stefan O. Schönland[23], Ibrahim Yakoub-Agha[24]

[1]Trinity College Dublin, St. James's Hospital, Dublin, Ireland, [2]LUMC, Leiden, Netherlands, [3]EBMT Data Office Leiden, Leiden, Netherlands, [4]Heidelberg University Hospital, Heidelberg, Germany, [5]Institut Paoli Calmettes, Marseilles, France, [6]The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom, [7]Centre Hospitalier Universitaire de Nantes, Nantes, France, [8]Institut Universitaire du Cancer Toulouse, Toulouse, France, [9]Nottingham University Hospitals NHS Trust,, Nottingham, United Kingdom, [10]Hôpital Haut-Lévêque, Pessac, France, [11]University College London Hospitals NHS Foundation Trust, London, United Kingdom, [12]King's College Hospital NHS Foundation Trust, London, United Kingdom, [13]Erasmus MC Cancer Institute,, Rotterdam, Netherlands, [14]Karolinska Institutet, Karolinska Universitetssjukhuset, Stockholm, Sweden, [15]Leeds Teaching Hospital NHS Trust, Leeds, United Kingdom, [16]Barts Cancer Institute, Queen Mary University of London, London, United Kingdom, [17]Amsterdam UMC, Location VU, Amsterdam, Netherlands, [18]St. István and St. Laszlo Hospital, Budapest, Hungary, [19]University Hospital Brno, Brno, Czech Republic, [20]National and Kapodistrian University of Athens, Attiko Hospital, Athens, Greece, [21]San Giuseppe Hospital, Florence, Italy, [22]Ankara University, Ankara, Turkey, [23]University of Heidelberg, Heidelberg, Germany, [24]CHU de Lille, LIRIC, INSERM U995, Université de Lille, Lille, France

Background: Though autologous haematopoietic cell transplantation (auto-HCT) has been widely used in the treatment of transplant-eligible patients with myeloma over the last 25 years, practice has evolved significantly. We therefore performed a retrospective analysis of patients who underwent first auto-HCT for MM in EBMT centres between 1997 and 2018 in consecutive five-year cohorts: (1) 1993-1997, (2) 1998-2002, (3) 2003-2007, (4) 2008-2012 and (5) 2013-2017.

Methods: All data was extracted from MED-A and MED-B forms submitted by centres to the EBMT registry.

Results: The study was based on a total of 103,032 patients in 568 centres in 54 countries. Analysis revealed a seven-fold increase in transplant activity over this time period: (1) 5,246, (2) 12,554, (3) 21,153, (4) 28,390 and (5) 35,689. The median age at transplant increased from (1) 54 to (5) 61 years and the percentage of patients >65 years at transplant increased from (1) 3% to (5) 22%. Between 1993 and 1997, IgG, IgA and Light Chain (LC) MM constituted 58%, 22% and 16%, respectively. The corresponding percentages between 2013 and 2017 were 52%, 18% and 27%, respectively. MED-B data (2008-2012, 2013-2017) revealed evolving recent practice patterns in the choice of induction regimens: VTD: 11% to 32%; VCD: 5% to 20%; CTD 15% to 10%; VD: 19% to 7%; PAD 5% to 4%; VRD 2% to 3%; VAD: 8% to 3%. CR rates pre-transplant have increased from (1) 16% to (5) 21% and >PR rates pre- auto-HCT from (1) 65% to (5) 73%. Analysis of clinical practice in stem cell collection revealed increasing use of cylophosphamide-based mobilisation from (1) 31% to (5) 65%; the use of single agent G-CSF declined from (1) 69% to (5) 28%. G-CSF + Plerixafor was used in 3.5% of cases from 2008-2012 and 5% in 2013-2017.

The median number of stem cells collected (CD34+cells × 10^6/kg) has gradually increased from (1) 5.1 to (5) 6.5, though the median cell dose infused is essentially unchanged: (1) 3.6, (2) 4.1, (3) 4.0, (4) 3.8, and (5) 3.8. Almost all (99%) patients received peripheral blood (PB) stem cells. The number of months from diagnosis to auto-HCT has been stable since 1998: (1) 8.9, (2) 7.7, (3) 7.4, (4) 7.4, and (5) 7.3. Finally, three-year overall survival (OS) post-transplant has risen from 65% to 81% and three-year Progression-Free Survival (PFS) from 41% to 46%.

Conclusions: Myeloma is the commonest indication for Auto-HCT worldwide and our data revealed a seven-fold increase in the numbers of transplants over time with almost a quarter of patients in the most recent cohort being older than 65 years of age. The majority of patients (59%) treated between 2013 and 2017 received bortezomib-based triplet induction regimens: VTD: 32%; VCD: 20%; PAD 4%; VRD 3%. Data from a subset of centres reveal that cyclophosphamide-based stem cell mobilisation is currently performed in two-thirds of centres; only 5% receive G-CSF + Plerixafor. Finally, the OS and PFS rates have improved, likely reflecting the deeper responses achieved pre-transplant and the increasing availability of novel agents.

Disclosure: Hayden: Alnylam: Honoraria; Amgen: Honoraria. Goldschmidt: MSD: Research Funding; Janssen: Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; John-Hopkins University: Research Funding; Sanofi: Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; Molecular Partners: Research Funding; Bristol-Myers Squibb: Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; Chugai: Honoraria, Research Funding; Novartis: Membership on an entity's Board of Directors or advisory committees, Research Funding; Adaptive Biotechnology: Membership on an entity's Board of Directors or advisory committees; Janssen: Consultancy, Research Funding; Dietmar-Hopp-Stiftung: Research Funding; John-Hopkins University: Research Funding; Amgen: Consultancy, Research Funding; Celgene: Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding;

Takeda: Membership on an entity's Board of Directors or advisory committees, Research Funding; Mundipharma: Research Funding. Blaise: Pierre Fabre medicaments: Honoraria; Molmed: Consultancy, Honoraria; Sanofi: Honoraria; Jazz Pharmaceuticals: Honoraria. Byrne: Ariad/Incyte: Honoraria, Speakers Bureau. Hulin: Celgene: Consultancy, Honoraria; Janssen, AbbVie, Celgene, Amgen: Honoraria. Benjamin: Gilead: Honoraria; Takeda: Honoraria; Novartis: Honoraria; Amgen: Honoraria; Eusapharm: Consultancy; Servier: Research Funding; Allogene: Research Funding; Pfizer: Research Funding. Cook: Celgene: Consultancy, Honoraria, Research Funding, Speakers Bureau; Karyopharm: Consultancy, Honoraria, Speakers Bureau; Sanofi: Consultancy, Honoraria, Speakers Bureau; Takeda: Consultancy, Honoraria, Research Funding, Speakers Bureau; Janssen: Consultancy, Honoraria, Research Funding, Speakers Bureau. Gribben: Acerta/Astra Zeneca: Consultancy, Honoraria, Research Funding; Celgene: Consultancy, Honoraria, Research Funding; Abbvie: Consultancy, Honoraria, Research Funding; Janssen: Consultancy, Honoraria, Research Funding. Mayer: AOP Orphan Pharmaceuticals AG: Research Funding. Beksac: Celgene: Consultancy; Amgen: Consultancy; Janssen&-Janssen: Consultancy; Takeda: Consultancy. Schönland: Janssen: Membership on an entity's Board of Directors or advisory committees, Research Funding; Prothena: Membership on an entity's Board of Directors or advisory committees, Research Funding; Takeda: Membership on an entity's Board of Directors or advisory committees, Research Funding; Medac: Other: Travel Grant.

Myelodysplastic syndromes

O124.

Allogeneic Hematopoietic Cell Transplantation of Adult Patients with Chronic Myelomonocytic Leukemia. A Nordic Retrospective Study

Lone Smidstrup Friis[1], Eileen Wedge[2], Ingunn Dybedal[3], Maria Creignou[4], Elisabeth Ejerblad[5], Fryderyk Lorenz[6], Olle Werlenius[7], Mette Skov Holm[8], Lars Nilsson[9], Astrid Olsnes Kittang[10], Petar Antunovic[11], Peter Rohon[12,13], Jakob Werner Hansen[1], Mette Klarskov Andersen[1], Martin Jädersten[4], Eva Hellström-Lindberg[4], Kirsten Grønbæk[2], Per Ljungman[4]

[1]Copenhagen University Hospital, Copenhagen, Denmark, [2]University of Copenhagen, Copenhagen, Denmark, [3]Oslo University Hospital, Oslo, Norway, [4]Karolinska Institutet, Stockholm, Sweden, [5]Uppsala University Hospital, Uppsala, Sweden, [6]University Hospital of Umeå, Umeå, Sweden, [7]Sahlgrenska University Hospital, Gothenburg, Sweden, [8]Aarhus University Hospital, Aarhus, Denmark, [9]Skåne University Hospital, Lund, Sweden, [10]Haukeland University Hospital, Bergen, Norway, [11]Linköping University Hospital, Linköping, Sweden, [12]University Hospital Olomouc, Olomouc, Czech Republic, [13]University Hospital Bratislava, Slovak Republic, Bratislava, Czech Republic

Background: The outcomes after allogeneic hematopoietic cell transplantation (allo-HCT) of chronic myelomonocytic leukemia (CMML) have been disappointing, with long term overall survival (OS) around 30%. The disease is very heterogenous and unpredictable with a lack of prognostic scoring systems validated for patients undergoing allo-HCT. In this study we describe the outcome of allo-HCT in a Nordic CMML sample in relation to different prognostic factors.

Methods: 60 patients with CMML undergoing allo-HCT in the period 2008-2015 from Denmark, Sweden and Norway were included. MED A data were extracted from the EBMT registry and supplementary clinical data were collected from participating centers. Next generation sequencing (NGS) was carried out on stored bone marrow from the time of transplantation for 45 patients.

Patient- and transplantation characteristics: Median age: 62 years (31-71), Karnofsky: 90 (70-100), Male/female: 44/16. Disease status at allo-HCT: CR: 15 (25%), Improvement: 27 (45%), Progression: 9 (15%), No treatment: 9 (15%). Conditioning: NMA/RIC: 24 (40%), RTC/MAC: 36 (60%). Stem cell source: BM: 7 (12%), PBSC: 53 (88 %). HLA-Matched MRD: 20 (35%), MUD: 35 (58%) and MMUD: 5 (8 %). CMV-matched: 42 (70 %).

Results: 56 patients (97 %) engrafted. OS after 1, 3 and 5 years was: 62% (CI: 48.7-73.4); 54% (CI: 40.2-65.5) and 47% (CI: 33.7-59.8), respectively, with a median follow up of 5.4 years. Cumulative incidence of relapse and transplant related mortality (TRM) after 3 years: 24% (0.14-0.36) and 26% (0.15-0.37), respectively. 17 patients (30%) developed acute GvHD (grade 2-4) and 32 patients (57%) chronic GvHD. 42 of 45 patients (93%) had at least 1 mutation detected by NGS. 32 patients (71%) had ≥ 3 mutations. The most frequent mutations were: TET2 (38%), RUNX1 (33%), ASXL1 (31%), NRAS (18%), SRSF2 (11%) and ZRSR2 (11%). In univariate analyses NRAS mutations had a significant negative impact on 3-years OS ($p = 0{,}001$), whereas mutation in SRSF2 or ZRSR2 had a positive impact ($p = 0{,}011$). Development of chronic GvHD was associated with a significantly better 3-years OS ($p = 0.011$). CMV-status, donor-match, stem cell source, type of conditioning or treatment prior to allo-HCT did not have significant impact on OS in univariate analyses. This was

also found for CPSS, CPSS-mol and disease status at allo-HCT.

Conclusions: The study supports previous reports that NRAS mutations have a negative impact on OS. The finding that SRSF2/ZRSR2 mutations may have a favorable prognostic impact needs to be confirmed in larger studies. It is confirmed that development of chronic GvHD is the price CMML patients often pay for being long-term survivors after allo-HCT.

There is still much room for improvement in results after allo-HCT for CMML and a need for validation of prognostic scoring tools in order to better select patients who will benefit from transplantation.

Disclosure: Nothing to declare.

O125.

Decitabine Monotherapy Before Allogeneic Stem Cell Transplantation Resulted in Superior Survival for Myelodysplastic Syndrome Patients with Excess Blasts

Yan Yu[1,2,3], Bingyu Yang[1,2,3], Zhao Zeng[1,2,3], Lijun Wen[1,2,3], Suning Chen[1,2,3], Aining Sun[1,2,3]

[1]Soochow University, Suzhou, China, [2]The First Affiliated Hospital of Soochow University, Suzhou, China, [3]Institute of Blood and Marrow Transplantation, Suzhou, China

Background: Hypomethylating agents are considered the standard of care for higher-risk myelodysplastic syndrome (MDS) patients and are commonly used for bridge treatment before allogeneic stem cell transplantation (allo-SCT) or rescue treatment in relapsed MDS after transplantation. However, there is no consensus on whether decitabine monotherapy before allo-SCT is necessary and affects overall survival and relapse after transplantation.

Methods: Therefore, we retrospectively analyzed a cohort of 287 adult MDS patients who underwent allo-SCT from a single center.

Results: Interestingly, the overall survival (OS) after allo-SCT of patients treated with decitabine (DAC) monotherapy was better than that of patients treated with intensive chemotherapy (ICT) combined with DAC (3-year OS rates: 73 m vs 63 m, P=0.041). Especially in MDS patients with excess blasts, the OS after allo-SCT of DAC monotherapy (3-year OS rate: 86 m) still exceeded that of other cohorts: supportive care with bridging DAC treatment (3-year OS rate: 55 m, P=0.010), supportive care without bridging DAC treatment (3-year OS rate: 68 m, P=0.098), and ICT combined with DAC (3-year OS rate: 59 m, P=0.014). However, the combination of ICT and DAC was significantly superior to DAC monotherapy for MDS patients with DNMT3A or TP53 variants. In addition, the DNMT3A gene variants SNP rs1042522 and SNP rs76208147 were independent prognostic factors for OS after transplantation.

Conclusions: In summary, DAC monotherapy is considered to be the most appropriate initial therapy before allo-SCT for myelodysplastic syndrome patients with excess blasts, except for MDS patients with DNMT3A or TP53 variants.

Disclosure: Nothing to declare.

Non-infectious early complications

O126.

Impact of Donor-Directed HLA Allo-Antibodies on Primary Graft Failure After Unrelated Donor Allogeneic Haematopoietic Cell Transplantation

Maria M. Cuadrado[1,2], Chloe Anthias[1,3], Raymond Fernando[1], Richard M. Szydlo[1,4], Steven G. E. Marsh[1,2], Neema P. Mayor[1,2], Ronjon Chakraverty[2,5], J. Alejandro Madrigal[1,2], Katy Latham[1]

[1]Anthony Nolan Research Institute, Royal Free Hospital, London, United Kingdom, [2]UCL Cancer Institute, Royal Free Campus, London, United Kingdom, [3]Royal Marsden NHS Foundation Trust, Sutton, London, United Kingdom, [4]Imperial College, London, United Kingdom, [5]University College London Hospitals, London, United Kingdom

Background: Primary Graft Failure (GF) is an infrequent but serious complication following allogeneic haematopoietic cell transplantation (HCT). Donor-directed HLA allo-antibodies (DSAs) are known to increase the risk of graft rejection, especially in the haploidentical HCT setting. However, few studies have been performed in unrelated donor HCT and there is currently no consensus of how to interpret the strength of DSAs, measured by mean fluorescent intensity (MFI) in solid phase assays and its impact on donor selection strategy or recipient intervention.

Methods: We report a case-control study of patients from a transplant registry in the UK who received an unrelated donor HCT between 1996-2011. Cases were recipients with primary GF (defined as failure to achieve neutrophils >0.5 × 10^9/L 30 days post HCT) and controls were those surviving recipients who engrafted 30 days post HCT. Pre-transplant plasma of these recipients were analysed to determine the presence and specificity of anti-HLA antibodies using the Luminex-based single antigen bead assays (One Lambda). Samples were considered positive for DSA based on a background adjusted for MFI > 500.

Results: We analysed 538 patients, 35 (6.5%) cases and 503 (93.5%) controls. Median age was 42 years (2-70), 444

(83%) were T-depleted, 259 (48%) received a myeloablative conditioning and the graft source was bone marrow (BM) in 235 (44%). Diagnoses included acute leukaemia ($n = 240$), MDS ($n = 97$), non-Hodgkin's lymphoma ($n = 63$), Hodgkin's lymphoma ($n = 30$), CML ($n = 63$), CLL ($n = 23$), multiple myeloma ($n = 20$) and other ($n = 2$). HLA matching was 12/12 in 66 (12%), 11/12 in 253 (48%), 10/12 in 133 (25%) and 9/12 or lower in 77 (15%). Among the cases, one (3%) presented two DSAs both against DPB1 compared to 12 recipients (2%) with DSAs in the control group.

The MFI of the DSAs of the patient with GF was 20,381 and 20,086 respectively (against HLA-DPB1) while the MFI of the DSAs of recipients who had engrafted was below 8000 (against HLA-DPB1, -A and -C).

In a multivariate analysis, parameters significantly associated with primary GF were stem cells from BM (OR: 7.5, 95% CI = 2.5-23) and myeloablative conditioning (OR: 7.7, 95% CI= 2.3-26). Other factors including T-depleted, CMV matching, ABO group, EBMT risk score, and disease type did not predict for GF. As BM harvest and myeloablative conditioning had an important impact on GF, we reanalysed the cohort to those that had received BM HCT with myeloablative conditioning. A total of 139 patients were identified, 24 (17%) of which were cases and 115 (83%) controls. The variable related to GF identified in this subgroup was HLA mismatching (OR:2.4, 95% CI=0.97-6.1).

Conclusions: Our study shows that most primary GF cases after unrelated donor HCT are not caused by DSAs. BM harvest, myeloablative conditioning and HLA mismatching were associated with GF. The presence of DSAs with high MFI, determined in this study to be over 20,000 MFI, might be a risk for GF. Intermediate or low MFIs (MFI < 8000) did not seem to have an impact on GF although more studies need to be performed to support our findings and to improve donor selection strategies.

Disclosure: Nothing to declare.

O127.

Eltrombopag Treatment Aided in Platelet Recovery and Reduced Platelet Infusion for Patients with Post-Transplantation Thrombocytopenia

Fei Gao, Yanmin Zhao, Jimin Shi, Yi Luo, Yanmin Tan, Jian Yu, Xiaoyu Lai, He Huang

The First Affiliated Hospital, Zhejiang University, Hangzhou, China

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) markedly improves the outcomes of patients with hematologic disorders. However, the development of post-transplantation thrombocytopenia is a common and severe complication, which not only diminishes the quality of life but also leads to fatal bleeding events. Eltrombopag (EPAG), a novel oral thrombopoietin receptor agonist (TPO-RA), has shown promising effects in thrombocytopenia due to immune thrombocytopenic purpura (ITP) and refractory severe aplastic anemia (rSAA). However, the effectiveness of EPAG for patients with post-transplantation thrombocytopenia still needs to be evaluated.

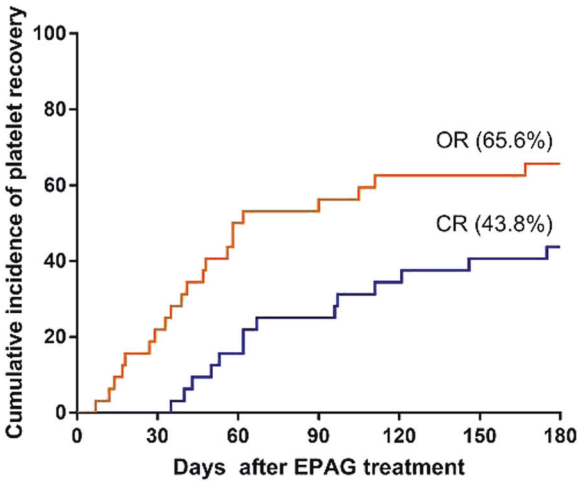
Methods: From September 2017 to July 2019, 32 patients with post-transplantation thrombocytopenia were enrolled in our study, including 15 patients with poor graft function (PGF) and 17 patients with secondary failure of platelet recovery (SFPR). All of them fulfilled the following conditions: (1) age ≥14 years; (2) absence of relapse or grade III-IV acute GVHD at the time of enrollment. The initial dose of EPAG was 25 mg daily for patients weighing < 50 kg and 50 mg daily for patients weighing ≥50 kg. If no obvious drug toxicity was observed during the first week, the dose was increased by 25 mg every one or two weeks, up to the maximum dose of 100 mg per day.

Results: In this cohort, the median treatment duration was 74 (range, 14-398) days. To date, 21 (65.6%) patients achieved overall recovery (OR) with platelets exceeded 50×10^9/L. 14 (43.8%) patients with platelet counts ≥100 × 109/L were defined as complete recovery (CR), and the other 7 patients were defined as partial recovery (PR). Among responding patients, 18 (85.7%) of them discontinued or tapered this drug and 16 (76.2%) of them successfully maintained their best response. During hospitalization, responding patients received much lower median platelet infusion units per month than those patients with no response (NR) (11 vs 47, P< 0.001). After a median follow up time of 313 (range, 24-791) days, the cumulative incidence of overall survival was 81.3% (100% for responded patients and 45.5% for non-responders, P< 0.001).

In univariate analysis, patient characters such as age, gender, sex mismatch and ABO blood mismatch were not associated with platelet recovery. Compared with PGF subgroup, patients in SFPR subgroup experienced a higher rate of OR (82.4 vs 46.7%, P=0.034). In addition, disease type was also associated with OR ($P = 0.073$). Patients with decreased megakaryocytes (Megk) before EPAG treatment had a lower CR rate (30.4 vs 77.8%, P=0.022). It was also observed that the CR rate was lower in patients with splenomegaly (18.2 vs 57.1%, P=0.061). In multivariate logistic analysis, PGF was identified as the only independent risk factor for OR ($P = 0.041$, HR=5.333). MegK amounts ($P = 0.025$, HR=14.638)

and splenomegaly ($P = 0.042$, HR=11.278) were identified as independent risk factors for CR.

Conclusions: In conclusion, EPAG treatment showed a good possibility of platelet recovery among patients with post-transplantation thrombocytopenia, with declined requirement for platelet infusion.



OR rate(%)	21.9	50.0	56.3	62.5	62.5	65.6
CR rate(%)	0.0	15.6	25.0	34.4	40.6	43.8

[Cumulative incidence of platelet recovery]

Disclosure: Nothing to declare.

O128.

Impact of Fluid Overload (FO) in Post-Transplant Cyclophosphamide-Based GVHD Prophylaxis After Allogeneic Hematopoietic Cell Transplantation for Hematological Diseases

Diana Tran, Dongyun Yang, Janny M. Yao, Salman Otoukesh, Haris Ali, Shukaib Arslan, Amandeep Salhotra, Ibrahim Aldoss, Karamjeet Sandhu, Vinod Pullarkat, Anthony Stein, David Snyder, Guido Marcucci, Auayporn Nademanee, Stephen J. Forman, Ryotaro Nakamura, Monzr M. Al Malki

City of Hope, Duarte, CA, United States

Background: Post-transplant cyclophosphamide (PTCy) is an effective graft-versus-host disease (GvHD) prophylaxis in patients undergoing allogeneic hematopoietic cell transplant (HCT). The use of aggressive hydration has been shown to reduce the incidence of hemorrhagic cystitis, a common side effect of PTCy, but may lead to fluid overload (FO). FO has been linked with higher non-relapse mortality (NRM) in HCT patients. We hypothesize that aggressive hydration associated with PTCy will contribute to fluid overload; leading to higher NRM, and worse survival outcomes.

Methods: We retrospectively identified 277 consecutive patients who received HCT with PTCy at City of Hope from 07/2009 to 12/2018. Baseline cardiac (EF>50%) and renal (CrCl >60 mml/min) functions were confirmed within 30 days of conditioning. FO was graded based on weight gain, need for diuretic therapy, and FO-related organ failure requiring ventilation or hemodialysis initiation (between day 3 to day 8). The associations of FO with NRM and relapse, disease free survival (DFS), and overall survival (OS) were examined using cumulative incidence curves and Gray's test, and Kaplan-Meier curves and log-rank test in the univariate analyses, respectively. Fine and Gray, and Cox regression models were used in the multivariable analyses that adjusted patient baseline demographic, disease, and transplant characteristics.

Results: Patient's median age was 47 (range: 2-75) and they received HCT either from a haploidentical (76.5%), matched (2.9%), or mismatched donors (20.6%). Diagnoses included: acute leukemia (60%), MPN/MDS (18.4%), lymphoma (11.9%) and non-malignant diseases (9%). DRI was intermediate in 37.9% of patients and high/very high in 34%. HCT comorbidity index was more than 2 in 40% of this cohort. Myeloablative regimen was used in 44% of patients who most received total body irradiation (82%). Reduced intensity/non-myeloablative conditioning regimen included Fludarabine/Melphalan (58.7%) and Fludarabine/Cyclophosphamide (41.3%). Most of patients (79.8%) received peripheral stem cells as graft source.

All 277 patients experienced some degree of FO between day 3-8 (grade 1 = 62.5%, grade 2 = 29.2%, and grade 3 or 4 = 8.3%). With median follow up of 23.9 months (range: 4.1-64.4), patients with FO grade 3 or 4 had significantly higher NRM at 1 year compared to patients with FO grade 1 and 2 (61.4 vs. 11.8 and 22.6%; respectively $p < 0.001$) with no significant difference in relapse rate (grade 1 = 20.6%, grade 2 =13.4%, grade 3 or 4 = 9.2%; $p = 0.15$). At 2 years, DFS and OS were also significantly worse in FO grade 3 or 4 patients (19.6%; 24.8%, respectively) compared to FO grade 1 and 2 (grade 1 = 56.3%; 61.2%; grade 2 = 58.5%; 63.8%, respectively) ($p < 0.001$). In multivariable analysis, weight gain percentage was associated with an increase in NRM (p value < 0.001).

Conclusions: FO is common during HCT using PTCy. Our data demonstrated that high grade FO is associated with poor outcome, and may serve as an early clinical indicator for developing multi-organ dysfunctions. While FO may be a result rather than a cause of MOF, it is a potentially modifiable factor by careful monitoring and early control of fluid balance.

Disclosure: nothing to disclose.

O129.

Incidence, Risk Factors, and Outcomes of Patients with Transplant-Associated Thrombotic Microangiopathy After Stem Cell Transplant: A Multi-Institutional Analysis

Christopher Dandoy[1], Seth Rotz[2], Priscila Badia[3], Anna Klunk[4], Christine Higham[5], Christopher Dvorak[5], Christin Duncan[6,7], Michelle Schoettler[6,7], Leslie Lehmann[6,7], Maria Cancio[8], James Killinger[8], Blachy Davila[9], Zoe Ann Kasprzyk[9], Rachel Phelan[10], Kris Mahadeo[11], Sajad Khazal[11], Nahal Lalefar[12], Madhav Vissa[12], Deepika Bhatla[13], Nicholas Gloude[14], Eric Anderson[14], Jefferey Huo[15], Philip Roehrs[15], Jeffrey Auletta[16], Stella Davies[1], Ranjit Chima[1], Sonata Jodele[1]

[1]*Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States*, [2]*Cleveland Clinic, Cleveland, OH, United States*, [3]*Phoenix Children's Hospital, Phoenix, AZ, United States*, [4]*Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States*, [5]*UCSF Benioff Children's Hospital, San Fransisco, CA, United States*, [6]*Boston Children's Hospital, Boston, MA, United States*, [7]*Dana-Farber Cancer Institute, Boston, MA, United States*, [8]*MSKCC, New York, NY, United States*, [9]*National Children's Hospital, Washington D.C, DC, United States*, [10]*Medical College of Wisconsin, Milwaukee, WI, United States*, [11]*MD Anderson Cancer Center, Houston, TX, United States*, [12]*UCSF Benioff Children's Hospital, Oakland, CA, United States*, [13]*Saint Louis University, Saint Louis, MO, United States*, [14]*Rady Children's Hospital-San Diego, San Diego, CA, United States*, [15]*Atrium Health, Charlotte, NC, United States*, [16]*Nationwide Childrens Hospital, Columbus, OH, United States*

Background: Transplant-associated thrombotic microangiopathy (TA-TMA) is a severe complication of hematopoietic stem cell transplant (HSCT). The aim of this study was to determine the incidence, risk factors and outcomes for patients who develop TA-TMA following HSCT through a multicenter analysis.

Methods: All patients were prospectively screened for TA-TMA at participating centers with daily

CBC, renal panel, and blood pressure; twice weekly LDH; and weekly urine analysis, urine protein to creatinine from the start of the preparative regimen through the first 30 days. All labs were transitioned to weekly from day +30 to +100. TA-TMA was diagnosed if 1) pathologic evidence of TA-TMA (e.g., renal biopsy with evidence of TA-TMA), *or* if meeting laboratory/clinical markers diagnostic for TA-TMA (4 of 7 concurrent markers are required) including elevated LDH, schistocytes on peripheral blood smear, *de novo* thrombocytopenia or anemia, hypertension >99% for age, proteinuria, and/or terminal complement activation (elevated plasma sC5b-9). Each site retrospectively reviewed the data from screened patients from their respective center, and these data were aggregated to determine outcomes.

Results: 614 patients (359 males, 58%) received TA-TMA screening at 13 pediatric centers from January 1, 2017 through March 30, 2019. Median age at time of transplant was 5.4 years (IQR 2.8-14.3). The majority of patients underwent transplant for malignancy (n = 384;63%) followed by immune dysfunction (n = 105;17%). TA-TMA was diagnosed in 98 patients (16%) at a median of 22 days (IQR 14-44) post-transplant. In autologous HSCT recipients ($n = 192$), 10% ($n = 19$) were diagnosed with TA-TMA, the majority (n = 12) were diagnosed with TA-TMA after the second of two autologous transplants for neuroblastoma (25% incidence of TA-TMA). In allogeneic HSCT patients ($n = 422$), TA-TMA was diagnosed in 79 patients (19%). Patients with TA-TMA had significantly increased bloodstream infections (37/98;38% vs. 107/516,21%; p=< 0.001) and higher need for intensive care admission (52/98,53% vs. 80/516,16%; p=< 0.001) in the first 100 days over those without TA-TMA. The mean total hospitalization days in the first 100 days after HSCT was significantly higher in the TA-TMA group over those without TA-TMA (68 days, 95%CI 63-74 vs. 43 days, 95%CI 41-45; p=< 0.001). Additionally, the mean number of days spent in the intensive care unit was significantly higher in patients with TA-TMA (1.6 days, 95%CI 1.1-2.2 vs. 10.1 days, 95%CI 6.4-14; p=< 0.001). Non-relapsed mortality during the first 6 months was significantly higher in allogeneic HSCT recipients with TA-TMA (20/98,20% vs. 15/516,3%; p=< 0.0001). In patients diagnosed with TA-TMA, 51% (50/98%) were treated with eculizumab.

Conclusions: In this multi-center cohort we report a high incidence of TA-TMA after pediatric HSCT. Patients with TA-TMA have higher morbidity and mortality when compared to patients without TA-TMA.

Clinical Trial Registry: n/a

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

O130.

Use of Eculizumab in Children with Haematopoietic Stem Cell Transplantation Associated Thrombotic Microangiopathy - A Multicenter Retrospective Study on Behalf of IEWP and PDWP EBMT

Peter Svec[1], Reem Elfeky[2], Jacques-Emmanuel Galimard[3], Christine Higham[4], Benedicte Neven[5], Arnaud

Dalissier[3], Troy C. Quigg[6], David Bueno Sanchez[7], Su Han Lum[8], Maura Faraci[9], Theresa Cole[10], Herbert Pichler[11], Maribel Benitez[12], Julia Horakova[1], Marta Gonzalez -Vicent[13], Asaf Yanir[14], Franca Fagioli[15], Paul G. Schlegel[16], Nicolas von der Weid[17], Stephen Robinson[18], Gergely Krivan[19], Carsten Speckman[20], Beki James[21], Simona Lucija Avcin[22], Yves Bertrand[23], Marta Verna[24], Petr Riha[25], Katharine Patrick[26], Simone Cesaro[27], Krzysztof Kalwak[28], Marc Bierings[29], Zoltan Prohaszka[30], Arjan Lankester[31], Selim Corbacioglu[32]

[1]National Institute of Children's Diseases, Bratislava, Slovakia, [2]UCL Great Ormond Street Institute of Child Health, London, United Kingdom, [3]EBMT Paris Study Office, Saint Antoine Hospital, Sorbonne University, Paris, France, [4]UCSF Benioff Children's Hospital, San Francisco CA, CA, United States, [5]Hôpital Necker, INSERM, Paris, France, [6]Texas Transplant Institute, Methodist Children's Hospital, San Antonio, TX, United States, [7]Hospital Infantil La Paz, Madrid, Spain, [8]Great North Children`s Hospital, Newcastle-Upon-Tyne, United Kingdom, [9]Institute G. Gaslini, Genova, Italy, [10]The Royal Children's Hospital Melbourne, Melbourne, Australia, [11]St. Anna Kinderspital /Medical University of Vienna, Vienna, Austria, [12]Hospital Universitari Vall d'Hebron, Barcelona, Spain, [13]Hospital Infantil Universitario 'Niño Jesus', Madrid, Spain, [14]Schneider Children's Medical Center Of Israel, Petach-Tikva, Israel, [15]Ospedale Infantile Regina Margherita, Torino, Italy, [16]University Children's Hospital, Wuerzburg, Germany, [17]University Children's Hospital Basel, Basel, Switzerland, [18]Bristol Royal Hospital for Children, Bristol, United Kingdom, [19]Central Hospital of Southern Pest, Budapest, Hungary, [20]University of Freiburg Medical Center, Freiburg, Germany, [21]St James's Institute of Oncology, Leeds, United Kingdom, [22]University Children's Hospital Ljubljana, Ljubljana, Slovenia, [23]Institut d`Hematologie et d`Oncologie Pediatrique, Lyon, France, [24]Fondazione MBBM, Milano Bicocca University, Monza, Italy, [25]University Hospital Motol, Charles University, Prague, Czech Republic, [26]Sheffield Children's Hospital NHS Foundation Trust, Sheffield, United Kingdom, [27]Universitaria Integrata Verona, Verona, Italy, [28]Wroclaw Medical University, Wroclaw, Poland, [29]Princess Maxima Centre for Pediatric Oncology, Utrecht University Children's Hospital, Utrecht, Netherlands, [30]Semmelweis University, Budapest, Hungary, [31]Leiden University Hospital, Leiden, Netherlands, [32]University of Regensburg, Regensburg, Germany

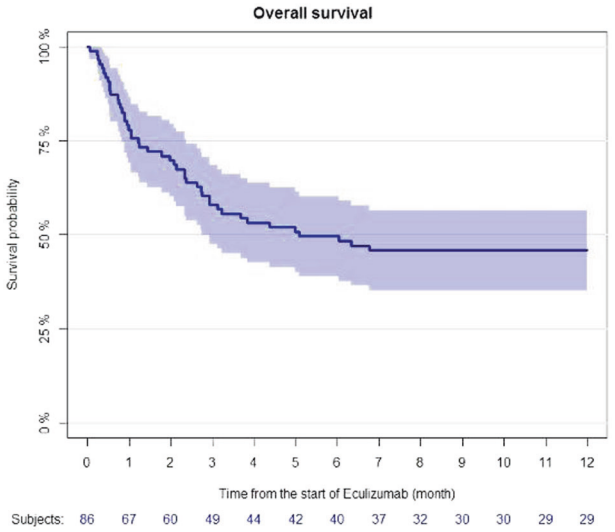
Background: The complement blockade by humanized monoclonal antibody Eculizumab is used to treat Transplantation-Associated Thrombotic Microangiopathy (TA-TMA) in recent years. The published evidence is rather scarce for this specific off-label Eculizumab indication. We report the real-life multicenter experience of 86 children and adolescents diagnosed with TA-TMA and treated with Eculizumab, on behalf of the IEWP and PDWP of the EBMT.

Methods: This is a retrospective multicenter study (29 centers), including pediatric (<18yrs) HSCT patients with TA-TMA treated with Eculizumab between January 2014 and May 2019. Five different sets of defined TA-TMA diagnostic criteria were used. Descriptive results are presented in term of median (minimum-maximum) for continuous variables. Outcomes were cumulative incidence of TA-TMA resolution and the overall survival. Death was a competing event for TA-TMA resolution. TA-TMA resolution was defined clinically by treating physician. Cumulative incidences and survival probabilities are presented with their 95% confidence intervals (CI).

Results: The cohort included 80 alloHSCTs (incl. 22 haploHSCTs) and 6 autoHSCTs, with an equal proportion of malignant and non-malignant disorders. Median age at transplant was 7.4 yrs (0.3-17.4). The median time from HSCT to TA-TMA manifestation was 88 days (7-834). Most centers applied the Cincinnati (Jodele S, 2014) diagnostic criteria (75%, n=62 pts), although only in 41 sC5b-9 monitoring was available. The median time from TA-TMA diagnosis to start Eculizumab treatment was 6 (0-135) days. Most patients received initially Eculizumab in a weekly dosing (68%, n=55), only 21% ($n = 17$) had a more frequent application. The standard dose (600mg /900mg) was given to 79% of pts ($n = 67$). The median duration of treatment for those resolving TA-TMA was 90 (3-517) days, with a median of 11.5 (1-87) Eculizumab doses applied. Sixty-six percent of alloHSCT pts ($n = 53$) developed acute GvHD prior to TA-TMA onset, with grade III-IV aGvHD in 37 pts. At 6 months from the beginning of Eculizumab treatment, the cumulative incidence of TA-TMA resolution was 41% [30-51] and the overall survival was 50% [40-61] (Graph 1). Forty-one of the 42 patients without TA-TMA resolution died. Among these, 39 were HSCT-related, the transplantation related mortality primarily attributed directly to TA-TMA or to infections as the second most common reason. Among the 44 patients with resolved TA-TMA, 8 died (3 for relapse, 2 infection, 1 GvHD, 2 other reasons). In univariate analysis, renal replacement therapy, intensive care unit admission and respiratory symptoms were significantly associated with both lower TA-TMA resolution and OS, while gastrointestinal bleeding associated with lower rates of OS.

Conclusions: In this multicenter retrospective EBMT study, severe TA-TMA in children represents an HSCT complication with very poor prognosis even with complement blockade using the monoclonal antibody Eculizumab.

Based on these results and considering the published data (Jodele S. et al., 2016, 2018) - the risk and response-based dose-intensity adjustment of Eculizumab and improving the chance to identify the proposed high-risk TA-TMA with detailed complement monitoring (CH50, sC5b-9, eculizumab drug level monitoring) deserve attention in future prospective trials. Focus on better understanding the interplay between acute GvHD and TA-TMA should be part of the trial designs.



[Graph 1: Overall survival of TA-TMA patients since initiation of Eculizumab]

Disclosure: Christine Higham received salary support from Jazz Pharmaceuticals.

Troy C. Quigg is on the speakers bureau for Alexion Pharmaceuticals and received honoraria for educational presentations on the diagnosis and management of thrombotic microangiopathies and atypical HUS.

David Bueno Sanchez received payment from Alexion Pharmaceuticals for advisory board membership and conference grants.

O131.

Reduced Post-Transplant Cyclophosphamide Doses in T-Cell Replete Haploidentical Hematopoietic Stem Cell Transplantation in Elderly Patients with Hematologic Malignancies

Remy Dulery[1,2], Claire Goudet[3], Antonio Bianchessi[1,4], Angela Granata[3], Samia Harbi[3], Valerio Maisano[3], Christian Chabannon[3], Florent Malard[1,2], Eolia Brissot[1,2], Simona Sestili[1], Clemence Mediavilla[1,2], Anne Banet[1,2], Zoé Van de Wyngaert[1,2], Annalisa Paviglianiti[1], Ramdane Belhocine[1], Stéphane Ederhy[1], Thomas Pagliardini[3], Faezeh Legrand[3], Lucas Castagna[3], Didier Blaise[3,5], Mohamad Mohty[1,2], Sabine Furst[3], Raynier Devillier[3]

[1]Saint Antoine Hospital, Paris, France, [2]Sorbonne University, INSERM UMRs 938, Centre de Recherche Saint-Antoine (CRSA), Paris, France, [3]Institut Paoli Calmettes, Marseille, France, [4]Università degli Studi di Pavia, Pavia, Italy, [5]Aix-Marseille University, Marseille, France

Background: Haploidentical (haplo) hematopoietic stem cell transplantation (HSCT) has become feasible with the use of post-transplant cyclophosphamide (PT-Cy), which reduces the risk of graft-versus-host disease (GVHD). However, PT-Cy is associated with toxicities, especially in elderly patients, which may be correlated with the total dose. Thus, we compared the outcomes with reduced PT-Cy total dose at 80 mg/kg to those with PT-Cy at 100 mg/kg in elderly patients undergoing haplo HSCT.

Methods: Eighty-five patients were included according to the following criteria: peripheral blood stem cells haplo HSCT, hematologic malignancy and age >65 years. Patients with cardiac comorbidities and age>60 years were also included. From 2014 to 2018, PT-Cy was administered at 100 mg/kg divided in 2 doses. Starting from 2018, the dose was 40 mg/kg/day on day+3 and day +4.

Results: Median age was 68 years (range, 60-77) and 62% of patients were males. Sorror comorbidity index score was 3 and higher in 39 patients (46%). Patients were transplanted for acute leukemia ($n = 31$, 36%), myelodysplastic syndrome ($n = 31$, 36%), myeloproliferative neoplasm ($n = 9$, 11%), lymphoma ($n = 10$, 12%) or multiple myeloma ($n = 2$, 2%). Disease risk index was high or very-high in 35 patients (41%). Disease status at transplantation was complete remission in 41 patients (48%). Conditioning regimens were non-myeloablative Baltimore ($n = 57$, 67%) or thiotepa-based (thiotepa - busulfan - fludarabine in 16 patients or Flamsa-like sequential in 12 patients). GVHD prophylaxis included cyclosporine and mycophenolate mofetil in all patients. Antithymocyte globulin was administered in 31 patients (36%). Thirty-three patients received PT-Cy at 80 mg/kg and 52 received 100 mg/kg. There was no significant difference between the 2 groups in terms of age, gender, comorbidity score, disease status, disease risk index, type of conditioning regimen and use of ATG. The median follow-up was 12.1 months (range, 7-21) and 32.5 months (range, 17-57) in patients receiving PT-Cy at 80 mg/kg and 100 mg/kg, respectively.

The cumulative incidence (CI) of acute grade II-IV and grade III-IV GVHD was 33% and 15% with PT-Cy at 80 mg/kg and 35% and 13% with 100 mg/kg ($p = 0.84$ and $p = 0.87$, respectively). The CI of chronic GVHD was

30% and 29% with PT-Cy at 80 mg/kg and 100 mg/kg, respectively ($p = 0.73$). The CI of severe chronic GVHD was 12% in both groups. Platelet recovery was significantly delayed with 100 mg/kg compared to 80 mg/kg (median of 36 versus 29 days, respectively, $p = 0.047$). Grade 2-3 BK-virus associated hemorrhagic cystitis and cardiac events occurred in 3% and 33% of patients with 80 mg/kg compared to 13% and 42% with 100 mg/kg.

Non-relapse mortality was 18% and 33%, progression free-survival 70% and 52%, overall survival 74% and 56% and GVHD-free, relapse-free survival 56% and 44% with 80 mg/kg and 100 mg/kg, respectively (p values were not significant in multivariate Cox adjusted model).

Conclusions: Reducing PT-Cy doses at 80 mg/kg is a safe and valid approach in elderly patients underdoing haplo. Compared to 100 mg/kg, BK-virus associated hemorrhagic cystitis was less frequent, platelet recovery was improved and the outcomes were similar without increasing the risk of GVHD.

Disclosure: Nothing to declare.

O132.

ABO Isoagglutinin Levels in Guided Management of ABO Incompatibility in Allogeneic Hematopoietic Cell Transplantation

Eleni Gavriilaki, Ioanna Sakellari, Natassa Konstantinou, Despina Mallouri, Zoi Bousiou, Marianna Masmanidou, Ioannis Batsis, Aliki Xochelli, Athanasios Anastasiadis, Maria Gkanidou, Achilles Anagnostopoulos

G. Papanicolaou Hospital, Thessaloniki, Greece

Background: Our group has previously shown that pure red cell aplasia (PRCA) does not worsen outcomes post allogeneic hematopoietic cell transplantation (HCT). Despite renewed interest in the role of ABO isoagglutinin levels, relevant studies are scarce. In the present study we aimed to investigate the impact of ABO isoagglutinin levels on guiding management of ABO incompatibility compared to our historic control group.

Methods: We retrospectively reviewed data in our prospectively acquired database of HCT recipients treated at our JACIE-accredited Unit (01/2001- 6/2019). Patient data including details of transplantation procedure, disease status, graft-versus-host-disease (GVHD), disease-free (DFS) and overall survival (OS) were extracted. Charts from patients with ABO incompatibility were re-reviewed to identify diagnostic and therapeutic features. ABO isoagglutinin levels have been measured since 2014 in patients with ABO incompatibility; sequentially in PRCA. Therefore, we divided our group into the historic control (up to 2013) and the current treatment period (2014-2019).

Results: Among 645 HCT recipients, 147 (23%) had ABO incompatibility (144 major, 41 minor, 39 bidirectional). Of these, 86 were transplanted in the early, compared to 61 in the current period. Incidence of ABO incompatibility did not differ between treatment periods (21% versus 26%). In total, 29 patients developed PRCA at a median of 32 (14-115) post-transplant day; 23 in the early and 6 in the late period ($p = 0.012$). Among pre-transplant factors, treatment period ($p = 0.003$) and major incompatibility ($p< 0.001$) independently predicted PRCA diagnosis. The effect of treatment period may be attributed to measurement of isoagglutinin levels. The latter guided management of non-hemolytic anemia leading to a reduced number of patients in need of intervention for PRCA. A titer of 512 or higher was associated with the development of PRCA ($p< 0.001$), that required plasma exchange in all but one cases ($p = 0.023$). Erythropoietin was administered in all PRCA patients, steroids in 15/29 and plasma exchange in 11/29 with a median of 9 (5-15 sessions). One patient presented with PRCA due to pre-existing anti-D alloimmunization that resolved with erythropoietin, corticosteroids and 9 plasma exchange sessions.

With a follow-up of 184 months (5-562) in surviving patients, PRCA did not affect DFS and OS ($p = 0.351$ and $p = 0.447$). In the multivariate model, favorable OS was predicted only by early disease phase at transplant ($p = 0.001$) and sibling donors ($p = 0.006$) and total body irradiation at conditioning ($p< 0.001$). Similarly, PRCA was not associated with acute or chronic GVHD. Interestingly, neither reduced intensity conditioning nor transplant period had significant effects on HCT outcomes.

Conclusions: Our real-world data in a large cohort of HCT recipients confirm previous reports that ABO incompatibility does not affect outcomes. ABO isoagglutinin levels emerge as a helpful tool in guiding proper diagnosis and management in these patients. Future prospective studies will clarify their role in clinical practice.

Disclosure: Nothing to declare.

O133.

Methylprednisolone Stratified Intervention Based on Risk Classification in the Treatment of Pre-Engraftment Syndrome After Unrelated Cord Blood Transplantation: A Prospective, Non-Randomized, and Open-Label Study

Xiaoyu Zhu[1,2], Baolin Tang[1], Jiang Zhu[1], Kaidi Song[1], Linlin Jin[2], Huilan Liu[1], Changcheng Zheng[1], Liangquan

Geng[1], Xuhan Zhang[1], Wen Yao[1], Xiang Wan[1], Juan Tong[1], Guangyu Sun[1], Zimin Sun[1,2]

[1]The First Affiliated Hospital of USTC, University of Science and Technology of China, Hefei, China, [2]Blood and Cell Therapy Institute, University of Science and Technology of China, Hefei, China

Background: Pre-engraftment syndrome (PES) is a common immune reaction prior to neutrophil engraftment after unrelated cord blood transplantation (UCBT), with a unique clinical manifestation of non-infectious fever and skin rash. The reported incidence of PES ranges from 20% to 78%, and median onset time is 7 (5-14) days. The main treatment for PES is methylprednisolone (MP). Studies showed that PES was associated with a high incidence of acute GVHD and but not with transplant-related mortality (TRM), relapse, or overall survival (OS). Our previous study found that multiple clinical symptoms and occurrence within 7 days after transplantation were two independent high risk factors affecting 180-day TRM in PES patients. One high risk factor was scored as 1. PES could be divided into low- (score 0), intermediate- (score 1), and high (score 2) risks, and different doses of MP stratified intervention could significantly improve the prognosis of high-risk PES patients. This study was conducted to validate the efficacy of MP stratified treatment based on the risk score classification in a large, varied population.

Methods: 340 hematological malignancy patients who underwent UCBT from September 2016 to December 2018 in our transplantation center were enrolled into this study. When patients occurred PES, they were divided into low, intermediate, and high-risk according to two high risk factors, and treated with different doses of MP, 0.5mg/kg/d for low-risk, 1mg/kg/d for intermediate-risk and 2mg/kg/d for high-risk. The primary endpoint was 180-day TRM.

Results: Among 340 hematological malignancy patients, 100 (29.4%) patients had no PES, the other 240 (70.6%) occurred PES. In 240 PES patients, risk score was low in 152 subjects (63.3%), intermediate in 67 (27.9%), and high in 21 (8.8%). All the patients were follow up until 10th July 2019. The cumulative incidence of neutrophil engraftment was significantly higher in PES than no-PES group (96.3% vs 89.0%, P=0.013). There was no significant difference in 180d-TRM between PES and no-PES group (18.8% vs 16.0%, P=0.579), and also among low, intermediate and high-risk PES groups (18.4% vs 14.9% vs 33.3%, P=0.236). However, grade II~IV and III~IV acute GVHD were significantly higher in PES group than in no-PES group (32.5% vs 18.0%, P=0.009; 26.7% vs 13.0%, P=0.007), which were highest in high-risk PES group. 1-year relapse rate, extensive chronic GVHD, OS, and DFS did not differ between PES and no-PES groups, and among different risks of PES groups. Compared to the previous PES patients without stratification treatment, the 180-day TRM of intermediate and high risk PES patients was significantly reduced and the 1-year OS, DFS, and GRFS were increased after MP stratification therapy. Although MP stratified therapy could significantly improve the prognosis of high-risk PES patients, acute GVHD and GRFS were still the worst compared with other risks of PES patients.

Conclusions: PES after UCBT is benefit for engraftment, but should be graded according the risk scoring system. Different doses of MP stratified therapy can significantly improve the prognosis of PES patients, and are worthy to clinical application. But how to improve the outcomes of high-risk PES patients remains to be further studied.

Clinical Trial Registry: This trial was registered at www.chictr.org.cn as ChiCTR-ONC-16009013.

Disclosure: Nothing to declare.

O134.

Pretransplant Nutrition Measures and Systemic Inflammatory Response Predict Outcome After Allogeneic Hematopoietic Cell Transplantation

Hartmut Bertz, Gabriele Ihorst, Robert Zeiser, Jürgen Finke

University of Freiburg, Freiburg, Germany

Background: In recent years several risk scores have been established to predict the outcome of patients before their alloHCT according OS, PFS, NRM or acute/chronic GvHD incidence. The nutrition status, especially severe malnutrition (defined as low serum albumin), and the systemic inflammatory response (increased C-reactive protein) are playing an important factor in oncology patients regarding outcome. They have not been evaluated so far in alloHCT and are, except the Body Mass Index (BMI) >35 kg/m², not established risk factors. Therefore, we evaluated all patients receiving their first alloHCT since 1996 with special look on CRP and serum albumin or their combination (Glasgow Prognostic Score; GPS) or the BMI at admission for outcome after alloHCT in comparison with established risk scores.

Methods: The 1665 consecutive patients (median age 53 years; range 16-79) received their first alloHCT for mainly myeloid malignancies (60%). Peripheral blood stem cells (PBSC) was the primary graft (89%) for the mainly male patients (58%) transplanted not in CR1/CP1 or > CR2 (63%). In all patients BMI, CRP, serum albumin, EBMT-score and the HCT-CI were statistically evaluated for the

above listed outcomes. Additionally the GPS was evaluated, which is an established risk score in patients with oncological malignancies. It is the combination of CRP < or> 10mg/l and sALB < or> 3.5 mg/dl in combination: score 0 both measures in normal range, score 1 one and score 2 both measures out of range.

Results: Of the evaluated 1658 pts. n=646 had an increased CRP or n=45high BMI (>35kg/m²), n=296 a low serum albumin or n=47 very low BMI (< 18.5kg/m²). We observed the following GPS: 0 ($n = 923$), 1 ($n = 531$) and 2 ($n = 211$). In a multivariate model the significant risk factors beside others were for OS or PFS a GPS 1 (HR 1.335 p< .0001) or 2 (HR 1.960 p< .0001). The same results were observed for PFS (GPS 1: HR 1.291 p< .0001; GPS 2 HR 1.818 p< .0001). Interestingly, not only the combination, but each measure of the GPS (CRP >10mg/l or serum albumin < 3.5 mg/dl) are significantly influencing OS and PFS in multivariate analysis. For NRM only GPS 2 (HR1.853 p< .0001) had a significant influence, as well as an elevated CRP for aGvHD °III-IV (HR 1.293; p= 0.0492). The GPS has no impact on relapse incidence, aGvHD °III-IV/°II-IV and or any cGvHD. Evaluating BMI, the standard clinical nutrition measure, neither very low < 18.5 kg/m² nor high BMI >35 kg/m² had a statistically influence in any outcome at all.

Conclusions: In our comprehensive analysis malnutrition (measured as low albumin) and/or systemic inflammatory response (elevated CRP) and their combination (GPS) have an high significant impact as pretransplant measures on the outcome after alloHCT and should be examined. Whether pretransplant nutrition and exercise is improving nutrition, inflammation and patients outcome should be evaluated with intensive prehabilitation programs.

Disclosure: Noting to declare.

O135.

A Multi-Centre, Multi-National, Prospective Observational Registry Study of Defibrotide in Patients Diagnosed with Severe Veno-Occlusive Disease/ Sinusoidal Obstruction Syndrome (VOD/SOS) After Haematopoietic Cell Transplantation (HCT)

Mohamad Mohty[1], Marta Lisa Battista[2], Didier Blaise[3], Elisabetta Calore[4], Simone Cesaro[5], Natalia Maximova[6], Katia Perruccio[7], Cecile Renard[8], Marco Zecca[9], Myriam Labopin[1], Raj Hanvesakul[10], Robert J. Ryan[11], Fabio Ciceri[12], Sarah Lawson[13]

[1]Hôpital St Antoine, Sorbonne University, INSERM UMRs 938, Paris, France, [2]University of Udine, Udine, Italy, [3]Institut Paoli Calmettes, Marseille, France, [4]University Hospital of Padova, Padova, Italy, [5]Ospedale della Donna e del Bambino, Verona, Italy, [6]IRCCS Burlo Garofolo, Trieste, Italy, [7]Santa Maria della Misericordia Hospital, Perugia, Italy, [8]Institute of Pediatric Hematology and Oncology, Lyon, France, [9]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [10]Jazz Pharmaceuticals, Oxford, United Kingdom, [11]Jazz Pharmaceuticals, Philadelphia, PA, United States, [12]IRCCS San Raffaele Scientific Institute, Milan, Italy, [13]Birmingham Children's Hospital, Birmingham, United Kingdom

Background: Severe hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication of haematopoietic cell transplantation (HCT). The most severe form of VOD/SOS is associated with multi-organ dysfunction/failure (MOD/MOF) and a mortality rate of >80% if untreated. A European disease registry of patients with severe VOD/SOS post-HCT who were treated with defibrotide was established to collect safety and outcome data and assess patterns of defibrotide utilisation post-approval.

Methods: This multi-centre, multi-national, prospective, observational study (NCT03032016), performed by the EBMT, included patients with severe VOD/SOS post-HCT who were treated with defibrotide and enrolled from April 2015 to July 2018. Investigators diagnosed VOD/SOS using classical/standard criteria (including but not limited to hyperbilirubinaemia, hepatomegaly, ascites, and weight gain >5%). Severity grading criteria were not predefined in the protocol; investigators graded VOD/SOS severity based on typical clinical practice. Patients with renal, pulmonary, or cerebral dysfunction were diagnosed as having MOD/MOF. Patients who received defibrotide for purposes other than the approved indication (VOD/SOS prophylaxis, non-severe VOD/SOS treatment, or thrombotic microangiopathy) were also registered. There were no specific exclusion criteria; however, treating physicians were alerted to contraindications, special warnings, and precautions detailed in the defibrotide SmPC. The primary endpoint was incidence rate of serious adverse events (SAEs) of interest (haemorrhage, hypotension, coagulopathy, allergic/hypersensitivity reactions, injection-site reaction, infection/septicaemia, thromboembolic events) up to 12 months post-HCT in patients with severe VOD/SOS. Secondary endpoints included Day 100 survival and overall rate of VOD/SOS (and MOD/MOF, if present) resolution (investigator-defined) up to 12 months post-HCT.

Results: Overall, data from 62 patients with severe VOD/SOS were analysed; MOD/MOF was diagnosed at registration in 36 (58%) patients. Median age was 14.5 (range: 0-68) years, with 34 (55%) patients aged <18 years. Fifty-five

(89%) patients received allogeneic HCT. Primary diseases included acute myeloid leukaemia (23%), precursor lymphoid neoplasms (23%), myelodysplastic syndrome/myeloproliferative disease (19%), and solid tumours (11%). Median length of defibrotide exposure was 16.5 (IQR: 11.0-25.0) days.

SAEs of interest occurred in 19 (31%; 95% CI: 19-42%) patients. The most common by category were infection (n = 14 [23%; 95% CI: 12-33%]) and bleeding events (n = 8 [13%; 95% CI: 5-21%]). The most common individual SAEs of interest (≥5% of patients) were pneumonia (8%), gastrointestinal bleeding (6%), and sepsis (6%). Death occurred in 31 (50%) patients, with VOD/SOS indicated as cause of death in 13/31 (42%) patients.

The Kaplan-Meier-estimated survival rate at Day 100 was 73% (95% CI: 60-82%). The median Kaplan-Meier-estimated survival post-HCT was not yet reached. VOD/SOS resolved in 47 (76%) patients; the cumulative rate of VOD/SOS resolution with death as a competing event at Day 100 was 73% (95% CI: 59-82%). MOD/MOF resolution was achieved in 19/36 (53%) patients with MOD/MOF at VOD/SOS diagnosis.

Conclusions: Among patients with severe VOD/SOS post-HCT (including those with MOD/MOF), the incidence of SAEs of interest was consistent with that observed in previous defibrotide clinical trials. Defibrotide treatment resulted in Day 100 survival and VOD/SOS resolution rates consistent with reports of defibrotide use in the post-approval setting.

Clinical Trial Registry: ClinicalTrails.gov (ID number: NCT03032016)

Disclosure: *Mohamad Mohty:* has received honoraria and research funding from Jazz Pharmaceuticals

Marta Lisa Battista: no conflicts of interest to disclose

Didier Blaise: has received honoraria from Jazz Pharmaceuticals

Elisabetta Calore: no conflicts of interest to disclose

Simone Cesaro: no conflicts of interest to disclose

Natalia Maximova: no conflicts of interest to disclose

Katia Perruccio: no conflicts of interest to disclose

Cecile Renard: no conflicts of interest to disclose

Marco Zecca: no conflicts of interest to disclose

Myriam Labopin: has received honoraria from Jazz Pharmaceuticals

Raj Hanvesakul: employee of and holds stock ownership and/or stock options in Jazz Pharmaceuticals

Robert J. Ryan: employee of and holds stock ownership and/or stock options in Jazz Pharmaceuticals

Fabio Ciceri: no conflicts of interest to disclose

Sarah Lawson: has received consultancy honorarium from Jazz Pharmaceuticals.

O136.

Defibrotide Treatment for Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome (VOD/SOS) After Haematopoietic Cell Transplantation (HCT): Outcomes by Severity and Multi-Organ Failure Status in an Observational Registry Study

Mohamad Mohty[1], Marta Lisa Battista[2], Didier Blaise[3], Elisabetta Calore[4], Simone Cesaro[5], Natalia Maximova[6], Katia Perruccio[7], Robert Wynn[8], Marco Zecca[9], Myriam Labopin[1], Vian Amber[10], Robert J. Ryan[11], Sarah Lawson[12]

[1]Hôpital St Antoine, Sorbonne University, INSERM UMRs 938, Paris, France, *[2]University of Udine, Udine, Italy*, *[3]Institut Paoli Calmettes, Marseille, France*, *[4]University Hospital of Padova, Padova, Italy*, *[5]Ospedale della Donna e del Bambino, Verona, Italy*, *[6]IRCCS Burlo Garofolo, Trieste, Italy*, *[7]Santa Maria della Misericordia Hospital, Perugia, Italy*, *[8]Royal Manchester Children's Hospital, Manchester, United Kingdom*, *[9]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*, *[10]Jazz Pharmaceuticals, Oxford, United Kingdom*, *[11]Jazz Pharmaceuticals, Philadelphia, PA, United States*, *[12]Birmingham Children's Hospital, Birmingham, United Kingdom*

Background: Severe hepatic VOD/SOS is a potentially life-threatening complication of HCT; the most severe form is associated with multi-organ dysfunction/failure (MOD/MOF) and a mortality rate of >80% if untreated. A European disease registry of patients with VOD/SOS post-HCT who received defibrotide collected safety and outcome data post-approval.

Methods: This multi-centre, multi-national, prospective, observational study (NCT03032016), performed by the EBMT, enrolled patients with VOD/SOS post-HCT, including severe VOD/SOS, and who received defibrotide, regardless of indication, from April 2015 to July 2018. VOD/SOS was diagnosed by the investigator using classical/standard criteria (including but not limited to hyperbilirubinaemia, hepatomegaly, ascites, and weight gain >5%). Investigators graded VOD/SOS severity based on typical clinical practice. Patients with renal, pulmonary, or cerebral dysfunction, as judged by the investigator, were diagnosed with MOD/MOF. The primary endpoint was incidence of serious adverse events (SAEs) of interest up to 12 months post-HCT in patients with severe VOD/SOS. Secondary endpoints included Day 100 survival and overall rate of VOD/SOS (and MOD/MOF, if present) resolution (as defined by the investigator) up to 12 months post-HCT.

This exploratory subgroup analysis evaluated outcomes in patients with non-severe VOD/SOS and those with severe VOD/SOS, including MOD/MOF.

Results: Overall, 104 defibrotide-treated patients with VOD/SOS post-HCT were enrolled: 42 had non-severe VOD/SOS (median age: 13.1 years [range: 0-69]) and 62 had severe VOD/SOS, of which 26 had no MOD/MOF (median age: 11.7 years [range: 1-65]) and 36 had MOD/MOF (median age: 21.1 years [range: 0-68]). Overall, 83%, 81%, and 94% of patients had received allogeneic HCT, respectively.

SAEs of interest occurred in 8/42 (19%) patients with non-severe VOD/SOS. Among patients with severe VOD/SOS, 7/26 (27%) with no MOD/MOF and 12/36 (33%) patients with MOD/MOF experienced an SAE of interest.

The Kaplan-Meier-estimated Day 100 survival rate was 91% (95% CI: 77-96%) in patients with non-severe VOD/SOS; among patients with severe VOD/SOS, Day 100 survival was 85% (95% CI: 64-94%) in patients with no MOD/MOF and 64% (95% CI: 46-77%) in patients with MOD/MOF. The median Kaplan-Meier-estimated survival post-HCT was not reached in patients with non-severe VOD/SOS or severe VOD/SOS with no MOD/MOF and was 249.5 days (95% CI: 83-not reached) in patients with MOD/MOF. Among patients who died, death due to VOD/SOS occurred in 0/11 patients with non-severe VOD/SOS and, in the severe VOD/SOS population, in 2/10 and 11/21 patients with no MOD/MOF and with MOD/MOF, respectively. In patients with non-severe VOD/SOS, the cumulative incidence of VOD/SOS resolution at Day 100 was 95%. The cumulative incidence of VOD/SOS resolution at Day 100 in the severe VOD/SOS population was 88% in those without MOD/MOF and 61% for those with MOD/MOF. Resolution of MOD/MOF was achieved in 19/36 (53%) patients.

Conclusions: Among patients with VOD/SOS post-HCT, the safety profile of defibrotide was consistent with previous reports. Rates of Day 100 survival and VOD/SOS resolution were consistent with previous reports of defibrotide in the post-approval setting, with progressively better outcomes observed in patients with less severe disease.

Clinical Trial Registry: ClinicalTrials.gov (ID number: NCT03032016)

Disclosure: *Mohamad Mohty:* has received honoraria and research funding from Jazz Pharmaceuticals

Marta Lisa Battista: no conflicts of interest to disclose

Didier Blaise: has received honoraria from Jazz Pharmaceuticals

Elisabetta Calore: no conflicts of interest to disclose

Simone Cesaro: no conflicts of interest to disclose

Natalia Maximova: no conflicts of interest to disclose

Katia Perruccio: no conflicts of interest to disclose

Robert Wynn: no conflicts of interest to disclose

Marco Zecca: no conflicts of interest to disclose

Myriam Labopin: has received honoraria from Jazz Pharmaceuticals

Vian Amber: employee of and holds stock ownership and/or stock options in Jazz Pharmaceuticals

Robert J. Ryan: employee of and holds stock ownership and/or stock options in Jazz Pharmaceuticals

Sarah Lawson: has received consultancy honorarium from Jazz Pharmaceuticals

O137.

Introduction of New Pediatric EBMT Criteria for VOD Diagnosis: Is it Life-Saving or Money-Wasting?

Zofia Szmit, Ewa Gorczyńska, Anna Król, Marek Ussowicz, Monika Mielcarek-Siedziuk, Jowita Frączkiewicz, Krzysztof Kałwak

Department of Pediatric Hematology/Oncology and BMT Wroclaw Medical University Supraregional Center of Pediatric Oncology Cape of Hope, Wrocław, Poland

Background: Hepatic veno-occlusive disease (VOD) is an unpredictable and potentially fatal complication following hematopoietic stem cell transplantation (HSCT). Proper diagnosis and immediate treatment is crucial for general outcome of patients with VOD. Therefore diagnostic criteria, adequately tailored for pediatric population, seem to be essential. Those criteria, recently established by EBMT, may change the conception of VOD in the future. The aim of this single-centre prospective cohort study was to evaluate the new VOD diagnostic criteria in comparison with the historically used Seattle and Baltimore criteria. Furthermore, a presumable impact of the new criteria on patients' outcome and cost effectiveness was assesed.

Methods: Prospective cohort study included all 315 HSCT procedures performed in Department of Pediatric Hematology, Oncology and Bone Marrow Transplantation in Wrocław between January 2016 and August 2019, particularly focusing on patients diagnosed with VOD according to new Pediatric EBMT VOD diagnostic criteria. Defibrotide (DF) was used according to expanded- access protocol and administered to every patient with VOD. Collected data were compared to results of previous VOD research conducted in our center during years 2001-2015.

Results: In analyzed period, 26 (8.3%) patients with median age of 3.5 yrs were diagnosed with VOD; 11 post auto-HSCT and 15 post allo-HSCT. Median day post HSCT at diagnosis was +16 (8-25). Five (19.3%) patients were diagnosed more than 21 days post HSCT (historically classified as "late onset"). Refractory thrombocytopenia (RT) was the earliest and most consistent VOD symptom,

fulfilled by 100% of children. Only five (19.3%) patients presented with hyperbilirubinemia >2mg/dl at the moment of diagnosis, while 17 (69.2%) met the criterion of a rising serum bilirubin level on three consecutive days. Nineteen (76%) cases remained anicteric during the whole course of VOD. Duration of DF administration varied from 4 to 34 days (median: 16.5), with 96.2% response rate. One patient died with active VOD. Overall survival (OS) in VOD cohort was 88.5%. If using Baltimore criteria only 6 patients would be diagnosed and therefore would receive proper treatment for VOD. According to Modified Seattle criteria, 16 patients would be diagnosed with VOD. Median diagnosis delay based on Modified Seattle Criteria was 3 days. Before year 2016, VOD incidence in our center was 4.9%, with 74% DF response rate ($p = 0.033$) and 56.2% OS ($p = 0.008$). After implementing new criteria length of hospitalization for patients diagnosed with VOD decreased by median of 12 days (54 vs 42; $p = 0.009$).

Conclusions: The new EBMT VOD diagnostic criteria justify the differences in various aspects of the disease between children and adults and offer the potential for early diagnosis. According to up-to-date studies, pre-emptive intervention in VOD is crucial for patients' outcomes. The superiority of immediate diagnosis, especially in correlation with the expanded-access DF treatment protocol was confirmed by our study. Due to the possibility of shortening the treatment and length of hospital stay, the new EBMT VOD criteria seem to have improved the outcomes of patients suffering from VOD post HSCT.

Disclosure: Nothing to declare.

O138.

Prospective Pilot Study on Frailty and Function Assessment During Clinics in Allogeneic Hematopoietic Cell Transplantation

Maria Queralt Salas[1], Eshetu G Atenafu[2], Arijit Nag[1], Ora Bascom[2], Leeann Wilson[2], Wilson Lam[1], Arjun Datt Law[1], Ivan Pasic[1], Zeyad Al-Shaibani[1], Dennis (Dong Hwan) Kim[1], Fotios V Michelis[1], Armin Gerbitz[1], Jeffrey Howard Lipton[1], Auro Viswabandya[1], Jonas Mattsson[1], Shabbir M. H. Alibhai[3], Rajat Kumar[1]

[1]*Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada*, [2]*Princess Margaret Cancer Center, Toronto, Canada*, [3]*University Health Network, Toronto, Canada*

Background: A Frailty and Functionality assessment was specifically designed at our Centre to be implemented using existing resources. We aim to share the experience implementing this evaluation and, correlate results with post-transplant outcomes.

Methods: Frailty and Functionality assessment has become part of the standard of care at our Centre since July 2018. The evaluation is done at first consultation and across all ages. The assessment consists of a Clinical Frailty Scale (CFS), Instrumental Activities of Daily Living Test (IADL), Grip Strength, Timed up and Go test (TUGT), Self-Health Related questionnaire (SHR), Single question of Falls and Albumin and C-Reactive Protein (CRP) Level.

All patients provided informed consent. Data was analyzed prospectively and updated in November 2019. Median follow-up was 5.3 months (range: 0.7-14.8). A Univariate Cox Regression analysis was done to correlate results provided by the Frailty and Functionality assessment with overall survival (OS) The impact of this evaluation in non-relapse mortality (NRM) was explored with Grey test.

Results: Between July 2018 and September 2019, 280 patients were evaluated. Median time required to perform the entire evaluation ranged between 5-6 minutes. No patient was missed and less than 5% of the parameters were missed and mostly during early implementation.

The impact of results provided by the Frailty and Functionality evaluation in post-transplant outcomes was analyzed in 168 consecutive patients. Main baseline characteristics were as follow: median age was 58 years (range: 19-76), 95 (56%) patients were previously diagnosed with acute myeloid leukemia, 38 (23.4%) had a Karnofsly performance status between 70%-80%, 54 (32.1%) an HCT-CI score ≥3 and 115 (68.4%) received reduced intensity conditioning regimen.

A TUGT > 10 seconds (HR 2.9 (95% CI 1.4-5.9); P=0.003), raised CRP (HR 4.4 (95% CI 2-9.6); P< 0.001), and hypoalbuminemia (HR 2.1 (95% CI 1-4.3); P=0.043) were significant risk factors for worse OS.

CFS ≥3 (HR 3.1 (95%CI 1.3-7.2); P=0.009), TUGT > 10 seconds (HR 3.47 (95%CI 1.5-7.9); P=0.003), SHR questionnaire B, C.D.E (HR 3.8 (95% CI 1.9-7.9); P< 0.001), elevated CRP (HR 11.7 (95% CI 3.4-40.7); P< 0.001), and hypoalbuminemia (HR 4.6 (95% CI 1.9-11.2); P< 0.001), were significant predictors for worse NRM.

No parameter had a significant impact in the cumulative incidence of acute GVHD.

Conclusions: With selected brief tools, Frailty and Functionality can be assessed as part of routine clinical practice in alloHCT without extra waiting time for patients or additional human resources or recurrent costs.

Some parameters correlated with main post-transplant outcomes. However, larger number of patients and longer follow-up will help to evaluate the different assessment modalities as prognostic tools in allo-HSCT and their wider applicability.

Multicenter validation of the current evaluation is desirable to demonstrate the true potential of this evaluation

Clinical Trial Registry: No applicable.

Disclosure: Nothing to declare.

O139.

Histologic Features of Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy with and Without Concomitant Acute Graft-Versus-Host Disease

Michelle Ehmann, Michael Medinger, Benjamin Bodenmann, Noemie Bollinger, Sarah Kraft, Dominik Heim, Dimitrios Tsakiris, Claudia Lengerke, Alexandar Tzankov, Jakob Passweg, Thomas Menter

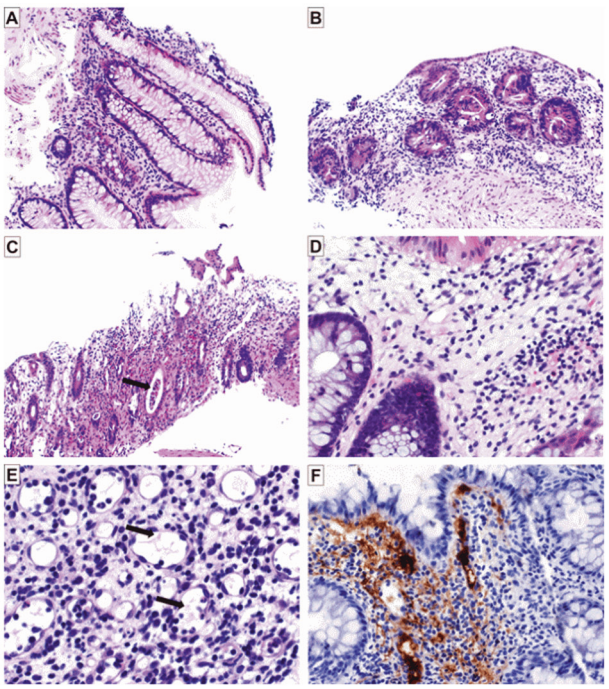
Universitätsspital Basel, Basel, Switzerland

Background: Transplant-associated thrombotic microangiopathy (TA-TMA) significantly affects transplant-related morbidity and mortality. The lack of sensitive and specific diagnostic tests for TA-TMA often results in delayed treatment. The aim of our study is to see whether biopsies could add additional information in the diagnosis of TA-TMA in patients with clinical diagnosed TA-TMA.

Methods: We assessed 660 patients for TA-TMA suffering from either AML n=248, ALL n=79, CML n=23, CLL n=36, lymphoma/myeloma n=127, MDS/MPN n=124 or bone marrow failure n=22, who had undergone allo-HSCT between 2006 and 2016s. Sixty-five (9.8%) of these patients matched the established clinical diagnostic criteria for TA-TMA. Of these 51/65 (78.5%) patients had undergone 74 biopsies to rule in /rule out GvHD, of these 13/74 (17.6%) were skin; 52/74 (70.3%) gastrointestinal tract (Fig. 1A) and 9/74 (12.1%) other biopsies were available for analysis. Of these 51 patients, 43 had concomitant aGvHD grade ≥2. A control group consisted of 10 patients with GvHD without clinical evidence of TA-TMA.

Results: Patients with TA-TMA had significantly higher aGvHD grade compared to patients without TA-TMA ($p = 0.041$). Regarding histological criteria for intestinal TA-TMA (El-Bietar et al. BBMT 2015), patients with TA-TMA had a significantly difference regarding loss of glands ($p = 0.001$) (Fig. 1B + 1C) stained positive for fibrin ($p = 0.014$) (Fig. 1F), and microthrombi ($p = 001$), whereas no significant differences were found regarding intraluminal schistocytes ($p = 0.616$) (Fig. 1E), total mucosal denudation ($p = 0.185$), endothelial cell separation ($p = 1.0$), endothelial cell swelling ($p = 0.201$) (Fig. 1D), and mucosal hemorrhage ($p = 0.073$). Overall, the correlation of clinical diagnosis of TA-TMA with histological signs of TA-TMA was low and many of the intestinal TA-TMA criteria are seen more often in biopsies with GvHD but without TA-TMA (loss of glands, total denudation of areas of mucosa, endothelial cell swelling, and positive fibrin staining). Of the 51 patients with clinical diagnosis of TA-TMA intestinal histological criteria were fulfilled in: 24 (47%) (loss of glands), 18 (35.35%) (endothelial cell swelling), 18 (35.3%) (fibrin positivity), 14 (27.55%) (total mucosal denudation), 13 (25.5%) (mucosal hemorrhages), 10 (19.6%) (microthrombi), 2 (3.9%) (intraluminal schistocytes), and 0 (0%) (endothelial cell separation). Of these 51 patients with TA-TMA 43 had aGvHD ≥ II, histological diagnosis of aGvHD was confirmed in 98%. In the control group with clinically diagnosed aGvHD without TA-TMA, histology confirmed aGvHD in 100%. 10/10 (100%) patients displayed loss of glands, 8/10 (80%) (fibrin positivity), 7/10 (70%) endothelial cell swelling, 6/10 (60%) total denudation of areas of mucosa, and 1/10 (10%) microthrombi.

Conclusions: We could demonstrate that although some features are more often seen in TA-TMA, patients, many of the histologic alterations described in TA-TMA patients might be more likely attributed to co-occuring aGvHD. This study points to a considerable overlap of aGvHD und TA-TMA both clinically and histologically. The risk/benefit-ratio of biopsies (bleeding, infection, perforations) should taken into account to rule out / in GvHD; but in the diagnosis of TA-TMA, especially with concomitant GvHD, the risk of biopsies is more prominent than the benefit to fortify the diagnosis of intestinal TA-TMA.



[Figure 1: Histologic features of gastrointestinal GvHD and putative correlates of TMA]

Disclosure: Nothing to declare.

O140.

High Survival Rate of Pediatric Patients with Primary Graft Failure WHO Undergo a Second Procedure. The Experience of 3 Spanish Pediatric Transplant Units

Laura Alonso[1], Marta González-Vicent[2], Belen Fernandez[3], Maria Isabel Benitez[1], Blanca Molina[2], Yasmina Mozo[3], Maria Luz Uria[1], Jesus Fernandez[4], Luisa Sisinni[3], David Bueno[3], Miguel Ángel Diaz Perez[2], Antonio Perez-Martinez[3], Cristina Diaz de Heredia[1]

[1]Hospital Maternoinfantil Vall d'Hebron, Barcelona, Spain, [2]Hospital Niño Jesus, Madrid, Spain, [3]Hospital Infantil La Paz, Madrid, Spain, [4]Banc de Sang i Teixits, Barcelona, Spain

Background: Primary graft failure (PGF) is defined as the failure of stem cells to engraft. This is a serious complication after hematopoietic stem cell transplantation (HSCT) and risk factors have been described. However, once it is diagnosed, there are not currently available treatment guidelines and thus patient management is individualised, depending on patient's status, donor availability and previous transplant characteristics. In addition, the outcome of this group of patient's remains largely unknown and published series usually include adult patients and primary and secondary graft failures.

Considering this background, this study seeks to describe the management and outcome of pediatric patients diagnosed with primary graft failure in 3 Spanish transplant units.

Methods: Retrospective review of the pediatric patients diagnosed with PGF in Hospital Vall d'Hebron, Hospital La Paz and Hospital Niño Jesús between January 2011 and August 2019.

PGF was defined as ANC< 0.5 x10E9/l by day +28 or day +42 in unrelated cord blood transplant or absence of donor chimerism.

Results: Thirty-one pediatric patients were diagnosed with PGF out of a total of 700 allogeneic HSCT performed (incidence of 4.4%).

Median age at transplant was 5.3years (0.36-14). Base line diagnosis was malignant disease in 16 patients and non-malignant in 15. Stem cell donors were matched sibling 1, unrelated donor 6, haploidentical 15, unrelated cord blood 8, MMRD 1.

Factors influencing graft failure: Anti-HLA antibodies were found in 1 patient and macrophage activation syndrome in 4. Stem cell product cellularity was clearly below the standard in 2 cases. One patient had previously experienced a secondary graft failure.

Twenty four (78%) of patients underwent a second transplant procedure. Median time between the 2 transplant procedures was 56 days (34-210). A different donor was used in 75% of the cases and the most frequent second HSCT donor was haploidentical (16). Sixteen of the 24 patients (67%) engrafted after the second HSCT and 2 further patients engrafted after a 3th HSCT. Overall rescue rate of patients who underwent further HSCT was 75%.

Sixteen patients (50%) are alive, 3 of whom present autologous reconstitution. None of the patients who did not received a second transplant survived. Main causes of death are disease relapse (1), infection in aplasia after graft failure (3), infection after engraftment (3), GVHD (1), other organ toxicity (7).

Conclusions: To the best of our knowledge, this is the largest series assessing the outcome of pediatric patients diagnosed with primary graft failure. Survival of patients with PGF who undergo a rescue HSCT is reassuring and every effort should be made to take these patient to a second transplant.

Disclosure: Nothing to declare.

O141.

Chemotherapy-Induced GUT Mucosal Injury Initiates Microbial Disruption in Stem Cell Transplant Recipients

Lenneke van Groningen[1], Hannah Wardill[2], Stijn van der Aa[2], Rita Ferreira da Silva[2], Alex Kurilshikov[2], Walter van der Velden[1], Hermie Harmsen[2], Wim Tissing[2], Nicole Blijlevens[1]

[1]Radboud University Medical Centre, Nijmegen, Netherlands, [2]University Medical Center Groningen, Groningen, Netherlands

Background: Haematopoietic stem cell transplantation (HSCT) is associated with gut dysbiosis, hypothesised to drive lethal complications. Dysbiosis has been largely attributed to widespread antibiotic use in HSCT recipients, with little appreciation for the impact of gastrointestinal mucositis (GI-M), posing consequences for preventive and therapeutic interventions. The current prospective study aimed to longitudinally characterize the composition of the faecal microbiota and short chain fatty acid (SCFA), relative to GI-M progression in HSCT recipients with constrictive use of antibiotics.

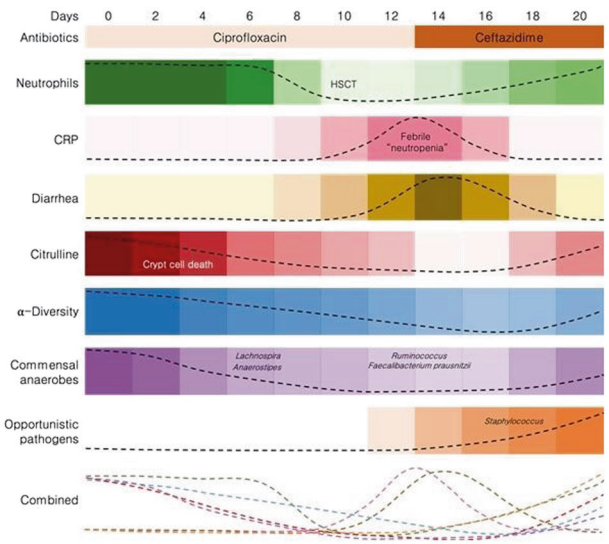
Methods: Data and biospecimens were collected from adult (>18 years) autologous or allogeneic HSCT recipients treated with melphalan or cyclophosphamide-based conditioning regimens. Patients with pre-existing bowel disease, a creatinine level > 150 μmol/L, creatinine clearance < 50 mL/min, using pre- or probiotics or those who could not fulfil the standard infectious protocol, defined as ciprofloxacin prophylaxis and ceftazidime in case of neutropenic fever, were excluded. Faecal and blood samples were collected twice weekly, with the first sample taken before HSCT and prophylactic antibiotics. Plasma citrulline was used as a marker of mucosal injury and 16S Illumina sequencing was performed to assess faecal microbiota composition. Faecal SCFAs were assessed using gas chromatography.

Results: Included were 31 (26 autologous and 5 allogeneic) HSCT recipients, predominantly male (87.1%), with a median age of 57.5 years. GI-M was characterized as decreasing citrulline levels with a nadir on day 11-20 post-HSCT (9.09 ± 3.70 mg/ml P< 0.0001 compared to baseline), which returned to baseline on day≥20.

Dysbiosis was characterized by a loss of Clostridiales-associated taxa, downregulated 15.71% - 25.18% in the early- and mid-mucositis phases, with a significant decrease in 11-20 days post-treatment (median(IQR): D0 = 63.66 (28.41-88.16%); D11-20 = 14.35(5.55-52.38)%). These changes were paralleled by an increase of opportunistic Staphylococcus with 9.44% (adjP=0.0053). Dysbiosis was accompanied by profound losses in acetic acid (P< 0.0001), butyric acid (P< 0.0001), iso-valeric acid (P< 0.0001) and iso-butyric acid (P< 0.0001).

Linear regression analyses demonstrated a significant association between microbial diversity and plasma citrulline levels in an uncontrolled state (R = 0.565, P = 3e-13), as well as when standardized per patient (R = 0.388, P = 1.00e06) and patient + sampling time point (R = 0.388, P = 1.95e-06).

Conclusions: The changes encountered in the gut microbiota occurred early on, i.e. the first two weeks after start of conditioning, with the patients receiving only ciprofloxacin during that period (Figure 1). Since the impact of ciprofloxacin on the gut microbiota is negligible, this underlines a direct causative role of GI-M in gut dysbiosis post HSCT. This in contrast to studies that only focus on antimicrobials driving dysbiosis in HSCT. In order to preserve a healthy gut microbiota in HSCT interventions should acknowledge the role of GI-M, as excluding all antibiotics will not prevent dysbiosis and can result in increased gram-negative bloodstream infections.



[Figure 1]

Disclosure: Nothing to declare

Non-infectious late effects, quality of life and fertility

O142.

Allogeneic Stem-Cell Transplantation in AML and MDS Using Conditioning Regimens with Different Dose-Intensities; 15 Years Later

Avichai Shimoni, Noga Shem-Tov, Ivetta Danylesko, Ronit Yerushalmi, Arnon Nagler

Chaim Sheba Medical Center, Tel-Hashomer, Israel

Background: Allogeneic stem-cell transplantation (SCT) with both myeloablative (MAC) and reduced-intensity conditioning (RIC) is effective therapy in AML and MDS. There is paucity of data on long-term outcome (beyond 10 years) following RIC due to the relative recent introduction of this approach. We previously reported on the role of dose intensity in a group of 112 patients with AML/MDS given SCT with different regimens during 1999-2004 (*Leukemia* 2005). Overall-survival (OS) was similar with MAC and RIC in patients given SCT in remission, but was inferior in patients given RIC in active disease due to high post-SCT relapse rates.

Methods: We have now updated SCT outcomes in the same cohort with median follow up of 16 years (range, 15-19) in order to better predict long-term outcomes.

Results: Results. Eighty-five patients had AML and 17 had MDS. Fifty-eight had active disease at SCT (>10% marrow blasts). The donor was HLA-matched sibling (n = 64) or matched-unrelated (n = 48). Forty-five patients met eligibility criteria for standard MAC and were given intravenous-busulfan (ivBu, 12.8 mg/kg) and cyclophosphamide (BuCy). Sixty-seven patients were given RIC with fludarabine and ivBu (6.4 mg/kg, FB2, n=41) or reduced-toxicity conditioning (RTC) with fludarabine and myeloablative doses of ivBu (12.8 mg/kg, FB4, n=26). The median age of RIC, RTC and MAC recipients was 57, 51 and 42 years, respectively (p = 0.001). In all, 31 patients are alive and 81 have died, 49 relapse, 32 non-relapse mortality (NRM). Active disease at SCT and poor-risk cytogenetics were the most significant factors predicting reduced OS in multivariable analysis, HR 2.8 (p = 0.0002) and 2.2 (p = 0.004), respectively. There was a trend for better 15-year OS with BuCy (p = 0.06). Relapse rates were higher after RIC/RTC than MAC throughout the follow-up period. The rate was 49%, 50 and 27%, 5 year after SCT and 54%, 50% and 31% after 15 years (p = 0.16), respectively. NRM rates were higher after MAC in the initial 5 years after SCT but approached each other in the late post-SCT course. NRM rate was 12%, 23% and 22% (p = 0.18), 5 year after SCT and 24%, 31% and 29% after 15 years (p = 0.77), respectively. Thus, OS was similar within the first 5 years after SCT, 39% 31% and 49% respectively (p = 0.86), but there was a trend for better OS after MAC later on, 19%, 22% and 40%, 15 years after SCT, respectively (p = 0.19). Forty-five patients were alive 5 years after SCT, 14 died later on, 3 of relapse and 11 NRM (6 second malignancies, 4 lung/ heart disease, 1 chronic GVHD). The expected OS for the next 10 years was 60%, 63% and 82%, respectively (p = 0.20).

Conclusions: With long-term follow-up of >15 years, RIC/RTC is an acceptable alternative to MAC in ineligible patients. NRM is lower after RIC/RTC in the early post SCT period, but late NRM negates this early advantage. Relapse rates are higher after RIC/RTC throughout the course. Due to these observations, it seems there is an advantage of MAC that may become apparent 10 years after SCT.

Disclosure: Nothing to disclose.

O143.

Employment Status and Return to Work After Allogeneic Hematopoietic Cell Transplantation: Results from a Nationwide Survey

Saiko Kurosawa[1,2], Takuhiro Yamaguchi[3], Ayako Mori[2], Tomoko Matsuura[2], Takehiko Mori[4], Heiwa Kanamori[5], Tadakazu Kondo[6], Shuko Sakamoto[7], Nobuharu Fujii[8], Tatsuo Ichinohe[9], Miho Nara[10], Tomoya Maeda[11], Shin Fujisawa[12], Yuichiro Nawa[13], Yukinori Nakamura[14], Hitoshi Minamiguchi[15], Yasushi Onishi[16], Kuniko Takano[17], Miyako Takahashi[18], Takahiro Fukuda[2]

[1]Ina Central Hospital, Nagano, Japan, [2]National Cancer Center Hospital, Tokyo, Japan, [3]Tohoku University, Sendai, Japan, [4]Keio University, Tokyo, Japan, [5]Kanagawa Cancer Center, Yokohama, Japan, [6]Kyoto University, Kyoto, Japan, [7]Aomori Prefectural Central Hospital, Aomori, Japan, [8]Okayama University Hospital, Okayama, Japan, [9]Hiroshima University Hospital, Hiroshima, Japan, [10]Akita University Hospital, Akita, Japan, [11]Saitama Medical University International Medical Center, Saitama, Japan, [12]Yokohama City University Medical Center, Yokohama, Japan, [13]Ehime Prefectural Central Hospital, Matsuyama, Japan, [14]Yamaguchi University, Yamaguchi, Japan, [15]Shiga University of Medical Science, Otsu, Japan, [16]Tohoku University Hospital, Sendai, Japan, [17]Oita University Hospital, Oita, Japan, [18]National Cancer Center, Tokyo, Japan

Background: Employment and return to work (RTW) are important outcomes for long-term survivors after allogeneic hematopoietic cell transplantation (allo-HCT). To examine the employment and RTW status and their influencing factors in allo-HCT recipients, we conducted a cross-sectional questionnaire study.

Methods: Patients were eligible if they (1) were at work at the time of diagnosis, (2) were aged 20-64 years at survey, and (3) survived ≥2 years without relapse. Questionnaire included patient- and transplant-related factors, characteristics of work at diagnosis (employment pattern, job contents, number of employees, occupational health staff, etc.), characteristics of HCT centers (area, long-term follow-up clinic, etc.), and issues related to resignation (termination of employment) and RTW after allo-HCT. All subjects provided informed consent in accordance with the Declaration of Helsinki.

Results: From November 2017 to December 2018, 1,904 patients were recruited at outpatient clinics of 72 participating centers. Response rate was 60% (n = 1,150), and 1,048 eligible participants were included in the analysis. Males accounted for 61%, the median age was 43 at allo-HCT (range, 19-62) and 50 at survey (22-64), and the median time after allo-HCT was 5 years (2-30). At the time of diagnosis, 72% of participants were regularly employed, 14% non-regular, and 13% were self-employed or freelance. As for job contents categorized by indoor/outdoor and light/physical work, 45% had indoor/light duty, 31% indoor/physical work, 12% outdoor/light, and 11% outdoor/physical. At diagnosis, 27% of participants had occupational health staff. After allo-HCT, 38% experienced hospital readmission, and 25% was taking immunosuppressant at

survey. From the time of diagnosis to survey, 41% participants experienced resignation, and the most frequent timing of the first resignation was "after HCT" (46%), followed by "before the 1st treatment after diagnosis" (27%). Multivariate analysis for resignation showed that female gender, older age (60s at HCT vs 30s), non-regular employment (vs regular), and indoor/physical work (vs indoor/light duty) were significantly associated with a higher risk of resignation. We also found that self-employed/freelance (vs regular), having occupational health staff, and 10 years or longer of employment were associated with a lower risk of resignation. The incidences of RTW with some accommodations such as flexible schedule and reduced work hour were 58%, 77%, and 87%, respectively, at 1, 2, and 5 years after allo-HCT, while those of RTW without accommodations were 41%, 59%, and 70%. Among 896 participants who returned to work after allo-HCT, 30% experienced leave of work after RTW, mostly because of physical issues.

Conclusions: In a nationwide patient-reported outcome questionnaire study, we found that 41% of 1,048 allo-HCT survivors experienced resignation throughout the course of treatment, and the most frequent timing of the first resignation was after allo-HCT. Up to 87% of survivors finally returned to work after allo-HCT, however, the possibility of RTW without any accommodation was lower, and 30% of those who once returned to work experienced leave of work. Early detection and continuous intervention may be important in survivorship care after allo-HCT, especially for patients with negative predictive factors.

Disclosure: Nothing to declare.

O144.

Functional Outcome Measures in Hematopoietic Stem Cell Transplant (HSCT): Focus on the 2-Minute Walk Test

Erin Sweetser[1,2,3], Daniel Couriel[1,2,3], Catherine Lee[1,2,3], Christopher Barnes[1,2,3], Christopher Noren[1], Kayla Woodring[2,3], Ed Wicklander[2,3]

[1]University of Utah Health, Salt Lake City, UT, United States, [2]Huntsman Cancer Institute, Salt Lake City, UT, United States, [3]University of Utah, Salt Lake City, UT, United States

Background: Hematopoietic stem cell transplantation (HSCT) is a curative strategy for a large number of hematologic and non-hematologic conditions. One of the challenges in understanding outcomes in HSCT is the lack of adequate metrics of success. Our hypothesis is that functional outcome measures of impairment can add important, objective information that may correlate with morbidity, quality of life and survival. The 2MWT is an established predictor of prognosis in multiple clinical scenarios, but has not been tested as a prognostic factor in the pre transplant setting.

Methods: We prospectively evaluated 85 consecutive patients who received an allogeneic transplant between Jan 2018 and July 2019. Of these, 66 underwent the 2MWT, the short performance physical battery (SPPB) and a timed up-and-go (TUG) as part of a comprehensive physical therapy evaluation performed by the same provider in all cases. The 2MWT is a method of self-paced walking ability and functional capacity, and we considered a threshold of 145 meters to demonstrate poor endurance. The SPPB encompasses balance, gait speed, and lower extremity strength, and a score of less than 9 is associated with lower extremity function and increased fall risk. TUG tests the capacity of transfer, walking and turning, and is a measure of fall risk. A value of < 10 seconds is associated with low fall risk.

Results: A total of 19/66 pts (29%) demonstrated poor functional endurance pre-transplant, as shown by a 2MWT score of < 145 meters. Six patients (9%) had poor SPPB (< 9) and TUG (>10s) scores, and 83% ($n = 5$) of these had a 2MWT test of < 145. The majority of surviving patients ($n = 41$, 87%) had a pre-transplant 2MWT >145 meters, and the 1-year overall survival for this group was 86% versus 55% for a 2MWT < or = 145 meters (HR=3.5, $p = 0.02$ 95% CI 1.23-10). In the group with a poor 2MWT, 7/9 (78%) deaths were due to transplant-related causes.

Conclusions: In this single institution experience, the 2MWT correlated with other functional outcome measures like the TUG and SPPB. A 2MWT < 145 meters was associated with a significantly higher mortality, mainly due to transplant related causes. The 2MWT warrants further study in larger series of patients, as it may be an easy, reproducible and objective functional metric with prognostic value.

Disclosure: Daniel Couriel: Seattle Genetics, Incyte, Fresenius

Other Authors: Nothing to declare.

O145.

Fertility in Adult Female Allogeneic Stem Cell Recipients

Markus Ditschkowski, Marie Latos, Rashit Bogdanov, Vesna Klisanin, Michael Koldehoff, Lambros Kordelas, Rudolf Trenschel, Dietrich W. Beelen

University Hospital Essen, Essen, Germany

Background: Information about reproductive potential in female recipients of allogeneic HCT is essential for recovering life balance. Therefore, we aimed to estimate prevalence of reproductive capacity in long-term surviving females by a single center data evaluation. Furthermore, we tried to identify factors potentially contributing to fertility preservation.

Methods: Five hundred fifty-seven female pts in a presumably fertile age of younger than 35 years received allogeneic HSCT between February 1976 and August 2013. In this cohort 194 pts (35%) were identified as long-term survivors applying to the HCT outpatient clinic once a year. In these long-term survivors median age at HCT was 27 years (16-35), median donor age 32 (4-63) and median post-transplant follow-up 202 months (31-481). Seventy-six pts (39%) received grafts from matched unrelated (bone marrow (BM) n=18; peripheral hematopoietic stem cells (PHSC) n=58) and 118 (61%) from matched sibling donors (BM n=77, PHSC n=41). Underlying diseases were acute leukemia ($n = 85$), myeloproliferative diseases ($n = 70$), MDS ($n = 4$), Hodgkin's disease ($n = 1$), lymphoma ($n = 10$), M. Glanzmann ($n = 1$), PNH ($n = 4$), SAA ($n = 19$). Sixty-one pts received conditioning with alkylating agents, 133 with total body irradiation (TBI). Pts were divided into groups 1 (gravidity/ reproductive group) and 2 (non-reproductive group). Out of a random sample of 50 women, 38 (76%) responded to a questionnaire focusing on pre- and post-transplant fertility status and pregnancy.

Results: Cohort data: pregnancy was observed in 18 pts after HCT equivalent to a motherhood prevalence of 9.3%. Median age at HCT was 24 (16-28) years in group 1 and 27 (16-35) in remaining pts (group 2). Three pts experienced repeated pregnancies and one woman had an uncomplicated twin birth. One woman sustained AML-relapse postpartum. Of all group 1 women, 10 initially suffered from non-malignant and 8 from malignant diseases in chronic phases or first complete remission. Twelve group 1 pts were treated with myeloablative and 6 with non-myeloablative conditioning regimen. In group 1, total body irradiation (TBI) using 2 Gy was applied to 1 pt and fractionated 4 × 2,5 Gy were given to 4 pts. Comparison between groups 1 and 2 shows that the proportion of non-malignant diseases was higher in group 1 ($p< 0.001$) and that likewise the frequency of very young pts< 25 years was higher in group 1 ($p< 0.001$). Furthermore, significantly higher numbers of pregnancy were observed after conditioning with Treosulfan compared with other regimen ($p = 0.0065$). Repeated pregnancy exclusively occurred after chemo-conditioning using Treosulfan or Melphalan. The proportion of advanced disease stages was not different between groups ($p = 0.79$). Questionnaire: data from 8 pts of group 1 and 30 pts of group 2 could be included. An unmet motherhood wish was stated by 21% before and 42% after HCT. Median age of post-transplant pregnancy was 30 years, median time 97 months after HCT. In 50% pts reported on unplanned pregnancies. Median time of delivery was the 39th week of gestation. No reference of miscarriages.

Conclusions: Post-transplant pregnancy is possible even after ovotoxic TBI. HCT at younger ages, non-malignant diseases and conditioning with Treosulfan could be shown to have fertility preserving potential.

Disclosure: Nothing to declare.

Paediatric issues

O146.

Prospective Open-Label Phase II Trial of Individualized Anti-Thymocyte Globulin Shows Improved Early CD4+ T-Cell Reconstitution After Pediatric Allogeneic Hematopoietic Cell Transplantation: The Parachute-Trial

Rick Admiraal[1,2], Stefan Nierkens[1,2], Robbert Bredius[3], Marc Bierings[1,2], Ineke van Vliet[4], Marta Lopez Yurda[1], Birgitta Versluijs[1,2], Caroline Lindemans[1,2], Michel Zwaan[1], Jaap Jan Boelens[1,5]

[1]Princess Maxima Center for Pediatric Oncology, Utrecht, Netherlands, [2]University Medical Center Utrecht, Utrecht, Netherlands, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Erasmus MC, Rotterdam, Netherlands, [5]Memorial Sloan Kettering Cancer Center, New York, NY, United States

Background: Rabbit anti-thymocyte globulin (ATG) is used in allogeneic hematopoietic cell transplantation (HCT) to prevent graft-versus-host-disease (GvHD) and graft failure (GF). Its main and unpredictable toxicity includes poor immune reconstitution associated with increased relapse, viral reactivations and subsequently higher mortality. Early (< 100 days) CD4+ T-cell reconstitution has been associated with improved overall survival[1]. Based on pharmacokinetic and pharmacodynamic (PKPD) studies we developed an individualized ATG dosing regimen aiming for optimal CD4+ T-cell recovery while maintaining a strong anti-GvHD effect.

Methods: We performed an open label, phase II historically controlled non-randomized prospective clinical

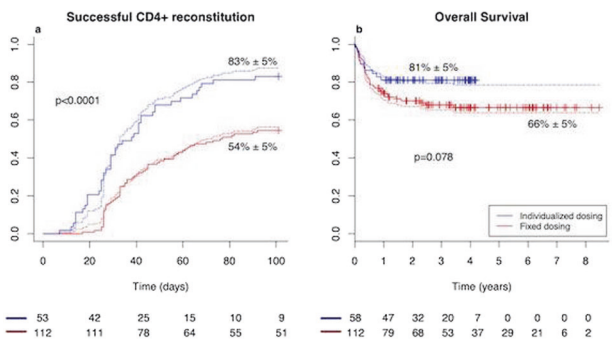
trial investigating individualized versus fixed dosing of ATG (Thymoglobulin). Individualized dosing was based on the results from a previous validated population PKPD model[1,2] with cumulative doses varying between 2 to 10 mg/kg starting based on weight, recipient lymphocyte counts before first dose of ATG and stem cell source, starting day -9. Primary endpoint was successful CD4+ T-cell reconstitution (CD4+ >50/mm^3 at 2 consecutive timepoints within 100 days after HCT[1]) in patients alive without relapse or graft failure <100 days. Secondary endpoints were overall survival, event free survival, GvHD and graft failure. Results were compared to a previously described historical cohort receiving a fixed cumulative ATG dose of 10mg/kg starting day -5[1]. Minimal follow-up was 1 year. Power was based on 20% effect size with α=0.05 and β=0.10. Multivariate Cox proportional hazard and Fine-Gray competing risks were used. The study was registered in the Dutch Trial Registry (NTR4960).

Results: We included 58 patients between 2015-2018, and compared to 112 historical controls (table 1). CD4+ reconstitution was significantly better in the individualized dosing group: 83% versus 54% in the fixed dosing group; HR 2.4 (95% CI 1.6-3.6), p< 0.0001 (Figure 1a). The individualized group showed a trend towards improved survival (81% vs. 66%; HR 0.54 [95% CI 0.27-1.07], p = 0.078; Figure 1b) and event free survival (79% vs 61%: HR 0.52 [95% CI 0.27-1.01], p = 0.052). No differences were seen in grade 3-4 acute GvHD (7% vs.6%; HR 1.44 [95% CI 0.47-4.44], p = 0.53), and graft failure (5% vs 5%; HR 1.61 [95% CI 0.38-6.83], p = 0.52).

Conclusions: Individualized ATG dosing significantly increases the chance of rapid immune reconstitution without affecting the incidence of aGvHD and graft failure. Together, this is an important step towards predictable CD4+ T cell reconstitution and improved survival changes.

References:

1: Admiraal et al, Lancet Haem 2015
2. Admiraal et al, Clin PK 2015



[Successful T-cell immune reconstitution and overall survival]

	Individualized	Fixed	*p*
Number of patients (n)	58	112	
Age at transplant (years)	7.4 (2.8-13.2)	6.5 (2.1-12.4)	0.97
Starting day of ATG (days before HCT)	9 (9-9)	4.2 (4-5)	<0.05
Cumulative dose of ATG (mg/kg)	9 (6-10)	10 (9.8-10.2)	<0.05
Graft source: marrow and peripheral blood	29 (50)	70 (62)	<0.05
Graft source: cordblood	29 (50)	42 (38)	
Diagnosis: malignancy	21 (36)	46 (41)	<0.05
Fully Matched Graft [n(%)]	38 (66)	60 (54)	0.17
Median (IQR) unless otherwise specified			

[Patient Characteristics]

Clinical Trial Registry: Dutch Trial Registry (NTR4960) https://www.trialregister.nl/trial/4836

Disclosure: None.

O147.

EBMT Lessons from 40 Years of High Dose Chemotherapy (HDT) and Stem Cell Transplantation (SCT) In Neuroblastoma. A Report From the Paediatric Working Party

Ruth Ladenstein[1], Ulrike Poetschger[2], Penelope Brock[3], Roberto Luksch[4], Victoria Castel[5], Shifra Ash[6], Vassilios Papadakis[7], Geneviève Laureys[8], Josef Malis[9], Walentyna Balwierz[10], Ellen Ruud[11], Per Kogner[12], Henrik Schroeder[13], Ana Forjaz de Lacerda[14], Maja Beck-Popovic[15], Pavel Bician[16], Miklos Garami[17], Evgenia Glogova[2], Dominique Valteau-Couanet[18], Selim Corbacioglu[19]

[1]St. Anna Children's Hospital and Children's Cancer Research Institute (CCRI), Medical University, Vienna, Austria, [2]Children's Cancer Research Institute (CCRI), Medical University, Vienna, Austria, [3]Great Ormond Street Hospital, London, United Kingdom, [4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [5]Hospital Universitario y Politecnico La Fe, Valencia, Spain, [6]Schneider Children's Medical Center of Israel, Tel Aviv University, Petach Tikvah, Israel, [7]Agia Sofia Children's Hospital, Athens, Greece, [8]University Hospital Ghent, Ghent, Belgium, [9]University Hospital Motol, Prague, Czech Republic, [10]Jagiellonian University Medical College, Krakow, Poland, [11]Rikshospitalet, Oslo, Norway, [12]Karolinska University Hospital, Stockholm, Sweden, [13]University

Hospital of Aarhus, Aarhus, Denmark, [14]*Portuguese Institute of Oncology, Lisboa, Portugal*, [15]*University Hospital Lausanne, Lausanne, Switzerland*, [16]*Clinic of Pediatric Oncology and Hematology, University Children's Hospital, Banska Bystrica, Slovakia*, [17]*Semmelweis University of Budapest, Budapest, Hungary*, [18]*Institut Gustave Roussy, Villejuif, France*, [19]*University Hospital Regensburg, Regensburg, Germany*

Background: Evaluation of EBMT registry data in Neuroblastoma to explore trends in indication and outcomes over 40 years.

Methods: Since 1980, 9165 patients (pts) < 18 years with Neuroblastoma, 5319 (58%) males, have been registered in the EBMT data base from 236 European centers in 42 countries with only 406 (4%) allogeneic SCTs in total. HDT indications were primary metastatic or high-risk local disease in 7685 patients (pts) with a median age at SCT of 3.7 (0.01-8), and relapse in 753pts, median age 5.7(1.2-18). Busulfan based combinations (BU) were used in 3733pts (57%), Treosulfan containing regimens (TREO) in 191pts (3%), total body irradiation (TBI) based regimens in 581pts (9%) whilst 2042pts had other various combinations (31%). The time from SCT until December 2019 is 12.7 years and the median observation time from SCT to the last follow up evaluation is 5.5 years.

Results: The 5-yrs. overall survival (OS) is 42% and the 5-yrs. Event Free Survival (EFS) is 35%. The OS in 1243pts between 2 and 18 years of age is 39% and 64% for 7883pts below 2 years. EFS (OS) after autologous SCT in 8720 pts was 36% (43%) and a 100-day TRM 3%. 2801 autologous SCT were given before 2000 with an EFS (OS) of 32% (37%) and a 100-day TRM of 5%. For 5919pts with autologous SCT 2000 or later the EFS (OS) is 39% (47%) and the 100-day TRM is 2%.

The EFS (OS) during primary treatment is 37% (44%) and 22% (27%) after relapse.

The EFS (OS) rates are related to the status at HDT with 44% (49%) for first complete remission (CR1:2763pts), 35% (42%) for very good /partial remission (VGPR /PR: 3869pts), 24% (35%) for stable disease (SD:321pts), 11% (20%) for primary refractory disease (PRD: 226pts), 32% (41%) for relapsed patients in CR2 (318pts), 22% (24%) if sensitive (SR: 56pts) and 14% (16%) if untreated, stable or resistant (RU, SDR, RR: 359 pts). A repetitive HDT approach was given to 1170pts with an OS of 39% compared to 45% for 6233 pts with single HDT ($p = 0.001$). In pts with single HDT after the year 2000, EFS (OS) after BU, TREO, TBI and other conditioning regimens was 42 (52%), 34 (44%), 39% (51%) and 35% (42%). Cox regression analysis showed that age, the status at HDT and the year of transplant and conditioning regimen had a significant impact on EFS. Busufan based HDT is still superior. 406 pts received allogeneic SCT: the latter compared to autologous SCT as significantly worse with OS (EFS) of 16% (19%) versus 36% (43%), respectively.

Conclusions: Important favorable prognostic factors of neuroblastoma like very young age and response prior HDT are still highly prognostic and in line with prospective trials. Others like double transplants need cautious interpretation as mostly applied after multiple lines of conventional treatments or at relapse in the EBMT data base. Hence more recently reported superiority in the front line setting is not visible yet. The role of immunotherapy post HDT cannot be studied within the EBMT data base.

Disclosure: No conflict of interest.

O148.

Incidence of Secondary Malignancies After TBI/VP16 Conditioning for Childhood All - Results of the Prospective ALL-SCT-BFM-2003 Trial

Anna Eichinger[1], Evgenia Glogova[2], Rita Beier[3], Tayfun Güngör[4], Daniel Stachel[5], Peter Lang[6], Martin Sauer[7], Brigitte Strahm[8], Ansgar Schulz[9], Bernd Gruhn[10], Angela Wawer[11], Hedwig Deubzer[12], Selim Corbacioglu[13], Ingo Müller[14], Christina Peters[2], Michael Albert[1]

[1]Dr. von Hauner University Children's Hospital, Ludwig-Maximilians-Universität, Munich, Germany, *[2]St. Anna Children's Cancer Research Institute, Vienna, Austria*, *[3]University Duisburg-Essen, Essen, Germany*, *[4]University Children's Hospital, Zurich, Switzerland*, *[5]Children's Hospital, Universitätsklinikum Erlangen, Erlangen, Germany*, *[6]University Children's Hospital, Tübingen, Germany*, *[7]Medizinische Hochschule Hannover, Hannover, Germany*, *[8]University of Freiburg, Freiburg, Germany*, *[9]University Medical Center Ulm, Ulm, Germany*, *[10]Jena University Hospital, Jena, Germany*, *[11]Technische Universität München, Munich, Germany*, *[12]Charité Universitätsmedizin, Berlin, Germany*, *[13]University of Regensburg, Regensburg, Germany*, *[14]University of Hamburg, Hamburg, Germany*

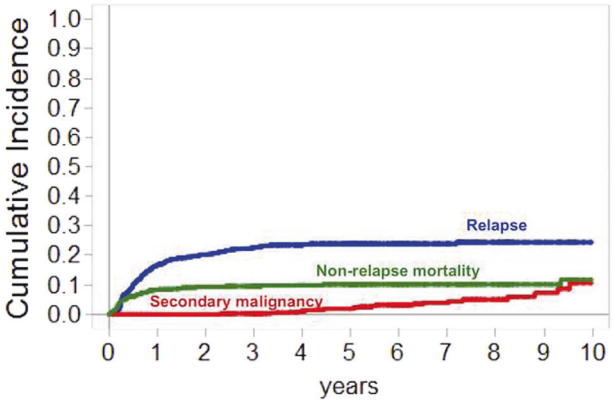
Background: Outcome of childhood ALL patients after allogeneic HSCT has substantially improved over the past decades, emphasizing the importance of morbidity and mortality of late sequelae such as secondary malignancies.

Methods: In the prospective multicenter ALL-SCT-BFM-2003 trial and its subsequent extension registry 705

patients <18 years with high-risk ALL in remission received allogeneic HSCT following either 12 Gy TBI/VP16 (≥2 years; 84% of patients) or Bu/Cy/VP16 (<2 years; 16%) conditioning from 2003 to 2015. We analyzed the incidence, outcome and risk factors for secondary malignancies in this cohort.

Results: After a median follow-up of 5.3 years (0.01-15.4) the probability of overall survival for the entire cohort was 0.70 ± 0.02 and 0.64 ± 0.03 at 5 and 10 years respectively. Event-free survival (death, relapse, secondary malignancy as events) was 0.64 ± 0.02 and 0.53 ± 0.04 respectively. Thirty-three secondary malignancies were reported in 29 patients (4%). These malignancies occurred at a median of 5.3 years (1.7-13.4) after HSCT and were reported as thyroid cancer ($n = 12$), MDS (4), osteosarcoma (3), glioblastoma (3), colon carcinoma (2), basal cell carcinoma (2), breast cancer (2), squamous cell carcinoma (2), Ewing sarcoma, parotid carcinoma and rhabdomyosarcoma (1 each). One patient was diagnosed with a cancer predisposition syndrome. Of these 29 patients, 20 (69%) are alive at a median follow-up of 4.6 years (0.0-6.79) after diagnosis of their first secondary malignancy. The 5-, 8- and 10- year cumulative incidences of a secondary malignancy in this cohort (with relapse and death as competing events) were 0.02 ± 0.01, 0.05 ± 0.01 and 0.11 ± 0.03 respectively (figure 1). In univariate and multivariate analyses, neither age at HSCT, donor type, acute GVHD °III/IV, chronic GVHD, CMV status or type of conditioning constituted a significant risk factor for the development of a secondary malignancy. Age below 10 years, female donors in male recipients and the use of TBI were associated with hazard ratios >2 but were not significant risk factors at p-values of 0.052, 0.053 and 0.216 respectively. However, secondary malignancies occurred exclusively in patients who had received TBI/VP16 conditioning.

Conclusions: These long-term follow-up data from a prospective multicenter study reveal a worrisome and increasing incidence of secondary malignancies after allogeneic HSCT in children with ALL who received TBI/VP16 conditioning. Longer follow-up of cohorts like these are pivotal to better assess incidence of secondary malignancies, additional risk factors and long-term outcome. This is especially relevant as TBI/VP16 conditioning results in superior short-term EFS compared to chemotherapy conditioning in children with ALL. It is crucial to identify patients with cancer predisposition and to design safer conditioning regimens especially for younger children. Life-long, thorough follow-up and heightened awareness is obligatory in children after TBI conditioning.



[Figure 1: Cumulative incidences of relapse, non-relapse mortality and first secondary malignancy.]

Clinical Trial Registry: Clinical Trial registry number NCT01423747.
https://clinicaltrials.gov/ct2/show/NCT01423747

Disclosure: CP received study support and travel grants from Amgen, Medac, Neovii, Sanofi. MA received travel support from Neovii, Medac. AE, EG, RB, DS, PL, MS, BS, HD, IM, BG, AS, AW, TG, SC report no conflict of interest related to this work.

MA and CP contributed equally.

O149.

Outcome and Risk Factors of Autoimmune Cytopenia After Hematopoietic Cell Transplantation for Children with Primary Immunodeficiency

Su Han Lum[1], Sabeena Selvarajah[1], Angela Deya-Martinez[1], Peter McNaughton[1], Ali Sobh[1], Sheila Waugh[1], Shirelle Burton-Fanning[1], Liz Newton[1], Julie Gandy[1], Zohreh Nademi[1], Stephen Owens[1], Eleri Willliams[1], Marieke Emonts[1,2], Terry Flood[1], Andrew Cant[1], Mario Abinun[1,2], Sophie Hambleton[1,2], Andrew Gennery[1,2], Mary Slatter[1,2]

[1]Great North Children's Hospital, Newcastle upon Tyne, United Kingdom, [2]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom

Background: Studies focusing on post-HCT AIC in large cohorts of patients transplanted for primary immunodeficiency (PID) are lacking. We conducted a retrospective analysis of incidence, risk factors, outcome of post-HCT AIC in children with PID and B-lymphocyte function following rituximab treatment.

Methods: Between January 1987-December 2018, 502 PID patients who underwent first allogeneic HCT for PID at our centre were included in the study. Cumulative incidence (CI) of post-HCT AIC was calculated using a competing risk analysis, considering death as a competing event. Fine-and-Gray test was used to identify risk factors of AIC; selected variables were: gender, age at transplant, indication for HCT (SCID versus non-SCID), pre-HCT AIC, donor type (MFD versus MUD versus MMFD/MMUD versus HID), donor-recipient ABO matching (ABO compatible versus major versus minor versus bidirectional mismatched), stem cell source (marrow versus PB versus CB), ex-vivo T-cell depletion (TCD), stem cell doses, conditioning regimen (none versus MAC versus RTC versus RIC), serotherapy (none versus alemtuzumab versus ATG), graft-versus-host disease (GvHD) prophylaxis, acute GvHD, chronic GvHD and viraemia. B-lymphocyte immune reconstitution kinetics were compared between surviving patients with post-HCT AIC without rituximab ($n = 18$), post-HCT treated with rituximab ($n = 12$) and controls ($n = 24$).

Results: Thirty-six (5-year CI, 9%) developed post-HCT AIC, median onset at 6.5 months (range, 2.5 months - 18.2 years). On univariate analysis, pre-HCT AIC, mismatched donor, alemtuzumab, ATG, acute GvHD and chronic GvHD were significantly associated with post-HCT AIC. After multivariate analysis, alemtuzumab (SHR 9.0, 95% CI, 1.50-54.0, p=0.02) was independently associated with post-HCT AIC. Corticosteroid and high-dose IVIg (2gm/kg) achieved remission in 50% ($n = 18$), additional rituximab led to remission in 25% ($n = 9$), and the remaining 25% were treated with various modalities including sirolimus ($n = 5$), bortezomib ($n = 3$), mycophenolate mofetil ($n = 2$), splenectomy ($n = 2$), and second HCT ($n = 3$). The mortality of post-HCT AIC reduced from 25% (4/16) prior to 2011 to 5% (1/20) after 2011. The median follow-up of 5.8 years (range, 0.4-29.1) showed that 26 of 30 survivors (87%) were in complete remission, 4 (13%) were in remission with sirolimus and low dose steroid. Of 12 survivors treated with rituximab, immunoglobulin substitution was discontinued in 7 (52%), and 5 (48%, median follow-up 10.5 years) required on-going IVIg replacement. The median interval between HCT and rituximab was 1.95 years (range, 0.96-19.9) in patients who were IVIg dependent and 0.73 (range, 0.30-2.3) in patients who were IVIg-free on last follow-up (p=0.17). B-lymphocyte immune reconstitution kinetics were significantly slower in patients with post-AIC receiving rituximab.

Conclusions: 5-year CI of post-HCT AIC in children with PID was 9% and there is risk of very late onset post-HCT AIC in patients with Artemis and RAG1 mutations, and activated PI3 delta syndrome. The change of treatment strategy has reduced the mortality in affected patients in our cohort. An alemtuzumab pharmacokinetic study might play a role in reducing the incidence of post-HCT AIC. Sirolimus is an effective steroid-sparing immunomodulator in patients with refractory and frequently relapsing post-HCT AIC.

Disclosure: Nothing to declare.

O150.

EBMT Survey on 40 Years of High-Dose Chemotherapy (HDT) and Stem Cell Transplantation (SCT) in Ewing Tumours (ET). A Report from the Paediatric Working Party

Ruth Ladenstein[1], Evgenia Glogova[2], Christelle Dufour[3], Edoardo Lanino[4], Jean Michon[5], Paul Veys[6], Roberto Luksch[7], Uta Dirksen[8], Krzysztof Kalwak[9], Stefan Burdach[10], Henk van den Berg[11], Boris Afanasyev[12], Franco Locatelli[13], Emmanuelle Nicolas-Virelizier[14], Shifra Ash[15], Nathalie Gaspar[16], Jeremy Whelan[17], Philippe Brault[18], Ulrike Poetschger[19], Selim Corbacioglu[20]

[1]St. Anna Children's Hospital and Children's Cancer Research Institute (CCRI), Medical University, Vienna, Austria, [2]Children's Cancer Research Institute (CCRI), Medical University, Vienna, Austria, [3]Institut Gustave Roussy, Paris, France, [4]Institute G. Gaslini, Genova, Italy, [5]Institut Curie, Paris, France, [6]UCL Great Ormond Street Institute of Child Health, London, United Kingdom, [7]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [8]University Hospital Essen, Essen, Germany, [9]Wroclaw Medical University, Wroclaw, Poland, [10]Children's Hospital Munich Schwabing, Munich, Germany, [11]Emma Children's Hospital, AMC, Amsterdam, Netherlands, [12]First State Pavlov Medical University of St. Petersburg, St. Petersburg,, Russian Federation, [13]IRRCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, [14]Centre Leon Berard, Lyon, France, [15]Schneider Children's Medical Center of Israel, Tel Aviv University, Petach, Tikvah, Israel, [16]Gustave Roussy, Villejuif, France, [17]UCL Hospitals NHS Foundation Trust, London, United Kingdom, [18]Institut Curie Hospital, Paris, France, [19]Children's Cancer Research Institute (CCRI), Medical University, Vienna, Austria, [20]University Hospital Regensburg, Regensburg, Germany

Background: Evaluation of EBMT registry data of Ewing Tumors <18 years to explore trends in indication and outcomes over 40 years.

Methods: Since 1980, 2890 patients (pts) <18 years (yrs) with Ewing tumours, 1650 males (57%), have been registered in the EBMT data base from 234 European centres in 39 countries with only 87 (3%) allogeneic SCTs of the total. MAT indications were primary metastatic disease or high-risk local disease (tumour size and/or poor response) in 2036 (70%) pts and relapse in 486 (19%) pts.

The median age is 14 yrs (range, 1 to 18). Peripheral blood stem cells were used in 2442 pts (86%). Busulfan based combinations were used in 1306 pts (63%), Treosulfan containing regimens in 289 pts (14%), Total body irradiation (TBI) in 82 pts (4%), whilst 408 pts had various other combinations (20%). The median survival time is 4.5 yrs after allogeneic and 5.7 yrs after autologous SCTs.

Results: The 5-year Event Free (Overall) Survival (EFS/OS) was 41% (47%) in 2803 pts with autologous SCT, 44% (51%) during primary treatment and 29% (34) after relapse, and 19% (22%) for 87 allogeneic SCT ($p< 0.001$). In the total cohort a steady improvement in EFS is observed: ≤1990 21%, 1990 to ≤2000 36%, and >2000 43% ($p< 0.001$). EFS according to age show 47% for ≤5 yrs, 45% for >5 to ≤10 yrs, and 38% for >10 yrs ($p< 0.001$). In the autologous SCT group the EFS of localized disease is 36% and 33% for metastatic pts. The remission status prior HDT/SCT has a major impact in this group: EFS in first complete remission (CR1: 967 pts) is 57%, in partial remission (PR: 885 pts) 36%, but only 16% in 139 pts with stable or primary refractory disease (SD/PRD) ($p< 0.001$). In relapse pts with a second CR (CR2: 256 pts)) prior to HDT still had a 42% EFS, whilst pts with residual disease (211 pts) do significantly worse with <20% ($p< 0.001$). A single autologous HDT/SCT procedure (1871 pts) results in 42% 5-yr EFS whereas repetitive regimes, likely to reflect less favourable pts (394 pts), in 35% ($p< 0.001$). In primary treatments TBI regimens are worse with EFS of 37%, whilst non TBI regimens result in 46% with autologous HDT/SCTs ($p< 0.018$). In pts with single HDT after the year 2000, EFS after BU, TREO, TBI and other conditioning regimens was 51%, 19%, 54% and 30%. In these patients, a Cox proportional hazards regression model identifies age, response status, and MGT regimens as independent risk factors.

Conclusions: This EBMT Ewing data set holds important information for decision making processes and suggests exploring in more depth the results and roles of Busulfan versus Treosulfan in front line trials.

Clinical Trial Registry: NCT00987636.

Disclosure: Nothing to declare.

O151.

Allogeneic Hematopoietic Stem Cell Transplantation for BCR/ABL1-Negative Myeloproliferative Neoplasms in Children - Retrospective Report on Behalf of I-BFM SCT Committee and EBMT Pediatric Diseases WP

Jacek Wachowiak[1], Jacques-Emmanuel Galimard[2], Arnaud Dalissier[2], Abdelghani Tbakhi[3], Amal Al-Seraihy[4], Miguel Angel Diaz[5], Gerard Socie[6], Petr Sedlacek[7], Miguel Abboud[8], Dietrich Beelen[9], Ivana Bodova[10], Claire Freycon[11], Jean-Hugues Dalle[12], Alina Ferster[13], Bernd Gruhn[14], Rose-Marie Hamladji[15], Marianne Ifversen[16], Charlotte Jubert[17], Gergely Krivan[18], Alphan Kupesiz[19], Franco Locatelli[20], Katharine Patrick[21], Stephen Robinson[22], Polina Stepensky[23], Ali Unal[24], Paul Veys[25], Robert Wynn[26], Adriana Balduzzi[27], Selim Corbacioglu[28]

[1]Poznan University of Medical Sciences, Poland, Poland, [2]EBMT Paris Study Office, Saint Antoine Hospital, INSERM UMR 938, Sorbonne University, Paris, France, [3]King Hussein Cancer Center, Amman, Jordan, [4]King Faisal Specialist Hospital and Research Center, Riyadh, Riyadh, Saudi Arabia, [5]Hospital Niño Jesús, Madrid, Spain, [6]Saint Louis Hospital, Paris, France, [7]Hospital Motol Charles University, Prague, Czech Republic, [8]American University of Beirut, Beirut, Lebanon, [9]University of Essen, Essen, Germany, [10]University Children's Hospital, Bratislava, Slovakia, [11]Grenoble University Hospital, Grenoble, France, [12]Robert Debré Hospital Université de Paris, Paris, France, [13]Hôpital and Universitaire des Enfants Reine Fabiola, Brussels, Belgium, [14]Jena University Hospital, Jena, Germany, [15]Centre Pierre et Marie Curie, Alger, Algeria, [16]Copenhagen University Hospital, Copenhagen, Denmark, [17]CHU de Bordeaux, Bordeaux, France, [18]United St. Istvan and St. László Hospital, Budapest, Hungary, [19]Akdeniz University, Antalya, Turkey, [20]IRCCS Bambino Gesù Children's Hospital, Rome, Italy, [21]Sheffield Children's Hospital, Sheffield, United Kingdom, [22]University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom, [23]Hadassah Hebrew University Medical Centre, Jerusalem, Israel, [24]Erciyes University, Kayseri, Turkey, [25]Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom, [26]Royal Manchester Children's Hospital, Manchester, United Kingdom, [27]Ospedale San Gerardo, Monza, Italy, [28]University Hospital of Regensburg, Regensburg, Germany

Background: Classical BCR/ABL1-neg myeloproliferative neoplasms (BCR/ABL1-neg MPN) (polycythemia vera, PV; essential thrombocythemia, ET; primary myelofibrosis, PMF) are rare hematological malignancies in children, however when PMF or post-ET/PV-myelofibrosis occurs allo-HSCT remains the only one curative treatment approach. So far, no study analyzed outcomes of allo-HSCT in a larger group of children with BCR/ABL1-neg MPN.

Methods: This retrospective registry-based analysis was performed in 42 children (0.4-18 years, median 7.6; male-64.3%, female, 35.7%) with *BCR/ABL1*-neg MPN (PMF, n=35; ET, n=4; PV, n=2; post-ET-myelofibrosis, n=1) transplanted from MSD ($n = 24$, 57%), UD ($n = 10$, 24%), other related donor ($n = 5$, 12%) or unrelated cord blood ($n = 3$, 7%) and reported to EBMT Registry between 2000 - 2018. Conditioning was chemotherapy-based in 40 (95%) patients, whilst FTBI-based was used in 2 (5%). Twenty

one (50%) patients received hematopoietic stem cells (HSC) from bone marrow, 18 (43%) from peripheral blood, and 3 (7%) from cord blood. Outcome measures were as follows: cumulative incidence (CI) of granulocytes recovery (≥0.5x10^9/L), CI of acute GvHD (aGvHD) and chronic GvHD (cGvHD), CI of non-relapse mortality (NRM), relapse incidence (RI), probability of overall survival (OS), and progression-free survival (PFS). Cumulative incidences and survival probabilities are presented with their 95% confidence interval. At time of analysis the median follow-up was 5 years (IC: 2.1-6.6 years).

Results: The day +60 CI of granulocytes recovery was 88.1% (72.3-95.2). The day +100 CI of aGvHD II-IV was 42.6% (27.0-57.4), while III-IV 10% (3.1-21.7). The 4-year CI of cGvHD was 21.4% (7.4-40.1), including extensive cGvHD 10.1% (2.5-24.1). The 4-year CI of NRM was 27.1% (13.7-42.4), and RI 18.8% (8.0-33.0). For the whole study group the estimated 2- and 4-year PFS was 54.1% (39.9%-73.4%), while 2-year and 4-year probability of OS was 62.3% (45.0-76.0) and 54.9% (39.9-73.4), respectively. In univariate analysis, children transplanted from MSD in comparisons with those transplanted from other donors presented lower 100 days incidence of aGvHD II-IV (27.6% vs 61.1%, $p = 0.02$) and lower 2-year NRM (9.4% vs 53.8%, $p = 0.004$) as well as higher probability of 2-year PFS (68.0% vs 32.5%, $p = 0.04$) and a nearly significant 2-year OS (76.6% vs 40.0%, $p = 0.0506$). In addition, 2-year NRM was significantly lower (5% vs 48.4%, $p = 0.005$) and 2-year OS significantly higher (83.8% vs 41%, $p = 0.04$) in children receiving bone marrow compared with those grafted with HSC from other sources.

Conclusions: Primary myelofibrosis is a major indication for allo-HSCT among classical BCR/ABL1-neg MPN in children. Allo-HSCT in children with classical BCR/ABL1-neg MPN is feasible. The outcome after transplantation from MSD is satisfactory, whereas results of transplantation from alternative donors are poor, mainly due to unacceptably high NRM and low PFS. Thus, there is an urgent need for a prospective studies to improve safety and anti-leukemic efficacy of allo-HSCT from alternative donors in children with classical BCR/ABL1-neg MPN along with redefinition of indications for allo-HSCT based on molecular risk factors specific for these neoplasms and their eligibility to novel targeted treatment approaches.

Disclosure: Nothing to declare.

O152.

Transplant-Associated Thrombotic Microangiopathy: Assessing, Containing, and Extinguishing the Firestorm

Sonata Jodele[1,2], Christopher E. Dandoy[1,2], Adam Lane[1,2], Ashley Teusink-Cross[1,2], Kasiani C. Myers[1,2], Gregory Wallace[1,2], Adam Nelson[1,2], Nicholas J. Gloude[1,2], Stella M. Davies[1,2]

[1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States, [2]University of Cincinnati, Cincinnati, OH, United States

Background: Transplant associated thrombotic microangiopathy (TA-TMA) is a significant cause of transplant morbidity and mortality with high incidence in pediatric HSCT recipients. Overactivated complement measured as elevated sC5b-9 in blood along with nephrotic range proteinuria are high-risk features of TA-TMA. Our previous prospective observational study showed dismal survival of 16.7% at 1 y post-transplant in untreated subject with TA-TMA who presented with both high risk features. Following this study, we changed our clinical practices to offer complement blocking therapy to all subjects with high risk TA-TMA.

Methods: We summarized clinical outcomes of HSCT recipients diagnosed with TA-TMA (2012-2018) by performing retrospective review. All patients at our institution are prospectively monitored for TA-TMA as standard of care and classified into risk groups: high risk (have both high-risk features-elevated sC5b-9 and nephrotic range proteinuria), moderate risk (have one high risk feature), low risk (have no high risk features).

Results: Total of 130 pediatric patients were diagnosed with TA-TMA: 64 were classified as high risk, 48 as moderate risk and 18 as low risk TA-TMA. HSCT recipients with high risk TA-TMA were treated with the terminal complement blocker eculizumab as first line therapy. Moderate and low risk patients did not receive any TA-TMA targeted therapy.

We demonstrated 1y post-HSCT survival of 66% in eculizumab treated patients with high risk TA-TMA. Responding patients benefited from a brief but intensive eculizumab therapy course using pharmacokinetically guided dosing, requiring a median of 11 doses of eculizumab (IQR 7-20). Eculizumab therapy was well tolerated and without increase in the incidence of blood stream infections. Therapy was discontinued due to resolution of TA-TMA at a median of 66 days (IQR 41-110). Subjects with higher complement activation measured by elevated blood sC5b-9 at the start of therapy were less likely to respond to treatment (OR =0.15, p-value 0.0014), and required more doses of eculizumab [r = 0.43, p-value = 0.0004]. Patients with intestinal bleeding had the fastest eculizumab clearance, required the highest number of eculizumab doses (20 vs 9, $p = 0.0015$), and had lower 1y survival (44% vs 78%, $p = 0.01$).

1y post-transplant survival for subjects with moderate TA-TMA (untreated) was similar to those with high risk

TA-TMA receiving eculizumab therapy (71% vs 66%, $p = 0.4$). Elevated sC5b-9 was associated with reduced survival to a greater degree than proteinuria in moderate risk TA-TMA. Patients with mild TA-TMA (untreated) had 94% survival.

Conclusions: Complement blockade with eculizumab is an effective therapeutic strategy for high risk TA-TMA, but some patients with severe disease still lack a complete response, prompting us to search for additional targetable endothelial injury pathways. Moderate risk patients who present with complement system activation may also benefit from TA-TMA therapy as their outcomes are likely to be further improved by early targeted interventions, and this will be tested in future cases.

Disclosure: COI related to this work - SJ and SMD have US pending patent application under review

COI disclosures outside this work: SJ and SMD have NIH funded study with the study drug provided by Alexion pharmaceuticals, SJ received travel support from Omeros and consultancy fees from Omeros, Arcus Medica and Magnolia Innovations. SMD has consultancy fees from Novartis and travel and research support from Prolacta. Other authors have no disclosures.

O153.

Is the EBMT Risk Score Predictive of Outcomes in Paediatric Acute Leukemia?

Fanette Bernard[1], Jacques-Emmanuel Galimard[2], Arnaud Dalissier[2], Amal El-Seraihy[3], Jean-Hugues Dalle[4], Chakradhara Rao S. Uppugunduri[5], Boris Afanasyev[6], Frederic Baleydier[1], Marco Zecca[7], Franco Locatelli[8], Chybicka Alicja[9], Franca Fagioli[10], Stephen Robinson[11], Adriana Balduzzi[12], Alessandra Biffi[13], Yves Chalandon[14], Peter Bader[15], Selim Corbacioglu[16], Marc Ansari[1,5]

[1]Geneva University Hospital, Geneva, Switzerland, [2]EBMT Paris Study Office, Saint Antoine Hospital, INSERM UMR 938, Sorbonne University, Paris, France, [3]King Faisal Specialist Hospital & Research Centre, Ryadh, Saudi Arabia, [4]Robert Debré Hospital, Paris, France, [5]University of Geneva, Geneva, Switzerland, [6]First State Pavlov Medical University of St. Petersburg, St Petersburg, Russian Federation, [7]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [8]IRRCS Ospedale Pediatrico Bambino Gesù, Sapienza University of Rome, Rome, Italy, [9]Cape of Hope Wroclaw Medical University, Wroclaw, Poland, [10]Onco-Ematologia Pediatrica Centro Trapianti Cellule Staminali, Torino, Italy, [11]Bristol Royal Hospital for Children, Bristol, United Kingdom, [12]Università di Milano Bicocca Ospedale San Gerardo, Monza, Italy, [13]Padua University, Padua, Italy, [14]Haematology Division and Bone Marrow Transplantation Unit, Geneva, Switzerland, [15]University Hospital Frankfurt, Goethe University, Frankfurt am Main, Germany, [16]University Hospital of Regensburg, Regensburg, Germany

Background: The EBMT risk score uses 5 factors to estimate risks associated with haematopoietic stem cell transplantation (HSCT) in patients. This score was validated in an adult cohort but never validated in children. Moreover, age is not further discriminated in patients under 20 years. The aim of this study was to assess the EBMT score in paediatric allogeneic HSCT for acute lymphoblastic leukaemia (ALL) and acute myeloid leukemia (AML) and to verify a modified EBMT score with age classes adapted to paediatrics.

Methods: This is a retrospective EBMT registry-based analysis on behalf of the PDWP. Patients aged under 18 years who underwent a first allogeneic HSCT between 2006 and 2014 for ALL or AML were included. Analyses were conducted separately for ALL and AML. Outcomes were overall survival (OS), leukaemia-free survival (LFS) and relapse incidence (RI) as well as non-relapse mortality (NRM). Multivariable analyses were performed using Cox proportional hazard models. Risk factors (disease stage at transplant, time from diagnosis to transplant, donor type and donor/recipient gender match) were coded as in the original EBMT score. To build the paediatric-adapted score, we selected factors that significantly impacted outcomes and added a new age-variable designed according to published age-related risk factors in each disease : in ALL 2-10 years of age scored 0, >10-18 years scored 1, 0-< 2 years scored 2, while in AML 0-10 years scored 0 and >10 years scored 1.

Results: 4685 ALL and 2989 AML patients with a median age at transplant of 9.4 and 9.9 years and a median follow-up of 4.8 and 4.2 years respectively were included.

In ALL, disease stage remained significant for all outcomes in multivariable analysis ($p< 0.05$), time from diagnosis to HSCT influenced OS, LFS, RI but not NRM while donor type influenced all outcomes but RI. Similar results were found in AML for disease stage and donor type. Time from diagnosis to transplant influenced RI and NRM ($p< 0.05$) but not OS and LFS. In both diseases, gender-match had no impact on outcomes. In a multivariate analysis, the impact of the EBMT score was still significant in all outcome analyses in ALL and AML ($p< 0.001$). The paediatric-adapted score included all previous factors except gender-match along with the new age-variable and scored from 0 to 6 in ALL and 0 to 5 in AML. In ALL, 5 year-OS decreased from 80.1% in score 0 to 31.5% in score 5-6. NRM increased from 4.8% to 33.4% respectively ($p< 0.001$). In AML, 5 year-OS decreased from 68.1% for

score 0 to 39.8% for score 4-5. NRM increased from 4.3% to 28.1% respectively (p< 0.001). The impact of the modified score as a continuous variable in the multivariate analysis was significant on all outcomes in ALL and AML (p< 0.001).

Conclusions: The EBMT risk score can be used in paediatric patients with acute leukaemia as a pre-transplant tool to estimate outcomes and help in defining risk-adapted strategies. Our paediatric-adapted EBMT risk score could improve the predictive value of this score for children.

Disclosure: Nothing to declare

O154.

TCRαβ+/CD19+-Depletion in Hematopoietic Stem Cells Transplantation from Matched Unrelated and Haploidentical Donors in Children with High-Risk Acute Myeloblastic Leukemia in First Complete Remission

L. Shelikhova, O. Molostova, S. Radygina, M. Dunaykina, A. Livshits, S. Kovrygin, S. Blagov, D. Shasheleva, S. Kozlovskaya, D. Balashov, R. Khismatullina, E. Kurnikova, A. Kazachenok, I. Muzalevsky, I. Kalinina, L. Khachatryan, J. Olshanskaya, E. Raykina, D. Litvinov, G. Novichkova, A. Maschan, M. Maschan

'Dmitry Rogachev National Medical Research Centre for Pediatric Hematology, Oncology and Immunology', Moscow, Russian Federation

Background: Among children with acute myeloid leukemia (AML) with high-risk genetic features and/or poor response to therapy alloHSCT performed in CR1 provides best chance of leukemia-free survival. Choice of donor and overall strategy of preparative regimen and graft-versus-host disease (GvHD) prevention remain an area of active research. Depletion of ab T cells was developed to improve the outcomes of hematopoietic stem cell transplantation (HSCT) by decreasing the incidence of GVHD while maintaining the anti-leukemia effects and infection control. We report here the results of a retrospective outcome research in a cohort of children with high-risk AML, who received ab T cell-depleted HSCT in CR1.

Methods: A total of 74 pediatric patients with AML (29 female, 45 male, median age 7.8 years, range 0.4-23) underwent allogeneic HSCT between May 2012 and August 2019. Forty-eight pts received haploidentical graft, 26 a graft from matched unrelated donor (MUD). All patients were in CR1 and transplanted according to institutional AML protocol (high-risk genetics ($n = 54$), poor response to induction therapy ($n = 16$) and M6/M7 morphology ($n = 21$)).

All pts received treosulfan/fludarabine-based preparative regimen, either melphalan ($n = 43$) or thiotepa ($n = 31$) were added as a second agent. Three regimens of GvHD prophylaxis were used. Regimen 1 ($n = 20$): hATG 50 mg/kg and post-HSCT tacro/mtx; regimen 2 ($n = 34$): thymoglobulin 5mg/kg, rituximab 200 mg/m2 and bortezomib on day +2, +5; regimen 3 ($n = 19$): tocilizumab at 8 mg/kg on day -1 and post-transplant bortezomib and abatacept at 10 mg/kg on day +2, +7, +14, +28. TCRαβ +/CD19+ depletion of HSCT with CliniMACS technology was implemented in all cases. Median follow-up is 3,8y (3mo - 7.5y)

Results: Primary engraftment was achieved in 71 (95%) of 74pts (1pt died before engraftment, 2 received 2nd HSCT), the median time to neutrophil and platelet recovery was 13 and 14 days, respectively. All engrafted pts achieved complete donor chimerism by day +30. Transplant-related mortality was 8.5 % (95% CI: 4-18). The cumulative incidence (CI) of relapse at 3.8 years was 17% (95%CI:10-28) for the whole cohort.

Cumulative incidence (CI) of acute GvHD grade ≥ II was 18.9% (95% CI: 12-30), grade III-IV 5.4 % (95%CI: 2-14) and chronic GvHD - 12% (95% CI: 7-23). No correlation between donor type and GvHD was noted. pEFS was 75% (95%CI: 64-85) for the whole cohort, in Haplo group it was 82% (95%CI: 72-94), as compared to 62% (95%CI:43-80) in the MUD group, $p = 0.08$. pOS was 81% (95%CI: 71-94) for the whole cohort, in Haplo group it was 91% (95% CI:83-99), as compared to 65% (95%CI:47-84) in the MUD group, $p = 0.011$.

Conclusions: This analysis indicates that αβ T-depleted HSCT from haploidentical donors provides a high chance of long-term survival in a cohort of children with high-risk AML in CR1 and is associated with a low burden of GVHD and non-relapse mortality. We suggest that due to easy logistics donor choice for children with high-risk AML in CR1 should be reconsidered in favor of haploidentical donors

Disclosure: Nothing to declare

O155.

The Great Ormond Street (GOS) Paediatric Co-Morbidity Score for Outcome Post-Hematopoietic Stem Cell Transplantation

Reem Elfeky[1,2], Natalia Builes[3], Soumya Perinparajah[2], Joe Standing[2], Robert Chiesa[1], Giovanna Lucchini[1], Arina Lazareva[1], Maria Gabelli[1], Persis Amrolia[1,2], Paul Veys[1,2], Kanchan Rao[1]

[1]Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom, [2]Institute of Child

Health, UCL, London, United Kingdom, [3]*Hospital Pablo Tobon Uribe, Medellin, Colombia*

Background: HCT-CI is an important tool in risk assessment pre-transplant, but its relevance to paediatric population remains unclear. We propose a new score that captures morbidities in this population.

Methods: Between January 2006-December 2016, 950 patients received one or more allo-HSCTs at a median age of 3.3 years for malignant ($n = 274$) or non-malignant disease ($n = 676$). Cox-proportional hazard analysis was performed where 2-year non-relapse mortality (NRM) was the endpoint and co-morbidities included transplant- and patient- related factors. Co-morbidities significant in univariable analysis ($p< 0.1$) were included in the multivariable analysis; with each co-morbidity assigned a weight based on its hazard ratio (HR) as follows; 0 if HR< 0.5, 1 if 0.5 ≥ HR< 1.5, 2 if 1.5 ≥ HR< 2.5, 2 if 2.5 ≥HR< 3.5, 4 if HR ≥3.5. Each patient was evaluated for a total score using these weights then all patients were divided into 5 risk groups using their scores; Group 0: no co-morbidity, Group 1; scores 1-2, Group 2; scores 3-4, group 3; scores 5-6, group 4; scores 7-8 and Group 5; scores ≥ 9.

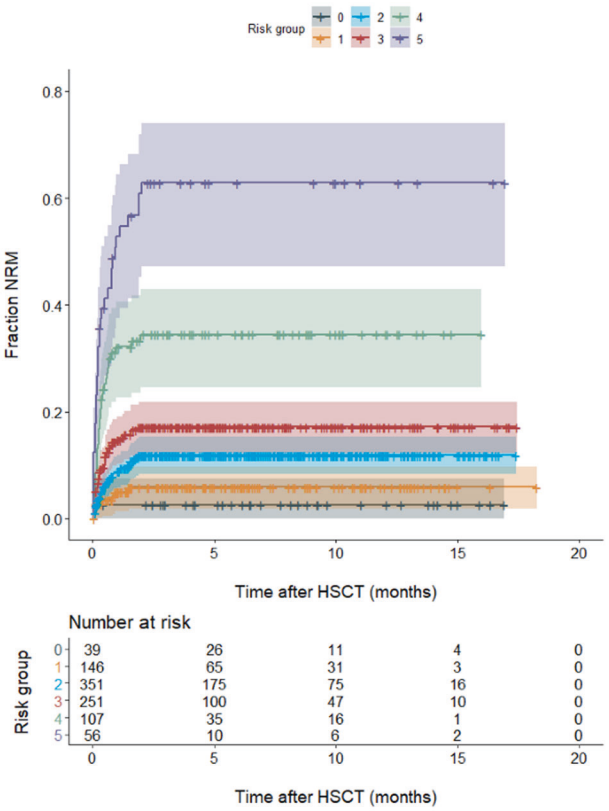
Results: The HCT-CI score was not valid among our studied cohort with multiple co-morbidities being dropped from the analysis due to the absence of patients with the co-morbidity or no reported NRM with the co-morbidity. The highest risk factors in our score were haplo-HSCT, assisted ventilation at D0, respiratory viral infection at D0, PRES, bilirubin ≥ 33 mmol/l and creatinine ≥ 1.5 mg/dl. Table 1 summarises co-morbidities included in the score. For groups 0-5; 2- year NRM was found to be 2.5%, 5%, 10%, 16.3%, 33.6% and 60.7%; respectively (figure 1).

Conclusions: We have created a new scoring system to predict 2-year NRM in children undergoing HSCT. We believe this score has several advantages over previous scoring systems and may guide physicians to counsel appropriately and perhaps make different therapeutic decisions based on this knowledge

Co-morbidity	Prevelance of co-morbidity (n)	Prevelance of NRM (n)	Hazard ratio	Weighted score
More than 1 transplant	84	18	1.44	1
Haplo-HSCT, MMFD/ MMUD/MMSD, MUD	70, 257, 326	29, 52, 52	4.46, 1.57, 1.12	4, 2, 1
Use of serotherapy, Continuation of prednisolone therapy >0.3 mg/kg beyond D0	620, 70	117, 27	1.96, 1.94	2, 2
Heart valve disease, Any cardiac abnormality	23, 42	6, 11	1.52, 1.08	2, 1
Assisted ventilation at D0, Assisted ventilation at any time point pre-HSCT, Any lung structural abnormality	6, 109, 31	3, 26, 9	5.75, 0.84, 1.94	4, 1, 2
CNS infection, Epilepsy, PRES, CNS structural abnormality	17, 8, 7, 14	8, 3, 4, 6	2.13, 1.03, 3.54, 2.15	2, 1, 4, 2
Chronic diarrhoea, Acute infectious diarrhoea at D0, TPN dependency	67, 13, 72	17, 5, 18	1.14, 2.07, 1.02	1, 2, 1
Presence of respiratory viral infection D-10-D0, Presence of CMV viraemia D-10-D0, Continuation of anti-microbial therapy beyond D0	39, 31, 158	16, 12, 36	3.45, 2.15, 0.98	3, 2, 1
ALT: 52-130 IU/L, ALT more than 130 IU/L, Bilirubin ≥ 33 mmol/L, Creatinine ≥ 1.5 mg/dl	222, 76, 21, 8	48, 20, 10, 3	1.74, 1, 3.82, 2.83	2, 1, 4, 3

Table (continued)

[GOS Paediatric Co-morbidity Score for outcome post-HSCT]



[2-year NRM based on the new score]

Clinical Trial Registry: not relevant

Disclosure: Nothing to disclose. Elfeky R and Builes N have equal contribution and are considered first co-authors.

O156.

Elevated Macrophage Activation Markers sCD163 and Mannose Receptor are Associated with Occurrence of aGVHD and SOS After Pediatric Allogeneic HSCT

Laura Louise Fosgrau Hergel[1], Katrine Kielsen[1], Sarah Wegener Weischendorff[1], Marianne Segelcke Rosenkrantz Ifversen[1], Claus Nielsen[1], Henning Grønbæk[2], Klaus Gottlob Müller[1]

[1]Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark, [2]Aarhus University Hospital, Aarhus, Denmark

Background: Acute graft-versus-host disease (aGVHD) and sinusoidal obstruction syndrome (SOS) are potentially severe complications after allogeneic HSCT. Both complications are thought to be propagated by innate immune mechanisms, involving release of proinflammatory cytokines from activated macrophages in response to tissue damage induced by the conditioning regimen.

The haptoglobin-hemoglobin receptor CD163 and the mannose receptor are expressed on the plasma membrane of human macrophages and are shed into the circulation upon inflammatory activation.

We investigated the role of macrophage activation in the development of aGVHD and SOS by measuring circulating levels of soluble CD163 (sCD163) and soluble mannose receptor (sMR) in pediatric HSCT.

Methods: We included 93 Danish children and adolescents undergoing HSCT between 2010-2018. Median age was 8.5 years (range: 1.1-17.6). Diagnoses included AML ($n = 9$), ALL ($n = 27$), other malignancies ($n = 21$) and benign disorders ($n = 36$). Donors were either MSD ($n = 29$), MUD ($n = 52$) or MMUD ($n = 12$). Stem cell source was either BM ($n = 89$) or PB ($n = 4$). All patients received myeloablative conditioning based on either TBI ($n = 25$) or high dose chemotherapy alone ($n = 68$).

Plasma levels of sCD163 and sMR were measured with ELISA before start of conditioning, at the day of HSCT and at day +7, +14, +21, +30, +90 and +180 after HSCT. Fifty-six healthy children with a median age of 12.5 years (range 7.7-17.7) were included as controls.

Results: Plasma levels of sCD163 and sMR increased from pre-conditioning and peaked at day +30 after HSCT ($p = 0.035$ and p=1.396e-07 respectively) and gradually declined thereafter.

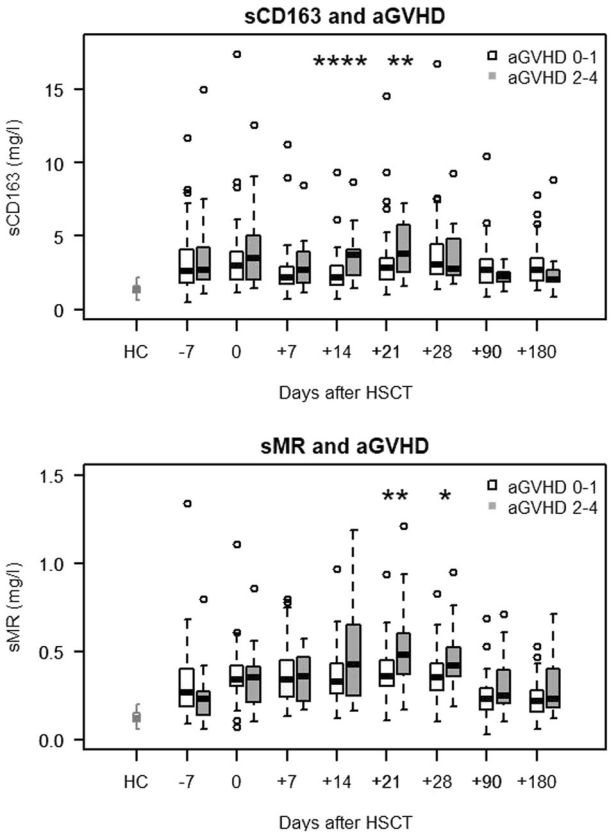
Both markers were elevated at all time points compared to healthy controls (all p< 0.0001). Patients with malignant diagnoses had significantly increased levels of sCD163 and sCD206 before conditioning than patients with benign disorders (sCD163: 2.91 mg/l (IQR: 2.11 - 4.14) vs. 2.19 mg/l (IQR: 1.63 - 3.25), $p = 0.016$, sCD206: 0.27 mg/l (IQR:0.21 - 0.42) vs. 0.22 mg/l (IQR: 0.13 - 0.28), $p = 0.032$) Both markers were significantly elevated at day +21 in patients receiving TBI-based conditioning (all p< 0.01).

Patients with grade 2-4 aGVHD ($n = 26$) had significantly higher levels of sCD163 and sMR between day +14 and +28 post-HSCT compared to patients with grade 0-1 aGVHD (Fig. 1).

sCD163 and sMR levels were positively correlated with same-day plasma levels of bilirubin and ALT from day of HSCT to 6 months post-transplant (all p< 0.05). In line with this, sCD163 levels were increased in patients fulfilling the Seattle criteria for SOS ($n = 11$) at day +21 post-HSCT compared to patients without SOS (median: 4.82 mg/l (IQR; 3.17 - 5.77) vs. median 2.85 mg/l (IQR; 2.20 - 3.80), $p = 0.045$).

Conclusions: Plasma levels of sCD163 and sMR were elevated in children undergoing HSCT, and increased levels of both markers were associated with the occurrence of aGVHD and liver dysfunction.

These findings suggest that macrophage activation plays a key role in the innate immune response involved in induction of hepatocellular damage, SOS and aGVHD and may prove clinically useful as predictive biomarkers for the course and severity of these complications.



[Figure 1: Levels of sCD163 and sMR during the first 180 days of transplantation according to grade of aGVHD.]

Disclosure: Nothing to declare

O157.

The Efficacy and Toxicity of Unmanipulated DLI After Haploidentical EX-VIVO T-Cell Depleted Stem Cell Transplantation in Children - A Retrospective Cohort Study

Gustav Sundén[1], Jacek Toporski[1], Ladislav Krol[1,2], Josefina Dykes[1], Albert N. Békássy[1], Cornelis Jan Pronk[1,2], Dominik Turkiewicz[1,2]

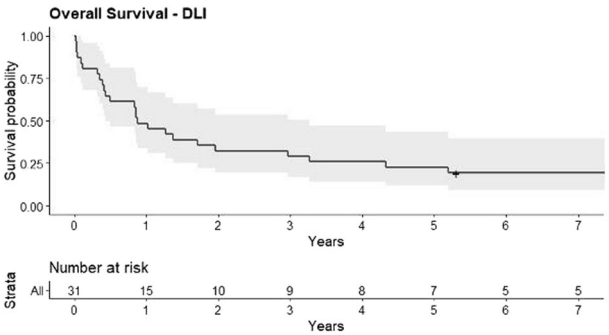
[1]Skåne University Hospital, Lund, Sweden, [2]Lund University, Lund, Sweden

Background: Unmodified donor lymphocyte infusions (DLI) have been used to prevent or treat relapse or infectious complications after allogeneic hematopoietic stem cell transplantation (SCT). However, data regarding their efficacy and safety in children after ex-vivo T-cell depleted (TCD) haploidentical SCT (haploSCT) is scarce

Methods: In a single-centre retrospective study frequency, safety and efficacy of unmodified DLI was evaluated in children who underwent TCD haploSCT between 2001 and 2018. Inclusion criteria were: age < 18 years at time of haploSCT, ex-vivo TCD of the graft +/- short course of MMF as a GvHD prophylaxis and singed informed consent to prospectively register demographic and transplantation-related data

Results: The study included 54 (32 male and 22 female) patients who underwent 64 transplants, at a median age of 5,9 years (1 month - 17,9 years). Indications for transplantation included: solid tumours (18), haematological malignancies (24) and non-malignant diseases (11). Majority of patients received conditioning containing Fludarabine (120-160mg/m2), Thiotepa (10mg/kg) and Melphalan (120-140 mg/m2). To prevent graft rejection, serotherapy with either OKT3 or ATG-F/Grafalone was used. Ex-vivo TCD was performed either by negative selection of CD3+ / TCRab+ cells, or, in a single case, positive selection of CD34+ cells. Median follow up time was 806 days (range 16 days-14 years). A total number of 81 unmodified DLIs was given to 31 patients. In 21 cases, DLIs were given as treatment to patients with measurable malignancy at or after transplantation (19) or active viral infection (AdV 1, EBV 1). Ten patients transplanted in complete remission but considered to be at high risk of disease recurrence, received DLI prophylactically. The median number of DLIs per patient was 2 (1-14). The average interval from haploSCT to DLI was 37 days (16-358). The median dose of CD3+ cells was 50×10^3/kg of recipient body weight (range 1×10^3-1×10^6), and 25×10^3/kg (range 1×10^3-2×10^5) for the first infusion only. For patients who received DLI, EFS reached 0.17 (95% CI:0.03-0.30) and OS 0.19 (95%CI:0.05-0.33). Cumulative incidences of post-DLI non-relapse mortality (NRM) and relapse (RI) were 0.13 (95%CI: 0.05- 0.31) and 0.71 (95%CI: 0.55- 0.85), respectively. GvHD occurred in 16 patients (in 8 grade 1-2 and in eight grade 3-4) resulting in cumulative incidence of post-DLI aGvHD of 0.47 (95% CI: 0.31 - 0.66). Unmodified DLI, analysed as a time-dependent covariate in a Cox model adjusted for age, sex and diagnosis was associated with an increased risk of all-grade aGvHD (HR 3.00, 95%CI: 1.26 - 7.13), but not with NRM (HR 1.95, 95%CI: 0.51 - 7.53), when adjusted for age and sex. Two patients developed extensive chronic GvHD resulting in 1-year post-DLI cGvHD probability of 0.13 (95%CI: 0.06 - 0.39). Extensive cGvHD was not observed in patients who did not receive DLI. None of the patients developed DLI-associated bone marrow hypoplasia.

Conclusions: In summary, our data indicates significant risk for aGvHD, but not for NRM, associated with unmodified DLI after ex-vivo TCD haploSCT in children. Efficiency of DLI is difficult to assess due to heterogeneity of indications and lack of comparable control group. However, low survival probability suggests limited efficacy



[OS after DLI]

Disclosure: Nothing to declare

O158.

Haploidentical T-Cell Depleted HSCT Represents a Safe Therapeutic Alternative to MSD Transplantation in Patients with Transfusion-dependent ß-Thalassemia Major

Katharina Kleinschmidt, Juergen Foell, Beatrix Pfirstinger, Anja Troeger, Agnes Mayr, Pauline Dibbern, Andreas Brosig, Norbert Ahrens, Selim Corbacioglu

University Hospital Regensburg, Regensburg, Germany

Background: Despite the improved supportive care for transfusion-dependent thalassemia (TDT) patients, quality of life with conventional therapy remains compromised. Hematopoietic stem cell transplantation (HSCT) represents currently the only curative option. With a matched-sibling donor (MSD) availability < 20%, safe alternative donor HSCT regimens are crucial. T-cell depleted HSCT from a haploidentical donor (T-haplo-HSCT) represents a promising alternative.

Methods: Seven patients with TDT received a HSCT, 4 were transplanted with a $CD3^+/CD19^+$ or aß/$CD19^+$ T-haplo-HSCT (median age 14.5 years, range 3-23) whereas 3 received bone marrow (BM) from a MSD (median age 7 years, range 4-11). Indication for transplantation was TDT as standard of care for patients with MSD availability, and with beginning of transfusion-associated complications (iron overload, related organ dysfunction) in all T-haplo HSCT patients. All patients received an identical conditioning regimen consisting of treosulfan, thiotepa, fludarabine and ATG, with the only difference in the time of ATG application (at the beginning of conditioning in the T-haplo-HSCT setting, in the end in MSD HSCT). Immunosuppression (IST) consisted in all but one patient of tacrolimus (in one patient cyclosporine A) and mycophenolate mofetil.

Results: The overall survival of both MSD and T-haplo-HSCT patients is 100%, with a median follow-up (F/U) of 18 months in the MSD population (range 12-26) and 11 months in T-haplo-HSCT (range 4-40). Engraftment was achieved after a median of 31 days for MSD patients and 18 days for T-haplo-HSCT, after the infusion of a median of 4.9 $x10^8$ TNC/kg (range: 4.17-7.88) and $17x10^6$ $CD3^+/CD19^+$ or aß/$CD19^+$ depleted $CD34^+$ cells/kg (range: 9.45-23.4), respectively. No graft failure/rejection was observed. Mixed chimerism was observed more often in the MSD population (median 90.8%; range 42.2-96%); transfusion independence was achieved in all patients. In T-haplo-HSCT, the median chimerism is 100% (range 94.4-100%) after a median F/U of 11 months. In MSD, IST was terminated after a median of 149 days; in T-haplo-HSCT, IST was stopped in two patients after 113 and 214 days, in the remaining two patients IST is still ongoing due to a post-HSCT period of < 180 days. The incidence of transplant-related complications (TRM) was low: no case of acute or chronic graft-versus-host-disease (a/cGvHD) was observed in the MSD population. In the T-haplo-HSCT recipients, 3/4 patients experienced a grade I skin aGvHD which resolved in all cases with extracorporeal photopheresis. One patient, the oldest, experienced a grade I chronic skin cGvHD. No severe infectious complications occurred, with a timely (approximately at 6 months post-HSCT), chimerism-triggered withdrawal of IST. Whereas in MSD all patients reached CD4 counts >50/µl at day 125, in T-haplo-HSCT 3/4 patients reached CD4 counts >50/µl at day 145 with one patient remaining at F/U of 120 days. The conditioning regimen was well tolerated with no high-grade transplant related toxicity.

Conclusions: These preliminary data of a small patient cohort with TDT add confirmative evidence that T-haplo-HSCT represents a safe alternative for TDT patients without a MSD. Treosulfan demonstrated to be an excellent alternative to busulfan, with no case of veno-occlusive disease in this high-risk patient population.

Disclosure: Nothing to declare.

O159.

Alphabeta T and B-Cell Depleted HLA-Haploidentical Hematopoietic Stem Cell Transplantation (Tbdepl-Haplohsct) in Children with Non-Malignant Disorders

Pietro Merli[1], Federica Galaverna[1], Mattia Algeri[1], Daria Pagliara[1], Stefania Gaspari[1], Roberto Carta[1], Marco Becilli[1], Michele Massa[1], Emilia Boccieri[1], Rita Maria Pinto[1], Giulia Bozza[1], Luciana Vinti[1], Luisa Strocchio[1], Giovanna Leone[1], Giovanna Del Principe[1], Giuseppina Li Pira[1], Annalisa Ruggeri[1], Franco Locatelli[1,2]

[1]Bambino Gesù Children's Hospital, Rome, Italy, [2]University of Rome La Sapienza, Rome, Italy

Background: A number of hematological disorders, either inherited (including primary immmunodeficiencies, red blood cell disorders or selected metabolic diseases) or acquired (i.e. severe aplastic anemia) can be cured with an allogeneic HSCT. Historically, the outcome of children transplanted from an HLA-haploidentical relative was inferior to that of children given the allograft from an HLA-matched, either related or unrelated, donor. Here, we report the outcome of a large cohort of children (partially published in Bertaina et al., Blood 2014) affected by non-malignant disorders who received a TBdepl-haploHSCT at our Center.

Methods: Between 02/2011 and 06/2019, 60 patients were treated at Bambino Gesù Children's Hospital; median age at HSCT was 3.6 years (range 0.3-16.1). Patients had many different disorders (see Table for details on patients and transplants characteristics). All patients received a conditioning regimen, which varied according to the original disease. As previously described, all patients were

given pre-transplant anti-thymocyte globulins to modulate bi-directional donor/recipient alloreactivity and rituximab to prevent PTLD. No patient received any post-transplant GvHD prophylaxis.

Results: primary donor cell engraftment was obtained in 46 patients, while 3 patients experienced secondary graft failure (GF); the cumulative incidence of either primary or secondary GF was 28.3% (95% CI 15.9-38.8). The vast majority of this event was recorded in children with disorders known to be associated with an increased GF risk (i.e., HLH, thalassemia, severe aplastic anemia or osteopetrosis). Fourteen of the 17 patients with either primary or secondary GF were successfully retransplanted (2 with a mismatched unrelated cord blood unit, the other from either the same donor or the other parent); the remaining 3 children died because of infectious complications before retransplant (PCP in a SCID patients (already present before HSCT), *E. faecium* sepsis in a SAA patients and *P. aeruginosa* sepsis in an HLH patient)). Three additional patients died of infectious complications (1 because of CMV pneumonia and 2 of disseminated adenovirus infection), this leading to a TRM of 10%. Median time to neutrophil and platelet recovery was 13 and 10 days, respectively. Eight patients developed grade II acute GvHD (no patient developed grade III or IV aGVHD), this resulting into a cumulative incidence of 13.9%. Among patients at risk, only one developed mild chronic GvHD. With a median follow-up of 62 months (range 3 - 105), the 5-year probability of overall and disease-free survival for the entire cohort of patients is 90% (95% CI 79.0-95.4).

Counting graft failure and death for any cause as events, 5-year EFS is 66.7% (95% CI 53.2-77.0).

Conclusions: these results indicate that TBdeplhaploHSCT is an effective option for children with different life-threatening nonmalignant disorders, either congenital or acquired. Prompt availability of this type of transplant saves time, thus limiting infectious risk and making this an attractive choice in particular subsets of patients (e.g., SCID patients). The low incidence of both acute and chronic GvHD preserves a good quality of life in patients with non-malignant diseases and long life-expectancy.

Clinical Trial Registry: NCT01810120

Disclosure: Merli: Novartis: Honoraria; Sobi: Consultancy; Amgen: Honoraria; Bellicum: Consultancy. Algeri:Miltenyi: Honoraria; Atara Biotherapeutics: Consultancy, Honoraria; Bluebird bio: Consultancy, Honoraria. Locatelli: Novartis: Consultancy, Advisory Board; Miltenyi:Honoraria; bluebird bio: Consultancy; Bellicum: Consultancy, Advisory Board; Amgen: Honoraria, Advisory Board.

O160.

Survey of Transplant Associated Macrophage Activation Syndrome (TAMAS) Following Allogeneic Hematopoietic Stem Cell Transplantation in Children and Young Adults

Petr Sedlacek[1], Cristina Diaz de Heredia[2], Akif Yesilipek[3], Pietro Merli[4], Priya Marwah[5], Stalin Ramprakash[6], Giorgio Ottaviano[7], Selim Corbacioglu[8]

[1]University Hospital Motol, Charles University Prague, Prague, Czech Republic, [2]Hospital Vall d'Hebron, Barcelona, Spain, [3]Akdeniz University, Antalya, Turkey, [4]IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy, [5]Bangalore, Bangalore, India, [6]Jaipur, Jaipur, India, [7]Ospedale San Gerado, Clinica Pediatrica dell'Universita, Monza, Italy, [8]University of Regensburg, Regensburg, Germany

Background: Macrophage activation syndrome (MAS) is a serious and historically rare life-threatening complication now increasingly observed in recipients of allogeneic HSCT. Excessive uncontrolled and dysregulated immune activation with proliferation of T lymphocytes and macrophages leads to hyperinflammatory responses with hypercytokinemia and hemophagocytosis. Similar but different from other primary or secondary hemophagocytic lymphohistiocytosis (HLH) there is no suitable definition for transplant associated MAS (TAMAS). Available HLH criteria do not reflect the specificity of MAS presenting in patients following allogeneic HSCT and therefore should be used cautiously. A retrospective survey was initiated by the Pediatric Diseases Working Party (PDWP) of the EBMT for a better understanding of the particularities and features of TAMAS. Our aim is to propose a definition for TAMAS based on this survey, which in the future may help to collect valid prospective data. Universally accepted criteria may help to identify the disease early and initiate efficient targeted therapies.

Methods: Twenty-one centers from 11 countries (Austria, Denmark, Germany, Hungary, India, Italy, The Netherlands, Poland, Slovakia, Spain and Turkey) participated in this retrospective study. Data of 45 patients age 0.5-21.6 years (median 9), who underwent their first alloHSCT since 2005 and were diagnosed with TAMAS according to local center criteria, were collected. Transplant indications were malignant diseases ($n = 20$), primary immunodeficiencies ($n = 5$), bone marrow failure syndromes ($n = 18$) and others ($n = 2$). Conditioning regimens varied substantially, reflecting a wide spectrum of diseases, but were defined as myeloablative (MAC) in 33 patients or

reduced (RIC) in 12 patients respectively. Primary grafts were bone marrow ($n = 26$), cord blood ($n = 4$), peripheral blood stem cells ($n = 7$) or in vitro T-cell depleted peripheral blood stem cells ($n = 8$). Seven patients were transplanted from MSD, 21 from MUD and 17 from haploidentical family donor.

Results: Following first HSCT 13 patients failed to reach primary engraftment, further 32 engrafted granulocytes on day 9-33 (median 21). Eighteen (40%) patients had to be infused with a second allogeneic graft for graft failure 23-560 days (median 75) after 1.HSCT. TAMAS was diagnosed in median 34 days (11-672) following 1.HSCT ($n = 38$) or 2. HSCT ($n = 7$). 13 patients (29%) suffered from aGvHD grade II-IV; in 23 patients (51%) viremia was detected. Seventeen patients (38%) died due to TRM 0 - 294 days (median 33) after diagnosis of TAMAS, further 2 died of primary disease progression. Twenty-six patients are alive (OS 26/45; 58%) after 1st ($n = 16$) or 2nd HSCT ($n = 10$) 1-104 months (median 18) after presentation of TAMAS.

Strenght of association of clinical and laboratory manifestations to TAMAS:

Strong: primary or secondary cytopenia in 42/45 (93%), ferritin above 5 000 ng/mL in 36/41 (88%), persistent fever in 39/45 (87%), triglycerides above 265 mg/dL in 15/17 (88%)

Moderate: marrow hemophagocytosis in 20/33 (61%), max sCD25 above 2400 UI/mL in 8/15 (53%)

Weak: splenomegaly in 17/42 (40%), fibrinogen below 150 mg/dL in 8/36 (22%), any neurological involvement in 12/45 (27%)

Conclusions: TAMAS is a serious complication associated with high mortality. Current criteria for HLH should be adapted for patients developing TAMAS.

Clinical Trial Registry: for Pediatric Diseases Working Party EBMT.

Disclosure: nothing to declare.

O161.

Impact of AB0 Incompatibility, Age And Stem Cell Source on Outcome Parameters in MSD HSCT for Hemoglobinopathies: A Retrospective Study on Behalf of the PDWP

Katharina Kleinschmidt[1], Josu de la Fuente[2], Jacques-Emmanuel Galimard[3], Arnaud Dalissier[3], Giorgio La Nasa[4], Jean-Hugues Dalle[5], Abdelghani Tbakhi[6], Yves Bertrand[7], Xavier Poiré[8], Gulsun Karasu[9], Gérard Michel[10], Despina Moshous[11], Hakan Ozdogu[12], Emel Ünal[13], Catherine Paillard[14], Akif Yesilipek[15], Selim Corbacioglu[1]

[1]University Hospital Regensburg, Regensburg, Germany, [2]Imperial College London, London, United Kingdom, [3]EBMT Paris Study Office, Saint Antoine Hospital, INSERM UMR 938, Sorbonne University, Paris, France, [4]R. Binaghi Hospital, ATS Sardegna, Cagliari, Italy, [5]Robert Debré Hospital, Paris Diderot University, Paris, France, [6]King Hussein Cancer Centre, Amman, Jordan, [7]University Hospital of Lyon, Lyon, France, [8]Universitaires Saint-Luc, Brussels, Belgium, [9]Bahcesehir University, Göztepe Medicalpark Hospital, Istanbul, Turkey, [10]Aix-Marseille University, Timone Children's Hospital Marseille, Marseille, France, [11]APHP, Hôpital Universitaire Necker-Enfants Malades, Paris, France, [12]Baskent University, Ankara, Turkey, [13]Ankara University, Ankara, Turkey, [14]Hôpital de Hautepierre, Strasbourg, France, [15]Akdeniz University, Antalya, Turkey

Background: Matched sibling donor (MSD) hematopoietic stem cell transplantation (HSCT) in hemoglobinopathies is standard of care, however factors like age, graft source and AB0 mismatch (MM) might impact on outcome. MM is usually not considered a barrier to successful HSCT, however major MM is a potential risk factor for hemolysis, delayed RBC engraftment, and pure red cell aplasia.

Methods: A retrospective registry-based analysis using the PDWP-EBMT database investigated the influence of AB0 MM on OS, incidence of second transplant as indicator of graft failure, acute GvHD grade II-IV, chronic GvHD and neutrophil (PNN) engraftment (>0.5) in children and young adults, transplanted with a MSD for Thal and SCD between 1985-2018.

Results: 955 patients ($n = 593$ Thal; n=362 SCD) were included. The median age at HSCT was 7.4 years (y; 0.5-45.1) for Thal and 10y (1.1-46.1) for SCD. Conditioning was mostly busulfan-based (>85%). ATG was applicated in 56.7% of Thal and 78.7% of SCD patients. 19.7% of Thal and 14.1% of SCD patients were transplanted with major MM, and 15.3%/18.2% with minor MM, respectively. The median follow-up (F/U) was 4.5 and 3.8 years in Thal and SCD patients, respectively. The 4y-OS was excellent with 91.1% for Thal (95% CI: 88.7-93.6) and 96.1% for SCD (95% CI: 94-98.2). In univariate analysis, no significant difference in terms of OS, second SCT, a/cGvHD or PNN-engraftment with regard to AB0 compatibility was observed. However, a significantly lower 4y-OS was seen in Thal-patients with blood group 0 of 86.2% (80.4-92) versus non-0 of 95.9% (93.4-98.4; $p = 0.002$). Moreover, with 87.3% (79.3-92.3) versus 90.5% (87.4-92.9; $p= 0.06$) a trend to a lower PNN-engraftment at day +30 was shown in Thal-patients with a major MM compared to patients with no or minor MM. This was confirmed in multivariate analysis, where the HR of missing PNN-engraftment was 1.32 (1.06-1.66) in patients with major MM (95% CI; $p = 0.02$). The major impact on OS was age at SCT: In Thal-

patients, the OS was 93.9% (90.9-96.9) in patients ≤ 7y compared to 88.7% (85-92.5) >7y ($p = 0.02$), with an even higher level of significance with ≤ 13y (93.5%; 91.1-95.9) and >13y (83.5%; 76.8-90.2; $p = 0.0001$). Multivariate analysis confirmed this with an HR=1.33 (CI: 1.14-1.55; $p = 0.0003$). In SCD, a similar trend was observed with an OS of 98.6% (97-100) in patients ≤ 13y, compared to 91% >13y (85.6-96.3%; $p = 0.001$). The cell source impacted significantly on d30 PNN-engraftment in univariate and multivariate analysis: 88.1% (84.8-90.8) in case of BM compared to 96.5% (90.4-98.8) for PBSC ($p = 0.001$). The d100 CI of grade II-IV aGvHD was 11.6% (8.1-15.8) in patients ≤ 7y and 16.4% (12.4-20.9; $p = 0.08$) >7y. For cGvHD, the impact of age was: 17.5% (13-22.7) >7y compared to 10% (6.3-14.8) in ≤ 7 ($p = 0.03$), and 25.1% (17.2-33.7) >13y versus 10.5% (7.4-14.1; p< 0.0001) ≤ 13y.

Conclusions: Outcomes for both, Thal and SCD, transplanted from a MSD are excellent but are significantly influenced by age and graft source. The moderate impact of the recipients' blood group in MSD is remarkable, might be more evident in alternative donor HSCT and allows selection in haploidentical setting.

Disclosure: Nothing to declare.

Stem cell donor

O162.

Donor-Recipient HLA Matching for Unrelated Donor Hematopoietic Stem Cell Transplantation Outcomes: A Study from the Cellular Therapy and Immunobiology Working Party (CTIWP) of the EBMT

Annalisa Ruggeri[1], Carlheninz Mueller[2], Katya Mauff[3], Lisbeth de_Wreede[3], Lotte wieten[4], Luca Vago[5], Jorinde Hoogenboom[3], Gerard Socie[6], Riitta Niittyvuopio[7], Ibrahim yakoubagha[8], Charles crawley[9], Eleni tholouli[10], Claude Eric Bulabois[11], Goda Choi[12], Edouard forcade[13], Anne Huynh[14], Stig Lenhoff[15], Virginie Gandemer[16], Fabio Ciceri[5], Nicolaus Kröger[17], Natacha Maillard[18], Maija Itäla-Remes[19], Vanderson rocha[20], Chiara bonini[21], Christian Chabannon[22], Katharina Fleischhauer[23]

[1]OPBG, Roma, Italy, [2]BMT Unit, Essen, Germany, [3]EBMT Data Office Leiden, Leiden, Netherlands, [4]University Hospital Maastricht, Maastricht, Netherlands, [5]San Raffaele Hospital, Milano, Italy, [6]APHP, Hôpital St Louis, Université de Paris, INSERM UMR 976, Paris, France, [7]HUCH Comprehensive Cancer Center, Helsinki, Finland, [8]CHU de Lille, Lille, France, [9]Addenbrookes Hospital, Cambridge, United Kingdom, [10]Manchester Royal Infirmary University NHS Foundation Trust, Manchester, United Kingdom, [11]CHU Grenoble Alpes, Université Grenoble Alpes, Grenoble, France, [12]University Medical Center Groningen (UMCG), Groningen, United Kingdom, [13]CHU Bordeaux, Bordeaux, France, [14]CHU Institut Universitaire du Cancer Toulouse, Toulouse, France, [15]Skanes University Hospital, Lund, Sweden, [16]Centre Hospitalier Universitaire de Rennes, Rennes, France, [17]University Hospital Eppendorf, Hamburg, Germany, [18]Hopital La Miletrie, Poitiers, France, [19]Turku University Hospital, Turku, Finland, [20]Sao Paolo University, Sao Paolo, Brazil, [21]San Raffaele Hospital, Milano, Italy, [22]Institut Paoli-Calmettes, Aix-Marseille University, INSERM CBT-1409, Marseille, France, [23]University Hospital Essen, Essen, Germany

Background: Optimal HLA matching is associated with clinical outcome of unrelated donor(UD) hematopoietic-cell-transplantation (HCT), but a comprehensive analysis addressing this question in European EBMT transplant centers is lacking. On behalf of the CTIWP-EBMT, we have addressed this issue in adults receiving an UD-HCT from 2000 to 2015.

Methods: 8985 cases of UD-HCT with available 6-loci high resolution HLA-A, -B, -C, -DRB1, -DQB1, -DPB1 typing for both patient and donor matched for at least 7/8 HLA-A,B,C,DRB1 alleles were selected. Median follow-up was of 36.8 months, main diagnosis was acute leukemia (AL,52%), disease stage was early in 45% of cases. UD-HCT were performed with PB in 86.02%, in-vivo T-cell-depletion (TCD) in 72.1% and reduced-intensity-conditioning regimen in 57.9% of cases.

HLA data were validated using the HLAcore library and a haplotype based probability check from the German Donor Registry. Pairs were stratified by: 1) In the overall cohort, HLA-A, -B, -C, -DRB1 matching status (8/8 N=7016 and 7/8 N=1799) and 2) in informative 8/8 matched pairs, HLA-DPB1 matching status as identical (22.3%), permissive (43.4%) or non-permissive (34.4%) by the 3-group T Cell Epitope (TCE3) model, or by the 4-group TCE4 model.

Results: 5-years-OS, RFS and relapse were 47%, 41% and 33%, respectively.

In multivariate-analysis, a single mismatch at HLA-A, -B, -C, -DRB1 (7/8) was associated with significantly higher risk of death compared to 8/8;(HR 1.14, p< 0.001). Other variables significantly associated with OS were patient (HR 1.14, p< 0.001) and donor age (HR 1.08, p< 0.001), CMV serostatus (HR 1.1, $p = 0.008$), AL (HR 1.14 v.s. MDS+MPN, p< 0.001 and HR 1.32, p< 0.001 v. s. Others), intermediate and advanced disease status (HR 1.21, p< 0.001 and HR 1.66, p< 0.001) and HCT-year (HR 0.98, p< 0.001). The hazards of

NRM, grade II-IV aGvHD and RFS were significantly higher in the 7/8 compared to the 8/8 group (HR 1.34, p< 0.001, HR 1.16, p< 0.001 and HR 1.1, $p = 0.02$, respectively), but no associated withlower risks of relapse (HR 0.93, $p = 0.22$).

In 8/8 matched HCT, when comparing with the HLA-DPB1 TCE3 permissive group, NRM was higher in the non-permissive and lower in the HLA-DPB1 allele-matched group (1.14, $p = 0.04$ and 0.87, $p = 0.08$). OS was not significantly different in both the non-permissive (HR 1.06, $p = 0.20$) and the allele-matched group (HR 0.99, $p = 0.8$). Also RFS was similar between the 3 groups (HR 1.03, $p = 0.43$ and HR 1.07, $p = 0.14$, respectively). Grade II-IV aGvHD was lower in the allele-matched compared to the permissive group (HR 0.86, $p = 0.08$), and higher for the non-permissive group (HR 1.14, $p = 0.049$).

Conclusions: In large independent cohort of UD-HCT from EBMT performed mostly from PB with in-vivo-TCD, single allele mismatch at HLA-A, -B, -C, -DRB1 was independently associated with lower OS and RFS, higher risk of NRM and aGvHD and no difference in relapse. We also confirm the negative effect of non-permissive HLA-DPB1 mismatches on NRM and aGvHD. The results from this new dataset validate current paradigms in donor selection and provide an important new platform for testing new questions in donor selection and HCT immunobiology.

Disclosure: Nothing to declare.

O163.

Presence of Age-Related Clonal Hematopoiesis (ARCH) in Donor Does Not Increase the Risk of Late Secondary Malignancies After Allogeneic Hematopoietic Stem Cell Transplantation

Kyoung Ha Kim[1,2], Tae Hyung Kim[1,3,4], Jae-Sook Ahn[4,5], Ivan Pasic[1], Zeyad Al-Shaibani[1], Arjun Law[1], Wilson Lam[1], Fotios Michelis[1], Armin Gerbitz[1], Auro Viswabandya[1], Jeffrey Lipton[1], Rajat Kumar[1], Jonas Mattsson[1], Zhaolei Zhang[3,4], Tamir Biezuner[6], Liran Shlush[6], Dennis Dong Hwan Kim[1]

[1]University of Toronto, Princess Margaret Cancer Centre, Toronto, Canada, [2]Soonchunhyang University, Soonchunhyang University Hospital, Seoul, Korea, Republic of, [3]University of Toronto, Toronto, Canada, [4]Donnelly Centre for Cellular and Biomolecular Research, University of Toronto, Toronto, Canada, [5]Chonnam National University Hwasun Hospital, Hwasun, Korea, Republic of, [6]Weizmann Institute of Science, Rehovot, Israel

Background: Age-related clonal hematopoiesis (ARCH) is known to be associated with increasing susceptibility to both hematologic and solid malignancies. Recent studies reported that the presence of ARCH in stem cell donors may not adversely affect transplant outcomes after allogeneic hematopoietic stem cell transplantation (allo-HCT). However, its long-term impact on the risk of late secondary malignancy (LSM) after allo-HCT remains unknown. We have reported that LSMs were observed in 209 of 2415 allo-HCT recipients with 6.3% of incidence at 10 years (Biol Blood Marrow Transplant, 2017). The risk of LSM after allo-HCT was double compared to that in the general population. The present study aimed to analyze the impact of the presence of donor's ARCH on the risk of LSM after allo-HCT.

Methods: Genomic DNA was extracted prior to allo-HCT from 372 donor/recipient pairs of peripheral blood samples between 2000 and 2007 at the Princess Margaret Cancer Centre, Canada. To detect ARCH, we applied bar-coded error-corrected sequencing using modified molecular inversion probe capture protocols (Gen Research, 2013) at Weizmann Institute of Science (Rehovot, Israel), targeting 34 genes covering ARCH-associated mutations along with other AML-related mutations. Bar-coded next-generation sequencing (NGS) library was generated and processed (ASH 2019 # 4514). For statistical analysis, the cumulative incidence of LSM was calculated considering relapse/death as competing events.

Results: Transplant characteristics are as following: male ($n = 223$, 59.9%); median age, 48 years (range, 17-71); myeloablative conditioning ($n = 267$, 71.8%). Median age of donors ($n = 299$) was 48 years (range, 11-75). 284 patients (76.3%) had an HLA identical sibling donor. A total of 30 mutations were detected in 25 donors (6.7%), while 47 mutations were detected in 41 recipients (11.02%). The most frequently mutated genes in the donors were *DNMT3A* ($n = 10/25$, 40%), *TET2* ($n = 4/25$, 16%), and *TP53* ($n = 3/25$, 12%). There was no difference in baseline and transplant characteristics between the recipients according to presence or absence of ARCH in the donors. Similarly, there were no differences in outcomes including overall survival ($p = 0.701$), cumulative incidence of relapse ($p = 0.71$), non-relapse mortality ($p = 0.7$), acute graft-versus-host disease (GVHD, $p = 0.762$) or chronic GVHD ($p = 0.8$).

With a median follow-up of 13 years (range 0.3-18.2 years) among survivors, a total of 56 of the 372 patients ($n = 56/372$, 15.1%) had a diagnosis of LSM at median of 8.4 years after allo-HCT. The most frequent LSM subtypes were non-melanoma skin ($n = 27$, 48%), lung ($n = 5$, 8.9%), prostate ($n = 5$, 8.9%), and hematological cancers ($n = 5$, 8.9%). Four cases had a donor carrying ARCH ($n = 4/25$, 16%) and 52 cases had a donor without carrying ARCH ($n = 52/347$, 15.0%) ($p = 0.326$). The incidence of LSM at 10 years was comparable in recipients with and

without an ARCH-carrying donor: 10.0% versus 8.8%, respectively ($p = 0.421$). No statistical difference in the LSC subtypes was noted between the recipients according to presence or absence of ARCH in the donors.

Conclusions: The present study suggests the presence of ARCH in donor does not increase the risk of LSM after allo-HCT.

Disclosure: Nothing to declare.

O164.

Serious Events and Adverse Reactions in Relation to Blood Stem Cell Donation Reported to WMDA in 2018

Monique Jöris[1], Mirjam Fechter[2], Thilo Mengling[3], Lydia Foeken[1]

[1]WMDA, Leiden, Netherlands, [2]Matchis, Leiden, Netherlands, [3]DKMS gemeinnützige GmbH, Tübingen, Germany

Background: The World Marrow Donor Association (WMDA) has set up a unique central global reporting system for WMDA member organisations for reporting adverse events and reactions among unrelated blood stem cell donors and recipients. With this Serious (Product) Events and Adverse Reactions (S(P)EARs) system, WMDA can collect and analyse information on S(P)EARs with the aim to gain insight in the occurrence of these, the causes and relation to blood stem cell donation and the provision of unrelated stem cell products.

Methods: WMDA member organisations are encouraged to report their S(P)EARs to WMDA. In 2018, the data collection has been done through the online questionnaire platform SurveyGizmo, following by a data analysis using Excel. All reported S(P)EARs were evaluated by the WMDA S(P)EAR committee and unclear or incomplete data were checked by a representative of the WMDA office.

Results: In 2018, the S(P)EAR committee received and considered 206 S(P)EAR reports from 18 organisations in 14 countries. Twenty-four (24) reports were considered not to be a S(P)EAR. The type of (SP)EARs reported were as follows: 151 (83%) harm to donor, 15 (8%) harm to recipient and 16 (9%) risk of harm. The majority ($N = 94$, 52%) of the S(P)EARs involved long term (>=30 days after collection) harm to donor and reports associated with HPC-Apheresis donations ($N = 137$, 75%).

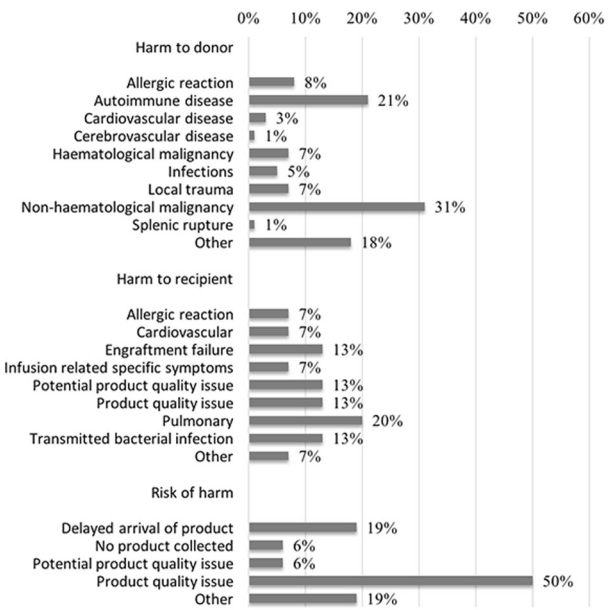
In graph 1 the types of reports are listed. The majority of the harm to donor reports were malignancies ($N = 57$, 38%) and autoimmune disorders ($N = 31$, 21%). A pulmonary disorder or symptom ($N = 3$, 20%) was the most common harm to recipient reported and half of the reported risk of harm incidents involved a product quality issue ($N = 8$, 50%).

The committee assessed each report for causation using the imputability tool. This tool is used to assess the likelihood that an adverse event/reaction in a donor or recipient is related to the process of donation or to a safety or quality defect in the transplanted tissue or cells. In 2018, 21% ($n = 38$) of reports were assessed as having definite, 12% ($n = 21$) probable, 7% ($n = 13$) possible, 44% ($n = 80$) unlikely and 11% ($n = 20$) excluded imputability. Five percent ($n = 10$) of reports were not assessable.

During 2018, 21,745 unrelated blood stem cell donations have taken place worldwide. These involved 2,783 HPC-Cord donations; 14,998 HPC-Apheresis donations and 3,964 HPC-Marrow donations. This means that for 0,25% ($N = 7$) of the HPC-Cord donations, in 0,91% ($N = 137$) of the HPC-Apheresis donations and in 0,86% ($N = 34$) of the HPC-Marrow donations a S(P)EAR has been reported.

Conclusions: The report rate of S(P)EARs in unrelated blood stem cell donation is below 1% for all cell types. However, we do believe there is a certain degree of underreporting of S(P)EARs to the WMDA. In the past year a new reporting system has been developed and implemented which should increase the user friendliness for reporters as well as improve communication about the reports.

It is important to emphasize that in addition to events and reactions in connection to a donation, any malignancy, severe autoimmune disorder, and donor death should be reported.



[Type of problem per S(P)EAR type.]

Disclosure: The authors declare no conflict of interest.

O165.

The Improvement in Overall Survival from Unrelated Donor Transplant in Australia and New Zealand is Driven by a Reduction in Transplant Related Mortality

David Kliman[1], Steven Tran[2], David Gottlieb[3,4], Nada Hamad[4,5,6], Leonie Wilcox[2], John Moore[5,6]

[1]Alfred Health, Melbourne, Australia, [2]ABMTRR, Sydney, Australia, [3]Westmead Hospital, Sydney, Australia, [4]University of Sydney, Sydney, Australia, [5]St Vincent's Hospital, Sydney, Australia, [6]University of New South Wales, Sydney, Australia

Background: Matched unrelated donors (MUDs) are the most common stem cell source for allogeneic transplantation (alloSCT) worldwide and this is also true for the transplant population in Australia and New Zealand (ANZ). Historically, non-relapse mortality (NRM) was substantially higher using MUDs compared to matched siblings, though recent international data suggest this gap is decreasing. We aimed to determine whether NRM following MUD alloSCT has reduced for ANZ patients and delineate which factors have contributed.

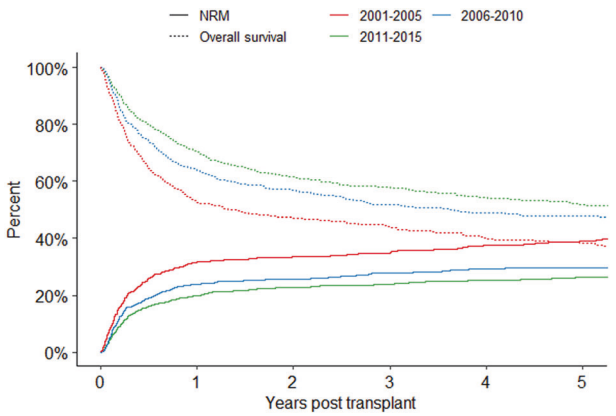
Methods: We analysed data from the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR). Adult (age >16 years) patients were included if they had a received a first alloSCT utilising a MUD during 2001-2015. Data collected included basic demographics, disease indication and risk, degree of HLA match, transplant year, cell source, CD34 dose, CMV serostatus, conditioning regimen, T-cell depletion and performance status. The patient group was divided into 3 cohorts according to quinquennium. Outcomes included overall survival (OS), progression-free survival (PFS) as well as incidences of NRM and disease relapse. Probability of OS and PFS were calculated using Kaplan Meier method while cumulative incidences of relapse and NRM were estimated accounting for competing risks. Independent predictors of outcome were determined from cox regression, accounting for time-dependent covariates where required.

Results: A total of 2565 patients received first MUD alloSCT between 2001-2015. Changes over time included increasing patient age, utilisation of peripheral blood stem cells, reduced intensity conditioning and T-cell depletion. Two-year OS increased from 47% in 2001-2015 to 61% in 2011-2015 (p< 0.001). This was attributed to a fall in NRM from 34% to 23% during that period (p< 0.001) with no appreciable change in relapse. Pre-transplant factors associated with NRM included age, degree of HLA match, disease phase, time to transplant and female gender. T-cell depletion and transplantation for Acute Lymphoblastic Leukaemia adversely impacted NRM during the 2001-2005 period only. As expected the development of acute or chronic graft-versus host disease (GVHD) increased NRM risk.

Conclusions: Survival following MUD SCT has improved by almost 15% over the past decade, driven by improvements in NRM. This has occurred despite increasing recipient age and appears to be due to better donor selection, transplantation earlier in the disease course and refinement of T-cell depletion doses. Prevention of significant GVHD remains paramount in light of the adverse impact on outcomes.

Variable	HR (95% CI)	P-value
Grade 3-4 acute GVHD	4.61 (3.73-5.69)	<0.001
T-cell depletion (2001-2005)	2.20 (1.31-3.70)	0.003
Transplant for ALL (2001-2005)	2.17 (1.13-4.17)	0.020
Chronic GVHD	1.55 (1.14-2.10)	0.005
Disease Phase Advanced	1.40 (1.08-1.80)	0.010
Time to SCT >180 days	1.38 (1.03-1.84)	0.031
Gender Female	1.28 (1.05-1.57)	0.017
Age (per 10 years)	1.27 (1.16-1.40)	<0.001
HLA group- not well matched	1.24 (1-1.54)	0.048

[Multivariate analysis for NRM]



[OS probability and NRM incidence by year]

Clinical Trial Registry: The study was approved by the steering committee of the ABMTRR.

www.abmtrr.org

Disclosure: Nothing to declare.

O166.

Alloreactivity Against HLA-DPB1 in Host-Versus-Graft Direction is Associated with Increased Risk of Graft Failure After Matched Unrelated Donor Transplantation for Nonmalignant Diseases

Alberto Cardoso Martins Lima, Margareth Kleina Feitosa, Luciana Nasser Dornelles, Geovana Borsato do Amaral, Gisele Loth, Samantha Nichele, Vaneuza Araújo Moreira Funke, Samir Kanaan Nabhan, Noemi Farah Pereira, Carmem Bonfim, Ricardo Pasquini

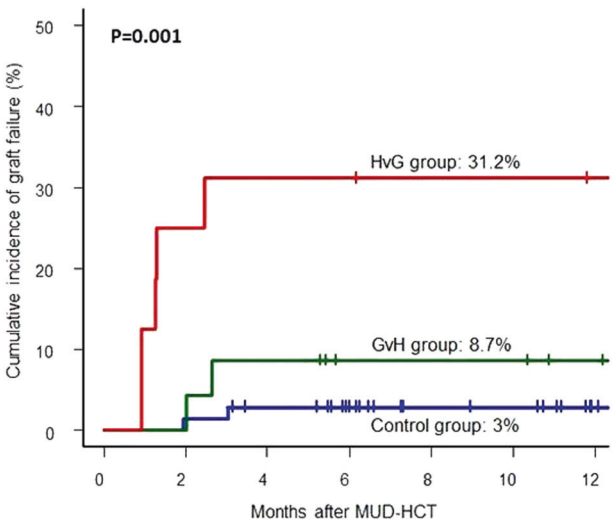
Federal University of Parana, Curitiba, Brazil

Background: The presence of T-cell epitope (TCE) non-permissive HLA-DPB1 mismatches (NP-MM) and HLA-DP donor-specific antibodies (DSA) have been associated with deleterious outcomes after matched unrelated donor hematopoietic cell transplantation (MUD-HCT) for malignant diseases. However, the role of anti-DPB1 alloreactivity has not been clearly defined in the context of MUD-HCT for nonmalignant diseases (NMD). In this retrospective single-center study, we hypothesized that NP-MM in host-versus-graft (HvG) direction and/or HLA-DP DSA would confer increased risk of graft failure (GF) in patients with NMD who underwent MUD-HCT.

Methods: All donor-patient pairs were matched at high resolution for HLA-A, -B, -C, -DRB1 and -DQB1 (10/10 match). HLA-DPB1 mismatches permissiveness was assessed with IMGT/TCE-3 algorithm version 2.0. HLA-DP DSA were determined using Luminex Single Antigen Beads kit. Patients were divided into 3 groups according to the alloreactivity direction: HvG (NP-MM in HvG direction and/or DSA positive; n=16), graft-versus-host (GvH) (NP-MM in GvH direction and DSA negative; n=23), and control group (CON) (12/12 Match/Permissive mismatches and DSA negative; n=67). Gray test was used to estimate the cumulative incidence of GF. Death with sustained engraftment was considered a competing event for GF. A Fine-Gray regression model was used to identify the risk factors for GF in the multivariate analysis. The prognostic effect of GF on overall survival (OS) was assessed through a Cox regression model, using GF as a time-dependent variable. Statistical analysis was performed using EZR software.

Results: Between January 2008 and December 2017, 106 patients with NMD received a first MUD-HCT at Federal University of Parana, Curitiba, Brazil. All patients received bone marrow as the graft source, and 101 of them (95.3%) had in vivo T-cell depletion with ATG. The most prevalent NMD were inherited bone marrow failures (48.1%) and acquired severe aplastic anemia (34.9%). Median age of patients was 10 years (IQR: 6.25, 15.75). Of 106 donor-recipient pairs, 20 (18.9%) were 12/12 matched, 47 (44.3%) had permissive mismatches, 25 (23,6%) had NP-MM in GvH direction, and 14 (13.2%) had NP-MM in HvG direction. Only 3 out of 106 patients (2.8%) had anti-DP DSA. Overall, nine of 106 patients (8.49%) experienced GF. Out of the nine GF, two were primary GF and seven secondary GF. Median time from transplant to secondary graft loss was 61 days (range: 38-92). All GF occurred in patients transplanted with HLA-DPB1 mismatched donors. One-year cumulative incidence of GF was 31.2%, 8.7%, and 3% for HvG, GvH and CON groups, respectively ($P = 0.001$). In multivariate analysis, the risk of GF was significantly increased in the HvG group as compared to GvH and CON groups (HR 8.53; 95% CI:2.6-28.3; P< 0.001). No other covariate influenced the risk of graft loss. GF as time-dependent variable was significantly associated with inferior OS (HR 9.6; 95 % CI: 2.8-31.8; P < 0.001).

Conclusions: Our results suggest that anti-DPB1 HvG alloreactivity is associated with increased risk of GF after MUD-HCT for nonmalignant diseases. Considering HLA-DPB1 TCE-3 permissiveness along with HLA-DP DSA status may optimize unrelated donor search for patients with NMD. Further studies are warranted to validate these findings.



[One-year cumulative incidence of graft failure]

Disclosure: Nothing to declare

Stem cell mobilization, collection and engineering

O167

Two Year Analysis of a Prospective Phase I/II Clinical Trial in Adults Using TCR Alpha/Beta Depleted Stem Cell Transplantation from Matched Related and Unrelated Donors.

Moniek A. de Witte[1], Anke Janssen[1], Clara A. Nijssen[1], Anna van Rhenen[1], Rick Admiraal[1], Lotte van der Wagen[1], Monique C. Minnema[1], Eefke Petersen[1], Reinier A. P. Raymakers[1], Kasper Westinga[1], Constantijn J. M. Halkes[1], Jaap Jan Boelens[2], Jurgen Kuball[1]

[1]*University Medical Center Utrecht, Utrecht, Netherlands*, [2]*Memorial Sloan Kettering Cancer Center, New York, NY, United States*

Background: Key requirement to implement maintenance therapy after allogeneic stem cell transplantation (allo-SCT) is rapid engraftment without severe complications.

Methods: Here we report the 2 year analysis of a multicenter prospective single-arm phase I/II study assessing the safety and feasibility of transplantation of TCRalpha/beta depleted stem cells from matched related or unrelated donors using the CliniMACS System (Miltenyi Biotec, Germany) in combination with a reduced toxicity myeloablative conditioning in adult patients. The conditioning regimen consisted of ATG (Thymoglobulin®) 1.5mg/kg i.v. days -12 to -9; fludarabine i.v. 40 mg/m^2 days -5 to -2 and busulfan i.v. (Busilvex®) days -5 to -2 (cumulative AUC of 80-90mg*h/L), followed by 28 days of MMF. Primary endpoint was the incidence of acute GVHD at day 100.

Results: 35 patients were enrolled in 2 centers (10 female and 25 male patients; median age 59 years, range 19 - 69 years), including 9 AML, 4 ALL, 2 CML, 5 MM, 1 NHL, 4 MDS (high risk), 4 MDL (low risk), 4 MPN and 2 CMML. Donors included 4 MRD, 21 10/10 matched MUD and 10 9/10 matched MUD. The median number of CD34+ cells and αβ TCR cells/kg was 6.1x 10^6 (range, 1.9-10) and 16.3x10^3 (range, 0-136), respectively. One primary graft failure was observed. Primary engraftment of ANCs > 500 cells/μL was reached at a median of 14 days (range 9 - 48 days) and of platelets > 20 cells/μL at a median of 17 days (range 10 - 99).

The median time of follow-up was 35 months (range 24-42). Immune reconstitution (IR) was analyzed up to 1 year. Median numbers of CD3/CD4+ and CD3/CD8+ T cells were 192 cells/ul (range 34-497) and 273 cells/ul (range 10-727). The median numbers of NK were 256 cells/ul (range 62 - 565) and of γδ T cells 14 cells/ul (range 1-46).

The cumulative incidence (CI) of aGVHD grade II-IV and III-IV at day 100 was 26% (+/- 13%) and 14% (+/- 9%). 54% of patients received a prophylactic DLI at day 100 (reasons for not receiving DLI were either development of GVHD or early relapse/progression). The CI of aGVHD grade II-IV and III-IV at 2 years was 37% (+/- 15%) and 17% (+/- 10%). The CI of CMV reactivation was 37% (+/- 16%) and of EBV reactivation 49% (+/- 18%). The CI of relapse was 29% (+/- 6%) and the TRM was 32% (+/- 15%) at 2 years. Kaplan Meier estimates of the EFS and OS were 42% (+/- 8%) and 54% (+/- 8%) at 2 years. The total CI of cGVHD was 26% (+/-8%), 14% (+/- 6%) being extensive.

Conclusions: Allo-SCT of αβ T cell depleted PBMCs from matched related or unrelated donors, in combination with early ATG and a myeloablative reduced toxicity conditioning regimen, resulted in favorable rates of primary engraftment. While the incidence of cGVHD at 2 years was low, the incidence of aGVHD II-IV and III-IV was rather high as compared to previous reports by others. Addition of CD19 depletion may reduce the incidence of aGVHD and subsequent TRM.

Clinical Trial Registry: https://www.trialregister.nl/trial/4767

Disclosure: COI: Dr. Kuball reports grants from Gadeta, Novartis, and Miltenyi Biotech. He is scientific co founder and scientific advisor of gadeta (www.gadeta.nl) and inventor on multiple patents on γδ TCR receptors γδTCR ligands, and isolation strategies for engineered immune cells.

Funding for this study was provided by KWF UU 2015-7553 to M.A.d.W; ZonMW 43400003 and VIDI-ZonMW 917.11.337, KWF UU 2010-4669, UU 2013-6426, UU 2014-6790, and UU 2015-7601, Vrienden van het UMCU, AICR 10-0736, and 15-0049 to J.K.

Stem cell source

O168.

Optimizing Outcomes of Acute Leukemia After Transplants with Single Unrelated Cord Blood Units Selected According to Current International Recommendations for Cell Dose and HLA Match

Hanadi Rafii[1,2], Kenzey Chantal[1,2], Fernanda Volt[1,2], Jaime Sanz[3], Gerard Michel[4], Jean Hugues Dalle[5], Katharina Kleinschmidt[6], Etienne Baudoux[7], Sergy Querol[8], Annalisa Ruggeri[1,9], Christian Chabannon[10], Eliane Gluckman[1,2]

[1]*Eurocord, Hopital Saint-Louis, APHP, University of Paris, IRSL, EA3518, Paris, France*, [2]*Monacord, Centre Scientifique, Monaco, Monaco*, [3]*Hospital Universitario La Fe, Valencia, Spain*, [4]*Aix-Marseille University and La Timone Children's Hospital, Marseille, France*, [5]*Hopital Robert Debré, Assistance Publique - Hôpitaux de Paris, Paris, France*, [6]*University Children's Hospital, Regensburg,*

Germany, [7]*CHU de Liege, Liege, Belgium*, [8]*Catalan Blood and Tissue Bank, Barcelona, Spain*, [9]*Ospedale Bambino Gesù, Rome, Italy*, [10]*Paoli-Calmettes Institute, INSERM CBT1409, Marseille, France*

Background: Cell dose and HLA matching have been described as important factors for selection of single-unit cord blood (sCBU) for transplantation.

Methods: Retrospective study aiming to assess the impact, on cord blood transplant (CBT) outcomes, of optimal selection of sCBU based on current published international guidelines for donor choice. Eligibility criteria: 1) adults or children with acute leukemia (AL) in first or second complete remission (CR) who received unrelated sCBT; 2) pre-cryopreservation total nucleated cell (TNC) dose ≥ $2.5x10^7$/kg; 3) and ≤2/6 HLA disparities between CBU and recipient. Patients with prior allogeneic transplantation were excluded. All transplants were performed in EBMT centres between January 2001 and December 2017.

Results: 1509 patients ($n = 999$; 66% aged< 18 years) with AL (53% acute lymphoblastic leukemia (ALL); 47% acute myeloid leukemia (AML)) were included; 54% were in CR1 ($n = 818$) and 46% in CR2 ($n = 691$). The median age at CBT was 10 (0.3-68) years (y). Myeloablative conditioning was administered to 85% and total body irradiation to 45% of patients (dose ≥8Gy in 35%). 71% of patients received antithymocyte globulin. Recipients and sCBU were 6/6 HLA-matched (13%) or had one (46%) or two (41%) HLA mismatches (HLA-MM), considering typing at antigen level for HLA-A and HLA-B and allele level for HLA-DRB1. The median follow-up for survivors was 56 months (0.8-204).

The cumulative incidence (CI) of neutrophil recovery was 88.6% (87- 90.2) at day 60, with a median time of 21 (5-72) days (d). The 100d CI of grade II-IV acute GVHD was 30.7% (28.4 - 33.2) and was significantly higher in ALL (34% vs 26% in AML; *p< 0.001*). The 3y-CI of chronic GVHD was 23.9% (21.6-26.5); 8% of patients had the extensive form. The 3y-CI of relapse was 22.3% (19.6-25.6) for patients in CR1 and 28.7% (25.3-32.4; $p = 0.02$) for those in CR2. The 3y-CI of non-relapse mortality was 26.8% (24-30.2) in the CR1 group and 26.7% (23.5-30.3; $p = 0.68$) in the CR2. At 3y follow-up, leukemia free survival (LFS) was 47% ± 1 (50% for CR1; 44% for CR2; $p = 0.02$) and overall survival (OS) was 52% ± 1 (55% for CR1 and 49% for CR2; $p = 0.01$). In multivariate model, age ≥18y and positive recipient CMV serology were associated with shorter LFS [HR1.52; CI 1.23-1.88, *p< 0.001* and HR1.22, CI 1.05-1.42, $p = 0.01$ respectively] and worse OS [HR1.45, CI1.16-1.80, $p = 0.001$ and HR1.25, CI 1.07-1.46, $p = 0.005$ respectively].

There was significant difference in transplant-related mortality (TRM) between CBT with HLA-MM=2 and HLA-MM=0-1 (HR1.24, CI 1.01-1.55; $p = 0.04$). Other factors associated with higher TRM were age ≥18y (HR1.41; CI 1.09-1.82; $p = 0.009$), positive recipient CMV serology (HR 1.41, CI 1.14-1.75; $p = 0.002$) and time interval between diagnosis and CBT ≥9months (HR1.30, CI 1.05-1.60; $p = 0.01$). At last follow-up, 707 (47%) patients died mainly because of TRM ($n = 413$) and disease progression ($n = 281$). Infections and GVHD were the most common causes of TRM.

Conclusions: Selection of sCBU based on recommended cell dose and HLA criteria results in good engraftment and survival. When cell dose (TNC ≥ $2.5x10^7$/kg) is respected, other factors such as HLA disparity have an impact on outcomes.

Disclosure: An analysis on behalf of Eurocord and the CTIWP.

Nothing to disclose.

CAR-based Cellular Therapy – clinical

O169.

Abstract already published.

O170.

CD19-Targeted CAR-T Cell Therapy for 32 B-Cell Acute Lymphoblastic Leukemia (B-ALL) Patients WHO Relapsed After Allogeneic Hematopoietic Stem Cell Transplantation (ALLO-HSCT)

Xian Zhang[1,2], Junfang Yang[1], Jianping Zhang[1], Jingjing Li[1,2], Wenqian Li[1], Peihua Lu[1,2]

[1]*Hebei Yanda Lu Daopei Hospital, Langfang, China*, [2]*Beijing Lu Daopei Institute of Hematology, Beijing, China*

Background: Patients with ALL who have relapsed after allo-HSCT have a dismal prognosis. CAR-T cell therapy has shown great success for treating relapsed/refractory B-ALL. Here we have assessed the initial response, duration of remission, and safety, especially cytokine release syndrome (CRS), graft-versus-host disease (GVHD) incidence after CD19 CAR-T therapy for B-ALL patients who relapsed after transplant.

Methods: From February 2016 to May 2019, 32 patients with B-ALL who relapsed post allo-HSCT were enrolled from four different clinical trials. The median age was 22

(2-55) years old. Median bone marrow blasts were 23.89% (0.03-92.43%) before CAR-T infusion, and 12/32 (37.5%) patients had received at least one prior donor lymphocyte infusion. No patients had active GVHD before CAR-T except for one patient who had limited chronic skin GVHD not requiring treatment.

The second generation CD19 CAR-T cells were produced from purified T cells either from transplant donors (12) or patients (20). They contained either a 4-1BB co-stimulatory signal domain in 23 patients or a CD28 domain in 9 patients.

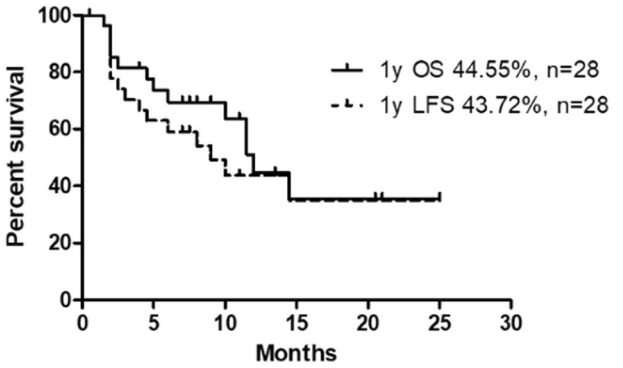
All patients received a conditioning regimen of IV fludarabine (30mg/m^2/d) and cyclophosphamide (250mg/m^2/d) for 3 days followed by a single infusion of CAR-T cells with a median dose of 2 x10^5 (0.083-10x10^5) cells/kg.

Results: With a median follow-up of 237 (30-789) days, 28/32 (87.5%) patients achieved complete remission (CR) on D30 after CAR-T-cell infusion, and 27/32 (84.4%) were minimal residual disease (MRD)-negative CR. For the 28 CR patients, one-year overall survival (OS) was 44.6% and leukemia-free survival (LFS) was 43.6% (Figure 1). Eight patients who achieved MRD-negative CR underwent a 2nd allo-HSCT at a median time of 76 (39-329) days after CAR-T (2 from matched-unrelated donors, 6 from haploidentical donors). Six out of 8 patients remained in LFS at a median follow up of 333(200-763) days but the other two died from infection. For the remaining 20 CR patients, 5 patients remained in LFS at a median of 386 (270-611) days but 8 patients subsequently relapsed at a median of 165 (46-240) days. Of the 8 relapsed patients, 3/10 (30.0%) patients whose CAR-T-cells were manufactured from donor, and 5/18 (27.8%) from autologous CAR-T-cells. Seven patients died from non-relapse mortality.

Only 24/32 (75.0%) patients had grade I-II CRS, and 3/32 (9.4%) had grade II-IV CRS. Total 5/32 (15.6%) patients developed neurotoxicity with 4 of grade III and 1 of grade IV.

After CAR-T therapy, 9/32 patients developed GVHD including 7 with grade II-III acute GVHD and 2 with localized chronic GVHD. Of note, 5/12 (41.7%) patients whose CAR-T cells were manufactured from transplant donors developed GVHD, versus 4/20 (20.0%) ($p = 0.24$) for those whose CAR-T were autologous.

Conclusions: Our study demonstrates that a high CR rate can still be achieved through CAR-T therapy even for those who relapsed after allo-HSCT without increasing CRS or neurotoxicity. A second consolidation allo-HSCT may be considered for those who achieved MRD-negative CR after CAR-T. Receiving CAR-T cells that manufactured from transplant donors may result in a trend towards higher GVHD rate compared to autologous CAR-T cells. GVHD should be carefully watched and managed.



[Figure 1. OS &LFS of the 28 patients achieved CR after CAR-T therapy]

Clinical Trial Registry: www.clinicaltrials.gov NCT03173417, NCT02546739; www.chictr.org.cn ChiCTR1800016541, ChiCTR-IIh-116008711.

Disclosure: Nothing to declare.

O171.

International Prognostic Index Predicts Outcomes in Patients with Relapsed and Refractory Large Diffuse B Cell Lymphoma Treated with Commercial CAR T Cells

Marta Garcia-Recio[1], Kitsada Wudhikarn[2], Martina Pennisi[2], Rosalia Alonso-Trillo[3], Jessica Flynn[2], Shouval Roni[2], Yakup Batlevi[2], Mari Lynne Silverberg[2], Connie W Batlevi[2], Renier Brentjens[2], Dahi Parastoo[2], Sean Devlin[2], Claudia Diamonte[2], Sergio Giralt[2], Elizabeth Halton[2], Josel Ruiz[2], Molly Maloy[2], Elena Mead[2], Lia Palomba[2], Bianca Santomasso[2], Craig Sauter[2], Michael Scordo[2], Shah Gunjan[2], Jae Park[2], Miguel-Angel Perales[2]

[1]HUSE, Palma, Spain, [2]MSKCC, New York, NY, United States, [3]Puerta de Hierro, Majadahonda, Spain

Background: CD19-targeted chimeric antigen receptor (CAR) T cells have shown excellent activity against relapsed/refractory (R/R) B cell malignancies with manageable early toxicities and a suggested safe late toxicity profile. Many of the CAR T cells early and late side effects could due to baseline disease and patient characteristics, which may also have an impact on overall (OS) and progression-free survival (PFS). Indexes routinely used to predict outcomes in patients with DLBCL (IPI or age adjusted IPI) have not been tested in patients receiving CAR T cells. The objective of this study is to determine if IPI and/or age adjusted IPI (a-IPI) assessed pre-leukapheresis can be used to predict early toxicities and outcomes in adult patients with R/R DLBCL after receiving commercial CAR T cells. Charlson Comorbidity

Index (CCI) and HCT-CI were calculated to assess comorbidities.

Methods: Between February 2018 and June 2019, 60 consecutive adult patients with R/R DLBCL received FDA-approved CD19 CAR T cell products (axicebtagene ciloleucel or tisagenlecleucel) at our center. Comorbidities were collected from medical records pre-leukapheresis and after bridge therapy. IPI and a-IPI were calculated pre-leukapheresis. High disease burden was defined as >= 3 for IPI, >= 2 for a-IPI, >= 2 for CCI and >= 3 for HCT-CI. All statistical analyses were performed by R program version 3.6.0.

Results: 60 patients with R/R DLBCL were included in this study with a median follow-up of 206 days (24-562). Median age was 63 (19.5-85.9), 43 (71.6%) received axicebtagene ciloleucel and 17 (28.3%) received tisagenlecleucel. Eight patients were excluded from the final analysis of IPI and a-IPI due to unconfirmed stage and only 15 patients were evaluable for HCT-CI (pulmonary functional tests not available). Of the remaining 52 evaluable patients, 45 (75%) had advanced stage (III-IV). Additionally, 52% were high risk by IPI, 50% by a-IPI, 20% by CCI and 47% by HCT-CI. High risk IPI (HR 2.85, $p = 0.035$) and a-IPI (HR 6.13, $p = 0.001$) were associated with inferior PFS, while high risk a-IPI was also associated with inferior OS (HR 7.38, $p = 0.008$). High risk IPI was also associated with increased risk of neurotoxicity (HR 2.53, $p = 0.048$). High risk HCT-CI was predictive of CRS (HR 3.53, $p = 0.018$) and any toxicity (CRS and neurotoxicity) (HR 1.69, $p = 0.069$) (Table 1). Comorbidities assessed by CCI could not predict neither outcomes or toxicity.

Conclusions: In this cohort of 52 evaluable patients with R/R DLBCL treated with commercial CAR T cells, we showed that the international prognostic indexes (IPI and a-IPI) can predict survival outcomes. In addition, the IPI determined pre-leukapheresis can also predict neurotoxicity in this patient population. These results may help with patient selection as well toxicity mitigation in high risk patients with R/R DLBCL. Results for HCT-CI need further validation due to the small sample of evaluable patients.

Disclosure: Dr. Garcia-Recio reports honoraria from Janssen and Takeda. Dr. Gunjan received research funding from Janssen and Amgen. Dr. Batlevi C reports consultancy and membership on Juno therapeutics. Dr. Brentjens is consultant for Juno and Celgene. Dr. Palomba is member of Pharmacyclics and consultant for Noble Insights. Dr. Santomasso is consultant for Kite/Gilead, Juno/Celgene and Novartis. Dr. Sauter is consultant for Juno Therapeutics, Sanofi-Genzyme, Spectrum Pharmaceuticals, Novartis, Genmab, Precision Biosciences, Kite/Gilead, Celgene and GSK. He received research support from Juno Therapeutics and Sanofi-Genzyme. Dr. Scordo is consultant for McKinsey & Company and Angiocrine Bioscience. Dr. Park is consultant for Allogene, Amgen, AstraZeneca, Autolus, GSK, Incyte, Kite Pharma, Novartis and Takeda. Dr. Giralt is consultant and received research funding for Amgen, Actinium, Celgene, Johnson & Johnson and Takeda. He received research funding from Miltenyi and he is consultant for Jazz Pharmaceuticals, Novartis, Kite and Spectrum Pharmaceuticals. Dr. Perales reports honoraria from Abbvie, Bellicum, Celgene, Bristol-Myers Squibb, Incyte, Merck, Novartis, Nektar Therapeutics, Omeros, and Takeda. He serves on DSMBs for Cidara Therapeutics, Servier and Medigene, and the scientific advisory boards of MolMed and NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead and Miltenyi Biotec. He serves in a volunteer capacity as a member of the Board of Directors of American Society for Transplantation and Cellular Therapy (ASTCT) and Be The Match (National Marrow Donor Program, NMDP), as well as on the CIBMTR Cellular Immunotherapy Data Resource (CIDR) Committee. Dr. Pennisi, Dr. Wudhikarn, Flynn J., Maloy M., Silverberg ML, Batlevi Y., Shouval R., Devlin S., Dr. Parastoo, Diamonte C., Halton E., Ruiz J, Maloy M and Dr. Mead have nothing to declare.

O172.

Abstract already published.

O173.

Real-World Evidence of the use of Tisagenlecleucel for Patients with Relapsed/Refractory Agressive B-Cell Lymphomas. The Spanish Experience

Gloria Iacoboni[1], Eva Catala[1], J. M. Sanchez Pina[2], Rebeca Bailen[3], Alberto Mussetti[4], J. M. Sancho[5], J. M. Ribera[5], Anna Sureda[4], Mi Kwon[3], Mari Liz Paciello Coronel[2], Francesc Bosch[1], Pere Barba[1]

[1]Vall d'Hebron University Hospital, Barcelona, Spain, [2]12 de Octubre University Hospital, Madrid, Spain, [3]Gregorio Marañon University Hospital, Madrid, Spain, [4]ICO-IDIBELL, L'Hospitalet de Llobregat, Spain, [5]ICO-IJC-Hospital Germans Trias i Pujol, Badalona, Spain

Background: Tisagenlecleucel (tisa-cel) is a chimeric antigen receptor (CAR) T-cell therapy approved for relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) based on results of a phase 2 trial. However, little is known on patient outcome in the commercial setting in Europe.

Methods: We evaluated in a retrospective study the safety and efficacy of tisa-cel in R/R DLBCL patients treated in 5 Spanish centers. All consecutive patients with

this diagnosis who underwent apheresis for tisa-cel from December 2018 to November 2019 were included. Cytokine-release syndrome (CRS) and immune-effector cells associated neurotoxicity syndrome (ICANS) were graded according to the ASTCT criteria. Overall survival (OS) and progression-free survival (PFS) were evaluated from the time of cell infusion. Disease response was assessed in infused patients and in all patients who underwent apheresis.

Results: Forty-five patients underwent apheresis: 38 patients (84%) received tisa-cel, while 7 (16%) patients did not, mainly due to disease progression ($n = 6$). Demographic and clinical characteristics of patients receiving tisa-cel are summarized in table 1. All patients received fludarabine and cyclophosphamide as lymphodepleting chemotherapy. Six (16%) of the 38 infused products were out of specification according to EMA requirements. Median follow-up for survivors was 5 months (range 1-10). Seventeen (45%) patients developed CRS of any grade at a median of 2 days (range 0-10) after infusion. Grade 2-4 and 3-4 CRS occurred in 8 (21%) and 2 (5%) patients, respectively. Seven (18%) patients developed ICANS, all of them but one (grade 2) were grade 1. One patient developed macrophage activation syndrome. Four (11%) were transferred to the intensive care unit. A median of 1 dose of tocilizumab was administered to 12 patients, and steroids were used in 7 patients for a median of 10 days. Only one patient received additional therapy (siltuximab and anakinra) for CAR-T-related complications. Microbiologically documented infections occurred in 9 (24%) patients (6 bacterial, 2 fungal, and 1 viral). Of the 36 evaluable patients for disease response, best reponse achieved was complete remission (CR) ($n = 9$, 25%), partial remission (PR) ($n = 13$, 36%) [overall response rate (ORR) of 61%], stable disease ($n = 3$) and progressive disease ($n = 12$). Considering the 45 patients who underwent apheresis (*intention to treat*), CRs and PRs were observed in 20% and 29%, respectively (ORR of 49%). Estimated 6-month PFS and OS were 33% and 68%, respectively. At last follow-up, 9 (24%) of the 38 patients had died at a median of 48 days (range 25-181) after CAR-T infusion, all but one due to progression.

Conclusions: Tisagenlecleucel can achieve disease response with a good safety profile in patients with R/R DLBCL treated in the real-world setting in a European country.

Characteristic	Patients
Median age (range)	53 (23-72)
Male gender, n (%)	23 (64)
ECOG PS, median (range)	1 (0-2)
Previous auto-HSCT, n (%)	12 (33)
Previous lines of therapy, median (range)	3 (2-5)
LDH at the time of CAR-T therapy (>1.5xUNL), n (%)	22 (61)

[Table 1. Clinical and demographic characteristics of infused patients.]

Disclosure: G.I.: Consultancy from Celgene, Novartis, Gilead. Speaker from Roche, AbbVie, Janssen. P.B.: Consultancy from Amgen, Celgene, Gilead, Jazz Pharmaceuticals, Novartis, Pfizer. Speaker from Amgen, Celgene, Novartis, Pfizer, Roche. Travel and accommodations from Jazz Pharmaceuticals, Novartis, Pfizer.