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ABSTRACTS COLLECTION

The 46th Annual Meeting of the European Society for Blood and Marrow Transplantation: Physicians Award Winners (O001-O009)

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Physicians award winners

Van Bekkum Award

O001.

Results of the Ebmt Saawp Phase III Prospective Randomized Multicenter Race Study of Horse Atg and Ciclosporin with or Without Eltrombopag in Naïve Saa Patients

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Background: Standard immunosuppressive therapy (IST) for severe/very severe aplastic anemia (SAA/vSAA) patients not eligible for transplantation is horse antithymocyte globulin (hATG) plus ciclosporin (CsA). We report an open-label, phase III, randomized trial of hATG and CsA with or without EPAG in naive patients with SAA/vSAA (clinicaltrials.gov, NCT02009747).

Methods: From July 2015 to April 2019, 197 treatment-naive patients were enrolled (6 countries and 24 sites), stratified on disease severity, age and center. Patients were randomized to either standard IST (hATG 40 mg/kg x4d and CsA 5 mg/kg/d; arm A) or standard IST + EPAG (experimental arm B) at the dose of 150 mg/d from day +14 until 6 months (m) (or 3m, in case of early complete response (CR)). The primary endpoint was hematological CR at 3m. Secondary endpoints included overall survival (OS), hematological response at 6m, clonal evolution and number and allele burden of somatic myeloid mutations (central laboratory, King's College London, UK). The study was powered to detect an increase in CR from 7% in arm A to 21% in arm B at 3m, requiring at least 96 patients per arm.

Results: One-hundred-one and 96 patients were randomized to arm A and arm B, respectively. Baseline characteristics were comparable between the 2 arms, including median age (52 and 55 years in arms A and B), age stratum (age < 40 was 35.6% in arm A and 30.2% in arm B), disease severity (vSAA was 33.7% in arm A and 35.4% in arm B), and presence of a PNH clone (59.2% in arm A and 45.2% in arm B). Median follow-up was 18 months. The primary endpoint was reached with 3m CR rates of 9.9% and 21.9% in arms A and B (pooled Odds Ratio 3.2, $p = 0.012$). Overall response (OR=CR +PR) rates were 31.7% and 59.4%, respectively. At time of analysis, OR at 6m for patients alive, not being transplanted and without clonal evolution was 50.0% in arm A vs 76.3% in arm B (Odds Ratio: 3.8). SAEs were comparable in both arms. Eight patients came off study prematurely in arm A and 7 in arm B requiring second-line transplantation. Clonal evolution occurred in 1 patient in arm A (karyotype abnormality 6.5m after randomization) and in 3 patients in arm B (2 karyotypic abnormalities and 1 MDS after 6.2, 6.3 and 12.0m after randomization). High sensitivity NGS analysis was performed using a 31 gene target molecular bar coded panel. At time of this analysis, samples were available from 163 patients at baseline, and 132 at 6m follow up with no difference in term of somatic myeloid mutations (baseline: VAF >1% 38.2% in arm A vs 36.6% in arm B). During the study, 22 patients died (14 in arm A, OS of 83.2% at 24m and 8 in arm B, OS 86.3% at 24m) ($p = 0.142$).

Conclusions: This practice changing phase III trial support the combination of hATG, CsA and EPAG as the next first line standard- of-care for SAA/vSAA patients not eligible fortransplantation.

RPDL, CD and AMR equally contributed

Clinical Trial Registry: clinicaltrials.gov, NCT02009747

Disclosure: The study was founded by Novartis and Pfizer, which provided also Eltrombopag and ATGAM, respectively.

Basic science award

O002.

Jun Activation in Dermal Fibroblasts Promotes Fibrosis and Inflammation in Sclerodermatous Graft-vs-host Disease in Mice and Humans

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Background: Chronic graft-vs-host disease (cGVHD) remains a major obstacle to the success of allogeneic hematopoietic cell transplantation. Sclerodermatous GVHD (sclGVHD) is one of the most devastating forms of cGVHD. Its pathophysiology involves chronic inflammation, cell-mediated and humoral immunity, and ultimately tissue fibrosis.

Methods: We established (i) a new MHC-matched, miAg-mismatched mouse model (AKR/J >BALB.k) of sclGVHD. Scl-tissues were examined by FACS, H&E-, immunohistochemistry- (IHC), and immunofluorescence (IF) staining. (ii) We analyzed human tissue microarrays (TMA) of 45 primary sclGVHD samples by IHF and IF. (iii) Dermal fibroblasts were isolated from fresh human sclGVH biopsies and subjected to ATACseq +/- deletion of JUN by CRISP-Cas9 and ChiPseq. (iv) Human sclGVHD fibroblasts were implanted under the kidney capsule of NOD-scid IL2Rɣ-/- mice to study the effects of in vivo inhibition of profibrotic pathways.

Results: (i) In our sclGVHD mouse model recipients of T-cell replete grafts developed severe scleroderma with massive skin thickening, collagen deposition, and extensive

fibrosis with mixed inflammatory infiltrates. Fibroblasts strongly expressed JUN, a transcription factor involved in acute phase responses that regulates gene expression in response to cytokines, growth factors, infections. Likewise, CD47, an immune checkpoint protein that prevents phagocytic removal of cells by macrophages was strongly co-expressed in fibroblasts in sclGVHD. (ii) Our findings were confirmed in 45 archived sclGVHD biopsies, which also demonstrated strong expression and activation of JUN and CD47 in dermal fibroblasts. (iii) Next, we isolated primary fibroblasts from fresh human sclGVHD biopsies to analyze chromatin accessibility across the genome by ATAC-seq. Chromatin accessibility to the JUN promotor, but also to the IL-6 promotor and CD47 enhancer and promotor was wide open in sclGVHD fibroblasts, whereas in normal fibroblasts the JUN promotor was only minimally accessible. CRISPR-Cas9 knock-down studies on sclGVHD fibroblasts revealed that the IL-6 promotor, and the CD47 enhancer+promotor were regulated by JUN, as with JUN deletion promotor binding accessibility to IL-6 and CD47 was significantly decreased. Furthermore, JUN activity regulated key members of the Hedgehog pathway (GLI1, PTCH1 and PTCH2), as their chromatin accessibility was decreased with JUN deletion. These correlative findings were confirmed by JUN ChIP seq. (iv) Finally, in xenograft models with established human sclerotic cell growth under the kidney capsule, treatments with anti-CD47/IL-6 antibodies, vismodegib (a Hh pathway inhibitor), or nintedanib (a TKI, targeting e.g., PDGFR, FGFR, VEGFR) - but not with placebo - were able to resolve established fibrosis by blocking the activation of JUN (pJUN) and its profibrotic downstream pathway members IL-6 and pSTAT3, as assessed by phospho flow.

Conclusions: In summary, we demonstrate a new mechanism in which chronic inflammation perpetuates fibrosis via activation of JUN, CD47, IL-6, and the Hedgehog pathway, which form the heart of a profibrotic signature in sclGVHD. Our findings are of particular interest, as (i) these pathways have been implicated in tissue fibrogenesis in other contexts (Wernig et al. PNAS2017), and (ii) indicate potential targets for therapeutic interventions using Hedgehog-inhibitors, anti-CD47 and IL-6R antibodies.

Disclosure: Nothing to declare

Presidential symposium

O003.

Superior event-free Survival with Blinatumomab Versus Chemotherapy in Children with high-risk First Relapse Of b-cell Precursor Acute Lymphoblastic Leukemia: A Randomized, Controlled Phase 3 Trial

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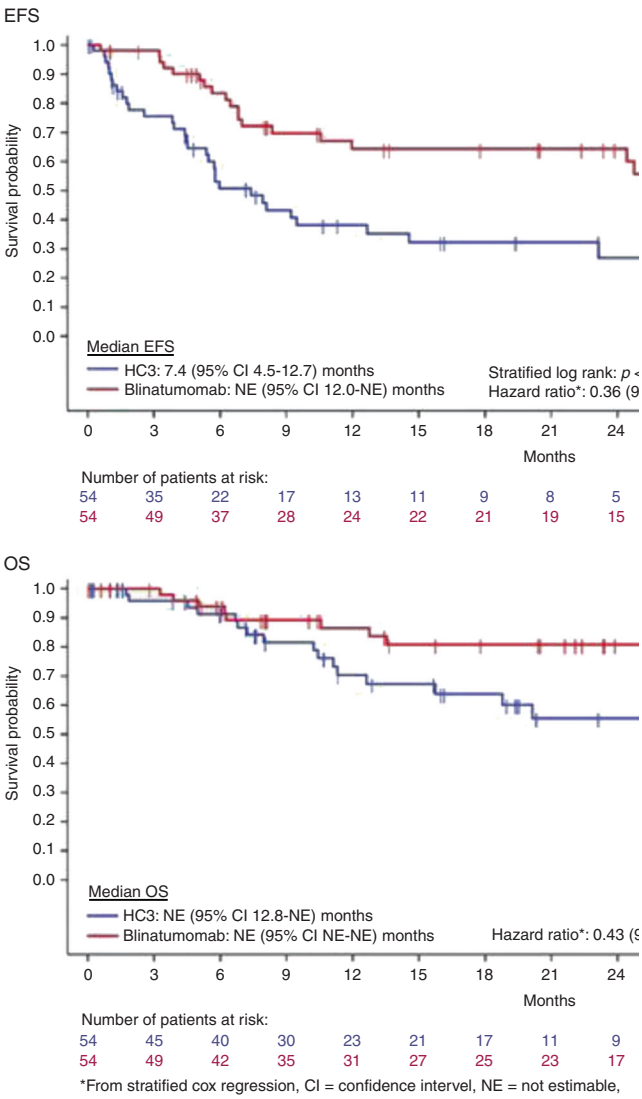
Background: Children with high-risk (HR) first-relapse B-cell precursor acute lymphoblastic leukemia (BCP-ALL) are candidates for allogeneic hematopoietic stem cell transplant (alloHSCT) when a second complete morphological remission (CR2, M1 marrow) is achieved. Immuno-oncotherapy with blinatumomab, a bispecific T-cell engager (BiTE®) molecule, is efficacious in children with relapsed/refractory BCP-ALL. We conducted an open-label randomized controlled phase 3 trial comparing blinatumomab with high-risk consolidation (HC) 3 chemotherapy as pre-transplant consolidation therapy for children with HR first-relapse BCP-ALL.

Methods: Children with M1 (< 5% blasts) or M2 (< 25% and ≥ 5% blasts) marrow were randomized 1:1 after induction therapy and cycles of HC1 and HC2 chemotherapy, administered according to the IntReALL HR 2010, ALL-REZ BFM 2002, ALL R3, COOPRALL, and AIEOP

ALL REC 2003 protocols, to receive a third consolidation course with blinatumomab (15 μg/m^2/day for 4 weeks) or HC3 (dexamethasone, vincristine, daunorubicin, methotrexate, ifosfamide, PEG-asparaginase); intrathecal chemotherapy (methotrexate/cytarabine/prednisolone) was administered before treatment. Stratification variables included age, marrow status at end of HC2, and minimal residual disease (MRD) after induction (evaluated in a local laboratory). Patients with CR2 (M1 marrow) after blinatumomab or HC3 proceeded to alloHSCT. The primary endpoint was event-free survival (EFS; from randomization until relapse date or M2 marrow after a CR, failure to achieve CR at end of treatment, second malignancy, or death from any cause). Secondary endpoints included overall survival (OS), cumulative incidence of relapse, MRD status (evaluated in a central laboratory by PCR), and incidence of adverse events (AEs). Two interim analyses were planned at approximately 50% and 75% of total EFS events.

Results: Enrollment was terminated for benefit (blinatumomab group) based on a predefined efficacy threshold at the 50% EFS events interim analysis. From November 10, 2015, to July 17, 2019 (data as-is snapshot), 108 patients were enrolled and randomized, 54 (50%) to blinatumomab and 54 (50%) to HC3. Patient baseline characteristics were comparable between treatment groups; most patients had completed treatment (blinatumomab, 91%; HC3, 89%). Events were reported for 18/54 (33.3%) and 31/54 (57.4%) blinatumomab- and HC3-randomized patients, with a median EFS of "not reached" and 7.4 months, respectively (Figure 1). Blinatumomab reduced risk of relapse by 64% vs HC3 (hazard ratio 0.36, 95% confidence interval [CI] 0.19-0.66, $p < 0.001$). In addition, OS favored blinatumomab vs HC3 (hazard ratio 0.43, 95% CI 0.18-1.01) (Figure 1). MRD remission (MRD < 10^{-4}) was seen in 43/46 (93.5%) blinatumomab-randomized and 25/46 (54.3%) HC3-randomized patients. Grade ≥ 3 treatment-emergent AEs were reported by 30/53 (57%) and 41/51 (80%) patients in the blinatumomab and HC3 groups, respectively. As expected, grade ≥ 3 neurologic events occurred more frequently with blinatumomab than HC3; no grade ≥ 3 cytokine release syndrome events were reported. Types of alloHSCT conditioning regimens received by patients as well as types of donors were balanced between groups.

Conclusions: Blinatumomab monotherapy as consolidation therapy before alloHSCT in children with HR first-relapse BCP-ALL leads to significantly better EFS, lower risk of recurrence, and fewer grade ≥ 3 treatment-emergent AEs vs HC3, suggesting a new standard-of-care treatment for these patients.



[Figure 1: Kaplan–Meier Curves for EFS and OS]

Clinical Trial Registry: www.ClinicalTrials.gov, NCT02393859

Disclosure: Franco Locatelli is a consultant for Amgen. Gerhard Zugmaier, Joan Morris, Abeera Mohammad, and Noemi Mergen are employees and stockholders of Amgen. Carmelo Rizzari has received honoraria from Amgen. Rosanna Parasole is a consultant for Jazz Pharma, Servier, Baxalta, Pfizer, and Boehringer Ingelheim. Bernd Gruhn, Thomas Klingebiel, Christin Linderkamp, Christian Flotho, Arnaud Petit, Concetta Micalizzi, Cornelia Eckert, and Mary Sartor have nothing to disclose. Anja Moericke's institution has received financial compensation for this study from Amgen. Ondrej Hrusak has performed MRD investigations funded by Amgen. Christina Peters is a consultant for Amgen and has received travel grants from Amgen. Vaskar Saha is a consultant for Amgen and has received honoraria from Amgen. Arend von Stackelberg is a

consultant for Amgen, Shire, Novartis, Roche, and Morphosys.

O004.

Results of Bmt Ctn Protocol 1101 a Multicenter Phase Iii Randomized Trial of Transplantation of Double Umbilical Cord Blood vs. Hla-haploidentical-related Bone Marrow

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Background: On the basis of encouraging data from two parallel multi-center phase II trials, one with dUCB and the other, haplo-BM, a phase III randomized trial was conducted in the United States to better understand the relative efficacy of the two donor types in adults with hematologic malignancy sponsored by NHLBI and NCI.

Methods: The primary outcome was a comparison of 2-year progression-free survival (PFS) between treatment arms using an intent-to-treat analysis. A sample size of 205 patients per arm aimed at providing 80% power for a two-sided test to detect a 15% increase in 2-year PFS in the haplo-BM arm. The conditioning regimen and GVHD prophylaxis for dUCB transplant was fludarabine (FLU) 200mg/m^2, cyclophosphamide (Cy) 50 mg/kg, total body irradiation (TBI) 200 cGy and cyclosporine with mycophenolate mofetil (MMF). The corresponding regimens for haplo-BM transplant were Flu 150 mg/m^2, Cy 29 mg/kg, TBI 200 cGy and post-transplant Cy 100 mg/kg, tacrolimus and MMF.

Results: The trial did not achieve its targeted accrual and was closed early. Thirty-three centers enrolled 368 patients between June 2012 and June 2018 (90% targeted accrual); 186 patients were randomized to dUCB and 182 to haplo-BM with randomization stratified by transplant center. Twenty-five percent of patients were not Caucasians. Twenty-six patients (7%) did not proceed to transplantation and 17 patients (5%) did not receive transplantation with the assigned donor type. Primary patient disease, disease status, age, sex, performance score and cytomegalovirus serostatus were balanced between treatment groups. The median follow-up of patients was 25 months after dUCB and 24 months after haplo-BM transplantation. The 2-year PFS did not differ significantly between treatment arms (Table 1); the 2-year difference in PFS was 6.1% (95% CI -5.2 - 17.4). Using multivariable analysis, there was no significant difference in PFS within the first 2 years after randomization between treatment arms after adjustment for age, performance score, disease, disease status, and transplant center (HR 1.27, 95% CI 0.92 - 1.75, $p = 0.162$). Except for lower non-relapse mortality (NRM) and higher overall survival after haplo-BM transplantation, other outcomes were similar between treatment arms (Table 1).

Conclusions: Although the trial did not record the expected 15% difference in 2-year PFS between treatment arms in adults with hematologic malignancy, lower NRM and higher overall survival favor haplo-BM transplantation to dUCB transplantation.

Outcome	dUCB	Haplo-BM	*p* value
PFS	35% (95% CI 28–42)	41% (95% CI 34–48)	0.409
NRM	18% (95% CI 13–24)	11% (95% CI 7–16)	0.039
Relapse/ progression	47% (95% CI 40–54)	48% (95% CI 41–56)	0.968
Overall survival	46% (95% CI 38–53)	57% (95% CI 49–64)	0.037

[Table 1. Point estimates of BMT CTN 1101 Outcomes]

Clinical Trial Registry: NCT 01597778

Disclosure: Claudio G Brunstein, MD, PhD: Gamida, research funding; Magenta research funding; Astex research funding;

Steven M. Devine, MD: Orca Bio consultant; Janssen consultant; Magenta consultant

Joseph P McGuirk, DO: Kite Pharma Advisory Board and Honoraria; Juno Therapeutics Advisory Board

O005.

Treosulfan Exposure in Pediatric Hematopoietic Stem Cell Transplantation is Associated with Early Toxicity but not with event-free Survival

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Background: Treosulfan-based (Trecondi®) conditioning is increasingly utilized in pediatric HSCT for both malignant and non-malignant diseases. In a first report of an ongoing prospective observational study, we demonstrated the relationship between treosulfan exposure and early toxicity. In the current report on the overall study cohort, we evaluated the relationship between treosulfan exposure, early toxicity and clinical outcome.

Methods: Patients transplanted in the pediatric transplant units in Leiden and Rome between June 2011 and January 2019 receiving treosulfan-based conditioning for non-malignant diseases were included. Children < 1 year received a lower dose of the drug (10 g/m^2) than children ≥ 1 year (14 g/m^2). Serum was collected to determine treosulfan concentration and subsequently calculate exposure. The relationship between exposure and early toxicity [i.e., mucosal, skin, hepatic and neurological toxicity until 28 days after HSCT], and clinical outcome [engraftment, acute GvHD (aGvHD), chimerism, Overall Survival (OS) and Event-Free Survival (EFS) with events defined as graft failure, extensive chronic GvHD, relapse and death] was analyzed using logistic or Cox regression analysis.

Results: A total of 114 consecutive pediatric patients were included in the study. Disease categories were immunodeficiencies (34%), hemoglobinopathies (49%), bone marrow failure (16%) and metabolic disease (1%). The median age at HSCT was 5.2 years (0.2-18.8); 73 patients (63%) were male. Donors were HLA-identical siblings (30%), matched unrelated (45%) or mismatched related (25%). Treosulfan was combined with either fludarabine and thiotepa (TFT: 68%) or fludarabine only (TF: 32%). Graft source was mainly BM (66%), followed by PBSC (24%) and CB (10%).

High treosulfan exposure (>1750 mg*hr/L) ($p = 0.006$) and young age ($p = 0.005$) proved significant risk factors for mucositis. High treosulfan exposure was also a risk factor for skin toxicity (p=0.03).

Cumulative incidence of engraftment was 97.3% (95%CI 93.7–100.0). Median time to neutrophil and platelet engraftment was 20 days (9–43) and 24 days (8–94), respectively. Grade 2-4 aGvHD occurred in 11.9% of patients. Eighty-five patients were evaluable for 1-year chimerism and 67% achieved ≥90% donor chimerism. Mixed chimerism was more prevalent in children < 2 years old (56% vs 23% in children ≥2 years old, p< 0.001). OS and EFS at 2 years were 88% and 72%, respectively. Interestingly, OS and EFS of infants under the age of 2 years was 97% and 78%, respectively. In contrast to early toxicity parameters, the occurrence of aGvHD, 1-year chimerism, OS or EFS were not associated with treosulfan exposure.

Conclusions: This is the largest prospective pediatric cohort reporting on treosulfan exposure and clinical outcome. We demonstrate a relationship between treosulfan exposure and mucosal and skin toxicity, which is most pronounced in young children. Treosulfan-based conditioning is safe and effective, particularly in infants. In contrast to early toxicity, we found no association between treosulfan exposure and survival, chimerism or EFS. PK-guided individualized dosing may be instrumental to reduce early toxicity. Follow up data of this study will also be valuable to study the relationship between treosulfan exposure and long-term toxicity, including fertility.

Disclosure: Nothing to declare.

O006.

Randomized Phase 3 Trial Evaluating the Efficacy and Safety of Ruxolitinib vs Best Available Therapy in Patients with Steroid-Refractory Acute Graft vs Host Disease (AGVHD)

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Background: REACH2 (NCT02913261), is a randomized, phase 3, open-label, multicenter trial, evaluating the efficacy and safety of ruxolitinib (RUX) compared to best available therapy (BAT) for the treatment of patients with steroid-refractory (SR)-acute graft-versus-host disease (aGvHD).

Methods: Patients were aged ≥12 years, had undergone allo-HSCT, developed grade II-IV aGvHD, and were refractory to corticosteroids. Patients were randomized (1:1) to RUX (starting dose 10mg bid) or BAT (per standard of care). Crossover to RUX was permitted among BAT-assigned patients who did not respond by Day 28 or lost response thereafter. Primary endpoint was overall response rate (ORR) at Day 28. The key secondary endpoint was durable ORR at Day 56 (patients who responded at Day 28 and maintained response at Day 56). Other endpoints included duration of response (time from first response to aGvHD progression or addition of systemic therapy) and safety.

Results: 309 patients were randomized to RUX (n = 154) or BAT (n = 155). Baseline characteristics were balanced between the arms; median (range) age was 54.0 (12-73) years (9 patients aged 12-< 18 years), and 59.2% were male. At randomization, 34.3%, 46.3% and 19.4% of patients had grades II, III and IV aGvHD respectively. At primary analysis, 18 patients (5.8%) were on randomized treatment and 243 patients (78.6%) had discontinued; reasons for discontinuation included: lack of efficacy, RUX: 20.8% vs BAT: 43.9%; adverse event (AE) 16.9% vs 3.2%, and death 16.2% vs 14.2% respectively.

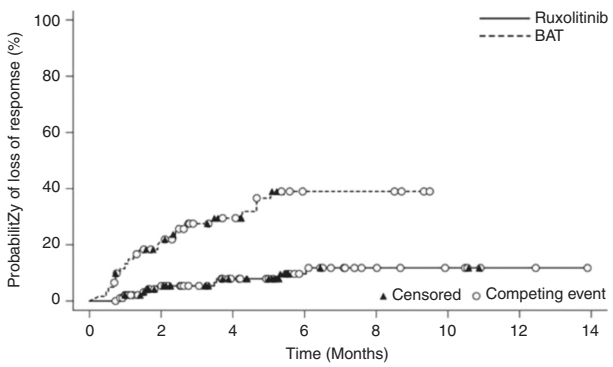
RUX performed better than BAT at all endpoints. ORR at Day 28: 62.3% for RUX vs 39.4% for BAT patients (odds ratio [OR] 2.64; p < 0.0001); proportion of patients with a complete response: 34.4% vs 19.4% respectively. Durable ORR at Day 56: 39.6% for RUX vs 21.9% for BAT patients (OR 2.38; p = 0.0005) (Table). Estimated cumulative incidence rate of loss of response shown in Figure 1.

The most common cause of on-randomized-treatment deaths was aGvHD (RUX: 21 [13.8%], BAT: 21 [14.0%]). Up to Day 28, AEs ≥ grade 3 occurred in 77.6% RUX and 78.0% BAT patients. Most commonly reported AEs by investigators in the RUX vs BAT arm were thrombocytopenia (27.0% vs 15.3%), anemia (21.7% vs 18.7%), platelet count decrease (14.5% vs 13.3%) and neutropenia (13.2% vs 9.3%). Infections of any type occurred in 61.2% RUX and 54.7% BAT patients (grade 3 infections occurred in 22.4% and 18.7% of patients, respectively).

Conclusions: Results from REACH2, the first successful randomized phase 3 trial of RUX in patients with SR-aGvHD, demonstrate the statistically significant superior efficacy of RUX vs BAT. The safety profile was consistent with that expected for RUX and patients with aGvHD.

Endpoint	RUX (*n* = 154)	BAT (*n* = 155)	Odds Ratio (95% Confidence Interval); *P* value
ORR at Day 28, n (%)	96 (62.3)	61 (39.4)	2.64 (1.65, 4.22); <0.0001
Complete response	53 (34.4)	30 (19.4)	
Partial response	43 (27.9)	31 (20.0)	
Durable ORR at Day 56, n (%)	61 (39.6)	34 (21.9)	2.38 (1.43, 3.94); 0.0005
Complete response	41 (26.6)	25 (16.1)	
Partial response	20 (13.0)	9 (5.8)	
Median duration of response, days (range)	168 (22–423)	101 (10–289)	

[Table. Efficacy Results]



[Figure 1: Cumulative incidence curve of loss of response]

Clinical Trial Registry: ClinicalTrials.gov: NCT02913261

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O007.

Host T Cells in Skin and Gut Survive Stem Cell Transplantation and Contribute to Acute GVHD

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Background: Graft-versus-host-disease (GVHD) is a significant cause of morbidity and mortality following stem cell transplantation (SCT). Donor T cells are thought to play a critical role in disease but a contribution from host T cells has not been previously explored, as it is presumed that host T cells are depleted by SCT conditioning.

Methods: We investigated the role of host T cells in GVHD using prospective and retrospective human studies and a humanized mouse model.

Results: Prospectively, patient skin and blood was collected prior to SCT and at ~30 days post-SCT, and along with donor infusion product, were analyzed using fluorescence in situ hybridization with immunofluorescence staining (FISH-IF), short tandem repeat analysis, and/or high throughput TCR sequencing to quantify host vs donor T cell chimerism. The majority of T cells in skin post-SCT derived from host skin T cells pre-SCT rather than from donor cells. Comparatively, the majority of T cells in blood post-SCT were donor-derived. We then retrospectively studied patient skin samples biopsied during active acute GVHD using FISH-IF. All 26 patients studied contained host T cells in skin during acute GVHD, with a median 46.5% host T cells. Chimerism was independent of conditioning regimen, GVHD prophylactic regimen, or host patient age. Multispectral immunofluorescence staining revealed that host T cells consisted of both $CD4^+$ and $CD8^+$ T cell subsets, and immunohistochemistry demonstrated that the vast majority were αβ not γδ T cells. Host T cells were observed throughout skin including the epidermis and dermal-epidermal junction, the main sites of damage during acute skin GVHD. Studies in acute gut GVHD similarly demonstrated host T cells present in both colon epithelium and lamina propria, and of both $CD4^+$ and $CD8^+$ T cell subsets. Despite the presence of host T cells in skin and gut during acute GVHD, T cells in blood were primarily donor-derived in paired specimens. In situ, a subset of host T cells expressed the proliferation marker, Ki67, and pro-inflammatory cytokines, IFNγ and IL-17, and host T cells were observed directly adjacent to donor antigen presenting cells. Finally, a humanized mouse model showed that donor monocytes could activate host skin resident memory T cells to generate a GVHD-like dermatitis in the absence of donor T cells.

Conclusions: This data demonstrate that host T cells survive SCT in peripheral tissues and appear to play a pathogenic role in acute GVHD. Importantly, this signifies a novel avenue of research in GVHD and potential for clinical intervention in prevention and/or treatment of disease.

Disclosure: Nothing to Declare

O008.

Pre-transplant Mrd Negativity Predicts Favorable Outcomes of car-t Therapy Followed by Haploidentical Hsct for Relapsed/refractory Acute Lymphoblastic Leukemia: A multi-center Retrospective Study

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Background: Recently chimeric antigen receptor T cells (CAR-Ts) have been successful in improving treatment outcomes for relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) by targeting CD19 or CD22, but relapse after CAR-T therapy is supposed a main obstacle. It remains controversial whether these patients could benefit from consolidative allo-HSCT after CAR-T therapy.

Methods: We designed a multi-center retrospective study to assess the efficacy and safety profiles of CAR-T therapy followed by haplo-HSCT from 11 domestic centers. Patients with minimal residual disease (MRD) negative complete remission (CR) after CAR-T therapy were divided into 3 groups: CAR-T treatment without transplant (Non-transplant group), haplo-HSCT with pre-transplant MRD negativity (MRD- group) and haplo-HSCT with pre-transplant MRD positivity (MRD+ group).

Results: 80, 41 and 17 patients were included in non-transplant group, MRD- group and MRD+ group, respectively. 2-year leukemia free survival (LFS) were 47.2%, 48.5% and 88.5% in non-transplant group, MRD+ group and MRD- group, respectively. Statistically higher LFS were found in MRD- group in contrast to non-transplant group ($p = 0.0019$) and MRD+ group ($p = 0.0065$), but no statistical difference were found between non-transplant group and MRD+ group ($p = 0.7424$). 2-year overall survival (OS) were 46.7%, 50.7% and 87.8% in non-transplant group, MRD+ group and MRD- group, respectively. Statistically higher OS were found in MRD- group in contrast to non-transplant group ($p = 0.0048$) and MRD+ group ($p = 0.0267$), but no statistical difference between non-transplant group and MRD+ group ($p = 0.6066$). Haplo-HSCT is the only independent factor associated with poor LFS ($P< 0.05$) and OS ($P< 0.05$) between non-transplant group and transplant group (MRD+ group and MRD- group together). MRD positivity at the time of haplo-HSCT is the only independent factor associated with poor LFS ($P< 0.05$) and OS ($P< 0.05$) in transplant patients. There were no statistical difference about cumulative incidence (CI) of grade III~IV aGVHD, CIs of cGVHD requiring systemic steroid therapy between the 2 transplant groups. The 1-year and 2-year CIs of infection including bacteria, CMV viremia and EBV viremia were not statistically significant among the 3 groups.

Conclusions: Haplo-HSCT after CAR-T treatment could greatly improve LFS and OS without increasing risks of treatment-related toxicity. Moreover, we confirmed that achieving pre-transplant MRD negativity after CAR-T treatment is a suitable basis for haplo-HSCT.

Clinical Trial Registry: www.chictr.org ChiCTR1900023957

Disclosure: Nothing to declare

Jian-Jian Luan award

O009.

Ofatumumab as Part of Reduced Intensity Conditioning in High Risk b-cell Lymphoma Patients: Results from a Prospective Multicenter Phase-II Trial

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Background: Allogeneic stem cell transplantation (AlloSCT) with reduced intensity conditioning (RIC) is potentially curative for high-risk non-Hodgkin lymphoma (NHL). However, best conditioning regimen is not fully established and new strategies to decrease transplant-related toxicity are under investigation. Anti-CD20 monoclonal antibodies have not been widely used in AlloSCT, and particularly there are no data about Ofatumumab (OFA) and its effect on graft versus host disease (GVHD) and long-term response.

In the GELTAMO group we designed a phase II clinical trial (NCT01613300) with OFA-RIC regimen for high-risk NHL. Primary endpoint was grade 3-4 acute GVHD rate, and secondary endpoint was complete response (CR) rate.

Methods: Inclusion criteria: less than a partial response (PR) after two lines of chemotherapy, relapse or evidence of measurable disease 3 months after an autologous SCT (ASCT). Conditioning regimen: OFA 300mg (day -20), 2000mg (days -13, -6), 1000mg (days +1, +8) plus fludarabine 150mg/msq (days -7 to -3) and melphalan 70mg/msq (days -2, -1). In case of relapse < 12 months after ASCT, patients received Thiotepa 5mg/msq (day -8). GVHD prophylaxis was based on sirolimus plus tacrolimus.

Results: Between 2012 and 2015, 33 patients from 6 centers were included and finally 31 were evaluable.

Median age was 51 years (30-65). Donor was HLA identical in 23 (74%). Diagnosis were: 21 (68%) diffuse large B cell lymphoma (DLBCL), 5 (16%) mantle cell lymphoma (MCL), 2 (6%) follicular lymphoma (FL) and 3 (10%) transformed NHL. Seventeen (55%) patients had relapsed after ASCT, 23 (74%) received ≥3 previous lines of treatment and 12 (39%) never achieved CR pre-AlloSCT (8 PR, 4 stable disease (SD)).

OFA infusions were well tolerated, with grade 1–2 cutaneous rash (n=5), grade 1 headache (1) and grade 2 allergic reactions (1), all of them fully resolved. No grade >2 toxicity was observed.

Response at day +100 was CR in 25 (81%), PR in 1 (3%) and progression in 3 (10%). Two patients were not evaluable due to early mortality.

Twenty-four out of 31 patients (77%) developed aGVHD, including 7/24 (30%) grade 1 gut GVHD (global grade 2) diagnosed by biopsy. Grade 3-4 aGVHD incidence was 16% (n = 5). In 75% of patients (18/24), aGVHD resolved and only 2 cases relapsed, so 71% of them were aGVHD-free at day +100. Chronic GVHD occurred in 14/26 (54%) patients alive at day +100, mild or moderate in 97%.

Seven patients relapsed/progressed after a median of 3 months (1-27), 4 of them with active disease pre-AlloSCT. Seventeen patients (55%) died due to progression (5), infections (10) and GVHD (2). With a median follow up of 48 months for surviving patients, estimated progression free and overall survival were 50% at 24 months.

Conclusions: OFA-RIC regimen is safe and effective, achieving 81% of CR in this population of high-risk B-cell NHL. Acute GVHD remain as the main complication. However, although 76% developed aGVHD, in 75% of them GVHD achived CR, suggesting that severity of aGVHD could be mitigate by OFA.

Clinical Trial Registry: NCT01613300

Disclosure: Nothing to declare