proportional hazards regression. Due to limited number of veno-oclusive disease (VOD) episodes (4), we did not include VOD in the analysis. We examined for potential confounding variable of age, donor, conditioning regimen (Bu cyclophosphamide or Bu fludarabine), disease risk index (DRI) grouped as low/intermediate or high/very high, graft source, thymoglobulin use, GVHD prophylaxis used. Of these, only age and DRI were significant and included in the Cox regression model. Kaplan-Meier (K-M) curves were examined for outcome of RFS and overall survival (OS).

Pts with a steady area under the curve (AUC) were considered those in whom AUC achieved was within 15% of goal AUC. In order to address the study question, we divided pts into those in whom calculated AUC was within 15% of target AUC (23 pts) and pts in whom AUC was higher/lower by ≥15% based on the first dose pharmacokinetics (21 pts). We also compared outcomes of pts who needed a change of Bu dose ≥15% (14 pts) to pts who required a dose change of ≥15% (30 pts).

Descriptive statistics for background characteristics, disease and SCT variables are summarized in Figure 1. Acute and chronic GVHD also did not show any significant difference as an outcome of interest, as shown in Figure 2. Survival analysis did not show a significant difference in RFS between groups of AUC [HR = 1.6 (52.4-7.7), P = .42] or Bu dose [HR = 3.6 (.88-14.4), P = .08], despite adjustment for age and DRI. K-M curves for OS for AUC groups are shown in Figure 3. Non-parametric tests for differences in time to neutrophil (P = .1 for AUC groups, P = .9 for Bu dose groups) and platelet engraftment (P = .7 for AUC groups, P = .6 for Bu dose groups) showed no significant differences between groups.

Conclusion: Therapeutic Bu dosing using first dose pharmacokinetics is an acceptable way to dose Bu, despite the transitory variations in AUC levels. The fluctuations that occur due to initial dose determination do not appear to affect outcomes. Additional research with a larger sample size is needed to more confidently describe these relationships.

Differential Toxicity Profile of Busulfan and Treosulfan on Endothelial Cells in Vitro—Relevance to Hematopoietic Stem Cell Transplantation

Balaji Balakrishnan, Ezhilpavai Mohanan, Raveen Stephen Stallon Illangeswaran, Alok Srivastava, Vikram Mathews, Poonkuzhali Balasubramanian. Department of Haematology, Christian Medical College, Vellore, India

Hematopoietic stem cell transplant (HSCT) is an established curative treatment option for hematological malignancies and non-malignant diseases. However, its success is limited by regimen related toxicity (RRT) caused by conditioning regimen drugs. RRT involves damage to the endothelioma leading to complications including sinusoidal obstruction syndrome. Among different conditioning drugs, busulfan (Bu) and treosulfan (Treo) (a structural analog of Bu) although used widely in HSCT, exhibit differences in their toxicity profile, the reason still being unclear. Here we compared the effect of these two drugs on endothelial cells to identify the factors causing the differences in toxicity.

To evaluate the cytotoxic effect of Bu and Treo, we incubated HHSEC and SK-HEP1 cells with Bu (200, 300 & 500μM) and Treo (3, 10 & 30μM) for 48 hours at previously reported concentrations in vitro (Danylesko et al., 2012). Bu induced a profound morphological change from cobble-stone to a fibroblast-like spindle shaped elongated cells by 12 h eventually floating due to dose dependent damage while this morphological change was not observed with Treo. However, both Bu and Treo induced a dose dependent increase in soluble ICAM-1 levels with a concomitant decrease in the total cellular ICAM-1 levels suggesting endothelial activation. Further, Bu treatment induced a dose dependent increase in apoptosis (55% in HHSEC & 39% in SK-HEP1 cells) while Treo (3, 10 & 30μM) for 48 hours at previously reported concentrations in vitro (Danylesko et al., 2012). Bu induced a profound morphological change from cobble-stone to a fibroblast-like spindle shaped elongated cells by 12 h eventually floating due to dose dependent damage while this morphological change was not observed with Treo. However, both Bu and Treo induced a dose dependent increase in soluble ICAM-1 levels with a concomitant decrease in the total cellular ICAM-1 levels suggesting endothelial activation. Further, Bu treatment induced a dose dependent increase in apoptosis (55% in HHSEC & 39% in SK-HEP1 cells) while Treo, even at 30μM induced minimal apoptosis (22% in HHSEC & 24% in SK-HEP1 cells) demonstrating that despite activating endothelial cells, Treo caused little/no damage to them. However, Treo induced an increase in acidic vesicular organelles (AVO) and LC3 levels suggesting that the minimal apoptosis to Treo could be due to autophagy. The gene expression profiling by using “Endothelial cell biology RT PCR array” showed maximal upregulation of inflammatory (up to 21 fold), apoptosis related genes (450 fold) due to initial dose determination do not appear to affect outcomes. Additional research with a larger sample size is needed to more confidently describe these relationships.
Results: Patients with CRS as determined by the attending physician (104pts). The most common diagnosis was AML (45%) followed by lymphoma (24%) and MDS (13%). The median time of transplant was 42 days, range 10-168 days. The most common manifestations of severe CRS included fever (100%), respiratory failure (75%), hypotension (83.3%), hepatic failure (25%), renal failure (33.3%). Several patients (4%) suffered neurotoxicity and severe CRS was associated with poor overall survival and higher transplant related mortality. Therapy directed against IL-6 may decrease treatment related mortality. Future prospective studies are warranted in studying the role of CRS prophylaxis and treatment to prevent transplanted related mortality while preserving relapse free survival in peripheral blood haplo-HCT patients.

Conclusion: CRS is common after T-cell replete haplo-HCT and severe CRS is associated with poor overall survival and higher transplant related mortality. Therapy directed against IL-6 may decrease treatment related mortality. Future prospective studies are warranted in studying the role of CRS prophylaxis and treatment to prevent transplanted related mortality while preserving relapse free survival in peripheral blood haplo-HCT patients.

**452**

Early Fluid Overload is a Serious Toxicity Associated with an Increased Risk of Non-Relapse Mortality after Ex-Vivo CD34-Selected Allogeneic Hematopoietic Cell Transplantation

Carlos Rondon-Clavo 1, Michael Scordo 1, Patrick Hilden 2, Gunjan L. Shah 3, Christina Cho 4, Molly Maloy 1, Esperanza B. Papadopoulos 5, Ann A. Jakubowski 1, Richard J. O'Reilly 4, Boglarka Gyurkocza 1, Hugo Castro-Malaspina 1, Roni Tamari 1, Brian C. Shaffer 1, Miguel-Angel Perales 1, Edgar A. Jaimes 1, Sergio A. Giralt 1

1 Department of Medicine, Adult Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, NY; 2 Department of Biostatistics and Epidemiology, Memorial Sloan Kettering Cancer Center, New York, NY; 3 Department of Medicine, Adult Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, NY; 4 Department of Medicine, Adult Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, NY; 5 Department of Medicine, Cancer Institute, New Jersey, New Jersey

Background: Early fluid overload is a frequent and serious complication after ex-vivo CD34-selected allogeneic hematopoietic cell transplantation (allo-HCT). The purpose of this study was to describe the incidence and impact of early fluid overload in adult patients undergoing allo-HCT at Memorial Sloan Kettering Cancer Center (MSKCC). We hypothesized that early fluid overload could be associated with non-relapse mortality (NRM).

Methods: We retrospectively analyzed 424 adult patients who underwent allo-HCT with CD34-selected peripheral blood stem cells at MSKCC between 2010 and 2017. We defined early fluid overload as the presence of fluid overload (weight gain ≥ 5% of body weight) on post-transplant day 0. We compared patient characteristics, early fluid overload incidence, and outcomes between patients with and without early fluid overload.

Results: Among 424 patients, 178 (42.3%) developed early fluid overload. Patients who developed early fluid overload were more likely to be older (median age 55 vs 47 years, P = 0.007), have poorer performance status (median PS 1 vs 0, P = 0.001), and receive non-myeloablative conditioning (74.5% vs 57.6%, P < 0.001). Early fluid overload was associated with higher risk of NRM (HR 3.72, 95% CI 2.15, 6.42, P < 0.0001) and non-relapse mortality (HR 2.39, 95% CI 1.39, 4.09, P = 0.002). The association between early fluid overload and non-relapse mortality was independent of conditioning intensity and early infections.

Conclusion: Early fluid overload is a serious toxicity associated with increased risk of non-relapse mortality after ex-vivo CD34-selected allogeneic hematopoietic cell transplantation.

**451**

T-Cell Replete Peripheral Blood Haploidentical Donor Transplant is Frequently Associated with Cytokine Release Syndrome Which Responds to IL-6 Inhibition—Updated Outcomes Data with Longer Follow-Up

Ramzi Abboud 1, Michael Slade 1, Jesse Keller 2, Kathryn Trinkaus 1, Camille Abboud 1, John F. DiPersio 1, Armin Ghobadi 1, Todd Fehniger 2, Rizwan Romee 1, Bone Marrow Transplantation & Leukemia Section, Division of Oncology, Washington University School of Medicine, St. Louis, MO; 2 Department of Medicine, Division of Oncology, Washington University in St Louis, St Louis, MO; 3 Biostatistics Shared Resource, Siteman Cancer Center, Washington University School of Medicine, Saint Louis, MO; 4 Oncology, Washington University School of Medicine, St Louis, MO

Background: Outcomes for haploidentical transplantation appear to be excellent, however, this novel approach brings toxicities that are particular to its biological and clinical milieu. We previously described occurrence of severe cytokine release syndrome (CRS) after haplo-HCT. Severe CRS was associated with poor clinical outcomes, including transplant related mortality, overall survival, and neutrophil engraftment (Abboud et al., BBMT, 10/2016).

Methods: We performed a retrospective review of patients who underwent haplo-HCT transplantation at our institution from 7/2009 through 1/2017. Patients were stratified into 3 categories by grade of CRS experienced: none (grade 0), mild (grade 1-2) and severe (grade 3-4). Outcomes were assessed.

A total of 169 patients were identified, median age at transplant of 52 (19-73), and 40% (67) had active disease at the time of transplant. The most common diagnosis was AML (104 pts). Patients with CRS as determined by the attending physician could be treated with the IL-6 receptor inhibitor tocilizumab at a dose of 6-8 mg/kg.

Results: We found a high incidence, 89%, of CRS in our haplo-HCT patients. Among a total of 169 patients, 27 (16%) experienced severe CRS, 108 (64%) had mild CRS, and 17 (10%) patients had no evidence of CRS. The most common manifestations of severe CRS included: fever (100%), respiratory failure (75%), hypotension (83.3%), hepatic failure (25%), renal failure (33.3%). Several patients (4%) suffered neurotoxicity or cardiomyopathy.

The patients who suffered from severe CRS had significantly worse overall survival (P < .0001) and transplant related mortality (P < .015). Median overall survival was not met for patients with no or mild CRS. Median overall survival for patients with severe CRS was 7.5 months. By contrast, 89% of patients with no or mild CRS survived beyond 7.5 months. Transplant related mortality was significantly higher in the severe CRS group at 100 days (20.8% versus 7.8%) and one year (30.7% versus 11.9%).

A total of 14 (8%) patients were treated with tocilizumab. Ten of them had severe CRS—four had grade 3 and six had grade 4. Mean and median progression free survival in patients with severe CRS who received tocilizumab was 283 days and 96 days, compared with 283 days and 155 days in those who did not receive tocilizumab. The patients who suffered from both minor and severe CRS and were treated with tocilizumab trended towards a lower transplant related mortality.

Conclusion: CRS is common after T-cell replete haplo-HCT and severe CRS is associated with poor overall survival and higher transplant related mortality. Therapy directed against IL-6 may decrease treatment related mortality. Future prospective studies are warranted in studying the role of CRS prophylaxis and treatment to prevent transplanted related mortality while preserving relapse free survival in peripheral blood haplo-HCT patients.