Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR REGIMEN-RELATED TOXICITY AND SUPPORTIVE CARE
Salt Lake City, UT
Sunday April 24, 2022, 6:45 AM – 8:15 AM MDT

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1. Introduction

Dr. Bipin Savani opened the meeting at 6:50 am by welcoming the working committee members for attending the Regimen-Related Toxicity and Supportive Care Working Committee (RRTWC) meeting. He introduced the RRTWC leadership and discussed the disclosures of the committee and the CIBMTR. Dr. Stadtmauer then stated the goals and limitations of the RRTWC and introduced Dr. Chhabra to the podium to continue.

2. Accrual Summary (Attachment 2)

The accrual summary was not presented in order to provide more time for the discussion of RT studies that are ongoing, published or presented in the last year, and the proposed studies to be presented at the meeting.

3.

Presentations, published or submitted papers

Dr. Chhabra gave an overview of the studies published and submitted in the past year. He also presented new areas of data collection on both the TED and CRF forms, rules of authorship, goals, expectations, and limitations. Dr. Chhabra brought up the importance of contributing at each step of the study.

a. **RT17-01** Farhadfar N, Dias A, Wang T, Fretham C, Chhabra S, Murthy HS, Broglie L, D'Souza A, Gadalla SM, Gale RP, Hashmi S, Al-Homsi AS, Hildebrandt GC, Hematti P, Rizzieri D, Chee L, Lazarus HM, Bredeson C, Jaimes EA, Beitinjaneh A, Bashey A, Prestidge T, Krem MM, Marks DI, Benoit S, Yared JA, Nishihori T, Olsson RF, Freytes CO, Stadtmauer E, Savani BN, Sorror ML, Ganguly S, Wingard JR, Pasquini M. Impact of pretransplantation renal dysfunction on outcomes after allogeneic hematopoietic cell transplantation. ***Transplantation and Cellular Therapy. 2021 May 1; 27(5):410-422. doi:10.1016/j.jtct.2021.02.030. Epub 2021 Feb 26. PMCID:PMC8168834.***
b. **RT18-02** Abou-Ismail MY, Fraser R, Allbee-Johnson M, Metheny III L, Ravi G, Ahn KW, Bhatt NS, Lazarus HM, de Lima M, El Jurdy N, Hematti P, Beitinjaneh AM, Nishihori T, Badawy SM, Sharma A, Pasquini MC, Savani BN, Sorror ML, Stadtmauer E, Chhabra S. Does recipient body mass index inform donor selection for allogeneic haematopoietic cell transplantation? ***British Journal of Haematology. doi:10.1111/bjh.18108. Epub 2022 Mar 14.***
c. **RT18-03** Patel SS, Ahn KW, Khanal M, Bupp C, Allbee-Johnson M, Majhail NS, Hamilton BK, Rotz SJ, Hashem H, Beitinjaneh A, Lazarus HM, Krem MM, Prestidge T, Bhatt NS, Sharma A, Gadalla SM, Murthy HS, Broglie L, Nishihori T, Freytes CO, Hildebrandt GC, Gergis U, Seo S, Wirk B, Pasquini MC, Savani BN, Sorror ML, Stadtmauer EA, Chhabra S. Non-infectious pulmonary toxicity after allogeneic hematopoietic cell transplantation. ***Transplantation and Cellular Therapy. doi:10.1016/j.jtct.2022.03.015. Epub 2022 Mar 18.***
d. **RT18-01a** Expanded Definitions in the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) Better Classifies Comorbidity in Children and Young Adults with Non-Malignant Diseases. (L Broglie/B Friend/G Schiller/M Thakar /M Sorror) ***Submitted.***
e. **RT18-01b** Adapting the HCT-CI Applicability for Children, Adolescents, and Young Adults with Hematologic Malignancies Undergoing Allogeneic Stem Cell Transplantation. (B Friend/L Broglie/G Schiller/M Thakar/M Sorror) ***Submitted.***
f. **RT18-S1** Differential use of the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) among adult and pediatric HCT physicians. (L Broglie/B Friend) ***Submitted****.*

4. Studies in progress (Attachment 3)

Dr. Chhabra presented the studies in progress. The older studies will be given priority to finish this year. The rest of the studies are on schedule to meet their current goals.

a. **RT19-01** Analysis of comorbidity-associated toxicity at a regimen-based level (R Shouval/ B Savani/ A Nagler) **Analysis**
b. **RT19-02** Hemorrhagic cystitis as a complication of hematopoietic stem cell transplantation in the post-transplant cyclophosphamide graft-versus-host disease prophylaxis era compared to other allogeneic stem cell transplants (K Adekola/ N Ali/ O Frankfurt/ L Metheny/ J Moreira/ M de Lima) **Datafile prep**
c. **RT20-01** Toxicities of older adults receiving allogeneic hematopoietic cell transplant compared to younger patients. (R Jayani/H Murff) **Protocol development**

5. Proposals

Future/proposed studies

a. **PROP 2109-09/ PROP 2110-02/ PROP 2110-257** Validating the HCT-CI score and exploring additional prognostic factors in patients undergoing second allogeneic transplants (Attachment 4).

Dr. Stadtmauer introduced Dr. Tomas. The hypothesis of this proposal is that HCT-CI is an

accurate determinant of non-relapse survival and overall survival in pediatric and adult patients received their second allogeneic transplant.

The CIBMTR identified n=4982 cases of second allo transplant in reported between 2008-2019 for all ages and for malignant and non-malignant diseases.

The aims of this proposal are to validate the HCT-CI as a predictor of non-relapse mortality in second transplant. identify determinants of non-relapse mortality in second transplant. The secondary aims of this proposal are to validate the HCT-CI as a predictor of overall survival in second transplant and to identify comorbidities that influence non-relapse mortality in second transplant.

Dr. Rangarajan discussed the potential use of the modified HCT-CI score developed in the RT18-01 study by Drs. Broglie and Friend. Dr. Tomas recommended both the modified and original score be examined. Dr. Stadtmauer asked about other pediatric data that we haven't collected that would be important to assess? Dr. Friend confirmed the examination of BMI, mechanical ventilation, and nutritional status are important to consider in this population as well. Dr. Silver discussed the differences in primary graft failure and relapse on second transplant and recommended the groups be split by indication for transplant. There was discussion around the separation of malignant and non-malignant disease and pediatric and adult patients. Dr. Dvorak discussed that due to the population of this proposal there could potentially be multiple manuscripts produced from this proposal. Dr. Stadtmauer recommended the regimen from the first allogeneic transplant be included in the analysis for the second transplant.

b. **PROP 2109-25** Correlation of melphalan dose with regimen-related toxicity in multiple myeloma patients undergoing autologous transplant (Attachment 5).
Dr. Stadtmauer invited Dr. Krem to the podium to present. The hypothesis of this proposal is Mel 140 will have more reduced toxicity related outcomes than Mel 200 with the same level of disease control. Additionally, due to patient selection, Mel 140 will correlate with frailty and NRM.

The CIBMTR found n=7033 adult patients with auto transplant for multiple myeloma who received melphalan conditioning regimen reported between 2008 and 2019. Of those, there were n=6014 who received standard Mel 200 conditioning.

The primary aim of the study is to examine non-relapse mortality for Mel 140 and Mel 200. Secondary aims include examining differences in regimen-related toxicities, infection, relapse, progression-free survival, overall survival, secondary malignancies, and cause of death will be described between the two regimens.

Dr. Stadtmauer asked about the exclusion criteria and the lack of exclusion for cases with previous auto transplant and lower does used for salvage. Dr. Krem recommended including these cases and including a variable for prior auto as there are a number of second transplants performed. Dr. Wall discussed measures of frailty and recommended partnering with institutions with robust assessments for geriatric patients.

c. **PROP 2110-23** Allogeneic hematopoietic cell transplantation (HCT) in patients 75 years and older-utilization and outcomes (Attachment 6).

Dr. Savani invited Dr. Artz to the podium to present the proposal. The hypothesis of this proposal is that the utilization of HCT in older populations is safe in the modern era with increased transplant rates and rates of non-relapse mortality.

The CIBMTR found n=392 adults over 75 years old transplanted for AML, ALL, and MDS between 2008 and 2019.

The primary aim or the proposal is to compare utilization of HCT for older patients o(75 years and older) over time. The secondary aims are to describe the utilization by driving factors, to examine non-relapse mortality, overall survival, leukemia free survival and GVHD at 1 and 2 years. Additional aim includes exploring risk of 75 years and older on non-relapse mortality compared to a slightly younger group (70-74 years) adjusting for common transplant factors such as HCT-CI, donor match, and performance score.

Dr. Savani asked about what the upper age limit for transplants at institutions is and asked about the collection of cases that were not selected for transplant due to age. The CIBMTR does not collect that information. Dr. Krem discussed the inclusion of older cases a cellular therapy inclusion and commented that secondary studies can answer with direct contact to centers regarding the cases not recommended to transplant due to age. The discussion included identifying an age cut off for transplants in older patients.

d. **PROP 2110-51** Trends of major organ injuries amongst children and young adults following allogeneic hematopoietic cell transplantation for hematologic malignancies (H Rangarajan/P Satwani) (Attachment 7).

Dr. Savani invited Dr. Rangarajan to the podium to present the proposal. The hypothesis of the proposal is that major organ toxicities in the first 100 days after transplant have decreased over time for children and young adults who received allogeneic transplants for hematologic malignancies. These decreases in toxicities have led to lower transplant related mortality.

The CIBMTR found n= 6210 pediatric and young adult patients (<30 years old) for AML and ALL who received allogeneic transplant between 2008 and 2019

The primary aim is to evaluate the trends in organ toxicities after allo transplant and to differentiate into the pulmonary, renal, CNS, liver, cardiac, and genitourinary systems. Secondary aims include comparing outcomes of non-relapse mortality, overall survival, acute GVHD between those with major organ toxicities and those without. Additional aim is to examine risk factors associated with major organ injuries.

Dr. Savani asked about the interactions between conditioning regimen, disease, and infection complications. Dr. Rangarajan, infection could be looked at as bias or confounding factor if the proposal is accepted. Dr. Friend asked about the broad time period in the proposal and asked for clarity on how time periods would be examined in the study. Dr. Rangarajan suggested time would be split to look at trends over every 5 years. Dr. Stadtmauer asked about availability of data related to the testing and confirmation of toxicities. Dr. Phelan commented that data is available for some toxicities but is center

reported, some testing available for review such as echocardiogram and MRIs available for a small subset of the patients. Primarily the data is reliant on the physician reporting. There was a question raised on how the organ function would be examined in the study. Dr. Rangarajan mentioned the analysis could look at any organ injuries compared to none. It was discussed primary analysis focus on the factors related to toxicity and subset analysis of cases where organ toxicity occurs and the impact on the outcomes.

e. **PROP 2110-80/ PROP 2110-244/ PROP 2110-315** Incidence, risk factors and outcomes of acute cardiac complications after post-transplant cyclophosphamide based GVHD prophylaxis; A Retrospective Analysis from CIBMTR Database (Attachment 8).

Dr. Stadtmauer invited Dr. Poonsombudlert to the podium to present the proposal. The hypothesis of this proposal is use of PT-Cy increased risk of cardiac events and those who develop adverse cardiac events (ACE) have worse short- and long-term outcomes after transplant.

The CIBMTR identified n= 5561 (n=2089 with PT-Cy) adult cases with hematologic malignancies who received their first allogeneic transplant reported between 2017-2019.

The primary aim of the proposal is evaluate incidence of ACE by GVHD prophylaxis and identify pre-transplant risk factors associated with the development of ACE. Secondary aims are to examine overall survival, disease-free survival and non-relapse mortality by ACE development.

Dr. Stadtmauer commented that the PT-Cy and mis-matched donor is a package, will that make the comparison more difficult? Adding more years may increase the matched donors who received PT-Cy. Dr. Krem commented on the heterogeneity of cyclophosphamide use and total *cyclophosphamide dose. Dr. Poonsombudlert recommended cumulative dose should be looked at if the data is available. Limitation is pre-transplant exposure and dosing.*

Dr. Stadtmauer invited Dr. Friend to the podium to present the results of RT18-01 (a and b) which expanded the HCT-CI in the pediatric population for non-malignant and malignant patients.

Dr. Stadtmauer closed the session at 8:10am.

Working committee Overview Plan for 2022-2023		
Study Number and Title	**Current Status**	**Chair Priority**
RT18-01: A modified HCT risk assessment tool for pediatric and young adult patients undergoing alloHCT.	Submitted	1
RT19-01: Analysis of comorbidity-associated toxicity at a regimen based level.	Analysis	1
RT19-02: Hemorrhagic cystitis as a complication of HCT in the Pt-Cy GVHD prophylaxis era compared to other alloHCTs.	Datafile preparation	2
RT20-01: Toxicities of older adults receiving allogeneic hematopoietic cell transplant compared to younger patients	Datafile preparation	3
EL22-02: PT-Cy related cardiomyopathy in allo transplants	Protocol development	3

Oversight Assignments for Working Committee Leadership (May 2022)

Edward Stadtmauer	**RT22-01:** PT-Cy related cardiomyopathy in allo transplant
Bipin Savani	**RT19-01: A**nalysis of comorbidity-associated toxicity at a regimen based level.
	RT19-02: Hemorrhagic cystitis as a complication of HCT in the Pt-Cy GVHD prophylaxis era compared to other alloHCTs.
Mohamed Sorror	**RT18-01:** A modified HCT risk assessment tool for pediatric and young adult patients undergoing alloHCT.
	RT20-01: Toxicities of older adults receiving allogeneic hematopoietic cell transplant compared to younger patients