MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR REGIMEN-RELATED TOXICITY AND SUPPORTIVE CARE
Orlando, FL
Saturday February 22, 2020, 12:15 – 2:15 pm

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1. **Introduction**
   Dr. Stadtmauer opened the meeting at 12:15 pm by welcoming the working committee members for attending the Regimen-Related Toxicity and Supportive Care Working Committee (RRTWC) meeting. He introduced the RRTWC leadership, welcomed the incoming chair Dr. Mohamed Sorror and thanked Dr. Shin Mineishi for his contributions to the committee over the year. Dr. Stadtmauer then stated the goals and limitations of the RRTWC and introduced Dr. Chhabra to the podium to continue.

2. **Accrual summary**
   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. **RT13-02** Sabloff M, Chhabra S, Wang T, Fretham C, Kekre N, Abraham A, Adekola K, Auletta JJ, Barker C, Beitinjaneh AM, Bredeson C, Cahn J-Y, Diaz MA, Freytes C, Gale RP, Ganguly S, Gergis U, Guinan E, Hamilton B, Hashmi S, Hematti P, Hildebrandt G, Holmberg L, Hong S, Lazarus HM, Martino R, Muffly L, Nishihori T, Perales M-A, Yared J, Mineishi S, Stadtmauer EA, Pasquini MC, Loren AW. *Comparison of high doses of total body irradiation in myeloablative conditioning*

prior to hematopoietic cell transplantation. ***Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation.*** doi:10.1016/j.bbmt.2019.08.012. Epub 2019 Aug 29.

b. **RT14-01** Parikh SH, Satwani P, Ahn KW, Sahr NA, Fretham C, Abraham AA, Agrawal V, Auletta JJ, Abdel-Azim H, Copelan E, Diaz M-A, Dvorak CC, Frangoul HA, Freytes CO, Gadalla SM, Gale RP, George B, Gergis U, Hashmi S, Hematti P, Hildebrandt GC, Keating AK, Lazarus HM, Myers K, Olsson RF, Prestidge T, Rotz S, Savani BN, Shereck E, Williams KM, Wirk B, Pasquini MC, Loren AW. *Survival trends in infants undergoing allogeneic hematopoietic cell transplant.* ***Journal of the American Medical Association Pediatrics.*** doi:10.1001/jamapediatrics.2019.0081. Epub 2019 Mar 18. PMC6503511.

c. **RT14-02** Epperla N, Li A, Logan B, Fretham C, Chhabra S, Aljurf M, Chee L, Copelan E, Freytes CO, Hematti P, Lazarus HM, Litzow M, Nishihori T, Olsson RF, Prestidge T, Saber W, Wirk B, Yared JA, Loren A, Pasquini M. *Incidence, Risk Factors for and Outcomes of Transplant-Associated Thrombotic Microangiopathy*. ***British Journal of Haematology***. **In press.**

d. **RT14-03** Zinter MS, Logan BR, Fretham C, Sapru A, Abraham A, Aljurf MD, Arnold SD, Artz A, Auletta JJ, Chhabra S, Copelan E, Duncan C, Gale RP, Guinan E, Hematti P, Keating AK, Marks DI, Savani BN, Olsson R, Ustun C, Williams KM, Pasquini MC, Dvorak CC. *Comprehensive prognostication in critically ill pediatric hematopoietic cell transplant patients: Results from merging the Center for International Blood and Marrow Transplant Research (CIBMTR) and Virtual Pediatric Systems (VPS) Registries.* ***Biology of Blood and Marrow Transplantation.*** doi:10.1016/j.bbmt.2019.09.027. Epub 2019 Sep 26.

e. **RT17-01a** Dias A, Farhadfar N, Wang T, Fretham C, Murthy H, Logan B, Mineishi S, Savani B, Stadtmauer E, Chhabra S, Wingard JR, Ganguly S, Pasquini MC. *Impact of Renal Dysfunction Measured By Estimated Glomerular Filtration Rate (eGFR) on Outcomes after Allogeneic Hematopoietic Cell Transplantation (HCT)*. ***Presented at ASH, December 2019.***

f. **RT17-01b** Farhadfar N, Murthy H, Wang T, Fretham C, Dias A, Logan B, Mineishi S, Savani B, Stadtmauer E, Chhabra S, Ganguly S, Wingard JR, Pasquini MC.
Development of the Renal Adjusted Hematopoietic Cell Transplant Comorbidity Index (RA-HCT-CI) Using Different Levels of Renal Dysfunction According to Estimated Glomerular Filtration Rate (eGFR). ***Presented at TCT, February 2020.***

g. **RT18-04** Broglie L, Fretham C, Al-Seraihy, George B, Kurtzberg J, Loren A, MacMillan M, Martinez C, Davies SM, Pasquini M. *Pulmonary complications in pediatric and adolescent patients following allogeneic hematopoietic cell transplantation.* ***Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation.*** doi:10.1016/j.bbmt.2019.06.004. Epub 2019 Jun 12.

4. Studies in progress

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. **RT17-01** Allogeneic hematopoietic stem cell transplant outcome of patients with end stage renal disease on dialysis (N Farhadfar/A Dias/JR Wingard/H Murthy/S Ganguly) **Manuscript preparation**

b. **RT18-01** A Modified Hematopoietic Cell Transplantation (HCT) Risk Assessment Tool for Pediatric and Young Adult Patients Undergoing Allogeneic Transplantation**.** (B Friend/L Broglie/G Schiller/M Thakar/M Sorror) **Analysis**

c. **RT18-02** The effect of obesity on outcomes after alternative donor stem cell transplants (M Abou-Ismail/G Ravi/L Metheny/M de Lima) **Datafile preparation**

d. **RT18-03** An Analysis of Non-Infectious Pulmonary Toxicities in Total Body Irradiation versus Chemotherapy-Based Conditioning Regimens after Allogeneic Hematopoietic Cell

Transplantation for Hematologic Malignancies (S Patel/B Hamilton/N Majhail/C Ustun) **Datafile preparation**

e. **RT19-01** Analysis of comorbidity-associated toxicity at a regimen-based level (R Shouval/ B Savani/ A Nagler) **Protocol development**

f. **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) **Protocol development**

5. Proposals

Future/proposed studies

Dr. Chhabra provided information on the proposals received this year. There were 23 proposals for the RRTWC. Seventeen were dropped due to overlap with current or recent studies or feasibility issues, which left six proposals to be presented at the meeting. The proposal themes were seropositivity (CMV, HTLV), toxicities, prior cancer diagnosis, post-transplant cyclophosphamide and prognostic tools for transplant. Dr. Chhabra invited Dr. Mineishi to the podium.

a. **PROP 1911-167** CMV Serotype and Graft Failure (M Pamukcuoglu/ M Arora) (Attachment 4)
Dr. Mineishi introduced Dr. Pamukcuoglu. The hypothesis is that graft failure may occur from dominant recipient CMV positive NK/T cells as opposed to donor CMV positive NK/T cells. The aim is to determine the impact of pre-transplant recipient/donor CMV serotype on graft failure. The CIBMTR identified 9592 cases of first allo with peripheral blood grafts between 2008 and 2018 for all hematologic malignancies and conditioning intensities.
The primary aim of the study is to determine the impact of pre-transplant donor/recipient CMV status on graft failure.
There was discussion around the definition of graft failure, and the variability of data collected. There was discussion around Letermovir for prevention of CMV reactivation and loss of grafts. Exploring CMV as an infection post-transplant. Letermovir is not approved in pediatric patients, differs by center and peripheral blood. Since primary graft failure incidence is <5%, might be important to include bone marrow and non-malignant cases to increase numbers. Non-malignant cases have higher graft failure. Olsson et al. published study on graft failure with pediatric cases included and found CMV serostatus was not a significant predictor for graft failure based on patient data between 1995 and 2008.

b. **PROP 1911-181** Significance of a prior cancer diagnosis as exclusion criteria in clinical trials among patients with Hematological malignancies undergoing hematopoietic stem cell transplant (HSCT) (A Kansagra/ S Hashmi/ B Savani/ M Hamadani/ S Devine) (Attachment 5)
Dr. Mineishi introduced Dr. Anderson. The hypothesis of this study is there is no difference in progression-free survival between patients on clinical trials where there are guidelines or acceptance of cases with prior cancers and standard of care patients.
The CIBMTR found 1000 cases of adults with AML or MDS transplanted between 6/2/2011 and 4/18/2014 with similar criteria to the BMT-CTN 0901 clinical trial cohort.
The primary aim of the study is to evaluate overall and progression-free survival for both cohorts. The secondary aim is to evaluate the risk of secondary malignancy after transplant.
Dr. Pasquini commented that there does not appear to be a strict exclusion of prior cancers in the BMT CTN 0901 cohort and the type of prior malignancy may matter. Curative cancer treatment is the endpoint with competing outcomes. Dr. Anderson said within a population of transplants in-situ cancers and melanoma may make a difference. There was a comment that this might not be the right clinical trial to compare it to. The impact of cancer on outcomes is important to study, and the FDA is interested in reducing barriers to clinical trials. Dr. Stadtmauer questioned how the population was chosen. Dr. Pasquini commented that the

comparison does not have to solely be to CTN 0901 but to a combination of clinical trials potentially.

c. **PROP 1911-198** Outcomes and safety of hematopoietic stem cell transplants from HTLV positive donors and HTLV positive recipients (M Janakiram/ G Okov) (Attachment 6)
Dr. Savani introduced Dr. Janakiram. The hypotheses of this proposal are as follows; 1) patients who receive transplants for HTLV-1 positive donors with have the same outcomes as transplants from HTLV-1 negative donors, 2) the rate of secondary malignancies will be similar between groups, 3) the rate of secondary malignancies will be similar in HTLV-1 positive recipients for both auto and all transplants, 4) the progression-free survival and non-relapse mortality will be comparable between cohorts.
The CIBMTR identified 31,919 cases who received their first allo transplant for any donor or graft source between 2008 and 2018 (26,839 HTLV-1 negative recipients, 217 HTLV-1 positive recipients, and 4863 unknow HTLV-1 seropositivity). Additionally, there were 13,577 cases of auto transplants with any graft source between 2008 and 2018.
The primary aims are to examine progression-free survival, non-relapse mortality, and secondary malignancies. The secondary aims are to examine overall survival and incidence of HTLV-1 related complications.
There was discussion around the impact of this study and partnership with other registries. There was a comment about feasibility of comparing 217 HTLV-1 positive recipients to 2500 HTLV-1 negative cases. Dr. Janakiram responded that a matching pair analysis may assist with this issue. Dr Yared from University of Maryland raised the question that the HTLV-1 positive donors in the allo transplants may be related donors. There was a question as to how long HTLV associated cancers develop. Dr. Janakiram stated these cancers take around 30 years to develop. There was discussion that the endpoint might need to include the 30 year follow-up and second primary malignancies. There was discussion regarding reaching out to centers to verify HTLV status. There was a comment that donors may be excluded on HTLV status, if this is not the case, donors increase and there may be a need for a different end point.

d. **PROP 1911-234** Patterns of Veno-Occlusive Disease in Patients with AML and ALL in the era of Monoclonal Antibodies and Antibody Drug Conjugates (L Gowda/ M Byrne/ P Kebriaei/ D Porter) (Attachment 7)
Dr. Savani introduced Dr. Kebriaei. The hypothesis is that the risk of VOD has changed with new drugs for treatment of acute leukemias.
The CIBMTR identified 664 cases who underwent allo transplant and received monoclonal antibodies prior to transplant for AML or ALL between 2008-2019.
The primary aim is to evaluate the incidence and severity of VOD of patients treated pre-transplant with gemtuzamab or inotuzamab. The secondary aims are to examine the timing of VOD, mortality and morbidity for monoclonal antibodies, risk factors for VOD, predictors of survival for VOD, impact of antibodies on VOD risk, severity and death, relapse, non-relapse mortality and acute and chronic GVHD for those who developed VOD.
There was a comment that gemtuzamab does not lead to increased risk for VOD. There was a comment that the granularity of the CIBMTR data may be insufficient and that the dosing information and schedule would be important and those have changed over time but are not available in the registry. There was discussion around the changes in gemtuzumab use and the availability of date of use and resolution of VOD. There was discussion regarding the methodology of this study given not all the data are applicable to all cases. There was discussion around the availability of ICU stays and defibrotide information which are not captured during the entire study period. There was a comment that this study might have low statistical power. It was commented that this would be a better study than what has been published so far.

f. **PROP 1911-46** The PTCY-CI and PTCY-CDRI: prognostic tools for the use of post-transplant cyclophosphamide based GVHD prophylaxis regimens in allogeneic stem cell transplants for malignant conditions (R Shapiro/ R Romee/ A Bashey) (Attachment 8)
Dr. Stadtmauer introduced Dr. Shapiro. The hypotheses of this study is PT-Cy impacts non-relapse mortality and should be included in HCT-CI and DRI scores to accurately predict risk scores.
The CIBMTR identified 8353 cases of adults who received PT-Cy for the first allo transplant for a hematologic malignancy.
The primary aim is to validate the HCT-CI and DRI risk score using PT-Cy prophylaxis regimens.
The secondary aims are to develop novel HCT-CI and DRI risk scores which incorporate transplant related factors including PT-Cy use.
Dr. Stadtmauer commented that most of the cases in this proposal are haploidentical. There was discussion that PT-Cy has already been tested in HCT-CI and DRI. Dr. Shapiro commented that the importance of looking at PT-Cy in these risk scores is there will be lower non-relapse mortality with use which may impact scoring systems. Dr. Pasquini commented that HCT-CI has been looked at in PT-Cy setting and it has been validated as a predictor for NRM. There was discussion that the intensity of conditioning may be important to HCT-CI scores where lower intensity related to increased scores. Dr. Sorror commented that reclassifying risk with PT-Cy compared to other immune suppression and different setting does not produce different scores or better predictive models. There was a comment that with a new score it would increase the number of scores physicians need to consider when treating patients.

g. **PROP 1911-60** Toxicities of Older Adults Receiving Allogeneic Hematopoietic Cell Transplant Compared to Younger Patients (R Jayani/ H Muff) (Attachment 9)
Dr. Stadtmauer introduced Dr. Jayani. The hypothesis of the study is that older adults experience a higher rate of toxicities than younger patients.
The CIBMTR identified 24,581 cases of adults who underwent allo transplant between 2008 and 2018 (15,794 <60 years old, 8,787 60+ years old).
The primary aim of the study is to understand the toxicities that most impact older adults.
Secondary aims include evaluating the frequency of organ toxicity early after transplant, late effects of transplant in both groups, impact of comorbidities on organ toxicity and late effects and acute and chronic GVHD rates and severities.
There was discussion of the cut point for age, 70+ years might be more standard with CIBMTR studies, age could also be evaluated continuously or by decade. There was a comment that continuous age would allow model flexibility. There was discussion around quantifying toxicities as individual toxicities and as a sum score. There was a comment that older people are predisposed to more toxicities and important to modify regimens impact potential toxicities.
Dr. Pasquini commented that is a different endpoint looking at all the toxicities and a breakdown by regimen. There was a comment that ICU information, HCT-CI and pulmonary toxicities are important. Dr. Sorror commented that groups with increased toxicity of management might be the same as younger. Dr. Stadtmauer mentioned this might be a complimentary study to the BMT-CTN study looking at non-relapse mortality and toxicity with a composite endpoint and examining regimen related tool.

The meeting was adjourned at 2:15 pm.

Working committee Overview Plan for 2020-2021							
Study number and title	**Current status**	**Goal with date**	**Total hours to complete**	**Total hours to 2021 goal**	**Hours allocated to 6/30/2020**	**Hours allocated 7/1/2020-6/30/2021**	**Total Hours allocated**
RT17-01: AlloHCT outcome of patients with end stage renal disease on dialysis.	Manuscript preparation	Submit by April 2020 Published by July 2021	60	60	50	10	**60**
RT18-01: A modified HCT risk assessment tool for pediatric and young adult patients undergoing alloHCT.	Analysis	Submit by May 2020 Published by July 2021	110	120	110	10	**120**
RT18-02: The effect of obesity on outcomes after alternative donor stem cell transplants.	Data file preparation	Manuscript preparation by May 2020 Submitted by July 2021	200	200	130	70	**200**
RT18-03: An analysis of non-infectious pulmonary toxicities in regards to conditioning regimens, graft source and early vs. delayed engraftment.	Data file preparation	Manuscript preparation by May 2020 Submitted by July 2021	160	160	90	70	**160**

RT19-01: Analysis of comorbidity-associated toxicity at a regimen based level.	Data file preparation	Analysis by July 2020 Submitted by July 2021	290	290	180	110	**290**
RT19-02: Hemorrhagic cystitis as a complication of HCT in the Pt-Cy GVHD prophylaxis era compared to other alloHCTs.	Protocol development	Data file preparation by July 2020 Manuscript preparation by July 2021	330	260	100	160	**260**
RT20-01: Toxicities of older adults receiving allogeneic hematopoietic cell transplant compared to younger patients	Protocol pending	Protocol Development by July 2020 Analysis by July 2021	330	200	0	200	**200**

Oversight Assignments for Working Committee Leadership (March 2020)	
Edward Stadtmauer	**RT18-02:** The effect of obesity on outcomes after alternative donor stem cell transplants.
Bipin Savani	**RT18-03:** An analysis of non-infectious pulmonary toxicities in regards to conditioning regimens, graft source and early vs. delayed engraftment.
	RT19-01: Analysis 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