MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR GRAFT-VERSUS-HOST DISEASE
Orlando, FL
Thursday, February 16, 2023, 12:45 - 2:15 PM

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Statistician:	**TBD**

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1. Introduction

The CIBMTR Working Committee for Graft-Versus-Host Disease met on Thursday, February 16th, 2023 at 12:45 PM. Dr. MacMillan welcomed the attendees and introduced the working committee leadership. Dr. Pidala was thanked for his contributions to the working committee during his acting time as a chair, and Dr. Zachariah DeFilipp was welcomed as the incoming chair. Dr. MacMillan discussed the committee's goals, expectations, and limitations, the proposal scoring process, and rules of authorship. Two exciting new opportunities were shared: (1) for early career investigators to work with CIBMTR, (2) CIBMTR's new Patient-Reported Outcomes (PRO) Protocol and data collection. Attendees were also encouraged to attend the Collaborative Session, especially as there was one proposal from the committee being presented.

2. Accrual Summary

The accrual tables were included in the meeting materials but were not reviewed in the interest of time.

3. Presentations, published or submitted papers

Updates on the committee's presentations, published or submitted papers were included in the meeting materials but were not discussed at the meeting.

a. **GV17-03** Saliba RM, Alousi AM, Pidala J, Arora M, Spellman SR, Hemmer MT, Wang T, Abboud C, Ahmed S, Antin JH, Beitinjaneh A, Buchbinder D, Byrne M, Cahn J, Choe H, Hanna R, Hematti P, Kamble RT, Kitko CL, Laughlin M, Lekakis L, MacMillan ML, Martino R, Mehta PA, Nishihori T, Patel SS, Perales M, Rangarajan HG, Ringdén O, Rosenthal J, Savani BN, Schultz KR, Seo S, Teshmia T, Van der Poel M, Verdonck LF, Weisdorf D, Wirk B, Yared JA, Schriber J, Champlin R, Ciurea S. Characteristics of Graft-versus-Host Disease (GvHD) after Post-transplant Cyclophosphamide

versus Conventional GvHD Prophylaxis. ***Transplantation and Cellular Therapy. 2022 Oct;28(10):681-693. doi: 10.1016/j.jtct.2022.07.013.***

b. **GV18-01a** Lee CJ, Wang T, Chen K, Arora M, Brazauskas R, Spellman SR, Kitko C, MacMillan ML, Pidala JA, Auletta JJ, Badawy SM, Bhatt N, Bhatt VR, Cahn J, DeFilipp Z, Diaz MA, Farhadfar N, Gadalla S, Gale RP, Hashem H, Hashmi S, Hematti P, Hong S, Hossain NM, Inamoto Y, Lekakis LJ, Modi D, Patel S, Sharma A, Solomon S, Couriel DR. Association of Chronic Graft-versus-Host Disease with Late Effects Following Allogeneic Hematopoietic Cell Transplantation for Children with Hematologic Malignancy. ***Transplantation and Cellular Therapy. 2022 Oct;28(10):712.e1-712.e8. doi: 10.1016/j.jtct.2022.07.014.***

c. **GV18-01b** Lee CJ, Wang T, Chen K, Arora M, Brazauskas R, Spellman SR, Kitko C, MacMillan ML, Pidala JA, Badawy SM, Bhatt N, Bhatt VR, Cahn J, DeFilipp Z, Diaz MA, Farhadfar N, Gadalla S, Hashmi S, Hematti P, Hossain NM, Inamoto Y, Lekakis LJ, Sharma A, Solomon S, Lee S, Couriel DR. Severity of Chronic Graft-versus-Host Disease and Late Effects Following Allogeneic Hematopoietic Cell Transplantation for Adults with Hematologic Malignancy. ***Submitted.***

d. **GV21-01** Farhadfar N, Al-Mansour Z, Wang T, Chen K, Pidala J, MacMillan ML, Kitko CL, Spellman SR, Wingard JR, Lee SJ. Racial, Ethnic and Socioeconomic Disparity in Outcomes of Patients with Chronic Graft-Versus-Host Disease: A CIBMTR Analysis. ***Poster presentation, ASH 2022.***

4. Studies in progress

The committee did not share updates on in-progress studies, though they were referenced in the meeting materials.

a. **GV18-02** Comparison of bacterial blood stream infection incidence in allogeneic stem cell transplantation patients with and without acute graft vs host disease (Wallis W/ Alousi AM/ Gulbis A) **Manuscript Preparation.**

b. **GV19-01** Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients (Gillis N/ Padron E/ Lazaryan A) **Manuscript Preparation.**

c. **GV20-01** Machine learning models and clinical decision support tool for acute and chronic graft-versus-host disease in patients with acute myelogenous leukemia undergoing allogeneic transplants (Kindwall-Keller T/ Lobo B) **Analysis.**

d. **GV20-02** Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly-multiplexed proteomics assay: MHC-PepSeq (Sandhu K/ Altin J/ Askar M/ Nakamura R) **Data File Preparation.**

e. **GV21-01/GV22-03** Racial, ethnicity and socioeconomic disparity in outcome of patients with graft versus host disease (Farhadfar N/ Wingard JR/ Al-Mansour Z/Rashid N) **Analysis.**

f. **GV21-02** Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation: A validation study (Pidala J/ Logan B/ Martens M) **Analysis.**

g. **GV22-01** Acute and chronic graft versus host disease in infants and toddlers following hematopoietic cell transplantation (Nishitani M/ Duncan C/ Graham R/ Qayed M) **Protocol Development.**

h. **GV22-02** Chronic GVHD Risk Index: A clinical risk assessment score for development of moderate-severe chronic graft-versus-host disease after hematopoietic cell transplantation (Im A/ Pavletic S) **Protocol Development.**

5. Future/proposed studies

a. **PROP 2210-62/2210-75** The Effect of Graft-Versus-Host Disease Prophylaxis on Survival after HLA-Matched Hematopoietic cell transplantation (HCT): a CIBMTR analysis (McCurdy S/ Pashna M/ Mehta R)

The proposal was presented by Dr. Rohtesh Mehta. The study hypothesizes that PTCy use will be associated with improved GRFS and less NRM compared to other GVHD prophylaxis strategies in recipients receiving reduced intensity or myeloablative conditioning regimens. Proposal feasibility analysis of CIBMTR data found N=169 patients receiving PTCy, and N=2,091 CNI+MTX, N=153 CNI+MTX+ATG in the comparator groups. The population was restricted to patients age 18 or older undergoing first alloHCT for AML, ALL or MDS, from matched related or unrelated donors from 2010-2020. The following questions and comments were addressed during the Q&A:

i. Will the study involve a sub-analysis of PM vs BM grafts? There may not be enough numbers in some of the comparator groups to detect any significance but it would be worth either adjusting for in a multivariate model or performing a sub-analysis, pending statistical input.
ii. Is the aim to assess GRFS at 1 or 2-years post-HCT? Ideally 2 as in the RIC setting GRFS at 1-year is already known.
iii. Should the study focus on MAC conditioning and PB? That may be more practice changing than results from the current proposed cohort. A recent clinical trial performing a similar investigation in RIC did not include ATG so this remains unexplored, and it is common practice to use MUD + ATG but the results are still not well-known.
iv. How will the study adjust for diverse disease risk and comorbidity index due to bias in patient selection deemed fit for PTCy use? There is no statistical analysis that can adequately account for that.

b. **PROP 2210-76** PTCy/CNI with or without MMF in HLA-matched donor HCT (Mehta R)

The proposal was presented by Dr. Rohtesh Mehta. The study hypothesizes that MMF when added to PTCy/CNI is associated with a higher risk of aGVHD than PTCy/CNI alone in HCTs using HLA-matched donors, based on single center data from MD Anderson. Proposal feasibility analysis of CIBMTR data showed N=627 receiving PTCY+MMF, N=243 PTCy w/o MMF, N=671 CNI+MMF, N=5,390 CNI w/o MMF. The following questions and comments were addressed during the Q&A:

i. In the single center study, what factors determine the use of MMF? Around 2014-15 PTCy+TAC use became standard due to a single institutional clinical trial. Then, emerging data from CTN study showed PTCY+TAC+MMF is standard.
ii. How can one differentiate GI toxicity vs GVHD due to MMF use? It is possible to differentiate MMF toxicity histologically, though the criteria were not discussed in detail.
iii. A comment was made that the timing of MMF discontinuation varies with the donor, so the later onset of GVHD could be impossible to disentangle.
iv. The timing of administration of the PTCy (+TAC) group will differ, which could cause some issues. This is why there are two other comparator groups for CNI+MMF and CNI alone (w/o PTCy).
v. How will patients that receive PTCy+TAC+sirolimus fit into these groups? Also, how will the analysis account for patients who are intended to receive a drug to day +35 but due to toxicities or cytopenias, adjustments are made? We will not have the start or stop dates of administration.
vi. In pediatrics, MMF dosing is performed (adjustment based on pharmacokinetics). This is not standard in adults, and not even in all pediatric centers. This cannot be adjusted for since the data is not captured, and would be a limitation.

c. **PROP 2210-108** Determining the optimal anti-thymocyte globulin dosing in patients with hematologic malignancies undergoing allogeneic hematopoietic cell transplant (Gallogly M/ Metheny L)

Dr. Molly Gallogly presented the proposal. The study aims to determine the optimal ATG dose based on conditioning intensity, donor, and graft source, as dosage and timing varies widely by

center. Study feasibility assessment of CIBMTR data found N=2,499 patients undergoing first alloHCT for AML, ALL or MDS between 2008-2019 registered to the CRF track and receiving ATG. The following questions and comments were addressed during the Q&A:

i. A concern was expressed that the timing and pharmacokinetics of ATG will be significant confounders. If the forms capture absolute lymphocyte count on the starting day of ATG this may be helpful to adjust for.
ii. The forms only capture total dose and not fractioned dosage and timing.
iii. The type of ATG is captured. Since the source differs geographically, this would be a US-based analysis.
iv. Other published research has shown AUC-based dosing patterns impact outcomes, and CIBMTR's data may not be able to provide such granularity.
v. Patient characteristics would also impact dosing and outcomes, would the study account for this by subgroup analysis or other? The goal would be to determine optimal dosing within each subgroup, but at this time it is unknown if the sample size and data will have enough power.

d. **PROP 2210-155** ATG versus PTCy for peripheral blood matched-sibling donor hematopoietic cell transplantation (Arcuri L/ Hamerschlak N)

Dr. Leonardo Arcuri presented the proposal. The study hypothesizes that GVHD outcomes will be the same between PTCy and ATG in the HLA-matched donor setting with peripheral blood and myeloablative conditioning. Study feasibility of CIBMTR data found N=5,257 patients age 18-60 undergoing first alloHCT for AML or MDS receiving ATG + CNI (N=4,131) or PTCy + CNI (N=1,126) in the HLA-matched + PB + MAC setting. The following questions and comments were addressed during the Q&A:

i. The differences in ATG dosing may have an impact on outcomes, how will this be accounted for? This is not the aim of the study; the aim is to show that any ATG use is comparable to PTCy and various doses have been effective.
ii. Regardless of the results, this may not change practice or people's minds, a randomized study may be the best or only way to change practice.
iii. Is there overlap with the first study that was presented? Why do the numbers differ? The years, diseases, donors, conditioning regimen, and other factors differ.

e. **PROP 2210-23** Post-Transplant Cyclophosphamide (PTCy) vs. Anti-Thymocyte Globulin (ATG) in Patients with Acute Leukemia (AL) and Myelodysplastic Syndrome (MDS) receiving HLA-Mismatched Unrelated Donor (MMUD) Hematopoietic Cell Transplant (HCT). A CIBMTR Analysis (Jimenez A / Shaffer B)

Dr. Antonio Jimenez Jimenez presented the proposal. The main objective of the study is to assess if the use of PTCy in MMUD transplants would improve outcomes compared to the current standard with ATG. Study feasibility of CIBMTR data found N=620 ATG and N=164 PTCy among recipients age 18+ of first alloHCT for AML, ALL or MDS with a MMUD from 2010-2020. The following questions and comments were addressed during the Q&A:

i. Will the study look at the impact of individual allele mismatch? This is a great question, though the numbers in the PTCy arm are likely too small.
ii. The PTCy arm is the same as the population of the ACCESS trial, which is a prospective trial and is still accruing. Although this study would include a comparison of PTCy vs ATG, will the study be a duplicate? There is some overlap with other studies, but if patients up to 2020 are included this would provide an advantage. This question also remains a high priority in racial and ethnic minorities.
iii. The feasibility tables show ATG is more common before 2015 and PTCy more common after. Even after adjusting for the year of transplant, is this a fair comparison? In Dr.

Jimenez's single-center experience, this analysis has been done and the advantages of PTCy persisted after these and other factors, such as for toxicity management.

iv. How will the study adjust for the graft source imbalance between the two groups? The statisticians will help inform this adjustment.

f. **PROP 2210-203** Allogeneic stem cell transplant (Allo- SCT) in patients older than 70 years using posttransplant cyclophosphamide (PTCy) based Graft versus Host disease (GVHD) prophylaxis: An analysis from the CIBMTR database (Nath R/ Zhou Z)

Dr. Rajneesh Nath presented the proposal. The study aims to determine how frequently alloHCTs occur in patients over age 70 using PTCy-based GVHD prophylaxis, describe the baseline characteristics, and investigate outcomes. Study feasibility of CIBMTR data showed N=439 patients meeting the selection criteria between 2008-2020 and registered to the CRF track. The study also proposes a potential comparison to an aged 60-70 cohort. The following questions and comments were addressed during the Q&A:

i. A suggestion to investigate what regimens are defined as myeloablative in this age group.

ii. Is it worth waiting to complete this study in 1-2 years because of a recent BMT CTN presentation on PTCy use? There would be more patients at that time, but it is an urgent question due to the intensity of Cytoxan. The population also differs as it allows MAC and includes broader donor types.

iii. A suggestion that a comparison aspect of the study would be helpful to know the organ toxicity prevalence.

iv. Should relapse be analyzed as separate endpoint instead of the proposed composite GRFS, because there is concern PTCy is associated with long term relapse. Relapse could be included as a secondary outcome.

v. Is PTCy dose collected? It was added to the F2100 within the last couple of years.

vi. A suggestion to consult with the protocol team of BMT CTN 1703.

vii. The oldest patient in the feasibility tables was 88. Would it be worth comparing 70-79 vs 80+? The sample size is likely too small.

6. Dropped proposed studies

g. **PROP 2209-17** GvHD prediction using machine learning. *Overlap with CIBMTR study GV20-01; insufficient detail about methods.*

h. **PROP 2210-07** Does early phase grade 1-2 mild or moderate skin GVHD have a benefit on OS and DFS after ASCT? *Unclear comparator group; lower scientific impact relative to other proposals.*

i. **PROP 2210-54** Impact of the additional immunosuppressant option on graft versus host disease and outcomes in patients who receive post-transplant cyclophosphamide for graft versus host disease prophylaxis. *Heterogeneous population; lower scientific impact relative to other proposals.*

j. **PROP 2210-127** Outcomes of Patients with Acute Myeloid Leukemia (AML) and Measurable Residual Disease (MRD) Undergoing Allogeneic Transplantation using Post-Transplant Cyclophosphamide versus Conventional Graft-versus-Host Disease (GvHD) Prophylaxis. *Limited MRD data availability; heterogeneous population.*

k. **PROP 2210-158** Effect of chronic graft-versus-host disease treatment on primary disease relapse. *Heterogeneous population; chronic GVHD severity correlated with type and number of treatments used.*

l. **PROP 2210-294** Optimal duration of ruxolitinib after acute and chronic GVHD: real world practices after 2020. *Duration of ruxolitinib influenced by many factors; lower scientific impact relative to other proposals.*

7. Concluding Notes

a. The meeting adjourned at about 2:15 PM.

b. *After the new proposals were presented, each participant in the meeting had an opportunity to score each proposal electronically using the Tandem app or website. Based on the voting results, current scientific merit, available number of relevant cases, and the impact of the study on the field, the following proposal was accepted to move forward to be added to the committee's active studies:*

PROP 2210-62/75/76/203 The effect of calcineurin inhibitor vs post transplant cyclophosphamide (with or without mycophenolate mofetil) based graft-vs-host disease prophylaxis on HLA matched hematopoietic cell transplantation. *After the meeting the working committee leadership combined these proposals, and they were accepted as one study.*

PROP 2209-15 Incidence of chronic graft versus host disease in cryopreserved versus fresh peripheral blood allogeneic hematopoietic stem cell grafts. *This study was presented at the Collaborative Working Committee Session but accepted as a study within the Graft-versus-Host Disease Working Committee.*

Working Committee Overview Plan for 2023-2024		
Study Number and Title	**Current Status**	**Priority**
GV18-02 Comparison of bacterial blood stream infection incidence in allogeneic stem cell transplantation patients with and without acute graft vs host disease	Manuscript Preparation	**1**
GV19-01 Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients	Manuscript Preparation	**1**
GV20-01 Machine learning models and clinical decision support tool for acute and chronic graft-versus-host disease in patients with acute myelogenous leukemia undergoing allogeneic transplants	Analysis	**2**
GV20-02 Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly-multiplexed proteomics assay: MHC-PepSeq	Data File Preparation	**2**
GV21-01/GV22-03 Racial, ethnicity and socioeconomic disparity in outcome of patients with graft versus host disease	Analysis	**2**
GV21-02 Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation: A validation study	Analysis	**1**
GV22-01 Acute and chronic graft versus host disease in infants and toddlers following hematopoietic cell transplantation	Protocol Development	**3**
GV22-02 Chronic GVHD Risk Index: A clinical risk assessment score for development of moderate-severe chronic graft-versus-host disease after hematopoietic cell transplantation	Protocol Development	**3**
GV23-01 The effect of calcineurin inhibitor vs post transplant cyclophosphamide (with or without mycophenolate mofetil) based graft-vs-host disease prophylaxis on HLA matched hematopoietic cell transplantation	Protocol Pending	**3**
GV23-02 Incidence of chronic graft versus host disease in cryopreserved versus fresh peripheral blood allogeneic hematopoietic stem cell grafts	Protocol Pending	**3**