Not for publication or presentation

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR GRAFT SOURCES & MANIPULATION
Houston, TX
Thursday, February 21, 2019, 2:45 – 5:15 pm

Co-Chair:	**Asad Bashey, MD, PhD, Northside Hospital, Atlanta, GA** **Telephone: 404-255-1930; E-mail: abashey@bmtga.com**
Co-Chair:	**Ian McNiece, PhD, CellMED Consulting, Miami, FL** **Telephone: 305-510-7057; E-mail: aussiflier@aol.com**
Co-Chair	**Claudio Brunstein, MD, PhD, University of Minnesota, Minneapolis, MN;** **Telephone: 612-625-3918 , E-mail: bruns072@umn.edu**
Scientific Director:	**Mary Eapen, MBBS, MS, CIBMTR Statistical Center, Milwaukee, WI;** **Telephone: 414-805-0700: E-mail: meapen@mcw.edu**
Statistical Director:	**Mei-Jie Zhang, PhD, CIBMTR Statistical Center, Milwaukee, WI;** **Telephone: 414-456-8375; E-mail: meijie@mcw.edu**
Statistician:	**Andrew St. Martin, MS, CIBMTR Statistical Center, Milwaukee, WI;** **Telephone: 414-805-0682; E-mail: astmartin@mcw.edu** **Molly Johnson, MPH, CIBMTR Statistical Center, Milwaukee, WI;** **Telephone: 414-805-2258, E-mail: mhjohnson@mcw.edu**

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1. **Introduction**
   Dr. Brunstein opened the meeting at 2:45 pm by welcoming the working committee members for attending the Graft Sources and Manipulation Working Committee (GSWC) meeting. He introduced the GSWC's leadership, and disclosed their conflicts of interest per CIBMTR policy. The minutes from the 2018 GSWC Tandem meeting were approved. Dr. Brunstein then presented the GSWC's membership guidelines, goals and expectations, as well as a brief reminder about the CIBMTR's rules of authorship. He also presented information on data sources (TED vs CRF), showed US transplant trends by donor type, and highlighted the Advisory Committee metrics for the committee. Members in the audience were directed to the CIBMTR's website for additional information. Dr. Brunstein concluded the introduction by referring the committee to Attachment 3 in the materials for a detailed description of current studies in progress.

2. **Published/submitted papers and studies in progress**
   Dr. Brunstein then invited Dr. Bashey to present GS17-02: *T-replete haploidentical cell transplantation using post-transplant cyclophosphamide for AML, ALL, and MDS: Effect of transplant conditioning regimen intensity on outcomes* (oral presentation at ASH 2018, manuscript preparation). Dr. Eapen then presented the results of GS18-02: *Impact of race on relapse after haploidentical transplantation with post-transplant cyclophosphamide compared to cord blood (manuscript preparation).*

3. **Future/proposed studies**
   a. **PROP 1809-05** This proposal was seeking to compare outcomes between haploidentical transplants with post-transplant cyclophosphamide and cord blood transplants for adult and pediatric patients

with acute leukemia or MDS receiving myeloablative conditioning. Dr. Karen Ballen presented the proposal.

The CIBMTR identified 1212 haploidentical transplants with post-transplant cyclophosphamide (434 BM, 778 PBSC) and 1793 cord blood transplants occurring between 2008 and 2018. These transplants were all myeloablative conditioning.

The primary objective of this proposal was to compare leukemia-free survival between haploidentical and cord blood transplants. Secondary objectives included hematopoietic recovery, acute and chronic GVHD, relapse, treatment related mortality, and overall survival.

There was some discussion about the age cutoff, as patients older than 55 were excluded. It was mentioned that since this proposal was including myeloablative conditioning only, there would be very few patients older than 55 who would be eligible, though possibly expanding to include patients up to 60 years old was suggested. Additionally, it was recommended that high resolution HLA typing be used for the cords, as prior work has shown this to be an important factor. However, high resolution typing will only be available in a subset of the cords, and it may not be feasible. Finally, there were comments on incorporating data on donor specific antibodies and recipient parity, which unfortunately is unavailable.

A comment was made that this proposal might be a significant overlap to work done by Dr. Rohtesh Mehta with the Graft vs Host Disease Working Committee. That study was GV16-01. It did not compare haploidentical to cord blood transplants in children. Among the adults, there was a comparison between haploidentical and cord blood transplants. However, GV16-01 included ~140 haploidentical transplants and ~40 used myeloablative regimen and haploidentical transplants were considered as a single group. The purpose of PROP 1809-05 is to compare outcomes after myeloablative haploidentical and cord blood transplants in young adults. As such we confirm there is minimal overlap between GV16-01 and PROP 1809-05.

This proposal received a high priority score from the committee and was accepted.

b. **PROP 1811-01** This proposal was looking to compare the incidence of graft failure in the setting of post-transplant cyclophosphamide between haploidentical, matched sibling, and matched unrelated donor HCT in acute leukemia and MDS. Dr. Cindy Lynn Hickey presented the proposal.

The CIBMTR identified 1018 adults transplanted for AML, ALL, or MDS with a haploidentical donor, 105 transplanted with a matched sibling donor, and 178 transplanted with a matched unrelated donor. These transplants occurred from 2012 to 2018 and had uniform GVHD prophylaxis of post-transplant cyclophosphamide, calcineurin inhibitor, and mycophenolate or methotrexate.

The primary objective of this proposal was to determine the incidence of graft failure in haploidentical donor HCT recipients compared to matched sibling and matched unrelated donor HCT recipients. Secondary objectives included determining the effect of post-transplant cyclophosphamide on the need for CD34+ selected stem cell boosts, identifying risk factors for graft failure, overall survival for patients with graft failure, efficacy of stem cell boosts as a treatment for graft failure, and second transplant compared to stem cell boosts as treatment for graft failure.

The main discussion around this proposal was the definition of graft failure. It was mentioned that chimerism data could be used to identify graft failures when available, and consulting with centers when it was unclear whether a graft failure had occurred. It was also mentioned that primary and secondary graft failures would both be considered.

It was again suggested that data on donor specific antibodies would strengthen the study, and it was mentioned that centers could be contacted to determine if they have any DSA data available for the study.

This proposal received a high priority score and was accepted.

c. **PROP 1811-52** This proposal was seeking to compare outcomes following bone marrow and peripheral blood grafts from matched sibling or matched unrelated donors in the post-transplant cyclophosphamide setting. Dr. Rotesh Mehta presented the proposal.

The CIBMTR identified 250 bone marrow and 589 peripheral blood grafts from matched sibling and matched unrelated donors from 2012 to 2018. These transplants all had uniform GVHD prophylaxis of post-transplant cyclophosphamide, calcineurin inhibitor, and mycophenolate or methotrexate. The diseases included AML and ALL in complete remission, and MDS.

The primary objectives of this proposal was to compare acute and chronic GVHD, relapse, treatment-related mortality, progression-free survival, overall survival, GRFS, and CRFS between bone marrow and peripheral blood grafts. Secondary objectives included incidence of infection, engraftment, and donor chimerism.

The main concern raised regarding this proposal was the potential overlap with an accepted graft sources study, GS18-01. That study is a comparison of haploidentical and matched unrelated donor transplants with post-transplant cyclophosphamide. As this proposal is comparing bone marrow and peripheral blood in the setting of post-transplant cyclophosphamide with wither matched sibling or matched unrelated donors, there overlap is not substantial.

Dr. Bashey asked Dr. Mehta what the standard of care or the baseline would be in this analysis, which Dr. Mehta asserted would be the bone marrow grafts from the matched sibling donors.

This proposal was not accepted.

d. **PROP 1811-119** This proposal was seeking to determine the impact of G-CSF on *in-vivo* T-cell depleted allogeneic hematopoietic cell transplantation. Dr. Nina Orfali presented the proposal.

The CIBMTR identified 1325 patients who received prophylactic G-CSF and 1350 patients who did not receive prophylactic G-CSF from 2007 – 2018. Prophylactic G-CSF was defined as administration -3 to +10 days from transplant. All of these patients received ATG, and were transplanted for AML, ALL, or MDS. Donor type included matched sibling, matched unrelated, and mis-matched unrelated donors.

The primary objective of this proposal was to compare the effect of G-CSF on relapse and relapse-related mortality between patients who received ATG. Secondary objectives included treatment-related mortality, overall and event-free survival, acute and chronic GVHD, and infection.

The only question raised during the discussion was whether data on the source and dose of ATG was available, which was confirmed that it is available.

This proposal received a high priority score from the committee and was accepted.

e. **PROP 1811-133/1811-121** These two proposals were both seeking to compare alternative donor selection for transplantation for aplastic anemia, and were presented as a single proposal. Dr. Queralt Salas presented the proposal.

The CIBMTR identified 67 haploidentical donor transplants with post-transplant cyclophosphamide, 299 matched unrelated donor transplants, and 52 cord blood transplants for aplastic anemia between 2008 and 2018.

The primary objective of this proposal was to compare overall survival between haploidentical donor, matched unrelated donor, and cord blood transplants. Secondary objectives included non-relapse mortality, graft failure, acute and chronic GVHD, and engraftment.

There were two main concerns raised regarding this proposal. First, there were substantial discrepancies in the year of transplants between the donor types such that a direct comparison of the 3 donor types would be difficult. While the MUD transplants were relatively consistent from 2008 to 2018, the cord blood transplants occurred in the early time period and tapered off, whereas the haploidentical transplants occurred in the later years. Dr. Zhang commented that adjustment for transplant period could not be done. The second main concern was the low number of patients eligible for the study. It would be difficult to adjust for confounders in the multivariable analysis, and the analysis would be underpowered.

This proposal was not accepted.

f. **PROP 1811-143** This proposal was seeking to identify factors influencing poor graft function following allogeneic bone marrow transplantation. Dr. Ashish Bajel presented the proposal on behalf of Dr. Emma Leitinger, who could not be in attendance.

The CIBMTR identified 2160 adults transplanted for acute leukemia in complete remission from HLA-identical siblings or unrelated donors. These transplants occurred over the time period between 2013 and 2017.

The primary objective of this proposal was to document the incidence of poor graft function in the presence of full donor chimerism. The secondary objective was to identify risk factors associated with poor graft function.

Dr. McNiece suggested that including graft quality data would strengthen the analysis, such as TNC and CD34 counts. Someone mentioned that the analysis may be difficult with the definition of poor graft function presented due to underlying cytopenias. It was also brought up that the timing of chimerism reported is not consistent and donor chimerism at day 30 may not be available for all patients. Additionally, there was a question about whether data on interventions is available, which Dr. Eapen confirmed was not available.

This proposal was not accepted.

g. **PROP 1811-173** This proposal was looking to compare alternative donor transplants and matched unrelated donor transplants for AML and MDS among patients with a high comorbidity-age composite index. Dr. Shivaprasad Manjappa presented the proposal.

The CIBMTR identified 2186 haploidentical transplants with post-transplant cyclophosphamide, 4783 matched unrelated donor transplants, and 1053 cord blood transplants for AML and MDS. These transplants were all for adults older than 40 years, and occurred between 2008 and 2018.

The main objective of this proposal was to compare overall survival between alternative donors and matched unrelated donors for patients with a high comorbidity-age index. Secondary objectives non-relapse mortality, progression-free survival, relapse, engraftment, GVHD, and graft failure.

One of the discussion points raised was that disease severity would need to be adjusted for, and it was recommended that DRI either be incorporated in the comorbidity index itself, or adjusted for in the multivariable analysis. Additionally, it was brought up that this proposal might overlap with previous work done by the Acute Leukemia Working Committee.

This proposal was not accepted.

h. **PROP 1811-176** This proposal was seeking to study the impact of cell dose on outcomes following haploidentical bone marrow transplants. Dr. Nosha Farhadfar presented the proposal.

The CIBMTR 543 haploidentical donor transplants with post-transplant cyclophosphamide for hematologic malignancies between 2008 and 2018.

The primary objective was the impact of bone marrow cell dose on overall survival. Secondary objectives included the impact of cell dose on engraftment, acute and chronic GVHD, non-relapse mortality, relapse, and progression-free survival.

The main concern raised about this proposal was that John's Hopkins recently published on the effect of bone marrow cell dose for haploidentical donor transplantation, and there was concern about how much this analysis would add to the field. Additionally, there was concern that some of the Hopkins patients from that publication might be included in this proposal.

There were several suggestions to strengthen the study, including looking at donor age and other donor factors, as well as ABO incompatibility. Someone also suggested adding peripheral blood transplants to the analysis.

This proposal was not accepted.

i. **PROP 1812-03** This proposal was seeking to compare conditioning intensities in adult cord blood transplants for AML, ALL, and MDS. Dr. Ioannis Politikos presented the proposal.

The CIBMTR identified 548 adult cord blood transplants with TBI200/Cy/Flud as conditioning, 127 transplants with TBI400/Cy/Flud/Thio as conditioning, and 415 transplants with TBI1320-1375/Cy/Flud as conditioning. These transplants occurred from 2008 to 2018.

The main objective of this proposal was to compare progression-free survival between the different conditioning regimens. Secondary objectives included hematopoietic recovery, acute and chronic GVHD, relapse, transplant-related mortality, and overall survival.

The only suggestion from the committee was to limit the study population to the double cord blood unit transplants, as the single cords were limited in numbers.

This proposal was not accepted.

j. **PROP 1812-09** This proposal was looking to compare haploidentical donors with unrelated donors as second allogeneic transplants following relapse or progression of AML, ALL, or MDS. Dr. Vanderson Rocha presented the proposal.

The CIBMTR identified 225 haploidentical donor transplants with post-transplant cyclophosphamide and 140 unrelated donor transplants. These were all second allogeneic transplants following relapse or progression, and occurred between 2013 and 2018.

The primary objective of this proposal was to compare overall survival following second haploidentical and matched unrelated donor transplants for relapse or progression. Secondary objectives included relapse, non-relapse morality, disease-free survival, acute and chronic GVHD, and graft failure.

A main discussion point was how to address the haploidentical patients who had a different donor for the second transplant compared to those who had the same donor for both transplants. It was recommended that the haploidentical donor group be split into two groups: those with the same haplo donors for the first and second allogeneic transplants and those with different haplo donors for the first and second transplants. Dr. Fuchs reported that the policy at Hopkins is to automatically use a different donor if the patient relapsed or progressed, and that the decision of whether to use the same donor may be center driven.

It was asked what the role of haploidentical DLI would be in this study. Dr. Rocha suggested that since DLI's typically don't involve conditioning, haplo DLI's would not be considered for this analysis. It was also recommended to exclude the MDS due to small numbers, which Dr. Rocha agreed with. Finally, it was mentioned that it would be important to know when the relapse occurred following the first transplant, as that will be an important factor in the outcomes following the second transplant.

This proposal was not accepted.

Meeting adjourned at 5:00 pm

Working Committee Overview Plan for 2019-2020

Study number and title	Current status	Goal with date	Total hours to complete	Total hours to goal	Hours allocated to 6/30/2018	Hours allocated 7/1/2018-6/30/2019	Total Hours allocated
GS16-02: Haploidentical vs MUD HCT in older patients	Submitted	Published – May 2019	10	**10**	10	0	**10**
GS17-02: Myeloablative vs reduced intensity conditioning in Haploidentical transplantation	Manuscript preparation	Published – June 2019	10	**10**	10	0	**10**
GS18-01: Comparison of outcomes after HCT from haploidentical donor with PT-Cy, MUD with PT-Cy, and MUD with CNI	Protocol development	Submitted – April 2020	310	**310**	0	310	**310**
GS18-02: Impact of race on relapse after haploidentical with PT-Cy vs cord blood	Manuscript preparation	Submitted – August 2019	80	**70**	70	10	**80**
GS18-03: Comparison of outcomes of reduced intensity transplantation in lymphoma patients using haploidentical related donors versus unrelated cord blood	Manuscript preparation	Submitted – July 2019	80	**70**	70	10	**80**

GS18-04: Haploidentical donor with PT-Cy vs MUD for MDS	Data file preparation	Submitted – October 2019	200	**200**	130	70	**200**
GS19-01: Comparison of myeloablative haplo or CB in Acute Leukemia	Protocol pending	Manuscript preparation – January 2020 Submitted – July 2020	330	**330**	0	330	**330**
GS19-02: Graft Failure in MDS and Acute Leukemia with PT-Cy	Protocol pending	Data file preparation – June 2020	330	**100**	0	100	**100**
GS19-03: Impact of G-CSF on in-vivo T-cell depleted Allogeneic Hematopoietic Cell Transplantation	Protocol pending	Data file preparation – April 2020	330	**100**	0	100	**100**

Oversight Assignments for Working Committee Leadership (March 2019)

Ian McNiece	**GS16-02:** Donor selection: Biologic child vs. HLA-matched sibling or Haplo-identical relative vs. HLA-matched sibling. Can post-transplant cyclophosphamide overcome the HLA barrier?
Asad Bashey	**GS17-02:** Myeloablative versus reduced intensity conditioning in haploidentical transplantation.
Ian McNiece	**GS18-01:** Comparison of outcomes after HCT from haploidentical donor with PT-Cy, MUD with PT-Cy, and MUD with CNI.
Asad Bashey	**GS18-02:** Impact of race (African Americans vs. Caucasians) on relapse after haploidentical with PT-Cy vs cord blood
Claudio Brunstein	**GS18-03:** Comparison of Outcomes of Reduced Intensity Transplantation in Lymphoma Patients Using Haploidentical Related Donors vs. Unrelated Cord Blood (joint study with EBMT)
Asad Bashey	**GS18-04:** Haploidentical donor with PT-Cy vs MUD for MDS.
Claudio Brunstein	**GS19-01:** Comparison of myeloablative haplo or CB in Acute Leukemia
Asad Bashey	**GS19-02:** Graft Failure in MDS and Acute Leukemia with PT-Cy
Ian McNiece	**GS19-03:** Impact of G-CSF on in-vivo T-cell depleted Allogeneic Hematopoietic Cell Transplantation