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A G E N D A
CIBMTR WORKING COMMITTEE FOR GRAFT SOURCES & MANIPULATION
Houston, TX
Thursday, February 21, 2019, 2:45 – 4:45 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**

- **Introduction**
  a. Minutes and Overview Plan from February 2018 meeting (Attachment 1)

- **Accrual summary** (Attachment 2)

- **Presentations, published or submitted papers**

  a. **GS17-03** Keesler DA, Martin AS, Bonfim C, Seber A, Zhang M-J, Eapen M. Bone marrow versus peripheral blood from unrelated donors for children and adolescents with acute leukemia. ***Biol Blood Marrow Transplant 24(12):2487-2492.***

  b. **GS15-01** McCurdy SR, Zhang M-J, St Martin A, Al Malki MM, Bashey A, Gaballa S, Keesler DA, Hamadani M, Norkin M, Perales M-A, Reshef R, Rocha V, Romee R, Solh M, Urbano-Ispizua A, Waller EK, Fuchs EJ, Eapen M. Effect of donor characteristics on haploidentical transplantation with posttransplantation cyclophosphamide. ***Blood Advances 2(3):299-307.***

  c. **GS16-02** Perales M-A, Tomlinson B, Zhang M-J, St. Martin A, Lazarus HM, Marks DI, Romee R, Solh M, Wagner JE, Weisdorf D, de Lima M, Eapen M. Outcomes after T-replete haploidentical transplantation using post-transplant cyclophosphamide compared to matched unrelated donor transplantation for acute myeloid leukemia in remission in older adults. ***Submitted***

d. **GS16-03** Robinson TM, Fuchs EJ, Zhang M-J, St Martin A, Labopin M, Keesler DA, Blaise D, Bashey A, Bourhis J-H, Ciceri F, Ciurea SO, Devine SM, Mohty M, McCurdy SR, Milpied N, McNiece IK, Rocha V, Romee R, Socie G, Yakoub-Agha I, Soiffer RJ, Eapen M, Nagler A. Related donor transplants: Has posttransplantation cyclophosphamide nullified the detrimental effect of HLA mismatch? ***Blood Advances 2(11):1180-1186.***

e. **GS17-02** Solomon S, Shah N, Fatobene G. Myeloablative vs reduced intensity conditioning in haploidentical transplantation. ***Oral presentation at ASH meeting in San Diego, CA, December 2018*.**

4. Studies in Progress (Attachment 3)

a. **GS17-02** Myeloablative vs reduced intensity conditioning in haploidentical transplantation (S Solomon/N Shah/ G Fatobene) **Manuscript Preparation**
b. **GS18-01** Transplant outcomes after HLA haploidentical donor transplantation with post-transplant cyclophosphamide (PTCy) vs matched unrelated donor transplantation with and without PTCy in AML, ALL, and MDS patients (R Romee et al) **Data File Preparation**
c. **GS18-02** Impact of race on relapse after haploidentical transplantation with PT-Cy vs cord blood (S Soloman) **Manuscript Preparation**
d. **GS18-03** Comparison of outcomes of reduced intensity transplantation in lymphoma patients using haploidentical related donors vs unrelated cord blood (G Fatobene/ V Rocha/ S Montoto) **Analysis**
e. **GS18-04** Comparison of Outcomes with Haploidentical and Matched Unrelated Donors for Hematopoietic Stem Cell Transplantation in Myelodysplastic Syndromes (A Viswabandya/ B Tomlinson/ M Grunwald/ H Elmariah) **Data File Preparation**

5. Future/proposed studies

a. **PROP 1809-05** Comparison of Myeloablative Haploidentical or Umbilical Cord Blood Transplantation for Pediatric and Adult Patients with Acute Leukemia (J Wagner/ K Ballen) (Attachment 4)
b. **PROP 1811-01** Graft Failure in MDS and Acute Leukemia Patients After Allogeneic Stem Cell Transplantation Receiving Post Transplant Cyclophosphamide (C Hickey/ R Romee/ C Cutler/ N Majhail) (Attachment 5)
c. **PROP 1811-52** Bone marrow (BM) versus peripheral blood (PB) graft in adults undergoing HLA matched related or unrelated donor hematopoietic cell transplantation (HCT) with post-transplantation cyclophosphamide (PTCy) (R Mehta/ A Alousi) (Attachment 6)
d. **PROP 1811-119** Impact of G-CSF on *in-vivo* T-cell depleted Allogeneic Hematopoietic Cell Transplantation (N Orfali/ J J Boelens/ K Van Besien) (Attachment 7)
e. **PROP 1811-133/1811-121** Comparing outcomes between HLA-haploidentical and HLA-matched unrelated donor allogeneic transplants in patients with aplastic anemia (Q Salas/ S Prem/ A Sureda/ R Kumar/A Sharma/ N Bhatt) (Attachment 8)
f. **PROP 1811-143** Factors influencing poor graft function post allogeneic bone marrow transplantation (E Leitinger) (Attachment 9)
g. **PROP 1811-173** Alternative donor stem cell transplants compared to matched unrelated donor transplants in the treatment of AML and MDS for patients with high comorbidity-age composite index (S Manjappa/ L Metheny/ M de Lima/ B Cooper) (Attachment 10)
h. **PROP 1811-176** Impact of Cell Dose on Haploidentical Bone Marrow Stem Cell Transplantation Outcome (N Farhadfar/ H Murthy/ J Hsu/ J Wingard) (Attachment 11)
i. **PROP 1812-03** Evaluation of the Impact of Conditioning Intensity in Adult Cord Blood Transplantation Recipients Treated for Acute Leukemia or Myelodysplasia (MDS) (L Politikos/ J Barker/ C Brustein) (Attachment 12)

j. **PROP 1812-09** The Role of Alternative Donors and HLA Disparity in Second Allogeneic Stem Cell Transplantation for Relapsed Hematologic Malignancies (G Fatobene/ P Imus/ E Fuchs/ V Rocha) (Attachment 13)

Dropped proposed studies

a. **PROP 1812-01** Haploidentical Transplant with Posttransplant Cyclophosphamide vs. HLA-Matched Unrelated Donor Transplant for Adult Acute Lymphoblastic Leukemia. *Overlap with current study LK18-02.*
b. **PROP 1812-02** Comparison of the Impact of Minimal Residual Disease before Allogeneic Stem Cell Transplantation in Adult Patients with Acute Lymphoblastic Leukemia between Unrelated Cord Blood vs. Conventional Marrow and Blood Grafts. *Data unavailable*

6. Other Business

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR GRAFT SOURCES & MANIPULATION
Salt Lake City, UT
Thursday, February 22, 2018, 2:45 – 4:45 pm

Co-Chair:	**Vanderson Rocha, MD, PhD, Churchill Hospital, Oxford, United Kingdom; Hospital das Clínicas da Universidade de São Paulo and Hospital Sírio-Libanês, Brazil Telephone: 44 1865 572326; E-mail: vanderson.rocha@ouh.nhs.uk; rocha.vanderson@hotmail.fr**
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**
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**

1. Introduction

Dr. Bashey 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, taking time to thank Dr. Rocha for his time as a co-chair. He also welcomed Dr. Claudio Brunstein as the incoming co-chair, and acknowledged Dr. Arnon Nagler, Chair of the Acute Leukemia Working Party of the EBMT, and Dr. Eliane Gluckman, Director of Eurocord who were in attendance. The minutes from the 2017 GSWC Tandem meeting was approved. Dr. Bashey then presented the GSWC's membership guidelines, goals and expectations. He also gave a brief reminder about the CIBMTR's rules of authorship. He closed the introduction by presenting information on data sources (TED vs CRF), showing US transplant trends by donor type, and by directing the committee to the CIBMTR's website for additional information.

2. Published/submitted papers and studies in progress

Dr. McNiece then invited Dr. Shannon McCurdy to present GS15-01: *Related donor transplants: has post-transplantation cyclophosphamide nullified the detrimental effect of HLA mismatch?* (published in Blood Advances). Dr. Miguel Perales presented the results of GS16-02: *Outcomes after T-replete HLA-haploidentical transplantation using post-transplant cyclophosphamide compared to matched unrelated donor transplantation for acute myeloid leukemia in remission in older adults* (manuscript preparation), and Dr. Nagler presented the results for GS16-03: *Selecting between HLA-matched siblings and HLA-haploidentical related donors for acute leukemia in the era of post-transplant cyclophosphamide: The CIBMTR and Acute Leukemia Working Party, EBMT* (submitted). The committee was directed to the GSWC packet for details on the other studies currently in progress.

3. Future/proposed studies

a. **PROP 1710-20/1711-41/1711-48/1711-68/1711-148** These five proposals were all seeking to compare outcomes between alternative donors with post-transplant cyclophosphamide as GVHD prophylaxis. They were combined into a single proposal, and Dr. Miguel Perales presented on the proposal on behalf of the other investigators.

The CIBMTR identified 1616 adults transplanted for AML, ALL, or MDS with a haploidentical donor with post-transplant Cytoxan (PT-Cy), 124 transplanted with a matched unrelated donor with PT-Cy, and 39 transplanted with a 7/8 unrelated donor. These transplants occurred over the time period between 2013 and 2017.

The primary objective of this proposal was to compare overall survival in adult patients transplanted with haploidentical donor with PT-Cy, matched unrelated donor with PT-Cy, and mismatched-unrelated donor with PT-Cy. Secondary objectives included comparing progression-free survival, engraftment, relapse and non-relapse mortality, and acute and chronic GVHD.

Based on the number of available patients eligible for the study, it was recommended to focus the study on haplo PT-Cy compared to MUD PT-Cy.

It was asked if it would make sense to add a matched unrelated donor group with standard GVHD prophylaxis as a comparison group. Dr. Rizwan Romee submitted a proposal looking to compare matched unrelated donors with PT-Cy to matched unrelated donors with standard prophylaxis, and the GSWC leadership decided to further combine the proposals, resulting in a study that will compare haplo PT-Cy, MUD PT-Cy, and MUD CNI + MMF/MTX.

This proposal, along with Dr. Romee's proposal, received a high priority score from the committee, and was accepted as a combined study.

b. **PROP 1711-51/1711-84/1711-91/1711-99** These four proposals were all seeking to compare outcomes between haploidentical and unrelated donor allogeneic transplants in patients with MDS. They were combined into a single proposal, and Dr. Michael Grunwald presented the proposal on behalf of the other investigators.

The CIBMTR identified 373 adults transplanted for MDS with a haploidentical donor, 1644 transplanted with a matched unrelated donor, and 248 transplanted with a mismatched unrelated donor. These transplants occurred over the time period between 2012 and 2017.

The primary objective of this proposal was to compare overall survival in adult patients transplanted for MDS, CMML, and MPN with haploidentical donor with post-transplant cyclophosphamide HCT, , matched unrelated donor HCT, and mismatched unrelated donor HCT. Secondary objectives included comparing non-relapse mortality, engraftment and graft failure, relapse, disease-free survival, and acute and chronic GVHD. The three disease groups would be analyzed separately.

It was suggested to restrict the study to CMML and MDS based on the eligible patients. Another person recommended looking at the distribution of biological markers.

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

c. **PROP 1711-15** This proposal was looking to investigate the impact of racial background on outcomes following haploidentical HCT and cord blood HCT. Dr. Scott Solomon presented the proposal.

The CIBMTR identified 2115 Caucasian haploidentical HCT recipients, 550 African American haploidentical recipients, 1582 Caucasian cord blood recipients, and 277 African American cord blood recipients. These patients were all adults transplanted for hematologic malignancies, and the transplants occurred over the time period between 2008 and 2017.

The primary objective of this proposal was to compare overall survival between the 4 donor and race groups. Secondary objectives included comparing acute and chronic GVHD, and relapse and non-relapse mortality, and disease free-survival.

This proposal was based on the findings from Drs. Bashey's and Solomon's single center study which showed a lower risk of relapse among African American haploidentical recipients compared to Caucasian haploidentical recipients, and much of the discussion was centered around why that might be.

Several recommendations for the proposal were also raised, including the addition of socio-economic factors in the analysis, time to transplant, availability of samples for sequencing, and how reliable race data is captured by the CIBMTR. It was also asked why Hispanics were excluded from the proposal, which was due to the limited numbers of eligible patients. Similarly, there were too few patients of other race to be included in the analyses.

This proposal was received the highest priority score from the committee, and was therefore accepted.

d. **PROP 1711-56** This proposal was seeking to compare outcomes from haploidentical, MUD, and cord blood HCT for pediatric patients with acute leukemia. This was a proposed CIBMTR/EBMT collaborative study. Dr. Alice Bertaina presented the proposal.

The CIBMTR identified 192 haploidentical transplants, 251 matched unrelated donor transplants, and 708 cord blood transplants occurring between 2008 and 2017. Similarly, the EBMT identified 895 haploidentical transplants, 1990 MUD transplants, and 1156 cord blood transplants from 2007 to 2014.

The primary objective of this proposal was to compare overall survival in pediatric acute leukemia patients transplanted with a haploidentical donor, a matched unrelated donor, or a cord blood donor. The secondary objectives included comparing disease-free survival, treatment-related mortality, and GVHD. Additionally, comparing different haploidentical transplant techniques was an aim.

Dr. Eliane Gluckman reported that the EBMT/Eurocord are updating the 2012 presentation at ASH and submission of that paper. That publication was delayed because of the heterogeneity of haplo-strategies. Therefore they waited to accrue more transplants for a meaningful comparison. The US data had only 192 haplo-identical transplants with ~40% using the PT-Cy approach. The remaining haplos were either T-cell depleted BM grafts or CD34 selected PB. As the European study is in its final stages (data analyses/manuscript preparation) the current

proposal would not add to the literature and would have to be limited to N. America. If that were the case, the numbers of haplo-identical transplants are few for a robust comparison.

This proposal was not accepted.

e. **PROP 1711-117** This proposal was seeking to compare outcomes between haploidentical transplants with post-transplant cyclophosphamide and cord blood transplants for lymphoma. Dr. Vanderson Rocha presented this proposal. Dr. Rocha approached the EBMT Lymphoma Working party and its leadership have confirmed their interest in joining this effort.

The CIBMTR identified 497 haploidentical transplants with post-transplant cyclophosphamide and 203 cord blood transplants for lymphoma between 2008 and 2017. These transplants were all reduced intensity conditioning.

The primary objective of this proposal was to compare overall, disease-free survival, relapse, non-relapse mortality, GVHD, and GRFS between haploidentical and cord blood transplants. There were planned subset analyses for patients with diffuse large B-cell lymphoma, follicular lymphoma, and Hodgkin lymphoma.

There were no comments raised by the committee.

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

f. **PROP 1711-168** This proposal was seeking to compare outcomes between matched unrelated donors with post-transplant cyclophosphamide and matched unrelated donors with standard care of calcineurin inhibitor containing GVHD prophylaxis in AML, ALL, and MDS. Dr. Rizwan Romee presented the proposal.

The CIBMTR identified 112 MUD transplants with post-transplant cyclophosphamide and 525 MUD transplants with TAC + MMF as GVHD prophylaxis. These transplants occurred over the time period between 2013 and 2017.

The primary objective of this proposal was to compare acute and chronic GVHD in 8/8 MUD HCT's with PT-Cy or TAC + MMF. Secondary objectives included relapse, non-relapse mortality, overall survival, GRFS, and hematopoietic recovery.

It was pointed out that dosage of cyclophosphamide given as GVHD prophylaxis might be important information to analyze, however dosage of cyclophosphamide is only collected for conditioning, not for GVHD prophylaxis. It was also asked how many of the MUD PT-Cy patients received PT-Cy alone compared to a calcineurin inhibitor in addition to the cyclophosphamide. There were roughly ten patients that were given PT-Cy alone, so they were excluded from the initial pool of eligible patients.

As this proposal was similar to the combined proposals seeking to compare MUD PT-Cy and haploidentical PT-Cy, the GSWC leadership decided to further combine the proposals, resulting in a study that will compare haplo PT-Cy, MUD PT-Cy, and MUD CNI + MMF/MTX.

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

Meeting adjourned at 4:15 pm

Working Committee Overview Plan for 2017-2018

a. **GS15-02**: Long-term outcomes of 100-day survivors of HCT survivors by donor source. Analysis by June 2018, manuscript submission by July 2019.
Statistical hours allocated - Through June 2018: 160; July 2018 - June 2019: 150; To completion: 310

b. **GS16-02:** Comparison of outcomes after haplo-identical related donor vs. HLA-matched unrelated donor transplant in patients aged > 50 years. This study is currently in manuscript preparation, and the goal is to be submitted by May 2018.
Statistical hours allocated - Through June 2018: 70; July 2018 - June 2019: 10; To completion: 70

c. **GS16-03:** Related donor transplants: has post-transplantation cyclophosphamide nullified the detrimental effect of HLA mismatch? This study was submitted for peer review.
Statistical hours allocated - Through June 2018: 10; July 2018 - June 2019: 0; To completion: 0

d. **GS17-02:** Myeloablative versus reduced intensity conditioning in haploidentical transplantation. The study protocol is currently being developed for this study, and the goal is manuscript preparation by July 2018, and to be submitted by October 2018.
Statistical hours allocated - Through June 2018: 240; July 2018 - June 2019: 70; To completion: 310

e. **GS18-01:** Comparison of outcomes after HCT from haploidentical donor with PT-Cy, MUD with PT-Cy, and MUD with CNI. Work will begin on this study in the next academic year, and the goal is to submit by May 2019.
Statistical hours allocated - Through June 2018: 0; July 2018 - June 2019: 310; To completion: 310

f. **GS18-02:** Impact of race (African Americans vs. Caucasians) on relapse after haploidentical with PT-Cy vs cord blood. The goal is data file preparation by June 2018, with a submission goal of June 2019.
Statistical hours allocated - Through June 2018: 60; July 2018 - June 2019: 250; To completion: 310

g. **GS18-03:** Comparison of Outcomes of Reduced Intensity Transplantation in Lymphoma Patients Using Haploidentical Related Donors vs. Unrelated Cord Blood. The goal is protocol development and data file preparation by July 2019.
Statistical hours allocated - Through June 2018: 0; July 2018 - June 2019: 60; To completion: 350

h. **GS18-04:** Haploidentical donor with PT-Cy vs MUD for MDS. The goal is protocol development and data file preparation by July 2019.
Statistical hours allocated - Through June 2018: 0; July 2018 - June 2019: 60; To completion: 310

Oversight Assignments for Working Committee Leadership (March 2017)

Claudio Brunstein	**GS15-02:** Long-term outcomes of 100-day survivors of HCT survivors by donor source.
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.

Accrual Summary for Graft Sources and Manipulation Working Committee

Characteristics of patients reported to the CIBMTR between 2000 and 2018

Characteristics	Registration N (%)	Research N (%)
Number of cases	**189672**	**66054**
Donor type		
HLA-identical sibling donor HCT	77694	19994
Bone marrow	21589 (28)	5614 (28)
Peripheral blood	54160 (72)	14139 (71)
Umbilical cord blood	557 (<1)	241 (1)
Identical twin donor HCT	1040	496
Bone marrow	157 (15)	77 (16)
Peripheral blood	878 (84)	417 (84)
Umbilical cord blood	5 (<1)	2 (<1)
HLA mismatched related donor HCT	13153	4926
Bone marrow	4385 (33)	1650 (33)
Peripheral blood	8366 (64)	3045 (62)
Umbilical cord blood	402 (3)	231 (5)
Unrelated donor HCT	90836	38411
Bone marrow	23138 (25)	10710 (28)
Peripheral blood	54407 (60)	18979 (49)
Umbilical cord blood	13291 (15)	8722 (23)

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TO: Graft Sources and Manipulation Working Committee Members

FROM: Mary Eapen, MBBS, MS; Scientific Director for the Graft Sources Working Committee

RE: Studies in Progress Summary

GS17-02: Myeloablative vs reduced intensity conditioning in haploidentical transplantation (S Solomon/N Shah/G Fatobene): The aim of this study is to compare outcomes for haploidentical donor transplantation using myeloablative or reduced intensity conditioning regimens. We are in the final stages of manuscript preparation and plan to have this submitted in February 2019.

GS18-01: Transplant outcomes after HLA haploidentical donor transplantation with post-transplant cyclophosphamide (PTCy) vs matched unrelated donor transplantation with and without PTCy in AML, ALL, and MDS patients (R Romee et al): The aim of this study is to compare outcomes following haploidentical donor and matched unrelated donor transplantation in the setting of a uniform GVHD prophylaxis with post-transplant cyclophosphamide. Furthermore, a comparison against matched unrelated donors with standard GVHD prophylaxis will be done to determine if PTCy is a preferable platform in both haploidentical and unrelated donor settings. We delayed starting this study to allow for further accrual of MUD's with PTCy, and we plan to start data file preparation in July 2019.

GS18-02: Impact of race on relapse after haploidentical transplantation with PT-Cy vs cord blood (S Solomon): The primary aim of this study is to compare outcomes following haploidentical transplantation with post-transplant cyclophosphamide among Caucasian and African American recipients. A secondary aim to compare is to compare outcomes following haploidentical donor transplantation with PT-Cy and cord blood transplantation among African American recipients. We have completed the analysis, and this study is currently in manuscript preparation. We plan to submit this by March 2019.

GS18-03: Comparison of outcomes of reduced intensity transplantation in lymphoma patients using haploidentical related donors vs unrelated cord blood (G Fatobene/ V Rocha/ S Montoto): This study is a collaboration between the CIBMTR, Eurocord, and EBMT. The aim is to compare outcomes following haploidentical donor and cord blood transplantation among lymphoma patients. This study is currently in analysis, and we plan to have this study submitted by June 2019.

GS18-04: Haploidentical donor transplantation with PT-Cy vs MUD for MDS (M Grunwald et al) The aim of this study is to compare outcomes following haploidentical donor transplantation and matched unrelated donor transplantation for MDS. The study is currently in data file preparation, and the plan is to be in manuscript preparation by June 2019.

Proposal: 1809-05

Title:
Comparison of Myeloablative Haploidentical or Umbilical Cord Blood Transplantation for Pediatric and Adult Patients with Acute Leukemia

John Wagner, MD, wagne002@umn.edu, University of Minnesota
Karen Ballen, MD, KB3TC@virginia.edu, University of Virginia

Hypothesis:
Two-year leukemia free survival (LFS) with myeloablative conditioning and umbilical cord blood transplantation (UCBT) is improved compared **to** Haploidentical (haplo) transplantation after myeloablative conditioning and post-transplant cyclophosphamide (PTCy).

Specific aims:
- To determine the relapse rate after myeloablative conditioning for haplo and UCBT
- To determine days to neutrophil and platelet engraftment after myeloablative conditioning for haplo and UCBT
- To determine rates for acute and chronic graft vs host disease (GVHD) after myeloablative conditioning for haplo and UCBT
- To determine overall survival (OS) at 2 years after myeloablative conditioning for haplo and UCBT
- To determine transplant related mortality (TRM) at 1 year after myeloablative conditioning for haplo and UCBT

Endpoints:
- Primary: The primary aim of this study is to describe the risk factors for LFS at 2 years in patients treated with MAC and determine the impact of donor source.
- Secondary: Evaluate the incidence of hematopoietic recovery by day 60, acute and chronic GVHD at 100 days and 2 years respectively, relapse at 2 years, transplant-related mortality at 1 year, and overall survival at 2 years.

Scientific impact:
The choice of graft source is an important one that transplant physicians face every day. Many centers are moving to haplo because of the donor availability, ease of immediate post transplant period, and cost. (Versluis J) Most of the data from the US Bone Marrow Transplant Clinical Trials Network (CTN) has focused on outcomes after reduced intensity conditioning. (Brunstein CG Fuchs EJ) Relapse remains the most common cause of treatment failure after HCT. (Ponce DM)
Recently, minimal residual disease after induction therapy has been studied as an important prognostic factor for patients with acute leukemia. (Canaani J) Milano and colleagues have demonstrated that UCBT is associated with a lower risk of relapse for patients with leukemia and minimal residual disease, when compared to matched unrelated donor transplant. (Milano F)
In this study, we compare outcomes between UCBT and haplo after myeloablative conditioning.

Scientific justification:
While ideally this question should be answered in a randomized trial, this trial will not likely be funded or completed. The CIBMTR now has accrued enough haplo patients to answer this crucial question.

Patient eligibility population:

Inclusion criteria:

- Patients with Acute Myeloid Leukemia, Acute Lymphoid Leukemia, and Myelodysplasia
- Age <55 years
- First BMT
- MAC
    - CIBMTR definitions
- HSC Sources
    - T-replete haploidentical HSC (PBSC or BM) defined as 2 or more antigen-level mismatches among HLA-A, -B, -C, and -DRB1
    - 4/6 Unrelated UCB based on high resolution typing at HLA A, B, C, DRB1 (single and double)
- GVHD Prophylaxis
    - For haploidentical only, Post Transplant Cyclophosphamide (PTCy) +Calcineurin Inhibitor (CNI)) ± other
    - For UCB, CNI + other

Exclusion Criteria:

- Ex-vivo T-cell depletion
- Use of ATG or alemtuzumab in conditioning
- PT-Cy as single GVHD prophylaxis
- Combined Haplo-UCB transplants

Variables to be analyzed:

Patient-related:

- Patient age at HCT: <18, 18-29 vs. 30-55
- Karnofsky performance score: ≥90 vs. <90
- HCT-CI: 0 vs. 1-2 vs. ≥3
- Race: Caucasian vs. not Caucasian

Disease-related:

- Time from diagnosis to HCT, months: < 6 vs. 6-<12 vs. ≥ 12
- Disease Risk Index (DRI): low vs. intermediate vs. high/very high
- AML vs ALL vs MDS

Transplant-related:

- Donor/Recipient CMV status: -/+ vs. +/- vs. +/+ vs. -/-
- TBI-based MAC vs. chemo-based MAC
- GVHD prophylaxis
- UCB HLA match (6-8/8 vs 3-5/8)
- Cell dose
- Single vs Double

Conflicts of interest:

None

References:

1. Brunstein CG Fuchs EJ, Carter SJ, et al. "Alternative donor transplantation after reduced intensity conditioning: results of parallel phase 2 trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts." *Blood* 118.2 (2011): 282-88.

2. Canaani J, Labopin M, Hunag XJ, et al. "Minimal residual disease status predicts outcome of acute myeloid leukemia patients T - cell replete haploidentical transplantation." *British Journal Hematology* doi:10.1111/bjh.15540 (2018): 1-10, e pub ahead of print.
3. Milano F, Gooley T, Wood B, et al. "Cord Blood Transplantation in Patients with Minimal Residual Disease." *New England Journal of Medicine* 375 (2016): 944-53.
4. Ponce DM, Hilden P, Devlin SM, et al. "High disease-free survival with enhanced protection against relapse after double-unit cord blood transplantation when compared with T cell-depleted unrelated donor transplantation in patients with acute leukemia and chronic myelogeneous leukemia." *Biology Blood Marrow Transplant* 21 (2015): 1985-93.
5. Versluis J, Labopin M, Ruggeri A, et al. "Alternative donors for allogeneic hematopoietic stem cell transplantation in poor-risk AML in CR q." *Blood Advances* 1.7 (2017): 477-485.

Table1. Characteristics of patients who underwent first myeloablative haploidentical donor or UCB HCT for hematologic malignancies and reported to CIBMTR, 2008-2018

Characteristic	Haplo-BM	Haplo-PB	UCB
Number of patients	434	778	1793
Age at transplant, years			
< 18	124 (29)	22 (3)	837 (47)
18 – 30	74 (17)	169 (22)	297 (17)
31 – 50	83 (19)	303 (39)	429 (24)
> 50	153 (35)	284 (37)	230 (13)
Disease			
AML	238 (55)	443 (57)	891 (50)
ALL	116 (27)	228 (29)	709 (40)
MDS	80 (18)	107 (14)	193 (11)
Conditioning regimen			
TBI + Cy	74 (17)	16 (2)	182 (10)
TBI + Flud	69 (16)	357 (46)	81 (5)
TBI + Cy + Flud	13 (3)	19 (2)	1053 (59)
TBI + Other	3 (<1)	14 (2)	64 (4)
Bu + Cy	113 (26)	223 (29)	202 (11)
Flud + Bu	65 (15)	122 (16)	98 (5)
Flud + Mel	91 (21)	26 (3)	74 (4)
Bu + Mel	6 (1)	1 (<1)	39 (2)
GVHD prophylaxis			
PT-Cy + CNI + MMF	434	778	0
CNI + MMF	0	0	1668 (93)
CNI + MTX	0	0	125 (7)
Year of transplant			
2008 – 2012	92 (21)	32 (4)	1030 (57)
2013 – 2018	342 (79)	746 (96)	763 (43)

Proposal: 1811-01

Title:
Graft Failure in MDS and Acute Leukemia Patients After Allogeneic Stem Cell Transplantation Receiving Post Transplant Cyclophosphamide

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Hypothesis:
We hypothesize that the use of post-transplant cyclophosphamide (PTCy) after hematopoietic cell transplant (HCT) increases the chance of engraftment failure and poor graft function.
Furthermore, we also hypothesize that CD34 selected stem cell boost is an effective treatment option for engraftment failure and poor graft function in both HLA matched and haploidentical HCT recipients.

Specific aims:
The primary goal of this study is to determine the potential impact of PTCy and/or graft source on engraftment failure (primary and or secondary) in AML, ALL and MDS patients after HLA haploidentical and HLA matched transplantation.

- Aim 1: To determine incidence of engraftment failure in haploidentical donor HCT recipients who received PTCy vs. HLA matched donor transplant recipients who also received PTCy in addition to the standard of care GvHD prophylaxis.
- Aim 2: To determine incidence of engraftment failure in HLA matched transplant recipients who received vs who did not receive PTCy for GvHD prophylaxis regimens.

<u>Additional objectives include:</u>

- To determine the effect of PTCy on the need for CD34+ selected stem cell boosts and/or second transplants.
- To determine potential predisposing risk factors for engraftment failure.
- To determine survival outcomes in patients with engraftment failure.
- To determine efficacy of stem cell boosts as a treatment for poor engraftment.
- To determine outcomes of second transplants vs. stem cell boosts as treatment for poor engraftment.

Scientific impact:
Allo-HCT offers a potential curative option for several hematological disorders that would otherwise result in fatal outcomes. The optimal donor cells would come from a HLA-matched sibling, however only 30% of patients will find a matching donor. For this reason, several other donor strategies have been explored including matched unrelated, umbilical cord and haplo-identical. Haploidentical stem cells have become a particularly appealing donor source as >95% of patients will find an available donor. The donors, which include parents, siblings or children of the patient, are often highly motivated and rapidly available.
One of the biggest challenges with haploidentical HCT, however, is the intense bi-directional alloreactivity of naïve CD4+ T cells resulting in high incidence of graft rejection and graft-vs-host disease (GVHD).[1] Strategies such as using in vivo or ex vivo T-cell depletion to prevent GVHD have been associated with unacceptable increased rates of non-relapse mortality and delayed immune reconstitution.[2] To overcome

this, a different tactic of using unmanipulated T-cells for haploidentical HCT with the addition of post-transplant cyclophosphamide (PTCy) has been studied with great success.[3] Cyclophosphamide is an antineoplastic agent that has a well-established role in conditioning prior to allogeneic HCT. There have been several studies, however, that have proven its role in preventing graft rejection and GVHD when given on days 3 and 4 post-transplantation.[4-5] When compared to match unrelated donor (MURD) transplant in acute myeloid leukemia (AML), PTCy showed lower rates of GVHD and comparable overall survival (OS).[6] Similarly, haploidentical HCT using PTCy was compared to HLA-matched siblings (MRDs) and HLA-matched unrelated donors (MUDs) for various hematological malignancies and showed equivalent rates of non-relapse mortality (NRM), acute GVHD and disease free survival (DFS).[7]
Despite the promising outcomes using PTCy, the rate of graft failure has been reported to be as high as 12-43% in haploidentical transplant recipients.[8-12] It is difficult to determine if this is due to PTCy effect or the haploidentical stem cell source itself. For this reason, it is important to determine the rates of graft failure with PTCy and see if there are differences observed in the haploidentical vs. non-haploidentical HCT populations. If in fact use of PTCy does increase the chance of engraftment failure, strategies such as using a two-step transplant technique (described by Thomas Jefferson Kimmel Cancer Center) involving infusion of fixed donor T-cells, followed by PTCy and then CD34 positive cells[13] or prophylactic CD34 boosts will need to be considered for future transplants. Alternatively, ways to overcome graft failure such as increased number of stem cells at the time of transplant or decreasing potential risk factors, could also potentially change current clinical practice. As far we know, this question has not been investigated in the literature.

Scientific justification:
Posttransplant cyclophosphamide and graft failure has been an observed complication in haploidentical transplant since early clinical studies. O'Donnell et al (2002) conducted a pivotal trial demonstrating 2/3 (67%) graft rejection in patients with high risk hematological malignancies who received T-cell replete haploidentical bone marrow grafts after nonmyeloablative conditioning with fludarabine and low dose total body irradiation followed by PTCy. To overcome this, 2 days of cyclophosphamide was added to the conditioning regiment resulting in 2/10 (20%) graft failure.[11] The established non-myeloablative Johns Hopkins University regimen using fludarabine, cyclophosphamide, low dose body irradiation followed by PTCy was used in several further studies showing improved rates in graft failure, however still ranging from 12-20%[14-16] This rejection rate is still significantly higher than non-myeloablative, 4-5%,[17-18] and myeloablative, 0.1-5%,[19] regimens used in the non-haploidentical transplant setting. The role of PTCy vs the known risk factor of a HLA-mismatched graft in graft failure requires further investigation.

Patient eligibility population:
Inclusion:
- Age ≥18 years
- Diagnosis of MDS, AML or ALL
- Any patient who underwent 1st allogeneic HCT between 2012-2017

Exclusion:
- T cell depleted HCT recipients
- Mismatched unrelated donor recipients
- Cord blood HCT recipients
- Patients who have received ATG as part of their conditioning
- Recipients of 2nd allogeneic HCT
- HLA matched patients having received PTCy as a single agent for GVHD prophylaxis

Data requirements:

Baseline patient/disease characteristics:

- Age at transplant
- Sex
- Ethnicity
- Diagnosis
- Time from diagnosis to HCT: 0-6 versus 6-12 versus ≥12 months and continuous
- Prior lines of therapy
- Remission status at the time of transplant
- CMV status
- ABO blood type
- Donor chimerism at days +30, +100, +180
- Karnofsky Performance Score (≥90 vs <90 and continuous)

Donor characteristics:

- Donor age
- Donor sex
- Donor relationship to patient
- CMV status
- ABO blood type
- Relationship to patient
- GVHD prophylaxis
- Conditioning regimen including myeloablative versus reduced intensity conditioning

Graft characteristics:

- Graft type: peripheral versus bone marrow
- Sibling vs. matched related vs. haploidentical donor
- Number and direction of HLA mismatches in HLA-haploidentical HCT patients
- Conditioning regimen (reduced intensity vs. myeloablative)
- CD34+ and lymphocyte cell counts
- Fresh or frozen product

Outcomes

- Primary and secondary graft failure (defined by ANC <500 and/or platelet count <20,000 and/or donor chimerism less than 5% anytime >/= 28 days after stem cell transplantation)
- Need for CD34+ selected stem cell boosts and/or second transplant
- Efficacy of stem cell boosts as treatment for poor engraftment
- Outcomes of second transplants vs. stem cell boosts
- Event-free survival (survival without relapse)
- Non-relapse mortality
- Relapse rates
- Acute GVHD, including cumulative incidence of grades all grades and grade 3-4 aGVHD
- Chronic GVHD, including cumulative incidence of all grades and moderate/severe GVHD

Study design:

This will be a retrospective cohort analysis. All patients who have undergone an allogenic HCT using between 2012-2017 will be screened to determine whether they meet inclusion criteria for the study. Upon data collection, we will be able to compare the rate of graft failure and need for stem cell boost in patients with PTCy Haplo vs. PTCy non-haplo vs. non PTCy (non haplo) patients.

Continuous variables between groups will be compared with Mann-Whitney U-testing. Dichotomous variables between groups will be compared with chi-squared testing or Fisher's exact test, when appropriate. Cumulative incidence will be measured with the cumulative incidence function. Time-to-event functions will be measured using Kaplan-Meier curves and the log-rank test. Univariate Cox proportional hazards regression analysis will be used to determine patient and disease variables that modified overall survival, with chronic GvHD treated as a time-dependent variable. Multivariate Cox proportional hazards regression analysis will be used to determine patient and disease variables that modified overall survival. Variables will be fit using the backward selection method with a p-value of <0.05 considered as significant. However, donor type will be held in all steps of model building.

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Characteristics of patients who underwent first HLA-identical sibling donor of MUD HCT for AML, ALL, or MDS, with PT-Cy + CNI + MMF/MTX and reported to CIBMTR (CRF-level), 2012-2018

Characteristic	Haplo	HLA Sibling	MUD
Number of patients	1018	105	178
Age at transplant, years			
Median (range)	59 (18-81)	59 (22-76)	64 (20-75)
18 – 30	127 (12)	8 (8)	11 (6)
31 – 50	219 (22)	24 (23)	28 (16)
> 50	672 (66)	73 (70)	139 (78)
Disease[1]			
AML	521 (51)	57 (54)	89 (50)
ALL	197 (19)	13 (12)	17 (10)
MDS	300 (29)	35 (33)	72 (40)
Graft type			
Bone marrow	361 (35)	39 (37)	55 (31)
Peripheral blood	657 (65)	66 (63)	123 (69)
Conditioning regimen intensity			
MAC	402 (39)	51 (49)	88 (49)
RIC/NMA	616 (61)	54 (51)	90 (51)
Year of transplant			
2012	15 (1)	3 (3)	7 (4)
2013	78 (8)	4 (4)	11 (6)
2014	126 (12)	13 (12)	13 (7)
2015	167 (16)	26 (25)	41 (23)
2016	217 (21)	28 (27)	49 (28)
2017	213 (21)	25 (24)	44 (25)
2018	202 (20)	6 (6)	13 (7)

[1] AML and ALL in CR; MDS limited to RA/RARS/RCMD/RAEB-1/RAEB-2

Proposal: 1811-52

Title:
Bone marrow (BM) versus peripheral blood (PB) graft in adults undergoing HLA matched related or unrelated donor hematopoietic cell transplantation (HCT) with post-transplantation cyclophosphamide (PTCy)

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Hypothesis:
We hypothesize that there will be no differences in the outcomes (acute or chronic GVHD, relapse, PFS or OS) after BM vs PB HCT with PTCy in patients with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), or chronic myeloid leukemia (CML) with HLA matched sibling (MSD) or unrelated (MUD) donor.

Specific aims:
The goal of the proposed study is to compare the following outcomes after BM or PB HCT, by conditioning intensity (myeloablative or RIC) and donor type (HLA-mated related or unrelated) –
The following outcomes will be assessed:

- GVHD-free relapse free survival (GRFS)
- Chronic GVHD-free relapse-free survival (CRFS)
- grade II-IV and grade III-IV acute GVHD
- systemic therapy-requiring chronic GVHD
- relapse
- non-relapse mortality (NRM)
- progression free survival (PFS)
- overall survival (OS)
- Cumulative incidence of viral infections (reactivation of CMV, HHV-6, EBV, or adenovirus and BK cystitis)
- Neutrophil and platelet engraftment
- Graft failure
- Need for CD34+ stem cell boost post-HCT
- Donor chimerism

If there are sufficient numbers of patients, subgroup analysis of outcomes by disease will be done.

Scientific impact:
Multiple studies, including a randomized clinical trial, assessed the outcomes of BM vs PB graft with different types of donors and conditioning intensity. However, how these graft sources differ in the era of novel GVHD prophylaxis regimens, such as PTCy, is unclear.
Although PB is the more commonly used graft than BM despite a randomized study showing significantly higher risk of cGVHD with PB graft in MUD; however, that study used tacrolimus or cyclosporine and methotrexate for GVHD prophylaxis. In the era where PTCy is being used increasingly in HLA-matched HCT, no study directly compared the outcomes of BM vs PB grafts with this GVHD prophylaxis regimen.

Scientific justification:
A phase III randomized trial showed significantly lower risk of cGVHD with BM than with PB grafts, with no differences in relapse, NRM, PFS or OS in patients undergoing MUD HCT. A majority (75-80% received myeloablative conditioning) and the GVHD prophylaxis was provided with tacrolimus or cyclosporine plus methotrexate.[1] A retrospective study of the data from the CIBMTR analysed the

impact of the higher risk of cGVHD after PB grafts on long term outcomes as compared to BM grafts in patients with MUD HCT who received myeloablative conditioning with tacrolimus or cyclosporine based GVHD prophylaxis. This study showed no significant differences in survival with PB or BM HCT, except for patients in early CML (1st chronic phase), where PB graft was associated with significantly higher NRM (59% vs 38% at 5-years) and worse OS (35% vs 56% at 5 years) than BM graft.[2] This was because the relapse rate was low in both PB and BM groups (6% vs 9% at 5-years) and there was little to gain from the graft-versus-leukemia effect generally associated with GVHD. In contrast, in patients with advanced stage MDS (refractory anemia with excess blasts), relapse rates were lower (23% vs 43%) but NRM was higher (44% vs 31%) after PB than with BM graft, resulting in similar OS. [2]
Two registry studies assessed the differences in outcomes after PB vs BM grafts in the setting of RIC MUD HCT.[3,4] A study by the EBMT included AML patients in first or second CR. GVHD prophylaxis was unknown in about half of the patients. The PBSC group had higher risk of acute aGVHD grade II-IV (27% vs 12%; P < 0.002), cGVHD at 2 years (43% vs 35%; P = 0.04), NRM (28% vs 13%; P = 0.004) than the BM group, but lower risk of relapse (46% vs 32%; P = 0.014), with no differences in LFS (46% vs 43%). In multivariate analysis, the PBSC group was associated with a higher incidence of aGVHD, higher NRM and a decreased relapse incidence with no difference of LFS.[4] A CIBMTR study included patients with AML, MDS and non-Hodgkin lymphoma who received calcineurin inhibitor (CNI) based GVHD prophylaxis with either methotrexate or mycophenolate mofetil (MMF). There was no difference in OS at 5 years with PBSC vs BM (34% vs 38% with CNI-MTX and 27% vs 20% with CNI-MMF). The risk of relapse were similar in PBSC vs BM with CNI-MTX GVHD prophylaxis, but the risk was significantly higher after BM when CNI-MMF GVHD prophylaxis was used. Moreover, regardless of the graft source, risks of grade II-IV and III-IV aGVHD, NRM and overall mortality were higher with CNI-MMF than with CNI-MTX GVHD prophylaxis.[3]
In the setting of MSD HCT, a randomized trial of PB or BM showed significantly higher risk of chronic GVHD with PB than with BM (73% vs 56%, p=0.021), without any differences in OS (49% vs 57%) or PFS (13% vs 28% for ALL; 62% vs 47% for AML, and 40% vs 48% for CML).[5] Another study confirmed high risk of cGVHD (61% vs 45% at 6-years) with no difference in risk of relapse with PB vs BM graft. However, NRM and PFS differed between PB and BM by disease and stage. For example, NRM was same in early leukemia and advanced CML with PB or BM graft, but higher with PB in early CML and higher with BM in advanced leukemia. PFS was lower with PB (41% vs 61%) but higher with PB (33% vs 25%) with advanced CML.[6]
Individual-patient data meta-analysis[7] of 9 randomized trials showed significantly higher risk of grade III-IV acute GVHD (OR = 1.39; 95% CI, 1.03 to 1.88), overall cGVHD (68% v 52% at 3 years; OR = 1.92; 95% CI, 1.47 to 2.49; P < 0.000001) and extensive cGVHD (47% v 31% at 3 years; OR = 1.89; 95% CI, 1.47 to 2.42; P < 0.000001) and significantly lower risk relapse (21% v 27% at 3 years; OR = 0.71; 95% CI, 0.54 to 0.93; P = 0.01) with PB with no differences in NRM. In patients with late-stage disease, OS (46% v 31% at 3 years; OR = 0.64; 95% CI, 0.46 to 0.90; P = 0.01) and PFS (41% v 27% at 3 years; OR = 0.63 95% CI, 0.45 to 0.87; P = 0.01) were significantly superior with PB grafts. [7]
Post transplantation cyclophosphamide is a novel GVHD prophylaxis strategy that was initially used with haploidentical HCT,[8-10] but is being used with MSD and MUD HCT as well. [11-15] Two studies assessed its role as a single agent for GVHD prophylaxis with myeloablative with MSD and MUD HCT with BM graft.[11,12] In these studies, the cumulative incidences of acute GVHD grades II-IV (43-51%) and grades III-IV (10-15%) and chronic GVHD (10-14%), and 2-years NRM (16-17%), relapse (22%), PFS (39-62%) and OS (55-67%). [11,12] An EBMT study in patients with acute leukemia who underwent MDS or MUD HCT and received PT-Cy alone or in combination with other immunosuppressive drugs showed that BM graft was associated with lower risk of extensive cGVHD in patients with acute leukemia after MSD or MUD HCT with PTCy based GVHD.[15]One study used PTCy with cyclosporine with PB graft in patients undergoing MSD and MUD HCT.[13] The cumulative 1-year incidence of NIH-defined chronic GVHD was 16%, grades 2-4 and 3-4 acute GVHD were 77% and 0%, respectively. At 2 years, the cumulative incidences of NRM and recurrent malignancy were 14% and 17%, respectively, with an estimated OS of 70%. [13] Another study used PTCy with tacrolimus and MMF in patients with

a variety of haematological malignancies who underwent MSD and MUD HCT with PB graft.[14] The cumulative incidence of grades II-III aGVHD was 12% and nobody developed grade IV aGVHD. At 2 years the cumulative incidence of NIH-defined cGHVD requiring systemic immunosuppression was 7%, NRM was 3%, relapse was 46% and OS was 77%. [14]
GRFS and other long term outcomes after BM vs PB grafts in the MUD setting were recently evaluated by a CIBMTR study. This study showed superior GRFS with BM, likely due to significantly higher incidence of IST-requiring cGVHD in the PB group; however, no patient in that study received PTCy.[16] How the inclusion of PTCy alters these outcomes in the setting of HLA-matched HCT is unknown, although this has been assessed in the HLA-mismatched HCT setting. One study by the CIBMTR[17] and another by the Acute Leukaemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT)[18] assessed outcomes after BM vs PB haploidentical HCT using PTCy and showed conflicting results. The CIBMTR study which included patients with myeloid or lymphoid malignancies showed a higher risk of relapse and lower risks of acute and chronic GVHD with BM (n=481) than PB grafts (n=190), which translated into superior GRFS with BM. The EBMT showed similar risk of chronic GVHD, relapse, non-relapse mortality, DFS or OS after BM (n=260) or PB (n=191), but significantly higher risk of grade II-IV and grade III-IV acute GVHD with PB graft in patients with ALL or AML in first or second complete remission. As haploidentical HCT is a unique entity and may offer greater degree of graft-versus-leukemia effect related to HLA mismatch as well as NK cell alloreactivity, the results of these studies cannot be extrapolated to patients with MSD or MUD HCT.

Patient eligibility population:
Inclusion criteria:

- Adults, ages ≥ 18 years
- MSD or MUD HCT
- PB or BM graft
- Year 01/2000- 12/2015
- Hematological malignancies including acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS) or chronic myeloid leukemia (CML)
- Any conditioning regimen – myeloablative versus RIC (with or without in-vivo T-cell depletion using ATG/ALG/ Campath)
- Any GVHD prophylaxis with post-transplantation cyclophosphamide.

Exclusion criteria:

- Prior allogeneic HSCT
- Solid organ malignancies
- Recipients of HSCT with ex vivo graft manipulations - such as CD34+ selected or T-cell depleted grafts

Primary outcomes:
GVHD-free, relapse-free survival (GRFS): Grade III-IV acute GVHD, chronic GVHD, disease relapse/progression and death are treated as events. There will be no competing risks. This event will be summarized by a survival curve. Patients will be censored at second transplant or date of last follow-up.
Chronic GVHD-free relapse-free survival (CRFS): chronic GVHD, disease relapse/progression and death are treated as events. There will be no competing risks. This event will be summarized by a survival curve. Patients will be censored at second transplant or date of last follow-up.
Acute GVHD III-IV: Time to the development of Grade III-IV acute GVHD using the Glucksberg grading system. The event will be summarized by the cumulative incidence estimate, where death without Grade III-IV acute GVHD will be treated as a competing risk. Patients will be censored at second transplant or date of last follow-up.

Chronic GVHD requiring systemic IST: Time to the development of limited or extensive chronic GVHD. The event will be summarized by the cumulative incidence estimate, where death without chronic GVHD will be treated as a competing risk. Patients will be censored at second transplant or date of last follow-up.
Relapse/Progression: Time to the recurrence of the underlying malignancy for which the allogeneic HCT was performed. The event will be summarized by the cumulative incidence estimate with NRM treated as a competing risk. Patients will be censored at second transplant or date of last follow-up.
Overall survival: Time to death from any cause. The event will be summarized by a Kaplan-Meier survival curve. Patients are censored at the date of last follow-up. There are no competing risks.

Secondary outcomes:
Acute GVHD III-IV: Time to the development of Grade III-IV acute GVHD using the Glucksberg grading system. The event will be summarized by the cumulative incidence estimate, where death without Grade III-IV acute GVHD will be treated as a competing risk. Patients will be censored at second transplant or date of last follow-up.
Chronic GVHD: Time to the development of any (limited or extensive) chronic GVHD. The event will be summarized by the cumulative incidence estimate, where death without chronic GVHD will be treated as a competing risk. Patients will be censored at second transplant or date of last follow-up.
Disease-free survival (DFS): Time to treatment failure (death or relapse/progression). This event will be summarized by a Kaplan-Meier survival curve. Patients will be censored at second transplant or date of last follow-up. There are no competing risks.
Non relapse mortality (NRM): Time to death without relapse/progression. The event will be summarized by the cumulative incidence estimate with relapse/progression treated as a competing risk. Patients will be censored at second transplant or date of last follow-up.
Engraftment: Time to achieving an absolute neutrophil count $\geq$ 500/mm^3 for 3 consecutive days by day 100 post-transplant, in patients surviving a minimum of 14 days post-transplant. Patients will be censored at second transplant or date of last follow-up.
Incidence of primary and secondary graft failures
Incidence of CD34+ stem cell boost
Cumulative incidence of viral reactivations, including CMV, HHV-6, EBV, or adenovirus, and BK cystitis at any time after HCT.

Baseline characteristics:
- Patient Age $\geq$18
- Patient Gender
- Patient Race/ethnicity
- Disease (AML, ALL, MDS, CML)
- Performance status (<90 vs $\geq$90)
- Disease status at HCT- CR1, CR2, relapsed, PIF, CP1, CP2
- Revised disease risk index (rDRI): low/intermediate vs high/very high
- HCT-CI (0-2 vs $\geq$3)
- HLA match [allele-level at HLA-A, -B, -C, and -DRB1]
- Major ABO mismatch (yes/no)
- Donor-recipient gender (female-donor-to-male vs. all others)
- Donor-recipient CMV status
- Donor age
- Conditioning regimen – (a) myeloablative vs (b) reduced intensity/non-myeloablative
- GVHD prophylaxis regimen
- In vivo T cell depletion (ATG/ALG or alemtuzumab) – yes/no
- TNC dose x10^7/kg: <2.5, 2.5-<5, $\geq$5
- CD34 dose x10^6/kg: <2.5, 2.5-<5, $\geq$5

- CD3 dose x10^6/kg: <0.2, 0.2-<2, ≥2
- Year of HCT
- Follow-up

Other data needed for outcome analysis:

- Graft failure (yes/no)
- Relapse (Yes/No)
- Progression (Yes/No)
- Acute GVHD grade II-IV (Yes/No)
- Acute GVHD grade III-IV (Yes/No),
- Chronic GVHD (Yes/No)
- Systemic-therapy requiring chronic GVHD (Yes/No),
- Death (yes/no),
- Cause of death
- Viral infections – CMV reactivation, EBV, adenovirus, BK cystitis. (cumulative incidence and time from HCT)
- IX. Sample Requirements (if study will use biologic samples from the NMDP Research Sample Repository)
- N/A
- X. Study Design (Scientific Plan)

We will analyze patients with AML, ALL, CML or MDS who received BM versus PB graft for MSD or MUD HCT. We will use the Wilcoxon sign-rank test to compare characteristics across graft sources for continuous variables and the Chi-square test for categorical variables. The Kaplan-Meier estimates of GRFS and CRFS at 1- and 2-years will be calculated for both graft types, which will be compared using the log-rank test. Proportional hazards will be checked using martingale residuals. Multivariate analyses will be performed using Cox regression model to examine the independent impact of variables on GRFS and CRFS. If the adjusted factors violate the proportional hazards assumption, they will be adjusted through stratification. If the main testing variable (graft source) violates the proportional hazards assumption, the optimal cut point will be determined based on the maximum likelihood method with different hazard ratios (HR) within each time interval.
We will also estimate NRM, DFS and OS at 1-and 2-years using Kaplan-Meier method. We will also describe the distribution of GRFS and CRFS events across both graft sources at 1- and 2-years.

Data source:
CIBMTR Research Database.

Conflicts of interest:
None

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Characteristics of patients who underwent first HLA-identical sibling donor of MUD HCT for AML, ALL, or MDS, with PT-Cy + CNI + MMF/MTX and reported to CIBMTR (TED-level), 2008-2018

Characteristic	Bone marrow	Peripheral blood
Number of patients	250	589
Age at transplant, years		
Median (range)	51 (19-75)	59 (18-80)
18 – 30	32 (13)	58 (10)
31 – 50	93 (37)	124 (21)
> 50	125 (50)	407 (69)
Disease[1]		
AML	144 (58)	339 (58)
ALL	67 (27)	105 (18)
MDS	39 (16)	145 (25)
Donor		
HLA-identical sibling	128 (51)	226 (38)
Matched unrelated donor	122 (49)	363 (62)
Conditioning regimen intensity		
MAC	176 (70)	248 (42)
RIC/NMA	74 (30)	341 (58)
Year of transplant		
2012	18 (7)	24 (4)
2013	31 (12)	29 (5)
2014	35 (14)	47 (8)
2015	28 (11)	93 (16)
2016	51 (20)	105 (18)
2017	61 (24)	159 (27)
2018	26 (10)	132 (22)

[1] AML and ALL in CR; MDS limited to RA/RARS/RCMD/RAEB-1/RAEB-2

Proposal: 1811-119

Title:
Impact of G-CSF on *in-vivo* T-cell depleted Allogeneic Hematopoietic Cell Transplantation

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Hypothesis:
G-CSF adversely impacts the outcomes of allogeneic hematopoietic cell transplants (HCTs) performed using the *in-vivo* T-cell depleting antibodies anti-thymocyte globulin (ATG) and alemtuzumab.

Specific aims:
To determine the effect of prophylactic G-CSF use on outcomes of allogeneic HSCTs performed for acute lymphoid leukemia (ALL), acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) using *in vivo* T-cell depleting antibodies by examining:

- Cumulative incidence of relapse (RI) and relapse-related mortality (RRM)
- Cumulative incidence of non-relapse mortality (NRM)
- Overall survival (OS), event-free survival (EFS)
- The incidence and severity of acute and chronic graft versus host disease
- Novel composite endpoints - acute and chronic GVHD/relapse-free survival (GRFS) & chronic GVHD/relapse-free survival (CRFS)
- The incidence of opportunistic infection, viral reactivation and PTLD
- Lymphocyte recovery

Scientific impact:
Several studies - though not all, have shown a beneficial effect of ATG and alemtuzumab on the incidence of GVHD and overall outcomes after HCT.[1,2] The use of these i*n-vivo* T-cell depleting antibodies is currently considered standard of care by the EBMT for myeloablative peripheral blood stem cell transplants from HLA-identical sibling donors, matched unrelated donors and haplo-identical donors.[2] They are also increasingly being adopted into reduced intensity conditioning regimens.[2,3]
G-CSF is commonly used to hasten engraftment after allogeneic HCT. *In-vitro* studies suggest a detrimental interaction between G-CSF use and ATG on immune reconstitution.[4] Our study will investigate the clinical implications of such an interaction and evaluate a similar interplay between G-CSF and alemtuzumab. This data will guide the judicious use of G-CSF following *in vivo* T-cell depletion with the ultimate aim of improving post-transplant morbidity and mortality outcomes for patients. It may support the exploration of individualized ATG dosing and surveillance of residual ATG levels to guide the safety of G-CSF administration and optimize immune recovery. We expect it will also provide clinical basis for further mechanistic study of the interplay between G-CSF and ATG/alemtuzumab on donor immune cells.

Scientific justification:
In vivo depletion of recipient and donor T-lymphocytes using ATG or alemtuzumab is an increasingly used component of allogeneic HCT preparative regimens to reduce both graft rejection and graft-versus-host disease.[1,2] The beneficial effects of these serotherapies are tempered by their adverse effect on immune reconstitution. Excess toxicity to incoming donor T-lymphocytes is associated with an increased

probability of infection and viral reactivation, higher relapse rates in malignant disease and poorer overall survival.[1,5,6]

Both ATG and alemtuzumab directly deplete T-lymphocytes through Fas-mediated apoptosis, but also indirectly stimulate T-cell destruction through complement-mediated cytotoxicity (CDCC), antibody-dependent cellular phagocytosis (ADCP) by monocytes and macrophages and antibody-dependent cellular cytotoxicity (ADCC) by natural killer cells and granulocytes.[1,5] While ATG is a polyclonal product with IgG activity against other immune cells, its highest affinity is for naïve T-lymphocytes.[7,8] Pharmacokinetic studies have shown substantial interpatient variability in peak ATG concentration and elimination, with a half-life of up to 6 weeks observed in some patients.[8] Alemtuzumab is a monoclonal product specific for CD52, present on both T- and B-lymphocytes as well as on other immune cells. Treatment results in protracted lymphotoxicity and profound immunosuppression.[9]
Recent work in pediatric cohorts has shown that T-cell reconstitution in the presence of post-transplant residual ATG is more suppressed in cord blood transplantation (CBT) than it is in either bone marrow (BMT) or peripheral blood stem cell transplantation (PBSCT).[4,10] This differential effect is not explained by differences in ATG binding sites or in susceptibility to ATG-mediated cytotoxicity between CB- and BM-derived lymphocytes.[4,11] The majority of CBT recipients receive G-CSF within a week of stem cell infusion in order to hasten engraftment and reduce early infection – a practice less routinely followed in BMT or PBSCT. Recently published data proposes that this may be the critical variable sensitizing CB lymphocytes to the cytotoxic effects of ATG.[4] G-CSF drives myeloid precursor proliferation and differentiation while also functionally activating phagocytosis, at least partially through induction of the IgG receptor FcγRI.[12] G-CSF-primed neutrophils *ex vivo* display dramatically higher ADCP and ADCC for ATG-coated cells.[4] The administration of G-CSF post-transplantation in the presence of residual ATG or alemtuzumab may thus exaggerate donor lymphocyte clearance with detrimental effects on transplant outcomes.
Several groups have previously studied the impact of G-CSF on allogeneic transplant outcomes. A large retrospective CIBMTR registry analysis of 2719 patients and a published meta-analysis incorporating 18 studies including 9 prospective RCTs reported no effect of post-allogeneic transplant G-CSF on GVHD, TRM or survival.[13,14] Two further registry studies examining allogeneic transplants performed for pediatric and adult patients with leukemia actually suggested worsened TRM and overall survival following G-CSF administration.[15,16] The use of post-transplant G-CSF as a supportive measure thus remains controversial. Importantly, none of the aforementioned studies have considered the interaction of G-CSF with *in vivo* T-depleting serotherapy.[13-16] This interplay is likely to be complex and critical. In addition to hastening the myeloid-mediated phagocytosis of antibody-coated lymphocytes, G-CSF in isolation can modulate T-lymphocyte behavior - durably altering cytokine expression and inducing T-cell tolerance.[12] G-CSF-mobilized stem cells have been shown to have reduced T-cell proliferative responses and reduced natural killer cell activity.[17,18] These immunomodulatory effects may significantly intensify the adverse effects of ATG and alemtuzumab on immune reconstitution leading to higher rates of infection and relapse with ultimately inferior transplant outcomes. Given the expanding use of these serotherapies in modern transplantation practice, we must attempt to fully understand their potential synergistic immunotoxicity with G-CSF.

Patient eligibility population:
Inclusion:

- First allogeneic HCT for ALL, AML or MDS
- *In vivo* T-cell depletion with ATG (ATGAM/Thymoglobulin/ATG-Fresenius) or alemtuzumab
- Pediatric and adult patients (No age limitation)
- All HCT types (MRD, MUD, UCB, Haplo-identical, Combined Haplo/cord)
- All product types (BM, PB, UCB)

Exclusion:

- In-vitro T cell depletion
- Use of other cytokines e.g. GM-CSF after transplantation.

Data Requirements:

We require data on eligible patients obtainable from forms 2400, 2402, 2006, 2450, 2100 and 2150.

Pre-transplant variables	
• Patient age / sex • Disease / stage • Disease Risk Index • HCT-Co-morbidity index • Type of conditioning • ATG source / dose / timing	• Alemtuzumab dose / timing • HCT type • Product type • Donor HLA matching • CD34+ cells in graft • CD3+ cells in graft
• **Post-transplant variables + outcomes**	
• G-CSF (Y/N) • Day G-CSF started • G-CSF Formulation / Indication • Time to neutrophil engraftment • Time to platelet engraftment • aGVHD Incidence / Organ / Grade • cGVHD Incidence / Organ / Grade • Post-transplant lymphocyte analysis o (CD3+/CD4+/CD8+ and timing)	• PTLD Incidence • Incidence of clinically significant infection • Viral infection (BK, CMV, ADV, EBV,HHV6)/ o Lymphocyte count at time of diagnosis • Relapse incidence / Relapse mortality • Non-relapse mortality (NRM) • Overall survival (OS) • Event-Free Survival (EFS) • GVHD-free/Relapse-free survival (GRFS)

Study design:

We propose a retrospective cohort analysis comparing post-transplant G-CSF exposure vs. no G-CSF exposure in patients with acute leukemia or myelodysplastic syndromes receiving either ATG or alemtuzumab as GVHD prophylaxis prior to allogeneic HSCT.

Our primary outcome of interest is cumulative incidence of relapse-related mortality (RRM). We estimate that the risk for RRM is increased by at least 50% in the G-CSF group. This estimate is based on observations of increased RRM in patients with excessively high post-transplant ATG levels and extrapolating that G-CSF enhances the lymphotoxicity of ATG in a manner that is in some part analogous to high residual ATG levels.[4,6] To detect an increase in CI RRM from 17% at one year to 25% with a power of 90% would require a samples size of approximately 400 patients in each group.

Secondary outcomes include cumulative incidence of relapse, non-relapse mortality, overall survival and event-free survival. We will examine the incidence and severity of acute and chronic graft versus host-disease and the composite measures GRFS and CRFS. Further outcomes of interest include the incidence of opportunistic infection, viral reactivation and PTLD as well as lymphocyte recovery as a measure of immune reconstitution. The primary limitation of our study is the variability in drug prescribing between patients. We expect differences in the formulation, dose and duration of G-CSF treatment, differences in the dosing and formulation of ATG and differences in alemtuzumab dosing.

Standard statistical methodology will be used for description of cohorts and analysis of outcomes - cumulative incidences calculated using the method of Gray, probabilities of survival to be determined

using Kaplan-Meier estimation with calculation of significance using log-rank testing and 95% confidence intervals calculated using the Greenwood formula. Adjustment for covariates will be necessary using Cox regression analysis for survival endpoints and Fine-Gray competing risk models for cumulative incidence endpoints.

Conflicts of Interest:
None

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Table1. Characteristics of patients who underwent first allogeneic HCT for AML, ALL, or MDS and received ATG, 2007-2018

Characteristic	G-CSF[1]	No G-CSF
Number of patients	1325	1350
Recipient age		
< 10	44 (3)	60 (4)
10 – 18	65 (5)	48 (4)
18 – 30	93 (7)	98 (7)
31 – 40	97 (7)	87 (6)
41 – 50	139 (10)	165 (12)
51 – 60	321 (24)	329 (24)
61 – 70	465 (35)	462 (34)
> 70	101 (8)	101 (7)
Disease		
AML	574 (43)	642 (48)
ALL	168 (13)	144 (11)
MDS	583 (44)	564 (42)
Donor		
HLA-identical sibling	161 (12)	167 (12)
Matched unrelated donor	911 (69)	929 (69)
Mismatched unrelated donor	253 (19)	254 (19)
Graft type		
Bone marrow	263 (20)	178 (13)
Peripheral blood	1062 (80)	1172 (87)
Conditioning regimen intensity		
MAC	816 (62)	708 (52)
RIC	476 (36)	557 (41)
NMA	33 (2)	85 (6)

[1]Planned G-CSF was defined as administration -3 to +10 days from HCT

Study Proposals 1811-121/1811-133

Comparison of donor selection for transplantation for aplastic anemia

PROP 1811-121 (A Sharma/ N Bhatt)

Title: Alternative Donor Transplantation for Severe Aplastic Anemia

PROP 1811-133 (Q Salas/ S Prem/ A Sureda/ R Kumar)

Title: Comparing outcomes between HLA-haploidentical and HLA-matched unrelated donor allogeneic transplants in patients with aplastic anemia

Table 1. Characteristics of patients who underwent first haploidentical or unrelated donor HCT for severe aplastic anemia (CRF-level), 2008-2018

Characteristic	Haploidentical	MUD	UCB
Number of patients	67	299	52
Age at transplant, years			
< 18	24 (36)	102 (34)	37 (71)
18 – 30	22 (33)	81 (27)	10 (19)
31 – 50	13 (19)	55 (18)	3 (6)
> 50	8 (12)	61 (20)	2 (4)
Graft type			
Bone marrow	55 (82)	259 (87)	0
Peripheral blood	12 (18)	40 (13)	0
Umbilical cord blood	0	0	52
Conditioning regimen			
TBI/Cy	66 (99)	59 (20)	3 (6)
TBI/Cy/Flu	0	148 (49)	26 (50)
Flu/Mel	0	10 (3)	7 (13)
Cy/Flu	0	62 (21)	15 (29)
Cy alone	1 (1)	20 (7)	1 (2)
GVHD prophylaxis			
PT-Cy + CNI + MMF	67	0	0
CNI + MMF/MTX	0	299	52
TX year			
2008	0	41 (14)	13 (25)
2009	0	26 (9)	11 (21)
2010	0	7 (2)	6 (12)
2011	0	10 (3)	5 (10)
2012	0	8 (3)	3 (6)
2013	1 (1)	25 (8)	2 (4)
2014	5 (7)	48 (16)	3 (6)
2015	22 (33)	46 (15)	2 (4)
2016	8 (12)	41 (14)	4 (8)
2017	17 (25)	43 (14)	3 (6)
2018	14 (21)	4 (1)	0

Proposal: 1811-121

Title:
Alternative Donor Transplantation for Severe Aplastic Anemia

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Hypothesis:
Clinical outcomes of allogeneic hematopoietic cell transplantation for severe aplastic anemia with alternative donors (haploidentical, cord blood) are comparable to matched sibling and matched unrelated donor transplants

Specific Aims:
Primary: To compare the effect of donor type on overall survival (OS) of patients receiving alloHCT for SAA.
Secondary:

1. To study neutrophil recovery and platelet recovery following HCT
2. To assess treatment-related mortality (TRM) and incidence of graft rejection
3. To study acute graft-vs-host disease (GVHD), chronic GVHD
4. To study 1-year and 3-year GVHD-free disease-free survival

Scientific impact:
While an allogeneic matched sibling donor hematopoietic cell transplantation (alloHCT) has emerged as a first line treatment for acquired severe aplastic anemia (SAA) and HLA-matched unrelated donor allogeneic HCT remains the treatment of choice for those who do not respond upfront immunosuppressive therapy, several patients do not have a matched related or unrelated donor. Umbilical cord blood and haploidentical donors are attractive options to expand this treatment modality to those patients who lack a matched donor option. However, there are few studies that have systematically evaluated the outcomes following alternative donor transplantation for SAA. A large analysis utilizing the CIBMTR database will allow hematologists and transplant physicians to clearly define the outcomes after alternative donor HCT in patients with SAA, identify prognostic markers for improved outcomes, and help to elucidate the utility of alternative (haploidentical and cord blood) donors against the standard matched-donor transplants.

Scientific justification:
AlloHCT from a matched sibling donor (MSD) is the first line treatment strategy for younger patients (less than 40-45 years of age) with SAA.[1-3] Salvage alloHCT with an HLA-matched unrelated donor (MUD) is recommended for patients with refractory SAA, but many patients, especially minorities, are unable to find a MUD in the registry.[4]
Donor availability has remained a major limitation to the expansion and success of BMT in SAA. About 50% to 60% patients of Caucasian descent, 20% Asian and 17% African American patients find a fully HLA-matched and available MUD.[4] At the same time, haploidentical donors (HAPLO) are available for nearly all patients and can be acquired immediately.[5] This is particularly crucial for patients with very severe aplastic anemia (vSAA) who need prompt therapy.[1] Additionally, in recent years more umbilical cord blood (UCB) transplants have been performed for SAA. Placental lymphocytes are immunologically

naive, thus allowing for transplantation of UCB units with high degrees of donor-recipient HLA disparity which otherwise would be associated with much higher risks of GVHD when compared to using bone marrow or PBPC grafts.[4,6]
Alternative donor (UCB and HAPLO) transplants have historically been associated with higher risks of graft failure, graft-versus-host disease (GVHD), and transplant-related mortality as compared to MSD transplantation.[4] But with advances in in-vivo regulation of T-cells, optimized conditioning regimens, and improved supportive care, outcomes following alternative donor transplants are improving. Data from Eurocord and Japan Cord Blood Bank suggest high graft failure rates and hence UCB transplants for SAA have remained rather sparse.[7,8]
A few small studies and case series have evaluated outcomes following alternative donor transplantation for SAA.[5-7,9-14] Lu and colleagues reported similar 3-year overall survival in young patients with SAA (n=89; HAPLO: 41, MUD: 48) undergoing HCT with HAPLO and MUD donors (80.3% vs 89.6%, p=0.21)[5]. While the cumulative incidence of acute GVHD was higher with HAPLO donors, chronic GVHD, disease free survival, and GVHD free failure free survivals were similar in both groups. A larger systematic analysis utilizing the data from the CIBMTR database will help assess the outcomes following transplant for this rare disorder comprehensively. An ongoing CIBMTR study (Proposal 1511-71) is currently evaluating the impact of conditioning regimens on transplant outcomes after MSD and MUD transplants but excludes HAPLO and UCB donor transplants. We plan to compare outcomes following HAPLO and UCB donor transplants to the current standard of care (MSD and MUD transplants).

Patient eligibility population:
Inclusion Criteria:

- Patients with SAA who underwent alloHCT at participating CIBMTR centers between 1995 and 2015
- All donor types and graft sources

Exclusion Criteria:

- SAA patients who had disease progression to MDS or AML prior to alloHCT

Data requirements:
This proposed study will require no supplemental data to be collected. The current data is included in the disease specific CIBMTR collection forms.

Study design:
This study is an observational retrospective registry analysis of all patients who received an allogeneic HCT for SAA between 1995 and 2015.

Transplant outcomes (OS, other secondary endpoints) will be evaluated for all patients and compared among different donor types/graft sources. OS estimates will be calculated utilizing Kaplan-Meier analysis and compared utilizing the log-rank test. Cumulative incidences of neutrophil and platelet engraftment, graft failure and GVHD (chronic and acute) will be performed utilizing the cumulative incidence procedure to account for competing risks, and comparison will be performed utilizing the Fine-Gray test.

Differences between groups will be evaluated utilizing the Chi-squared test or Fisher's exact test for categorical variables, two-sample test for proportions, or the Wilcoxon rank sum test for medians.

Prognostic variables (such as age at transplant, previous immunosuppressive therapy, conditioning intensity and regimen etc.) will be evaluated for their impact on OS, graft failure and other secondary endpoints utilizing univariate analysis and multivariate analysis by cox proportional hazards analysis.

Conflicts of interest:
None

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Proposal: 1811-133

Title:
Comparing outcomes between HLA-haploidentical and HLA-matched unrelated donor allogeneic transplants in patients with aplastic anemia

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Hypothesis and scientific justification:
Allogeneic hematopoietic stem cell transplantation (alloHSCT) up-front, or after failure to respond to immunosuppressive therapy (IST), is a therapeutic option for eligible patients diagnosed with aplastic anemia (AA) with the aim of achieving sustained engraftment with minimal regimen-related toxicities and graft versus host disease (GVHD). The choice between these two therapies depends today on variables such as recipients' age, severity of the disease, and availability of a matched donor.

A Human Leukocyte Antigen (HLA) matched sibling donor is considered the first choice. However, approximately 70% of patients do not have a suitable matched sibling donor (MSD) available for transplantation. Alternatives such as matched unrelated donors (MUD) can be identified for only 50% to 60% of patients with the donor search and procurement process requiring a median of 4 months. In addition, despite the expansion of MUD registries, donor availability can often be uncertain particularly for under-represented ethnic minorities which may be subject to prolonged and unproductive registry searches. Using haploidentical donors reduces this uncertainty to a large degree as almost all patients have an immediately available related donor with whom they share a single HLA haplotype.

First, considering that the recipient age, the time from diagnosis to alloHSCT, and prior failure to IST treatment are known to be risk factors for the worst outcome in patients diagnosed with AA; the choice of a haploidentical donor instead a MUD, would potentially decrease the time from diagnosis to alloHSCT, the need of prior or several lines of IST, and would might decrease the median age of the recipients when they are sent for alloHSCT.

Secondary, AA is more common in Asia and other developing countries compared to the West; and in those countries there is considerable delay from diagnosis to transplantation. Using haploidentical donors would reduce the cost, time delay and would overcome the difficulty of finding a suitable donor for ethnic minorities.

Finally, the selection of a haploidentical donor will also provide a more reliable source of donor stem cells or lymphocytes if even further interventions are required. Regarding that graft failure and the potential need of undergo a second alloHSCT in AA may be higher than in other diseases, show the safety and efficacy of the use of this donor source is important.

We hypothesize that the use of haploidentical donors is safe and effective for patients diagnosed with aplastic anemia. In addition, we want to compare the outcome of allogeneic stem cell transplant using haploidentical donors and unrelated donor in these group of patients.

Objectives:

Primary objective:

- To determine the safety and efficacy of the use of haploidentical donor in patients diagnosed with AA.

Secondary objectives:

- To analyze differences in outcome of HSCT using 10/10 or 9/10 match unrelated donors versus haplodentical donors for patients diagnosed with AA.
- To compare the following outcomes between the two groups:
    - Cumulative incidence of Non Relapse Mortality (NRM) at day +100
    - Cumulative incidence of relapse/progression
    - Neutrophil and platelet recovery
    - Incidence of Graft failure

Study population:

Patients (all ages) who underwent allogeneic stem cell transplant for aplastic anemia using a 10/10 or 9/10 match unrelated donor and a haploidentical donor.

Inclusion criteria:

- Patients diagnosed with aplastic anemia undergoing first allo-HCT between 2000-2017, reported to the CIBMTR.
- Eligible donors include, unrelated donors (HLA 10/10 and 9/10) and haploidentical donors
- Patients who receive transplants in centers with a minimum follow up of 6 months will be included.

Exclusion criteria:

- Non eligible donors include identical twin or match related donors

Outcomes:

Main definitions:

- OS: time to death at 1, 3 and 5 years. Death from any cause will be considered an event. Surviving patients will be censored at time of last follow-up.
- Cumulative incidence of disease relapse (graft failure) at 1, 3 and 5 years, with TRM as competing event.
- TRM: Cumulative incidence of TRM at day +100 and 1, 3 and 5 year. TRM is defined as death without preceding disease relapse/progression. Relapse/progression and death are competing events.
- Acute GVHD: Cumulative incidence of grade II-IV acute GVHD per consensus criteria at day +100, with death as competing risk.
- Chronic GVHD: Cumulative incidence of limited and extensive chronic GVHD at 1 year. With death as competing risk.
- Hematopoietic recovery:
    - Time to neutrophils (ANC) > 0.5 $x10^9$/L sustained for three consecutive days. This endpoint will be evaluated at 28-day and 100-day after HCT.
    - Time to achieve a platelet count of >20 x 10^9/L independent of platelet transfusions for 7 consecutive days within 28 and 100 days post-transplant.
    - This endpoint will be evaluated at 28-day and 100-day after HCT.

Datat requirements:
Utilizing data collected by CIBMTR from pre and post alloHSCT from patients diagnosed with aplastic anemia who underwent first allogeneic stem cell transplant between 2000-2017.
Patients who receive transplants in centers with a minimum follow up of 6 months will be included.

The parameters to be assessed are outlined in **table 1** below.

Type of data	**Data point**	**Specific data**
Patient Specific	Patient specific characteristics	Age at transplant (Date of birth) Gender Race Country of transplant (if available) Significant comorbidities Grade of AA Date of diagnosis Interval from diagnosis to transplant Transfusion status prior to transplant Infections one week prior to conditioning Prior immunosuppressive therapy: Yes/No. Type of IST.
Transplant information	Transplant date	Transplant date
	Transplant information	Donor type: MUD vs Haploidentical donor HLA mismatch Donor-recipient gender match Donor-recipient ABO mismatch Donor age (if available) Donor relation (if haploidentical donor)
	Conditioning regimen	Conditioning regimen description
	GVHD prophylaxis	Calcineurin based T cell depletion Others
	Graft characteristic	Stem cell source (BM or PBSC)
Outcome Measures	Engraftment	Neutrophil engraftment date Platelet engraftment date
	Post-transplant complications	VOD: Yes/No. Grade if available. Resolved: Yes/no Platelet refractoriness: Yes/No CMV reactivation: yes/no. Date of first reactivation EVB reactivation: yes/no. PTLD yes/no
	GVHD	Acute GVHD (aGVHD) Incidence of grade II-IV acute GVHD (aGVHD) (subset evaluating grade III-IV aGVHD) Date of onset of aGVHD

		Grade Organ involved Response to treatment (Yes/no) Chronic GVHD (cGVHD) Incidence of chronic GVHD (aGVHD) (subset evaluating moderate and severe cGVHD) Date of onset of aGVHD Grade Organ involved Response to treatment (Yes/no)
	Mortality	Death yes/no Time to mortality Day 100, 6 months and 2 year mortality Treatment related mortality at 6 months and 1 year Cause of mortality Patient alive with no graft failure and absence of active GVHD: Yes/No
	Graft failure	Graft failure (primary and secondary) Date of the graft failure Second transplant: Yes/No. Date of the second transplant

Variables to be analyzed:

Main effect:

- **Haploidentical donor vs unrelated donor**
- An internal analysis will be done comparing 9/10 MUD with haplodentical donors.

Patient-related:

- Age at HCT, years: 0-10, 11-18, 18-39; 40-59, 60-70, >70 years.
- Karnofsky performance score: ≥80% vs. <80%.
- HCT-CI score: ≤3 vs >3.

Disease-related:

- Chemosensitivity at HCT: chemosensitive vs. chemoresistant vs. untreated.
- BM involvement at HCT: yes vs no.
- Requirement of transfusional support
- IPSS, DIPSS and DDIPS score
- Prior use of Ruxolitinib: Clinical response: yes vs no.
- Splenectomy: yes vs no.

Transplant-related (allo-cohort):

- Donor type: HLA-identical siblings vs unrelated donors.
- Conditioning regimen: MAC vs RIC/NMA.
- Graft type: bone marrow vs peripheral blood.
- GVHD prophylaxis: calcineurin inhibitors based vs other groups .
- ATG or alemtuzumab use for *in vivo* T cell depletion.
- Year of HCT: Continuous (auto and allo cohorts).
- Donor older than 50: yes vs no.

- Female donor/Male recipient: yes vs no.
- Negative donor/Positive recipient CMV status: yes vs no.
- Maior ABO mismatch: yes vs no
- VOD yes/no.
- Platelet refractoriness: Yes vs no.
- Graft failure (primary and secondary): Yes vs no.
- CMV reactivation Yes vs no
- EBV reactivation Yes vs no

Study design:

Study characteristics:

- Multicenter
- Retrospective
- observational.

The aim of this study is to compare the clinical outcomes after allogeneic stem cell transplantation between patients who receive graft from haploidentical donors between unrelated donors.

The CIBMTR data base would provide data for the variables of interest. The cohort of patients would be classified in two main groups: patients who received MUD grafts and haploidentical donors. In addition, an internal analysis will be done to compare the outcome between 9/10 MUD and haploidentical donors. Baseline characteristics will be reported using descriptive statistics (counts and percentages). Comparisons between categorical variables would be done using c2 test.

The main variable of interest will be overall survival (OS) and it will be calculated from the date of transplant to the date of death or last date of follow-up. OS would be calculated using the Kaplan-Meier product-limit method and the impact of variables will be assessed using the Log-rank test. None-relapse mortality would be estimated using the cumulative incidence method to account for death and graft failure as competing risks. Survival rates would be assessed at 1, 3 and 5 years. Acute and chronic GHVD rates would be assessed using the cumulative incidence method while considering death and graft failure as competing risks. Acute GVHD would be analyzed at day 100. Chronic GVHD would be analyzed at 1 year. Graft-versus-host disease-free, relapse-free survival (GRFS) will be calculated at 1 year.

Covariates of interest to survival outcome would be: interval from diagnosis to transplant, age at transplant (≤40 vs >40 years), prior IST, stem cell source, neutrophil recovery, platelet recovery, primary graft failure, secondary graft failure and acute and chronic GVHD. Cox Proportional hazards regression will be used to assess the impact of covariates of interest in the survival outcome. Results will be expressed as hazard ratio (HR).

All P-values will be 2-sided and for the statistical analyses, $P < 0.05$ will be considered to indicate a statistically significant result.

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Proposal: 1811-143

Title:
Factors influencing poor graft function post allogeneic bone marrow transplantation

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Hypothesis:
Pre- and post-transplant factors are associated with poor graft function despite successful engraftment and absence of disease relapse

Specific aims:
To document the incidence of poor graft function in the presence of full donor myeloid chimerism
To identify risk factors for poor graft function post allogeneic bone marrow transplantation

Rationale:
The incidence of poor graft function post engraftment is poorly defined, and estimates range from 5-27%(1-3). There is significant morbidity and mortality associated with poor donor graft function post allogeneic bone marrow transplant (1, 4). Further elucidating rate of poor graft function and stratifying risk of poor graft function pre-transplantation may influence decision-making.

Background:
Graft dysfunction is an important outcome as it is associated with a significantly poorer overall survival, with 3 year survival rates as low as 25%, and a 14-fold increase in non-relapse-related mortality(2, 4). Graft-related factors increasing risk of graft dysfunction include disparate donors (including haploidentical, unrelated donors and cord transplants), stem cell dose, ABO incompatibility, T-cell depletion, and reduced intensity conditioning(1, 3, 5-7). Recipient factors include age (increasing risk of graft failure with increasing age), male sex, splenomegaly ≥10cm after D+30, viral infections (CMV, HHV6, HHV8), septicaemia, and administration of myelotoxic agents such as ganciclovir(1, 3, 5, 6). Additional proposed recipient and graft factors include degree of prior treatment, underlying haematologic disease (2, 4, 5, 9). Additional transplant factors include the presence of graft-versus-host-disease (GVHD)(2, 6, 8, 9). Importantly, increased cell doses do not necessarily result in improved graft function and may result in poorer survival at doses over 10x108/kg, though higher rates of thrombocytopenia have been noted with stem cell doses of ≤4x108/kg (5, 6, 8). Interrogating the large CIBMTR database will help identify risk factors associated with poor graft function despite complete donor chimerism and absence of disease relapse.

Project design:
Retrospective review of patients with poor graft function post allogeneic bone marrow transplantation in the context of complete donor myeloid chimerism (≥95%) and the absence of disease relapse to identify contributing factors. We will include all allogeneic transplants for haematologic diseases (malignant and non-malignant).

For the purposes of this study, graft dysfunction will be defined as:

- Evidence of donor engraftment based on CD3neg chimerism of 95% or higher beyond day 30; and
- Simultaneous cytopenias in a 2 or more cell lines defined as a platelet count of ≤30x109, neutrophil count of ≤0.5x106, and haemoglobin of ≤85g/L; and
- Absence of disease relapse

Patient eligibility criteria:

Inclusion criteria:

- All patients post allogeneic bone marrow transplant for a haematologic disorder, either malignant or non-malignant, with donor myeloid chimerism of ≥95%.
- First allogeneic transplant for haematologic disorder
- Age ≥ 18 years
- Year of HCT 2000-2016

Exclusion criteria:

- Death or relapse before day 30
- Umbilical cord blood and haplo-identical transplants

From this patient group we will compare incidence of graft dysfunction, as defined above, with a number of proposed risk factors as outlined below to try to both identify and quantify their impact on graft function.

The variables we propose to collect are:

Pre- and peri-transplant factors:

- Patient demographics
- Age
- Sex
- Comorbidities (if available) – HCT-CI
- Indication for transplant
- Disease status pre-transplant
- Presence of splenomegaly (10cm below costal margin) where known
- Therapy prior to transplant and number of cycles
- Transplant details
- Donor type (matched related donor, matched unrelated donor, mismatched unrelated donor)
- Donor age
- Mismatch presence and details
- ABO donor/recipient
- CMV donor/recipient
- Graft source – BM versus peripheral blood stem cells
- Conditioning regime – MAC vs RIC
- T cell depletion
- GVHD prophylaxis
- Death and cause of death where applicable

Post-transplant factors:

- Illness/organ dysfunction during transplant
- Early organ toxicity and severity (if data available)
- ICU admission
- Ventilatory support
- CMV
- Presence of reactivation
- Presence of CMV disease
- Treatment required
- Duration and type of treatment where treatment required
- GVHD
- Presence of acute and chronic GVHD
- Severity of GVHD

- Resolution of GVHD
- Treatment of GVHD
- Graft function
- Chimerism as available
- Patients meeting criteria for poor graft function at any within 12 months post-transplant
- Duration of poor graft function
- Resolution of graft dysfunction

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Table 1. Characteristics of patients who underwent first HLA-identical sibling or unrelated donor HCT for AML or ALL in remission and reported to CIBMTR, 2013-2017

Characteristic	N (%)
Number of patients	2610
Age at transplant, years	
Median (range)	55 (18-78)
18 – 30	327 (13)
31 – 50	736 (28)
> 50	1547 (59)
Disease	
AML	1966 (75)
ALL	644 (25)
Disease status	
CR1	2101 (80)
CR2	509 (20)
Donor type	
HLA-identical sibling	887 (34)
8/8 Unrelated	1470 (56)
7/8 unrelated	253 (10)
Conditioning regimen intensity	
MAC	1555 (60)
RIC/NMA	1055 (40)
Graft type	
Bone marrow	419 (16)
Peripheral blood	2191 (84)
TX year	
2013	506 (19)
2014	709 (27)
2015	591 (23)
2016	476 (18)
2017	328 (13)

Proposal: 1811-173

Title:
Alternative donor stem cell transplants compared to matched unrelated donor transplants in the treatment of AML and MDS for patients with high comorbidity-age composite index

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Hypothesis:
We hypothesize that outcomes of alternative donor stem cell transplants (haploidentical or cord blood) are comparable to Matched unrelated donor (MUD) transplant among patients with high comorbidity- age index score.

Specific aims:
Primary aim:

- To compare overall survival (OS) between those who had a MUD (8/8 or 7/8) allogeneic hematopoietic cell transplant (allo HCT) versus those transplanted using an alternative donor (haploidentical or cord blood)

Secondary aims:

- To compare NRM (Non-relapse Mortality), progression free survival (PFS), relapse, engraftment (of both neutrophils and platelets) and graft failure rate between MUD allo HCT and alternative donor transplants.
- To compare acute and chronic GVHD rate between those with MUD allo HCT versus alternative donor transplants.
- To analyze if stem cell source is an important factor in affecting the outcome in this group of patients.

Scientific impact:
The results from this study will guide us in choosing the appropriate donor stem cell source to achieve the best outcome possible for patients with high comorbidity- age index.

Scientific justification:
Advances in the understanding of pathobiology of stem cell transplants and use of reduced intensity conditioning (RIC) regimens have made it possible for allo HCT to be offered to an increasing number of patients for the treatment of AML and MDS including older adults. Availability of alternative donor stem cell sources (haploidentical and cord blood) has also contributed to increase in number of patients being offered transplant as a treatment option.
Haploidentical HCT (haplo HCT) has been shown to have outcomes comparable to MRD, MUD in AML and MDS.[1] Similarly, a recent analysis from CIBMTR also showed equivalent OS in patients with AML using either MUD (8/8) or haploidentical donor making it a viable alternative donor source.[2] Cord blood

transplant (UCB) is another alternative donor option considered for patients without an identified matched donor, including for some older patients over the age of 55.[3]
A comparative study of haplo HCT and MUD HCT among older patients (60 years and older), from the EBMT data showed similar outcomes including transplant related mortality (TRM), acute GVHD, PFS, OS, except for higher chronic GVHD in pts who underwent MUD allo HCT(HR 2, p = 0.01, 95% CI 1.17-3.47).[4]
UCB was compared with HLA 8/8 and 7/8 matched unrelated donors among pts age above 50 in a CIBMTR study by Weisdorf et al.[3] In this study, TRM was higher and PFS was lower with UCB (35% and 28%, respectively) when compared to 8/8 MUD (27% and 39%, respectively) but chronic GVHD was lowest (28%) compared to 53% and 59% in 8/8 and 7/8 HLA- MUD transplants. These studies as detailed above have demonstrated the viability of alternative donor transplants among older patients.
Decisions regarding the suitability of a patient for allo HCT and the choice of regimen is made by taking into account disease-specific, transplant and patient-specific factors that can predict transplant outcomes and age has been one of the key factors considered in deciding transplant eligibility of a patient. Traditionally transplant outcomes have been thought to be worse with increasing age of the patient and most clinical trials use arbitrary age cut-offs. However, age as a predictor of transplant outcomes has been inconsistent especially with the use of RIC conditioning regimen.[5-8]
In a multi- institute study, Sorror et al showed that Comorbidity- age index (HCT-CI + age composite index- that adds 1 additional point to HCT-CI score for age >40) was a better indicator of a patients biological age and predicted NRM and OS with c-statistic estimates for prediction of NRM (0.664 v 0.556; P .001) and survival (0.682 v 0.560; P .001) respectively, when compared with age.[9]
As previously discussed in the text above, studies have primarily focused on feasibility of alternative donors among older adults. However, rather than age, 'comorbidity -age index' is a better indicator of an individual's biological age and a better predictor of how well a patient will tolerate an allo HCT. Patients with higher scores on the comorbidity-age index score (3-4 vs. ≥ 5) tend to have worse transplant outcomes and no data is available on whether transplant outcomes from different donor choices are comparable in this cohort of patients. Information from this study would aid in selecting appropriate donor stem cell source for future transplants to improve the chances of achieving the best outcome possible in this patient population who have a higher risk of poor outcomes.

Patient eligibility population:
Inclusion criteria:

- Patients undergoing allo HCT for hematologic malignancies (AML and MDS) from Haploidentical, Cord blood and MUD (8/8 or 7/8)
- Age ≥ 18 years
- Transplant between 2008 and 2017

Exclusion criteria:

- Ex-vivo T-cell depletion
- PT-Cy as single-agent GVHD prophylaxis
- Combined Haplo-Cord transplants
- Second allo HCT

Data requirements:
The following variables will be collected using CRF forms and analyzed:
Patient related variables

- Patient age at HCT
- Patient gender: male vs. female
- KPS: ≥90 vs. <90 and continuous

- Time from diagnosis to HCT
- Race: White vs. African American vs. Hispanics vs. others
- Comorbidities
- HCT-CI
- HCT-CI/age (3-4 vs. ≥5)

Disease related variables

- Disease (AML, MDS)
- For AML- Baseline laboratory/cytogenetic/molecular risk group (favorable, intermediate, poor) and for MDS (Baseline laboratory/ cytogenetics and IPSS-R score)
- Disease status at transplant
- Induction/Low intensity therapy received prior to transplant

Transplant related variables

- Conditioning type (Myeloablative vs. Non-Myeloablative/Reduced-intensity) according to CIBMTR definition10
- TBI-based conditioning if ablative (Yes vs. No)
- Graft type: peripheral blood vs. marrow
- GVHD prophylaxis
- Donor/Recipient CMV status: -/+ vs. +/- vs. +/+ vs. -/-
- Time from diagnosis to HCT: 0-6 vs. 6-12 vs. ≥ 12 months and continuous

Study design:

Patient characteristics will be compared with Chi-square or Wilcoxon statistics for categorical and continuous variables as appropriate. Univariate probabilities of OS and PFS will be calculated using the Kaplan-Meier estimator with log-rank test for univariate comparisons. Cumulative incidence of NRM and relapse will be estimated by Fine and Gray's method of competing risk analysis. Multivariate analysis will be performed by step-wise Cox proportional hazard model retaining variables significant at .05.

Conflicts of interest:

None

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Table 1. Characteristics of patients 40 years or older who underwent first allogeneic HCT for AML or MDS and reported to CIBMTR. 2008-2018

Characteristic	Haploidentical	MUD	UCB
Number of patients	2186	4783	1053
Age at transplant, years			
Median (range)	61 (40-88)	62 (40-83)	59 (40-81)
40 – 50	333 (15)	603 (13)	221 (21)
51 – 60	648 (30)	1333 (28)	344 (33)
61 – 70	934 (43)	2209 (46)	418 (40)
≥ 70	271 (12)	638 (13)	70 (7)
HCT-CI			
0 – 2	1048 (48)	2283 (48)	531 (50)
3 – 4	707 (32)	1497 (31)	336 (32)
≥ 5	431 (20)	1003 (21)	186 (18)
HCTCI/age			
0 – 2	750 (34)	1606 (34)	398 (38)
3 – 4	717 (33)	1562 (33)	347 (33)
≥ 5	719 (33)	1615 (34)	308 (29)
Disease			
AML	1466 (67)	2109 (44)	789 (75)
MDS	720 (33)	2674 (56)	264 (25)
Graft type			
Bone marrow	751 (34)	660 (14)	0
Peripheral blood	1435 (66)	4123 (86)	0
Umbilical cord blood	0	0	1053
Year of transplant			
2008	41 (2)	360 (8)	100 (9)
2009	56 (3)	397 (8)	112 (11)
2010	53 (2)	283 (6)	112 (11)
2011	74 (3)	235 (5)	104 (10)
2012	88 (4)	298 (6)	101 (10)
2013	140 (6)	535 (11)	116 (11)
2014	185 (8)	673 (14)	103 (10)
2015	312 (14)	660 (14)	123 (12)
2016	375 (17)	652 (14)	101 (10)

Characteristic	Haploidentical	MUD	UCB
2017	426 (19)	570 (12)	72 (7)
2018	436 (20)	120 (3)	9 (<1)

Proposal: 1811-176

Title:
Impact of Cell Dose on Haploidentical Bone Marrow Stem Cell Transplantation Outcome

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Hypothesis:
Cell dose of the bone marrow graft predicts haploidentical transplant outcomes

Specific aims:
- To investigate the impact of bone marrow graft cell dose on haploidentical hematopoietic stem cell transplant (HSCT) outcomes.
- To identify the optimal cell dose of bone marrow graft for haploidentical HSCT.

Scientific justification:
Over the past decade, bone marrow transplantation (BMT) has been used to treat numerous malignant and nonmalignant hematologic diseases. An adequate bone marrow stem cell dose is recognized as one of the most important donor factors influencing the outcome of hematopoietic stem cell transplantation (HSCT). Numerous studies have demonstrated that infusion of larger numbers of bone marrow cells improve survival after HSCT [1-5]. In a retrospective study of 572 patients with acute myeloid leukemia (AML) who underwent MRD allogeneic transplant using bone marrow grafts[1], a nucleated cell dose above the mean (2.6 x 10^8 TNC/kg recipient body weight) was associated with lower non-relapse mortality, disease relapse and improved disease-free survival, neutrophil, and platelet engraftment. There was no relationship seen between the dose of TNC and the risk of acute GVHD. Patients who received >3.8 x 10^8 TNC/kg were shown to have 30% increase in disease-free survival compared to patients who received < 1.6x10^8 TNC/kg. A subsequent study evaluated the effect of TNC dose on graft function and transplant outcomes in 905 allogeneic bone marrow graft recipients (753 MRD, 30 MMUD, 135 MUD) [2]. A higher TNC doses was associated with faster engraftment, lower TRM and better OS. The effect of cell dose was more pronounced in patients older than 30 years, with advanced disease, and with alternative donors. Currently, a TNC dose of 3 x 10^8/kg or higher in bone marrow grafts is generally accepted as an optimal for transplant outcomes, although more recent data has begun to question its significance.
Recently, haploidentical hematopoietic stem cell transplantation has been increasingly used for treatment of hematologic malignancies, primarily due to development of post-transplant cyclophosphamide as an effective strategy for GVHD prophylaxis. The bone marrow is the predominant graft source used for haploidentical transplantations. The optimal bone marrow cell dose for T-cell replete haploidentical transplant is not known. Given the continued growth of haploidentical stem cell transplantation in adults over the past decade, we sought to determine whether there is a correlation between cell dose of bone marrow graft and clinical outcome in haploidentical HSCT.

Scientific impact:
Several studies have identified CD34+ and MNC cell dose as a critical factor affecting stem cell transplantation outcome. Most of these studies primarily focused on MRD and MUD peripheral blood or bone marrow grafts. In the absence of a suitable HLA matched sibling donor, haploidentical donors are

increasingly considered due to donor availability and a relatively lower treatment related mortality [7]. The effect of donor graft cell dose (CD34+, TNC) on clinical outcomes in haploidentical bone marrow HSCT has not been well characterized. This study will be the first to identify the optimal bone marrow graft cell dose for haploidentical HSCT.

Patient eligibility population:

- Patients aged 18 years or older who have underwent first haploidentical bone marrow transplant for hematologic malignancies from 2006 – 2017
- Patients who received manipulated grafts, such as ex-vivo T cell depletion or CD34+ selection, will be excluded.
- Haploidentical transplants without post-transplant cyclophosphamide for GVHD prophylaxis will be excluded

Outcomes:

Primary outcome:

- To investigate the impact of bone marrow graft cell dose (TNC and CD34+) on overall survival (OS).

Secondary outcomes:

- Incidence of grade II-IV and grade III-IV acute and chronic GVHD
- Cumulative incidence of Non-relapse mortality (NRM)
- Relapse/progression-free survival (PFS)
- Time to engraftment: Defined as time between day of transplantation and recovery of neutrophils and platelets.
- GVHD free/relapse free survival (GFRS)
- Primary graft failure (failure to achieve ANC>500/mm^3 for three days or donor chimerism < 5% (If information available)

Variables:

Main effect:

- Bone marrow graft Cell dose (CD34+ and TNC dose) – continues variable or patient can be divided into 4 quartiles

Patient-related:

- Age at transplant: continuous & by age group: decades
- Gender: male vs. female
- Karnofsky performance status at transplant: ≥ 90 vs. < 90 vs. missing
- HCT comorbidity index at transplant: 0 vs 1-2 vs ≥ 3 vs. missing
- Race/ethnicity: Caucasian vs. others vs. missing
- Recipient BMI (normal vs overweight vs obese)

Disease-related:

- Disease type
- Remission status at HCT: CR vs PR vs. resistant vs. untreated/unknown
- Disease risk index

Transplant-related:

- Conditioning regimen: MAC vs. NMA
- TBI dose in conditioning regimen (none vs. ≤450 cGy vs. >450 cGy)
- GVHD prophylaxis: Post- transplant Cy +/- calcineurin inhibitor

- Donor-recipient sex match: male-male vs. male-female vs. female-male vs. female-female vs. missing
- Donor-recipient CMV status: -/+ vs. others vs. missing
- Year of transplant: continuous
- Donor-recipient blood group ABO match (Matched, minor mismatch, major mismatched, not reported)
- Donor specific anti-HLA antibody (if available)
- Degree of match (Number of mismatches)

Statistical analysis:
This study aims at assessing the impact of TNC cell dose on outcome of haploidentical HSCT. Categorical variables were compared using the X^2 test. The probability of OS is calculated using the Kaplan-Meier estimator. The probabilities of neutrophil and platelet recovery, acute and chronic GVHD, non-relapse mortality and relapse were calculated using the cumulative incidence method. To study the association between clinical outcomes and TNC cell dose, Cox regression models is used for acute and chronic GVHD, NRM, relapse and OS. Results are expressed as hazard ratio (HR) together with the 95% confidence interval (CI).

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Table1. Characteristics of patients who underwent first bone marrow haploidentical donor HCT for hematologic malignancies in the US and reported to CIBMTR (CRF level), 2008-2018

Characteristic	N (%)
Number of patients	543
Age at transplant, years	
18 – 30	70 (13)
31 – 50	116 (21)
> 50	357 (66)
Disease	
AML	254 (47)
ALL	85 (16)
MDS	131 (24)
Non-Hodgkin lymphoma	62 (11)
Hodgkin lymphoma	11 (2)
Conditioning regimen intensity	
MAC	127 (23)
RIC	416 (77)
Patients with TNC available	405
TNC dose per actual weight, median (IQR) ($\times 10^8$/kg)	2.8 (2.1 – 3.8)
TNC dose per ideal weight, median (IQR) ($\times 10^8$/kg)	3.7 (2.7 – 4.6)
Patients with CD34 available	425
CD34 dose per actual weight, median (IQR) ($\times 10^6$/kg)	2.9 (1.8 – 4.0)
CD34 dose per actual weight, median (IQR) ($\times 10^6$/kg)	3.5 (2.4 – 4.9)

Proposal: 1812-03

Title:
Evaluation of the Impact of Conditioning Intensity in Adult Cord Blood Transplantation Recipients Treated for Acute Leukemia or Myelodysplasia (MDS)

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Hypothesis:
Intermediate intensity conditioning (Cy/Flu/Thio/TBI400) is associated with superior progression-free survival (PFS) compared to non-myeloablative (NMA, Cy/Flu/TBI200) or myeloablative high-dose TBI conditioning (Cy120/Flu/TBI1320-1375) in adults undergoing cord blood transplantation (CBT) for the treatment of acute leukemia/ MDS.

Specific aims:
To compare adult CBT outcomes in adult recipients of three different conditioning regimens: NMA, intermediate intensity, and high dose TBI-based ablation. Primary endpoint will be progression-free survival (PFS). Secondary endpoints will include ANC recovery, Platelet recovery, incidence of aGVHD and cGVHD, incidence of relapse and transplant-related morality (TRM), overall survival (OS) and cause of death.

Scientific impact:
MSKCC has developed an intermediate intensity CBT using Cy50/Flu150/Thio10/TBI400 in order to overcome the limitations of high TRM with high-dose TBI-based ablative conditioning, and the limitation of both relapse and TRM after NMA conditioning. Long term outcomes with intermediate intensity dCBT are promising. However, how the results compare to contemporary series of adult CBT recipients conditioned with high dose ablative or NMA regimens is not known. This question will be the focus of the current CIBMTR study proposal. If our primary hypothesis is confirmed this may support further investigation of intermediate intensity CBT in preference to either NMA or high dose conditioning.

Scientific justification:
CB is a standard alternative hematopoietic stem cell (HSC) source for patients in need of allogeneic HSC transplantation who lack suitable HLA-matched related or unrelated donors, especially ethnic and racial minority patients[1]. Double-unit CBT has successfully extended the application of CBT to adults without adequately sized CB units[2], and single- and double-unit CBT outcomes are comparable to matched unrelated donor HSCT[3-7]. Several factors have contributed to improving CBT outcomes over time including the increasing availability of quality CB units, modern CB graft selection guidelines, and advancements in supportive care. However, the optimal conditioning regimen for CBT in adults with hematologic malignancies is not established.
Early experience with dCBT after Cy120/Flu75/TBI1320 was notable for high rates of engraftment[8]. This strategy was subsequently investigated in a prospective multicenter trial of 56 adult patients[9]. While high rates of engraftment and low rates of relapse (11% at 3 years) were achieved, success was limited by a relatively high incidence of TRM (39% at 3 years). NMA CBT using Cy/Flu/TBI200 has been investigated as an alternative to mitigate the morbidity and TRM associated with high dose conditioning with a lower TRM at the expense of a higher incidence of relapse (31% at 3 years)[10-12].

In order to minimize TRM and morbidity while maintaining high rates of engraftment and disease control, our center has investigated a novel intermediate intensity conditioning (Cy50/Flu150/Thio10/TBI400) for CBT[13]. In an updated analysis of 102 adult patients conditioned with the MSKCC regimen (median age 50 years), we observed a high incidence of CB engraftment (97%), low incidence of relapse (11% at 2 years), and relatively low TRM (14% at 2 years) (*Politikos et al, ASH 2018 and TCT 2019*). With a median follow-up of 27 months, the 2-year PFS and OS are 74% and 82% respectively. Other centers in North America have adopted the MSKCC regimen to overcome the limitations of NMA and high-dose TBI regimens. For example, in a retrospective University of Colorado[14] study, the intermediate intensity MSKCC regimen was associated with significantly lower relapse incidence and improved OS in comparison to the standard NMA regimen. How the intermediate intensity MSKCC CBT conditioning regimen compares to high-dose TBI ablative conditioning and NMA conditioning in a larger multi-center analysis is unknown.

Patient eligibility population:

Patient age:

- 21-65 years

Transplant period:

- 1/2012-12/2017
    - First CBT only (prior allograft excluded).
    - Unrelated CBT only

Diagnoses:

- Acute Leukemia (AML/ALL/biphenotypic)
- Myelodysplastic Syndromes (MDS)

Graft criteria:

- units with $\geq$ 4/6 HLA-A, -B antigen, -DRB1 allele match to the recipient.
- single units with a TNC dose $\geq 2.5 \times 10^7$ cells/kg or $\geq 1.5 \times 10^7$ cells/kg for each unit of a double-unit graft.
- Patients who additionally received CD34+ selected haploidentical grafts will be included in the study.

Conditioning regimens:

- Non-Myeloablative: Cy50/Flu200/TBI200
- Intermediate intensity: Cy50/Flu150/Thiotepa10/TBI400
- High-dose TBI ablative: Cy120/Flu75/TBI1320-1375

GVHD prophylaxis:

- Calcineurin inhibitor (CNI) + MMF

Data requirements:

Patient demographics:

- Age
- Gender
- Weight
- Race
- CMV serostatus
- Karnofsky Performance Score
- HCT-CI if available

Disease characteristics:

- diagnosis (AML, ALL, biphenotypic, MDS)

- Remission status at transplant (for Acute Leukemia: CR1, CR2, Refractory and for MDS: Early, Advanced)
- Disease Risk Index if available (or CIBMTR disease risk category)

Transplant characteristics:

- Number of CB units (1 or 2)
- HLA-match of CB units (HLA-A, -B antigen, -DRB1 allele, and 8-allele HLA match grade if available)
- Haploidentical CD34+ selected graft supplementation (yes or no)
- Use of ATG (yes or no)
- CB unit cell dose (TNC and, if available, CD34+)
- Year of transplant
- **conditioning regimen (NMA vs Intermediate intensity vs TBI- Ablative)** - this is the main effect variable and all other variables should be tabulated per conditioning regimen in Table 1.

Transplant outcomes:

- Survivor follow-up
- ANC recovery
- PLT recovery
- aGVHD (day of onset and max. grade)
- cGVHD (day of onset and grade)
- Relapse
- transplant-related mortality
- Primary cause of death

Analysis of conditioning groups needs to be balanced for critical patient variables (eg age).

Sample requirements:
To be determined.

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Conflicts of interest:
None

Table 1. Characteristics of patients who underwent first UCB HCT for AML, ALL, or MDS and reported to CIBMTR, 2008-2018

Characteristic	TBI200/Cy/Flud	TBI400/Cy/Flud/Thio	TBI1320-1375/Cy/Flud
Number of patients	548	127	415
Number of centers	59	12	54
Age at transplant, years			
Median (range)	60 (18-74)	53 (19-70)	36 (18-68)
18 – 30	33 (6)	11 (9)	143 (34)
31 – 50	92 (17)	45 (35)	222 (53)
> 50	423 (77)	71 (56)	50 (12)
Disease			
AML	357 (65)	87 (69)	226 (54)
ALL	87 (16)	18 (14)	150 (36)
MDS	104 (19)	22 (17)	39 (9)
Number of cord units			
Single	44 (8)	1 (<1)	77 (19)
Double	504 (92)	126 (99)	338 (81)
Year of transplant			
2008	41 (7)	7 (6)	38 (9)
2009	71 (13)	4 (3)	46 (11)
2010	54 (10)	6 (5)	60 (14)
2011	54 (10)	7 (6)	47 (11)
2012	36 (7)	12 (9)	45 (11)
2013	73 (13)	8 (6)	42 (10)
2014	66 (12)	13 (10)	40 (10)
2015	64 (12)	16 (13)	31 (7)
2016	45 (8)	30 (24)	38 (9)
2017	37 (7)	20 (16)	26 (6)
2018	7 (1)	4 (3)	2 (<1)

Proposal: 1812-09

Title:
The Role of Alternative Donors and HLA Disparity in Second Allogeneic Stem Cell Transplantation for Relapsed Hematologic Malignancies

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Hypothesis:
We hypothesize that second hematopoietic stem cell transplantation using an HLA-haploidentical donor followed by posttransplant cyclophosphamide for relapsed/progressing hematologic malignancies will result in superior outcomes compared to other second donors, and HLA-disparity relative to first allogeneic hematopoietic cell transplant will be associated with improved survival rates.

Specific aims:
Primary endpoint: To compare adjusted overall survival (OS) in adult patients with relapsed/progressing hematologic malignancies by donor type (8/8 HLA-matched donor vs. 7/8 HLA-matched donor vs. unrelated cord blood [UCB] vs. haploidentical stem cell transplant with posttransplant cyclophosphamide [Haplo-PTCY]).

Secondary endpoints:
- To compare adjusted relapse/progression rate (RR), disease-free survival (DFS), nonrelapse mortality (NRM), acute and chronic graft-versus-host disease (GVHD) and graft failure after a second allogeneic stem cell transplant by graft type (8/8 HLA-matched donor vs. 7/8 HLA-matched donor vs. unrelated cord blood vs. Haplo-PTCY).
- Provided that the sample size allows, to compare the OS, RR and DFS in recipients of allografts from the above donors at first hematopoietic cell transplantation (HCT2) within each type of donor at HCT1, in order to determine the impact of HLA-disparity and change of donors on HCT2.
    - In the group receiving Haplo-PTCY at HCT1, the haploidentical donor category at HCT2 will be further divided into 1) Haplo-PTCY not harboring a new mismatched haplotype (same or different donors) AND 2) Haplo-PTCY harboring a new mismatched haplotype.
    - In the group receiving UCB at HCT1, the UCB donor category at HCT2 will be further divided into 1) 5-6/8 HLA-matched UCB transplant AND 2) 7-8/8 HLA-matched UCB transplant.
    - Compare graft failure, acute and chronic GVHD, relapse, non-relapse mortality, disease-free survival and overall survival after second HCT using an HLA-haploidentical donor + PTCy, where the second donor is mismatched to the first donor, versus second transplants from all other donor types

Scientific justification:
Options for the treatment of relapsed hematologic malignancies after allogeneic HCT are limited, and long-term prognosis is usually poor. Donor lymphocyte infusion (DLI) is associated with sustained clinical remission in chronic myeloid leukemia and posttransplant lymphoproliferative disease, yet only about 10-20% of patients with acute leukemias relapsing after allogeneic transplantation achieve complete

remission, which is usually short-lived.[1–4] In addition, DLI is associated with potentially life-threatening graft-versus-host disease, need for immunosuppressive therapy, bone marrow aplasia, and infections.[5] Second HCT is an alternative for such cases and has yielded long-term overall survival as high as 35% in patients with favorable risk factors. Most reports have not found any difference using the same or different donors.[5–12] However, studies addressing second transplantation for relapsed hematologic diseases have included none or only few transplants using alternative donors, including Haplo-PTCY, UCB, and 7/8 HLA-matched donors.

Among these alternative donor transplant options, Haplo-PTCY has increasingly been used worldwide according to CIBMTR and EBMT data.[13,14] In the second transplantation setting, it has the advantage of being relatively less costly and promptly available. Two German transplant centers performed 20 second Haplo-PTCY and showed an engraftment of 85% and encouraging 45% OS rate at one year.[15] The Atlanta group also reported on the outcomes of 20 patients with relapsed malignancies following a first matched donor transplant who received second Haplo-PTCY, 31% of whom had persistent DFS at three years.[16] More recently, the Baltimore group showed a 4-year event-free survival of 36% in 40 patients who received second Haplo-PTCY for relapsed hematologic diseases. Interestingly, despite the caveat of the small sample size, the 20 patients who had received a haploidentical allograft harboring a new mismatched haplotype at HCT2 had superior overall survival compared to those whose allograft did not have a new haplotype mismatch, and the choice of a second haploidentical allograft was also found to have a trend for improved OS compared to other graft sources.[17] These findings suggest that second transplantation from donors with HLA-disparity in relation to the first donor might be beneficial in relapsed malignancies.

Therefore, given the gaps in knowledge on the role of alternative donors at HCT2 for relapsed malignancies, we propose a registry-based analysis to compare outcomes of alternative donor transplant recipients (i.e., Haplo-PTCY, UCB, and 7/8 HLA-matched) to 8/8 HLA-matched donor recipients at HCT2, and to investigate whether HLA-disparity at HCT2 relative to HCT1 yields a survival benefit in this setting.

Study population:

Inclusion criteria:

- Patients age 18 – 70 years;
- Diagnosis of relapsed/progressing hematologic malignancies: acute myeloid leukemia, chronic myeloid leukemia, myelodysplastic syndrome, acute lymphoblastic leukemia, B-cell or T-cell Non-Hodgkin lymphomas, Hodgkin lymphoma;
- First and second allogeneic stem cell transplant with any of the following graft types: 8/8 or 7/8 HLA-matched related or unrelated donor, allele-level 5-8/8 HLA-matched unrelated cord blood (single or double units) or haploidentical related donor with posttransplant cyclophosphamide (cases using the same donor as the first transplant are to be included).

Exclusion criteria:

- More than one previous allogenic stem cell transplant;
- Haploidentical transplantation with any other GVHD prophylaxis except for posttransplant cyclophosphamide;
- 8/8 or 7/8 HLA-matched related or unrelated donor or unrelated cord blood hematopoietic transplantation using posttransplant cyclophosphamide as GVHD prophylaxis;
- UCB transplants receiving less than 3.0×10^7 total nucleated cells infused/kg.
- Second allogeneic transplants performed for the sole indication of graft failure

Data Requirements:

Patient-related:

- Age at HCT, years: by quartiles and continuous.
- Sex: male vs. female.
- Karnofsky performance score: ≥ 90% vs. < 90%.
- HCT comorbidity index at transplant 0, 1, 2, and ≥ 3.
- Race: White vs. Black vs. Asian/pacific islander vs. other vs. others .
- Recipient CMV serostatus: positive vs. negative.

Disease-related:

- Time from first transplant to relapse/progression: < 6 months vs. 6 months to 1 year vs. ≥ 1 year and continuous.
- Disease status at 1st and 2nd transplants: complete remission vs. partial remission vs. chemorefractory vs. untreated.
- Number of prior lines of therapy before the 2nd transplant: continuous.
- Type of post-relapse salvage therapy: none vs. donor lymphocyte infusion vs. chemotherapy vs. radiotherapy vs. other.

Transplant-related (1st and 2nd transplants):

- Donor genotypic gender: female vs. male.
- Donor age: continuous;
- Donor type: 8/8 HLA-matched donor vs. 7/8 HLA-matched donor vs. unrelated cord blood vs. haploidentical related donor with posttransplant cyclophosphamide.
- Graft source: Bone marrow vs. peripheral blood vs. cord blood.
- Conditioning intensity: myeloablative vs. reduced intensity.
- Conditioning regimens: most common types, categorical.
- GVHD prophylaxes: most common types, categorical.
- Total and CD34+ cell dose: continuous
- Year of HCT: continuous.
- T-cell depletion: yes vs. no.
- Acute GVHD (only 1st transplant): none or grade 1 vs. grade 2-4 vs. grade 3-4.
- Chronic GVHD (only 1st transplant): none vs. limited vs. extensive OR none vs. mild vs. moderate/severe.
- Same donor as first transplant (only 2nd transplant, not applicable to UCB): yes vs. no.
- Donor CMV status

Primary outcome:

Overall survival (OS): Time to death. Death from any cause will be considered an event. Surviving patients will be censored at last follow up. The outcome of OS will be adjusted for all pretransplant variables that are significantly associated with OS in multivariate analysis. OS will be calculated using the Kaplan–Meier method for both groups, summarized by survival curves.

Secondary outcomes:

Diasease-free survival (PFS): PFS is defined as survival without disease relapse/progression. Disease relapse/progression and death are treated as events. Surviving patients will be censored at last follow up. PFS will be calculated using the Kaplan–Meier method for both donor types, summarized by survival curves.

Relapse/progression rate (RR): Disease recurrence or progression (either morphological or molecularly). Patients will be censored at date of last follow-up. The event will be summarized by the cumulative incidence estimate, with nonrelapse mortality treated as a competing risk.
Nonrelapse mortality (NRM): Death without relapse/progression. The event will be summarized by the cumulative incidence estimate, with relapse/progression treated as a competing risk. Patients will be censored at date of last follow-up.
Acute GVHD: Development of Grades II-IV and III-IV acute GVHD using the Glucksberg grading system.[18] The event will be summarized by the cumulative incidence estimate, where death without Grade III-IV acute GVHD and graft failure will be treated as competing risks. Patients will be censored at date of last follow-up.
Chronic GVHD: Development of chronic GVHD.[19] The event will be summarized by the cumulative incidence estimate, where death without chronic GVHD and graft failure will be treated as competing risks. Patients will be censored at date of last follow-up.
Neutrophil recovery: The first of 3 measurements on different days with an ANC >500/µL after transplant. Death and relapse will be competing risks.
Platelet recovery: The first of 3 measurements on different days with a platelet count >20,000 after transplant with no platelet transfusions in the prior 7 days. Death and relapse will be competing risks. The event will be summarized by the cumulative incidence estimate.
Graft failure: Primary and secondary graft failure will be considered together. Primary graft failure is defined as failure to achieve absolute neutrophil count (ANC) of 0.5 x 10^9/L for three consecutive days or donor chimerism <5% in any compartment (T-cell chimerism ≤5%, unsorted blood or marrow chimerism) at all measurements and additional hematopoietic stem cells were required to restore hematopoiesis. Secondary graft failure is defined as need for additional hematopoietic stem cells because the recipient's hematopoietic recovery declined indefinitely after the initial hematopoietic recovery (ANC was greater than or equal to 0.5 × 10^9/L for three consecutive days, and then declined to below 0.5 × 10^9/L for three consecutive days or donor chimerism <5% in any compartment). When there is recurrent disease, it is assumed that graft failure is related to disease recurrence and not considered an event for this study.

Study design:
This study aims to the role of donor choice at second allogeneic hematopoietic transplantation. Descriptive tables of patient, disease-, and transplant-related factors will be created. The tables will list mean/median and range for continuous variables and percent of total for categorical variables. Probabilities of PFS and OS will be calculated using the Kaplan-Meier estimator accounting for competing risks. Comparison of survival curves will be made using the log-rank test. Cumulative incidence of NRM, relapse/progression, acute and chronic GVHD, and hematologic recovery will be calculated while accounting for competing events. Multivariate analyses will be performed using Cox proportional hazards models for various outcomes. A stepwise model building approach will then be used to identify the significant risk factors associated with the outcomes. The donor type will always be included in the Cox models. A backward stepwise model selection approach will be used to identify all other significant risk factors. Factors which are significant at a 5% level will be kept in the final model. The potential interactions between main effect and all significant risk factors will be tested.

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Table 1. Characteristics of patients who underwent second allogeneic HCT following relapse or progression of AML, ALL, or MDS and reported to CIBMTR. 2008-2018

Characteristic	Haploidentical	URD
Number of patients	225	140
Age at transplant, years		
Median (range)	50 (19-77)	57 (19-76)
18 – 30	39 (17)	22 (16)
31 – 50	78 (35)	30 (21)
> 50	108 (48)	88 (63)
Disease		
AML	148 (66)	77 (55)
ALL	41 (18)	18 (13)
MDS	36 (16)	45 (32)
Conditioning regimen intensity		
MAC	44 (20)	46 (33)
RIC/NMA	181 (80)	94 (67)
Graft type		
Bone marrow	23 (10)	10 (7)
Peripheral blood	202 (90)	130 (93)
TX year		
2013	6 (3)	18 (13)
2014	44 (20)	27 (19)
2015	51 (23)	27 (19)
2016	42 (19)	26 (19)
2017	37 (16)	32 (23)
2018	45 (20)	10 (7)