Introduction
a. Minutes and Overview Plan from February 2017 meeting (Attachment 1)

Accrual summary (Attachment 2)

Presentations, published or submitted papers


4. **Studies in Progress** *(Attachment 3)*

a. **GS15-02** Long term outcomes of 100-day survivors of hematopoietic stem cell transplant by cell source (W Hwang/ C Brunstein) Protocol Development

b. **GS16-02** Outcomes in haploidentical vs matched unrelated donor transplants in older patients (MA Perales/B Tomlinson/M de Lima) Manuscript Preparation

c. **GS16-03** Donor selection for allogeneic stem cell transplantation: HLA-haploidentical children, siblings, or parents versus HLA-matched siblings (E Fuchs/T Robinson/A Nagler) Manuscript Preparation

d. **GS17-02** Myeloablative vs reduced intensity conditioning in haploidentical transplantation (S Solomon /N Shah/G Fatobene G) Protocol Development

5. **Future/proposed studies**


b. **PROP 1711-51/1711-84/1711-91/1711-99** Comparison of alternative donor transplant for MDS and MPS (A Viswabanndya/B Tomlinson/M Grunwald/ H Elmariah, et al.) (Attachment 5)

c. **PROP 1711-15** Impact of Racial Background on Survival Following Haploidentical Donor Transplantation (HIDT) with Post Transplant Cyclophosphamide (PTCy) for Adults with Hematologic Malignancies and Comparison with Race-Specific Outcomes following Umbilical Cord Blood Transplantation (UCBT) (S Solomon) (Attachment 6)

d. **PROP 1711-56** A retrospective observational CIBMTR/EBMT study on the efficacy of alternative donor/stem cells sources in pediatric patients with acute leukemia (A Bertaina) (Attachment 7)

e. **PROP 1711-117** Comparison of Outcomes of Reduced Intensity Transplantation in Lymphoma Patients Using Haploidentical Related Donors vs. Unrelated Cord Blood (G Fatobene) (Attachment 8)

f. **PROP 1711-168** Outcomes after 8/8 matched unrelated donor (MUD) transplantation using post transplant cyclophosphamide (PTCy) vs. standard of care calcineurin inhibitor containing graft versus host disease prophylaxis in AML, ALL and MDS patients (R Romee) (Attachment 9)

**Dropped proposed studies**

a. **PROP 1706-02** Correlation of bone marrow harvest quality control parameters and engraftment after allogeneic stem cell transplantation. *Low scientific impact.*

c. PROP 1711-07 Comparison of outcomes in adult patients with acute lymphoblastic leukemia following allogeneic stem cell transplantation, with haploidentical matched unrelated, matched related donor or umbilical cord transplants. Small sample size.

d. PROP 1711-08 Umbilical Cord Stem Cell Transplantation for Acute Myeloid Leukemia not in Complete Remission. Low scientific impact.

e. PROP 1711-14 Impact of donor selection and recipient age for non-myeloablative/ reduced intensity conditioning allogeneic transplantation with haplo-identical donor with post-transplant cyclophosphamide for older adults with acute myeloid leukemia and myelodysplastic syndrome. Overlap with current studies GS15-01/GS16-02.

f. PROP 1711-23 Comparison of outcomes between t-cell replete haploidentical and HLA-matched (related or unrelated) donor HCT in ALL. Small sample size.

g. PROP 1711-46 Outcomes after alternative donor transplantation in children and young adults with hematologic malignancies. Small sample size.

h. PROP 1711-95 Which donor source is preferable for patients 60 years and older undergoing non-myeloablative/ reduced intensity conditioning transplant: a matched sibling or matched unrelated donor or haploidentical donor? Overlap with current study GS16-02.

i. PROP 1711-115 Impact of donor choice on the outcomes of second allogeneic hematopoietic cell transplantation for the treatment of relapse. Overlap with previous publication.


k. PROP 1711-118 Haploidentical Transplant with Post-transplant Cyclophosphamide vs. HLA-Matched Unrelated Donor Transplant for Adult Acute Lymphoblastic Leukemia. Small sample size.

l. PROP 1711-125 Comparing Outcomes between Young Haploidentical Donor Using Post-Transplant Cyclophosphamide and Older HLA-Matched Related Donor (8/8) hematopoietic cell transplant In Lymphoma patients. Overlap with current study GS15-01.

m. PROP 1711-126 Comparing Outcomes between Young Haploidentical Donor Using Post-Transplant Cyclophosphamide and Older HLA-Matched Related Donor (8/8) hematopoietic cell transplant In Acute Myeloid Leukemia and Myelodysplastic Syndrome. Overlap with current studies GS16-02/GS16-03.

n. PROP 1711-135 Mixed Donor Chimerism in Pediatric and Adult Patients post Allogeneic Hematopoietic Stem Cell Transplantation and Relationship to Clinical Outcomes. Small sample size and supplemental data needed.

o. PROP 1711-152 Retrospective study of the prognostic significance of non-HLA donor factors in post-transplantation cyclophosphamide (PTCy)-based HLA-haploidentical allogeneic blood or bone marrow transplantation (alloBMT). Overlap with current study GS15-01.

p. PROP 1711-153 Outcomes in patients with acute leukemia or myelodysplastic syndrome with high or very high risk DRI are improved in recipients of cord blood compared to those transplanted with an HLA-matched or mismatched donor. Overlap with current study LK16-02.

q. PROP 1711-158 In the absence of an HLA identical related or unrelated donor, which is the best strategy? Overlap with current studies GS16-02/GS16-03.

r. PROP 1711-165 The Impact of CD34 and CD3 Cell Dose in T cell Replete Haploidentical Hematopoietic Cell Transplant Using Post-transplant Cyclophosphamide. Supplemental data required.

6. Other Business
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. Perales for his time as a co-chair. He also welcomed Dr. Ian McNiece as the incoming co-chair, and acknowledged Dr. Arnon Nagler, Chair of the Acute Leukemia Working Party of the EBMT, who was in attendance. The minutes from the 2016 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 presentations

Dr. Bashey continued to present a brief summary of the committee’s publications within the past 5 years. GSWC has published 6 studies on alternative donors and grafts, 6 studies on donor selection, 2 studies on graft processing, and 1 study on transplant strategy, for a total of 15 publications.

The three submissions/publications from the 2016 academic year were then highlighted. Dr. Bashey summarized GS14-02: Donor-recipient sex in allogeneic stem cell transplantation: what really matters? (published in Haematologica) and GS16-01: Comparison of peripheral blood stem cells to bone marrow for t-replete HLA-haploidentical donor transplantation using post-transplant cyclophosphamide (submitted). Dr. Claudio Brunstein was then invited to present summary of GS13-02: The effect of inter-unit HLA matching in double umbilical cord blood transplantation for acute leukemia (In press – Haematologica).
3. Studies in Progress

In the interest of time, Dr. Bashey directed the committee members to refer to the GSWC packet for details on studies currently in progress.

4. Future/proposed studies
   a. PROP 1610-09/1611-03/1611-124 These three proposals were all seeking to compare outcomes between umbilical cord blood, haploidentical, and matched unrelated donor allogeneic transplants in patients with AML. They were combined into a single proposal, and Dr. Armin Rashidi presented on the proposal on behalf of the other investigators.

   The CIBMTR identified 413 adults transplanted for AML with a haploidentical donor, 192 transplanted with a single cord blood unit, 604 transplanted with a double cord blood unit, and 1772 transplanted with a matched unrelated donor. These transplants occurred over the time period between 2008 and 2016.

   The primary objective of this proposal was to compare overall survival in adult AML patients transplanted with cord blood HCT, haploidentical donor with post-transplant cyclophosphamide HCT, and matched unrelated donor HCT. Secondary objectives included comparing relapse-free survival, relapse and non-relapse mortality, acute and chronic GVHD, and GVHD-free relapse-free survival (GRFS). Additionally, cord blood HCT and haploidentical HCT will be compared for patients with high or very high risk AML (based on DRI), and when the cord blood unit is stratified for optimality based on total nucleated cell dose and HLA match.

   Several of the discussion points were related to exclusion of comparison groups in the analysis. First, a question was raised as to why 7/8 unrelated donors were not included in the analysis. An additional question asked why matched or mismatched unrelated donor HCT with post-transplant cyclophosphamide were excluded. Dr. Rocha informed the committee that previous studies had already looked at various combinations of donor types, and that the novel idea in this proposal was haploidentical donor HCT compared to cord blood HCT. Although the EBMT has published such a comparison, the haploidentical donor group from Europe includes several haploidentical strategies.

   One committee member pointed out that there would be no point in investigating the effect of DRI on outcomes in AML patients alone, as DRI was designed to be able to study multiple malignancies at the same time. For a defined population like AML the study must consider disease status and cytogenetic risk. The committee was in agreement with this point.

   When asked for clarification, Dr. Rashidi informed the committee that cord blood cell dose would not be used as selection criteria, and instead cell dose would be looked at in the analysis and a cut-point would be searched for.

   This proposal received a high priority score from the committee, and was accepted. However, due to previous publications and the distribution of conditioning regimens, GSWC leadership decided to limit this analysis to haploidentical donor with post-transplant cyclophosphamide HCT compared with cord blood HCT. Further refinement of the inclusion criteria may occur after careful review of conditioning regimens and considering the findings of prior CIBMTR publications on haploidentical and cord blood transplants.
b. **PROP 1611-30/1611-38/1611-116** These three proposals were all seeking to compare outcomes between umbilical cord blood, haploidentical, and matched related and unrelated donor allogeneic transplants in patients with ALL. They were combined into a single proposal, and Dr. Mahasweta Gooptu presented on the proposal on behalf of the other investigators.

The CIBMTR identified 187 adults transplanted for ALL with a haploidentical donor, 395 transplanted with a single or double cord blood unit, 418 transplanted with a matched related donor, and 445 transplanted with a matched unrelated donor. These transplants occurred over the time period between 2008 and 2016.

The primary objective of this proposal was to compare overall survival in adult ALL patients transplanted with haploidentical donor with post-transplant cyclophosphamide HCT, cord blood HCT, matched related donor HCT, and matched unrelated donor HCT. Secondary objectives included comparing non-relapse mortality, relapse, disease-free survival, and acute and chronic GVHD.

A concern was raised that if the goal of this study was to test for inferiority of the haploidentical transplants, the sample sizes available were too small, which was acknowledged by Dr. Gooptu. Dr. Perales additionally questioned how the analysis would address the discrepancy in conditioning regimens; most of the haploidentical transplants were reduced intensity, whereas the majority of the matched related and unrelated donor transplants were myeloablative. Another committee member added that graft type, too, was confounded between the main effect groups; while the haploidentical transplants were mostly half and half in terms of bone marrow or peripheral blood, the matched related and unrelated donor transplants were mostly peripheral blood. Dr. Gooptu suggested that both conditioning intensity and graft type could be added as variables in the multivariate modeling to adjust for confounding.

It was suggested that perhaps the analysis could be stratified by conditioning intensity. Dr. Tao Wang suggested this could be done in the reduced intensity setting between the haploidentical transplants and the cord blood transplants because most shared a common regimen of TBI+cyclophosphamide+fludarabine. He said it would be difficult, however, in the myeloablative setting, as the regimens were more varied.

It was also suggested that collaboration with EBMT would strengthen the analysis by providing additional cases. Proposal 1612-10 was also looking at comparing outcomes between haploidentical transplants and matched related and unrelated donor transplants in ALL patients, but as it was a collaborative proposal with the EBMT, it was kept separate. This combined proposal received and equally high priority from the committee as the collaborative proposal. However, even with the EBMT cases, it was decided that the disparity in regimen intensity between the donor groups could not be overcome, and therefore the study was deemed not feasible. It was suggested that allowing more time for the accrual of haploidentical patients might make this project feasible in a couple of years.

This proposal was not selected.

c. **PROP 1612-10** This proposal was for a collaborative study between the CIBMTR and EBMT looking to compare outcomes between haploidentical and matched related and unrelated donor transplants in adult patients with ALL. Though similar to Proposal 1611-30/1611-38/1611-116, it was presented
separately since it was a joint proposal with the Acute Leukemia Working Party of the EBMT. Dr. Stefan Ciurea presented the proposal.

The CIBMTR identified 187 adults transplanted for ALL with a haploidentical donor, 418 transplanted with a matched related donor, and 445 transplanted with a matched unrelated donor. These transplants occurred over the time period between 2008 and 2016.

The primary objective of this proposal was to compare overall survival, disease-free survival, and GVHD-free relapse-free survival (GRFS) in adult ALL patients transplanted with haploidentical donor with post-transplant cyclophosphamide HCT, matched related donor HCT, and matched unrelated donor HCT. Secondary objectives included comparing hematopoietic recovery, acute and chronic GVHD, and relapse and non-relapse mortality.

It was asked how many additional haploidentical transplant with post-transplant cyclophosphamide patients the EBMT would contribute to the analysis, and though Dr. Ciurea did not know the exact number, he estimated at least one hundred.

There was discussion about whether or not this proposal overlapped with previously published studies, though the consensus was it was not overlapping, especially with the inclusion of the EBMT patients.

As with the other ALL proposal, there was doubt that even a collaborative study between the EBMT and CIBMTR would not be able to overcome the disparity in conditioning regimens between the donor groups. Again, it was suggested that allowing more time for accrual of haploidentical patients may improve the feasibility of this project in a couple of years.

This proposal was not selected.

d. **PROP 1611-62** This proposal was seeking to compare outcomes from haploidentical and matched unrelated donor transplantation for adult MDS patients over the age of 50. Dr. Ben Tomlinson presented this proposal.


The primary objective of this proposal was to compare overall survival in adult MDS patients 50 years or older transplanted with a haploidentical donor or a matched unrelated donor. The secondary objectives included comparing disease-free survival, treatment-related mortality, and GVHD. Additionally, the identification of possible prognostic factors was an aim.

The main concern raised for this proposal was the small sample size available for the haploidentical transplants. The power for analysis would be quite limited with only 88 patients. It was suggested to try using matching in the analysis to limit potential confounding, although Dr. Wang suggested that matching could result in low power, and that it was not always a good option. It was also suggested that allowing more time for the accrual of haploidentical patients would be an option, and that this analysis might be more feasible in a few years.

This proposal was not accepted.
e. **PROP 1611-142** This proposal was seeking to compare outcomes between haploidentical transplants with post-transplant cyclophosphamide and 1-allele mismatched unrelated donor transplants. Dr. Giancarlo Fatobene presented this proposal.


The primary objective of this proposal was to compare overall, disease-free survival, hematopoietic recovery, relapse, graft failure, non-relapse mortality, and GVHD between haploidentical and 1-allele mismatched unrelated donor transplants. A secondary objective was to compare the outcomes by specific loci-mismatches (A, B, C, DRB1, DQ1).

A question was raised that since a previous study looked at matched unrelated donor compared to 1-allele mismatched unrelated donor transplants, would there be anything additional to learn in this study? Dr. Fatobene suggested that some centers continue to favor 1-allele mismatched unrelated donor transplants to haploidentical transplants, so an analysis comparing the two would be clinically relevant. The committee questioned, however, that any findings from this study would be enough impact to change the practices of the centers favoring 1-allele mismatched unrelated donor HCT’s.

Another main concern was why post-transplant cyclophosphamide use was excluded in the 1-allele mismatched unrelated donor group. Though the numbers were not known, it was estimated to be relatively small at this point. It was suggested that including pt-cy mismatched unrelated donors would be important in the analysis based on current trends, and that it might make sense to wait on this study until more cases could be accrued.

This proposal was not accepted.

f. **PROP 1609-04/1611-65/1611-107** These three proposals were all seeking to compare myeloablative versus reduced intensity conditioning in haploidentical transplantation, and were combined into a single proposal. Dr. Scott Solomon presented the proposal on behalf of the other investigators.

The CIBMTR identified 217 MAC and 482 RIC haploidentical transplants for AML/ALL, 18 MAC and 83 RIC haploidentical transplants for MDS, and 26 MAC and 302 RIC haploidentical transplants for NHL/HL. These transplants occurred over the time period between 2008 and 2016.

The primary objective of this proposal was to compare overall and disease-free survival between MAC and RIC haploidentical transplants with post-transplant cyclophosphamide. Secondary objectives included relapse, non-relapse mortality, acute and chronic GVHD, and hematopoietic recovery.

The main concern raised about this proposal was regarding confounding between the two groups. It was brought up that there could be differences in the health of patients receiving MAC and RIC transplants, but Dr. Solomon suggested the usual variables used to control for patient health could be used, such as age, co-morbidities, and KPS.
Another concern was that initially, only the Hopkins regimen was used initially, so there could be confounding. Dr. Wang suggested that propensity scoring could be used to address this.

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

Meeting adjourned at 4:30 pm
Working Committee Overview Plan for 2017-2018

a. **GS15-01**: Optimal donor selection for patients undergoing T-cell replete haplo-identical donor transplantation using post-transplant cyclophosphamide. This study is a priority. Manuscript submission by June 2017.
   **Statistical hours allocated** - Through June 2017: 160; To completion: 160

b. **GS15-02**: Long-term outcomes of 100-day survivors of HCT survivors by donor source. Develop protocol and study file by June 2017, manuscript submission by June 2018.
   **Statistical hours allocated** - Through June 2017: 0; July 2017 - June 2018: 310; To completion: 310

c. **GS15-03**: Disease risk index guided graft source selection (bone marrow or peripheral blood) for allogeneic HCT in adults with leukemia and lymphoma. Protocol development by June 2018.
   **Statistical hours allocated** - Through June 2017: 0; July 2017 - June 2018: 0; To completion: 310

d. **GS16-01**: Bone marrow or peripheral blood grafts for haplo-identical donor transplants: are there differences in outcomes? This study is a priority – it has been submitted. Published by June 2017.
   **Statistical hours allocated** - Through June 2017: 10; To completion: 10

e. **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? This study is a priority - we anticipate developing a protocol and study file by June 2017 and plan on submitting an abstract to the 2017 American Society of Hematology meeting. Manuscript submission by June 2018.
   **Statistical hours allocated** - Through June 2017: 140; July 2017 - June 2018: 70; To completion: 210

f. **GS16-03**: Comparison of outcomes after haplo-identical related donor vs. HLA-matched unrelated donor transplant in patients aged > 50 years. Analysis by June 2017, Manuscript submission by June 2018.
   **Statistical hours allocated** - Through June 2017: 140; July 2017 - June 2018: 150; To completion: 290

   **Statistical hours allocated** - Through June 2017: 0; July 2017 - June 2018: 160; To completion: 310

h. **GS17-02**: Myeloablative versus reduced intensity conditioning in haploidentical transplantation. Analysis by June 2018.
   **Statistical hours allocated** - Through June 2017: 0; July 2017 - June 2018: 160; To completion: 310
<table>
<thead>
<tr>
<th>Oversight Assignments for Working Committee Leadership (March 2017)</th>
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<tbody>
<tr>
<td><strong>Asad Bashey</strong></td>
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<tr>
<td><strong>Ian McNiece</strong></td>
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<td><strong>GS15-02</strong>: Long-term outcomes of 100-day survivors of HCT survivors by donor source.</td>
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<tr>
<td><strong>Vanderson Rocha</strong></td>
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<td><strong>GS16-03</strong>: Comparison of outcomes after haplo-identical related donor vs. HLA-matched unrelated donor transplant in patients aged &gt; 50 years.</td>
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<td><strong>Vanderson Rocha</strong></td>
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<td><strong>GS17-01</strong>: Comparing outcomes between cord blood and haploidentical transplants in patients with acute myeloid leukemia.</td>
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<td><strong>Asad Bashey</strong></td>
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<td><strong>GS17-02</strong>: Myeloablative versus reduced intensity conditioning in haploidentical transplantation.</td>
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Accrual Summary for Graft Sources and Manipulation Working Committee

Characteristics of patients reported to the CIBMTR between 2000 and 2017

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Registration</th>
<th>Research</th>
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<tbody>
<tr>
<td>Number of cases</td>
<td>170041</td>
<td>60577</td>
</tr>
<tr>
<td>Donor type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-identical sibling donor HCT</td>
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<td></td>
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<tr>
<td>Bone marrow</td>
<td>20836 (28)</td>
<td>5463 (28)</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>52383 (71)</td>
<td>13550 (71)</td>
</tr>
<tr>
<td>Umbilical cord blood</td>
<td>504 (1)</td>
<td>213 (1)</td>
</tr>
<tr>
<td>Identical twin donor HCT</td>
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<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>153 (15)</td>
<td>75 (16)</td>
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<tr>
<td>Peripheral blood</td>
<td>855 (84)</td>
<td>398 (84)</td>
</tr>
<tr>
<td>Umbilical cord blood</td>
<td>5 (1)</td>
<td>2 (&lt;1)</td>
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<tr>
<td>HLA mismatched related donor HCT</td>
<td></td>
<td></td>
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<tr>
<td>Bone marrow</td>
<td>3709 (34)</td>
<td>1352 (33)</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>6893 (63)</td>
<td>2515 (62)</td>
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<tr>
<td>Umbilical cord blood</td>
<td>365 (3)</td>
<td>212 (5)</td>
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<tr>
<td>Unrelated donor HCT</td>
<td></td>
<td></td>
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<tr>
<td>Bone marrow</td>
<td>22200 (26)</td>
<td>10580 (29)</td>
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<tr>
<td>Peripheral blood</td>
<td>49435 (59)</td>
<td>17824 (48)</td>
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<tr>
<td>Umbilical cord blood</td>
<td>12703 (15)</td>
<td>8393 (23)</td>
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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

GS15-02: Long term outcomes of 100-day survivors of hematopoietic stem cell transplant by cell source (W Hwang / C Brunstein): The aim of this study is to compare the effect of graft source on long term outcomes of 100-day survivors of hematopoietic stem cell transplantation for acute leukemia. This study was deferred in order to work on the several haploidentical studies. It is currently in protocol development, and we plan to have the data file preparation complete by June 2018.

GS16-02: Outcomes in haploidentical vs matched unrelated donor transplants in older patients (MA Perales/B Tomlinson/M de Lima): This study is looking at outcomes from haploidentical donor transplantation compared to matched unrelated donor transplantation for allogeneic HCT recipients with hematologic malignancies who are 50 years and older. This is currently in manuscript preparation, and we plan to submit this by the end of April 2018.

GS16-03: Donor selection for allogeneic stem cell transplantation: HLA-haploidentical children, siblings, or parents versus HLA-matched siblings (E Fuchs/T Robinson/A Nagler): This study is looking at outcomes from haploidentical donor transplantation based on donor-recipient familial relation. These outcomes will also be compared to outcomes following HLA-identical sibling donor transplantation. This study is currently in manuscript preparation, and we plan to submit this by the end of February 2018.

GS17-01: Comparing outcomes between cord blood and haploidentical transplants in patients with acute myeloid leukemia (R Romee): This study was going to compare transplant outcomes in haploidentical donor transplants for AML compared to cord blood donors. As this has substantial overlap with the GVHD Working Committee study GV16-01, this study was dropped.

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 plan to have this study in manuscript preparation by August 2018.
Study Proposals 1710-20/1711-41/1711-48/1711-68/1711-148

Comparison of alternative donors with post-transplant cyclophosphamide as GVHD prophylaxis

PROP 1710-20 (S Chhabra)

**Title:** For post-transplant cyclophosphamide-based GVHD prophylaxis, is survival after matched unrelated donor allogeneic transplantation better than haploidentical transplantation in Acute Myeloid Leukemia?

PROP 1711-41 (M Gooptu/ R Soiffer)

**Title:** A comparison of outcomes between haploidentical (HI) hematopoietic cell transplantation (HCT) with post-transplant cyclophosphamide (PT/Cy), matched unrelated donor (MUD) HCT with PT/Cy and MUD HCT with calcineurin-inhibitor (CI) based prophylaxis in AML/MDS: A retrospective cohort analysis

PROP 1711-48 (MA Perales)

**Title:** Post-transplant cyclophosphamide overcomes poorer outcomes usually seen with a 7/8 HLA mismatched unrelated donor and expands access to patients without alternative donors including a haploidentical related donor.

PROP 1711-68 (A Mussetti/ M Sanchez del Villar)

**Title:** HLA-mismatch in the setting of PT-CY based anti-GVHD prophylaxis: Is a matched related, matched unrelated, or haploidentical donor still an issue?

PROP 1711-148 (K Adekola/ SR Pingali/ J Galvin/ J Moreira)

**Title:** Use of Post-Transplant Cyclophosphamide in Allogeneic Hematopoietic Stem Cell Transplantation – HLA Mismatched Donors versus Haplo-identical donors versus fully Matched Unrelated Donor versus fully- Matched Related Donors
Table 1. Characteristics of adult patients who underwent first HCT for hematologic malignancy in the US and received post-transplant cyclophosphamide as GVHD prophylaxis, CIBMTR, 2013-2017

<table>
<thead>
<tr>
<th>Variable</th>
<th>Haploidentical</th>
<th>8/8 URD</th>
<th>7/8 URD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1616</td>
<td>124</td>
<td>39</td>
</tr>
<tr>
<td>Age at HCT, years</td>
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<tr>
<td>Median(range)</td>
<td>56 (18-88)</td>
<td>64 (21-82)</td>
<td>62 (26-75)</td>
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<tr>
<td>18 - 30</td>
<td>220 (14)</td>
<td>7 (6)</td>
<td>2 (5)</td>
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<td>31 - 40</td>
<td>172 (11)</td>
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<td>41 - 50</td>
<td>229 (14)</td>
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<td>51 - 60</td>
<td>400 (25)</td>
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<td>61 - 70</td>
<td>493 (31)</td>
<td>59 (48)</td>
<td>17 (44)</td>
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<tr>
<td>&gt; 70</td>
<td>102 (6)</td>
<td>13 (10)</td>
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<tr>
<td>Disease</td>
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<tr>
<td>AML</td>
<td>939 (58)</td>
<td>65 (52)</td>
<td>14 (36)</td>
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<tr>
<td>ALL</td>
<td>315 (19)</td>
<td>11 (9)</td>
<td>10 (26)</td>
</tr>
<tr>
<td>MDS</td>
<td>362 (22)</td>
<td>48 (39)</td>
<td>15 (38)</td>
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Proposal 1710-20

Title:
For post-transplant cyclophosphamide-based GVHD prophylaxis, is survival after matched unrelated donor allogeneic transplantation better than haploidentical transplantation in Acute Myeloid Leukemia?

Saurabh Chhabra, MD, schhabra@mcw.edu, Medical College of Wisconsin

Hypothesis:
We hypothesize that 8/8 HLA-matched unrelated donor (MUD) allogeneic hematopoietic cell transplantation (alloHCT) with post-transplant cyclophosphamide (PTCY)-based GVHD regimen will result in better survival in AML patients than T-cell replete PTCY-based haploidentical transplantation (haploHCT).

Scientific Impact:
The results of the study will have significant clinical implications: if the study conclusively demonstrates that OS is better with PTCY-based MUD alloHCT, it may encourage the use of MUD for alloHCT over haploHCT. On the other hand, if it turns out that there is no significant OS difference between the two groups, it may lend support to the use of more rapidly available haplo donor over MUD for alloHCT.

Specific aims:
Primary aim:
• To compare the overall survival (OS) in patients with receiving MUD alloHCT using PTCY to haploHCT with PTCY

Secondary aims:
• To compare the following outcomes between the two donor groups:
  • Leukemia-free survival (LFS)
  • Relapse rate (RR)
  • Non-relapse mortality (NRM)
  • Cumulative incidence of acute and chronic GVHD

Scientific justification:
Allogeneic hematopoietic cell transplant (HCT) remains the only curative therapy for many hematologic malignancies but it is limited by high non-relapse mortality (NRM), primarily from unpredictable control of graft-versus-host disease (GVHD). Acute myeloid leukemia (AML) is the most frequent indications for alloHCT [1]. Disease status and donor source are major determinants of outcomes for alloHCT. For patients with acute myeloid leukemia (AML) needing alloHCT, an HLA-matched sibling donor is considered the most optimal donor source [2]. An unrelated adult donor who is HLA-matched to the recipient at the allele-level (at HLA-A, -B, -C, and -DRB1) is considered the best alternative in the absence of an HLA-matched sibling [3]. When a matched sibling is not available, a matched unrelated donor (MUD) is considered the best alternative. The GVHD prophylaxis used most commonly in HCT is a calcineurin inhibitor (CNI) combined with a short course of methotrexate, which, in an unrelated donor setting, is often supplemented by antithymocyte globulin (ATG). Even so, 30% to 80% of allogeneic HCT patients will develop GVHD, suggesting that development of strategies to control this complication is key to broadening its clinical applicability [4].
For patients without a matched sibling donor or MUD, haploidentical donor is particularly attractive because it promises almost universal donor availability. Although the historically high transplant-related mortality, mostly because of delayed immune reconstitution, used to be a barrier to success in haploidentical donor related transplantation (haploHCT) [2], outcomes have significantly improved with the advent of high-dose post-transplantation cyclophosphamide (PTCY). HaploHCT performed using extensive in vivo or ex vivo T-cell depletion to prevent GVHD is associated with higher non-relapse mortality (NRM) and delayed immune reconstitution [5]. CY given post-HCT is a promising approach can be safely administered in high doses after alloHCT without hematopoietic stem cell toxicity, but targeting early-proliferating alloreactive T cells involved in GVHD onset [6, 7] and relatively sparing regulatory T cells and hematopoietic stem cells [8-10]. Patients treated in this manner usually receive standard post-transplant immune suppression with a CNI and mycophenolate mofetil (MMF) as well. The promising results of PTCY have invited retrospective comparisons of these haploHCT with those performed using MUD and have suggested similar survival outcomes for haploHCT using PTCY compared with MUD [11]. Three recent registry studies of lymphoid malignancies (two from the Center for International Blood and Marrow Transplant Research [CIBMTR] and another from EBMT) also suggested similar survival outcomes with lower incidence of chronic GVHD for haploHCT using PTCY compared with MRD and MUD transplantations [5, 12, 13]. A CIBMTR study [3] comparing transplantation outcomes after haploHCT using PTCY approach to those after MUD alloHCT in adults with AML confirm that in both the myeloablative and reduced intensity setting, OS after haploHCT was comparable to that after MUD alloHCT for AML although acute and chronic GVHD rates were higher with MUD alloHCT. Acute and chronic GVHD are lower when PTCY is used for GVHD prophylaxis.

A prospective single-center study suggested the superiority of PTCY-based approach over conventional CI-based prophylaxis for MUD alloHCT [14]: 86 patients with ALL and AML underwent MUD alloHCT using PTCY, tacrolimus, and MMF as GVHD prophylaxis. The control group comprised 125 consecutive historical control patients who received ATG, tacrolimus, and methotrexate or MMF. Cumulative incidences of grades II to IV, grades III to IV acute and chronic GVHD were significantly lower in the PTCY compared with the ATG group. PTCY-based prophylaxis was associated with reduced incidence of NRM and improved OS, event-free survival and GVHD/relapse-free survival.

While there is retrospective evidence for equivalent OS between haploHCT (PTCY-based) and MUD alloHCT (CNI-based) [3] and some evidence for superiority of PTCY-based MUD alloHCT over CNI-based MUD alloHCT [14], no comparisons have been reported between outcomes after PTCY-based MUD alloHCT and those after PTCY-based T-cell replete haploHCT. So, we propose a CIBMTR study to answer the question whether MUD alloHCT using PTCY for GVHD prophylaxis improves OS in patients with AML in remission compared to T cell-replete haploHCT, attributable to lower NRM and/or lower relapse risk after MUD compared to haploHCT. To put it differently, this study will try to answer the question whether PTCY can negate the effect of HLA disparity and result in the similar survival outcomes after both haploHCT and MUD alloHCT.

If Haplo-PTCY = MUD-CNI for OS,

And if MUD-PTCY > MUD-CNI for OS,

Is MUD-PTCY > Haplo-PTCY for OS?
Study population:
Inclusion criteria:
- AML patients, aged ≥18 years, undergoing first alloHCT using T-replete graft
- In CR1 or CR2 at HCT
- Using MA or RIC conditioning
- PTCY containing GVHD prophylaxis
- Peripheral blood or bone marrow
- 8/8 (HLA-A, -B, -C, and -DRB1) unrelated or haplo-identical donors

Exclusion Criteria:
- Patients undergoing graft manipulation strategies such as ex vivo T-cell depletion, CD34+ selection
- AML transplanted in relapse or primary induction failure.
- ATG or alemtuzumab containing regimens

References:
Proposal 1711-41

Title:
A comparison of outcomes between haploidentical (HI) hematopoietic cell transplantation (HCT) with post-transplant cyclophosphamide (PT/Cy), matched unrelated donor (MUD) HCT with PT/Cy and MUD HCT with calcineurin-inhibitor (CI) based prophylaxis in AML/MDS: A retrospective cohort analysis

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Robert Soiffer, MD, Robert_soiffer@dfci.harvard.edu, Dana-Farber Cancer Institute

Hypothesis:
HI HCT using PT/Cy as GVHD prophylaxis has resulted in similar survival outcomes, but superior acute and chronic GVHD outcomes compared to CI-based prophylaxis in MUD HCT(Ciurea et al, 2015). It is not entirely clear at this time, if this solely due to PT/Cy, although this is the proposed hypothesis. Further, it is not known if PT/Cy is better or worse than CI-based prophylaxis in the MUD setting. Finally, it is unclear if graft-versus-leukemia (GVL) effect is greater with a HI compared to a HLA-matched donor (in fact the concern has been greater relapses clinically with HI HCT). Thus, the optimal transplant strategy which minimizes both relapse and GVHD, in the absence of a MRD, is an open question

We hypothesize that acute and chronic GVHD outcomes are better with any approach using PT/Cy compared to CI-based prophylaxis. We further hypothesize that, disease-free survival (DFS) is superior or equivalent in patients undergoing MUD HCT using PT/Cy for AML/MDS, compared to the other two approaches.

Scientific impact:
In the absence of a HLA-matched donor, HI HCT using PT/Cy has become an important transplantation platform in AML and MDS. Acute and chronic GVHD rates have been found to be superior to MUD HCT using calcineurin-inhibitor (CI) based prophylaxis in some studies(Ciurea et al, 2015). It is unclear if this is solely attributable to PT/Cy, although this is the current hypothesis. PT/Cy has consequently been adopted in HLA-matched HCT and a large RCT is currently comparing non-CI based GVHD prophylaxis approaches (namely PT/Cy and T-cell depletion) with CI-based prophylaxis (BMT CTN #1301) (NCT02345850). In addition, although an enhanced graft versus leukemia (GVL) effect has been postulated in HI HCT, so far relapse rates have been increased or equivalent to MUD HCT(Ciurea et al, 2015; Luznik et al, 2010; Ringdén et al, 2016). Thus, the optimal transplant strategy to minimize both relapse and GVHD, in the absence of a MRD, is an open question. We propose to compare outcomes between HI HCT with PT/Cy, MUD HCT with PT/Cy and MUD HCT with CI-based prophylaxis, for AML/MDS, to help clarify this question.

Specific aims:
Primary objective: To compare disease-free survival (DFS) among patients undergoing HI HCT using PT/Cy, MUD HCT using PT/Cy and MUD HCT using CI-based prophylaxis, for AML/MDS patients, separately in the myeloablative (MA) and reduced-intensity (RIC) setting
Secondary Objective: To investigate the differences in incidence and severity of acute and chronic graft-versus-host-disease (GVHD), overall survival (OS) and GVHD relapse free survival (GRFS) in the three study cohorts
Scientific justification:
HCT remains the major consolidative and only potentially curative therapy in AML and MDS. The availability of a donor is the key limiting step in the transplant process. Matched related donors (MRD) are found for approximately 25-30% of patients. In the absence of a MRD, a matched unrelated donor (MUD) is usually sought, a process which typically delays the transplant by a few months, allowing a window for disease relapse. Furthermore, certain ethnic groups are poorly represented in the unrelated registries. Consequently, alternative donor transplants, particularly HI transplants utilizing PT/Cy, have emerged as a more readily available donor option and can now be performed safely and effectively (Luznik et al., 2008; Luznik & Fuchs, 2010).

The induction of immunologic tolerance by cyclophosphamide was elegantly demonstrated initially in mouse models by different investigators (Mayumi et al., 1986; Berenbaum & Brown, 1963). Investigators at Johns Hopkins first showed that non-myeloablative HI HCT with PT/Cy (50mg/kg on days +3 and +4 or only +3) resulted in acceptable engraftment with 2-year OS of 36%, cumulative incidence (CI) of NRM of 15% and relapse 51% at 1 year. (Luznik et al., 2008). Numerous subsequent studies have confirmed that PT/Cy is an effective and safe GVHD prophylaxis strategy. Myeloablative HI HCT with PT/Cy has also been safely performed with promising results (Solomon et al., 2014). In the largest myeloablative experience from Hopkins, using PT/Cy, tacrolimus and mycophenolate mofetil as GVHD prophylaxis, the 2-year OS was 57%, CI of relapse at 3 years was 44%, aGVHD (grade II-IV) at day 100 was 17% and II-IV 7% and cGVHD at 6 months was 16% (Symons et al., 2015). GVHD outcomes with this transplant platform appeared better than with HLA-matched transplant using CI-based prophylaxis. There has been a suggestion of enhanced GVL with HI donors, however this has not been proven clinically so far (Ringdén et al., 2016).

The promising results with PT/Cy in HI HSCT, has led to its adoption as a GVHD prophylaxis strategy (instead of CI-based prophylaxis), even in MRD and MUD HSCT. Luznik et al studied 117 patients (MRD=78, MUD=39) undergoing myeloablative HSCT with PT/Cy/CI/mycophenolate and found the actuarial 2-year OS was 55% for all patients, NRM at 2 years was 17%. The incidences of aGVHD grade II-IV was 43%, grade II-IV 10% and cGVHD 10% (median follow-up of 26.3 months). CI of relapse at 2 years was 44% (Luznik et al., 2010). A subsequent multi-institutional study found similar results with 2-year OS of 67% (Kanakry et al., 2014). Despite a somewhat higher CI of relapse than would be expected from HLA-matched HCT, the GVHD rates were reassuring. Consequently, PT/Cy is being compared to standard CI-based GVHD prophylaxis in a large randomized controlled trial of matched donors (MRD and MUD) (BMT CTN #1301) (NCT02345850), the results of which are eagerly awaited.

HI HCT using PT/Cy has never been compared head to head with MUD HCT using PT/Cy. However, in a large retrospective CIBMTR analysis comparing HI HSCT with PT/Cy with MUD HSCT using standard CI-based GVHD prophylaxis, OS was similar (45% vs 50%, p=0.38) (Ciurea et al., 2015). Furthermore, in the myeloablative setting, aGVHD (grade II-IV) at 3 months was better in the HI arm (16% vs 33%, P < .0001), as was 3-year chronic GVHD (30% vs 53%, P < .0001). Interestingly there was no difference in relapse rates at 3 years in the two arms (44% versus 39%, p=0.36). Although not an RCT, this suggested that HI HCT using PT/Cy could provide equivalent survival and superior GVHD outcomes compared to conventional MUDs, without compromising relapse risk.

In summary, it is not entirely clear at this time if the superior GVHD outcomes in HI HSCT using PT/Cy is strictly due to PT/Cy, although this is the likely hypothesis. There is also no clear evidence that GVL is greater with a HI donor or whether PT/Cy is better or worse than CI-based prophylaxis in the MUD.
setting. Thus, the optimal transplant strategy which minimizes both relapse and GVHD, in the absence of a MRD, is an open question. We propose to compare outcomes in HI HCT with PT/Cy, MUD HCT with PT/Cy and MUD HCT with standard CI-based prophylaxis for AML/MDS, which we hope, will help clarify this question. We propose to conduct separate analyses for MA and RIC HCT.

Study population:
All patients >18 years of age, with AML or MDS, who underwent first HSCT (using peripheral blood stem-cells or bone marrow) from 2008 to present, with MUD or HI donors using PT/Cy alone or with CI and mycophenolate or CI-based prophylaxis alone. Patients should have had 12 months of follow-up, and captured in the CIBMTR database.

Data requirements:
Clinical variables required from the database will include patient age, gender, ethnicity, HCT-CI, DRI, cytogenetic risk status for AML, IPSS for MDS, disease status (first complete remission or CR1/second CR or CR2/active disease), minimal residual disease status (when available), conditioning regimen, GVHD prophylaxis strategy, stem-cell source (bone marrow versus peripheral blood), incidence and grade of acute GVHD, incidence of stage of chronic GVHD, CMV donor-recipient serostatus, CMV reactivation with end-organ involvement, organ toxicity (type and grade), use of ATG and transplant center.

Study design:
The design of our study is a retrospective cohort analysis comparing the outcomes of DFS primarily, and OS, GRFS and acute and chronic GVHD (secondarily), between patients in these three cohorts.

References:


Proposal 1711-48

Title:
Post-transplant cyclophosphamide overcomes poorer outcomes usually seen with a 7/8 HLA mismatched unrelated donor and expands access to patients without alternative donors including a haploidentical related donor.

Miguel-Angel Perales, MD, peralesm@mskcc.org, Memorial Sloan Kettering Cancer Center

Hypothesis:
Using post-transplant cyclophosphamide overcomes poorer outcomes usually seen with a 7/8 HLA mismatched unrelated donor compared to 8/8 MUDs. Furthermore, it expands access to HCT by providing a good option for patients without a matched donor or a haploidentical related donor. Finally, it may allow broader donor selection based on other criteria such as KIR, for example.

Specific aims:
The specific aims are:
- Assess outcomes in 3 cohorts of patients: 1) recipients of 7/8 HLA mismatched donor with post-transplant cyclophosphamide; 2) recipients of 7/8 HLA mismatched donor using standard CNI-based prophylaxis and 3) recipients of haploidentical donors using post-transplant cyclophosphamide.
- General Outcomes to be examined include:
  - Engraftment (neutrophil, platelet), graft failure
  - NRM
  - acute GVHD (II-IV and II-IV)
  - chronic GVHD
  - relapse/progression
  - PFS/DFS
  - OS

Scientific justification:
Availability of an HLA-identical sibling (MRD) or suitably matched unrelated donor (MUD) has historically been a limiting factor in the application of allogeneic hematopoietic transplantation. Although almost all patients have an HLA-haploidentical family donor, it has only been recently with the introduction of by the Johns Hopkins group of the use of T-cell replete grafts and post-transplant cyclophosphamide (Haplo-post-HCT-CY) that this approach has yielded consistently positive outcomes (1-6). NRM rates of < 10% are usual and rapid reconstitution of immunity leads to a low rate of post-transplant infections. Although there has been significant uptake in the use of Haplo-post-HCT-CY, questions remain. In particular, not all patients will have a suitable haploidentical donor and in some cases the availability of multiple donors may allow selection based on additional criteria such as CMV status, KIR etc. We propose to compare outcomes in 3 cohorts of patients: 1) recipients of 7/8 HLA mismatched donor with post-transplant cyclophosphamide (7/8-PTCY); 2) recipients of 7/8 HLA mismatched donor using standard CNI-based prophylaxis (7/8-CNI); and 3) recipients of haploidentical donors using post-transplant cyclophosphamide (Haplo-PTCY). The 7/8-PTCY cohort is being tested in 2 prospective trials: 1) PTCY arm of BMT CTN 1203 included 7/8 donors (submitted to ASH); and 2) the ongoing CIBMTR 15-MMUD is specifically includes mismatched unrelated donors. Comparing 7/8-PTCY to 7/8-CNI will demonstrate that using PTCY results in superior outcomes to CNI-based GVHD prophylaxis. Comparing
7/8-PTCY to Haplo-PTCY will show similar results and demonstrate that using a mismatched unrelated donor with the right GVHD prophylaxis is a viable transplant option.

**Study population:**
This study will include adult patients with hematologic malignancies who received a first allogeneic using a 7/8 HLA mismatched donor with post-transplant cyclophosphamide, 7/8 HLA mismatched donor using standard CNI-based prophylaxis, or a haploidentical donor using post-transplant cyclophosphamide between 01/2008 and 12/2016.

Inclusion criteria:
- first allo-HCT between 2008 and 2016
- a 7/8 HLA mismatched donor with post-transplant cyclophosphamide, 7/8 HLA mismatched donor using standard CNI-based prophylaxis (tacro/CSA), or a haploidentical donor using post-transplant cyclophosphamide
- GVHD prophylaxis as noted – exclude ATG

**Data requirements:**
Utilizing data collected by CIBMTR from pre and post HCT, which includes pre-transplant essential data form #2400, post-transplant essential data form #2450, chimerism studies form #2451, selective post-transplant selective data form #2455 and 100 day post-HSCT data form #2100. The parameters to be assessed are outlined in table 1 below.

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<td>• Graft failure (primary and secondary)</td>
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GVHD

- Acute GVHD (aGVHD)
  - Incidence of grade II-IV acute GVHD (aGVHD) (subset evaluating grade III-IV aGVHD)
  - Time to aGVHD
- GVHD after day 100
  - Incidence of chronic GVHD (cGVHD)
  - Severity of GVHD after day 100

Mortality

- Time to mortality
- Day 100, 6 months and 1 year mortality
- Treatment related mortality at 6 months and 1 year
- Cause of mortality

Disease relapse

- Incidence of disease relapse
- Time to disease relapse

Study design:
A retrospective study will be conducted utilizing CIBMTR data. Patients will be eligible for inclusion if they received a first allogeneic HCT using a 7/8 HLA mismatched donor with post-transplant cyclophosphamide, 7/8 HLA mismatched donor using standard CNI-based prophylaxis (tacro/CSA), or a haploidentical donor using post-transplant cyclophosphamide. The objectives of this analysis are to determine outcomes in the 3 cohorts.

References:
Proposal 1711-68

Title:
HLA-mismatch in the setting of PT-CY based anti-GVHD prophylaxis: Is a matched related, matched unrelated, or haploidentical donor still an issue?

Alberto Mussetti, MD, alberto.mussetti@istitutotumori.mi.it, Istituto Nazionale dei Tumori di Milano
Matias Sanchez del Villar, MD, msanchez@alemana.cl., Clinica Alemana de Santiago

Hypothesis:
Our hypothesis is that a PT-Cy based strategy could neutralize differences between donors. If this will be confirmed, prospective studies addressing the same question could be made in order to possibly reduce the need for a MUD. This could dramatically reduce the time required to find a donor without a negative impact on transplant clinical outcomes.

Scientific impact:
Post-transplant Cyclophosphamide (PT-Cy) has recently emerged as an effective anti-GVHD prophylaxis. Its first clinical use was tested in the setting of haploidentical allogeneic hematopoietic cell transplantation (alloHCT). First studies by the Baltimore group showed an impressive reduction of cGVHD incidence when using PT-Cy plus tacrolimus/MMF. Extensive chronic GVHD ranging from 5% to 10% in the haploidentical setting was so promising that lead to the worldwide application of this very feasible anti-GVHD prophylaxis. After the confirmation of these results on larger cohorts of patients, haploidentical alloHCT with PT-Cy was compared to alloHCT from matched unrelated donor (MUD) and standard anti-GVHD prophylaxis in retrospective analysis in both myeloid and lymphoid malignancies. Surprisingly, haploidentical alloHCT groups had less cGVHD than alloHCT using MUD with standard anti-GVHD prophylaxis (tacrolimus/cyclosporine + methotrexate). Despite recent reports regarding outcome differences based upon graft source or conditioning regimen intensity, there are still several areas of uncertainty in the PT-Cy setting. In particular, there is a current interest in defining the influence of donor characteristics and graft cell composition on survival outcomes. A provocative study by Kasamon et al. showed that HLA-mismatch degree is not influencing clinical outcomes in the haploidentical alloHCT setting. We recently reported that neither donor characteristics (sex, age, donor-recipient relationship) have a strong influence in this setting (data will be presented at ASH 2017). Thus, current studies suggest that PT-Cy anti-GVHD prophylaxis could neutralize differences in terms of type of donor and HLA-mismatches.

A formal comparison between matched related donor (MRD) vs MUD vs haploidentical donor when using a PT-Cy based anti-GVHD prophylaxis has never been performed.

Our study could address for the first time if the type of donor (MRD vs MUD vs haploidentical) is still a matter when a PT-Cy based strategy is used.

Specific aims:
Primary aim:
• cGVHD: maximum extent of chronic GVHD, and time to cGVHD

Secondary aim:
• Hematopoietic recovery: time to neutrophil (ANC) recovery ≥0.5x10⁹/l; time to platelet recovery ≥ 20x10⁹/L
  • PFS: survival without progression. Patients are censored at time of last contact
- aGVHD: maximum overall grade of grade II-IV acute GVHD, we do not collect date of onset of acute GVHD
- RI: Time of relapse of the original malignancy post allo-HCT
- TRM: time to death without disease relapse
- OS: events are death from any cause. Surviving patients are censored at time of last contact
- Primary cause of death: according to Copelan algorithm, descriptive only

**Study population:**
This study will include adult patients of 18-70 years who received first allo-HCT between 01/2008 and 12/2015 for hematological malignancies using a MRD, MUD or haploidentical donor. AntiGVHD prophylaxis will be limited to PT-Cy based strategies. Three groups will be compared: MRD vs MUD vs haploidentical donors.

**Inclusion criteria for haploidentical cohort:**
- first allo-HCT in USA between 2008 and 2015
- Age 18-70 years old
- Graft manipulation with PT-Cy based strategy only as antiGVHD prophylaxis

**Inclusion criteria for MRD/MUD cohort:**
- first allo-HSCT in USA between 2008 and 2015
- Age 18-70 years old
- MRD or MUD
- >9/10 HLA matches
- Graft manipulation with PT-Cy based strategy only as antiGVHD prophylaxis

Both myeloablative and reduced intensity conditioning regimen will be included. Use of peripheral blood stem cells or bone marrow stem cells as a graft will be considered for the study. Recipients of prior allografts, non-malignant disease, leukemia in morphologic relapse or refractory disease will be excluded.

**Data requirements:**
Utilizing data collected by CIBMTR from pre and post HCT, which includes pre-transplant essential data form #2400, post-transplant essential data form #2450, selective post-transplant selective data form #2455 and 100 day post-HCT data form #2100, Six Months to Two Years Post-HCT Data #2200. The parameters to be assessed are outlined in table 1 below.

**Table 1 Data Requirements:**
Utilizing data collected by CIBMTR from pre and post HSCT, which includes pre-transplant essential data form #2400, post-transplant essential data form #2450, chimerism studies form #2451, selective post-transplant selective data form #2455 and 100 day post-HSCT data form #2100. The parameters to be assessed are outlined in table 1 below.
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</tr>
<tr>
<td></td>
<td>Reduced Intensity/ non-myeloablative</td>
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</tr>
<tr>
<td>GVHD prophylaxis</td>
<td>PT-Cy based + other (e.g. tacrolimus/MMF; CSA/MMF)</td>
<td></td>
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<tr>
<td>Graft characteristic</td>
<td>PBSC, BM</td>
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<table>
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<tr>
<th>Outcome Measures</th>
<th>Engraftment</th>
<th>Time to absolute neutrophil count ≥500 cells/mm³ for 3 consecutive laboratory readings</th>
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<tbody>
<tr>
<td></td>
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<td>Time to unsupported platelets ≥20 x 10⁸ cells/L and ≥50 x 10⁹ cells/L</td>
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<tr>
<td></td>
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<td>Donor-recipient chimerism</td>
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<tr>
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<td>For double-unit CBT recipients (initial engraftment of 1 unit vs 2 units)</td>
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<td>Graft failure (primary and secondary)</td>
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<table>
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<tr>
<th>GVHD</th>
<th>Acute GVHD (aGVHD)</th>
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<tr>
<td></td>
<td>Incidence of grade II-IV acute GVHD (aGVHD)</td>
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<tr>
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<td>(subset evaluating grade III-IV aGVHD)</td>
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<td></td>
<td>Time to aGVHD</td>
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<td></td>
<td>GVHD after day 100</td>
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<tr>
<td></td>
<td>Incidence of chronic GVHD (cGVHD)</td>
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<td>Severity of GVHD after day 100</td>
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<table>
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<tr>
<th>Mortality</th>
<th>Time to mortality</th>
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<tr>
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<td>Day 100, 6 months and 1 year mortality</td>
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<tr>
<td></td>
<td>Treatment related mortality at 6 months and 1 year</td>
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<td>Cause of mortality</td>
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<table>
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<tr>
<th>Disease relapse</th>
<th>Incidence of disease relapse</th>
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<td></td>
<td>Time to disease relapse</td>
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<table>
<thead>
<tr>
<th>Immune reconstitution</th>
<th>Incidence of EBV PTLD</th>
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<tbody>
<tr>
<td></td>
<td>Recovery of ALC, CD3+4+, CD3+8+ T lymphocytes</td>
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**Study design:**
A retrospective multicenter study will be conducted utilizing CIBMTR data. Patients will be eligible if they satisfied the criteria detailed in the “Patient eligibility population” section. Patients will then be stratified according to MRD/MUD or haplo-PTCy. The objective of this analysis is to compare these three approaches and their effects on allo-HCT outcomes.
References:
Proposal 1711-148

Title:
Use of Post-Transplant Cyclophosphamide in Allogeneic Hematopoietic Stem Cell Transplantation – HLA Mismatched Donors versus Haplo-identical donors versus fully Matched Unrelated Donor versus fully-Matched Related Donors

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Sai Ravi Pingali, MD, spingali@houstonmethodist.org, Baylor College of Medicine, Houston, TX
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Jonathan Moreira, MD, jonathan.moreira@northwestern.edu, Robert H. Lurie Comprehensive Cancer Center, Northwestern University

Hypothesis:
1. The inclusion of post-transplant cyclophosphamide as GVHD for patients with HLA mismatched donors leads to similar outcomes compared to patients who get a haplo-identical or other (related or unrelated) allogeneic stem cell transplant (HSCT)
2. There are similar outcomes in regards to GVHD in patients who get post-transplant cyclophosphamide regardless of the presence of donor HLA mismatch

Specific aims:
• To describe outcomes in patients who received post –transplant cyclophosphamide as part of GVHD prophylaxis in patients who had a HLA-mismatched donor versus haplo-identical donor versus other (MUD/MRD) donor allogeneic stem cell transplantation
• To describe and evaluate disease characteristics and characteristics of patients greater than 18 years old with hematologic malignancies that received post-transplant cyclophosphamide as part of their GVHD prophylaxis
• To evaluate survival outcomes, incidence and severity of acute and chronic GVHD, relapse rate and graft failure rates in patients who received post-transplant cyclophosphamide as part of their GVHD prophylaxis regimen.

Scientific justification:
Cyclophosphamide, historically was one of the first chemotherapy agents used as a preparative regimen for bone marrow transplantation given its immunosuppressive properties (1-5). In recent times it has also been re-invented as an agent to be used in the post- preparative regimen of stem cell transplantation as prophylaxis against GVHD (6-8). This was initially in the setting of a haplo-identical stem cell transplant (7). The use of post-transplant cyclophosphamide has been reported to result in comparable outcomes in patients who get a haplo-identical stem cell transplant compared to HLA matched related and unrelated donor stem cell transplantation(8-10). Specifically there has been an improvement in GVHD outcomes and subsequently non-relapse mortality for patients undergoing a haplo-identical stem cell transplant (11). This is very important because GVHD outcomes correlate with stem cell transplant recipient’s quality of life long-term.

Human Leukocyte antigen (HLA) histocompatibility is the most important factor to consider in a patient undergoing an allogeneic stem cell transplant. It has been shown that presence of HLA mismatch even at a single antigen increases the risk of non-relapse mortality associated with graft versus host disease (12, 13). This is regardless of whether the donor is related or unrelated. The ability to mitigate this risk in
patients getting a haplo-identical stem transplant by the use of cyclophosphamide post-transplant has revolutionized this type of stem cell transplant. As discussed above it has been shown that patients undergoing haplo-identical stem cell transplantation have similar outcomes compared to patients who undergo HLA matched related or unrelated donor stem cell transplantation. It has also been shown that certain types of HLA-mismatch for e.g. a mismatch at HLA-C antigen is associated with inferior outcomes compared to patients with HLA mismatch at HLA- A or HLA-B (14). It is therefore of importance to determine if the use of post-transplant cyclophosphamide in the post-preparative regimen mitigates this risk in different types of HLA mismatch be they be related or unrelated. It will also be important to determine if there are certain HLA mismatches that predict for worse outcomes in terms of risk of acute and chronic GVHD, relapse rates or graft failure, when post-transplant cyclophosphamide in used.

There is evidence that shows that post-transplant cyclophosphamide is not only being used in the haplo-identical transplantation setting, but also in other types of HLA mismatch ( related or unrelated), single or more(15, 16). We hypothesize that patient outcomes with different degrees of HLA mismatch will be similar to outcomes obtained in the haplo-identical stem cell transplantation setting. The ability to extend the donor pool by increasing the number of eligible donors for transplants that can safely be done without adverse outcomes in regards to graft versus host disease, relapse rate and graft failure presents an exciting prospect. This study will guide investigators when making decisions about donor eligibility in terms of HLA matching and could potentially lead to expansion of the donor pool for patients who need an allogeneic stem cell transplant.

**Study population:**
- All patients, age 18 years and older with a diagnosis of a hematologic malignancy
- Patients who received post-transplant cyclophosphamide as GVHD prophylaxis
- Received hematopoietic transplant from 2011 to 2017
- All donor sources are eligible – haplo-identical, all HLA-mismatch, MUDs, MSDs
- All transplant regimens are eligible

**Data requirements:**
- CIBMTR forms required to carry out this proposed study:
  - Recipient Baseline Data
  - Confirmation of HLA-typing
  - Post-HSCT Data
  - Acute Myelogenous Leukemia Pre-HCT Data
  - Acute Lymphoblastic Leukemia Pre-HCT Data
  - Chronic Myelogenous Leukemia Pre-HCT Data
  - Chronic Lymphocytic Leukemia Pre-HSCT Data
  - Myelodysplasia / Myeloproliferative Disorders Pre-HCT Data
  - Multiple Myeloma / Plasma Cell Leukemia Pre-HCT Data
  - Hodgkin and Non-Hodgkin Lymphoma Pre-HCT Data
  - Acute Myelogenous Leukemia Post-HCT Data
  - Acute Lymphoblastic Leukemia Post-HCT Data
  - Chronic Myelogenous Leukemia Post-HCT Data
  - Chronic Lymphocytic Leukemia Post-HSCT Data
  - Myelodysplasia / Myeloproliferative Disorders Post-HCT Data
  - Multiple Myeloma / Plasma Cell Leukemia Post-HCT Data
  - Hodgkin and Non-Hodgkin Lymphoma Post-HCT Data
• Pre-Transplant Essential Data: Disease Classification
• Post-Transplant Essential Data
• Recipient Death Data

Study design:
This is a retrospective study with review of CIBMTR database. Plan will be to analyze patients who received post-transplant cyclophosphamide as part of their GVHD prophylaxis who meet the inclusion criteria.

References:
Study Proposals 1711-51/1711-84/1711-91/1711-99

Comparison of alternative donor transplant for MDS and MPS

**PROP 1711-51** (A Viswabandya/ S Manjappa/ V Gupta/ R Romee)

**Title**: Outcomes of Allogeneic Stem Cell Transplantation with Alternate Donors (Haploidentical or Cord Blood) compared with Matched Unrelated Donor Transplant among Patients with Myelofibrosis.

**PROP 1711-84** (B Tomlinson/ T Nishihori/ M de Lima)

**Title**: Alternative donor allogeneic stem cell transplant in patients with myelodysplastic syndrome over the age of 50

**PROP 1711-91** (M Grunwald/ N Ghosh/ E Copelan)

**Title**: Comparison of Outcomes with Haploidentical and Matched Unrelated Donors for Hematopoietic Stem Cell Transplantation in Myelodysplastic Syndromes

**PROP 1711-99** (H Elmariah/ A Dezerni/ FJ Bolanos-Meade)

**Title**: Outcomes of HLA-haploidentical Allogeneic Blood or Marrow Transplantation with Post-Transplant Cyclophosphamide for Myeloproliferative Neoplasms and Myelodysplastic Syndrome/Myeloproliferative Neoplasm Overlap Syndromes
Table 1. Characteristics of patients who underwent first HCT for MDS/MPS in the US and reported to the CIBMTR, 2012-2017

<table>
<thead>
<tr>
<th>Variable</th>
<th>Haploidentical</th>
<th>8/8 URD</th>
<th>7/8 URD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>373</td>
<td>1644</td>
<td>248</td>
</tr>
<tr>
<td>Age at HCT, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median(range)</td>
<td>63 (20-78)</td>
<td>66 (20-83)</td>
<td>64 (18-81)</td>
</tr>
<tr>
<td>18 - 30</td>
<td>11 (3)</td>
<td>13 (&lt;1)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>31 - 40</td>
<td>6 (2)</td>
<td>24 (1)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>41 - 50</td>
<td>39 (10)</td>
<td>69 (4)</td>
<td>22 (9)</td>
</tr>
<tr>
<td>51 - 60</td>
<td>93 (25)</td>
<td>361 (22)</td>
<td>58 (23)</td>
</tr>
<tr>
<td>61 - 70</td>
<td>186 (50)</td>
<td>945 (57)</td>
<td>127 (51)</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>38 (10)</td>
<td>232 (14)</td>
<td>31 (13)</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA/RARS/RCMD</td>
<td>63 (17)</td>
<td>393 (24)</td>
<td>65 (26)</td>
</tr>
<tr>
<td>RAEB-1/RAEB-2</td>
<td>150 (40)</td>
<td>598 (36)</td>
<td>90 (36)</td>
</tr>
<tr>
<td>5q-syndrome</td>
<td>4 (1)</td>
<td>14 (&lt;1)</td>
<td>5 (2)</td>
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<tr>
<td>MDS - not specified</td>
<td>68 (18)</td>
<td>248 (15)</td>
<td>32 (13)</td>
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<tr>
<td>CMMoL</td>
<td>44 (12)</td>
<td>130 (8)</td>
<td>19 (8)</td>
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<tr>
<td>Polycythemia vera</td>
<td>13 (3)</td>
<td>70 (4)</td>
<td>6 (2)</td>
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<tr>
<td>Myelofibrosis</td>
<td>22 (6)</td>
<td>158 (10)</td>
<td>27 (11)</td>
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<tr>
<td>MPS - not specified</td>
<td>9 (2)</td>
<td>33 (2)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Graft type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>125 (34)</td>
<td>176 (11)</td>
<td>24 (10)</td>
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<tr>
<td>Peripheral blood</td>
<td>248 (66)</td>
<td>1468 (89)</td>
<td>224 (90)</td>
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<tr>
<td>Umbilical cord blood</td>
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<td>NA</td>
<td>NA</td>
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<tr>
<td>Conditioning intensity</td>
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<tr>
<td>Myeloablative</td>
<td>110 (29)</td>
<td>549 (33)</td>
<td>75 (30)</td>
</tr>
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<td>RIC/NMA</td>
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<td>1095 (67)</td>
<td>173 (70)</td>
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<tr>
<td>Myeloablative regimens</td>
<td></td>
<td></td>
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<tr>
<td>TBI + Cy + Flud</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>TBI + Cy</td>
<td>3 (&lt;1)</td>
<td>17 (1)</td>
<td>4 (2)</td>
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<tr>
<td>TBI + Flud</td>
<td>29 (8)</td>
<td>5 (&lt;1)</td>
<td>0</td>
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<tr>
<td>Bu + Cy</td>
<td>30 (8)</td>
<td>133 (8)</td>
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<tr>
<td>Bu + Flud</td>
<td>32 (9)</td>
<td>382 (23)</td>
<td>48 (19)</td>
</tr>
<tr>
<td>Flud + Mel</td>
<td>15 (4)</td>
<td>12 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Reduced intensity regimens</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>TBI + Cy + Flud</td>
<td>218 (58)</td>
<td>22 (1)</td>
<td>4 (2)</td>
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<td>Variable</td>
<td>Haploidentical</td>
<td>8/8 URD</td>
<td>7/8 URD</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>TBI + Cy</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>TBI + Flud</td>
<td>25 (7)</td>
<td>167 (10)</td>
<td>29 (12)</td>
</tr>
<tr>
<td>Bu + Flud</td>
<td>4 (1)</td>
<td>475 (29)</td>
<td>65 (26)</td>
</tr>
<tr>
<td>Flud + Mel</td>
<td>15 (4)</td>
<td>430 (26)</td>
<td>75 (30)</td>
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GVHD prophylaxis

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<th></th>
<th>PT-Cy + CNI + MMF</th>
<th>CNI + MMF</th>
<th>CN + MTX</th>
<th>CNI alone</th>
<th>Other</th>
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<tr>
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<td>373</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>392 (24)</td>
<td>62 (25)</td>
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<tr>
<td></td>
<td>0</td>
<td>909 (55)</td>
<td>129 (52)</td>
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<tr>
<td></td>
<td>0</td>
<td>194 (12)</td>
<td>22 (9)</td>
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<td>22 (9)</td>
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<tr>
<td></td>
<td>0</td>
<td>149 (9)</td>
<td>35 (14)</td>
<td>0</td>
<td>35 (14)</td>
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Year of transplant

<table>
<thead>
<tr>
<th>Year</th>
<th>Haploidentical</th>
<th>8/8 URD</th>
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<tr>
<td>2012</td>
<td>12 (3)</td>
<td>196 (12)</td>
<td>31 (13)</td>
</tr>
<tr>
<td>2013</td>
<td>26 (7)</td>
<td>298 (18)</td>
<td>51 (21)</td>
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<td>2014</td>
<td>54 (14)</td>
<td>350 (21)</td>
<td>56 (23)</td>
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<tr>
<td>2015</td>
<td>69 (18)</td>
<td>358 (22)</td>
<td>50 (20)</td>
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<tr>
<td>2016</td>
<td>101 (27)</td>
<td>377 (23)</td>
<td>46 (19)</td>
</tr>
<tr>
<td>2017</td>
<td>111 (30)</td>
<td>65 (4)</td>
<td>14 (6)</td>
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</table>
Proposal 1711-51

Title:
Outcomes of Allogeneic Stem Cell Transplantation with Alternate Donors (Haploidentical or Cord Blood) compared with Matched Unrelated Donor Transplant among Patients with Myelofibrosis.

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Shivaprasad Manjappa, MD, MPH, smanjappa@wustl.edu, Washington University in Saint Louis
Vikas Gupta, MD, FRCP, FRCPath, Vikas.Gupta@uhn.ca, Princess Margaret Cancer Center-University of Toronto
Rizwan Romee, MD, rromee@wustl.edu, Washington University in Saint Louis

Hypothesis:
We hypothesize that the outcomes of allogeneic stem cell transplantation in patients with risk-stratified myelofibrosis (MF) is comparable among those who undergo alternate donor transplantation (Haploidentical or cord blood) is similar to those undergoing matched unrelated donor transplantation.

Scientific impact:
We hope to conduct this CIBMTR study to better characterize the outcomes using an alternate donor source. If we were to find the survival of alternate donor transplant is equivalent to matched unrelated (8/8 or 7/8) transplant, then either a haploidentical or umbilical cord blood transplant can be considered as a suitable alternative for patients with MF. We also hope to analyze a large cohort of patients with MF who have undergone alternate donor transplantation to analyze the variables, which affect both short and long-term outcomes.

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 alternate donor (haploidentical or cord blood).

Secondary Aims:
• To compare engraftment (of both neutrophils and platelets) and graft failure rate between MUD Allo HCT and alternate donor transplants.
• To compare acute and chronic GVHD rate between those with MUD Allo HCT versus alternate donor transplants.
• To analyze if stem cell source is an important factor in affecting the outcome between these 2 groups of patients.

Scientific justification:
Allo HCT is currently considered as the only curative option in patients with myelofibrosis. Though the outcomes of matched related donor (MRD) and well-matched unrelated donor transplant are comparable, literature on outcomes using an alternate donor source is scarce. A European Blood and Marrow Transplantation (EBMT) registry study showed that the cumulative incidence of non relapse mortality (NRM) at 1 year was significantly lower among patients with completely matched donors in comparison to mismatched donors (12% vs. 38%), whereas the cumulative incidence of NRM did not differ between the HLA-identical sibling and the 10/10 matched unrelated group (10% vs. 13%).
MPN-Research Consortium (MPN-RC) found that with transplants from unrelated donors, the OS was 32%, significantly inferior to the sibling group (hazard ratio 3.9)\(^5\).

In the CIBMTR retrospective report, adjusted probabilities of survival at 5-yr were 56% for matched sibling donors (MSD), 48% for well-matched unrelated donors, and 34% for partially matched/mismatched unrelated donors\(^1\).

The outcome of 35 umbilical cord blood transplants (UCBT) in patients with MPN-MF reported to Eurocord showed that the 2-year OS and Event free survival (EFS) rates were 44% and 30%, respectively. All patients were given TBI-fludarabine-CY and the use of this regimen was associated with superior EFS in the population receiving reduced intensity conditioning (RIC) (44% versus 0%)\(^6\).

Haploidentical stem cell transplantation (Haplo HCT) is becoming increasingly popular in the last few years with some centers showing similar outcomes between MRD, MUD and haplotransplants in AML and MDS\(^7\). A recent analysis from CIBMTR showed equivalent OS in AML using either MUD (8/8) or haploidentical donor\(^8\). However, a similar type of analysis comparing MUD Allo HCT with Haplo HCT has not been done in MF to date.

A recently published small retrospective analysis showed improved outcome in alternate donor transplant patients and equivalent outcome between Haplo HCT and MRD\(^9\).

This type of large registry based analysis will help us in looking at the outcome using an alternate donor in this rare disease and will guide us in deciding whether an alternate donor transplant can be recommended to patients who lack an appropriately matched donor.

**Study population:**
- Patients with MF who have received either haploidentical or umbilical cord blood transplantation. This will be compared with those who had a MUD transplant.
- Age \(\geq\) 18 years

**Exclusion Criteria:**
- Those who had a 2\(^{nd}\) transplant

**Data requirements:**
Data would be obtained via that reported to the CIBMTR. Any patient who had received allogeneic stem cell transplantation in MF will be considered if he/she met inclusion criteria. The following variables would be collected and analyzed:
- Patient age
- Patient gender
- Patient race
- Time from hematologic diagnosis to HCT
- Recipient performance score (KPS 90-100 versus <90)
- Recipient HCT-CI (0-1 vs. \(\geq\)2)
- Disease risk index (low or intermediate, or high risk)
- IPSS risk category (Low, Intermediate, or High)
- DIPSS risk category (Low, Intermediate, or High)
• Primary MF vs. Post ET/PV Myelofibrosis
• JAK2V617F status (yes/no)
• JAK inhibitor prior to transplant (yes/no)
• Palpable splenomegaly >/= 10 cm (yes/no)
• Peripheral blood blasts >/=2% (yes/no)
• Thrombocytopenia (platelets less than 100,000/cmm) – yes/no
• MUD donor -8/8 vs. 7/8
• Donor gender
• Donor age
• Conditioning intensity (ablative vs. reduced-intensity/non-ablative)
• TBI-based conditioning (yes vs. no)
• Graft source (peripheral blood vs. marrow vs. umbilical cord)
• GVHD prophylaxis regimen (calcineurin inhibitor-based or not or Post transplant cyclophosphamide)
• Use of ATG (yes/no)

Study design:
Univariate probabilities of OS and progression free survival (PFS) will be calculated using the Kaplan-Meier estimator. The log-rank test will be used for univariate comparisons. Probabilities of hematopoietic recovery, aGVHD, cGVHD, NRM and relapse / progression will be calculated using cumulative incidence curves to accommodate competing risks. Potential risk factors for OS, NRM, relapse and PFS will be evaluated in multivariate analyses using Cox proportional hazards regression. The proportional hazards assumption will be tested. A stepwise selection procedure will be used to select significant covariates. Factors significantly associated with the outcome variable at a 5% level will be retained in the final model. Any variables with a p-value <0.05 will be deemed significant. First-order interactions between the main effect and significant covariates will be tested. An analysis evaluating the impact of aGVHD/cGVHD as time-dependent covariates on survival, NRM, relapse/progression, and PFS will be conducted. Adjusted 5-year survival probabilities will be estimated using the direct adjusted survival curves estimation methods.

References:


Proposal 1711-84

Title:
Alternative donor allogeneic stem cell transplant in patients with myelodysplastic syndrome over the age of 50

Benjamin Tomlinson, MD, Benjamin.Tomlinson@UHhospitals.org, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer center
Taiga Nishihori, MD, taiga.nishihori@moffitt.org, H. Lee Moffitt Cancer Center and Research Institute
Marcos de Lima, MD, Marcos.deLima@UHhospitals.org, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer center

Hypothesis:
Allogeneic stem cell transplant outcomes in older patients with myelodysplastic syndromes with haploidentical related donors and umbilical cord donors provide promising outcomes.

Specific aims:
Primary Objective:
Compare overall survival of allogeneic stem cell transplant recipients over the age of 50 with a diagnosis of myelodysplastic syndrome (MDS) who have received a haploidentical (haplo) allogeneic hematopoietic stem cell transplant (HSCT) with haploidentical related donor (haplo) vs umbilical cord blood (UCB) vs 7/8 mismatched unrelated donor (mMUD) HSCT as part of therapy from 2010-2016.

Secondary Objectives:
Evaluate treatment outcomes including disease-free survival (DFS), non-relapse related mortality (NRM), and rates of graft-versus-host-disease (GVHD) in recipients of haplo vs UCB vs 7/8 mMUD HSCT for MDS patients
Identify possible prognostic features for haplo, UCB, and mMUD for MDS in patients 50 and older.

Scientific justification:
Myelodysplastic syndrome (MDS) is a group of heterogeneous disorders with a wide range of clinical and biologic behaviors.(1) Hematopoietic stem cell transplant (HSCT) is the only potentially curative therapy for patients with MDS, but is not universally part of MDS treatment due the age, coexisting comorbidities and donor availability.(2) However, reduced intensity condition has permitted more patients over the age of 50 receive allogeneic stem cell transplant. While prospective trials are lacking, overall outcome data for MDS patients receiving alloSCT are encouraging. Large registry studies of RIC allogeneic HSCT for patients over the age of MDS have been published reviewing the European Group for Blood and Marrow Transplantation (EBMT) as well as the Center for International Blood and Marrow Transplant Research (CIBMTR) with older patients with MDS that help define rates of long term survival. These find survival rates upwards of 31-45%.(3, 4) CIBMTR reported the outcomes of 701 MDS patients who underwent allogeneic HCT between 2002 and 2006. They found similar long term outcomes for recipients of matched related donors and 8/8 matched unrelated donors, but inferior outcomes for unrelated donors with a single mismatched allele.(5) Numerous questions remain for this patient population, including the timing of HSCT and the role of alternative donor HSCT with haplo and UCB. Decision models currently inform the timing of HSCT, and BMT-CTN1102 will add further clarity, the role of haplo, UCB, and mMUD HCST are more poorly defined.(6, 7)
Aforementioned EBMT and CIBMTR registry studies clearly demonstrate the inferiority of 7/8 mMUD HCST for MDS patients. Available data for UCB stem cells in MDS suggest it may also be an inferior to matched unrelated donors. CIBMTR reported outcomes of 176 adults from 2004-2013 with MDS receiving UCB(8-10) 3 year treatment related mortality was high at 40%. 3-year DFS and OS were 28% and 31% respectively.(11) Eurocord and European Blood and Marrow Transplantation Group (EBMT) performed a comparative study of the outcomes of peripheral blood unrelated donor (n=502) versus umbilical cord blood (n=129) HCT using reduced-intensity conditioning in patients with MDS from 2005-2011.(12) For unrelated donors, 75% were 10/10 HLA matched and 21% were 9/10 HLA matched. NRM, OS and DFS were better after peripheral blood group compared to both umbilical cord and mismatched unrelated donor sources.(12)

Data for the use of haplo HSCT for MDS patients is more limited. EMBT recently reported outcomes of related HLA-mismatched donors from 2007-2014 on 228 patients. 194 patients were T-cell replete and received post-transplant cyclophosphamide (PTCY) for GVHD prophylaxis. 3-year OS was 38% versus 28% for post-Tx Cy GVHD vs other haploidentical transplants.(13) Chen et al reported on a series of 36 MDS patients who received T-cell depleted haplo HSCT with a two year leukemia free survival of 65%.(14) No other series solely focused on haplo in MDS has been published. Series of haplo HSCT in hematologic malignancies have included subsets of MDS patients. Di Stasi et al compared outcomes of haplo HSCT with replete grafts to matched donor HSCT for AML and MDS patients and found similar outcomes overall. This including 33 MDS patients.(15) Larger registry studies of haplo HSCT have not focused on MDS patients alone. Subsets of MDS patients were also included in a single institution reviews of older patients receiving haplo HSCT. Kasamon et al reported the single institution experience of T-cell replete haploidentical transplant with reduced intensity condition and post-transplant cyclophosphamide and evaluated survival outcomes relative to age. 35 patient with MDS were included. No differences in overall survival and disease free survival were associated with older age, though the number of MDS patients was not reported as a separate subgroup.(16)

Little comparative data for different sources of HCSTs for older MDS patients exists. The use of haplo HSCT for hematologic malignancies has been increasing and use of umbilical cord blood declining, likely due to the wide adoption of PTCY.(17, 18) At the same time, there is better understanding of the importance of HLA-C matching and the overall importance of UCB match on NRM.(19, 20) We propose to study the outcomes of MDS patients over the age of 50 receiving alternative donor stem cell transplants since 2010. This should test the hypothesis that alternative donor stem cell transplant provide promising outcomes, and could inform donor selection in MDS patients who do not have an HLA-matched related or unrelated donor.

**Study population:**

**Inclusion criteria**
- HSCT recipients over the age of 50 with a primary diagnosis of MDS undergoing first allogeneic stem cell transplant from 2010-2016 with UCB, haplo with PTCY, or 7/8 mMUD.

**Exclusion criteria**
- Prior allogeneic HSCT (prior autologous HSCT for other diagnosis permitted)
- Diagnosis of MDS/MPN crossover syndrome

**Data requirements:**

**Patient data**
- Age
• Gender
• Race
• KPS
• HCT-CI

MDS/Disease information
• Time from Diagnosis to HCT
• Baseline laboratory/Cytogenetic/molecular risk group (IPSS-R risk category)
  o Marrow blasts %
  o Peripheral blood blast %
• Therapy related MDS vs de novo MDS
• Disease status at time of HCT
• Therapy received prior to transplant (growth factors, azanucleosides, lenalidomide, high dose chemotherapy)

Allogeneic HSCT related data
• Year of allogeneic HSCT
• Condition regimen
• Conditioning regimen intensity (MAC vs RIC vs NMA)
• ATG use
• Donor source (7/8 mismatched unrelated, vs. UCB, vs. related haploidentical)
• Graft type (bone marrow versus mobilized peripheral blood)
• CD34 cell dose
• HLA match (UCB)
• Relationship of related donors
• Engraftment dates (neutrophils, platelets)
• GVHD prophylaxis
  o Tac/MTX vs. CSA/MTX vs. Tac/MMF vs. CSA/MMF vs. Tac/Rapa vs. PTCY (+/- others)
  o ATG, alemtuzumab
• GVHD occurrences and grade
• Time to relapse (if applicable)
• Time to death or last known contact
• Cause of death (non-relapse related vs relapse related)

Study design:
This will be a retrospective review of all patients meeting inclusion criteria. Patient and disease characteristics will be collected from the CIBMTR registry for patients with a primary diagnosis of MDS receiving HSCT from 2010 through 2016. Patients will be grouped into those receiving cells from haploidentical related donors with PTCY, umbilical cord blood, and 7/8 matched unrelated donors for comparison. Groups’ characteristics will be compared with Chi-square or Wilcoxon statistics for categorical and continuous variables respectively. Overall survival and disease free survival will be evaluated with Kaplan-Meier methods. Acute and chronic GVHD, treatment related mortality and MDS relapse will be calculated using cumulative incidence curves.

Potential patient, disease, and treatment related prognostic factors will be evaluated with multivariate analysis with Cox proportional hazards regression to study association between treatment groups and outcomes.
References:


Proposal 1711-91

Title:
Comparison of Outcomes with Haploidentical and Matched Unrelated Donors for Hematopoietic Stem Cell Transplantation in Myelodysplastic Syndromes

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Hypothesis:
Patients with myelodysplastic syndromes (MDS) undergoing haploidentical stem cell transplantation (haploSCT) with post-transplant cyclophosphamide (PT-Cy) have similar outcomes to those undergoing matched unrelated donor (MUD) SCT.

Scientific impact:
In MDS patients who lack a suitable matched sibling donor, alternative donor graft sources are necessary. This comparison of haploSCT and MUD SCT may inform future alternative graft selection. If outcomes with haploSCT are the same as or superior to outcomes with MUD SCT, a strong argument can be made for haploidentical relatives to be the preferred donor source in MDS patients who lack a matched sibling donor.

Specific aims:
- To compare overall survival (OS) for patients undergoing haploSCT and MUD SCT.
- To compare graft failure, acute and chronic graft-versus-host disease (GVHD) incidence, relapse-free survival (RFS), and non-relapse mortality (NRM) for haploSCT with PT-Cy versus MUD SCT.

Scientific justification:
Allogeneic SCT has been used effectively in advanced hematologic malignancies (Copelan 2006). The best donor for allogeneic SCT is generally considered to be a human leukocyte antigen (HLA) matched sibling. However, most patients lack an HLA matched related donor. MUD SCT has been used for decades in MDS patients with some success. Nevertheless, there can be significant obstacles to MUD SCT. Not all patients have an HLA identical MUD. Results with mismatched donors have been worse than with HLA-matched MUs. In addition, there can be substantial delays in arranging for MUD SCT. HaploSCT with PT-Cy has emerged as an effective approach to treat patients with MDS and other hematologic malignancies. Several reports, many of which also include AML patients, have described small numbers of MDS patients undergoing haploSCT with PT-Cy (Ciurea 2017, Slade 2017, Devillier 2016, Di Stasi 2014). A larger analysis of outcomes with haploSCT is needed.

Study population:
Patients aged ≥18 years who received their first allogeneic SCT after either myeloablative (MA) conditioning or reduced intensity conditioning (RIC) from a MUD or a haploidentical related donor (defined as ≥2 antigen level mismatches) for a diagnosis of MDS from 2010 to 2015 will be included. Graft source will include marrow or PBSC donors in both groups. The haploidentical related donor group
will be limited to those who received post-transplantation cyclophosphamide. Patients who underwent T cell depletion will be excluded from the study.

Data requirements:

Variables to be Analyzed:

Patient-related:
- Age: continuous or in groups
- Gender: male vs. female
- Karnofsky performance score: <90% vs. ≥90%
- Co-morbidity index: 0 vs. 1-2 vs. >2
- CMV status: recipient positive vs. recipient negative vs. unknown
- Ethnicity and race: Caucasian, African-American, other

Donor-related:
- Donor age: continuous or in groups
- Donor-recipient sex match: M/M, M/F, F/M, F/F, missing
- Donor-recipient CMV status match: +/-, +/+, -/-, -, missing

Disease-related:
- IPSS-R score at diagnosis: Very Low, Low, Intermediate, High, Very High
- IPSS-R score at time of transplant: Very Low, Low, Intermediate, High, Very High
- CIBMTR score (Shaffer 2016): low, intermediate, high, very high
- t-MDS: yes, no
- History of prior therapy: azacitidine, decitabine, lenalidomide, ESAs, induction (e.g., 7+3), none, other
- Number of prior therapies: 1, 2 vs ≥3
- Response to therapy: CR, HI, HI-E, HI-P, HI-N, SD, Prog from HI, Rel from CR, Progression to AML

Transplant-related:
- Date of allogeneic SCT
- Graft source: marrow vs PBSC
- Donor source
- For haploSCT, number of antigen level mismatches
- Preparative regimen: MA vs RIC
- GVHD prophylaxis
- Interval from diagnosis to transplant: <3, 3-6, 6-12, 12-24, vs. ≥ 24 months, missing
- Main effects: HaploSCT vs. MUD SCT (including MA and RIC groups combined); RIC haploSCT vs. RIC MUD SCT; if numbers permit, MA HaploSCT vs. MA MUD SCT

Study design:
Median values and ranges will be used for continuous variables and percentages for categorical variables. For each continuous variable, the study population will be initially split into quartiles and in two groups by the median. Patient, disease, and transplant related variables of the groups will be compared using Chi-square or Fischer exact test for categorical variables, and Mann-Whitney test for continuous variables. The probabilities of OS and DFS will be calculated using the Kaplan-Meier method and log-rank test for univariate comparisons. Probabilities of relapse, NRM, acute and chronic GVHD and engraftment will be calculated using cumulative incidence curves to accommodate for competing risk (Prentice 1978). The cumulative incidence of grade II-IV acute GVHD and chronic GVHD (limited and extensive) will also be determined using the competing risks method. The competing risks include
disease progression and death. Patients who do not experience GVHD or progression of disease and alive at the last follow-up will be censored. Associations among patient, disease, and transplant related variables and outcomes will be evaluated using a multivariate Cox proportional hazards regression. A stepwise selection multivariate model will be built to identify covariates that influence outcomes. Covariates with a $p<0.05$ will be considered significant.

References:

Proposal 1711-99

Title:
Outcomes of HLA-haploidentical Allogeneic Blood or Marrow Transplantation with Post-Transplant Cyclophosphamide for Myeloproliferative Neoplasms and Myelodysplastic Syndrome/Myeloproliferative Neoplasm Overlap Syndromes

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Hypothesis:
In patients with myeloproliferative neoplasms (MPNs), including classical BCR:ABL negative MPNs and myelodysplastic syndrome (MDS)/MPN overlap syndromes, we hypothesize that nonmyeloablative (NMA) haploidentical (haplo) allogeneic (allo) BMT with post-transplant cyclophosphamide (PTCy) yields similar overall survival (OS) when compared with NMA matched related donor (MRD) or matched unrelated donor (MUD) allo-BMT.

Scientific impact:
The use of NMA alloBMT with HLA-haplol related donors with PTCy has expanded the donor pool such that nearly every patient requiring a BMT has at least one rapidly available donor.1 To this point, no studies have evaluated outcomes using haplo donor BMT in MPNs and MDS/MPNs. We seek to evaluate outcomes of MPN and MDS/MPN patients after NMA haplo BMT with PTCy, and compare these outcomes to those following matched donor transplants through the CIBMTR.

AlloBMT offers a potential cure for many patients with MPNs or MDS/MPNs who are fit enough to tolerate potential toxicities. Even still, this therapy is limited by the availability of an acceptable donor. The vast majority of these patients included in current literature received transplants from MRDs or MUDs. MRDs are the preferred donor source but are only available for approximately 30% of patients.2 Given the advanced age of most patients with MPNs and MDS/MPNs, the available MRDs are also likely to be elderly, which has been correlated with adverse transplant outcomes.3,4 MUDs expand donor availability to up to 75% of patients, though there is a large ethnic disparity with some groups having only a 15-20% likelihood of finding a donor.2

Haplo alloBMT with PTCy is a popular platform for expanding the BMT donor pool. Multiple studies have demonstrated low transplant related mortality (TRM) of <20%, OS rates of 30-50%, and severe GVHD rates of 10% in a number of hematologic malignancies, comparable to historical outcomes with MRDs.1,5-8 For elderly patients, selected haplo donors are most commonly the offspring, who are younger and more likely to be healthy than an elderly matched sibling.

The low toxicity profile and ease of identifying a healthy haplo donor make this transplant platform optimal for diseases that typically affect the elderly, such as MPNs. These advantages raise the possibility that other factors, such as time to transplant, donor age or ABO matching, may be more significant predictors of outcome than choosing the closest HLA matched donor. Hence, large studies validating outcomes with haplo alloBMT with PTCy in this disease group are warranted.
Specific aims:
- In patients with MPNs or MDS/MPNs, to evaluate the OS following allogeneic NMA haplo BMT with PTCy in comparison to NMA MRD alloBMT and NMA MUD alloBMT.
- In patients with MPNs or MDS/MPNs, to evaluate rates of relapse and disease free survival (DFS) following haplo allo-BMT with PTCy in comparison to NMA MRD alloBMT and NMA MUD allo-BMT.
- In patients with MPNs or MDS/MPNs, to evaluate rates of nonrelapse mortality (NRM) following NMA haplo allo-BMT with PTCy in comparison to NMA MRD alloBMT and NMA MUD allo-BMT.
- In patients with MPNs or MDS/MPNs, to evaluate rates and time to engraftment following haplo allo-BMT with PTCy in comparison to NMA MRD alloBMT and NMA MUD allo-BMT.
- In patients with MPNs or MDS/MPNs, to evaluate rates of acute and chronic graft-versus-host disease (GVHD) following NMA haplo allo-BMT with PTCy in comparison to NMA MRD allo-BMT and NMA MUD allo-BMT.

Scientific justification:
The classical BCR:ABL negative MPNs are a group of myeloid neoplasms characterized by clonal proliferation of mature myeloid cells and absence of the BCR:ABL translocation.\(^9\) This group of diseases includes polycythemia vera (PV), essential thrombocytosis (ET) and myelofibrosis (MF). On the spectrum of MPNs, the MDS/MPNs are a group of clonal myeloid neoplasms with both dysplastic and proliferative features. In the adult population, MDS/MPNs include chronic myelomonocytic leukemia (CMML), atypical CML (aCML, BCR:ABL negative CML), and MDS/MPN unclassified (MDS/MPN-u).\(^9\) While these conditions may have relatively indolent courses, there exists the risk of progression to more severe phenotypes, acute myelogenous leukemia (AML), and death.

For PV and ET, 5-10% transform, with OS of 15-20 years from diagnosis.\(^10,11\) MF can occur secondary to PV and ET, or de novo, and has a more aggressive course with a ~15% risk of blast transformation and OS of ~6 years.\(^11\) The overlap MDS/MPNs tend to be more aggressive with median OS of less than 3 years and likelihood of transformation to AML exceeding 30%.\(^12,13\) Thus, while many patients with these diseases may be managed conservatively, there is a subgroup of patients with aggressive disease who require definitive curative treatment.

For both severe MPNs and the overlap MDS/MPNs, the only available curative therapy is allogeneic bone marrow or blood transplantation (alloBMT). Given the toxicity of this therapy, recent National Comprehensive Cancer Network (NCCN) guidelines and historical practice reserve BMT only for physically fit patients predicted to have poor prognosis based on factors such predictive scoring systems, mutational status, or progression to MF, MDS, or AML.\(^11,14-19\)

Studies evaluating BMT outcomes in these patients are limited mostly to retrospective analyses focused on patients with MF and CMML. For example, in one study of 438 adult patients <65 years with primary MF without evidence of AML, alloBMT resulted in significantly higher 5-year OS than chemotherapy alone for patients with intermediate risk disease (50% versus 41%) or high risk disease (32% versus 11%).\(^20\) For patients with MF secondary to PV or ET, prognosis after alloBMT appears more favorable with OS exceeding 60%, and relapse rates of 20-30%.\(^21,22\) In patients with MDS/MPN, alloBMT results have been mixed. In one study of 21 adults with CMML, long term disease free survival (DFS) was 39%, with an acceptable relapse rate of 25%.\(^23\) Another study of 18 patients showed similar survival, though a much higher relapse rate of 47%.\(^24\) A larger multicenter European study recently evaluated transplant outcomes in 251 CMML patients and 422 MPN patients after progression to AML.\(^25\) For CMML the 3-
year OS was 36%, DFS was 30%, and relapse rate was 43%, while the MPN group had an OS of 37%, DFS of 25%, and relapse rate of 50%.25

To this point, no studies have evaluated outcomes using haplo alloBMTs in MPNs and MDS/MPNs, though this donor source has proven a reasonably safe and efficacious strategy to expand the donor pool in other hematologic diseases.

**Study population:**

**Inclusion:**
- Patients having received a first allogeneic BMT (marrow or peripheral blood stem cell transplant) for MPN, MDS/MPN, or AML secondary to these conditions. MPNs include ET, PV, and MF. MDS/MPNs include CMML, atypical CML, or MDS/MPN-unclassified
- Age 18 or older
- Transplant between 2007-2016
- Patients will be included regardless of whether their transplant was performed as part of a clinical trial.

**Exclusion:**
- Patients who received myeloablative conditioning
- Patients for whom a BMT was performed for a malignancy other than those in the inclusion criteria.
- Patients who received a haplo alloBMT without the use of PTCy
- Patients who received umbilical cord blood transplant

**Study design:**

We intend to retrospectively evaluate relevant clinical outcomes for all patients in the CIBMTR database who received a NMA alloBMT for MPNs or MDS/MPNs from 2007-2016. Specifically, we plan to highlight outcomes for patients with these diseases following NMA HLA haplo allo-BMT with PTCy as compared to NMA matched related donor alloBMTs and NMA matched unrelated donor alloBMTs. Relevant demographic and clinical information will be obtained through the existing CIBMTR database. Data will be separated into three cohorts by donor type (MRD, MUD, haplo) to compare outcomes below:

1. Overall survival
2. Rates of engraftment and graft failure, including time to neutrophil and platelet recovery.
3. Rate of relapse, defined as disease persistence/recurrence after alloBMT.
4. DFS following alloBMT, defined as time to disease progression after alloBMT.
5. Rates of graft versus host disease (GVHD; acute grade II-IV, acute grade III-IV, chronic or both) following alloBMT.
6. Composite GVHD-free-relapse-free survival (GRFS).
7. Rates non-relapse mortality following alloBMT, defined as death in a patient in absence of active MPN, MDS/MPN, or AML.

Additionally, we propose univariate analysis to determine factors associated with the outcomes above to include:

1. Patient age at time of transplant
2. Diagnosis (MF, PV, ET, CMML, aCML, or MDS/MPN-u, secondary AML)
3. Disease status at time of transplant by IWG criteria26,27
4. Donor age at time of transplant.
5. Graft type (marrow or peripheral blood stem cells)
References:
Proposal 1711-15

Title:
Impact of Racial Background on Survival Following Haploidentical Donor Transplantation (HIDT) with Post Transplant Cyclophosphamide (PTCy) for Adults with Hematologic Malignancies and Comparison with Race-Specific Outcomes following Umbilical Cord Blood Transplantation (UCBT)

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Hypothesis:
We hypothesize that racial background may have different impact depending on the type of alternative donor transplant (HIDT, UCBT) which may impact donor preference.

Specific aims:
• To evaluate the risk-adjusted DFS and OS at 2 years post-transplant, according to racial background, in adult patients with hematologic malignancies who received a PTCy-based HIDT.
• To evaluate relapse risk, non-relapse mortality, acute and chronic GVHD at 2 years post-transplant, according to racial background, in adult patients with hematologic malignancies who received a PTCy-based HIDT.
• To compare race-specific outcomes between PTCy-based HIDT and UCBT in adult patients with hematologic malignancies.

Scientific justification:
Race is a social and biological construct that is based on the geographic region of origin of an individual’s ancestry.[1] The 2010 US Census categorizes race into 5 broad categories: White, Black/African-American, Asian, Native Hawaiian/Pacific Islander, and American Indian/Alaska Native. Racial disparity has been well documented among cancer patients in the United States.[2, 3] Of all racial/ethnic groups in the U.S., Blacks have the highest death rates for most types of cancers.[4] The causes of racial disparity in cancer outcomes are thought to be multifactorial, reflecting multiple social and economic factors, including socioeconomic strata, health literacy, as well as access to health insurance.[5]

Racial disparities have also been noted in outcomes of allogeneic transplant.[6-8] Certain aspects of allogeneic transplant may make it particularly susceptible to racial disparities. These include socioeconomic factors such as the expense and complexities of the procedures, as well as other potential social barriers (need for caregivers, transportation, etc.). Biological factors may also come into play such as the need for a diverse donor pool and potential genetic differences (variation in HLA and minor transplant antigen diversity, frequency of cytokine gene polymorphisms, etc.).

Allogeneic transplant is a potentially curative therapy for several life-threatening blood cancers and other diseases, however access to a suitable donor can vary significantly by race. Although HLA-matched unrelated donor (MUD) transplantation is a viable option for the 70% of patients without available matched sibling donors, the probability of finding an optimal (8/8, HLA-A, -B, -C, -DR, -DQ) MUD varies significantly by racial/ethnic group, ranging from 75% in white Europeans, to 30% to 40% in...
Mexican and Central/South Americans, to 15% to 20% in African Americans and black Caribbeans.[9] As less than one-fifth of black patients will have an acceptable MUD, alternative donor sources such as umbilical cord blood (UCB) and HIDT have greatly improved access to allogeneic transplant for these patients.

The importance of race as a predictor of allogeneic transplant outcome remains an important question. The largest analysis investigating the association of race with transplant outcome was conducted by Baker et al.[6] using data from the CIBMTR. The study included 5253 White, 368 Black, 445 Hispanic, and 141 Asian/Pacific Islanders who had received a myeloablative MUD transplant for acute leukemia, MDS, or CML between 1995 and 2004. In multivariate analysis, black patients had significantly worse OS (HR 1.47, p<0.01) due to higher risks of NRM (HR 1.56, p<0.01). In regards to UCB transplantation, Ballen et al.[7] evaluated 612 White, 145 Black, and 128 Hispanic patients receiving a single UCB transplant for acute leukemia, MDS or CML between 1995 and 2006. Again, in multivariate analysis, Black patients had worse overall survival (HR 1.3, p=0.02). However, it is worth noting that much of this effect was mitigated when patients with suboptimal cell dose (TNC <2.5 x 107/kg) were excluded from this analysis.

The impact of race on HIDT has not been formally studied. This is of particular relevance as HIDT has the capacity to dramatically increase donor availability for minority patients. At Northside Hospital (Atlanta, Georgia), about 20% of all allogeneic transplants are performed on black patients. Whereas black patients comprise <5% of all MUD transplants performed at our center, they make up about 40% of all of the HIDT performed. In a recently completed analysis of 205 consecutive PTCy-based HIDT for hematologic malignancies performed at Northside Hospital, we analyzed the influence of racial background on transplant outcomes (OS, DFS, relapse/progression, NRM and GVHD) – manuscript submission in progress. The cohort included 123 White (60%), 80 Black (39%) and 2 Asian (1%) patients. Median (range) age was 53 (19-75) and 61% were male. Disease type included AML (34%), NHL/HL/CLL (24%), MDS/MPN/CML (20%), and ALL (17%). DRI was low, intermediate, and high/very high in 15%, 47% and 38% respectively. Stem cell source was PBSC in 66%, and conditioning intensity was myeloablative in 42%. Follow-up for surviving patients was 36 (7-130) months.

In univariate analysis, black patients had significantly better OS and DFS compared with white patients (figure 1). This was due to a lower risk of relapse/progression in black patients with no significant difference in NRM (figure 2). The improvements in survival in black vs. white patients was seen in all subgroups – older vs. younger, higher vs. lower risk disease, myeloablative vs. RIC, and PBSC vs. marrow (figure 3). There were no significant differences between black and white patients in regards to grade 2-4 acute GVHD, grade 3-4 acute GVHD or moderate-to-severe chronic GVHD. However, any-grade chronic GVHD was higher in black patients due to a higher incidence of mild chronic GVHD (data not shown). While controlling for other significant covariates in multivariate analysis (table 1) such as age, DRI, sex, and year-of-transplant, black patients continued to show superior OS (HR 0.47, p=0.003), DFS (HR 0.49, p=0.003), and lower cumulative incidence of relapse/progression (HR 0.49, p=0.01).

In summary, available evidence from large CIBMTR-based registry studies suggests inferior survival for black adult patients following MUD and single cord blood transplantation. However, the importance of
racial background has not been evaluated following PTCy-based HIDT. In a single institution analysis of 205 consecutive patients receiving HIDT from our center for hematologic malignancy, black patients were shown to have superior survival in both univariate and multivariate analysis. We hope to confirm this data in a large registry analysis through the CIBMTR. We further propose to compare race-specific outcomes between PTCy-based HIDT and UCBT (single or double cord units) in adult patients with hematologic malignancies. A formal large retrospective analysis of the importance of racial background in the outcomes of PTCy-based HIDT and UCBT may be of great significance in helping to establish the standard of care for alternative donor choice for minority populations in the absence of a prospective randomized trial.

**Study population:**

**Inclusion Criteria:**
- Patients age 18 years or older
- Diagnosis of AML, ALL, MDS, NHL, HL, or CLL
- Undergoing a first allogeneic transplant from one of the donors below:
  - Haploidentical donor, using PTCy and either BM or PBSC as stem cell source
  - Cord blood, either single or double cord blood units.
- Allogeneic transplant performed 2004-2015
- Any conditioning intensity

**Exclusion Criteria:**
- Any ex vivo T cell manipulation
- In vivo T cell depletion with ATG or alemtuzumab
- Prior allogeneic transplant

**Data requirements:**

**The following CIBMTR forms will be used:**

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<td>2018</td>
<td>LYM</td>
<td>Hodgkin Lymphoma / Non-Hodgkin Lymphoma Pre-HCT Data</td>
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</tbody>
</table>
### Variables to be analyzed:

#### Patient-related:
- Age at HCT, years: <55 vs. ≥55 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. others
- CMV status: seropositive vs. seronegative.

#### Disease-related:
- Disease diagnosis
- Disease-Risk Index (low/intermediate vs. high/very high)

#### Transplant-related:
- Bone marrow vs. peripheral blood as a graft source
- Conditioning regimen: MA vs. RIC vs. NMA (using standard CIBMTR definitions); MA vs. RIC/NMA
- Year of HCT
- Donor/Recipient gender (F-to-M vs. other)
- Donor/Recipient CMV status (CMV- D/CMV+ R vs. other)
- HLA match
- Donor age - continuous
- Donor relationship – child vs. sibling vs. parent (UCBT-specific)
- Cell dose (single cord or combined cord dose of ≥3 x 10^7 vs. <3 x 10^7 nucleated cells/kg)

#### Outcomes:

**Primary:**

- **Disease-free survival (DFS):** DFS is defined as survival without relapse or progression. Disease relapse/progression and death are treated as events. Surviving patients will be censored at last follow up. The outcome of DFS will be adjusted for all pre-transplant variables that are
significantly associated with DFS in multivariate analysis. DFS will be calculated using the Kaplan–Meier method, summarized by a survival curves, and compared using the log-rank test.

**Secondary:**
- **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 pre-transplant variables that are significantly associated with OS in multivariate analysis. OS will be calculated using the Kaplan–Meier method, summarized by a survival curves, and compared using the log-rank test.
- **Relapse/Progression:** Recurrence or progression of the underlying malignancy. The event will be summarized by the cumulative incidence estimate, with NRM treated as a competing risk. Patients will be censored at date of last follow-up. The cumulative incidences of this endpoint will be compared between groups using the Gray’s test.
- **Non-relapse 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. The cumulative incidences of this endpoint will be compared between groups using the Gray’s test.
- **Acute GVHD onset:** Development of Grades II-IV and III-IV acute GVHD using the Glucksberg grading system. The event will be summarized by the cumulative incidence estimate, where death without acute GVHD will be treated as a competing risk. The cumulative incidences of this endpoint will be compared between groups using the Gray’s test.
- **Chronic GVHD onset:** Development of NIH grade moderate-to-severe or any grade chronic GVHD. The event will be summarized by the cumulative incidence estimate, where death without chronic GVHD will be treated as a competing risk. The cumulative incidences of this endpoint will be compared between groups using the Gray’s test.

**Study design:**
The study aims to assess the significance of race on outcomes of adult patients undergoing PTCy-based HIDT. Descriptive tables of patient, disease-, and transplant-related factors will be created. The tables will list median and range for continuous variables and percent of total for categorical variables. Probabilities of DFS and OS will be calculated using the Kaplan-Meier estimator. Comparison of survival curves will be made using the log-rank test. Cumulative incidence of NRM, relapse/progression, acute and chronic GVHD will be calculated while accounting for competing events. A secondary analysis will compare race-specific outcomes between PTCy-based HIDT and cord blood transplantation.

Multivariate analysis 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. Race (White vs. Black vs. Asian/pacific islander vs. others) will always be included in the Cox models because the primary goal of the study is to evaluate the impact of Race on survival outcomes. 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.

**References:**
2. Clegg, L.X., et al., Cancer survival among US whites and minorities: a SEER (Surveillance, Epidemiology,
Table 1. Characteristics of adult patients who underwent first haploidentical donor HCT with post-transplant cyclophosphamide or cord blood HCT for hematologic malignancies in the US and reported to the CIBMTR, 2008-2017

<table>
<thead>
<tr>
<th>Variable</th>
<th>Haploidentical</th>
<th>UCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>2832</td>
<td>2082</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>2115 (75)</td>
<td>1582 (76)</td>
</tr>
<tr>
<td>African-American</td>
<td>550 (19)</td>
<td>277 (13)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>148 (5)</td>
<td>174 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (&lt;1)</td>
<td>49 (2)</td>
</tr>
<tr>
<td>Age at HCT, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>55 (18-88)</td>
<td>50 (18-81)</td>
</tr>
<tr>
<td>18 - 30</td>
<td>409 (14)</td>
<td>402 (19)</td>
</tr>
<tr>
<td>31 - 40</td>
<td>324 (11)</td>
<td>340 (16)</td>
</tr>
<tr>
<td>41 - 50</td>
<td>419 (15)</td>
<td>358 (17)</td>
</tr>
<tr>
<td>51 - 60</td>
<td>718 (25)</td>
<td>478 (23)</td>
</tr>
<tr>
<td>61 - 70</td>
<td>802 (28)</td>
<td>458 (22)</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>160 (6)</td>
<td>46 (2)</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>1351 (48)</td>
<td>1077 (52)</td>
</tr>
<tr>
<td>ALL</td>
<td>418 (15)</td>
<td>384 (18)</td>
</tr>
<tr>
<td>MDS</td>
<td>431 (15)</td>
<td>296 (14)</td>
</tr>
<tr>
<td>NHL</td>
<td>472 (17)</td>
<td>261 (13)</td>
</tr>
<tr>
<td>HL</td>
<td>160 (6)</td>
<td>64 (3)</td>
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<td>Conditioning intensity</td>
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<td></td>
</tr>
<tr>
<td>MAC</td>
<td>1126 (40)</td>
<td>1060 (51)</td>
</tr>
<tr>
<td>RIC/NMA</td>
<td>1706 (60)</td>
<td>1022 (49)</td>
</tr>
<tr>
<td>Year of transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>92 (3)</td>
<td>229 (11)</td>
</tr>
<tr>
<td>2009</td>
<td>113 (4)</td>
<td>271 (13)</td>
</tr>
<tr>
<td>2010</td>
<td>123 (4)</td>
<td>249 (12)</td>
</tr>
<tr>
<td>2011</td>
<td>155 (5)</td>
<td>228 (11)</td>
</tr>
<tr>
<td>2012</td>
<td>185 (7)</td>
<td>218 (10)</td>
</tr>
<tr>
<td>2013</td>
<td>240 (8)</td>
<td>246 (12)</td>
</tr>
<tr>
<td>2014</td>
<td>322 (11)</td>
<td>218 (10)</td>
</tr>
<tr>
<td>2015</td>
<td>488 (17)</td>
<td>214 (10)</td>
</tr>
<tr>
<td>2016</td>
<td>541 (19)</td>
<td>176 (8)</td>
</tr>
<tr>
<td>2017</td>
<td>573 (20)</td>
<td>33 (2)</td>
</tr>
</tbody>
</table>
Proposal 1711-56

Title:
A retrospective observational CIBMTR/EBMT study on the efficacy of alternative donor/stem cells sources in pediatric patients with acute leukemia.

Alice Bertaina, MD, PhD, aliceb1@stanford.edu, Stanford University, Department of Pediatrics, Division of Stem Cell and Regenerative Medicine

Hypothesis:
Hematopoietic stem cell transplantation (HSCT) can be a curative therapy for children with both malignant and non-malignant diseases. Traditionally, both matched related and unrelated donors have been employed for either bone marrow or mobilized peripheral blood stem cells used for HSCT. More recently, alternative donor/sources of stem cells, including umbilical cord blood (UCB) and haploidentical donors have been used for patients lacking an appropriate matched donor.

UCB with up to 2 antigens mismatches can be used because of it reduce capacity to mediate graft-versus-host disease (GvHD), whereas both bone marrow and mobilized peripheral blood stem cells from haploidentical donors must be T-cell depleted, either \textit{ex vivo} or \textit{in vivo}, to reduce GvHD occurrence.

We believe that the time is appropriated 1) to compare the outcome of children with acute leukemia receiving HSCT from alternative donors, both UCB and haploidentical donors, to the outcome of children receiving HSCT from matched donors, and 2) to compare the outcome of patients receiving $\alpha\beta$ T-cell depleted haploidentical HSCT to patients receiving haploidentical HSCT utilizing other forms of \textit{ex vivo} and \textit{in vivo} T-cell depletion. The outcomes of the two evaluations would establish 1) if one of the 2 alternative donor/sources were superior and 2) for haploidentical donors, what the most successful strategy of T-cell depletion was. Patients will be evaluated for 1) rates of engraftment, 2) rates of acute and chronic GvHD, 3) rates of leukemia relapse, 4) transplant-related-mortality (TRM), 5) immune reconstitution as measured by the frequency of opportunistic infections, 6) leukemia-free survival (LFS) and overall survival (OS).

Scientific impact:
This study will offer to the pediatric community a clear picture of what in both Europe and US we can obtain employing alternative donor/sources of stem cells in children with acute leukemia. Indeed, the outcomes of the two evaluations would establish 1) if one of the 2 alternative donor sources were superior and 2) for haploidentical donors, what the most successful form of T-cell depletion was ($\alpha\beta$+ T-cell depletion vs other forms of \textit{ex vivo} and \textit{in vivo} T-cell depletion).

Specific aims:
It is the purpose of this analysis:

1) to compare the outcome of children with acute leukemia receiving HSCT from alternative donors, both UCB and haploidentical donors, to the outcome of children receiving HSCT from matched donors;
2) to compare the outcome of patients receiving $\alpha\beta$ T-cell depleted haploidentical HSCT to patients receiving haploidentical HSCT utilizing other forms of ex vivo and in vivo T-cell depletion.

We will evaluate the following endpoints:
1. PMN and PLT Engraftment (rate and kinetics);
2. Cumulative incidence of grade II-IV acute GvHD;
3. Cumulative incidence of grade III-IV acute GvHD;
4. Cumulative incidence of limited and extensive chronic GvHD;
5. Cumulative incidence of Relapse;
6. Cumulative incidence of non-relapse mortality;
7. Cumulative incidence of opportunistic infections;
8. Kaplan-Meyer estimate probability of Overall Survival;
9. Kaplan-Meyer estimate probability of Event-free survival (by ALL and AML);

Scientific justification:
The only study comparing UCB and haploidentical HSCT was made in 2014 by Eurocord and the PDWP of EBMT and the results are still unpublished (Locatelli F, ASH 2014). The last data published on the comparison between different strategies of T-cell depletion date to 2000 (Champlin RE et al, Blood 2000). To the best of my knowledge, only few reports reporting outcome of both T-cell depleted and unmanipulated haploidentical HSCT in children with acute leukemia are so far available in the literature.

As a scientific community, we need a large retrospective cohort of patients transplanted through these different approaches for comparing LFS. Only a joined US and European effort can be instrumental in achieving this goal.

Study population:
- Patients aged $\geq$ 3 months and < 21 years;
- Diagnosis of acute leukemia (ALL, AML);
- 1st HSCT;
- Patients transplanted using either UCB or haploidentical donor;
- ex-vivo T-cell depletion (CD34+ selection, CD3+/CD19+ T-cell depletion, $\alpha\beta$+ T-cell depletion) or
- in vivo T-cell depletion (i.e. post-HSCT Cyclophosphamide);
- CR at time of HSCT: (CR1 and CR2);
- HSCT performed in all pediatric CIBMTR and EBMT centers between 2000 and 2015.

Data requirements:
Data from the following forms will be needed: 2000 (recipient baseline data), 2010 (Acute Myelogenous Leukemia Pre-HCT Data), 2010 (Acute Lymphoblastic Leukemia Pre-HCT Data), 2100 (post-HSCT data), 2110 (Acute Myelogenous Leukemia Post-HCT Data), 2110 (Acute Lymphoblastic Leukemia Post-HCT Data), 2110 (Acute Lymphoblastic Leukemia Post-HCT Data).
Data), 2450 (Post-Transplant Essential Data), 2146 (fungal infection post-HSCT data), 2200 (6 months to 2 years post-HSCT data), 2300 (yearly follow up greater than 2 years post-HSCT data), and 2900 (recipient death data).

**Study design:**
This is a CIBMTR/EBMT retrospective observational study that aims to compare the efficacy of alternative donor/stem cell sources in pediatric patients affected by acute leukemia given.

**References**


Table 1. Characteristics of pediatric (≤18 years) patients who underwent first myeloablative haploidentical HCT, matched unrelated donor HCT, or cord blood HCT for acute leukemia in Europe and reported to the EBMT, 2007-2014

<table>
<thead>
<tr>
<th>Variable</th>
<th>Haploidentical</th>
<th>8/8 MUD</th>
<th>UCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>895</td>
<td>1990</td>
<td>1156</td>
</tr>
<tr>
<td>Age at HCT, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 - 4</td>
<td>136 (15)</td>
<td>383 (19)</td>
<td>369 (32)</td>
</tr>
<tr>
<td>4 - 12</td>
<td>388 (43)</td>
<td>909 (46)</td>
<td>533 (46)</td>
</tr>
<tr>
<td>12 - 18</td>
<td>371 (42)</td>
<td>698 (35)</td>
<td>254 (22)</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>383 (44)</td>
<td>713 (36)</td>
<td>438 (38)</td>
</tr>
<tr>
<td>ALL</td>
<td>491 (55)</td>
<td>1208 (61)</td>
<td>676 (59)</td>
</tr>
<tr>
<td>Acute undifferentiated leukemia</td>
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<td>7 (&lt;1)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Mixed phenotype, not specified</td>
<td>16 (1)</td>
<td>56 (3)</td>
<td>37 (3)</td>
</tr>
<tr>
<td>Mixed phenotype, B/myeloid</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Mixed phenotype, T/myeloid</td>
<td>2 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>2 (&lt;1)</td>
<td>3 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Disease status at transplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR1</td>
<td>279 (31)</td>
<td>868 (44)</td>
<td>520 (45)</td>
</tr>
<tr>
<td>CR2</td>
<td>265 (30)</td>
<td>776 (39)</td>
<td>441 (38)</td>
</tr>
<tr>
<td>Other</td>
<td>351 (39)</td>
<td>346 (17)</td>
<td>195 (17)</td>
</tr>
</tbody>
</table>
Table 2. Characteristics of pediatric (≤18 years) patients who underwent first haploidentical HCT, matched unrelated donor HCT, or cord blood HCT for acute leukemia in North America and reported to the CIBMTR, 2008-2017

<table>
<thead>
<tr>
<th>Variable</th>
<th>Haploidentical</th>
<th>8/8 MUD</th>
<th>UCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>192</td>
<td>251</td>
<td>708</td>
</tr>
<tr>
<td>Age at HCT, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 - 4</td>
<td>35 (18)</td>
<td>38 (15)</td>
<td>187 (26)</td>
</tr>
<tr>
<td>4 - 12</td>
<td>75 (39)</td>
<td>100 (40)</td>
<td>306 (43)</td>
</tr>
<tr>
<td>12 - 18</td>
<td>82 (43)</td>
<td>113 (45)</td>
<td>215 (30)</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>87 (45)</td>
<td>152 (61)</td>
<td>339 (48)</td>
</tr>
<tr>
<td>ALL</td>
<td>105 (55)</td>
<td>99 (39)</td>
<td>369 (52)</td>
</tr>
<tr>
<td>Disease status at transplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR1</td>
<td>103 (54)</td>
<td>153 (61)</td>
<td>345 (49)</td>
</tr>
<tr>
<td>CR2</td>
<td>89 (46)</td>
<td>98 (39)</td>
<td>363 (51)</td>
</tr>
<tr>
<td>Haploidentical strategy</td>
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<td></td>
</tr>
<tr>
<td>Post-transplant cyclophosphamide</td>
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<td>NA</td>
<td>NA</td>
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<tr>
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</tr>
<tr>
<td>T cell depletion</td>
<td>22 (11)</td>
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<td>NA</td>
</tr>
<tr>
<td>Plasma depletion</td>
<td>4 (2)</td>
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<td>NA</td>
</tr>
<tr>
<td>TCR Alpha/Beta depletion</td>
<td>9 (5)</td>
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<td>NA</td>
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<tr>
<td>RBC reduction</td>
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<td>NA</td>
</tr>
<tr>
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<tr>
<td>Year of transplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>8 (4)</td>
<td>35 (14)</td>
<td>103 (15)</td>
</tr>
<tr>
<td>2009</td>
<td>10 (5)</td>
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<tr>
<td>2010</td>
<td>9 (5)</td>
<td>29 (12)</td>
<td>93 (13)</td>
</tr>
<tr>
<td>2011</td>
<td>8 (4)</td>
<td>2 (&lt;1)</td>
<td>71 (10)</td>
</tr>
<tr>
<td>2012</td>
<td>6 (3)</td>
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<td>2013</td>
<td>12 (6)</td>
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<tr>
<td>2014</td>
<td>17 (9)</td>
<td>39 (16)</td>
<td>61 (9)</td>
</tr>
<tr>
<td>2015</td>
<td>28 (15)</td>
<td>49 (20)</td>
<td>70 (10)</td>
</tr>
<tr>
<td>2016</td>
<td>46 (24)</td>
<td>18 (7)</td>
<td>50 (7)</td>
</tr>
<tr>
<td>2017</td>
<td>48 (25)</td>
<td>1 (&lt;1)</td>
<td>9 (1)</td>
</tr>
</tbody>
</table>
Proposal 1711-117

Title:
Comparison of Outcomes of Reduced Intensity Transplantation in Lymphoma Patients Using Haploidentical Related Donors vs. Unrelated Cord Blood

Giancarlo Fatobene, MD, giancarlo.fatobene@hsl.org.br, Hospital das Clínicas da Universidade de São Paulo and Hospital Sírio-Libanês, Brazil
Vanderson G. Rocha, MD, PhD, vanderson.rocha@ouh.nhs.uk; rocha.vanderson@hotmail.fr, Churchill Hospital, Oxford, United Kingdom and Hospital das Clínicas da Universidade de São Paulo and Hospital Sírio-Libanês, Brazil

Hypothesis:
We hypothesize that reduced intensity transplantation using haploidentical related donors have superior survival outcomes following haploidentical transplantation with posttransplant cyclophosphamide compared to unrelated cord blood transplantation in adult patients with lymphoma, while the relapse rate and incidence of acute and chronic graft-versus-host disease are similar between these donor types.

Specific aims:
A) Primary endpoint – To compare the risk-adjusted overall survival (OS) in adult patients with lymphoma who received reduced-intensity transplantation using haploidentical related donors with posttransplant cyclophosphamide vs. unrelated cord blood.
B) Secondary endpoints – To compare the risk-adjusted relapse/progression rate (RR), progression-free survival (PFS), nonrelapse mortality (NRM), acute and chronic graft-versus-host disease (GVHD), GVHD-free, relapse-free survival (GRFS), Chronic-GVHD-free, relapse-free survival (CRFS) and hematopoietic recovery between reduced-intensity haploidentical transplant with posttransplant cyclophosphamide and unrelated cord blood transplant.

Scientific justification
Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative therapy for patients with advanced, relapsed, or refractory non-Hodgkin’s lymphoma (NHL), Hodgkin’s lymphoma (HL), and chronic lymphocytic leukemia (CLL). Comparative studies have reported lower relapse rates after allogeneic transplant compared to autologous transplant. However, the absence of an HLA-matched sibling donor and eventually the prohibitive delays in matched unrelated donor availability have been major challenges.

Haploidentical transplantation with posttransplant cyclophosphamide (Haplo/PTCY) and umbilical cord blood (UCB) are alternative sources of hematopoietic stem cells for the treatment of hematologic malignancies in patients lacking a human leukocyte antigen (HLA)-matched donor. The advantages of these alternative sources include prompt availability and decreased risk of graft-versus-host disease (GVHD) despite HLA mismatch. These attributes make HCT available to virtually any patient with adequate performance and disease status, particularly in ethnic and racial minorities. On the other hand, UCB HCT has been associated with increased NRM and delayed hematologic recovery besides its elevated costs, while data on the outcomes of Haplo/PTCY is smaller and relatively still recent compared to UCB and other donor types.

Both Haplo/PTCY and UCB HCT have been found to be effective in adult patients with lymphoma in...
many studies,\textsuperscript{11–13} as well as comparisons of both donor types to conventional matched donors seem encouraging. In fact, similar to the results found in acute myeloid leukemia,\textsuperscript{14} a large Center for International Blood and Marrow Transplant Research (CIBMTR) report encompassing 987 adult patients with lymphoma found no significant difference between Haplo/PTCY and matched sibling donors regarding NRM, RR, PFS and OS, while the incidence of chronic GVHD was significantly lower in the Haplo/PTCY group.\textsuperscript{15} Another CIBMTR study including 917 lymphoma patients showed no difference in terms of NRM, RR, and PFS between reduced-intensity Haplo/PTCY and matched unrelated transplants either.\textsuperscript{16} Similarly, a recent European Society for Blood and Marrow Transplantation including 709 adult patients with Hodgkin lymphoma found no significant differences in OS or PFS between Haplo/PTCY and matched sibling and unrelated donors, while the composite end point of CFRS was significantly better for Haplo/PTCY compared with matched sibling donor HCT.\textsuperscript{17} On the other hand, a small prospective trial comparing UCB vs. matched sibling donor HCT in 29 patients with advanced Hodgkin lymphoma suggested equivalent progression-free survival.\textsuperscript{18} Analogous results were found in a Japanese study of individuals with relapsed/refractory follicular lymphoma.\textsuperscript{19}

Data on the specific comparison of outcomes between UCB HCT and Haplo/PTCY in lymphoma patients is limited. A French study of patients with Hodgkin lymphoma undergoing nonmyeloablative and reduced-intensity Haplo/PTCY (n=34) or UCB HCT (n=37) demonstrated that the former group had superior 3-year GRFS compared to UCB recipients.\textsuperscript{20} To the best of our knowledge, there are no other disease-specific reports on transplant outcomes of lymphoma patients following Haplo/PTCY vs. UCB HCT. Although there is an ongoing prospective trial (BMT CTN 1101) comparing the two strategies, this study is recruiting different hematologic malignancies besides lymphoma. Thus, a large retrospective study specifically addressing lymphoma patients may be of importance in helping to choose the best alternative donor option while long-term results of that trial are awaited, may corroborate its findings, and provide addition insight into the granularity of this group of patients (e.g., impact of lymphoma histology).

**Study population:**

**Inclusion criteria:**

Patients age 18 – 65 years

- Diagnosis of Hodgkin or non-Hodgkin lymphoma (B and T-cell lymphomas)
- First reduced-intensity or nonmyeloablative conditioning transplants using (1) haploidentical related donors (mismatched by at least 2 or more HLA loci to donors) and posttransplant cyclophosphamide or (2) unrelated cord blood (single or double units) between 2008 and 2017.

**Exclusion criteria:**

- Prior allogeneic transplant.
- *Ex-vivo* graft manipulation (T-cell-depleted or CD34-selected grafts).

**Data Requirements:**

**Patient-related:**

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

**Disease-related:**

- Time from diagnosis to HCT: $< 1$ year vs. $\geq 1$ year and continuous
• Lymphoma histology: Hodgkin lymphoma vs. diffuse large B-cell lymphoma vs. follicular lymphoma vs. mantle cell lymphoma vs. mature T- and NK-cell lymphoma
• Disease-Risk Index: low vs. intermediate vs. high vs. very high risk
• Disease status: complete remission vs. partial remission vs. chemorefractory vs. untreated.
• History of prior autologous transplantation: yes vs. no

Transplant-related:

Outcomes:

Primary:
• **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 donor types, summarized by survival curves.

Secondary:
• **Progression-free survival (PFS):** PFS is defined as survival without relapse/progression of lymphoma. Disease relapse/progression and death are treated as events. Surviving patients will be censored at last follow up. The outcome of PFS will be adjusted for all pretransplant variables that are significantly associated with PFS in multivariate analysis. PFS will be calculated using the Kaplan–Meier method for both donor types, summarized by survival curves.
• **Relapse/progression rate (RR):** Recurrence or progression of lymphoma. Patients will be censored at date of last follow-up. The outcome of RR will be adjusted for all pretransplant variables that are significantly associated with RR in multivariate analysis. The event will be summarized by the cumulative incidence estimate, with nonrelapse mortality treated as a competing risk. The cumulative incidences of this endpoint will be compared between both donor types.
• **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. The outcome of NRM will be adjusted for all pretransplant variables that are significantly associated with NRM in multivariate analysis. The cumulative incidences of this endpoint will be compared between both donor types.
• **Acute GVHD:** Development of Grades II-IV and 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 date of last follow-up. The outcome of acute GVHD will be adjusted for all pretransplant variables that are significantly associated with acute GVHD in multivariate analysis. The cumulative incidences of this endpoint will be compared between both donor types.
• **Chronic GVHD**: Development of 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 date of last follow-up. The outcome of chronic GVHD will be adjusted for all pretransplant variables that are significantly associated with chronic GVHD in multivariate analysis. The cumulative incidences of this endpoint will be compared between both donor types.

• **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. Patients will be censored at date of last follow-up. The outcome of GRFS will be adjusted for all pretransplant variables that are significantly associated with chronic GRFS in multivariate analysis. GRFS will be calculated using the Kaplan–Meier method for both donor types, summarized by survival curves.

• **Chronic GVHD-free relapse-free survival (CRFS)**: Moderate or severe chronic GVHD, disease relapse/progression and death are treated as events. There will be no competing risks. Patients will be censored at date of last follow-up. The outcome of CRFS will be adjusted for all pretransplant variables that are significantly associated with chronic CRFS in multivariate analysis. CRFS will be calculated using the Kaplan–Meier method for both donor types, summarized by survival curves.

• **Neutrophil recovery**: The first of 3 measurements on different days with an ANC >500/µL after transplant. Death and relapse will be competing risks. The outcome of neutrophil recovery will be adjusted for all pretransplant variables that are significantly associated with neutrophil recovery in multivariate analysis. The event will be summarized by the cumulative incidence estimate. The cumulative incidences of this endpoint will be compared between both donor types.

• **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 outcome of platelet recovery will be adjusted for all pretransplant variables that are significantly associated with platelet recovery in multivariate analysis. The event will be summarized by the cumulative incidence estimate. The cumulative incidences of this endpoint will be compared between both donor types.

**Study design:**

This study aims to assess the impact of donor type on the outcomes of lymphoma undergoing allogeneic HCT. Descriptive tables of patient, disease-, and transplant-related factors will be created. The tables will list median and range for continuous variables and percent of total for categorical variables. Probabilities of PFS, OS, GRFS and CRFS will be calculated using the Kaplan–Meier estimator. 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 analysis 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 type of donor (Haplo/PTCY vs. UCB) will always be included in the Cox models because the primary goal of the study is to evaluate the impact of donor type on survival outcomes. 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. If statistically feasible, planned subset analyses will be performed for patients with: diffuse large B cell lymphoma, follicular lymphoma, Hodgkin lymphoma and chronic lymphocytic leukemia.
References:


Table 1. Characteristics of patients who underwent first reduced intensity haploidentical donor HCT with post-transplant cyclophosphamide or cord blood HCT for lymphoma in the US and reported to the CIBMTR, 2008-2017

<table>
<thead>
<tr>
<th>Variable</th>
<th>Haploidentical</th>
<th>UCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>497</td>
<td>203</td>
</tr>
<tr>
<td>Age at HCT, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>54 (18-76)</td>
<td>52 (20-73)</td>
</tr>
<tr>
<td>18 - 30</td>
<td>75 (15)</td>
<td>22 (11)</td>
</tr>
<tr>
<td>31 - 40</td>
<td>63 (13)</td>
<td>41 (20)</td>
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<td>41 - 50</td>
<td>70 (14)</td>
<td>33 (16)</td>
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<td>51 - 60</td>
<td>129 (26)</td>
<td>60 (30)</td>
</tr>
<tr>
<td>61 - 70</td>
<td>135 (27)</td>
<td>45 (22)</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>25 (5)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>369 (74)</td>
<td>158 (78)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>128 (26)</td>
<td>45 (22)</td>
</tr>
<tr>
<td>Disease status at transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>215 (43)</td>
<td>96 (47)</td>
</tr>
<tr>
<td>Partial response</td>
<td>225 (45)</td>
<td>82 (40)</td>
</tr>
<tr>
<td>Chemorefractory</td>
<td>53 (11)</td>
<td>23 (11)</td>
</tr>
<tr>
<td>Untreated</td>
<td>4 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Conditioning regimen (NMA/RIC)</td>
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<td></td>
</tr>
<tr>
<td>TBI + Cy + Flud</td>
<td>453 (91)</td>
<td>167 (82)</td>
</tr>
<tr>
<td>TBI + Cy</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>TBI + Flud</td>
<td>22 (4)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Bu + Flud</td>
<td>2 (&lt;1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Flud + Mel</td>
<td>19 (4)</td>
<td>27 (13)</td>
</tr>
<tr>
<td>Year of transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>34 (7)</td>
<td>16 (8)</td>
</tr>
<tr>
<td>2009</td>
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<td>2011</td>
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<td>2013</td>
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<td>2014</td>
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<td>2015</td>
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<tr>
<td>2016</td>
<td>69 (14)</td>
<td>19 (9)</td>
</tr>
<tr>
<td>2017</td>
<td>90 (18)</td>
<td>8 (4)</td>
</tr>
</tbody>
</table>
Proposal 1711-168

Title:
Outcomes after 8/8 matched unrelated donor (MUD) transplantation using post transplant cyclophosphamide (PTCy) vs. standard of care calcineurin inhibitor containing graft versus host disease prophylaxis in AML, ALL and MDS patients

Rizwan Romee, MD, rromee@wustl.edu, Washington University in St. Louis

Hypothesis:
We hypothesize that the use of high dose cyclophosphamide (PTCy) early after MUD transplantation leads to significantly lower incidence of graft versus host disease (GvHD) without increasing relapse rates.

Scientific impact:
Use of post transplant cyclophosphamide early after transplant (PTCy) has significantly improved outcomes after HLA haploidentical donor transplantation and has become the most popular regimen for this transplant modality.1,2,3 Recently PTCy has also been used in non haplo settings with encouraging results.4,5 However, there have been few reports where the use of PTCy alone for GvHD prophylaxis in non-haplo allo-HCTs was shown to be associated with increased GvHD.6,7 Evaluation of the efficacy of PTCy in reducing GvHD is needed to guide optimal use of this platform in a non-haplo transplant setting.

Specific aims:
- Compare outcomes of AML, ALL and MDS patients following 8/8 MUD transplantation with or without the use of high dose cyclophosphamide as part of GvHD prophylaxis regimen. Primary outcomes include overall survival and event-free survival (survival without relapse). Secondary outcomes include non-relapse mortality, relapse rates, graft failure, cumulative incidences of acute and chronic graft versus host disease (GvHD) and the composite end point of GvHD-free/relapse-free survival (GRFS).
- Compare incidence of key viral (CMV, EBV, and BK virus) and fungal infections in PTCy vs. non PTCy MUD transplant recipients.

Scientific justification:
In recent years PTCy is being increasingly used in the non-haplo transplant setting. However there are conflicting reports regarding transplant outcomes in non-haplo patients receiving PTCy as a single agent or in combination with calcineurin inhibitor containing standard of care GvHD prophylaxis regimens. The objective of this proposal to answer this relatively unexplored question of whether GvHD and relapse outcomes are significantly impacted by the use of PTCy in MUD transplant recipients with AML, ALL and MDS. There is also paucity of literature regarding impact of PTCy in non-haplo transplants on graft failure, delayed count recovery, and incidence of key post transplant infections like CMV, EBV, BK virus and fungal infections. We hope to be able to answer some of these key questions by retrospectively analyzing outcomes of matched unrelated donor transplant patients who receive PTCy alone or in addition standard of care calcineurin inhibitor containing GvHD prophylaxis regimens. We hope the results of our study will guide appropriate use of PTCy in a non-haplo transplant setting.
Study population:
Inclusion:
- Age >18 years
- 8/8 HLA matched unrelated donor transplants with un-manipulated peripheral blood (PB) or bone marrow (BM) grafts and PTCy alone, PTCy in combination with MMF and tacrolimus or standard of care calcineurin containing GvHD prophylaxis
- Patients with AML, ALL or MDS
- First allo-HCT between 2008-2016

Exclusion:
- Prior allogeneic HCT
- Ex-vivo T-cell depletion
- In-vivo T-cell depletion with anti-thymocyte globulin (ATG) or alemtuzumab (Campath) containing conditioning regimens

Data requirements:
- Baseline patient/disease characteristics
  - Age at transplant
  - Karnofsky Performance Score (>90 vs <90 and continuous)
  - Patient gender
  - HCT in primary induction failure versus relapse
  - # of prior relapses
  - Race
  - Duration of remission if relapsed
  - Time from diagnosis to HCT: 0-6 versus 6-12 versus >12 months and continuous
  - AML subtype
  - ALL type (T cells vs. B cells and Ph+ chromosome positivity status)
  - MDS IPSS-R score at the time of transplantation
  - Cytogenetics and relevant molecular / mutation information (FLT3 mutation, NPM etc)
  - Median blast percentage on pre-transplant bone marrow
  - Sorror Co-morbidity Index: 0 versus 1-2 versus >3
- Transplant characteristics
  - Graft type: peripheral versus marrow
  - Donor-recipient sex mismatch
  - CMV status of host and donor
  - TBI-based conditioning
  - GVHD prophylaxis
  - Conditioning regimen including myeloablative versus reduced intensity conditioning
  - Host and donor ABO type
- Outcomes
  - Overall survival
  - 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
- GFRS (GvHD-free/relapse-free survival)
- Graft failure
- Donor chimerism at day +30, +100 and 6 months after allo-HCT
- Median neutrophil and platelet recovery
- CMV reactivation
- EBV reactivation
- BK viruria
- Any reported fungal infection

Study design:
Retrospective cohort analysis evaluating key post transplant outcomes of AML, ALL and MDS patients receiving 8/8 MUD allo-HCT with 1.) Standard of care calcineurin inhibitor containing GvHD prophylaxis 2.) Standard of care calcineurin inhibitor containing GvHD prophylaxis plus PTCy 3.) PTCy alone for GvHD prophylaxis.

Death in remission will be considered a competing risk event for cumulative incidence of relapse. Graft failure, relapse, or death will be considered as competing risk events for cumulative incidence of acute and chronic GvHD. GRFS events will be defined at 1- and 2- years after HCT as the first occurrence of grade III–IV acute GvHD, extensive or systemic chronic GvHD requiring therapy, relapse, or death.

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.

References:

Table 1. Characteristics of adult patients who underwent first matched unrelated donor HCT for AML, ALL, or MDS in the US and reported to the CIBMTR, by GVHD prophylaxis, 2013-2017

<table>
<thead>
<tr>
<th>Variable</th>
<th>PT-Cy + CNI + MMF</th>
<th>TAC + MMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>112</td>
<td>525</td>
</tr>
<tr>
<td>Age at HCT, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median(range)</td>
<td>65 (21-82)</td>
<td>66 (18-83)</td>
</tr>
<tr>
<td>18 - 30</td>
<td>6 (5)</td>
<td>24 (5)</td>
</tr>
<tr>
<td>31 - 40</td>
<td>4 (4)</td>
<td>15 (3)</td>
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<td>41 - 50</td>
<td>13 (12)</td>
<td>35 (7)</td>
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<td>51 - 60</td>
<td>19 (17)</td>
<td>94 (18)</td>
</tr>
<tr>
<td>61 - 70</td>
<td>57 (51)</td>
<td>279 (53)</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>13 (12)</td>
<td>78 (15)</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
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<td>184 (35)</td>
</tr>
<tr>
<td>ALL</td>
<td>10 (9)</td>
<td>39 (7)</td>
</tr>
<tr>
<td>MDS</td>
<td>47 (42)</td>
<td>302 (58)</td>
</tr>
<tr>
<td>Graf type</td>
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<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>20 (18)</td>
<td>37 (7)</td>
</tr>
<tr>
<td>Peripheral blood</td>
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<td>488 (93)</td>
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<tr>
<td>Conditioning intensity</td>
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</tr>
<tr>
<td>MAC</td>
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<td>128 (24)</td>
</tr>
<tr>
<td>RIC/NMA</td>
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<td>397 (76)</td>
</tr>
<tr>
<td>Year of transplant</td>
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</tr>
<tr>
<td>2013</td>
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</tr>
<tr>
<td>2014</td>
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<td>2016</td>
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<td>4 (4)</td>
<td>19 (4)</td>
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