Not for publication or presentation

CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

A G E N D A
CIBMTR WORKING COMMITTEE FOR GRAFT-VERSUS-HOST DISEASE
Houston, TX
Wednesday, February 20, 2019 12:15 – 2:15 PM

Co-Chair:	**Amin Alousi, MD, MD Anderson Cancer Center, Houston, TX;** **Telephone: 713-745-8613; E-mail: aalousi@mdanderson.org**
Co-Chair:	**Joseph Pidala, MD, PhD, H. Lee Moffitt Cancer Center and Research Institute;** **Telephone: 813-745-2556; E-mail: joseph.pidala@moffitt.org**
Co-Chair:	**Madan Jagasia, MBBS, MS, Vanderbilt University Medical Center, Nashville, TN;** **Telephone: 615-936-8422; E-mail: madan.jagasia@vumc.org**
Scientific Director:	**Mukta Arora, MD, MS, University of Minnesota Medical Center, Minneapolis, MN;** **Telephone: 612-626-4105; E-mail: arora005@umn.edu**
Scientific Director:	**Stephen Spellman, MBS, CIBMTR Statistical Center, Minneapolis, MN;** **Telephone: 763-406-8334; E-mail: sspellma@nmdp.org**
Statistical Director:	**Tao Wang, PhD, CIBMTR Statistical Center, Milwaukee, WI;** **Telephone: 414-955-4339; E-mail: taowang@mcw.edu**
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Statistician:	**Michael Hemmer, MS, CIBMTR Statistical Center, Milwaukee, WI;** **Telephone: 414-805-4638; E-mail: mhemmer@mcw.edu**

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1. Introduction

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

b. Introduction of new incoming Co-Chair:
Margaret MacMillan, MD, MSc
University of Minnesota
Telephone: (612) 626-8094
E-mail: macmi002@umn.edu
Thank you to **Amin Alousi** for all of his contributions and input to the GVWC.

2. Accrual Summary (Attachment 2)

3. Presentations, published or submitted papers

a. **GV14-01a** Chhabra S, Liu Y, Hemmer MT, Costa L, Pidala JP, Couriel DR, Alousi AM, Majhail NS, Stuart RK, Kim D, Ringden O, Spellman SR, Arora M, Hamilton BK, et. al. ***Biology Blood Marrow Transplant.*** **2018 Aug 25.**

b. **GV14-01b** Hamilton BK, Liu Y, Hemmer MT, Costa L, Pidala JP, Couriel DR, Alousi AM, Majhail NS, Stuart RK, Kim D, Ringden O, Spellman SR, Arora M, Chhabra S, et. al. ***Submitted.***

c. **GV15-01b** Turcotte L, Wang T, Hemmer MT, Spellman SR, Arora M, Yingst A, Couriel DR, Alousi AM, Pidala J, Knight JM, Verneris MR. Proinflammatory cytokine and adipokine levels in adult unrelated marrow donors are not associated with hematopoietic cell transplantation outcomes. ***Biology Blood Marrow Transplant.*** **2018 Aug 23.**

d. **GV16-01a** Mehta R, Holtan S, Wang T, Hemmer MT, Arora M, Spellman SR, Alousi AM, Couriel DR, Pidala J, Weisdorf D. GVHD-free, relapse-free survival (GRFS) and chronic GVHD-free, relapse-free survival (CRFS) in alternative donor hematopoietic cell transplantation for adult patients with acute leukemia. ***Submitted.***

e. **GV16-01b** Mehta R, Holtan S, Wang T, Hemmer MT, Arora M, Spellman SR, Alousi AM, Couriel DR, Pidala J, Weisdorf D. GVHD-free, relapse-free survival (GRFS) and chronic GVHD-free, relapse-free survival (CRFS) in alternative donor hematopoietic cell transplantation for pediatric patients with acute leukemia. ***Submitted.***

f. **GV16-02** Saad A, Wang T, Hemmer MT, Spellman SR, Arora M, Lamb LS, Hashmi SK. Impact of T-cell dose on graft-versus-host disease risk after allogeneic HLA-matched peripheral blood stem cell transplantation. ***Poster presentation at ASH meeting in San Diego, CA, December 2018.***

g. **GV17-02** Im A, Wang T, Hemmer MT, Spellman SR, Arora M, Majhail NS, Pavletic SZ, Weisdorf DJ, Rashidi A, Hamilton BK. Risk factors of acute and chronic GVHD in haploidentical hematopoietic cell transplantation using post-transplant Cyclophosphamide. ***Poster presentation at TCT meeting in Houston, TX, February 2019.***

4. Future/proposed studies

a. **PROP 1803-03** Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients (N Gills/ E Padron/ A Lazaryan) (Attachment 3)

b. **PROP 1810-08/1811-55** Determining the optimal ATG dosing in conditioning regimen in patients with hematologic malignancies (M Byrne/ L Metheny/ M de Lima) (Attachment 4)

c. **PROP 1811-34** Cyclosporine vs tacrolimus based GVHD prophylaxis in children undergoing allogeneic hematopoietic cell transplantation (L Broglie/ P Satwani/ L Davis) (Attachment 5)

d. **PROP 1811-163** Racial and ethnic differences in patients with chronic graft versus host disease (N Farhadfar/ J Wingard/ S Lee) (Attachment 6)

Dropped proposed studies

e. **PROP 1811-158** Role of post-allogeneic hematopoietic cell transplant hypomethylating agents on the incidence and severity of graft-versus-host disease in patients with myelodysplastic syndrome and acute myeloid leukemia. *Small sample size of patients with valid date available for post-HCT hypomethylating agents.*

f. **PROP 1812-08** The impact of recipient abnormal Stimulator of Interferon Genes (STING) genotypes on acute and chronic graft-versus-host disease after matched unrelated donor allogeneic HCT. *Withdrawn.*

5. **Studies in progress** (Attachment 7)
   a. **GV17-01** Investigating antibiotic exposure and risk of acute GVHD in children undergoing HCT for acute leukemia (C Elgarten/ B Fisher/ R Aplenc) **Protocol Development**
   b. **GV17-03** Alterations in the characteristics and outcomes of GVHD following post-transplant Cy for haploidentical HCT and in patients over 60 at high risk for GVHD (R Saliba/ S Ciurea/ J Schriber) **Analysis**
   c. **GV18-01** Comparison of late effects among allogeneic hematopoietic cell transplantation survivors with and without chronic graft-versus-host disease (Lee CJ/ Couriel DR) **Protocol Development**
   b. **GV18-02** Comparison of antibacterial prophylaxis strategies and outcomes in allogeneic hematopoietic cell transplantation patients with acute graft-versus-host disease (Wallis W/ Alousi AM/ Gulbis A) **Data File Preparation**
   b. **GV18-03** Impact of chronic graft-versus-host disease on non-relapse mortality and disease relapse in transplant recipients (Bhatt V/ Lee SJ) **Protocol Development**

6. **Other Business**

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR GRAFT-VERSUS-HOST DISEASE
Salt Lake City, UT
Friday, February 23, 2018, 12:15 – 2:15 pm

Co-Chair:	**Daniel Couriel, MD, University of Utah, Salt Lake City, UT;**
	Telephone: 801-585-7121; E-mail: daniel.couriel@hci.utah.edu
Co-Chair:	**Amin Alousi, MD, MD Anderson Cancer Center, Houston, TX;**
	Telephone: 713-745-8613; E-mail: aalousi@mdanderson.org
Co-Chair:	**Joseph Pidala, MD, PhD, H. Lee Moffitt Cancer Center and Research Institute;**
	Telephone: 813-745-2556; E-mail: joseph.pidala@moffitt.org
Scientific Director:	**Mukta Arora, MD, MS, University of Minnesota Medical Center, Minneapolis, MN;**
	Telephone: 612-626-4105; E-mail: arora005@umn.edu
Scientific Director:	**Stephen Spellman, MBS, CIBMTR Statistical Center, Minneapolis, MN;**
	Telephone: 763-406-8334; E-mail: sspellma@nmdp.org
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	Telephone: 414-955-4339; E-mail: taowang@mcw.edu
Statistical Director:	**Ying Liu, PhD, CIBMTR, Medical College of Wisconsin, Milwaukee, WI;**
	Telephone: 414-955-8280, E-mail: yiliu@mcw.edu
Statistician:	**Michael Hemmer, MS, CIBMTR Statistical Center, Milwaukee, WI;**
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1. Introduction

The CIBMTR Graft-versus-Host Disease Working Committee (GVWC) was called to order at 12:15 pm on Friday, February 23rd, 2018, by Dr. Daniel Couriel. The GVWC Leadership was introduced to the GVWC members. Dr. Couriel introduced the new incoming GVWC Co-Chair, Dr. Madan Jagasia, who would be replacing Dr. Couriel, who had fulfilled his 5-year term as Co-Chair. Dr. Amin Alousi thanked Dr. Couriel for his contributions to the GVWC and presented him with a gift. Dr. Couriel reminded those in attendance that scanning their badges as they entered the conference room would include them in the GVWC email list, so they would receive invitations to participate in new studies seeking input. The voting sheet was explained and presenters were reminded they would be allowed 5 minutes to present, followed by approximately 5 minutes for discussion.

2. Accrual Summary (Attachment 2)

Mr. Stephen Spellman led this section. Due to time restraints, Mr. Spellman referenced that the accrual summary tables would not be presented at this meeting, but are available with the meeting materials online, and should be consulted while considering submitting a proposal idea. Mr. Spellman presented an overview of the CIBMTR, BMT CTN and Chronic GVHD Consortium research repository collections, and encouraged prospective investigators to utilize this resource to enhance their studies.

3. Presentations, published or submitted papers

Due to the full agenda, the 2017 presentations, published or submitted papers were mentioned, but not presented. Mr. Spellman noted that study **GV15-01a** was in press by ***Bone Marrow Transplant***, as of late January 2018.

a. **GV14-02** Qayed M, Arora M, Wang T, Spellman SR, Hemmer MT, Pidala J, Couriel DR, Alousi AM, Horan J. Influence of age on acute and chronic GVHD in children undergoing HLA-identical sibling BMT for acute leukemia: Implications for prophylaxis. ***Biology Blood Marrow Transplant.*** **2017 Nov; [Epub ahead of print].**

b. **GV13-01** Kumar AJ, Soyoung K, Hemmer MT, Arora M, Spellman SR, Pidala J, Couriel DR, Alousi AM, Loren AW. Graft versus host disease in recipients of male unrelated donor compared to parous female sibling donor transplants. ***Submitted.***

c. **GV15-01a** Turcotte L, Wang T, Hemmer MT, Spellman SR, Arora M, Couriel DR, Alousi AM, Pidala J, Knight JM, Verneris M. Donor body mass index does not predict graft-versus-host-disease following hematopoietic cell transplantation. ***Submitted.***

d. **GV15-02** Alousi AM, Wang T, Hemmer MT, Spellman SR, Arora M, Couriel DR, Pidala J, Weisdorf D. Peripheral blood versus bone marrow from unrelated donors: Bone marrow allografts have improved long-term overall and graft-versus-host disease, relapse-free survival. ***Submitted.***

e. **GV16-01** Mehta R, Holtan S, Wang T, Hemmer MT, Arora M, Spellman SR, Alousi AM, Couriel DR, Pidala J, Weisdorf D. Graft-versus-host disease-free relapse-free survival and chronic GVHD in alternative donor hematopoietic cell transplantation in adults and pediatric patients. ***Oral and poster presentation at ASH meeting in Atlanta, GA, December 2017.***

4. Future/proposed studies

Dr. Joseph Pidala led this section. Dr. Pidala began by reminding presenters they had 5 minutes to present, which would then be followed by 5 minutes of discussion, and also reminded the GVWC members how to vote on the voting sheets.

a. **PROP 1710-24** Predictive value of pre-transplant gene expression profile in unrelated stem cell donor on recipient risk and severity of post-transplant GVHD (S Lachance/A Brasey) (Attachment 3)
Dr. Silvy Lachance presented the proposal. Dr. Lachance hypothesizes that gene expression in healthy stem cells from unrelated donors regulates the risk of GVHD in recipients following HCT, and will test this by evaluating the gene expression profile of CD4 T cells from unrelated stem cell donors. Dr. Lachance stated that it has already been demonstrated in the HLA-identical sibling donor setting that some genes expressed by the donor significantly increases the GVHD risk in the recipient. The impact of this proposal is that a priori knowledge of GVHD risk would improve transplant outcomes by defining a more refined donor selection process and immunosuppression strategy. There are 109 adult patients who underwent first alloHCT between 2000-2005 for AML, ALL, CML, or MDS with a T-cell replete PBSC graft from a 10/10-matched unrelated donor and have at least 2 donor sample vials available.
A GVWC member asked how the analysis will adjust for different GVHD prophylaxis strategies, which would impact the rates of GVHD. Dr. Lachance said that the previous analysis she had worked on had examined other factors known to impact GVHD, and would follow that process here. Questions were

raised to clarify the goal of the proposal, which Dr. Lachance explained would use the prior work in the related donor population as a discovery cohort, and then use the unrelated donor population as a validation cohort to test those findings. Another GVWC member expressed some concern with the small sample size, and suggested using a matched case-control approach to the analysis.

b. **PROP 1711-122** Impact of GVHD prophylaxis on outcome of single UCB transplantation in patients with non-malignant disorders (M Ayas) (Attachment 4)
Dr. Mouhab Ayas presented the proposal. Dr. Ayas noted that there still remains no consensus as to the best GVHD prophylaxis strategy among UCB transplantation. A recent CIBMTR study analyzing UCB transplantation in acute leukemia patients found that ATG was associated with lower rates of aGVHD, but no GVHD prophylaxis regimen was found to have a significant effect on outcomes. The aims of this proposal are to analyze the incidence of GVHD after single UCB transplantation in patients with non-malignant disorders. There are 797 patients who underwent first alloHCT for non-malignant disease with a single cord blood unit from an unrelated donor between 2000-2016.
A GVWC member asked how the investigator would handle the certain disorders, in particular the patients with Severe Aplastic Anemia (SAA) that make up about 10% of the gathered population, as these disorders carry a higher risk of graft rejection and prior infection. It was further suggested to exclude the SAA patients from the population. It was noted that, even besides this issue with SAA, there exists a lot of disease heterogeneity among the non-malignant disorders. A GVWC member asked what the difference is between this proposal and the recent CIBMTR publication investigating UCB transplantation in acute leukemia that was referenced in Dr. Ayas' presentation. The difference is that the populations are different from that publication, which evaluated hematological malignancies, and this proposal, investigating non-malignant disease. Another clarification was made into whether certain GVHD prophylaxis regimens would be excluded, specifically ex-vivo and in-vivo T-cell depletion. Dr. Ayas said that in-vivo T-cell depleted grafts would likely be included in the population, as that was such a significant factor in the published analysis.

c. **PROP 1711-04** Risk stratification by time to onset of acute GVHD. (H Choe/ S Lee) (Attachment 5)
The proposal was presented by Dr. Hannah Choe. Dr. Choe stated that it is known that early onset aGVHD has been associated with worse outcomes. However, there is no consensus on the specific risk associated with the timing of aGVHD onset, or how to define "early" or "late" aGVHD. Dr. Choe also claimed that the time to onset of aGVHD has not been analyzed yet using CIBMTR data. The hypothesis of this proposal is that early onset of aGVHD indicates a higher risk of NRM, cGVHD and resistance to treatment. Dr. Choe used the number of days from aGVHD onset and neutrophil recovery to define "early aGVHD" (aGVHD occurring within 10 days after neutrophil engraftment) "intermediate aGVHD" (11-56 days) and "late aGVHD" ($\underline{\geq}$ 57 days). There were 1635 patients with "early aGVHD", 2197 patients with "intermediate aGVHD", and 862 patients with "late aGVHD."
A GVWC member pointed out that the impact of time to aGVHD onset within their center was evaluated recently, where HLA mismatch proved to be an important factor among mismatched donors. Dr. Choe said that this proposal will only include matched donors. Another GVWC member emphasized caution in stating or concluding that any increased NRM in the early aGVHD onset group should automatically be attributed to aGVHD. Dr. Choe agreed, saying other causes of death could be responsible besides GVHD, and caution would be taken in drawing conclusions. A question was asked if the CIBMTR data collection forms differentiate between engraftment syndrome and GVHD development. Unfortunately the forms cannot definitively differentiate between those 2 outcomes. Another GVWC member speculated that different conditioning intensities could also explain the difference in NRM, and Dr. Choe said intensity would be included in the analysis. It was also suggested to consider the using different cutoffs to define "early", "intermediate" and "late" aGVHD, as the median time to aGVHD onset appears to be about 10 days post-neutrophil recovery.

d. **PROP 1711-163** Comparison of antibacterial prophylaxis strategies and outcomes in alloHCT patients with acute GVHD (W Wallis/ A Alousi/ A Gulbis) (Attachment 6)
The proposal was presented by Dr. Whitney Wallis. Dr. Wallis stated that there is currently a lack of consensus regarding antimicrobial prophylaxis in patients with aGVHD. The goal of the proposal is to determine the impact that aGVHD grade II-IV has on the incidence of bacterial bloodstream infections (BSI) through 100 days post-transplant. More specifically, the proposal will examine the influence of specific organs involved in aGVHD and their impact on BSI through day-100. Dr. Wallis is proposing to send out a formal survey to transplant centers, to get more detailed center-practice data on antibacterial prophylaxis strategies. It was also mentioned that such a survey is being circulated by Shernan Holtan and Dan Wesidorf. This study could inform our knowledge of BSI in patients experiencing aGVHD and attempt to answer if commonly prescribed antibacterial strategies are affecting BSI in this population. This study could also lead to a future validation in a prospective clinical trial. There are 5765 patients who underwent their first alloHCT between 2010-2016 and experienced aGVHD grade II-IV and were treated with systemic corticosteroids.
It was asked whether the CIBMTR can identify whether BSI occurred prior to aGVHD, or vice versa. The CIBMTR data forms collect date of infection and aGVHD, so that information is available. Unfortunately, central line access dates are not known. A suggestion was made to include patients who did not develop aGVHD, to be used as a comparative group. When asked if this analysis will evaluate the role that steroid therapy for aGVHD will have on BSI incidence, Dr. Mukta Arora said that the entire population is restricted to patients receiving systemic corticosteroids. We could evaluate aGVHD organ involvement on BSI.

e. **PROP 1710-10** Evaluating different ATG dosing of anti-thymocyte globulin in conditioning regimens for matched related and unrelated donor transplants (L Metheny/ M de Lima) (Attachment 7)
The proposal was presented by Dr. Leland Metheny. Dr. Metheny stated that while there is evidence that ATG can reduce the incidence of cGVHD, the optimum dosing of ATG is not known. The hypothesis of this proposal is that lower ATG dose could reduce cGVHD incidence without increasing infection and relapse rates. This hypothesis will be tested in a cohort of hematological malignancies with matched related and unrelated donors. There are 5136 adult patients who underwent first alloHCT for a hematological malignancy from a matched related or unrelated donor between 2008-2015. 1046 of these patients received ATG as a part of their conditioning regimen or GVHD prophylaxis treatments, while the remaining 4090 patients did not receive ATG.
A GVWC member suggested including known risk factors for cGVHD as covariates in this analysis to provide a more nuanced conclusion. For example, in a patient at very low risk for cGVHD, a very low dose of ATG might be more beneficial than the optimum dose for patients at higher cGVHD risk. It was asked if the CIBMTR data forms collect the date of administration or the brand of the ATG product used and unfortunately, neither of these data points are collected. To avoid any misinterpretation with different brands of ATG, it was recommended to restrict the population to US centers. Another shortcoming pointed out by the GVWC was that, in a recent publication from a single center analysis, an important predictor in cGVHD is the absolute neutrophil and lymphocyte count in the blood at the time of ATG administration, which is a factor the CIBMTR data forms do not collect.

f. **PROP 1709-04** Impact of chronic GVHD on non-relapse mortality and disease relapse (V Bhatt/S Lee) (Attachment 8)
The proposal was presented by Dr. Vijaya Bhatt. The purpose of this proposal is to study the impact of cGVHD on non-relapse mortality (NRM) among older transplant recipients. Dr. Bhatt's hypothesis is that transplant recipients who develop cGVHD experience significantly higher rates of NRM compared to patients without cGVHD, and that this adverse effect is more pronounced in older patients. Dr. Bhatt stated that this potential study is relevant today as older patients are increasingly receiving allogeneic HCT and they may experience more severe complications arising from cGVHD. This study

could suggest beneficial treatment strategies for these older patients to prevent cGVHD and perhaps lower their risk for NRM. There are 19087 patients who were 40 years of age or older at time of transplant, who underwent first alloHCT for a hematological malignancy between 2000-2013.
A GVWC member asked if the cGVHD consortium database would have the data to answer this question. Dr. Bhatt stated that this was evaluated in the consortium, but there were only approximately 100 patients over the age of 60 at the time of transplant in the dataset. There was then a discussion about the strengths of the using the consortium dataset, which would collect NIH cGVHD severity levels in greater detail, versus the CIBMTR registry database, which would have a much larger number of older patients being transplanted to make the findings more universally appropriate. A question was asked of Dr. Arora if her publication, which validated a cGVHD risk score measurement, featured age as a risk factor for cGVHD. Dr. Arora confirmed that age was a risk factor for cGVHD in that prior publication, but noted that this study is asking a different question, pertaining to NRM specifically in an older population with CGVHD.

g. **PROP 1711-162** Comparison of late effects among alloHCT survivors with and without cGVHD (C Lee/ D Couriel) (Attachment 9)
Dr. Catherine Lee presented the proposal. Dr. Lee stated the cGVHD is a known risk factor for several late effects, but the cumulative incidence and rate of these late effects have not been longitudinally assessed from the time of cGVHD diagnosis compared to HCT survivors without cGVHD. Dr. Lee hypothesized that the incidence of late effects is greater in HCT survivors with cGVHD compared to those without cGVHD, and that the type of late effect will vary depending on cGVHD characteristics, such as time of onset, onset type and duration, grade, severity, and organ involvement. The proposed analysis will further group late effects into malignant versus non-malignant late effects, and then evaluate the most frequently occurring late effects individually. These data could provide rationale to examine treatment algorithms, alternative screening and primary or secondary prevention practices for late effects in survivors with or without cGVHD. There were 17610 patients who underwent first alloHCT for a hematological malignancy between 2000-2016, and were alive and disease-free 1 year post-transplant.
A suggestion from a GVWC member was to evaluate overall survival post-late effect, for those patients who did develop a late effect. A clarification was made that the CIBMTR forms collect data on "late effects" in many different categories, such as pulmonary, thyroid and secondary malignancies. A question was raised as to whether infection, specifically, is categorized as a late effect on the CIBMTR forms, which it is not. However, infection could be described as a cause of death. Another GVWC member suggested to include the pre-transplant Sorror HCT-CI score, as that has proven to be a good predictor for mortality.

Dropped proposed studies

These proposals were not presented at the meeting, and Dr. Arora briefly explained the issues stemming from each proposal and why it would not be considered at this time. Dr. Arora also discussed the difference between the CIBMTR CRF and TED forms, and the distinctions in the depth of data collected.

h. **PROP 1710-01** Comparison of GVHD-free, relapse-free survival of haploidentical transplants using post-transplant Cyclophosphamide versus HLA-matched donor transplants in patients with hematologic malignancies. *Overlapped with current study **GV17-03***.

i. **PROP 1711-89** Impact of pre-allogeneic HCT checkpoint inhibition on development of GVHD. *Small sample size, due to recent FDA approval of checkpoint inhibition.*

j. **PROP 1711-108** Outcomes of haploidentical alloHCT with post-transplant Cy versus single-locus HLA-mismatched related alloHCT without post-transplant Cy. *Small sample size of single-locus HLA-mismatched related donors.*

k. **PROP 1711-159** Impact of donor source on 5-year GRFS in pediatric patients with high-risk hematological malignancies (K Page/ J Kurtzberg). *Lack of 5-year follow-up and small sample size of haploidentical pediatric patients. Overlap with **GV16-01**.*

5. Studies in progress (Attachment 10)

Dr. Arora presented a slide that demonstrated the progress made on every GVWC study so far in the 2017/18 academic year, and the remaining milestones remaining and intended to accomplish.

a. **GV14-01** Comparison of mycophenolate versus methotrexate in combination with a calcineurin inhibitor for GVHD prophylaxis in allogeneic HCT (B Hamilton/ S Chhabra/ N Majhail/ L Costa/ R Stuart/ D Kim/ O Ringden) **Manuscript Preparation**
b. **GV 15-01b** Pro-inflammatory cytokine and adipokine levels in adult unrelated marrow donors are not associated with HCT outcomes (L Turcotte/ M Verneris/ J Knight) **Manuscript Preparation**
c. **GV16-02** The impact of the graft T cell dose on the outcome of allogeneic HLA-matched peripheral blood stem cell transplantation (A Saad/ S Hashmi/ M Sharma/ L Lamb) **Manuscript Preparation**
d. **GV17-01** Investigating antibiotic exposure and risk of acute GVHD in children undergoing HCT for acute leukemia (C Elgarten/ B Fisher/ R Aplenc) **Protocol Development**
e. **GV17-02** Risk factors of GVHD in T-replete haploidentical HCT using post-transplant Cy (A Im/ B Hamilton/ A Rashidi/ N Majhail/ S Pavletic/ D Weisdorf) **Data File Preparation**
f. **GV17-03** Alterations in the characteristics and outcomes of GVHD following post-transplant Cy for haploidentical HCT and in patients over 60 at high risk for GVHD (R Saliba/ S Ciurea/ J Schriber) **Data File Preparation**

6. Other Business

Hearing no other calls for business to discuss, Dr. Alousi ended the meeting at 2:00 pm.

After the new proposals were presented, each participant in the meeting had the opportunity to rate each proposal using paper ballots. Based on the voting results, current scientific merit, available number or relevant cases and the impact of the study on the field, the following studies will move forward as the committee's research portfolio for the upcoming year:

PROP 1711-163 Comparison of antibacterial prophylaxis strategies and outcomes in alloHCT patients with acute GVHD (W Wallis/ A Alousi/ A Gulbis)

PROP 1711-162 Comparison of late effects among alloHCT survivors with and without cGVHD (C Lee/ D Couriel)

PROP 1709-04 Impact of chronic GVHD on non-relapse mortality and disease relapse (V Bhatt/S Lee)

Working Committee Overview Plan for 2018 – 2019

a. **GV17-01** Investigating antibiotic exposure and risk of acute GVHD in children undergoing HCT for acute leukemia (C Elgarten / B Fisher / R Aplenc)
The aims of the study are to determine the association of antibiotics commonly administered for neutropenic fever with subsequent development of post-HCT aGVHD among pediatric patients undergoing HCT for acute leukemia. The hypothesis is that these patients who are exposed to antibiotics with activity against anaerobic commensal microorganisms are associated with an increased risk of aGVHD.
We anticipate the preliminary results of the analysis will be ready by August 2018. We further anticipate submitting an abstract for Tandem by October 2018 and receiving the initial draft of the manuscript by December 2018. The initial manuscript will be revised by February 2019 and circulated to the Writing Committee by March 2019. We finally expect to submit the final manuscript for publication by May 2019. 150 statistical hours have been allocated to accomplish these goals.

b. **GV17-02** Risk factors for GVHD and outcomes in T-replete HLA-haploidentical HCT using post-transplant Cyclophosphamide (A Im / B Hamilton / A Rashidi / S Pavletic / N Majhail / D Weisdorf)
The aims of the study are to describe the incidence, characteristics and risk factors for acute and chronic GVHD in patients undergoing post-transplant Cyclophosphamide-based T-replete haploidentical HCT, specifically evaluating the impact of conditioning regimen intensity and graft source on GVHD. Secondary aims are to evaluate the incidence of other outcomes, including OS, relapse, TRM, GRFS, hematopoietic recovery and CMV viremia.
We anticipate that the data file will be prepared for analysis by August 2018. We further anticipate that the analysis will be completed by September 2018, and are hopeful an abstract can be submitted to Tandem by October 2018. We expect that the initial draft of the manuscript will be received by December 2018. 180 statistical hours have been allocated to accomplish these goals.

c. **GV17-03** Characteristics and outcomes of acute and chronic GVHD after haploidentical related donor allogeneic HCT (R Saliba / S Ciurea / J Schriber)
The aims of the study are to compare aGVHD, cGVHD, OS and TRM between patients receiving post-transplant Cyclophosphamide-based GVHD prophylaxis with those receiving standard GVHD prophylaxis. Patients over the age of 60, and therefore at greater risk for GVHD, will also be specifically examined in a subset analysis.
We anticipate that the data file will be prepared for analysis by October 2018, and that the analysis will be completed by November 2018. We then anticipate receiving the initial draft of the manuscript by February 2019. 180 statistical hours have been allocated to accomplish these goals.

d. **GV18-01** Comparison of late effects among alloHCT survivors with and without cGVHD (C Lee/ D Couriel)
This study will test whether the cumulative incidence rate of late effects is greater among alloHCT survivors with cGVHD versus those without cGVHD.
We anticipate receiving the draft protocol by July 2018, and finalizing the protocol by February 2019. We further anticipate preparing the data file for analysis by April 2019 and to have preliminary analysis results by June 2019. 160 statistical hours have been allocated to accomplish these goals.

e. **GV18-02** Comparison of antibacterial prophylaxis strategies and outcomes in alloHCT patients with acute GVHD (W Wallis/ A Alousi/ A Gulbis)
This study will evaluate the cumulative incidence of bacterial blood stream infections in patients with aGVHD grade II-IV, and compare patients between centers that give antibiotics for antibacterial prophylaxis versus those centers that do not.
We anticipate receiving the draft protocol by July 2018. We further anticipate finalizing the protocol by May 2019. 60 statistical hours have been allocated to accomplish these goals.

f. **GV18-03** Impact of chronic GVHD on non-relapse mortality and disease relapse (V Bhatt/S Lee)
This study will evaluate the cumulative incidence of non-relapse mortality and relapse between patients who have cGVHD versus those without cGVHD, as well as between older versus younger patients.
We anticipate receiving the draft protocol by July 2018. We further anticipate finalizing the protocol by June 2019. 60 statistical hours have been allocated to accomplish these goals.

Oversight Assignment for Working Committee Leadership (March 2018)

Amin Alousi	**GV17-01** Investigating antibiotic exposure and risk of acute GVHD in children undergoing HCT for acute leukemia **GV17-02**: Risk factors for GVHD and outcomes in T-replete HLA-haploidentical HCT using post-transplant Cyclophosphamide
Joseph Pidala	**GV17-03** Characteristics and outcomes of acute and chronic GVHD after haploidentical related donor allogeneic HCT **GV18-01**: Comparison of late effects among alloHCT survivors with and without cGVHD
Madan Jagasia	**GV18-02**: Comparison of antibacterial prophylaxis strategies and outcomes in alloHCT patients with acute GVHD **GV18-03**: Impact of chronic GVHD on non-relapse mortality and disease relapse

Accrual Summary for the Graft-vs-Host Disease Working Committee

Characteristics of leukemia patients receiving allogeneic HCT between 1990-2018

Accrual Table 1. Leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Number of patients	**28668**	**3971**	**1351**	**33844**	**6535**
Number of centers	445	318	286	398	250
Age at transplant, years, median (range)	38 (<1-78)	38 (<1-88)	38 (<1-78)	42 (<1-83)	19 (<1-83)
Disease					
AML	11004 (38)	1766 (44)	577 (43)	12913 (38)	2986 (46)
ALL	5453 (19)	912 (23)	299 (22)	6425 (19)	2167 (33)
Other leukemia	1396 (5)	145 (4)	76 (6)	1704 (5)	272 (4)
MDS	4195 (15)	753 (19)	213 (16)	6950 (21)	840 (13)
CML	6620 (23)	395 (10)	186 (14)	5852 (17)	270 (4)
Sex					
Male	16781 (59)	2381 (60)	777 (58)	19847 (59)	3612 (55)
Female	11884 (41)	1590 (40)	574 (42)	13994 (41)	2923 (45)
Missing	3 (<1)	0	0	3 (<1)	0
Graft source					
Bone marrow	14943 (52)	1676 (42)	494 (37)	16860 (50)	-
Peripheral blood	12886 (45)	2184 (55)	811 (60)	16521 (49)	-
Missing	839 (3)	111 (3)	46 (3)	463 (1)	-
GVHD prophylaxis					
None	1317 (5)	123 (3)	299 (22)	499 (1)	31 (<1)
Ex-vivo T-cell depletion	1601 (6)	624 (16)	105 (8)	2940 (9)	31 (<1)
CD34 selection	415 (1)	234 (6)	37 (3)	577 (2)	202 (3)
Post-transplant Cy ± others	249 (<1)	1734 (44)	68 (5)	563 (2)	8 (<1)
Tac + MTX alone	3128 (11)	114 (3)	163 (12)	7679 (23)	199 (3)
Tac + MTX + others	967 (3)	41 (1)	46 (3)	3610 (11)	135 (2)
Tac + MMF alone	537 (2)	120 (3)	32 (2)	1445 (4)	932 (14)
Tac + MMF + others	184 (<1)	73 (2)	13 (<1)	736 (2)	306 (5)
Tac alone	219 (<1)	13 (<1)	29 (2)	758 (2)	158 (2)
Tac + others	465 (2)	12 (<1)	21 (2)	833 (2)	252 (4)
CsA + MTX alone	13520 (47)	593 (15)	239 (18)	8616 (25)	265 (4)
CsA + MTX + others	783 (3)	55 (1)	35 (3)	1999 (6)	128 (2)
CsA + MMF alone	804 (3)	24 (<1)	40 (3)	1257 (4)	2016 (31)
CsA + MMF + others	84 (<1)	4 (<1)	6 (<1)	355 (1)	372 (6)
CsA alone	2578 (9)	102 (3)	83 (6)	782 (2)	1110 (17)
CsA + others	858 (3)	32 (<1)	12 (<1)	386 (1)	277 (4)
Others	507 (2)	30 (<1)	39 (3)	300 (<1)	95 (1)
Missing	452 (2)	43 (1)	84 (6)	509 (2)	18 (<1)

Accrual Table 1. Leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Number of patients	**28668**	**3971**	**1351**	**33844**	**6535**
Conditioning regimen intensity					
Myeloablative	23407 (82)	2378 (60)	950 (70)	24259 (72)	4802 (73)
RIC	2475 (9)	452 (11)	158 (12)	6264 (19)	633 (10)
NMA	1280 (4)	913 (23)	103 (8)	1991 (6)	958 (15)
Missing	1506 (5)	228 (6)	140 (10)	1330 (4)	142 (2)
Grade of aGVHD					
None	13127 (46)	1699 (43)	720 (53)	11003 (33)	2628 (40)
Grade I	4649 (16)	631 (16)	171 (13)	5555 (16)	995 (15)
Grade II	3921 (14)	747 (19)	126 (9)	7296 (22)	1347 (21)
Grade III	3527 (12)	426 (11)	127 (9)	5144 (15)	833 (13)
Grade IV	1276 (4)	190 (5)	36 (3)	2740 (8)	369 (6)
Missing	2168 (8)	278 (7)	171 (13)	2106 (6)	363 (6)
Organ involvement of aGVHD					
Skin	975 (11)	280 (21)	41 (14)	2651 (17)	485 (19)
Skin + Liver	1356 (15)	106 (8)	22 (8)	1571 (10)	111 (4)
Skin + Liver + UGI	76 (<1)	9 (<1)	3 (1)	211 (1)	24 (<1)
Skin + Liver + LGI	1888 (21)	189 (14)	50 (17)	2572 (17)	239 (9)
Skin + Liver + UGI + LGI	263 (3)	39 (3)	13 (4)	677 (4)	99 (4)
Skin + UGI	345 (4)	71 (5)	13 (4)	1039 (7)	180 (7)
Skin + LGI	1626 (19)	255 (19)	59 (20)	2722 (18)	495 (20)
Liver	284 (3)	18 (1)	12 (4)	244 (2)	41 (2)
Liver + UGI	41 (<1)	5 (<1)	1 (<1)	52 (<1)	12 (<1)
Liver + LGI	319 (4)	29 (2)	3 (1)	319 (2)	58 (2)
Liver + UGI + LGI	82 (<1)	14 (1)	3 (1)	142 (<1)	37 (1)
UGI	299 (3)	88 (6)	8 (3)	723 (5)	161 (6)
LGI	688 (8)	106 (8)	30 (10)	960 (6)	218 (9)
UGI + LGI	246 (3)	58 (4)	22 (8)	485 (3)	156 (6)
Missing	296 (3)	92 (7)	13 (4)	836 (5)	222 (9)
Incidence of cGVHD					
No	18292 (64)	2921 (74)	982 (73)	19219 (57)	4784 (73)
Yes	9277 (32)	938 (24)	286 (21)	13029 (38)	1533 (23)
Missing	1099 (4)	112 (3)	83 (6)	1596 (5)	218 (3)
Maximum grade of cGVHD					
Limited	2983 (32)	278 (30)	80 (28)	2736 (21)	592 (39)
Extensive	6155 (66)	649 (69)	197 (69)	10072 (77)	912 (59)
Missing	139 (1)	11 (1)	9 (3)	221 (2)	29 (2)

Accrual Table 1. Leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Number of patients	**28668**	**3971**	**1351**	**33844**	**6535**
Overall severity of cGVHD					
Mild	3878 (42)	440 (47)	109 (38)	4444 (34)	875 (57)
Moderate	3278 (35)	307 (33)	97 (34)	3831 (29)	381 (25)
Severe	1916 (21)	172 (18)	67 (23)	2599 (20)	228 (15)
Missing	205 (2)	19 (2)	13 (5)	2155 (17)	49 (3)
Year of transplant					
1990-1994	8203 (29)	450 (11)	211 (16)	3103 (9)	33 (<1)
1995-1999	7078 (25)	523 (13)	292 (22)	6236 (18)	406 (6)
2000-2004	5346 (19)	422 (11)	185 (14)	7828 (23)	918 (14)
2005-2009	4120 (14)	383 (10)	264 (20)	8634 (26)	2114 (32)
2010-2014	2212 (8)	616 (16)	206 (15)	4366 (13)	2066 (32)
2015-2018	1709 (6)	1577 (40)	193 (14)	3677 (11)	998 (15)
Follow-up of survivors, months, median (range)	76 (<1-319)	19 (<1-300)	47 (<1-316)	72 (<1-314)	58 (<1-265)

Abbreviations: AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, CML=Chronic myelogenous leukemia, MDS=Myelodysplastic-myeloproliferative diseases, RIC=Reduced intensity conditioning, NMA=Non-myeloablative, Cy=Cyclophosphamide, Tac=Tacrolimus, MTX=Methotrexate, MMF=Mycophenolate mofetil, CsA=Cyclosporine, UGI=Upper gastrointestinal, LGI=Lower gastrointestinal.

Characteristics of non-leukemia patients receiving allogeneic HCT between 1990-2018

Accrual Table 2. Non-leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Number of patients	**13041**	**1675**	**1198**	**8989**	**3164**
Number of centers	436	239	269	324	210
Age at transplant, years, median (range)	26 (<1-79)	12 (<1-76)	27 (<1-77)	28 (<1-79)	5 (<1-73)
Disease					
NHL	3238 (25)	344 (21)	267 (22)	2982 (33)	521 (16)
HD	448 (3)	110 (7)	60 (5)	703 (8)	135 (4)
SAA	3324 (25)	251 (15)	172 (14)	1509 (17)	179 (6)
MM	1689 (13)	51 (3)	225 (19)	697 (8)	48 (2)
Inherited abnormalities of erythrocyte diff-or function	2785 (21)	252 (15)	178 (15)	874 (10)	514 (16)
SCID & other immune system disorders	604 (5)	479 (29)	181 (15)	868 (10)	718 (23)
Inherited abnormality of platelets	27 (<1)	5 (<1)	2 (<1)	39 (<1)	38 (1)
Histiocytic disorders	119 (<1)	58 (3)	19 (2)	354 (4)	227 (7)
Inherited disorders of metabolism	211 (2)	83 (5)	22 (2)	546 (6)	681 (22)
Others	596 (5)	42 (3)	72 (6)	417 (5)	103 (3)
Sex					
Male	7775 (60)	1041 (62)	680 (57)	5610 (62)	1902 (60)
Female	5266 (40)	634 (38)	518 (43)	3379 (38)	1262 (40)
GVHD prophylaxis					
None	508 (4)	45 (3)	354 (30)	90 (1)	27 (<1)
Ex-vivo T-cell depletion	582 (4)	389 (23)	77 (6)	881 (10)	17 (<1)
CD34 selection	239 (2)	157 (9)	32 (3)	327 (4)	52 (2)
Post-transplant Cy ± others	367 (3)	555 (33)	44 (4)	125 (1)	9 (<1)
Tac + MTX alone	917 (7)	23 (1)	54 (5)	1553 (17)	101 (3)
Tac + MTX + others	344 (3)	22 (1)	21 (2)	785 (9)	36 (1)
Tac + MMF alone	278 (2)	38 (2)	34 (3)	486 (5)	336 (11)
Tac + MMF + others	105 (<1)	33 (2)	11 (<1)	203 (2)	121 (4)
Tac alone	125 (<1)	11 (<1)	23 (2)	277 (3)	94 (3)
Tac + others	148 (1)	4 (<1)	11 (<1)	209 (2)	128 (4)
CsA + MTX alone	5687 (44)	204 (12)	207 (17)	1847 (21)	178 (6)
CsA + MTX + others	432 (3)	30 (2)	17 (1)	384 (4)	57 (2)
CsA + MMF alone	716 (5)	24 (1)	45 (4)	667 (7)	875 (28)
CsA + MMF + others	69 (<1)	1 (<1)	4 (<1)	126 (1)	115 (4)
CsA alone	1761 (14)	81 (5)	120 (10)	491 (5)	814 (26)
CsA + others	421 (3)	19 (1)	16 (1)	197 (2)	155 (5)
Others	173 (1)	21 (1)	22 (2)	117 (1)	39 (1)
Missing	169 (1)	18 (1)	106 (9)	224 (2)	10 (<1)

Accrual Table 2. Non-leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Number of patients	**13041**	**1675**	**1198**	**8989**	**3164**
Graft source					
Bone marrow	7878 (60)	854 (51)	543 (45)	4932 (55)	-
Peripheral blood	4855 (37)	771 (46)	638 (53)	3889 (43)	-
Missing	308 (2)	50 (3)	17 (1)	168 (2)	-
Conditioning regimen intensity					
Myeloablative	8035 (62)	765 (46)	662 (55)	3934 (44)	2008 (63)
RIC	1271 (10)	198 (12)	200 (17)	2367 (26)	471 (15)
NMA	2886 (22)	510 (30)	176 (15)	2164 (24)	598 (19)
Missing	849 (7)	202 (12)	160 (13)	524 (6)	87 (3)
Grade of aGVHD					
None	7393 (57)	867 (52)	811 (68)	3843 (43)	1532 (48)
Grade I	1739 (13)	221 (13)	97 (8)	1263 (14)	481 (15)
Grade II	1422 (11)	227 (14)	99 (8)	1488 (17)	522 (16)
Grade III	1227 (9)	154 (9)	75 (6)	1121 (12)	294 (9)
Grade IV	427 (3)	75 (4)	22 (2)	630 (7)	148 (5)
Missing	833 (6)	131 (8)	94 (8)	644 (7)	187 (6)
Organ involvement of aGVHD					
Skin	476 (15)	104 (23)	36 (18)	629 (20)	245 (26)
Skin + Liver	437 (14)	34 (7)	19 (10)	255 (8)	45 (5)
Skin + Liver + UGI	26 (<1)	0	0	35 (1)	7 (<1)
Skin + Liver + LGI	558 (18)	74 (16)	15 (8)	485 (15)	83 (9)
Skin + Liver + UGI + LGI	72 (2)	7 (2)	11 (6)	118 (4)	31 (3)
Skin + UGI	87 (3)	10 (2)	2 (1)	181 (6)	56 (6)
Skin + LGI	688 (22)	86 (19)	44 (22)	658 (20)	208 (22)
Liver	100 (3)	8 (2)	6 (3)	53 (2)	8 (<1)
Liver + UGI	8 (<1)	1 (<1)	2 (1)	10 (<1)	3 (<1)
Liver + LGI	111 (4)	13 (3)	5 (3)	104 (3)	27 (3)
Liver + UGI + LGI	16 (<1)	10 (2)	5 (3)	37 (1)	9 (<1)
UGI	83 (3)	20 (4)	5 (3)	129 (4)	31 (3)
LGI	277 (9)	38 (8)	27 (14)	275 (9)	85 (9)
UGI + LGI	57 (2)	16 (4)	11 (6)	90 (3)	46 (5)
Missing	90 (3)	34 (7)	9 (5)	166 (5)	70 (7)

Accrual Table 2. Non-leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Number of patients	**13041**	**1675**	**1198**	**8989**	**3164**
Incidence of cGVHD					
No	9729 (75)	1346 (80)	997 (83)	5652 (63)	2364 (75)
Yes	2798 (21)	277 (17)	148 (12)	2908 (32)	669 (21)
Missing	514 (4)	52 (3)	53 (4)	429 (5)	131 (4)
Maximum grade of cGVHD					
Limited	1030 (37)	106 (38)	61 (41)	694 (24)	307 (46)
Extensive	1694 (61)	167 (60)	83 (56)	2120 (73)	347 (52)
Missing	74 (3)	4 (1)	4 (3)	94 (3)	15 (2)
Overall severity of cGVHD					
Mild	1284 (46)	135 (49)	77 (52)	1076 (37)	370 (55)
Moderate	921 (33)	84 (30)	38 (26)	829 (29)	177 (26)
Severe	510 (18)	51 (18)	26 (18)	630 (22)	102 (15)
Missing	83 (3)	7 (3)	7 (5)	373 (13)	20 (3)
Year of transplant					
1990-1994	2784 (21)	221 (13)	140 (12)	577 (6)	23 (<1)
1995-1999	3135 (24)	219 (13)	236 (20)	1175 (13)	205 (6)
2000-2004	3450 (26)	241 (14)	157 (13)	2450 (27)	525 (17)
2005-2009	2020 (15)	232 (14)	257 (21)	2783 (31)	1071 (34)
2010-2014	632 (5)	223 (13)	209 (17)	976 (11)	911 (29)
2015-2017	1020 (8)	539 (32)	199 (17)	1028 (11)	429 (14)
Follow-up of survivors, months, median (range)	77 (1-316)	34 (<1-313)	52 (1-297)	72 (<1-312)	61 (<1-268)

Abbreviations: NHL=Non-Hodgkin lymphoma, HD=Hodgkin disease, SAA=Severe aplastic anemia, MM=Multiple myeloma, SCID=Severe combined immunodeficiency, RIC=Reduced intensity conditioning, NMA=Non-myeloablative, Cy=Cyclophosphamide, Tac=Tacrolimus, MTX=Methotrexate, MMF=Mycophenolate mofetil, CsA=Cyclosporine, UGI=Upper gastrointestinal, LGI=Lower gastrointestinal.

Unrelated Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired samples, recipient only samples and donor only samples.

Accrual Table 3. **Unrelated donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**18751**	**5365**	**3448**
Source of data			
CRF	9904 (53)	2470 (46)	2008 (58)
TED	8847 (47)	2895 (54)	1440 (42)
Number of centers	231	199	295
Disease at transplant			
AML	12782 (68)	3782 (70)	2223 (64)
ALL	5581 (30)	1464 (27)	1153 (33)
Other acute leukemia	388 (2)	119 (2)	72 (2)
AML Disease status at transplant			
First complete remission	6446 (50)	1924 (51)	970 (44)
Second complete remission	2591 (20)	762 (20)	469 (21)
Third, or greater, complete remission	257 (2)	70 (2)	50 (2)
Advanced or active disease	3341 (26)	989 (26)	687 (31)
Missing	143 (1)	37 (1)	43 (2)
ALL Disease status at transplant			
First complete remission	2643 (47)	730 (50)	464 (40)
Second complete remission	1641 (29)	402 (27)	344 (30)
Third, or greater, complete remission	466 (8)	120 (8)	111 (10)
Advanced or active disease	787 (14)	198 (14)	202 (18)
Missing	44 (1)	14 (1)	31 (3)
Recipient age at transplant			
0-9 years	1438 (8)	374 (7)	368 (11)
10-19 years	1942 (10)	493 (9)	476 (14)
20-29 years	2348 (13)	646 (12)	496 (14)
30-39 years	2259 (12)	605 (11)	468 (14)
40-49 years	2888 (15)	817 (15)	520 (15)
50-59 years	3605 (19)	1000 (19)	553 (16)
60-69 years	3569 (19)	1178 (22)	486 (14)
70+ years	702 (4)	252 (5)	81 (2)
Median (Range)	45 (0-84)	47 (0-79)	38 (0-76)

Accrual Table 3. **Unrelated donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**18751**	**5365**	**3448**
Recipient race/ethnicity			
Caucasian, non-Hispanic	15606 (85)	4459 (85)	2554 (82)
African-American, non-Hispanic	696 (4)	194 (4)	141 (5)
Asian, non-Hispanic	435 (2)	175 (3)	122 (4)
Pacific islander, non-Hispanic	23 (<1)	8 (<1)	9 (<1)
Native American, non-Hispanic	75 (<1)	21 (<1)	15 (<1)
Hispanic	1411 (8)	372 (7)	259 (8)
Other	18 (<1)	11 (<1)	10 (<1)
Unknown	487 (N/A)	125 (N/A)	338 (N/A)
Recipient sex			
Male	10386 (55)	2978 (56)	1960 (57)
Female	8365 (45)	2387 (44)	1488 (43)
Karnofsky score			
10-80	6508 (35)	1962 (37)	1048 (30)
90-100	11534 (62)	3120 (58)	2125 (62)
Missing	709 (4)	283 (5)	275 (8)
HLA-A B DRB1 groups - low resolution			
≤ 3/6	13 (<1)	16 (<1)	0
4/6	86 (<1)	42 (1)	14 (<1)
5/6	2655 (14)	674 (14)	531 (16)
6/6	15809 (85)	3927 (84)	2693 (83)
Unknown	188 (N/A)	706 (N/A)	210 (N/A)
High-resolution HLA matches available out of 8			
≤ 5/8	370 (2)	43 (1)	18 (1)
6/8	813 (4)	58 (2)	60 (3)
7/8	3761 (21)	687 (19)	502 (24)
8/8	13280 (73)	2800 (78)	1513 (72)
Unknown	527 (N/A)	1777 (N/A)	1355 (N/A)
HLA-DPB1 Match			
Double allele mismatch	4696 (30)	320 (28)	158 (30)
Single allele mismatch	8405 (54)	569 (49)	284 (53)
Full allele matched	2548 (16)	269 (23)	93 (17)
Unknown	3102 (N/A)	4207 (N/A)	2913 (N/A)
High resolution release score			
No	229 (2)	71 (44)	194 (70)
Yes	14457 (98)	92 (56)	83 (30)
Unknown	4065 (N/A)	5202 (N/A)	3171 (N/A)

Accrual Table 3. **Unrelated donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**18751**	**5365**	**3448**
KIR typing available			
No	10254 (55)	5300 (99)	3426 (99)
Yes	8497 (45)	65 (1)	22 (1)
Graft type			
BM	6595 (35)	1776 (33)	1489 (43)
PBSC	12145 (65)	3525 (66)	1957 (57)
BM+PBSC	4 (<1)	5 (<1)	1 (<1)
BM+UCB	0	1 (<1)	0
PBSC+UCB	7 (<1)	58 (1)	1 (<1)
Conditioning regimen			
Myeloablative	13747 (73)	3778 (70)	2623 (76)
RIC/Nonmyeloablative	4928 (26)	1574 (29)	781 (23)
TBD	76 (<1)	13 (<1)	44 (1)
Donor age at donation			
TBD/NA	95 (1)	666 (12)	29 (1)
0-9 years	8 (<1)	10 (<1)	0
10-19 years	548 (3)	155 (3)	81 (2)
20-29 years	8357 (45)	2110 (39)	1292 (37)
30-39 years	5304 (28)	1375 (26)	1076 (31)
40-49 years	3379 (18)	802 (15)	747 (22)
50+ years	1060 (6)	247 (5)	223 (6)
Median (Range)	31 (0-61)	30 (0-73)	33 (18-67)
Donor/Recipient CMV serostatus			
+ / +	4848 (26)	1537 (30)	872 (27)
+ / -	2104 (11)	636 (12)	420 (13)
- / +	6571 (36)	1707 (33)	1126 (34)
- / -	4946 (27)	1265 (25)	860 (26)
UCB / +	0	3 (<1)	0
UCB / -	0	1 (<1)	0
UCB / recipient CMV unknown	0	1 (<1)	0
Unknown	282 (N/A)	215 (N/A)	170 (N/A)

Accrual Table 3. **Unrelated donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**18751**	**5365**	**3448**
GvHD Prophylaxis			
Ex vivo T-cell depletion	539 (3)	133 (2)	160 (5)
CD34 selection	290 (2)	122 (2)	53 (2)
TAC + MMF ± others	2056 (11)	575 (11)	237 (7)
TAC + MTX ± others (except MMF)	8887 (47)	2528 (47)	1062 (31)
TAC + others (except MTX, MMF)	1003 (5)	345 (6)	136 (4)
TAC alone	470 (3)	150 (3)	64 (2)
CSA + MMF ± others (except Tacrolimus)	1002 (5)	242 (5)	226 (7)
CSA + MTX ± others (except Tacrolimus, MMF)	3015 (16)	763 (14)	1082 (31)
CSA + others (except Tacrolimus, MTX, MMF)	318 (2)	107 (2)	125 (4)
CSA alone	220 (1)	69 (1)	132 (4)
Other GVHD prophylaxis	302 (2)	87 (2)	57 (2)
Missing	649 (3)	244 (5)	114 (3)
Donor/Recipient sex match			
Male / Male	7375 (40)	2003 (38)	1301 (38)
Male / Female	5093 (27)	1391 (26)	871 (25)
Female / Male	2962 (16)	919 (17)	648 (19)
Female / Female	3231 (17)	932 (18)	604 (18)
UCB / Male	2 (<1)	31 (1)	0
UCB / Female	5 (<1)	28 (1)	1 (<1)
Unknown	83 (N/A)	61 (N/A)	23 (N/A)
Year of transplant			
1986-1990	119 (1)	17 (<1)	32 (1)
1991-1995	708 (4)	189 (4)	252 (7)
1996-2000	1320 (7)	475 (9)	430 (12)
2001-2005	2477 (13)	516 (10)	736 (21)
2006-2010	4581 (24)	957 (18)	740 (21)
2011-2015	6598 (35)	1865 (35)	877 (25)
2016-2019	2948 (16)	1346 (25)	381 (11)
Follow-up among survivors, Months			
N Eval	7780	2392	1242
Median (Range)	48 (1-337)	36 (1-325)	47 (1-337)

Abbreviations: CRF=Comprehensive report form, TED=Transplant essential data, AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, UCB=Umbilical cord blood, BM=Bone marrow, PBSC=Peripheral blood stem cells, RIC=Reduced intensity conditioning, TBD=To be determined, NA=Not applicable, Post-CY=Post-transplant Cyclophosphamide, TAC=Tacrolimus, MMF=Mycophenolate mofetil, MTX=Methotrexate, CsA=Cyclosporine.

* Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006). Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Unrelated Cord Blood Transplant Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired, recipient only and cord blood only samples.

Accrual Table 4. **Unrelated cord blood research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**3077**	**689**	**670**
Source of data			
CRF	2324 (76)	533 (77)	454 (68)
TED	753 (24)	156 (23)	216 (32)
Number of centers	135	111	154
Disease at transplant			
AML	1937 (63)	411 (60)	381 (57)
ALL	1060 (34)	259 (38)	268 (40)
Other acute leukemia	80 (3)	19 (3)	21 (3)
AML Disease status at transplant			
First complete remission	966 (50)	219 (53)	192 (50)
Second complete remission	548 (28)	104 (25)	104 (27)
Third, or greater, complete remission	51 (3)	6 (1)	11 (3)
Advanced or active disease	364 (19)	80 (20)	72 (19)
Missing	8 (<1)	1 (<1)	2 (1)
ALL Disease status at transplant			
First complete remission	477 (45)	108 (42)	122 (46)
Second complete remission	397 (37)	100 (39)	95 (35)
Third, or greater, complete remission	118 (11)	35 (14)	28 (10)
Advanced or active disease	68 (6)	16 (6)	23 (9)
Recipient age at transplant			
0-9 years	689 (22)	211 (31)	181 (27)
10-19 years	460 (15)	110 (16)	121 (18)
20-29 years	351 (11)	51 (7)	61 (9)
30-39 years	346 (11)	70 (10)	75 (11)
40-49 years	348 (11)	70 (10)	68 (10)
50-59 years	445 (14)	84 (12)	84 (13)
60-69 years	387 (13)	81 (12)	74 (11)
70+ years	51 (2)	12 (2)	6 (1)
Median (Range)	31 (0-81)	26 (0-75)	25 (0-78)

Accrual Table 4. **Unrelated cord blood research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**3077**	**689**	**670**
Recipient race/ethnicity			
Caucasian, non-Hispanic	1733 (59)	409 (63)	371 (62)
African-American, non-Hispanic	388 (13)	77 (12)	66 (11)
Asian, non-Hispanic	191 (7)	35 (5)	48 (8)
Pacific islander, non-Hispanic	16 (1)	2 (<1)	7 (1)
Native American, non-Hispanic	16 (1)	3 (<1)	6 (1)
Hispanic	572 (20)	126 (19)	101 (17)
Unknown	161 (N/A)	37 (N/A)	71 (N/A)
Recipient sex			
Male	1610 (52)	373 (54)	373 (56)
Female	1467 (48)	316 (46)	297 (44)
Karnofsky score			
10-80	813 (26)	173 (25)	159 (24)
90-100	2197 (71)	484 (70)	483 (72)
Missing	67 (2)	32 (5)	28 (4)
HLA-A B DRB1 groups - low resolution			
≤ 3/6	43 (1)	18 (3)	3 (<1)
4/6	1317 (45)	236 (44)	246 (39)
5/6	1287 (44)	211 (40)	301 (48)
6/6	311 (11)	67 (13)	74 (12)
Unknown	119 (N/A)	157 (N/A)	46 (N/A)
High-resolution HLA matches available out of 8			
≤ 5/8	1543 (59)	236 (60)	277 (55)
6/8	623 (24)	90 (23)	127 (25)
7/8	313 (12)	37 (9)	76 (15)
8/8	142 (5)	28 (7)	28 (6)
Unknown	456 (N/A)	298 (N/A)	162 (N/A)
HLA-DPB1 Match			
Double allele mismatch	391 (39)	30 (53)	28 (41)
Single allele mismatch	510 (51)	21 (37)	32 (47)
Full allele matched	92 (9)	6 (11)	8 (12)
Unknown	2084 (N/A)	632 (N/A)	602 (N/A)
High resolution release score			
No	105 (11)	21 (40)	22 (85)
Yes	818 (89)	32 (60)	4 (15)
Unknown	2154 (N/A)	636 (N/A)	644 (N/A)

Accrual Table 4. **Unrelated cord blood research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**3077**	**689**	**670**
KIR typing available			
No	2385 (78)	684 (99)	666 (99)
Yes	692 (22)	5 (1)	4 (1)
Cord blood number of units			
1	2021 (66)	0	494 (74)
2	1055 (34)	0	176 (26)
3	1 (<1)	0	0
Unknown	0 (N/A)	689 (N/A)	0 (N/A)
Graft type			
UCB	2938 (95)	630 (91)	633 (94)
BM+UCB	0	1 (<1)	0
PBSC+UCB	139 (5)	58 (8)	37 (6)
Conditioning regimen			
Myeloablative	2202 (72)	506 (73)	464 (69)
RIC/Nonmyeloablative	869 (28)	183 (27)	205 (31)
TBD	6 (<1)	0	1 (<1)
Donor age at donation			
TBD/NA	80 (3)	35 (5)	35 (5)
0-9 years	2752 (89)	544 (79)	578 (86)
10-19 years	158 (5)	62 (9)	30 (4)
20-29 years	28 (1)	13 (2)	7 (1)
30-39 years	27 (1)	22 (3)	11 (2)
40-49 years	11 (<1)	6 (1)	3 (<1)
50+ years	21 (1)	7 (1)	6 (1)
Median (Range)	3 (0-72)	4 (0-73)	4 (0-67)
Donor/Recipient CMV serostatus			
+ / +	803 (26)	154 (22)	146 (22)
+ / -	283 (9)	70 (10)	54 (8)
- / +	603 (20)	124 (18)	135 (20)
- / -	363 (12)	73 (11)	92 (14)
UCB / +	653 (21)	162 (24)	135 (20)
UCB / -	331 (11)	84 (12)	93 (14)
UCB / recipient CMV unknown	41 (1)	22 (3)	15 (2)

Accrual Table 4. **Unrelated cord blood research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**3077**	**689**	**670**
GvHD Prophylaxis			
Ex vivo T-cell depletion	16 (1)	6 (1)	2 (<1)
CD34 selection	108 (4)	42 (6)	30 (4)
TAC + MMF ± others	836 (27)	167 (24)	100 (15)
TAC + MTX ± others (except MMF)	125 (4)	38 (6)	35 (5)
TAC + others (except MTX, MMF)	108 (4)	29 (4)	18 (3)
TAC alone	69 (2)	20 (3)	10 (1)
CSA + MMF ± others (except Tacrolimus)	1530 (50)	306 (44)	358 (53)
CSA + MTX ± others (except Tacrolimus, MMF)	52 (2)	13 (2)	19 (3)
CSA + others (except Tacrolimus, MTX, MMF)	123 (4)	47 (7)	59 (9)
CSA alone	30 (1)	9 (1)	27 (4)
Other GVHD prophylaxis	62 (2)	5 (1)	10 (1)
Missing	18 (1)	7 (1)	2 (<1)
Donor/Recipient sex match			
UCB / Male	1610 (52)	373 (54)	372 (56)
UCB / Female	1467 (48)	316 (46)	297 (44)
UCB / recipient sex unknown	0	0	1 (<1)
Year of transplant			
1996-2000	0	1 (<1)	3 (<1)
2001-2005	55 (2)	53 (8)	11 (2)
2006-2010	1031 (34)	226 (33)	215 (32)
2011-2015	1520 (49)	268 (39)	342 (51)
2016-2019	471 (15)	141 (20)	99 (15)
Follow-up among survivors, Months			
N Eval	1409	350	315
Median (Range)	48 (1-176)	37 (2-187)	48 (1-145)

Abbreviations: CRF=Comprehensive report form, TED=Transplant essential data, AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, UCB=Umbilical cord blood, BM=Bone marrow, PBSC=Peripheral blood stem cells, RIC=Reduced intensity conditioning, TBD=To be determined, NA=Not applicable, Post-CY=Post-transplant Cyclophosphamide, TAC=Tacrolimus, MMF=Mycophenolate mofetil, MTX=Methotrexate, CsA=Cyclosporine.

* Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006). Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Related Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired, recipient only and donor only samples, Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006), Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Accrual Table 5. **Related donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**3007**	**481**	**181**
Source of data			
CRF	987 (33)	126 (26)	55 (30)
TED	2020 (67)	355 (74)	126 (70)
Number of centers	78	56	39
Disease at transplant			
AML	1980 (66)	297 (62)	118 (65)
ALL	946 (31)	170 (35)	60 (33)
Other acute leukemia	81 (3)	14 (3)	3 (2)
AML Disease status at transplant			
First complete remission	1215 (61)	189 (64)	72 (61)
Second complete remission	312 (16)	33 (11)	12 (10)
Third, or greater, complete remission	23 (1)	4 (1)	0
Advanced or active disease	423 (21)	69 (23)	32 (27)
Missing	7 (<1)	2 (1)	2 (2)
ALL Disease status at transplant			
First complete remission	597 (63)	112 (66)	43 (72)
Second complete remission	257 (27)	35 (21)	10 (17)
Third, or greater, complete remission	39 (4)	5 (3)	2 (3)
Advanced or active disease	53 (6)	18 (11)	5 (8)
Recipient age at transplant			
0-9 years	193 (6)	21 (4)	10 (6)
10-19 years	298 (10)	32 (7)	14 (8)
20-29 years	292 (10)	61 (13)	21 (12)
30-39 years	307 (10)	51 (11)	15 (8)
40-49 years	465 (15)	81 (17)	27 (15)
50-59 years	717 (24)	114 (24)	43 (24)
60-69 years	642 (21)	103 (21)	44 (24)
70+ years	93 (3)	18 (4)	7 (4)
Median (Range)	49 (1-76)	49 (1-76)	51 (1-74)

Accrual Table 5. **Related donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**3007**	**481**	**181**
Recipient race/ethnicity			
Caucasian, non-Hispanic	1944 (68)	248 (55)	117 (67)
African-American, non-Hispanic	269 (9)	34 (8)	9 (5)
Asian, non-Hispanic	132 (5)	47 (10)	13 (7)
Pacific islander, non-Hispanic	9 (<1)	1 (<1)	0
Native American, non-Hispanic	13 (<1)	1 (<1)	0
Hispanic	507 (18)	118 (26)	36 (21)
Unknown	133 (N/A)	32 (N/A)	6 (N/A)
Recipient sex			
Male	1710 (57)	274 (57)	101 (56)
Female	1297 (43)	207 (43)	80 (44)
Karnofsky score			
10-80	1132 (38)	215 (45)	81 (45)
90-100	1812 (60)	259 (54)	93 (51)
Missing	63 (2)	7 (1)	7 (4)
Graft type			
BM	737 (25)	91 (19)	50 (28)
PBSC	2265 (75)	387 (80)	130 (72)
BM+PBSC	2 (<1)	2 (<1)	0
BM+UCB	3 (<1)	1 (<1)	0
PBSC+UCB	0	0	1 (1)
Conditioning regimen			
Myeloablative	2162 (72)	335 (70)	129 (71)
RIC/Nonmyeloablative	840 (28)	145 (30)	50 (28)
TBD	5 (<1)	1 (<1)	2 (1)
Donor age at donation			
TBD/NA	22 (1)	1 (<1)	0
0-9 years	141 (5)	11 (2)	9 (5)
10-19 years	263 (9)	41 (9)	12 (7)
20-29 years	422 (14)	78 (16)	21 (12)
30-39 years	418 (14)	81 (17)	31 (17)
40-49 years	502 (17)	87 (18)	21 (12)
50+ years	1239 (41)	182 (38)	87 (48)
Median (Range)	45 (0-80)	43 (0-79)	48 (3-76)

Accrual Table 5. **Related donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**3007**	**481**	**181**
Donor/Recipient CMV serostatus			
+ / +	1259 (42)	252 (53)	89 (51)
+ / -	286 (10)	31 (7)	15 (9)
- /+	862 (29)	118 (25)	45 (26)
- / -	558 (19)	75 (16)	27 (15)
Unknown	42 (N/A)	5 (N/A)	5 (N/A)
GvHD Prophylaxis			
Ex-vivo T-cell depletion	38 (1)	10 (2)	1 (1)
CD34 selection	39 (1)	11 (2)	6 (3)
Post-CY + other(s)	570 (19)	83 (17)	29 (16)
Post-CY alone	23 (1)	6 (1)	3 (2)
TAC + MMF ± other(s) (except post-CY)	312 (10)	27 (6)	16 (9)
TAC + MTX ± other(s) (except MMF, post-CY)	1326 (44)	173 (36)	88 (49)
TAC + other(s) (except MMF, MTX, post-CY)	307 (10)	133 (28)	18 (10)
TAC alone	21 (1)	2 (<1)	0
CSA + MMF ± other(s) (except post-CY)	42 (1)	4 (1)	2 (1)
CSA + MTX ± other(s) (except MMF, post-CY)	239 (8)	18 (4)	13 (7)
CSA alone	24 (1)	6 (1)	0
Other(s)	30 (1)	3 (1)	2 (1)
Missing	36 (1)	5 (1)	3 (2)
Donor/Recipient sex match			
Male / Male	955 (32)	176 (37)	58 (32)
Male / Female	677 (23)	101 (21)	41 (23)
Female / Male	753 (25)	97 (20)	43 (24)
Female / Female	619 (21)	106 (22)	38 (21)
UCB / Male	2 (<1)	1 (<1)	0
UCB / Female	1 (<1)	0	1 (1)
Year of transplant			
2006-2010	224 (7)	20 (4)	14 (8)
2011-2015	1589 (53)	250 (52)	91 (50)
2016-2019	1194 (40)	211 (44)	76 (42)
Follow-up among survivors, Months			
N Eval	1817	305	106
Median (Range)	24 (1-124)	23 (3-100)	24 (2-96)

Abbreviations: CRF=Comprehensive report form, TED=Transplant essential data, AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, UCB=Umbilical cord blood, BM=Bone marrow, PBSC=Peripheral blood stem cells, RIC=Reduced intensity conditioning, TBD=To be determined, NA=Not applicable, Post-CY=Post-transplant Cyclophosphamide, TAC=Tacrolimus, MMF=Mycophenolate mofetil, MTX=Methotrexate, CsA=Cyclosporine.

* Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006). Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Proposal: 1803-03

Title:
Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients

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Hypothesis:
Donor-engrafted clonal hematopoiesis (CH) is associated with an increased risk of graft-versus- host disease (GVHD) among adult allogeneic hematopoietic cell transplant (alloHCT) recipients.

Specific aims:

- **Aim 1: Determine the prevalence of CH in matched sibling and unrelated alloHCT donors.** Using our custom next-generation sequencing (NGS) assay and pipeline, we will determine the prevalence of CH in alloHCT donors in the CIBMTR® Repository. We will include matched sibling donors ≥ 55 years old (n=300), matched sibling donors 40-54 years old (n=200), unrelated donors ≥ 55 years old (n=1500), and unrelated donors 40- 54 years old (n=500). We will explore differences in demographics (e.g., age, race, gender), environmental (e.g., smoking history, socioeconomic status), and clinical factors (e.g., CD34 dose) between those donors with and without CH mutations. Under the hypothesis of a shared predisposition for CH in related siblings, we will compare the prevalence of CH in sibling donors to that in unrelated donors. We will sequence a subset of paired recipient samples (n=500) to determine whether the patients' founding malignant mutations are similar to the CH mutations detected in sibling donors.
- **Aim 2: Determine if alloHCT from donors with CH is associated increased incidence of acute and chronic GVHD.** We will use outcome data for fully matched sibling and unrelated donor alloHCTs described in Aim 1. Our primary outcomes of interest will be recipient occurrence of grade II-IV acute GVHD and chronic GVHD. Multivariate analysis will be conducted to account for differences in other potentially relevant factors/ confounders such as age, peripheral blood source, female-to-male transplant, and T-cell depletion. Secondary endpoints will include cumulative incidence of relapse, secondary malignancies, non-relapse mortality, GVHD and relapse-free survival (GRFS), and cGVHD and relapse-free survival (CRFS).
- **Aim 3: Explore the molecular features of post-transplant donor T-cells within alloHCT recipients.** Recent evidence suggests that CH-positive donor cells are associated with an increased cGVHD risk in alloHCT recipients.[1] We hypothesize that characterization of donor T-cell molecular features will provide insights into the mechanism associated with cGVHD risk. We will collaborate with the CIBMTR Working Committee to identify a subset of case-matched recipient samples (i.e., with CH-positive donors and with CH- negative donors) collected 100 and/or 180 days post-HCT from the BMT CTN repository (e.g., 1301 and/or 1203). T-cells will be isolated utilizing double negative selection as previously described by our laboratory.[2] Both the positive and negative fractions will be used for the following exploratory analysis: (1) Perform NGS of unfractionated cells utilizing our CH panel described below (**7.0**) to determine if clonal expansion of CH mutations occurs relative to pre-transplant samples, as previously described in the setting of therapy-related leukemias.[3] (2) Perform NGS of the T-cell fraction utilizing our CH panel to determine if CH donor T-cells are derived from CH clones, as previously described.[2] (3) Perform T-cell immunophenotyping, focusing on TH_{17} polarization and T- regs, to determine if different proportions of T-cell subtypes are present in

recipients with CH-positive versus CH-negative donor cells, using methods previously described.[4]

Scientific impact:
The proposed study has the potential to inform the clinical utility of pre-HCT CH screening in donors, a practice which is not currently standard of care. Results of this study may provide evidence to modify selection of donors or post-HCT management of patients with CH-positive donors. First, *Aim 1* will provide the opportunity to validate data generated from a European cohort,[1] which would substantiate the clinical impact of the published study and lead to widespread adoption of CH profiling in sibling donor cells. Additionally, by including a range of donor ages, this study will build upon existing knowledge and provide the ability to explore whether age or CH status of donors is the primary driver of the known high rates of GVHD that occur with older alloHCT donors. This may also lead to clinically relevant optimization of donor selection in some HCT cases. Furthermore, inclusion of unrelated donors will provide novel data on the clinical impact of donor CH in unrelated alloHCTs. Because unrelated donor selection is primarily driven by donor age, our CH data may allow for molecularly rational selection of older unrelated donors, therefore expanding the overall donor pool. *Aim 3* is designed to begin to elucidate the mechanism of *how* donor CH mediates risk of GVHD. This will provide novel evidence for future management strategies in the setting of CH-positive alloHCTs and, for the first time, explore the impact of CH on the human lymphoid hematopoietic compartment. Finally, the CH status of donors generated through our research will be data available to CIBMTR that can be incorporated into future research studies.

Scientific justification:
Clonal hematopoiesis or clonal hematopoiesis of indeterminate potential (CH/CHIP) is defined by the presence of somatic mutations within genes associated with myeloid neoplasms (*e.g., DNMT3A, TET2, ASXL1*) in the peripheral blood of individuals without signs of hematologic abnormalities. CH is increasingly common as people age, with a prevalence of approximately 10% in healthy individuals over the age of 65 years.[5,6] The presence of CH is associated with poor outcomes, including a significantly increased risk of atherosclerotic cardiovascular disease, hematologic malignancies, all-cause mortality in non-cancer populations, and inferior overall survival in patients with solid tumors.[5-7]
Although CH was first described in non-cancer populations, its clinical relevance to cancer patients is rapidly becoming apparent. We, and others, have demonstrated that cancer patients with CH are at an increased risk of developing therapy-related myeloid neoplasms (t-MN) after treatment for their primary malignancy.[3,8] This association was also demonstrated in lymphoma patients undergoing *autologous* transplants, where individuals with pre-transplant CH mutations had a significantly increased incidence of t-MN and inferior overall survival.[9] Interestingly, in the setting of allogeneic transplants, we, and others, have demonstrated that CH can be transferred from donors to recipients, and the mutations may expand and undergo clonal evolution.[9,10] In a study of allogeneic HCT recipients with cytopenias, donor-engrafted CH was confirmed for the majority (5/6, 83%) of patients with unexplained cytopenias.[9] Donor cell leukemia has also been reported to arise from CH acquired from donors over the age of 60 years.[11]
GVHD is among the most critical clinical challenges for allogeneic HCT recipients. It has been demonstrated that GVHD is mediated by the Nlrp3 inflammasome, a multiprotein complex that is activated by disruptions in tissue homeostasis.[12] Specifically, HCT conditioning therapy results in activation of the Nlrp3 inflammasome, which results in the production and activation of interleukin-1β (IL-1β), caspase-1, and T_h17 cells. Interestingly, the mechanism by which CH increases atherosclerosis is also mediated by an immune response through Nlrp3 inflammasome activation.[11] Specifically, CH induces a pro-inflammatory state through clonal macrophages with increased Nlrp3 inflammasome activation, resulting in increased IL-1β secretion. Thus, activation of the Nlrp3 inflammasome in both donor-engrafted CH cells and in recipient gastrointestinal cells may contribute to increased risk for GVHD. The effective use of statins as prophylaxis for GVHD provides further evidence of shared etiology.[13] **Given the overlapping pathological mechanisms of GVHD and CH, we hypothesize that donor-engrafted CH confers an increased risk of GVHD for**

allogeneic transplant recipients.
A recent study conducted in allogeneic recipients with older donors (age ≥ 55 years) from ten transplantation centers in Germany and France explored the association between donor-engrafted CH and outcomes.[1] CH was identified in 80/500 donors (16%) and was significantly associated with faster leukocyte engraftment at 15 days post-HCT, higher cumulative incidence of chronic GVHD, and decreased cumulative incidence of relapse/progression. There was no association with non-relapse mortality or overall survival. Two recipients with donor CH (2.5%) versus zero without donor CH were diagnosed with donor cell leukemia. Patients with myelodysplastic syndrome or acute myeloid leukemia who underwent HCT in non-complete remission had *improved* survival when the donor harbored a CH mutation; there was a trend toward inferior survival in myeloproliferative neoplasm patients with donor CH. One hypothesis for the relapse benefit of donor-engrafted CH is that CH clones confer a competitive advantaged by competing, and suppressing, pathogenic malignant clones. The proposed study provides an unparalleled opportunity to investigate the clinical significance of donor CH in the setting of worldwide, including a majority of United States', allogeneic HCT recipients. The CIBMTR Research Database and Repository represent the ideal resource to determine the role of CH status in the screening of potential HCT donors and the management of recipients. The availability of standardized and comprehensive treatment and outcomes data provide the ability to conduct pragmatic research that is directly translatable to current HCT practice in the U.S. Beyond the potential to validate current findings, this study can elaborate on the biological mechanism through which the observations are occurring, which will further help to inform future studies and the management of HCT recipients with CH-positive donors.

Patient eligibility population:
This study will primarily focus on alloHCT donors. Donors for adult (age ≥ 18 years) patients with myeloid neoplasms (MDS, AML, CMML, MF) and no previous history of HCT who received reduced intensity or non-myeloablative conditioning regimens will be eligible for this study. Donors will be included if the patients underwent a matched alloHCT (matched at the allele-level at HLA-A, -B, -C, and -DRB1) using bone marrow or peripheral blood stem cell grafts. Donors for patients with engraftment failures will be excluded. For the matched unrelated HCT patients, recipients who received GVHD prophylaxis with a calcineurin inhibitor and mycophenolate or methotrexate will be included in analyses, while those who were treated with post-transplant cyclophosphamide will be excluded. We aim to include donors from a range of ages and both sibling and unrelated HCTs: sibling donors ≥ 55 years (n=300), matched sibling donors 40-54 years old (n=200), unrelated donors ≥ 55 years (n=1500), and unrelated donors 40-54 years old (n=500). This will allow us to explore the effect of both donor age and CH status on outcomes for alloHCT recipients. We aim to include observational data from all donor and recipient pairs who meet eligibility criteria and have banked blood, peripheral blood mononuclear cells, or DNA collected prior to HCT that are available for research. For *Aim 3*, a subset of matched-related HCT recipients who have day 100 and/or 180 post-HCT samples (listed above) available for research from CIBMTR CTN (e.g., 1301 and/or 1203) will be included to explore the clonal dynamics and T cell distribution of CH. For this *Aim 3.3*, patients with a history of grade 3-4 aGVHD or cGVHD at the time of sample collection will be excluded.

Data requirements/study outcomes:
Primary outcomes:

- Acute GVHD II-IV: Time from transplant to development of grade II-IV aGVHD, and grade III-IV using the Consensus grading system. The event will be summarized by the cumulative incidence estimate, where death or disease relapse without grade II-IV aGVHD will be treated as a competing risk. Patients will be censored at second transplant or date of last follow-up.
- Chronic GVHD: Time from transplant to the development of limited or extensive cGVHD. The event will be summarized by the cumulative incidence estimate, where death or disease relapse without

cGVHD will be treated as a competing risk. Patients will be censored at second transplant or date of last follow-up.

Secondary outcomes:

- Relapse: Time to the recurrence of the underlying malignancy for which the allogeneic HCT was performed. The event will be summarized by the cumulative incidence estimate with non-relapse mortality (NRM) treated as a competing risk. Patients will be censored at date of last follow-up.
- Leukemia-free survival: Time to treatment failure (death or relapse). This event will be summarized by a Kaplan-Meier survival curve. Patients will be censored at the date of last follow-up. There are no competing risks.
- Overall survival (OS): Time to death from any cause. The event will be summarized by a Kaplan-Meier survival curve. The time to event will be measured from the landmark date post-transplant. Patients will be censored at the date of last follow-up. There are no competing risks.
- Non-relapse mortality (NRM): Time to death without relapse. The event will be summarized by the cumulative incidence estimate with relapse treated as a competing risk. Patients will be censored at the date of last follow-up.
- GVHD and relapse-free survival (GRFS): Composite endpoint taking into account grade 3-4 acute GVHD, systemic therapy-requiring chronic GVHD, primary disease relapse, or death for any cause as events.
- cGVHD and relapse-free survival (CRFS): Composite time to event outcome defined as moderate to severe chronic GVHD, disease relapse, or death by any cause.

Aim 3 endpoints:

Clonal dynamics (*Aim 3.1*):

- CH clonal expansion: ≥ 2% increase in variant allele frequency (VAF) of the pre-HCT CH mutation in the recipient post-HCT sample
- CH clonal retraction: ≥ 2% decrease in VAF of the pre-HCT CH mutation in the recipient post-HCT sample
- Steady CH: no (or ± 1%) change in VAF of the pre-HCT CH mutation in the recipient post-HCT sample
- New mutations that emerge post-HCT will first be compared with donor pre-HCT samples, as there may be a lag between HCT and expression of donor-acquired mutations. Non-donor acquired mutations will be assumed to be pathogenic mutations and will be assessed in context of relapse.

Donor T-cell CH (Aim 3.2):

- This endpoint will focus on total T-cell fractions derived from recipient post-HCT samples. Presence of donor CH mutations in the T-cell fraction of recipient post- HCT samples will provide evidence demonstrating that the T-cell fraction was derived from the donor-engrafted CH clones.

T-cell polarization (*Aim 3.3*):

- Both CH and cGVHD are mediated by activation of the Nlrp3 inflammasome, which regulates Th_{17} differentiation.[11,12,14] Additionally, T-cells can adopt their functions (i.e., polarizations) in response to changing circumstances.[15] Therefore, we hypothesize that patients with CH-positive donors will have higher proportions of peripheral blood Th_{17} cells at the selected time points post-HCT compared to those with CH-negative donors. For this aim, we will compare the proportions of T-cell fractions within the post-HCT samples of recipients with CH-positive versus CH-negative donors. As exploratory analyses we will also test for associations between T-cell patterns and cGVHD onset, severity, and other outcomes listed below.

Variables to be analyzed:

Patient-related:

- Age
- Gender: male vs. female
- Karnofsky performance score: <90 vs. > 90

Disease-related:

- Disease: AML vs. MDS vs. CMML vs. MF
- Disease status at transplant: early vs. intermediate vs. advanced (CIBMTR)

Donor-related:

- Donor age: continuous and 40-55 vs. 55-65 vs. 65-75
- Donor smoking status
- Donor race
- CD34 dose
- Donor-recipient gender match: M/M vs. M/F vs. F/M vs. F/F
- Donor-recipient CMV serostatus: -/- vs. -/+ vs. +/- vs. +/+

Transplant-related:

- Graft source: bone marrow vs. peripheral blood
- Conditioning regimen
- Use of antithymocyte globulin (ATG) or alemtuzumab with conditioning
- Year of transplant

Sample requirements:

We request DNA isolated from peripheral blood or bone marrow from all donors who meet eligibility requirements (matched related, age at donation $\geq$ 55 years). DNA from samples stored in heparin tubes have performed sub-optimally in the past and is not ideal for library preparation. We would request 0.5µg of DNA, as quantified by Qubit (Thermo Fisher Scientific) or PicoGreen (Thermo Fisher Scientific). If quantified by Nanodrop (Thermo Scientific) or if the DNA integrity number (DIN) is < 5, we request 1µg of DNA, due to differences in measurement between the quantification methods and the need for sufficient input DNA. For Aim 3, we request recipient PBMC samples collected day 100 and/or 180 post-HCT. These time points were selected based on (1)sample availability in BMT CTN, (2) to assure adequate starting lymphocyte numbers for planned assays based on the trajectory of immune reconstitution, and (3) the fact that by day 100, most of the allo-HCT recipients will have achieved prevailing chimerism so the effect and detection of CH should be maximized. Sequential samples would allow for exploration of clonal evolution overtime.

Sample Assay/ Defining Clonal Hematopoiesis: Clonal hematopoiesis status of donors will be determined using our custom next-generation sequencing (NGS) panel and bioinformatics pipeline in collaboration with Moffitt Cancer Center Molecular Genomics Core. The NGS panel, which utilizes the Agilent SureSelect^{XTHS} technology, incorporates unique molecular identifiers (UMIs) to tag DNA molecules, improving ability to confidently call low frequency variants (i.e., $\leq$ 1% variant allelic frequency). The custom panel we designed includes coverage of complete exons from 76 common CH genes reported in non-cancer[5,6] and cancer[7] cohorts. We conduct NGS using a NextSeq 500 (Illumina) sequencer and target a coverage of 800-1000x. Our bioinformatics pipeline has been published previously[3,16] and includes NGS quality control and selection for known CH mutations, such as low frequency mutations previously reported in CH or known to be pathogenic for hematologic malignancies.

Study design:
This will be a retrospective observational study of matched-related and unrelated HCT donors and recipients within the CIBMTR database. Pairwise comparisons of demographic and baseline characteristics will be conducted using Mann-Whitney U, χ^2, or Fisher's exact tests, as appropriate. For Aim 1, prevalence of donor CH will be reported as a percentage and will be compared between matched-related and unrelated donors using a χ^2 test. Associations between CH status and demographic, environmental, and clinical factors will be assessed with logistic regression. For Aim 2, cumulative incidence of outcomes, such as GVHD, will be compared between recipients who received HCT from donors with and without CH using Gray's test. Fine and Gray competing risk regression will be used to assess competing risk of outcomes adjusted for relevant baseline and clinical factors. Overall survival will be compared using the Kaplan-Meier method and log-rank tests. For Aim 3, the association between models of clonal dynamics and T-cell fractions with outcomes will be assessed using a χ^2 test. Multivariate logistic regression will be used to adjust for relevant covariates. For all analyses, a p-value < 0.05 will be considered statistically significant.

Data source:
The CIBMTR Research Database, CIBMTR Sample Repository, and BMT CTN Repository (*Aim 3*) will be used for this study. The data will not be linked with any outside sources.

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Conflict of interest:
None

Characteristics of adult patients undergoing first allogeneic HCT from a related donor ≥ 40 years old between 2008-2018, with donor biospecimens available through the CIBMTR Repository.

	N (%)
Number of patients	**2820**
Number of centers	50
Samples available for recipient?	
Yes	2641 (94)
No	179 (6)
Recipient age at transplant	
Median (range)	58 (24-77)
20-29 years	6 (<1)
30-39 years	65 (2)
40-49 years	511 (18)
50-59 years	1100 (39)
60-69 years	1033 (37)
70+ years	105 (4)
Disease	
AML	1030 (37)
ALL	288 (10)
CML	105 (4)
MDS	432 (15)
CMMoL	45 (2)
Myelofibrosis	83 (3)
MPS	89 (3)
Other leukemia	144 (5)
NHL	402 (14)
HD	31 (1)
PCD/MM	119 (4)
Other malignancies	2 (<1)
Severe aplastic anemia	41 (1)
Inherited abnormlaities erythrocyte differentiation or function	1 (<1)
Histiocytic disorders	4 (<1)
Autoimmune diseases	1 (<1)
Other	3 (<1)
Graft type	
Bone marrow	118 (4)
Peripheral blood stem cells	2702 (96)
Conditioning regimen intensity, as reported by the center	
Myeloablative	1572 (56)
Reduced intensity	161 (6)
Non-myeloablative	1078 (38)

	N (%)
Missing	9 (<1)
Related donor age at transplant	
Median (range)	56 (40-81)
40-44	275 (10)
45-49	389 (14)
50-54	574 (20)
55-59	603 (21)
60-64	542 (19)
65-69	324 (11)
70+	113 (4)
GVHD prophylaxis	
Tac + MMF ± others (not Cy)	311 (11)
Tac + MTX ± others (not Cy, MMF)	1738 (62)
Tac ± others (not Cy, MMF, MTX)	456 (16)
CsA + MMF ± others (not Cy, Tac)	57 (2)
CsA + MTX ± others (not Cy, Tac, MMF)	153 (5)
CsA ± others (not Cy, Tac, MMF, MTX)	20 (<1)
Others (not Cy, Tac, CsA)	50 (2)
Missing	35 (1)
Year of transplant	
2008-2011	530 (19)
2012-2015	1596 (57)
2016-2018	694 (25)
Follow-up of survivors, months, median (range)	36 (<1-123)

Abbreviations: AML, Acute myeloid leukemia; ALL, Acute lymphoblastic leukemia; CML, Chronic myeloid leukemia; MDS, Myelodysplastic diseases; CMMoL, Chronic myelomonocytic leukemia; MPS, Myeloproliferative diseases; NHL, Non-Hodgkin lymphoma; HD, Hodgkin disease; PCD, Plasma cell disorders; MM, Multiple myeloma; Tac, Tacrolimus; MMF, Mycophenolate mofetil; Cy, Cyclophosphamide; MTX, Methotrexate, CsA, Cyclosporine.

Characteristics of adult patients undergoing first allogeneic HCT from an unrelated donor ≥ 40 years old between 2008-2018, with donor biospecimens available through the CIBMTR Repository.

	N (%)
Number of patients	**32**
Number of centers	15
Samples available for recipient?	
Yes	2641 (94)
No	179 (6)
Recipient age at transplant	
Median (range)	55 (25-76)
18-19 years	0
20-29 years	2 (6)
30-39 years	2 (6)
40-49 years	2 (6)
50-59 years	15 (47)
60-69 years	8 (25)
70+ years	3 (9)
Disease	
AML	11 (34)
ALL	1 (3)
CML	3 (9)
MDS	4 (13)
CMMoL	0
Myelofibrosis	2 (6)
MPS	0
Other leukemia	1 (3)
NHL	5 (16)
HD	2 (6)
PCD/MM	3 (9)
Severe aplastic anemia	0
Inherited abnormlaities erythrocyte differentiation or function	0
SCID and other immune system disorders	0
Graft type	
BM	8 (25)
PB	24 (75)
Conditioning regimen intensity, as reported by the center	
MAC	18 (56)
RIC	5 (16)
NMA	9 (28)
Missing	0
Unrelated donor age at transplant	

	N (%)
Median (range)	48 (40-69)
40-44	11 (34)
45-49	11 (34)
50-54	7 (22)
55-59	2 (6)
60-64	0
65-69	1 (3)
70+	0
GVHD prophylaxis	
Tac + MMF ± others (not Cy)	4 (13)
Tac + MTX ± others (not Cy, MMF)	22 (69)
Tac ± others (not Cy, MMF, MTX)	0
CsA + MMF ± others (not Cy, Tac)	0
CsA + MTX ± others (not Cy, Tac, MMF)	2 (6)
CsA ± others (not Cy, Tac, MMF, MTX)	4 (13)
Others (not Cy, Tac, CsA)	0
Missing	0
Year of transplant	
2008-2011	11 (34)
2012-2015	17 (53)
2016-2018	4 (13)
Follow-up of survivors, months, median (range)	35 (2-104)

Abbreviations: AML, Acute myeloid leukemia; ALL, Acute lymphoblastic leukemia; CML, Chronic myeloid leukemia; MDS, Myelodysplastic diseases; CMMoL, Chronic myelomonocytic leukemia; MPS, Myeloproliferative diseases; NHL, Non-Hodgkin lymphoma; HD, Hodgkin disease; PCD, Plasma cell disorders; MM, Multiple myeloma; Tac, Tacrolimus; MMF, Mycophenolate mofetil; Cy, Cyclophosphamide; MTX, Methotrexate, CsA, Cyclosporine.

Proposal 1810-08 / 1811-55

Title:
Determining the optimal anti-thymocyte globulin dosing in patients with hematologic malignancies.

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Hypothesis:
The optimal anti-thymocyte globulin (ATG) dosing is unknown and may be individualized based on conditioning intensity, donor choice, risk factors for acute graft versus host disease (GVHD), and recipient lymphocyte count.

Scientific impact:
To date, a large-scale analysis to identify the optimal dose of ATG has not yet been undertaken. Given the heterogeneity of the patients undergoing HCT, there may not be a single, optimal dose. Instead, ATG dosing may depend on intensity of the preparative regimen, donor characteristics, and recipient lymphocyte counts. The number of patients required to retrospectively determine the dosing of ATG in relation to these characteristics would be too significant for any one institution to undertake. The CIBMTR dataset would allow such an analysis to occur. This type of study could potentially inform ATG dosing as well as the design of a prospective analysis with personalized ATG dosing.

Specific aims:
1. Determine the optimal dose of ATG at which the risk of acute GVHD and risk of post-HCT infectious complications are balanced.
2. Investigate the differences in overall survival (OS), acute and chronic graft-versus-host-disease (GVHD), treatment-related mortality (TRM), relapse incidence (RI), and leukemia-free survival (LFS) based on variations in ATG dosing.
3. Identify whether patients with established risk factors for acute GVHD, including differences in graft source and conditioning intensity, benefit from higher ATG dosing than patients without these risk factors.
4. Assess whether low recipient absolute lymphocyte count (ALC) + ATG dosing predicts for post-transplant infectious complications, TRM, and shortened OS.

Scientific justification:
Patients undergoing allogeneic hematopoietic cell transplantation (HCT) receive immunosuppression to facilitate engraftment and reduce the incidence and severity of acute and chronic GVHD. At many centers, *in-vivo* T cell depletion is routinely undertaken to reduce the incidence and severity of GVHD, however, no standardized practice exists, and clinical experience is variable.

Early work established a correlation between ATG use, GVHD, and infectious complications. Initially, a total of 55 patients were randomized to 15mg/kg of rabbit ATG vs. no ATG. Those treated with ATG had significantly less grade III-IV GVHD, however, there was a higher incidence of lethal infections resulting in equivalent TRM between the two groups.[1] Separately, in an analysis of favorable risk leukemia patients undergoing matched related donor (MRD) HCT, patients received ATG 30mg/kg for 1-3 days. ATG use correlated with a lower rate of acute and chronic GVHD and a trend toward a higher mortality from sepsis and fungal infections.[2] In the reduced intensity conditioning (RIC) MRD setting, higher ATG

doses (7.5 to 10mg/kg) were associated significantly less GVHD at two years compared to patients receiving 2.5mg/kg of ATG.[3] Finally, 44% of patients receiving 4mg/kg of ATG developed acute and chronic GVHD compared to <15% of patients receiving 6-8mg/kg of ATG.[4]

Three retrospective analyses reported similar outcomes. In the first, Remberger and colleagues evaluated four different ATG doses in 162 patients receiving HCTs from matched unrelated donors (MUD). Lower ATG dosing was associated with a higher incidence of GVHD associated deaths whereas higher dosing was associated with more infectious deaths. Patient that received moderate doses of 6-8mg/kg experienced lower TRM and improved OS suggesting a possible target dosing range for recipients of unrelated donors.[5] In the second retrospective analysis, there was no significant difference in the cumulative incidence of acute GVHD, however, ATG dosing at 6mg/kg resulted in lower rates of CMV reactivation and bacterial infections, and an improved 1-year non-relapse mortality (NRM) and trend toward improved 1 year OS compared to 7.5mg/kg.[6] Finally, comparisons between ATG doses of 6mgk/kg vs. 7.5mg/kg in the RIC setting showed no significant difference in acute or chronic GVHD, NRM, relapse, PFS, and OS between groups.[7] As of yet, no large scale analysis has been undertaken to identify the optimal dosing.

We recently hypothesized that the target of ATG, recipient T cells, are highly variable and that in lymphopenic patients, ATG binds graft CD3+ T cells leading to undesirable consequences. While data suggest that the lymphocyte count and weight/body mass index are correlated in healthy subjects, little is known about this correlation after cytotoxic chemotherapy.[8,9] With a half-life of approximately 30 days, ATG may bind a significant number of graft T cells in lymphopenic recipeints.[10] Recent data from VUMC supports this hypothesis. In a retrospective analysis of ATG doses ranging from 5-10mg/kg, there was no difference in OS. Higher ATG doses were associated with a lower incidence of severe chronic GVHD but higher mortality due to infectious complications. In a multivariate analysis, high ATG doses in combination with a low ALC (10^{th} percentile, or 0.56 x 10^2/□L) on the first day of ATG administration was associated with a higher risk of death. Alternatively, high ALC (95th percentile, or 24.96 x 10^2/□L) was associated with a lower risk of death.[11]

Study population:

Inclusion Criteria:

- Patients with MDS, AML, and ALL transplanted between 2008 and 2018
- Age 18 to 70 years
- First HCT
- PBSC or BM
- HSC Sources: MUD, mMUD, MRD.
- Conditioning Intensity: Ablative, non-ablative, reduced intensity
- Received any dosing of ATG as a component of the preparative regimen

Exclusion Criteria:

- Ex-vivo T-cell depletion
- Haploidentical or cord blood transplant
- History of prior/Pre-HCT fungal infection
- Horse ATG

Data requirements:

Patient-related:

- Patient age at HCT: 18-29, 30-55, vs. 56-70

- Karnofsky performance score: ≥90 vs. <90
- HCT-CI: 0 vs. 1-2 vs. ≥3
- Race: Caucasian vs. not Caucasian
- Hematologic Findings Prior to the Preparative Regimen (Conditioning)
    - WBC
    - Lymphocytes (%)

Disease-related:

- Time from diagnosis to HCT, months: < 6 vs. 6 to <12 vs. ≥ 12
- AML, ALL vs. MDS
- Disease status at transplant: CR1 ≥ CR2 < CR
- Disease risk status (including cytogenetics)

Transplant-related:

- Stem cell source: PBSC vs. BM
- HLA Match: 10/10 or ≤ 9/10 related, 10/10 or ≤ 9/10 unrelated
- Conditioning intensity: MAC vs. RIC/NMA
- ATG
    - Total prescribed dose (mg/kg)
- TBI-based preparative regimen
- Female → Male vs. all others.
- Donor/Recipient CMV status: -/+ vs. +/- vs. +/+ vs. -/-
- GVHD prophylaxis
- Cell dose > 8 x 10^6 CD34+ cells/kg vs. ≤ 8 x 10^6 CD34+ cells/kg

Post-HCT Data:

- CMV reactivation
- EBV reactivation
- Development of PTLD
- Graft rejection rate; primary and secondary
- Acute GVHD:
    - Overall grade at diagnosis
    - Max grade at D+100
- Chronic GVHD:
    - Chronic GVHD at 6 months, 1 year, and 2 years
    - Max grade cGVHD (mild, moderate, severe)
    - Limited or extensive cGVHD
- Primary cause of death
    - Acute GVHD,
    - Chronic GVHD,
    - Infection
        - Not identified
        - Bacterial
        - Fungal
        - Viral
        - Protozoal
        - Other

    - Other
- Contributing cause of death
    - Acute GVHD
    - Chronic GVHD
    - Infection
        - Not identified
        - Bacterial
        - Fungal
        - Viral
        - Protozoal
        - Other
    - Other
- Overall Survival

Study design:

Patients meeting the above criteria will be divided based on the dosing of ATG received: ≤ 2.5mg/kg, 2.6 to 5mg/kg, 5.1 to 7.5mg/kg, 7.6 to 10mg/kg, and >10mg/kg. Descriptive statistics will be used to describe the characteristics of the patients in each group (i.e., conditioning intensity, graft characteristics, and other known risk factors for aGVHD). Next, the incidence and maximum grade of acute GVHD by the Glucksberg grading system will be determined for each of the groups and summarized by cumulative incidence probability, where death without aGVHD will be treated as a competing risk and reported with 95% confidence intervals. Cox proportional hazard models will assess the impact of aGVHD and infectious complications on TRM. In instances where aGVHD and infection is listed as both the primary and contributing cause of death (or the opposite), only the primary causes of death will be counted. OS calculations using Kaplan-Meier curves will be performed in each of the groups with median OS calculated for each of the five groups.

The following established risk factors for aGVHD will be assessed: TBI-based preparative regimen, ablative conditioning regimen, F → M donor, mMUD, and PBSCs will be assessed for each patient. Patients with 0-1 risks, 2 risks, and ≥ 3 risks factors will first have their incidence and max grade of aGVHD calculated to confirm that increasing risk factors are associated with a higher incidence of aGVHD. Patients in these groups will then be divided based on ATG dosing at 0 to 5mg/kg, 5.1 to 10mg/kg, and >10mg/kg with the cumulative incidence and max grade of aGVHD, TRM, and OS calculated in each group, as described above.

Finally, we will calculate pre-HCT absolute lymphocyte counts (ALC: WBC x % lymphocytes). In our prior work, the ALC on the first day of ATG administration, in combination with the ATG dose, predicted for inferior outcomes. Since these values are not available from the CIBMTR, we reviewed the charts of several unrelated donors and found a high incidence of lymphopenia prior to the start of conditioning chemotherapy which we believe will be a suitable substitute in this analysis. Recipient ALCs will be divided by decile with ATG dosing assessed in each decile (0 to 5mg/kg, 5.1 to 10mg/kg, and >10mg/kg). The incidence of aGVHD, infectious complications, TRM, and OS will be evaluated in the extremes of ALC values which is likely to be top and bottom 1-2 deciles. Depending on the preliminary analyses, discussions with the investigator may prompt further study in other deciles.

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Characteristics of adult patients undergoing first allogeneic transplant for AML, ALL, MDS and received ATG in conditioning regimen between 2008-2018, as registered to the CIBMTR.

	N (%)
Number of patients	**1768**
Number of centers	141
Recipient age	
Median (range)	57 (18-69)
18-29	174 (10)
30-39	178 (10)
40-49	223 (13)
50-59	490 (28)
60-69	703 (40)
Disease	
AML	938 (53)
ALL	213 (12)
MDS	617 (35)
Donor type	
HLA-Identical sibling	304 (17)
Matched unrelated donor	1114 (63)
Mismatched unrelated donor	350 (20)
Graft type	
Bone marrow	256 (14)
Peripheral blood	1512 (86)
Conditioning regimen intensity	
Myeloablative	978 (55)
Reduced intensity	679 (38)
Non-myeloablative	75 (4)
TBD	36 (2)
GVHD prophylaxis	
CD34 selection	86 (5)
Post-transplant Cy + others	7 (<1)
Tac + MMF ± others (not Cy)	369 (21)
Tac + MTX ± others (not Cy, MMF)	904 (51)
Tac + others (not Cy, MMF, MTX)	64 (4)
CsA + MMF ± others (not Cy, Tac)	142 (8)
CsA + MTX ± others (not Cy, Tac, MMF)	155 (9)
CsA + others (not Cy, Tac, MMF, MTX)	23 (1)
Others (not Cy, Tac, CsA)	17 (<1)
Missing	1 (<1)
Year of transplant	
2008-2011	802 (45)

	N (%)
2012-2015	748 (42)
2016-2018	218 (12)
Follow-up of survivors, months, median (range)	61 (3-124)

Abbreviations: AML = Acute myelogenous leukemia, ALL = Acute lymphoblastic leukemia, MDS = Myelodysplastic syndrome, TBD = To be determined, CY = Cyclophosphamide, TAC = Tacrolimus, MMF = Mycophenolate mofetil, MTX = Methotrexate, CsA = Cyclosporine.

Proposal: 1811-34

Title:
Cyclosporine versus Tacrolimus based Graft Versus Host Disease Prophylaxis in Children undergoing Allogeneic Hematopoietic Cell Transplantation

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Hypothesis:
Use of cyclosporine-based graft versus host disease (GVHD) prophylaxis results in lower rates of chronic GVHD compared to tacrolimus-based GVHD prophylaxis in children undergoing allogeneic hematopoietic cell transplantation (HCT).

Specific aims:
Primary aim:

- Compare the incidence of chronic GVHD (cGVHD) among children receiving alloHCT with cyclosporine based GVHD prophylaxis to those who receive tacrolimus based GVHD prophylaxis.

Secondary aims:

- Compare the incidence of acute GVHD (aGVHD) among children receiving alloHCT with cyclosporine based GVHD prophylaxis to those who receive tacrolimus based GVHD prophylaxis.
- Compare the incidence of relapse (for malignancies) or graft failure (for non-malignant diseases) among children receiving alloHCT with cyclosporine based GVHD prophylaxis to those who receive tacrolimus based GVHD prophylaxis.
- Compare neutrophil and platelet engraftment in children receiving alloHCT with cyclosporine based GVHD prophylaxis to those who receive tacrolimus based GVHD prophylaxis.
- Compare overall survival among children receiving alloHCT cyclosporine based GVHD prophylaxis to those who receive tacrolimus based GVHD prophylaxis.

Scientific impact:
The optimal GVHD prophylaxis regimen has not been defined for pediatric patients and current practice has been extrapolated from studies in adults. A prior CIBMTR study suggested the superiority of CSA and Methotrexate (MTX) compared to Tac/MTX for cGVHD outcomes, but Tac was an emerging therapy at that time. Despite these finding, use of Tac/MTX significantly increased and has largely replaced CSA as the most commonly used GVHD prophylaxis regimen. Analysis of GVHD outcomes in the more recent era, with more patients receiving Tac, may improve discriminative capacity between CSA and Tacrolimus and may result in practice changes that can ultimately result in decreased cGVHD and decreased long term morbidity in pediatric patients.

Scientific justification:
CSA and Tac are commonly used calcineurin inhibitors for prevention of acute GVHD (aGVHD). CSA has been utilized for more than 3 decades for aGVHD prevention but is associated with renal injury, neurotoxicity, hirsutism, and gum hypertrophy. Tac seems to have a better toxicity profile. In the 1990s studies in adults demonstrated the efficacy of Tac and suggested that it may be more potent in aGVHD prevention[1]. Subsequent studies in adults have shown that Tac-based GVHD prophylaxis regimens are equivalent to, or superior to cyclosporine based regimens, resulting in less aGVHD and improved

survival[2-6]. In addition, a recent study from the CIBMTR found decreased GVHD among patients who received MTX with a calcineurin inhibitor for GVHD prophylaxis during reduced intensity HCT, but outcomes were similar when CSA or Tac was used as the calcineurin inhibitor in this regimen[7]. However, there are few published studies comparing calcineurin inhibitors for GVHD prophylaxis in the pediatric population.

In children, the use of CSA and MTX had been the preferred GVHD prophylaxis regimen in the 1990s but practice has largely shifted with more pediatric patients receiving Tac-based regimens[8]. This practice change was based largely on results of studies in adults and the improved toxicity profile of Tac. However, in the pediatric population, a larger proportion of patients undergo HCT for non-malignant diseases and the majority of patients receive bone marrow as their stem cell source. These differences in practice for the pediatric population makes it difficult to extrapolate GVHD prophylaxis strategies from those used in adults.

Two recent studies performed by the Health Services Committee at the CIBMTR (HS13-02 and HS14-01) have demonstrated improved outcomes in pediatric patients who received CSA-based GVHD prophylaxis regimens. In patients with Sickle Cell Disease, utilization of CSA was associated with statistically significant lower incidence of chronic GVHD (HR 0.48, 95% CI 0.26-0.88), mortality (HR 0.33, 95% CI 0.12-0.91) and better GVHD-free, relapse-free survival (GRFS) (HR 0.49, 95% CI 0.28-0.86) compared to Tac[9]. In children with acute leukemia, regimens containing Tac were associated with a higher risk of cGVHD compared to CSA (HR 1.77, 95% CI 1.29-3.42)[10]. These studies were primarily focused on healthcare utilization and included only a small number of patients, but they suggest that larger studies are needed to better evaluate GVHD prophylaxis in pediatric patients. In addition, a recent single center study has suggested that single agent calcineurin inhibitor prophylaxis instead of 2 agents is safe and effective in pediatric patients[11]. In a CIBMTR study studying the effect of age on GVHD outcomes in children undergoing HCT for leukemia, CSA and Tac regimens were compared and Tac/MTX regimens were found to be associated with a higher risk of cGVHD (HR 2.4, 95% CI 1.22-4.74, p=0.012); there was no difference seen in incidence of aGVHD between CSA/MTX with Tac/MTX[12]. However, this study evaluated the years of 2000-2013, when Tac was still an emerging therapy with less than 30% of patient receiving Tac-based regimens. Since the eras studied in this paper, Tac use has continued to increase and has now surpasses CSA as the primary GVHD prophylactic regimen.

In summary, the association between clinical outcomes from CSA and tacrolimus in the pediatric population deserves to be further investigated with a larger cohort and focused on the more recent era, and including patients with non-malignant diseases, in hopes of providing guidance to the pediatric BMT community.

Patient eligibility population:

Inclusion criteria:

- First allogeneic HCT performed 2008-2018
- Age <21y at time of transplant
- Any indication (malignant or non-malignant diseases)
- Bone marrow at stem cell source
- Donor: 6/6 HLA matched sibling or 8/8 unrelated donor
- GVHD prophylaxis with CSA alone, CSA/MTX, CSA/MMF, Tacro alone, Tacro/MTX, Tacro/MMF

Exclusion criteria:

- Ex vivo T-cell depletion (CD34 selection, T-cell depletion)
- GVHD prophylaxis regimens except those noted above (Sirolimus, post-transplant Cy, Abatacept, etc)

- Peripheral blood stem cell or cord blood as graft source
- Mismatched donors (<6/6 HLA matched related donor, <8/8 unrelated donor) and syngeneic donors
- Embargoed centers and centers with 5-year completion index of <85%

Data requirements: (Variables to be described to be analyzed in bold)

Patient characteristics

- Age (<2y, 2-12y, 13-21y)
- Gender (male v female)
- Ethnicity (Caucasian v African American v Hispanic v Other)
- Indication (malignant v non-malignant disease)
- Performance Status (<90 v 90-100)
- Recipient CMV status (positive v negative v missing)

Transplant characteristics

- Donor-recipient sex match (M-M, M-F, F-F, F-M)
- Donor-recipient CMV status (+/+, +/-, -/+, -/-)
- Donor age (<18y, 18-29y, 30-49y, >50y)
- Donor (6/6 matched related, 8/8 unrelated)
- Conditioning Intensity (Myeloablative v Reduced Intensity)
- TBI (yes v no)
- GVHD prophylaxis (CSA alone, CSA/MTX, CSA/MMF, Tac alone, Tac/MTX, Tac/MMF)
- ATG or Campath use (yes v no v missing)
- Year of transplant (2008-2013, 2014-2018)

Outcomes

- Neutrophil engraftment (yes v no)
- Primary or secondary graft failure (yes v no)
- Relapse (for malignancies, yes v no)
- Grade II-IV aGVHD (yes v no)
- Grade III-IV aGVHD (yes v no)
- cGVHD (yes v no)
- Extensive cGVHD (yes v no)

Study design:

This will be a retrospective study utilizing the CIBMTR database. Children who underwent first allogeneic HCT using bone marrow grafts from matched related or matched unrelated donors will be included. Patient and transplant variables will be described using frequencies for categorical variables and median (range) for continuous variables.

The primary outcome of assessment is the incidence of chronic GVHD. The cumulative incidence method will be used, stratified by GVHD prophylaxis regimen (CSA alone, CSA/MTX, CSA/MMF, Tac alone, Tac/MTX, Tac/MMF). Death without GVHD will be a competing risk. Secondary outcomes include incidence of extensive cGVHD, aGVHD, neutrophil engraftment, relapse (for malignancies), and graft failure (for non-malignant diseases). Multivariable logistic regression will be used to assess the effect of GVHD prophylaxis on the development of cGVHD after adjusting for recipient age at transplant, gender, ethnicity, transplant indication, donor-recipient sex match, donor age, donor, conditioning intensity,

ATG/Campath use, and year of transplant. Subgroup analyses will be performed by disease indication (malignant and non-malignant) and by donor (matched related and matched unrelated).
The probability of survival at 1, 2, and 3 years after HCT will be assessed using Kaplan-Meier estimates, stratified by GVHD prophylaxis regimen and compared using log-rank testing. Patients will be censored at time of second HCT or donor cell infusion. Causes of death and frequency of hepatic and renal dysfunction at D100 will be described.

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Characteristics of pediatric patients undergoing first allogeneic BM transplant with a matched donor and receiving calcineurin inhibitor-based GVHD prophylaxis between 2008-2018, as reported to the CIBMTR.

	Tac + MMF	Tac + MTX	Tac	CsA + MMF	CsA + MTX	CsA
Number of patients	**168**	**445**	**15**	**184**	**740**	**93**
Number of centers	41	81	8	51	104	28
Patient age, years						
Median (range)	9 (<1-20)	10 (<1-20)	12 (<1-20)	7 (<1-20)	9 (<1-20)	7 (<1-20)
<2	19 (11)	36 (8)	2 (13)	41 (22)	87 (12)	23 (25)
2-4	22 (13)	46 (10)	2 (13)	29 (16)	122 (16)	11 (12)
5-9	44 (26)	122 (27)	2 (13)	41 (22)	185 (25)	24 (26)
10-14	39 (23)	120 (27)	4 (27)	33 (18)	160 (22)	19 (20)
15-17	22 (13)	73 (16)	1 (7)	27 (15)	110 (15)	11 (12)
18-20	22 (13)	48 (11)	4 (27)	13 (7)	76 (10)	5 (5)
Disease type						
Malignant	53 (32)	255 (57)	4 (27)	55 (30)	276 (37)	27 (29)
Non-malignant	115 (68)	190 (43)	11 (73)	129 (70)	464 (63)	66 (71)
Disease						
AML	18 (11)	125 (28)	1 (7)	30 (16)	127 (17)	6 (6)
ALL	12 (7)	78 (18)	1 (7)	16 (9)	79 (11)	12 (13)
CML	2 (1)	11 (2)	0	1 (<1)	14 (2)	2 (2)
MDS	8 (5)	17 (4)	0	3 (2)	20 (3)	1 (1)
MPS	3 (2)	12 (3)	0	2 (1)	16 (2)	5 (5)
Other leukemia	1 (<1)	4 (<1)	0	1 (<1)	6 (<1)	0
NHL	0	0	0	1 (<1)	1 (<1)	0
HD	9 (5)	5 (1)	0	1 (<1)	11 (1)	1 (1)
Severe aplastic anemia	17 (10)	77 (17)	6 (40)	25 (14)	182 (25)	18 (19)
Inherited abnormalities erythrocyte differentiation/function	70 (42)	78 (18)	2 (13)	46 (25)	214 (29)	25 (27)
SCID & other immune system disorders	16 (10)	26 (6)	2 (13)	43 (23)	44 (6)	17 (18)
Inherited platelet abnormalities	4 (2)	3 (<1)	0	0	1 (<1)	0
Inherited metabolism disorders	1 (<1)	4 (<1)	0	4 (2)	14 (2)	4 (4)
Histiocytic disorders	5 (3)	1 (<1)	1 (7)	10 (5)	8 (1)	2 (2)
Autoimmune diseases	1 (<1)	0	0	0	1 (<1)	0
Other	1 (<1)	1 (<1)	0	1 (<1)	0	0
Type of donor						
HLA identical sibling	117 (70)	258 (58)	9 (60)	116 (63)	550 (74)	89 (96)
8/8-matched unrelated	51 (30)	187 (42)	6 (40)	68 (37)	190 (26)	4 (4)

	Tac + MMF	Tac + MTX	Tac	CsA + MMF	CsA + MTX	CsA
Number of patients	**168**	**445**	**15**	**184**	**740**	**93**
Conditioning regimen intensity						
Myeloablative	103 (61)	303 (68)	2 (13)	92 (50)	493 (67)	33 (35)
Reduced intensity	46 (27)	47 (11)	4 (27)	35 (19)	38 (5)	5 (5)
Non-myeloablative	14 (8)	71 (16)	8 (53)	34 (18)	173 (23)	34 (37)
To be determined	3 (2)	14 (3)	0	15 (8)	11 (1)	3 (3)
Missing	2 (1)	10 (2)	1 (7)	8 (4)	25 (3)	18 (19)
Year of transplant						
2008-2013	71 (42)	246 (55)	10 (67)	93 (51)	409 (55)	37 (40)
2014-2018	97 (58)	199 (45)	5 (33)	91 (49)	331 (45)	56 (60)
Follow-up of survivors, months, median (range)	36 (3-123)	47 (3-127)	50 (12-121)	37 (3-124)	39 (3-122)	24 (3-120)

Abbreviations: Tac, Tacrolimus; MMF, Mycophenolate mofetil; MTX, Methotrexate, CsA, Cyclosporine; AML, Acute myeloid leukemia; ALL, Acute lymphoblastic leukemia; CML, Chronic myeloid leukemia; MDS, Myelodysplastic diseases; MPS, Myeloproliferative diseases; NHL, Non-Hodgkin lymphoma; HD, Hodgkin disease; PCD, Plasma cell disorders; MM, Multiple myeloma; SCID, Severe combined immunodeficiency.

Proposal: 1811-163

Title:
Racial and Ethnic Differences in Patients with Chronic Graft versus Host Disease

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Hypothesis:
There are racial and ethnic differences in clinical manifestations, severity, treatment patterns and outcome of patients with chronic graft versus host disease (GVHD).

Specific aims:
- To determine the racial differences in clinical manifestations and severity of chronic GVHD
- To determine impact of race on treatment patterns of patients with chronic GVHD
- To evaluate the impact of race on chronic GVHD treatment outcome

Scientific impact:
This study will characterize the role that race and ethnicity plays in the incidence, clinical presentation, treatment pattern, and outcomes of chronic GVHD. This will guide future studies to identify possible reasons for any differences and highlight interventions needed to mitigate the differences. Identification of disparities in chronic GVHD clinical presentation (organ involvement) can also help tailor treatment regimens.

Scientific justification:
Profound race-associated disparities in prevalence of several chronic diseases has been well documented. Genetic, physiological, and anatomic differences exist between races [1]. Structural cardiac differences and variations in pulmonary vasculature have been reported between difference races[2]. Based on the Multi-Ethnic study of Atherosclerosis (MESA), left ventricular mass is lowest in Asian and Caucasians and highest in blacks[3]. Changes in vascular endothelium and impaired nitric oxide balance is also noted in black patients leading to higher predisposition to vasculopathy[4-5]. Several data also suggest racial differences in pulmonary arterial hypertension (PAH) severity and response to PAH-directed therapy[6]. Many fibroproliferative diseases including systemic scleroderma[7], nephrosclerosis[8] and sarcoidosis are also more prevalent in African-derived populations than in European populations. Racial disparities in tumor presentation, histology, stage at diagnosis and response to therapy have also been well documented among patients with cancer. African Americans have the highest death rate and shortest survival of any racial and ethnic groups in the United States for most cancers[9-10]. The causes of these inequalities are thought to be multifactorial, and likely reflect racial differences in cancer biology in addition to socioeconomic disparities. Racial disparities have also been noted in outcomes of allogeneic stem cell transplant. An earlier CIBMTR study comparing transplant outcomes between ethnic populations who underwent MRD allo-HCT between 1990 and 1999 revealed a higher acute but not chronic GVHD risks for adult U.S. Whites compared with adults of Japanese descent[11]. However, among children, both acute and chronic GVHD risks were higher in U.S. Whites compared with the Japanese. More recent study comparing transplant outcomes after umbilical cord blood transplant (UCBT) between Japanese and White children with acute leukemia did not observe significant differences in acute GVHD or overall mortality[12]. Ballen et al,[13] also evaluated transplant outcomes in 612 White, 145 Black, and 128 Hispanic patients receiving a single UCBT for acute leukemia, MDS or CML between 1995 and 2006. In multivariate analysis, Black patients had worse overall survival. However, it is worth noting that higher mortality in Blacks was attributed to HLA disparity and suboptimal cell dose.

Chronic GVHD remains one of the major causes of late morbidity and mortality after allo-HCT affecting up to 70% of survivors. Corticosteroid treatment, the mainstay of therapy, is often not fully effective. Approximately 60% of patients do not have complete response[13]. Although several second line treatment options are available, currently the "trial-and-error system" is the only way to identify the treatment effective in the individual patient. With the armamentarium of treatment options available, identification of unique phenotypes can help to identify the likelihood of response to a drug in advance. Genetic, physiological, and anatomic differences between races may significantly alter the disease phenotype of chronic GVHD. Therefore, studies are needed to characterize the role that race and ethnicity plays in the prevalence, presentation, and outcomes of chronic GVHD. Unfortunately, minority groups are underrepresented in chronic GVHD clinical trials. Whether this difference in the ethnic and racial makeup of trial populations is due to differences in the background risk for the development of chronic GVHD, unequal access to medical care and resultant lower likelihood for members of racial minority groups to be diagnosed chronic GVHD, or differences in willingness to participate in treatment trials is unknown.

To our knowledge, the impact of racial disparity on clinical features and clinical course of patients with chronic GVHD has not been reported. Better understanding of racial disparities will minimize inequities, inform health policy, guide development of interventions targeted to eliminate disparities

Patient eligibility population:

- Patients age 18 years or older who have received first allogeneic transplant for hematologic malignancy (AML, ALL, MDS) from 2006 – 2017
- Only Caucasian, African American and Asian will be included
- Based on the number of patients available will decide whether include Haploidentical and umbilical cord transplant
- Patients who had recurrent malignancy before the onset of chronic GVHD will be excluded

Outcomes:

- To determine the impact of race and ethnicity on clinical characteristics of chronic GVHD.
- Severity of chronic GVHD at presentation (limited vs extensive or if NIH criteria available mild, vs moderate vs severe)
- Organ involvement at diagnosis

<u>Secondary outcome</u>

- Incidence of sclerotic GVHD (defined when cutaneous sclerosis, fasciitis, or joint contracture) at first presentation
- Proportions of patients treated initially with a single drug as opposed to 2 or more drugs
- Time to withdrawal of systemic immunosuppressive therapy (IST)
- Incidence of failure of frontline IST. Failure of frontline immunosuppression for chronic GVHD is defined as the initiation of the next line of IST for chronic GVHD regardless of the target organs. The next line of IST for chronic GVHD included either a change of systemic IST, the addition of another agent
- Overall survival after the diagnosis of chronic GVHD

Data Requirements:

Data regarding chronic GVHD can be obtained from post-transplant form 2100.

<u>Main effect:</u>

- Patient race: African American vs. Caucasian vs Asian-Pacific Islander

<u>Patient-related:</u>

- Age at HCT, years: cut-point determined statistically
- Sex: male vs female

- Karnofsky performance score: ≥90% vs. <90%
- Recipient CMV seropositivity (positive vs. negative vs. not reported)
- HCT comorbidity index at transplant 0-2 vs. ≥ 3
- Zip code

Disease-related:

- Diagnosis: AML vs ALL vs MDS
- Disease-Risk Index (low vs. intermediate vs. high/very high; and low/intermediate vs. high/very high)

Transplant-related:

- Donor type: HLA-identical sibling vs. matched URD vs haplo vs cord
- Donor race: see above
- Year of HCT: cut-point determined statistically
- Conditioning regimen intensity: MAC vs. NMA
- TBI dose in conditioning regimen (none vs. ≤450 cGy vs. >450 cGy)
- Prior grade 2-4 acute GVHD (Yes vs No)
- Graft source Bone marrow vs PBSC vs umbilical cord
- GVHD prophylaxis

Study design:

Race will be broken down into groups based on race and ethnicity: Caucasians, African Americans, and Asian pacific islander (or White non-Hispanic, white Hispanic, Black non-Hispanic, Black Hispanic, Asian based on the number available on registry). Patient, disease-, and transplant-related variables for the study cohorts will be described. The incidence of chronic GVHD will be calculated using the cumulative incidence estimator, adjusting for clinical variables with race/ethnicity forced into each model. The prevalence of organ involvement at the initial diagnosis of chronic GVHD will be calculated among the groups. The χ^2 or Fisher exact test will used to evaluate the significance of differences in proportions, and Wilcoxon rank sum tests were used to compare continuously valued outcomes and to evaluate the significance of differences in distributions among ordered categories for patients who develop chronic GVHD. The log-rank test will be used to compare subsequent survival among the racial/ethnic groups after development of chronic GVHD, adjusting for time since transplant.

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Characteristics of adult patients undergoing first allogeneic HCT for AML, ALL, MDS between 2006-2017, as reported to the CIBMTR.

	Caucasian	African-American	Asian/Pacific Islander
Number of patients	**13422**	**1034**	**1047**
Number of centers	254	143	137
Patient age, years			
Median (range)	55 (18-88)	48 (18-76)	47 (18-79)
18-29	1652 (12)	188 (18)	209 (20)
30-39	1383 (10)	166 (16)	187 (18)
40-49	2157 (16)	208 (20)	201 (19)
50-59	3564 (27)	257 (25)	259 (25)
60+	4666 (35)	215 (21)	191 (18)
Ethnicity of recipient			
Hispanic or Latino	1175 (9)	31 (3)	12 (1)
Not Hispanic or Latino	11535 (86)	970 (94)	808 (77)
Not applicable, non-resident of USA	527 (4)	22 (2)	219 (21)
Missing	185 (1)	11 (1)	8 (<1)
Disease			
AML	7806 (58)	640 (62)	654 (62)
ALL	2123 (16)	213 (21)	226 (22)
MDS	3493 (26)	181 (18)	167 (16)
Type of donor			
Cord blood	1493 (11)	235 (23)	203 (19)
HLA identical sibling	3715 (28)	239 (23)	351 (34)
Twin	52 (<1)	7 (<1)	6 (<1)
Haploidentical (1 mm)	92 (<1)	9 (<1)	6 (<1)
Haploidentical ($\geq$ 2 mm)	801 (6)	223 (22)	117 (11)
Matched other relative	175 (1)	23 (2)	18 (2)
Mismatched other relative (unknown matching)	97 (<1)	18 (2)	51 (5)
Other relatives	12 (<1)	1 (<1)	0
8/8-matched unrelated	5421 (40)	128 (12)	200 (19)
7/8-matched unrelated	1262 (9)	131 (13)	60 (6)
$\leq$ 6/8-matched unrelated	132 (<1)	15 (1)	13 (1)
Unrelated (unknown HLA)	116 (<1)	4 (<1)	18 (2)
Missing	54 (<1)	1 (<1)	4 (<1)
Graft type			
Bone marrow	1945 (14)	149 (14)	142 (14)
Peripheral blood stem cells	9968 (74)	647 (63)	702 (67)
Cord blood	1405 (10)	208 (20)	195 (19)
Missing	104 (<1)	30 (3)	8 (<1)

	Caucasian	African-American	Asian/Pacific Islander
Number of patients	**13422**	**1034**	**1047**
GVHD prophylaxis			
Ex-vivo T-cell depletion	194 (1)	25 (2)	7 (<1)
CD34 selection	312 (2)	44 (4)	22 (2)
Cyclophosphamide ± others	1004 (7)	224 (22)	113 (11)
Tac + MMF ± others	2451 (18)	217 (21)	104 (10)
Tac + MTX ± others	5536 (41)	295 (29)	305 (29)
Tac + others	685 (5)	35 (3)	53 (5)
Tac	231 (2)	20 (2)	12 (1)
CsA + MMF ± others	1420 (11)	108 (10)	168 (16)
CsA + MTX ± others	1146 (9)	48 (5)	220 (21)
CsA + others	119 (<1)	4 (<1)	10 (<1)
CsA	110 (<1)	3 (<1)	21 (2)
Others (not Cy, Tac, CsA)	134 (<1)	3 (<1)	5 (<1)
Missing	80 (<1)	8 (<1)	7 (<1)
Year of transplant			
2006	1468 (11)	64 (6)	125 (12)
2007	1458 (11)	65 (6)	53 (5)
2008	1530 (11)	82 (8)	75 (7)
2009	1373 (10)	70 (7)	66 (6)
2010	962 (7)	81 (8)	75 (7)
2011	753 (6)	59 (6)	53 (5)
2012	782 (6)	52 (5)	46 (4)
2013	1253 (9)	93 (9)	137 (13)
2014	1224 (9)	125 (12)	126 (12)
2015	1086 (8)	125 (12)	104 (10)
2016	882 (7)	122 (12)	102 (10)
2017	651 (5)	96 (9)	85 (8)
Follow-up of survivors, months, median (range)	61 (1-150)	38 (2-147)	13 (2-145)
Chronic GVHD			
No	7704 (57)	654 (63)	647 (62)
Yes	5475 (41)	358 (35)	380 (36)
TBD	243 (1)	22 (2)	20 (2)

Abbreviations: Tac = Tacrolimus, MMF = Mycophenolate mofetil, MTX = Methotrexate, CsA = Cyclosporine, TBD = To be determined.

Characteristics of adult patients undergoing first allogeneic HCT for AML, ALL, MDS between 2006-2017 and developed post-HCT chronic GVHD, as reported to the CIBMTR.

	Caucasian	African-American	Asian/Pacific Islander
Number of patients	**5475**	**358**	**380**
Number of centers	202	99	92
Patient age, years			
Median (range)	53 (18-78)	49 (18-75)	47 (18-74)
18-29	691 (13)	53 (15)	68 (18)
30-39	623 (11)	63 (18)	73 (19)
40-49	977 (18)	79 (22)	75 (20)
50-59	1506 (28)	85 (24)	100 (26)
60+	1678 (31)	78 (22)	64 (17)
Ethnicity of recipient			
Hispanic or Latino	494 (9)	13 (4)	5 (1)
Not Hispanic or Latino	4721 (86)	332 (93)	291 (77)
Not applicable, non-resident of USA	188 (3)	10 (3)	80 (21)
Missing	72 (1)	3 (<1)	4 (1)
Disease			
AML	3174 (58)	228 (64)	227 (60)
ALL	903 (16)	67 (19)	82 (22)
MDS	1398 (26)	63 (18)	71 (19)
Type of donor			
Cord blood	374 (7)	43 (12)	58 (15)
HLA identical sibling	1700 (31)	119 (33)	146 (38)
Twin	2 (<1)	0	0
Haploidentical (1 mm)	28 (<1)	3 (<1)	2 (<1)
Haploidentical ($\geq$ 2 mm)	188 (3)	75 (21)	32 (8)
Matched other relative	71 (1)	9 (3)	5 (1)
Mismatched other relative (unknown matching)	22 (<1)	1 (<1)	12 (3)
Other relatives	9 (<1)	1 (<1)	0
8/8-matched unrelated	2413 (44)	57 (16)	86 (23)
7/8-matched unrelated	556 (10)	47 (13)	27 (7)
$\leq$ 6/8-matched unrelated	56 (1)	3 (<1)	4 (1)
Unrelated (unknown HLA)	37 (<1)	0	7 (2)
Missing	19 (<1)	0	1 (<1)
Graft type			
BM	618 (11)	47 (13)	35 (9)
PB	4477 (82)	267 (75)	287 (76)
CB	367 (7)	42 (12)	58 (15)
Missing	13 (<1)	2 (<1)	0

	Caucasian	African-American	Asian/Pacific Islander
Number of patients	**5475**	**358**	**380**
GVHD prophylaxis			
Ex-vivo T-cell depletion	38 (<1)	7 (2)	0
CD34 selection	68 (1)	2 (<1)	2 (<1)
Cyclophosphamide ± others	239 (4)	63 (18)	25 (7)
Tac + MMF ± others	1030 (19)	75 (21)	38 (10)
Tac + MTX ± others	2623 (48)	137 (38)	147 (39)
Tac + others	362 (7)	14 (4)	28 (7)
Tac	82 (1)	7 (2)	6 (2)
CsA + MMF ± others	487 (9)	25 (7)	48 (13)
CsA + MTX ± others	442 (8)	25 (7)	77 (20)
CsA + others	26 (<1)	1 (<1)	3 (<1)
CsA	42 (<1)	2 (<1)	6 (2)
Others (not Cy, Tac, CsA)	25 (<1)	0	0
Missing	11 (<1)	0	0
Year of transplant			
2006	596 (11)	21 (6)	45 (12)
2007	634 (12)	23 (6)	15 (4)
2008	696 (13)	30 (8)	30 (8)
2009	649 (12)	28 (8)	34 (9)
2010	477 (9)	33 (9)	32 (8)
2011	333 (6)	13 (4)	20 (5)
2012	353 (6)	18 (5)	23 (6)
2013	533 (10)	36 (10)	60 (16)
2014	461 (8)	49 (14)	38 (10)
2015	363 (7)	37 (10)	38 (10)
2016	258 (5)	47 (13)	26 (7)
2017	122 (2)	23 (6)	19 (5)
Follow-up of survivors, months, median (range)	71 (3-150)	45 (6-147)	25 (3-145)

Abbreviations: Tac = Tacrolimus, MMF = Mycophenolate mofetil, MTX = Methotrexate, CsA = Cyclosporine.

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Graft-Versus-Host Disease Working Committee Members

FROM: Mukta Arora, MD, MS and Stephen Spellman, MBS; Scientific Directors for GVWC

RE: Studies in Progress Summary

GV17-01: Investigating antibiotic exposure and risk of acute GVHD in children undergoing HCT for acute leukemia (C Elgarten/ B Fisher/ R Aplenc)
This study aims to determine the association and impact of pre-transplant antibiotic exposures with subsequent development of aGVHD in pediatric leukemia patients. The hypothesis is that exposure to antibiotics with activity against anaerobic commensal microorganisms during the pre- and peri-transplant time periods will be associated with an increased risk of aGVHD. The study leadership discussed the plan for merging data between the CIBMTR and Pediatric Health Information System (PHIS) databases. In September 2018, the PHIS data was sent to the CIBMTR, and the study population, determined by clinical review and according to the number of patients included in both databases, was finalized in January 2019. The plan for the study is to present the protocol at the CIBMTR Statistical Meeting in February 2019 and circulate the protocol to form a Writing Committee in March 2019. Following that, the data file will be prepared and forwarded to PHIS for analysis by May 2019. The analysis results will then be presented at the CIBMTR Statistical Meeting by July 2019.

GV17-03: Alterations in the characteristics and outcomes of GVHD following post-transplant Cy for haploidentical HCT and in patients over 60 at high risk for GVHD (R Saliba/ S Ciurea/ J Schriber)
This study aims to compare outcomes between recipients of PT-Cy-based haploidentical HCT versus 8/8-matched unrelated donor with standard GVHD prophylaxis. In addition, a subset analysis will be performed comparing PT-Cy-based versus standard GVHD prophylaxis (irrespective of donor type). The draft protocol was received in June 2017 and was revised in May 2018 and ultimately presented at the CIBMTR Statistical Meeting in November 2018. After minor revisions, the protocol was circulated to form a Writing Committee in December 2018. The data file was prepared for analysis in January 2019. The plan for the study is for the analysis to be conducted by Dr. Rima Saliba and present the results at the CIBMTR Statistical Meeting by April 2019. The first draft of the manuscript will be received for initial review by June 2019.

GV18-01: Comparison of late effects among allogeneic hematopoietic cell transplantation survivors with and without chronic graft-versus-host disease (Lee CJ/ Couriel DR)
This study aims to compare the cumulative incidence of late effects between one-year survivors of allogeneic HCT diagnosed with chronic GVHD versus those without chronic GVHD. Furthermore, the effects of chronic GVHD onset, severity and organ involvement on late effects will be evaluated. Due to a shortage of statistical hours, there are no plans to progress this study until the 2019/2020 year.

GV18-02: Comparison of antibacterial prophylaxis strategies and outcomes in allogeneic hematopoietic cell transplantation patients with acute graft-versus-host disease (Wallis W/ Alousi AM/ Gulbis A)

This study aims to determine the incidence of bacterial bloodstream infections (BSI) in patients with acute GVHD II-IV. The study also, potentially, will compare the cumulative incidence of BSI in those patients from transplant centers that systematically give antibiotics as a part of antibacterial prophylaxis versus those patients from centers that do not administer antibacterial prophylaxis. The initial protocol was received in August 2018 and revised in December 2018. The protocol was then presented at the CIBMTR Statistical Meeting in February 2019. The plans for the study are to circulate the protocol to form a Writing Committee in March 2019 and then prepare the data file for analysis by May 2019.

GV18-03: Impact of chronic graft-versus-host disease on non-relapse mortality and disease relapse in transplant recipients (Bhatt V/ Lee SJ)
This study aims to compare non-relapse morality and disease relapse of older transplant recipients (≥40 years old) who experience post-HCT GVHD versus those who do not experience chronic GVHD. Further aims will be to determine the impact of baseline characteristics on chronic GVHD incidence, as well as the impact of chronic GVHD on non-relapse mortality and relapse among older patients (≥70 years old). Due to a shortage of statistical hours, there are no plans to progress this study until the 2019/2020 year.