Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR GRAFT-VERSUS-HOST DISEASE
Salt Lake City, UT
Saturday, April 23, 2022 12:15 PM - 1:45 PM

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1. **Introduction**
   a. Minutes from February 2021 meeting (Attachment 1)
   b. Introduction of new Scientific Director, Stephanie Lee.
      Thank you to Mukta Arora for all her contributions to the GVWC.

2. **Accrual Summary** (Attachment 2)

3. **Presentations, published or submitted papers**
   a. **GV18-03** Bhatt VJ, Wang T, Chen K, Kitko CL, MacMillan ML, Pidala JA, Al Malki MM, Badawy SM, Beitinjaneh A, Ganguly S, Hamilton B, Hildebrandt GC, Lekakis LJ, Liu H, Maziarz RT, Modi D, Murthy HS, Preussler JM, Sharma A, Spellman SR, Arora M, Lee SJ . Chronic Graft-versus-Host Disease, Nonrelapse Mortality, and Disease Relapse in Older versus Younger Adults Undergoing Matched Allogeneic Peripheral Blood Hematopoietic Cell Transplantation: A Center for International Blood and Marrow Transplant Research Analysis. ***Transplantation and Cellular Therapy. 2021 Oct 9;S2666-6367(21)01293-8. doi: 10.1016/j.jtct.2021.10.002.***
   b. **GV17-03** Saliba RM, Majid A, Pidala J, Arora M, Spellman SR, Hemmer MT, Wang T, Abboud C, Ahmed S, Antin JH, Beitinjaneh A, Buchbinder D, Byrne M, Cahn J, Choe H, Hanna R, Hematti P, Kamble RT, Kitko CL, Laughlin M, Lekakis L, MacMillan ML, Martino R, Mehta PA, Nishihori T, Patel SS, Perales M, Rangarajan HG, Ringdén O, Rosenthal J, Savani BN, Schultz KR, Seo S, Teshmia T, Van der Poel M, Verdonck LF, Weisdorf D, Wirk B, Yared JA, Schriber J, Champlin R, Ciurea S. Characteristics of Graft-versus-Host Disease (GvHD) after Post-transplant Cyclophosphamide versus Conventional GvHD Prophylaxis. ***Submitted.***

c. **GV18-01a** Lee CJ, Wang T, Chen K, Arora M, Spellman SR, Kitko C, MacMillan ML, Pidala JA, Auletta JJ, Badawy SM, Bhatt N, Bhatt VR, Cahn J, DeFilipp Z, Diaz MA, Farhadfar N, Gadalla S, Gale RP, Hashem H, Hashmi S, Hematti P, Hong S, Hossain NM, Inamoto Y, Lekakis LJ, Modi D, Patel S, Sharma A, Solomon S, Couriel DR. Association of Chronic Graft-versus-Host Disease with Late Effects Following Allogeneic Hematopoietic Cell Transplantation for Children with Hematologic Malignancy. ***Submitted.***

d. **GV18-02** Wallis W, Gulbis W, Wang T, Chen K, Kitko CL, MacMillan ML, Pidala JA, Riches ML, Spellman SR, Arora M, Alousi AM. Bacterial Prophylaxis in Patients with Acute GVHD; Who Is at Risk for Bloodstream Infections? ***Poster presentation, ASH 2021.***

e. **GV19-01** Gillis N, McNulty S, Wang T, Druley T, Chen K, Arora M, Kitko CL, MacMillan ML, Pidala JA, Padron E, Spellman SR, Lazaryan A. A Pilot Study Exploring the Link between Donor-Engrafted Clonal Hematopoiesis and Outcomes of Allogeneic Hematopoietic Cell Transplantation from Older Matched Sibling Donors. ***Poster presentation, Tandem Meetings 2022.***

4. Studies in progress (Attachment 3)

a. **GV18-01b** Comparison of late effects among adult allogeneic hematopoietic cell transplantation survivors with and without chronic graft-versus-host disease (Lee CJ/ Couriel DR) **Manuscript Preparation**

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

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

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

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

f. **GV21-01** Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease (Farhadfar N/ Wingard JR/ Al-Mansour Z) **Data File Preparation**

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

5. Future/proposed studies

a. **PROP 2108-02/2109-19/2110-72** Post-Transplant Cyclophosphamide vs *in vivo* T-Cell Depletion with Anti-Thymocyte Globulin or Alemtuzumab in Patients with Acute Leukemia or Myelodysplastic Syndrome undergoing Unrelated Donor Hematopoietic Cell Transplant (A Jimenez/L Arcuri/A Marinos/K Komanduri/N Hamerschlak/P Lulla) (Attachment 4)

b. **PROP 2110-193/2110-278** Comparative analysis of the incidence of graft versus host disease by age group in pediatric hematopoietic stem cell transplant recipients and impact on non-relapse mortality (M Nishitani/C Duncan/R Graham/M Qayed) (Attachment 5)

c. **PROP 2108-04** Chronic GVHD Risk Index: A clinical risk assessment score for development of moderate-severe chronic graft-versus host disease after hematopoietic cell transplantation (A Im/S Pavletic) (Attachment 6)

d. **PROP 2110-25/2110-266** A Risk-Score for Bronchiolitis Obliterans Syndrome after Allogeneic Hematopoietic Cell Transplantation (S Patel/R Mehta/C Ustun/A Alousi) (Attachment 7)
e. **PROP 2106-01** Incidence and Risk Factors for thromboembolism in patients with Chronic Graft-versus-Host Disease (N El Jurdi/M Arora) (Attachment 8)
f. **PROP 2110-24** Does race/ethnicity or socio-economic status impact the outcomes of patients with acute GVHD? (N Rashid/N Farhadfar) (Attachment 9)

Dropped proposed studies

g. **PROP 2109-06** Risk Factors For Engraftment Syndrome And Its Impact On Clinical Outcomes In Pediatric Allogeneic Stem Cell Transplant Recipients: A Contemporary Analysis. *Concern about accurate capture of engraftment syndrome; lower scientific impact relative to other proposals.*
h. **PROP 2109-23** Assessing if multiparous female donors increase the risk of graft vs host disease in HLA-Matched un-related and related allogenic stem cell transplant in the era of post-transplant cyclophosphamide. *Need for additional data collection; lower scientific impact relative to other proposals.*
i. **PROP 2110-30** Risk of cardiovascular disease, infections, secondary malignancies, and non-relapse mortality among patients who received sirolimus. *Concern about study population heterogeneity and ability to isolate effect of sirolimus; unclear feasibility; lower scientific impact relative to other proposals*
j. **PROP 2110-70** Comparing Patterns, Outcomes and Organ Involvement with Acute and Chronic Graft-versus-Host Disease Between Patients with Non-Malignant Diseases Undergoing Haploidentical Transplantation Using Post-Transplantation Cyclophosphamide vs. Matched Unrelated Donor Transplantation Using Calcineurin Inhibitors. *Overlap with CIBMTR study GV17-03.*
k. **PROP 2110-97** Is there differential benefit of alternative GVHD prophylaxis strategies among racial and ethnic groups? Graft-versus host disease-free relapse-free survival by race and ethnicity comparing post-transplant cyclophosphamide-based to calcineurin inhibitor plus methotrexate-based GVHD prophylaxis. *Minority sample size too small; transplant approach confounded by donor availability*.
l. **PROP 2110-122** Determining the optimal anti-thymocyte globulin dosing in patients with hematologic malignancies. *Data on ATG timing not available.*
m. **PROP 2110-169** Comparison of survival and graft versus host disease outcomes in alternate mismatched graft sources. *Overlap with published CIBMTR study GV16-01a.*
n. **PROP 2110-215** Effect of Graft-Versus-Host Disease Prophylaxis on Survival after Reduced Intensity Conditioning Hematopoietic cell transplantation for Older Adults: a CIBMTR analysis. *Overlap with CIBMTR study GV17-03.*
o. **PROP 2110-218** To compare CD3+ T-Cell Dose for Patients Receiving Allogeneic Peripheral Blood Stem Cell Transplants from Matched Related Donors using a propensity-matched study. *The primary single center study population is very small; lower scientific impact relative to other proposals.*
p. **PROP 2110-279** One Year Graft vs. Host Disease Relapse Free Survival in Acute Lymphoblastic Leukemia patients undertaking Matched Related or Matched Unrelated Allogeneic Stem Cell Transplant Using Post Transplant Cytoxan compared to conventional Graft vs Host Disease prophylaxis. *Limited sample size; overlap with published CIBMTR study GV16-01a.*
q. **PROP 2110-285** Sirolimus versus Tacrolimus in combination with post-transplant cyclophosphamide and MMF as a GVHD prophylaxis after allogeneic hematopoietic cell transplantation in patients with hematologic malignancies. *Limited sample size.*

r. **PROP 2110-324** Explore the optimal dose and length of post allogeneic hematopoietic stem cell transplant prophylactic immunosuppressant use. *Data on dosing and timing not available.*

s. **PROP 2110-329** Immunosuppression discontinuation after allogeneic hematopoietic stem cell transplantation. *Concern about reliability of late infection data; immunosuppression discontinuation not clearly defined at 1 and 2 years in CIBMTR database*

6. Other Business

MINUTES
CIBMTR WORKING COMMITTEE SESSION
Thursday, February 11, 2021, 1:00 - 4:00 pm
Co-Chair: Bronwen Shaw, MD, PhD; CIBMTR Statistical Center, Milwaukee, WI; E-mail: beshaw@mcw.edu
Co-Chair: John Wingard, MD; University of Florida, Gainesville, FL; E-mail: wingajr@ufl.edu

INTRODUCTION:

Dr. Wingard opened the virtual meeting at 1:00 pm by welcoming the working committee members and the presenters. He discussed the proposal selection and voting process. Though the pandemic amended the process for proposal selection, 368 working committee proposals were submitted and evaluated altogether by CIBMTR Working Committee Chairs and Scientific Directors. About 61% were screened out, 30% had less-relative scientific merit, and 3% were combined with overlapping proposals with relevant nature. 21 proposals (about 6%), were considered for advancing of further pro-development. The proposals were pre-recorded 5-minutes presentations of the 15 semi-finalists, which were presented by the principal investigators. Each presentation was followed by a 5-minute question and answer session, in which audience was invited to submit questions via live chat. For those not able to attend the live session, a link was posted with the session recording and voting was closed on Monday, February 15, 2021. Audience was also instructed on where to locate the scoring and voting links for the presentations. It was mentioned that over 1,000 Working Committee members voted on the first screening of these proposals. Dr. Shaw led the second part of the meeting starting with presentation #9.

GENERAL REMINDERS:

The following reminders were mentioned and posted via the chat option:

a. Thank you for participating in the CIBMTR Working Committee Session! Please cast your score here: https://mcwisc.co1.qualtrics.com/jfe/form/SV_7QwO1ZvzfPZV1NY to vote on the proposals that were presented during the session.
b. Several presenters provided their email addresses for any future communication.

PRESENTATIONS:

1. **Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis.** This proposal was presented by Dr. Ana Alarcon Tomas. The primary objective of this proposal is to describe the incidence rate, risk factors, characteristics, and outcomes of subsequent neoplasms in patients receiving post-transplant cyclophosphamide (PTCy) and compare it with calcineurin inhibitors-based graft-versus-host disease prophylaxis and the general population. The CIBMTR identified 64,935 patients ≥18 years of age who underwent a first allogeneic for a malignant disease between 2008-2017. 5,771 (9%) of these patients developed a subsequent neoplasm. Currently, there are no published studies on the incidence of subsequent neoplasms in patients who received post-transplant cyclophosphamide. The following questions were answered during the Q&A:
    a. How are we going to prove that these secondary neoplasms are related to post-transplant cyclophosphamide or cyclophosphamide in conditioning and not due to "by chance" itself- as in general population? This is a case-controlled study. For example, for each patient received with a post-transplant cyclophosphamide will be matched with at least three patients who didn't receive post-transplant cyclophosphamide. Characteristics including primary disease, HLA complexity, survival, follow up time etc. would be used for matching and reviewing survival will also allow us to see that this is because of PTCy and not by coincidence.

b. What is the median follow up time from transplant and subsequent malignancy in post-transplant cyclophosphamide group? I assume it is much shorter than other cohort? Information is not available for each median follow up time cohort. What is available is the median follow up for all patients and some numbers related to the type of diseases for each group. Dr. Rachel Phelan included in the chat that the median follow-up for the PT-Cy group is 38.2 months, and for the proposed control population is 60.3 months.
c. How is this in comparison with matched unrelated donor and cord transplants? Cord transplants will be excluded from the analysis because we don't think we can match those patients.
d. Do we have adequate follow up to answer this important question? We have follow-up for mantle hematological diseases but less time for solid tumors. However, when we saw the numbers that we have (around 5,000 - 5,700) subsequent neoplasms, the majority of cases occurred after the 1st - 5th year of post- transplant and have a 5-year median follow up. We think we have enough numbers to address this question now and we should not wait because it hasn't been published before. This is a noble study and if we wait for a longer median follow up, we might lose that opportunity to have it published first.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix A.

2. **Outcomes of chimeric antigen receptor-T cell therapy for patients with antecedent chronic lymphocytic leukemia (Richter's Syndrome)**. This proposal was presented by Dr. Farrukh Awan. The objective of this proposal is to assess outcomes in adult patients with chronic lymphocytic leukemia undergoing transformation to diffuse large B-cell lymphoma (Richter's Syndrome) and undergoing CAR-T therapy. The CIBMTR identified 36 patients underwent CAR-T for Richter's Syndrome from 2015-2019. The following questions were answered during the Q&A:
   a. I know that in the Ohio State paper have many patients that used concurrent Bruton Tyrosine Kinase (BTK) inhibitors. Will you be able to collect data on concurrent BTK inhibitors for these patients? Yes, this information is available through the CIBMTR dataset.
   b. Are you looking at diffuse large B-cell lymphoma derived Richter's Syndrome or chronic lymphocytic leukemia derived Richter's Syndrome? Yes, but it is difficult to determine a clonality between related and unrelated Richter's syndrome. Any studies that show similarities versus dissimilarities in the clone would be very helpful but unfortunately, previous studies have shown that this has been consistently difficult.
   c. You mentioned the opportunity of comparing to other treatment groups. Can you talk about that a little more? We can compare to patients with de novo diffuse large B-cell lymphoma. There are multiple approved and ongoing studies within CIBMTR of diffuse large B-cell lymphoma patients, who do undergo CAR-T therapy and look at toxicity outcomes and infectious outcomes, for example. There are efforts in place to look at outcomes of transplantation for patients with Richter's Syndrome, which can improve the impact of this project and be a competitor to those other ongoing studies.
   d. How many pts do we have? 36 patients
   e. How do you plan to deal with the very low patient numbers (n=36) to make meaningful conclusion? I agree that it is a small number, but it is substantial. Despite the small numbers, if the right competitors are used, such as those mentioned previously, this study can still provide an impactful dataset.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix B.

3. **Impact of graft versus host disease following allogeneic hematopoietic cell transplantation on leukemia free survival in hematologic malignancies**. This proposal was presented by Dr. Andrea Bauchat. The objectives of this proposal is to determine the impact of development of grade I-II acute graft versus host disease on relapse and leukemia-free survival, to assess the impact of development of grade III-IV acute graft versus host disease on relapse and leukemia-free survival, and to determine whether the impact of graft versus host disease on

relapse and leukemia-free survival is influenced by disease risk prior to HCT. The CIBMTR identified 1,345 children <18 years who received first HCT for acute lymphoblastic leukemia and acute myeloid leukemia receiving first allogeneic transplantation between 2008 - 2017. The following questions were answered during the Q&A:

a. What is the sample size of each sub-group: disease-risk index (DRI)-low, -intermediate, -high? Exact sample size not available but the high-risk group was less in comparison to others.
b. How will you factor in occurrence of chronic graft versus host disease in your analysis? Our main focus is on acute graft versus host disease because it will have more impact on our clinical practice. However, we will collect the data for the interactions of chronic graft versus host disease alone, and if the patient had a history of acute.
c. What is the biological basis for focusing this study on a pediatric population? The interest from our perspective is looking at the pediatric population compared to the adults. The literature on pediatric is severely lacking in comparison to adults and we need to expand on that for the patient population that we care for.
d. Are you going to separate acute myeloid leukemia and acute lymphoblastic leukemia numbers at DRI level? Yes, they are already divided from DRI protocol. Our acute lymphoblastic leukemia patients are about 1,300 and the acute myeloid leukemia are about 1,200.
e. Is the analysis going to be time dependent or landmark? Landmark
f. Do you have the date of this max acute graft versus host disease grade to take into account the time to event aspect of the effect? No
g. Do you have a plan to include/account for the various GVHD prophylaxis regimen "strengths?" We are taking into consideration of what GVHD prophylaxis regimen the patient uses. This data, which is already categorized, will show us the differences between trends.
h. What is the clinical benefit besides prognostic? This will help define a better foundation of which patients will benefit more from a little bit of graft versus host disease. If we can come up with a patient category that we see is beneficial to have exposure to a little bit of graft versus host disease, it can go forward with clinical trials and GVHD prophylaxis adjustment or manipulation to improve their Leukemia-free survival.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix C.

4. **Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant**. This proposal was presented by Dr. Christine Camacho-Bydume. The primary objective of this proposal is to determine if HLA evolutionary divergence (HED) of HLA class I alleles of HLA-A, -B, -C and HLA class II alleles of HLA-DR is associated with overall survival and relapse. The objective is to also evaluate association of HED with acute and chronic GVHD and treatment-related mortality (TRM). The CIBMTR identified pediatric and adult patients with acute myeloid leukemia, myelodysplastic syndromes, acute lymphoblastic leukemia, chronic myeloid leukemia, or lymphoma (non-Hodgkin or Hodgkin's lymphoma), who have received initial allogeneic 8/8 HLA-matched (HLA-A, -B, -C, -DR) transplant between 2008 - 2018. The following questions were answered during the Q&A:

   a. Could HLA diversity simply be a surrogate for race? How would you account for race in the study? Great question given there are particular HLA alleles that are more common in certain ethnic groups. We do think that evaluation of HED lows and highs within these different ethnicities can help to tease this out more, with potential to adjust for race more in this analysis. We think some of these differences in peptide binding grooves can help us to understand better the different peptides and how antigens are presented to T-cells.
   b. Extrapolating HLA data from solid tumors and checkpoint inhibitors and their antigen presentation is slightly challenging in context of allo donor T-cell interaction with antigen presented for bone marrow origin cancers. Yes, have to consider there could be some differences. Was a small previous study that

looked at this question, saw some signals there, larger population and different types of cancers, may be able to explore that more.

c. Leukemia (both lymphoblastic and myeloid) have low mutational burden as compared to melanoma and lung. Will the HED algorithm still work? Yes, we do expect to see differences in mutational burdens, and we do plan to look at the cohort at large to look at the disease subgroups to see more or less of this phenomenon in these groups. Do you have preliminary data in leukemias? There was a small study in Germany that looked at AML, to my knowledge only one that looked at leukemias. Mutational burden did see some differences, so we do expect it and also, besides the overall cohort, also plan to look at disease subgroups.
d. Given HED implications for infection surveillance, are you going to look at infectious sequelae differences? No, at the moment we have initially requested information in terms of tumor control, relapse, overall survival, graft versus host disease, and TRM. Not sure of availability of the other information but would be interesting to look at if available.
e. Would you please discuss the confounding effects of HLA mismatching for HLA-DRB3, 4, 5, DQ, and DP? Not known off the top of my head the percentages of mismatching differences in this cohort. For DR at least they will be matched, 8/8 matched, in terms of DP, don't have that info but if available it is something that can be looked at.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix D.

5. **Impact of IDH1 and IDH2 mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation**. This proposal was presented by Dr. Evan C. Chen. The primary objective of this proposal is to identify differences in survival outcomes between mutIDH1/2 and wtIDH1/2 acute myeloid leukemia patients and to assess the prognostic significance of disease features in mutIDH1/2 and wtIDH1/2 acute myeloid leukemia patients. The CIBMTR identified patients ≥ 18 years old with a diagnosis of normal karyotype acute myeloid leukemia, receiving first allogeneic HCT during CR1 in 2013 - 2019. The following questions were answered during the Q&A:
   a. Is there any concern that patients with IDH1/2 mutated acute myeloid leukemia would have received more intensive conditioning / therapy than IDH1/2 wild-type? Yes, and it's important to look at how conditioning intensity can be an important covariant, which is a variable captured in CIBMTR.
   b. Will you have registry information on the type and duration of use of IDH inhibitors before/after HCT? It's currently not available with CIBMTR.
   c. IDH mutations are usually seen in older subjects. How will you a priori adjust for this known association? Age will certainly be a covariant in our multi-variant analysis.
   d. How reliable are the wild-type patients as some may just not be tested for IDH mutations? It is double checked. There is a datapoint in the forms that indicate whether or not testing has been done, versus if testing was done and IDH was found to be absent.
   e. Do you have information what the numbers will be like when you divide your patient groups with concomitant mutations such FLT3 or p53 that may have an impact on outcomes? Yes, the numbers are about 20-40 for co-mutated for ITD and NPM1 patients. p53 not provided.
   f. Is there data in CIBMTR forms that collect use of IDH inhibitors pre transplant? Will you be able to study their impact on the transplant? I'm not aware of this data point being available in the forms but it is something that we should follow up on.
   g. How do you analyze its (or ITS?) with multiple mutations? With regards to double-mutated patients, IDH1, and IDH2 patients, which are generally rarely reported, we would look at the CIBMTR forms to ensure accurate data entry. In regard to analyzing IDH with other co-mutations, we would include co-mutations as a co-variant in a multi-variant analysis, should the sample size permit.

h. What about other mutations in Wild type IDH? We focus on NPM1 and FLT3-ITD because they are prevalent in the cytogenetic risk population. We will look at the other mutations to see if they have any relevance at all.
i. Do the data forms reliably collect information on use of IDH inhibitors pretransplant? Data point is not available.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix E.

6. **Characteristics and outcomes of adolescent and young adults with multiple myeloma treated with autologous hematopoietic cell transplant**. This proposal was presented by Dr. Christin B. DeStefano. The primary objective of this proposal is to describe patient and disease related characteristics of adolescent and young adults (AYAs) with multiple myeloma treated with early high dose melphalan and AutoHCT and to characterize response to AutoHCT, survival outcomes, SPMs, and infections of AYA multiple myeloma patients and AutoHCT. The CIBMTR identified 1,142 AYA multiple myeloma patients who underwent autologous hematopoietic cell transplant) between 2008 -2018. The following questions were answered during the Q&A:
   a. What will differentiate this study from MM18-03 "To compare the outcomes in young patients with multiple myeloma at diagnosis undergoing upfront autologous hematopoietic stem cell transplant with older patients in the US: progression-free and overall survival"? There appears to be substantial population overlap. The Scientific Director clarified via the chat function that MM18-03 included the years 2013-2017 and excluded patients less than 40 years from the outcome analysis owing to small numbers.
   b. How do you plan to control for differences between your AYA group and older control group which would be attributable to age? In total, there are about 1,700 TED and CRF cases. We can adjust the critical variables of these cases, such as stage, treatment rendered, and cytogenetics, for example, to control for differences.
   c. Will results be stratified according to different induction regimens? Yes, we will adjust those critical variables amongst the CRF cases where this information is available.
   d. A cohort going back to 1995 seems too outdated. What was the N for a more recent group (since 2010)? There were 1,142 AYA cases between 2008-2018.
   e. This is a long cohort 1995-2019 with lots of changes in induction treatment, novel agents and time to bone marrow transplant. How will this be controlled for? We are going to study induction regimens, post-transplant treatment, use of tandem transplants in our analysis.
   f. Will you be also studying the effect of post-transplant maintenance therapy? Also, any effect of extramedullary plasmacytomas in this AYA group? We will for cases where this information is available. Extramedullary plasmacytomas are a good focus, as AYA patients may have a more aggressive presentation of myeloma.
   g. Are plasma cell leukemias included in this analysis? No

   Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix F.

7. **Impact of measurable residual disease status on outcomes of AML in patients 18-65 years old in CR1 undergoing Allo-HCT**. This proposal was presented by Dr. Firas El Chaer. The objectives of this proposal is to determine if acute myeloid leukemia measurable residual disease (MRD) analysis as currently performed has prognostic value when measured prior to AlloHCT, to explore factors that may modify the risk associated with detectable acute myeloid leukemia MRD pre-AlloHCT, and identification, using MRD combined with other clinical factors, of patients most at risk of post-AlloHCT relapse. The CIBMTR identified 753 MRD positive and 1986 MRD negative adult patients receiving first AlloHCT for de-novo AML in CR1 in 2007-2018. The following questions were answered during the Q&A:

a. What kind of MRD data is collected? Depending on the individual participating centers, the methodology uses molecular or immunotherapy? MRD
b. What is the rate of missing MRD status and are those patients different from those with MRD data available? The answer is not included in this study.
c. Are you going to also study the effect of post-transplant maintenance in AML FLT3, IHD mutations on relapse and overall survival? One of the aims of this study is to have future studies look at post-transplant maintenance from this study.
d. What do you mean by most "recent" pre-conditioning MRD assessment? Would testing need to be completed within a specific time frame before conditioning? All patients who will be receiving a stem cell transplant are required to get a bone marrow biopsy and peripheral blood aspiration before transplantation. Within a month before the transplant, we would look at data point.
e. What is your working definition of MRD? A combination of molecular testing as well as immunotherapy by NFC.
f. Are all mutations equivalent when thinking about MRD? Absolutely not.
g. How sure are you that the MRD patients are really MRD negative? We can never be absolutely sure.
h. How are you going to account for the different sensitivity of methods used to determine MRD? Are ELN risk available at CIBMTR, since when? The way that CIBMTR reports the acute myeloid leukemia data is by reporting their cytogenetics and mutation analysis so we can calculate the data for this population. The point of this study is to look at the commercial availability of these tests and we can rely on it or if we should standardize one testing at all centers.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix G.

8. **Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease.** This proposal was presented by Dr. Nosha Farhadfar. The objectives of this proposal are to determine whether clinical manifestations and severity of chronic GVHD differ based on racial/ethnic and socioeconomical status (SES) differences, to determine whether treatment patterns of chronic GVHD differ based on racial/ethnic and SES differences, and to evaluate whether chronic GVHD treatment outcomes differ based on racial/ethnic and SES differences. The CIBMTR identified 17,665 patients, age 18 years or older, who have received first allogeneic transplant for hematologic malignancy (acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome) between 2008 - 2019. The following questions were answered during the Q&A:
   a. I like the idea for looking at outcomes based on race/ethnicity/SES but not sure if incidence should be a primary outcome because it will be dependent on donor type which is very different amongst the groups. The primary outcome of this study is to look at the outcome of patients who develop chronic graft versus host disease. We need to look at the whole cohort, report the incidence, and then focus on chronic graft versus host disease cohort as the primary endpoint of this study.
   b. How will you correct for the impact of race on HLA mismatch between recipients and donors due to the lower chance of identifying a fully matched donor in non-Hispanic white patients? For the same reason, should cord blood recipients be excluded? We are going to include both the donor type, graft source and degree of HLA matching as covariables in a multi-variable analysis. Cord blood recipients should not be excluded, as there was near 14% of Non-Hispanic black, 14% Hispanic, and 15% Asian who received cord transplant. Approximately 7-8% of cord transplants were received by Non-Hispanic whites. We do have the number to look into cords but if a statistician reviews and determines we don't have the power, then we can eliminate the cords.
   c. Is it possible to access constitutional DNA to look at ancestry information markers in this population? This information is not available for the population. The analysis will focus on self-reported race/ethnicity.
   d. All patients in your cohort from 2008 were not reported with NIH consensus criteria for chronic GVHD. Since you have large numbers, should you limit this to more recent time period? We do have all of the

information on graft versus host disease and whether it was limited or extensive. There is information on whether graft versus host disease is progressive, de-novo or interrupted. We have organ involvement and maximum grade of chronic graft versus host disease. NIH scoring is available for at least the past 4 years and maybe we can look at that group separately. Within the past 4 years, the population limited to NIH grading only in about 1,500 non-Hispanic white, 270 non-Hispanic black, and 200 Hispanic, who have developed chronic graft versus host disease.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix H.

9. **Time from diagnosis to transplant as an important contributor for post allogeneic stem cell transplant infections, immune reconstitution and its associated mortality/morbidity**. This proposal was presented by Dr. Lohith Gowda. The objectives of this proposal are to identify density and types of early and late infections (bacterial, viral and fungal) in patients that went to transplant a) <6 months b) between 6- 12 months and c) > 12 months from diagnosis; to identify T cell lymphocyte absolute numbers at days 100 and 180 and CD4/CD8 ratio for the timeline cohorts examining individual donor types; to evaluate the impact of bacterial, viral or fungal infections by day 100 and day 180 on 1-year post-transplant outcomes (relapse, non-relapse mortality, disease free survival, acute and chronic graft versus host disease); and to evaluate quantitative immunoglobulin levels at D+ 100 and + 180 if available. The CIBMTR identified 6,877 ≥ 18 years old patients who underwent first allogeneic transplants for AML in CR1, ALL in CR1 or MDS in the United States from 2012 to 2019. The following questions were answered during the Q&A:
    a. How many patients in the registry have the immune parameters you wish to assess? >2100
    b. How will you account for the type of treatment used prior to transplant? For example, treatments such as hypomethylating agents may require months of treatment before transplant versus induction chemo that works more quickly. We do have some variables that are available, such as types of therapy, and we can analyze levels of intensity of therapy (low to high) and post-transplantation outcomes. The exact number of how many patients who have had different intensities of therapies is not available.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix I.

10. **Efficacy and safety of CD19 directed CAR T-cell therapy for non-Hodgkin B-cell lymphomas with secondary central nervous system involvement**. This proposal was presented by Dr. Hamza Hashmi. The primary objective of this proposal. The CIBMTR identified 55 adult patients (age ≥ 18) who received CD19 CAR T-cell therapy for B-cell NHL with secondary central nervous system (CNS) involvement. The following questions were answered during the Q&A:
    a. How will you differentiate between immune effector cell-associated neurotoxicity syndrome (ICANS) and CNS relapse? ICANS will be documented as a neurotoxicity and CNS relapse will be when the form is filled out.
    b. Is this active CNS disease or previously treated CNS disease? The data received from CIBMTR looks at CNS disease at the time of diagnosis and the CNS disease that is present at the time of cellular therapy.
    c. Do you have any registry information on concomitant CNS therapy (chemo/radiation) pre, peri and post transplantation? Answer was not available at this time.
    d. How many patients are in your study? How will you define whether the patients have cleared their CNS involvement? There are currently 60 patients in the history of this data. Of the 60, 40 had this disease at the time of diagnosis and 20 had this disease at the time of cellular therapy. Whether the patients have cleared their CNS involvement, this information is not available at the time.
    e. Since this is your primary endpoint, how will you account for the differences of frequency of CRS and ICANS across different products (e.g. high in Yescarta, lower in Kymriah, low in Breyanzi)? If you look at the toxicity profile of CD19 therapy, they seem to be relatively similar.

f. Could you please include other agents such as anakinra, siltuximab, and other agents? Dasatinib for this populations for ICANS? Also, was CNS disease under control at CAR-T therapy? As for Anakinra, siltuximab, and other agents, I'm not sure if CIBMTR is capturing this data. As for dasatinib, I'm not sure if this information is available as well. Per Dr. Pasquini of CIBMTR in the live chat, he commented "we capture treatment of ICANS, like siltuximab, dasatinib has been reported as other treatment."
g. Will you have detail on the nature and extender features of secondary CNS involvement to associate with the toxicity and outcome? I only have the essential data with me but am hopeful that this comprehensive research will have further detail.
h. Will all the patients included have active CNS disease at the time of CAR-T or, are treated CNS disease are also included? They are both included, and we are able to tell who has had active disease with a prior history at the time they got the CAR-T therapy.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix J.

11. **Haploidentical donor versus matched donor allogeneic hematopoietic cell transplantation in patients with myelofibrosis**. This proposal was presented by Dr. Tania Jain. The primary objective of this proposal is to explore the impact of donor type on overall survival of patients undergoing HCT for myelofibrosis. The CIBMTR identified 1,640 patients ≥18 years old diagnosed with primary, post-ET or post-PV myelofibrosis and undergoing first HCT between 2013 and 2019. The following questions were answered during the Q&A:
    a. Are you also going to compare the effect of pretransplant Ruxo in haplo vs MUD/MRD? Also, are you going to look for graft failures as well in these patient populations? Yes, this will be included. We also do look at graft failures in these populations.
    b. Is there a difference in time from diagnosis to HCT across the groups? The median time from diagnosis to transplant for haploidentical patients was 38 months, while for HLA- identical sibling and URD 8/8 was 21 and 24 months, respectively.
    c. Are you including all conditioning regimens types: MAC, RIC and NMA? Yes, and they will be looked at for comparison in the univariable and may be taken to the multivariable analysis as well.
    d. For the graft failure or rejection analysis are you going to include spleen size? Ideally it should be included but the spleen size measurement has many variables and it may not be a clean assessment. We don't collect precise spleen size in our forms, but it can be analyzed as spleen size as splenomegaly, no splenomegaly or splenectomy.
    e. Can you comment on the bone marrow vs peripheral blood in the three groups? Peripheral blood is more common in the donor source (about 80%).

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix K.

12. **Assessing utilization and clinical outcome differences by sex and race in CAR-T for relapsed/refractory NHL**. This proposal was presented by Dr. Arushi Khurana. The objective of this proposal is to enhance our understanding of sex- and race-based differences in utilization of CAR-T vs AutoHCT and outcomes after CAR-T. The CIBMTR identified 1,133 patients to compare sex and race/ethnicity rates for first cellular infusion (AutoHCT vs. CAR-T) for relapsed/refractory non-hodgkins lymphoma patients from 2017 – 2019 (aim 1a). The CIBMTR identified 619 non-hodgkins lymphoma patients who relapse after first AutoHCT to describe subsequent treatment patterns (e.g. CAR-T, second AutoHCT, AlloHCT, other treatment, no treatment) by sex and race/ethnicity (aim 1b). The CIBMTR identified 1,253 patients to identify sex-and race-based differences in response to CD19 CAR-T in aggressive lymphomas (aim 2). The following questions were answered during the Q&A:
    a. Is there gender and race-based difference in SEER data with or without treatment for diffuse large B-cell lymphoma even before CAR T? Yes, that data does exist.

b. Can this be stratified by center/geography (private/public, large urban/rural)? Yes, it will be shown based on zip code (of patient and of recorded center), which will allow us to differentiate from urban/rural as well.
c. We saw almost no neurotoxicity in women so would you be plotting CRS and ICANS based on gender and race? Yes, and we believe CIBMTR is the best resource for this because of the larger numbers
d. How do you differentiate between larger trial centers vs less resourced centers? The information is reported based on the center type. Basing on academic or zip code, or city versus rural center, that will also be a way to differentiate the centers.
e. Would disease response status prior to cellular therapy be taken into account for analysis? Yes, that is one of the co-variants that will be included.
f. How reliable is the data you will get to study "access", as there are many factors, depending on patient specific factors (education, resource, finances, mobility, support, performance, etc.), center specific (criteria), and also access depends on the hematologist/oncologist who sees these patients in the community? Access to a center is not one of the main issues in this study. It is more about why some of these minorities receiving other treatments when they should be receiving cellular therapy at the time of indication.
g. Is there any way to take into account insurance issues? We do look at the insurance statuses as one of the co-variants.
h. Would it be possible to look at differences in access based on commercial CAR T vs. clinical trials? The majority of the patients from the forms received are from commercial CAR T.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix L.

13. **Optimal GVHD prevention strategy in older, robust patients with acute leukemias and myeloid malignancies undergoing myeloablative, matched donor hematopoietic cell transplantation**. This proposal was presented by Dr. Richard J. Lin. The primary objective of this proposal is to compare CRFS among patients ≥ 60 years old undergoing myeloablative conditioned, allogeneic hematopoietic cell transplantation with following graft versus host disease prophylaxis in 2 matched-pair analysis and to compare other transplant outcomes in the above 2 matched-pair analysis. The CIBMTR identified 1,301 patients at ≥ 60 years old at the time of first allo-HCT between 2010 and 2019, with any myeloablative conditioning defined by CIBMTR, 8/8 matched related or unrelated donor only, graft versus host disease prophylaxis (ex-vivo TCD/CD34+ selection versus PTCy-based versus Tac/MTX). The following questions were answered during the Q&A:
    a. What do you mean by "robust?" Is it based on KPS, HCT-CI, or just the fact that someone got MA. regimen? We use the definition of a patient getting a myelo-conditioning as a way of saying that they are robust by their transplant centers.
    b. Are patients with In-vivo T cell depletion (Campath or ATG) excluded from this analysis? T cell depletion and CD34 selection does include ATG and does not include Campath.
    c. Why do you pool post-CY and ex vivoCD34+ selection? Can we still consider ex vivoCD34 selection to be a promising transplant modality in 2021? We wanted to compare a 2-match pair analysis and not a direct comparison between CD34 selection and post-CY. We do know which will be better for an older patient.
    d. Why exclude TBI? For older patients, we don't consider TBI to be a conditioning regimen.
    e. How many patients with Tac/methotrexate prophylaxis had ATG? Answer was not available at the time of Q&A.
    f. Do we know GFR (creatinine) coming into allo in these groups? In this study, we didn't include the GFR (creatinine) as a variable but we have some evidence in older patients that does play a major role. I can discuss with our statistician on whether we can include this as a variable.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix M.

14. **Outcomes of elderly patients receiving CD-19 directed CAR-T therapy for B-cell lymphomas**. This proposal was presented by Dr. Sayeef Mirza. The primary objectives of this proposal to evaluate cumulative incidence grades, duration and median time to onset of CRS and CRES/ICANS in patients > 65 years of age receiving CD-19 directed CAR-T therapy, describe post CAR-T clinical outcomes and resource utilization in elderly, and identify disease biology, comorbidities and other clinical predictive markers of toxicity, response, and survival in elderly patients. The CIBMTR identified 1,036 patients (<65y,n=612; 65-74y, n=348; >75y, n=76) with the diagnosis of any B-cell lymphoid malignancy (indolent or aggressive lymphoma) receiving CAR-T cell product (CD19 target). The following questions were answered during the Q&A:
    a. Would you please also look at Incidence of pancytopenia, hypogammaglobulinemia and HLH in elderly versus younger in 3 cohorts <60, 60-75 ,>75? I think it's very important to look at this as the data becomes available to us. We are primarily looking at different age groups. We have 81 patients over the age of 75 and five patients over the age of 85. Overall, there are 435 (40 %) of the group are over 65 years old.
    b. How does this defer from the data presented by Dr. Pasquini last year in older patients? This data will be more helpful in including both CAR-T products.
    c. In case of CAR T was used for post-alloHCT relapse, would the donor age of the CART source be analyzed? This is something that we should include in our analysis.
    d. Are data on baseline geriatric scores or HCT-CI available for all? The answer was not available at the time of the Q&A.
    e. Do we have registry information on whether CAR-T production succeeded or not, when attempted? The answer was not available at the time of the Q&A but the moderator did state that on behalf of CIBMTR, this information is not captured.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix N.

15. **Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation**. This proposal was presented by Dr. Joseph Pidala. The primary objective of this proposal is to validate prediction models for immune suppression discontinuation (ISD) and ISD failure developed in prior DISCIS-defined population, explore ISD and ISD failure in a new population inclusive of full range of diversity in current HCT practices, construct and validate dynamic prediction models of ISD and ISD failure in the expanded population. The CIBMTR identified 20,031 patients with a hematologic malignancy who received an allogeneic HCT from matched sibling donor, matched or mismatched unrelated donor, umbilical cord blood or haploidentical donor between 2009-2018. The following questions were answered during the Q&A:
    a. Can you explain how the ISD data information was made feasible? We used CIBMTR follow up data in the previous analysis that led to the development of the prediction model for ISD that we intend to validate in this study.
    b. Can you provide more granularity on how the time of discontinuation of immune suppression will be defined? In the CIBMTR data, there is a hard stop date for a complete discontinuation of immune suppression. That granular data is available, and it was the data we used for the prior project. We used that hard stop of all systemic immune suppression because that's an unambiguous measure of success.
    c. Many with PTCY may be discontinuing by days 100 or 60- likely based on center practice rather than patient response, how will this be addressed? Our prior project was successfully addressed this issue, specifically within that study population. The first step in this project is to validate those findings. We will definitely be studying how immune suppression was performed and what are the subsequent outcomes.
    d. Do you plan to use age as one of the variables regarding likelihood to discontinue IST, or will you have a separate pediatric specific model? Yes, we will consider age as a variable and evaluate the need for a pediatric specific model.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix O.

CLOSING:

Dr. Shaw, on behalf of herself and co-chair, Dr. John Wingard, did thank presenters, conference organizers, and the CIBMTR staff for having coordinated this virtual session. She did mention that this session was recorded and encouraged attendees to take survey, as access would be available until Monday, February 15, 2021.

APPENDICES:

A. Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis.

1. How will authorship work for these studies? The same as usual, there are fewer studies being accepted but the process otherwise is the same
2. What if a higher risk of cancer is related to the almost uniform use of 2GyTBI in these patients rather than PTCY?
3. What is the breakdown of haploidentical versus matched sib/MUD in the post-transplant cyclophosphamide group?
4. How can we r/o genetic predisposition on samples and variables of TBI based conditioning therapies?
5. What is your sample size and follow-up period?
6. How long post BMT you will follow up? From where will you receive the SN data?
7. Will you be adjusting for chronic GVHD when looking at your outcome of SN?
8. Is this study statistically powered to detect a difference between PTCY and above a certain threshold? What is the threshold?
9. Will analysis be conducted separately for TBI/non-TBI and MAC/RIC conditioning? Are you evaluating all malignancies?
10. Since the total CY exposure is likely not that different in PTCY vs. BU/CY or CY/TBI, is your hypothesis that the timing of exposure to CY may lead to a difference in risk? And if so, why?
11. Information on skin cancers - ssc, bcc available?
12. Matching for HLA matching could be a limitation because the PTCY patients are more likely to receive haploidentical grafts.

B. Outcomes of chimeric antigen receptor-T cell (CAR-T) therapy for patients with antecedent chronic lymphocytic leukemia (Richter's Syndrome).

1. If patients had failed an auto or allo, how do you plan to compare to the results of auto? Isn't it a different group?
2. Can you please provide your thoughts if the small n will be able to generate meaningful results at this time?
3. Would you include both transformed lymphoma from other low-grade lymphoma and Richter's transformation?
4. Are there concerns about underreporting Richter's?
5. Since the numbers are small, can we go back to centers to establish clonality?

C. Impact of graft versus host disease following allogeneic hematopoietic cell transplantation on leukemia free survival in hematologic malignancies. *No additional questions*

D. Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant.

1. Does the HED algorithm take into account variations outside the peptide binding groove?

2. What is the size of the cohort you are looking at?

E. Impact of IDH1 and IDH2 mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation. *No additional questions*

F. Characteristics and outcomes of adolescent and young adults with multiple myeloma treated with autologous hematopoietic cell transplant.

1. How do you plan to control for differences between your AYA group and older control group?

G. Impact of MRD status on outcomes of AML in patients 18-65 years old in CR1 undergoing Allo-HCT.

1. How are you going to account for the different sensitivity of methods used to determine MRD? Are ELN risk available at CIBMTR, since when?
2. Hi Firas, How are defining the MRD?
3. The methods for MRD assessment may be quite heterogeneous, including the threshold of detection. How will you deal with the high likelihood of false MRD negative assessments from using inadequately sensitive quantification?
4. MRD test is different from different centers. How can you control for this?
5. How do you account for different MRD- cut-offs?
6. To clarify, if AML-MRD is to become a "precision medicine tool", does that mean is will be used to guide treatment decisions in addition to being prognostic?
7. How will control for the various methods for detecting MRD as different techniques have different sensitivities/accuracy?
8. if both multiparameter flow and NGS are available and are discordant on the same patient, how will that be analyzed?
9. is the MRD before alloSCT is the one to be analyzed?
10. Will this require more data from centers to answer some of the questions above?

H. Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease.

1. Is age significantly different in your Hispanic cohort? How do you adjust for it?
2. Was the MMUD recipient cohort limited to single antigen mismatch? Or all mismatches (understanding most MMUD will likely be single antigen MM)?
3. Do you have information on health insurance? Why not to study this question in a more homogeneous patient population to avoid the complexity and interactions in different factors?
4. Are there any other sociodemographic variables available that could be used to adjust for socioeconomic status, or is median income in the patient's ZIP code the only one?
5. Baker et al 2009 demonstrated no impact of household income on GVHD (acute or chronic) and only minimal impact of race on Grade III-IV aGVHD (none of cGVHD). Why do you think this null relationship should be pursued again?
6. Is there a plan to study as per continent distribution?
7. Is there a better index to gauge SES or poverty level?
8. Are Native American/Hawaiian/Pacific islanders being grouped elsewhere?

I. Time from diagnosis to transplant as an important contributor for post allogeneic stem cell transplant infections, immune reconstitution and its associated mortality/morbidity.

1. Do you plan to address the confounding influence of different factors leading to delay in transplant timing?
2. How are you going to account for number of cycles of chemotherapy versus no

chemotherapy as a confounder in the time delay?

J. Efficacy and safety of CD19 directed CAR T-cell therapy for non-Hodgkin B-cell lymphomas with secondary central nervous system involvement.

1. Is site-specific response (CNS vs. other lesions) and pattern of relapse/progression (CNS vs. systemic) available?
2. Why not to consider a comparative group?
3. Will you stratify patients according if they received IT chemo vs radiation therapy?

K. Haploidentical donor versus matched donor allogeneic hematopoietic cell transplantation in patients with myelofibrosis.

1. Availability of somatic mutations?
2. Is pretransplant Splenectomy data available? Are you going to factor this in the outcomes?
3. At least look at splenectomies?
4. What risk stratification is being used? DIPSS or DIPSS+?

L. Assessing utilization and clinical outcome differences by sex and race in CAR-T for relapsed/refractory NHL. *No additional questions*

M. Optimal GVHD prevention strategy in older, robust patients with acute leukemias and myeloid malignancies undergoing myeloablative, matched donor hematopoietic cell transplantation. *No additional questions*

N. Outcomes of elderly patients receiving CD-19 directed CAR-T therapy for B-cell lymphomas. *No additional questions*

O. Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation.

1. How is immune suppression stop defined in the CIBMTR database?
2. How long after HCT do you expect data regarding ongoing IST usage to be reliable since many patients leave the transplant center and are managed elsewhere long-term?
3. How long will you deal with restart IST?

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

Characteristics of leukemia patients receiving allogeneic HCT between 2008-2020

Accrual Table 1. Leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Number of patients	**6133**	**4033**	**571**	**13217**	**4855**
Number of centers	243	218	161	248	187
Age at transplant, years, median (range)	55 (0-78)	55 (0-88)	49 (1-77)	58 (0-83)	30 (0-81)
Disease					
AML	2623 (43)	1906 (47)	264 (46)	5444 (41)	2471 (51)
ALL	952 (16)	800 (20)	127 (22)	1672 (13)	1465 (30)
Other leukemia	298 (5)	158 (4)	32 (6)	640 (5)	219 (5)
MDS	1685 (27)	903 (22)	118 (21)	4099 (31)	642 (13)
MPN	575 (9)	266 (7)	30 (5)	1362 (10)	58 (1)
Sex					
Male	3599 (59)	2470 (61)	342 (60)	7799 (59)	2639 (54)
Female	2534 (41)	1563 (39)	229 (40)	5418 (41)	2216 (46)
Graft source					
BM	787 (13)	1147 (28)	85 (15)	2381 (18)	-
PBSC	5339 (87)	2852 (71)	486 (85)	10834 (82)	-
Missing	7 (<1)	34 (1)	0 (<1)	2 (<1)	-
GVHD prophylaxis					
Ex-vivo T-cell depletion	41 (1)	159 (4)	16 (3)	79 (1)	40 (1)
CD34 selection	99 (2)	155 (4)	14 (2)	226 (2)	265 (5)
Post-tx Cyclophosphamide +/- others	272 (4)	3028 (75)	77 (13)	837 (6)	6 (<1)
Tac + MTX	2480 (40)	87 (2)	143 (25)	4873 (37)	131 (3)
Tac + MTX + others	487 (8)	22 (1)	23 (4)	1979 (15)	44 (1)
Tac + MMF	455 (7)	203 (5)	27 (5)	962 (7)	974 (20)
Tac + MMF + others	118 (2)	48 (1)	11 (2)	554 (4)	272 (6)
Tac	164 (3)	35 (1)	20 (4)	378 (3)	110 (2)
Tac + others	354 (6)	14 (<1)	13 (2)	819 (6)	145 (3)
CsA + MTX	813 (13)	48 (1)	62 (11)	689 (5)	42 (1)
CsA + MTX + others	68 (1)	5 (<1)	6 (1)	216 (2)	20 (<1)
CsA + MMF	373 (6)	25 (1)	23 (4)	481 (4)	1817 (37)
CsA + MMF + others	30 (<1)	4 (<1)	3 (1)	245 (2)	340 (7)
CsA	87 (1)	12 (<1)	21 (4)	131 (1)	281 (6)
CsA + others	21 (<1)	6 (<1)	1 (<1)	50 (<1)	55 (1)
Others	62 (1)	24 (1)	9 (2)	160 (1)	100 (2)
Missing	209 (3)	158 (4)	102 (18)	538 (4)	213 (4)
Conditioning regimen intensity					

Accrual Table 1. Leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Myeloablative	3493 (57)	1659 (41)	304 (53)	6298 (48)	3103 (64)
Reduced intensity	1963 (32)	728 (18)	162 (28)	5325 (40)	683 (14)
Non-myeloablative	397 (6)	1421 (35)	68 (12)	926 (7)	871 (18)
Missing	280 (5)	225 (6)	37 (6)	668 (5)	198 (4)
Acute GVHD grade					
None	3007 (49)	1761 (44)	311 (54)	4686 (35)	1934 (40)
Grade I	789 (13)	678 (17)	75 (13)	2167 (16)	645 (13)
Grade II	1129 (18)	884 (22)	70 (12)	3334 (25)	1112 (23)
Grade III	641 (10)	329 (8)	52 (9)	1460 (11)	583 (12)
Grade IV	259 (4)	150 (4)	22 (4)	870 (7)	254 (5)
Missing	308 (5)	231 (6)	41 (7)	700 (5)	327 (7)
Organ involvement of aGVHD					
Skin	267 (13)	322 (24)	24 (17)	1002 (18)	349 (18)
Skin + Liver	124 (6)	50 (4)	6 (4)	216 (4)	40 (2)
Skin + Liver + UGI	21 (1)	7 (1)	4 (3)	51 (1)	15 (1)
Skin + Liver + LGI	85 (4)	49 (4)	8 (6)	264 (5)	83 (4)
Skin + Liver + UGI + LGI	94 (5)	32 (2)	7 (5)	262 (5)	75 (4)
Skin + UGI	168 (8)	95 (7)	7 (5)	562 (10)	162 (8)
Skin + LGI	268 (13)	191 (14)	20 (14)	894 (16)	309 (16)
Liver	74 (4)	22 (2)	10 (7)	93 (2)	29 (1)
Liver + UGI	19 (1)	10 (1)	0 (<1)	31 (1)	13 (1)
Liver + LGI	46 (2)	27 (2)	4 (3)	84 (1)	44 (2)
Liver + UGI + LGI	51 (3)	15 (1)	1 (1)	92 (2)	42 (2)
UGI	205 (10)	154 (11)	7 (5)	513 (9)	179 (9)
LGI	219 (11)	147 (11)	22 (15)	511 (9)	185 (10)
UGI + LGI	210 (10)	114 (8)	10 (7)	465 (8)	179 (9)
Missing	180 (9)	125 (9)	15 (10)	610 (11)	241 (12)
Incidence of cGVHD					
No	3130 (51)	2774 (69)	375 (66)	6924 (52)	3445 (71)
Yes	2853 (47)	1142 (28)	171 (30)	5864 (44)	1240 (26)
Missing	150 (2)	117 (3)	25 (4)	429 (3)	170 (4)
Maximum grade of cGVHD					
Limited	406 (14)	274 (24)	33 (19)	776 (13)	440 (35)
Extensive	2408 (84)	855 (75)	135 (79)	5006 (85)	772 (62)
Missing	39 (1)	13 (1)	3 (2)	82 (1)	28 (2)
Overall severity of cGVHD					
Mild	1023 (36)	523 (46)	53 (31)	2110 (36)	733 (59)
Moderate	989 (35)	379 (33)	61 (36)	2077 (35)	302 (24)
Severe	766 (27)	214 (19)	52 (30)	1517 (26)	161 (13)

Accrual Table 1. Leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Missing	75 (3)	26 (2)	5 (3)	160 (3)	44 (4)
Year of transplant					
2008-2009	1273 (21)	166 (4)	103 (18)	2500 (19)	1116 (23)
2010-2011	702 (11)	57 (1)	28 (5)	1295 (10)	951 (20)
2012-2013	807 (13)	238 (6)	90 (16)	1779 (13)	833 (17)
2014-2015	1372 (22)	804 (20)	105 (18)	2780 (21)	843 (17)
2016-2017	1092 (18)	1163 (29)	127 (22)	2356 (18)	671 (14)
2018-2020	887 (14)	1605 (40)	118 (21)	2507 (19)	441 (9)
Follow-up of survivors, months, median (range)	62 (0-157)	36 (0-147)	47 (2-145)	60 (0-156)	65 (1-155)

Abbreviations: AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, MDS=Myelodysplastic diseases, MPN=Myeloproliferative diseases, 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 2008-2020

Accrual Table 2. Non-leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Number of patients	**3142**	**1694**	**593**	**3755**	**2157**
Number of centers	220	192	145	226	168
Age at transplant, years, median (range)	19 (0-79)	21 (0-76)	22 (0-77)	26 (0-79)	5 (0-73)
Disease					
NHL	626 (20)	388 (23)	126 (21)	1012 (27)	411 (19)
HD	149 (5)	201 (12)	24 (4)	288 (8)	96 (4)
SAA	804 (26)	312 (18)	85 (14)	834 (22)	101 (5)
MM-PCD	173 (6)	52 (3)	102 (17)	255 (7)	40 (2)
Inherited abnormalities of erythrocyte diff-or function	1070 (34)	330 (19)	149 (25)	513 (14)	329 (15)
SCID & other immune system disorders	225 (7)	280 (17)	78 (13)	539 (14)	491 (23)
Inherited abnormality of platelets	4 (<1)	3 (<1)	0 (<1)	13 (<1)	26 (1)
Histiocytic disorders	31 (1)	52 (3)	7 (1)	139 (4)	153 (7)
Inherited disorders of metabolism	20 (1)	37 (2)	10 (2)	53 (1)	469 (22)
Others	40 (1)	39 (2)	12 (2)	109 (3)	41 (2)
Sex					
Male	1858 (59)	1027 (61)	347 (59)	2325 (62)	1302 (60)
Female	1284 (41)	667 (39)	246 (41)	1430 (38)	855 (40)
GVHD prophylaxis					
Ex-vivo T-cell depletion	9 (<1)	134 (8)	7 (1)	63 (2)	10 (<1)
CD34 selection	45 (1)	133 (8)	23 (4)	189 (5)	51 (2)
Post-tx Cyclophosphamide +/- others	138 (4)	983 (58)	24 (4)	204 (5)	2 (<1)
Tac + MTX	589 (19)	18 (1)	33 (6)	906 (24)	65 (3)
Tac + MTX + others	164 (5)	10 (1)	9 (2)	376 (10)	15 (1)
Tac + MMF	195 (6)	104 (6)	15 (3)	243 (6)	339 (16)
Tac + MMF + others	43 (1)	27 (2)	7 (1)	115 (3)	113 (5)
Tac	57 (2)	18 (1)	14 (2)	157 (4)	71 (3)
Tac + others	72 (2)	7 (<1)	3 (1)	144 (4)	76 (4)
CsA + MTX	840 (27)	41 (2)	107 (18)	425 (11)	57 (3)
CsA + MTX + others	66 (2)	2 (<1)	8 (1)	95 (3)	10 (<1)
CsA + MMF	204 (6)	48 (3)	30 (5)	269 (7)	710 (33)
CsA + MMF + others	16 (1)	2 (<1)	3 (1)	68 (2)	106 (5)
CsA	196 (6)	17 (1)	36 (6)	175 (5)	300 (14)
CsA + others	27 (1)	3 (<1)	4 (1)	40 (1)	44 (2)
Others	172 (5)	34 (2)	23 (4)	64 (2)	35 (2)

Missing	309 (10)	113 (7)	247 (42)	222 (6)	153 (7)
Graft source					
BM	1700 (54)	748 (44)	241 (41)	1752 (47)	-
PBSC	1440 (46)	941 (56)	352 (59)	2002 (53)	-
Missing	2 (<1)	5 (<1)	0 (<1)	1 (<1)	-
Conditioning regimen intensity					
Myeloablative	1032 (33)	471 (28)	224 (38)	1030 (27)	1236 (57)
Reduced intensity	770 (25)	336 (20)	126 (21)	1249 (33)	414 (19)
Non-myeloablative	993 (32)	660 (39)	113 (19)	1149 (31)	429 (20)
Missing	347 (11)	227 (13)	130 (22)	327 (9)	78 (4)
Acute GVHD grade					
None	2184 (70)	918 (54)	426 (72)	1811 (48)	1108 (51)
Grade I	268 (9)	214 (13)	34 (6)	530 (14)	274 (13)
Grade II	329 (10)	265 (16)	55 (9)	656 (17)	361 (17)
Grade III	168 (5)	123 (7)	31 (5)	337 (9)	183 (8)
Grade IV	96 (3)	69 (4)	14 (2)	182 (5)	94 (4)
Missing	97 (3)	105 (6)	33 (6)	239 (6)	137 (6)
Organ involvement of aGVHD					
Skin	75 (13)	115 (25)	23 (23)	273 (23)	162 (26)
Skin + Liver	29 (5)	16 (4)	6 (6)	40 (3)	11 (2)
Skin + Liver + UGI	6 (1)	0 (<1)	0 (<1)	5 (<1)	5 (1)
Skin + Liver + LGI	32 (5)	17 (4)	6 (6)	56 (5)	24 (4)
Skin + Liver + UGI + LGI	16 (3)	8 (2)	5 (5)	38 (3)	19 (3)
Skin + UGI	35 (6)	18 (4)	2 (2)	84 (7)	39 (6)
Skin + LGI	82 (14)	65 (14)	18 (18)	183 (16)	132 (21)
Liver	25 (4)	10 (2)	2 (2)	20 (2)	6 (1)
Liver + UGI	2 (<1)	1 (<1)	0 (<1)	3 (<1)	1 (<1)
Liver + LGI	14 (2)	23 (5)	3 (3)	29 (2)	15 (2)
Liver + UGI + LGI	13 (2)	11 (2)	2 (2)	21 (2)	9 (1)
UGI	57 (10)	37 (8)	5 (5)	80 (7)	29 (5)
LGI	98 (17)	56 (12)	14 (14)	135 (12)	67 (11)
UGI + LGI	55 (9)	31 (7)	10 (10)	89 (8)	51 (8)
Missing	53 (9)	47 (10)	5 (5)	111 (10)	63 (10)
Incidence of cGVHD					
No	2316 (74)	1255 (74)	489 (82)	2342 (62)	1602 (74)
Yes	756 (24)	378 (22)	82 (14)	1277 (34)	484 (22)
Missing	70 (2)	61 (4)	22 (4)	136 (4)	71 (3)
Maximum grade of cGVHD					
Limited	182 (24)	132 (35)	29 (35)	311 (24)	212 (44)
Extensive	559 (74)	243 (64)	49 (60)	922 (72)	259 (54)
Missing	15 (2)	3 (1)	4 (5)	44 (3)	13 (3)
Overall severity of cGVHD					

Mild	339 (45)	189 (50)	36 (44)	541 (42)	281 (58)
Moderate	219 (29)	114 (30)	25 (30)	364 (29)	119 (25)
Severe	170 (22)	64 (17)	14 (17)	311 (24)	69 (14)
Missing	28 (4)	11 (3)	7 (9)	61 (5)	15 (3)
Year of transplant					
2008-2009	554 (18)	98 (6)	107 (18)	721 (19)	501 (23)
2010-2011	65 (2)	35 (2)	45 (8)	225 (6)	412 (19)
2012-2013	189 (6)	103 (6)	75 (13)	403 (11)	378 (18)
2014-2015	727 (23)	307 (18)	128 (22)	840 (22)	404 (19)
2016-2017	691 (22)	443 (26)	122 (21)	716 (19)	288 (13)
2018-2020	916 (29)	708 (42)	116 (20)	850 (23)	174 (8)
Follow-up of survivors, months, median (range)	37 (1-158)	28 (0-151)	48 (0-151)	49 (2-151)	66 (0-163)

Abbreviations: NHL=Non-Hodgkin lymphoma, HD=Hodgkin disease, SAA=Severe aplastic anemia, MM=Multiple myeloma, SCID=Severe combined immunodeficiency, 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, 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 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	**22291**	**8204**	**4394**
Source of data			
CRF	10644 (48)	2860 (35)	2100 (48)
TED	11647 (52)	5344 (65)	2294 (52)
Number of centers	239	209	329
Disease at transplant			
AML	15294 (69)	5896 (72)	2918 (66)
ALL	6535 (29)	2123 (26)	1370 (31)
Other acute leukemia	462 (2)	185 (2)	106 (2)
AML Disease status at transplant			
CR1	8061 (53)	3434 (58)	1439 (49)
CR2	2975 (19)	1072 (18)	590 (20)
CR3+	330 (2)	95 (2)	67 (2)
Advanced or active disease	3783 (25)	1262 (21)	767 (26)
Missing	145 (1)	33 (1)	55 (2)
ALL Disease status at transplant			
CR1	3206 (49)	1180 (56)	585 (43)
CR2	1873 (29)	548 (26)	393 (29)
CR3+	558 (9)	157 (7)	139 (10)
Advanced or active disease	852 (13)	222 (10)	217 (16)
Missing	46 (1)	16 (1)	36 (3)
Recipient age at transplant			
0-9 years	1628 (7)	456 (6)	414 (9)
10-19 years	2196 (10)	608 (7)	544 (12)
20-29 years	2717 (12)	883 (11)	586 (13)
30-39 years	2624 (12)	902 (11)	565 (13)
40-49 years	3365 (15)	1168 (14)	649 (15)
50-59 years	4276 (19)	1537 (19)	744 (17)
60-69 years	4476 (20)	2088 (25)	732 (17)
70+ years	1009 (5)	562 (7)	160 (4)
Median (Range)	46 (0-84)	51 (0-82)	42 (0-77)
Recipient race/ethnicity			
Caucasian, non-Hispanic	18394 (83)	6781 (83)	3081 (70)
African-American, non-Hispanic	829 (4)	280 (3)	180 (4)
Asian, non-Hispanic	560 (3)	264 (3)	176 (4)
Pacific islander, non-Hispanic	28 (<1)	10 (<1)	16 (<1)

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 (%)
Native American, non-Hispanic	91 (<1)	27 (<1)	18 (<1)
Hispanic	1501 (7)	503 (6)	262 (6)
Missing	888 (4)	339 (4)	661 (15)
Recipient sex			
Male	12328 (55)	4538 (55)	2478 (56)
Female	9963 (45)	3666 (45)	1916 (44)
Karnofsky score			
10-80	7993 (36)	3189 (39)	1427 (32)
90-100	13531 (61)	4770 (58)	2734 (62)
Missing	767 (3)	245 (3)	233 (5)
HLA-A B DRB1 groups - low resolution			
<=3/6	18 (<1)	27 (<1)	2 (<1)
4/6	102 (<1)	52 (1)	20 (<1)
5/6	3025 (14)	936 (13)	655 (16)
6/6	18769 (86)	6427 (86)	3448 (84)
Unknown	377 (N/A)	762 (N/A)	269 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	397 (2)	67 (1)	29 (1)
6/8	856 (4)	75 (1)	74 (2)
7/8	4277 (20)	1011 (16)	675 (23)
8/8	16093 (74)	4982 (81)	2204 (74)
Unknown	668 (N/A)	2069 (N/A)	1412 (N/A)
HLA-DPB1 Match			
Double allele mismatch	6032 (29)	735 (25)	303 (26)
Single allele mismatch	10975 (54)	1519 (51)	608 (52)
Full allele matched	3499 (17)	728 (24)	266 (23)
Unknown	1785 (N/A)	5222 (N/A)	3217 (N/A)
High resolution release score			
No	2753 (12)	8177 (>99)	4297 (98)
Yes	19538 (88)	27 (<1)	97 (2)
KIR typing available			
No	13733 (62)	8195 (>99)	4365 (99)
Yes	8558 (38)	9 (<1)	29 (1)
Graft type			
Marrow	7426 (33)	2201 (27)	1584 (36)
PBSC	14835 (67)	5906 (72)	2799 (64)
BM+PBSC	4 (<1)	5 (<1)	2 (<1)
PBSC+UCB	17 (<1)	83 (1)	4 (<1)
Others	9 (<1)	9 (<1)	5 (<1)
Conditioning regimen			
Myeloablative	15757 (71)	5220 (64)	3106 (71)
RIC/Nonmyeloablative	6444 (29)	2965 (36)	1227 (28)

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 (%)
TBD	90 (<1)	19 (<1)	61 (1)
Donor age at donation			
To Be Determined/NA	238 (1)	748 (9)	57 (1)
0-9 years	6 (<1)	20 (<1)	1 (<1)
10-19 years	649 (3)	288 (4)	94 (2)
20-29 years	10374 (47)	3696 (45)	1829 (42)
30-39 years	6149 (28)	2046 (25)	1302 (30)
40-49 years	3712 (17)	1078 (13)	844 (19)
50+ years	1163 (5)	328 (4)	267 (6)
Median (Range)	30 (0-61)	29 (0-89)	32 (0-67)
Donor/Recipient CMV serostatus			
+/+	5842 (26)	2423 (30)	1147 (26)
+/-	2479 (11)	924 (11)	538 (12)
-/+	7880 (35)	2700 (33)	1439 (33)
-/-	5775 (26)	1904 (23)	1077 (25)
CB - recipient +	2 (<1)	9 (<1)	0
CB - recipient -	0	3 (<1)	0
CB - recipient CMV unknown	0	1 (<1)	0
Missing	313 (1)	240 (3)	193 (4)
GvHD Prophylaxis			
No GvHD Prophylaxis	73 (<1)	33 (<1)	24 (1)
TDEPLETION alone	62 (<1)	12 (<1)	17 (<1)
TDEPLETION +- other	512 (2)	137 (2)	140 (3)
CD34 select alone	132 (1)	42 (1)	26 (1)
CD34 select +- other	414 (2)	318 (4)	98 (2)
Cyclophosphamide alone	484 (2)	409 (5)	125 (3)
Cyclophosphamide +- others	1071 (5)	762 (9)	205 (5)
FK506 + MMF +- others	2289 (10)	767 (9)	291 (7)
FK506 + MTX +- others (not MMF)	10229 (46)	3546 (43)	1314 (30)
FK506 +- others (not MMF, MTX)	1174 (5)	500 (6)	161 (4)
FK506 alone	524 (2)	196 (2)	71 (2)
CSA + MMF +- others (not FK506)	1129 (5)	317 (4)	286 (7)
CSA + MTX +- others (not MMF, FK506)	3207 (14)	836 (10)	1224 (28)
CSA +- others (not FK506, MMF, MTX)	369 (2)	117 (1)	131 (3)
CSA alone	198 (1)	63 (1)	149 (3)
Other GVHD Prophylaxis	322 (1)	111 (1)	76 (2)
Missing	102 (<1)	38 (<1)	56 (1)
Donor/Recipient sex match			
Male-Male	8677 (39)	2997 (37)	1627 (37)
Male-Female	5998 (27)	2095 (26)	1097 (25)
Female-Male	3527 (16)	1330 (16)	814 (19)
Female-Female	3847 (17)	1390 (17)	788 (18)

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 (%)
CB - recipient M	7 (<1)	41 (<1)	0
CB - recipient F	10 (<1)	47 (1)	5 (<1)
Missing	225 (1)	304 (4)	63 (1)
Year of transplant			
1986-1990	132 (1)	18 (<1)	19 (<1)
1991-1995	776 (3)	190 (2)	214 (5)
1996-2000	1403 (6)	509 (6)	402 (9)
2001-2005	2554 (11)	529 (6)	781 (18)
2006-2010	4683 (21)	967 (12)	787 (18)
2011-2015	6769 (30)	1822 (22)	980 (22)
2016-2020	5476 (25)	3668 (45)	1063 (24)
2021	498 (2)	501 (6)	148 (3)
Follow-up among survivors, Months			
N Eval	8960	3802	1693
Median (Range)	60 (1-372)	26 (0-362)	37 (0-365)

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, MMF=Mycophenolate mofetil, MTX=Methotrexate, CsA=Cyclosporine.

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

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	**3536**	**899**	**880**
Source of data			
CRF	2571 (73)	634 (71)	527 (60)
TED	965 (27)	265 (29)	353 (40)
Number of centers	140	122	165
Disease at transplant			
AML	2221 (63)	529 (59)	505 (57)
ALL	1222 (35)	344 (38)	347 (39)
Other acute leukemia	93 (3)	26 (3)	28 (3)
AML Disease status at transplant			
CR1	1147 (52)	287 (54)	241 (48)
CR2	608 (27)	139 (26)	139 (28)
CR3+	62 (3)	8 (2)	22 (4)
Advanced or active disease	398 (18)	93 (18)	101 (20)
Missing	6 (<1)	2 (<1)	2 (<1)
ALL Disease status at transplant			
CR1	550 (45)	146 (42)	146 (42)
CR2	451 (37)	124 (36)	125 (36)
CR3+	143 (12)	51 (15)	48 (14)
Advanced or active disease	77 (6)	21 (6)	28 (8)
Missing	1 (<1)	2 (1)	0
Recipient age at transplant			
0-9 years	789 (22)	267 (30)	228 (26)
10-19 years	534 (15)	136 (15)	154 (18)
20-29 years	409 (12)	73 (8)	93 (11)
30-39 years	392 (11)	98 (11)	103 (12)
40-49 years	404 (11)	93 (10)	93 (11)
50-59 years	496 (14)	112 (12)	110 (13)
60-69 years	444 (13)	105 (12)	91 (10)
70+ years	68 (2)	15 (2)	8 (1)
Median (Range)	31 (0-83)	27 (0-76)	25 (0-78)
Recipient race/ethnicity			
Caucasian, non-Hispanic	1961 (55)	513 (57)	478 (54)
African-American, non-Hispanic	438 (12)	105 (12)	87 (10)
Asian, non-Hispanic	217 (6)	57 (6)	65 (7)

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 (%)
Pacific islander, non-Hispanic	22 (1)	3 (<1)	8 (1)
Native American, non-Hispanic	23 (1)	5 (1)	10 (1)
Hispanic	655 (19)	148 (16)	119 (14)
Missing	220 (6)	68 (8)	113 (13)
Recipient sex			
Male	1859 (53)	479 (53)	476 (54)
Female	1677 (47)	420 (47)	404 (46)
Karnofsky score			
10-80	973 (28)	243 (27)	226 (26)
90-100	2491 (70)	625 (70)	618 (70)
Missing	72 (2)	31 (3)	36 (4)
HLA-A B DRB1 groups - low resolution			
<=3/6	60 (2)	29 (4)	9 (1)
4/6	1514 (44)	329 (44)	323 (40)
5/6	1495 (44)	307 (41)	373 (47)
6/6	358 (10)	90 (12)	97 (12)
Unknown	109 (N/A)	144 (N/A)	78 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	1741 (58)	326 (59)	353 (54)
6/8	708 (24)	128 (23)	165 (25)
7/8	383 (13)	61 (11)	99 (15)
8/8	161 (5)	35 (6)	34 (5)
Unknown	543 (N/A)	349 (N/A)	229 (N/A)
HLA-DPB1 Match			
Double allele mismatch	487 (39)	65 (47)	64 (38)
Single allele mismatch	657 (52)	59 (43)	84 (50)
Full allele matched	115 (9)	14 (10)	20 (12)
Unknown	2277 (N/A)	761 (N/A)	712 (N/A)
High resolution release score			
No	2704 (76)	855 (95)	874 (99)
Yes	832 (24)	44 (5)	6 (1)
KIR typing available			
No	2846 (80)	894 (99)	876 (>99)
Yes	690 (20)	5 (1)	4 (<1)
Graft type			
UCB	3339 (94)	816 (91)	818 (93)
PBSC+UCB	179 (5)	83 (9)	58 (6)
Others	18 (1)	0	4 (<1)
Number of cord units			
1	2897 (82)	0	725 (82)
2	638 (18)	0	155 (18)
3	1 (<1)	0	0

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 (%)
Unknown	0 (N/A)	899 (N/A)	0 (N/A)
Conditioning regimen			
Myeloablative	2481 (70)	638 (71)	591 (67)
RIC/Nonmyeloablative	1047 (30)	260 (29)	287 (33)
TBD	8 (<1)	1 (<1)	2 (<1)
Donor age at donation			
To Be Determined/NA	125 (4)	58 (6)	66 (8)
0-9 years	3118 (88)	691 (77)	736 (84)
10-19 years	169 (5)	82 (9)	37 (4)
20-29 years	39 (1)	22 (2)	10 (1)
30-39 years	36 (1)	25 (3)	15 (2)
40-49 years	22 (1)	10 (1)	7 (1)
50+ years	27 (1)	11 (1)	9 (1)
Median (Range)	3 (0-72)	5 (0-73)	4 (0-67)
Donor/Recipient CMV serostatus			
+/+	894 (25)	196 (22)	185 (21)
+/-	304 (9)	88 (10)	68 (8)
-/+	697 (20)	166 (18)	167 (19)
-/-	407 (12)	97 (11)	113 (13)
CB - recipient +	804 (23)	213 (24)	208 (24)
CB - recipient -	386 (11)	115 (13)	118 (13)
CB - recipient CMV unknown	44 (1)	24 (3)	21 (2)
GvHD Prophylaxis			
No GvHD Prophylaxis	16 (<1)	7 (1)	4 (<1)
TDEPLETION alone	1 (<1)	0	0
TDEPLETION +- other	20 (1)	6 (1)	3 (<1)
CD34 select alone	0	1 (<1)	2 (<1)
CD34 select +- other	178 (5)	83 (9)	60 (7)
Cyclophosphamide alone	0	0	1 (<1)
Cyclophosphamide +- others	26 (1)	15 (2)	24 (3)
FK506 + MMF +- others	998 (28)	236 (26)	146 (17)
FK506 + MTX +- others(not MMF)	136 (4)	39 (4)	44 (5)
FK506 +- others(not MMF,MTX)	115 (3)	32 (4)	25 (3)
FK506 alone	77 (2)	19 (2)	10 (1)
CSA + MMF +- others(not FK506)	1681 (48)	372 (41)	431 (49)
CSA + MTX +- others(not MMF,FK506)	57 (2)	16 (2)	20 (2)
CSA +- others(not FK506,MMF,MTX)	135 (4)	53 (6)	64 (7)
CSA alone	24 (1)	12 (1)	29 (3)
Other GVHD Prophylaxis	66 (2)	7 (1)	15 (2)
Missing	6 (<1)	1 (<1)	2 (<1)
Donor/Recipient sex match			
CB - recipient M	1859 (53)	479 (53)	475 (54)

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 (%)
CB - recipient F	1677 (47)	420 (47)	404 (46)
CB - recipient sex unknown	0	0	1 (<1)
Year of transplant			
1996-2000	0	1 (<1)	3 (<1)
2001-2005	54 (2)	68 (8)	16 (2)
2006-2010	1055 (30)	228 (25)	244 (28)
2011-2015	1552 (44)	274 (30)	363 (41)
2016-2020	845 (24)	304 (34)	232 (26)
2021	30 (1)	24 (3)	22 (3)
Follow-up among survivors, Months			
N Eval	1593	428	409
Median (Range)	61 (1-196)	50 (3-213)	48 (1-199)

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, MMF=Mycophenolate mofetil, MTX=Methotrexate, CsA=Cyclosporine.

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	**4925**	**834**	**337**
Source of data			
CRF	1402 (28)	180 (22)	99 (29)
TED	3523 (72)	654 (78)	238 (71)
Number of centers	83	66	54
Disease at transplant			
AML	3214 (65)	506 (61)	206 (61)
ALL	1578 (32)	299 (36)	124 (37)
Other acute leukemia	133 (3)	29 (3)	7 (2)
AML Disease status at transplant			
CR1	2063 (64)	340 (67)	134 (65)
CR2	486 (15)	66 (13)	26 (13)
CR3+	38 (1)	13 (3)	1 (<1)
Advanced or active disease	619 (19)	83 (16)	45 (22)
Missing	8 (<1)	4 (1)	0
ALL Disease status at transplant			
CR1	974 (62)	195 (65)	76 (61)
CR2	437 (28)	69 (23)	31 (25)
CR3+	88 (6)	13 (4)	10 (8)
Advanced or active disease	78 (5)	22 (7)	7 (6)
Missing	1 (<1)	0	0
Recipient age at transplant			
0-9 years	330 (7)	47 (6)	22 (7)
10-19 years	545 (11)	69 (8)	32 (9)
20-29 years	521 (11)	103 (12)	34 (10)
30-39 years	498 (10)	86 (10)	42 (12)
40-49 years	707 (14)	133 (16)	41 (12)
50-59 years	1071 (22)	184 (22)	60 (18)
60-69 years	1061 (22)	177 (21)	93 (28)
70+ years	192 (4)	35 (4)	13 (4)
Median (Range)	49 (1-82)	49 (1-76)	50 (1-83)
Recipient race/ethnicity			
Caucasian, non-Hispanic	3103 (63)	426 (51)	208 (62)
African-American, non-Hispanic	437 (9)	68 (8)	18 (5)
Asian, non-Hispanic	225 (5)	77 (9)	19 (6)
Pacific islander, non-Hispanic	13 (<1)	1 (<1)	1 (<1)

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 (%)
Native American, non-Hispanic	20 (<1)	2 (<1)	1 (<1)
Hispanic	828 (17)	196 (24)	65 (19)
Missing	299 (6)	64 (8)	25 (7)
Recipient sex			
Male	2807 (57)	466 (56)	188 (56)
Female	2118 (43)	368 (44)	149 (44)
Karnofsky score			
10-80	1848 (38)	365 (44)	149 (44)
90-100	2974 (60)	458 (55)	177 (53)
Missing	103 (2)	11 (1)	11 (3)
Graft type			
Marrow	1216 (25)	153 (18)	80 (24)
PBSC	3685 (75)	674 (81)	251 (74)
UCB (related)	1 (<1)	3 (<1)	0
BM+PBSC	3 (<1)	3 (<1)	1 (<1)
BM+UCB	4 (<1)	1 (<1)	0
PBSC+UCB	0	0	5 (1)
Others	16 (<1)	0	0
Conditioning regimen			
Myeloablative	3371 (68)	555 (67)	215 (64)
RIC/Nonmyeloablative	1546 (31)	277 (33)	117 (35)
TBD	8 (<1)	2 (<1)	5 (1)
Donor age at donation			
To Be Determined/NA	4 (<1)	5 (1)	0
0-9 years	227 (5)	29 (3)	12 (4)
10-19 years	453 (9)	75 (9)	29 (9)
20-29 years	782 (16)	139 (17)	53 (16)
30-39 years	792 (16)	142 (17)	71 (21)
40-49 years	816 (17)	154 (18)	42 (12)
50+ years	1851 (38)	290 (35)	130 (39)
Median (Range)	43 (0-80)	42 (0-79)	41 (1-76)
Donor/Recipient CMV serostatus			
+/+	2081 (42)	395 (47)	147 (44)
+/-	484 (10)	67 (8)	28 (8)
-/+	1388 (28)	209 (25)	89 (26)
-/-	905 (18)	154 (18)	63 (19)
Missing	67 (1)	9 (1)	10 (3)
GvHD Prophylaxis			
No GvHD Prophylaxis	59 (1)	8 (1)	2 (1)
TDEPLETION alone	30 (1)	13 (2)	2 (1)
TDEPLETION +- other	33 (1)	8 (1)	3 (1)
CD34 select alone	41 (1)	9 (1)	4 (1)

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 (%)
CD34 select +- other	207 (4)	44 (5)	28 (8)
Cyclophosphamide alone	149 (3)	26 (3)	17 (5)
Cyclophosphamide +- others	1378 (28)	207 (25)	99 (29)
FK506 + MMF +- others	273 (6)	30 (4)	11 (3)
FK506 + MTX +- others(not MMF)	1876 (38)	250 (30)	117 (35)
FK506 +- others(not MMF,MTX)	401 (8)	172 (21)	23 (7)
FK506 alone	23 (<1)	3 (<1)	2 (1)
CSA + MMF +- others(not FK506)	60 (1)	8 (1)	4 (1)
CSA + MTX +- others(not MMF,FK506)	303 (6)	34 (4)	15 (4)
CSA +- others(not FK506,MMF,MTX)	0	2 (<1)	0
CSA alone	32 (1)	6 (1)	0
Other GVHD Prophylaxis	43 (1)	8 (1)	6 (2)
Missing	17 (<1)	6 (1)	4 (1)
Donor/Recipient sex match			
Male-Male	1596 (32)	297 (36)	110 (33)
Male-Female	1094 (22)	195 (23)	76 (23)
Female-Male	1207 (25)	164 (20)	76 (23)
Female-Female	1023 (21)	169 (20)	70 (21)
CB - recipient M	4 (<1)	2 (<1)	2 (1)
CB - recipient F	1 (<1)	2 (<1)	3 (1)
Missing	0	5 (1)	0
Year of transplant			
2006-2010	268 (5)	29 (3)	16 (5)
2011-2015	1778 (36)	266 (32)	79 (23)
2016-2020	2608 (53)	483 (58)	199 (59)
2021	271 (6)	56 (7)	43 (13)
Follow-up among survivors, Months			
N Eval	2780	469	182
Median (Range)	36 (1-148)	29 (3-122)	24 (3-121)

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, MMF=Mycophenolate mofetil, MTX=Methotrexate, CsA=Cyclosporine.

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Graft-Versus-Host Disease Working Committee Members

FROM: Stephanie Lee, MD, MPH and Stephen Spellman, MBS; Scientific Directors for GVWC

RE: Studies in Progress Summary

GV18-01b: Comparison of late effects among adult 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, who were age ≥ 18 years at time of 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. The results were presented during an oral presentation at TCT 2021. The plan is to have a manuscript prepared and submitted by July 2022.

GV18-02: Comparison of bacterial blood stream infection incidence in allogeneic stem cell transplantation patients with and without acute graft vs host disease (Wallis W/ Alousi AM/ Gulbis A)
This study aims to determine the incidence of bacterial bloodstream infections (BSI) in patients with acute GVHD II-IV. An existing finalized dataset from the CIBMTR's Infection Working Committee was found to be a suitable data source to address the questions posed in GV18-02. The results were presented as a poster presentation at ASH 2021. The plan is to have a manuscript prepared and submitted by July 2022.

GV19-01: Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients (Gillis N/ Padron E/ Lazaryan A)
This study aims to compare allo-HCT outcomes between recipients with older (≥ 55 years old) HLA-matched related donors without clonal hematopoiesis and recipients with young (< 25 years old) HLA-matched unrelated donors. Next-generation sequencing will be used to determine the prevalence of clonal hematopoiesis in the older donor samples obtained from the CIBMTR research sample repository. The results will be presented as a poster presentation during the Tandem Meeting 2022. The plan is to have a manuscript prepared and submitted by July 2022.

GV20-01: Machine learning models and clinical decision support tool for acute and chronic graft-versus-host disease in patients with acute myelogenous leukemia undergoing allogeneic transplants (Kindwall-Keller T/ Lobo B)
This study aims to develop a machine learning model to predict the risk of developing acute and chronic GVHD in adult AML patients based on patient, disease and transplant-specific factors. The end goal is to create a tool that will provide information to both physician and patient to support clinical decision-making regarding transplant. The protocol was reviewed at the CIBMTR Statistical Meeting in February 2021 and was circulated the Working Committee members. The analysis is currently underway.

GV20-02: Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly-multiplexed proteomics assay: MHC-PepSeq (Sandhu K/ Altin J/ Askar M/ Nakamura R)
This study aims to evaluate the performance of a risk score derived from the MHC-PepSeq assay in predicting the development of acute and chronic GVHD in recipients of allogeneic HCT from either an 8/8 matched donor with mismatch in HLA-DP or a 7/8 mismatched donor. The plan is to present the protocol at the CIBMTR Statistical Meeting in Spring 2022. Following approval, the protocol will be forwarded to form a Writing Committee and the data file will be prepared for analysis by July 2022.

GV21-01: Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease (Farhadfar N/ Wingard JR/ Al-Mansour Z)
This study aims to compare the clinical manifestations and severity of chronic GVHD between racial, ethnic, and socioeconomic groups among allogeneic HCT recipients who developed chronic GVHD. A secondary aim is to evaluate the impact of race and socioeconomic status on long-term outcomes after diagnosis of chronic GVHD. The protocol was presented at the CIBMTR Statistical Meeting in November 2021 for approval and was circulated to Working Committee members in December 2021. The plan is to have the analysis completed by July 2022.

GV21-02: Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation: A validation study (Pidala J/ Logan B/ Martens M)
This study aims to develop and validate prediction models for immune suppression discontinuation and immune suppression discontinuation failure in patients who received allogeneic HCT for hematologic malignancies. The protocol was presented at the CIBMTR Statistical Meeting in January 2022. The plan is to have the analysis completed by July 2022.

Study Title

Post-Transplant Cyclophosphamide (PTCy) vs *in vivo* T-Cell Depletion with Anti-Thymocyte Globulin (ATG) or Alemtuzumab in Patients with Acute Leukemia (AL) or Myelodysplastic Syndrome (MDS) undergoing Unrelated Donor (UD) Hematopoietic Cell Transplant (HCT)

Key Words

In vivo T-cell depletion, graft-versus-host disease, post-transplant cyclophosphamide, acute leukemia, unrelated donor, MDS

PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Antonio Jimenez Jimenez, MD MS Leonardo Javier Arcuri, MD PhD Alejandro Marinos, MD
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Institution name:	University of Miami Hospital Israelita Albert Einstein Baylor College of Medicine
Academic rank:	Assistant Professor of Medicine Physician and Clinical Trialist Clinical Fellow

Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

Yes (Dr Alejandro Marinos)

Do you identify as an underrepresented/minority?

Yes

Principal Investigator #2 (If applicable):

First and last name, degree(s):	Krishna Komanduri Nelson Hamerschlak, PhD Premal Lulla, MD
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Institution name:	University of Miami Hospital Israelita Albert Einstein Baylor College of Medicine
Academic rank:	Professor of Medicine Bone Marrow Transplantation Unit Director Assistant Professor of Medicine

Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

No

Do you identify as an underrepresented/minority?

Yes

We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

Antonio M. Jimenez Jimenez, MD

If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

NA

LETTER OF COMMITMENT:

Please note: A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:
https://www.cibmtr.org/Studies/Observational/StudyManagement/

CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

AMJJ: Co-author on "Outcomes after HCT for rare chronic leukemias: Evaluating outcomes of Allogeneic hematopoietic cell transplantation in T-cell prolymphocytic leukemias."

PROPOSED WORKING COMMITTEE:

Graft vs. Host Disease

Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

Yes

If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

Dr. Mary Eapen

RESEARCH QUESTION:

Does graft manipulation with post-transplant cyclophosphamide (PTCy) improve clinical outcomes in unrelated donor (UD) recipients, compared to *in vivo* T-cell depletion with anti-thymocyte globulin (ATG) or alemtuzumab?

RESEARCH HYPOTHESIS:

Post-transplant cyclophosphamide (PTCy) is associated with improved clinical outcomes in Acute Myeloid Leukemia (AML), Acute Lymphoblastic Leukemia (ALL) and Myelodysplastic Syndromes (MDS) patients undergoing HLA-matched (MUD) and mismatched unrelated donor (MMUD) transplantation.

SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.) Suggested word limit of 200 words:

Primary Objective:

- GVHD-free, relapse-free survival (GRFS): Will be defined as time to development of grade 3-4 acute GVHD, chronic GVHD requiring systemic therapy, relapse, or death from any cause. Patients are censored at last follow-up.

Secondary Objectives:

- Overall survival (OS): time to death. Death from any cause will be considered an event. Surviving patients are censored at the time of the last follow-up.
- Relapse-free survival (RFS): Will be defined as time to relapse or death from any cause. Patients are censored at the last follow-up.
- Non-relapse mortality (NRM): Cumulative incidence of NRM. NRM is defined as death without preceding disease relapse/progression. Relapse is the competing event.
- Relapse/Progression: Cumulative incidence of disease relapse/progression, with NRM as competing event.
- Incidence of acute and chronic GVHD: Cumulative incidence of acute and chronic GVHD, with death without the corresponding GVHD as the competing risk. Patients are censored at subsequent HCT or last follow-up.

Specific Aims:

We propose to evaluate the impact of in vivo graft manipulation strategy (PTCy vs. ATG or alemtuzumab) on clinical outcomes following UD HCT for patients with acute leukemias (AL) and MDS. To achieve this objective, we will:

AIM 1. Identify differences in post-transplant outcomes (GVHD-free, relapse free survival [GRFS], overall survival, leukemia-free survival, non-relapse mortality, relapse and acute and chronic GVHD) in AL/MDS patients receiving *in vivo* graft manipulation with PTCy versus ATG or alemtuzumab, following UD HCT.

AIM 2. Evaluate differences in post-transplant outcomes for AL/MDS patients receiving graft manipulation with PTCy versus ATG or alemtuzumab based on graft source, donor type (MUD vs. MMUD) and conditioning intensity.

SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

The optimal graft manipulation strategy to prevent graft-versus-host disease following HCT from an unrelated donor remains unknown. The current standard of care following unrelated HCT is administration of a calcineurin inhibitor and methotrexate in combination with anti-thymocyte globulin (ATG) or alemtuzumab. The use of post-transplant cyclophosphamide (PTCy) is an emerging prophylactic strategy that has proven successful in haploidentical transplantation, demonstrated satisfactory outcomes in the setting of matched unrelated HCT and promising results in a prospective trial for mismatched unrelated HCT. Nevertheless, there is a paucity of data comparing outcomes in unrelated donor HCT receiving post-transplant cyclophosphamide, alemtuzumab, or anti-thymocyte globulin for graft-versus-host disease prophylaxis.

To date, the comparison of these approaches has been restricted to single institutions, limited HCT indications, or recipients of single-antigen MMUD grafts. Answering this research question in a large multicenter cohort will provide HCT clinicians and scientists with critical information to improve clinical care and will add to the current body knowledge in unrelated matched and mismatched HCT, as emerging methodologies continue to be evaluated in this setting.

SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

Allogeneic Hematopoietic Cell Transplant (alloHCT) continues to be the preferred consolidation strategy for many patients with acute leukemias and myelodysplastic syndromes. MUDs are the preferred graft source for patients without matched sibling donors, and MMUD HCT is emerging as a suitable alternative donor source for patients without HLA-matched donors.

The use of post-transplant cyclophosphamide (PTCy) is an emerging prophylactic strategy that has proven successful in haploidentical transplantation, demonstrated satisfactory outcomes in the setting of matched unrelated HCT and promising results in a prospective trial for mismatched unrelated HCT.

Historically, mismatched UD HCT has been associated with poor outcomes given increased rates of GvHD, graft failure and infection, all resulting in high non-relapse mortality (NRM). The post-transplant cyclophosphamide (PTCy) platform has successfully overcome barriers related to HLA-mismatching in the haploidentical donor setting and is being increasingly recognized as a suitable strategy for UD transplants. PTCy-based GVHD prophylaxis in the mismatched UD HCT setting has shown to be safe and feasible in single institution studies. A recent prospective phase-II, multicenter NMDP trial demonstrated the effectiveness of PTCy in a cohort of 80 patients with hematologic malignancies (68% with a diagnosis of acute leukemias) receiving a mismatched UD bone marrow HCT, with a one-year OS of 76% and satisfactory rates of NRM, RFS, GRFS and GVHD. We retrospectively evaluated the outcomes of 73 adult patients (68% with a diagnosis of acute leukemia or MDS) who received a MMUD (>=1 mismatch at -A, -B, -C, -DRB1 alleles) at the University of Miami. PTCy prophylaxis resulted in superior OS (73.6% vs. 36.9%, P=0.002) RFS, GRFS and lower NRM compared to ATG-based TCS. A large multicenter, retrospective study evaluating the role of alternative donor HCT (N=125) for ALL in CR, demonstrated no differences in post-HCT outcomes among all different donor sources. Recent data from the Acute Leukemia Working Party (ALWP) of the EBMT, demonstrated superior outcomes for PTCy recipients (vs. ATG) in a cohort of 272 patients with AML, following a single-antigen (9/10) MMUD HCT. Cohort included patients with DQ mismatched grafts, and various GVHD prophylactic regimens following transplantation.

Clinical outcomes following PTCy MUD transplantation appear to be similar to those of mismatched related donor HCT (haplo-HCT) receiving PTCy, but direct comparisons of PTCy vs. traditional TCD (ATG or alemtuzumab) in the MUD setting are limited. Gooptu *et al*. carried out a retrospective review of the CIBMTR comparing patients who either received haploidentical or MUD HCT with GVHD prophylaxis with PTCy + CNI/MMF. There were no differences in graft failure, relapse, NRM, and disease-free and overall survival between donor types with MAC regimens, but the use of a MUD graft was associated with improved survival in the RIC cohort. Brisott *et al.*, on behalf of the ALWP of the EBMT, demonstrated comparable outcomes for PTCy recipients (vs. traditional TCD) in a cohort of 1626 patients with AML, following 10/10 HLA-MUD HCT in CR1.

Despite the expanding role of PTCy-based GVHD prophylaxis outside of the haplo-HCT setting, and the emerging use of MMUD as an alternative donor source, data comparing outcomes in UD HCT receiving PTCy vs. traditional TCD with ATG or alemtuzumab are limited. We propose a retrospective cohort study to evaluate differences in post-HCT outcomes for acute leukemia and MDS patients receiving graft manipulation with PTCy versus ATG or alemtuzumab following UD HCT. To our knowledge, no large, multi-center studies addressing this important question in the US have been conducted to date.

PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

Inclusion Criteria

- Patients with a diagnosis of AML and ALL in CR (< 5% blasts) or MDS (< 10% blasts) at transplant
- Ages 18 and older
- Recipients of a MUD (8/8 match at -A, -B, -C, -DRB1 alleles) or MMUD graft (>=1 mismatch at -A, -B, -C, -DRB1 alleles) between 2010-2020, receiving GVHD prophylaxis with CNI+MTX (ATG cohort) or CNI+MMF (PTCy cohort)

Exclusion Criteria

- *In vivo* graft manipulation other than ATG, alemtuzumab or PTCy
- *Ex vivo* TCD

Does this study include pediatric patients?

No

If this study does not include pediatric patients, please provide justification:

a. Strategies for TCD and GVHD prophylaxis are different in pediatric transplantation and they experience different morbidity and mortality from GVHD.
b. Pediatric patients with high-risk acute leukemias are more likely to receive transplant consolidation with haploidentical or CBT units (vs. MMUDs) if a fully-matched donor is not available. We therefore suspect that numbers will not be sufficient to answer the research question in the MMUD subgroup
c. Myelodysplastic syndrome (MDS) is a primarily disease of the elderly and rarely affects the pediatric population.

DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses.

Study main effect:

Choice of *in vivo* graft manipulation (PTCy vs. ATG or alemtuzumab) following UD HCT.

Variables to be described:

Patient-related:

• Age at transplant
• Gender
• Race
• Ethnicity: Hispanic vs. Non-Hispanic
• Karnofsky performance status at transplant: ≥ 90 vs. < 90
• HCT comorbidity index at transplant: 0 vs 1-2
vs ≥ 3

Disease-related:

Acute Leukemia Patients:

• CR status at HCT: CR1 vs ≥CR2
• Time to achieve CR
• MRD prior to transplant: yes/no
• CRi prior to transplant: yes/no
• Extramedullary disease: yes/no
• Disease
risk index
AML
Patients:
• Clinical onset of AML: *de novo* vs. transformed from MDS/MPN vs. therapy-related
• ELN genetic stratification
• White blood count at diagnosis: <10 vs. 10-100
vs. >100 x10^9/L
ALL Patients:
• Genetic stratification
• Lineage: B-cell vs T-cell
• Hyperleukocytosis at diagnosis (>30,000 for B-ALL, >100,000 for T-ALL)
• Ph+ status

MDS Patients:

- Disease status at HCT (CR, HI, NR/SD, etc.)
- IPSS-R
- Cytogenetic risk group
- Blast burden at diagnosis
- Pre-HCT therapy (HMA, lenalidomide, BSC, etc.)

Transplant-related:

- Conditioning intensity: Myeloablative conditioning (MAC) vs. reduced-intensity/non-myeloablative conditioning (RIC/NMA)
- Graft source: bone marrow vs. peripheral blood
- Degree of HLA match (8/8, ≤7/8)
- Donor age
- Donor-recipient sex match
- Donor-recipient CMV status
- Time from diagnosis to HCT
- Year of transplant
- An unique ID of the centers (not the actual CIBMTR ID, can be 1 to # of centers; to build random-effects models)

Outcomes:

- Death (and time from transplant to death)
- Relapse/Progression (and time from transplant to relapse/progression)
- Acute GVHD (grade and time to acute GVHD)
- Chronic GVHD (grade and time to chronic GVHD)
- Chronic GVHD requiring systemic therapy (and time to systemic therapy for chronic GVHD)

PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.

NA

SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems.

NA

NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

NA

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Table 1. Characteristics of adult patients receiving first alloHCT for AML/ALL/MDS with unrelated donor in 2010-2020, CRF track

Characteristic	PT-Cy	ATG/Alemtuzumab	Total
No. of patients	548	2136	2684
No. of centers	75	157	172
Age at HCT, years			
Median (range)	64 (18-82)	61 (18-83)	62 (18-83)
18-29	33 (6)	191 (9)	224 (8)
30-39	29 (5)	147 (7)	176 (7)
40-49	54 (10)	220 (10)	274 (10)
50-59	97 (18)	451 (21)	548 (20)
60-69	253 (46)	850 (40)	1103 (41)
≥70	82 (15)	277 (13)	359 (13)
Recipient sex			
Male	306 (56)	1271 (60)	1577 (59)
Female	242 (44)	865 (40)	1107 (41)
Primary disease for HCT			
AML	236 (43)	791 (37)	1027 (38)
ALL	78 (14)	269 (13)	347 (13)
MDS	234 (43)	1076 (50)	1310 (49)
Donor type			
Well-matched unrelated (8/8)	375 (68)	1741 (82)	2116 (79)
Partially-matched unrelated (7/8)	148 (27)	381 (18)	529 (20)
Mis-matched unrelated (<= 6/8)	25 (5)	14 (1)	39 (1)
Conditioning intensity			
MAC	217 (40)	915 (43)	1132 (42)
RIC	219 (40)	1044 (49)	1263 (47)
NMA	87 (16)	98 (5)	185 (7)
TBD	1 (<1)	34 (2)	35 (1)
Missing	24 (4)	45 (2)	69 (3)
GVHD prophylaxis			
Post-CY + other(s)	504 (92)	0 (0)	504 (19)
Post-CY alone	44 (8)	0 (0)	44 (2)
TAC + MMF +- other(s) (except post-CY)	0 (0)	467 (22)	467 (17)
TAC + MTX +- other(s) (except MMF, post-CY)	0 (0)	1080 (51)	1080 (40)
TAC + other(s) (except MMF, MTX, post-CY)	0 (0)	77 (4)	77 (3)
TAC alone	0 (0)	106 (5)	106 (4)
CSA + MMF +- other(s) (except post-CY)	0 (0)	124 (6)	124 (5)
CSA + MTX +- other(s) (except MMF, post-CY)	0 (0)	145 (7)	145 (5)
CSA + other(s) (except MMF, MTX, post-CY)	0 (0)	16 (1)	16 (1)
CSA alone	0 (0)	29 (1)	29 (1)
Other(s)	0 (0)	26 (1)	26 (1)
Missing	0 (0)	66 (3)	66 (2)

Characteristic	PT-Cy	ATG/Alemtuzumab	Total
ATG/Alemtuzumab			
ATG	0 (0)	1957 (92)	1957 (73)
Alemtuzumab	0 (0)	179 (8)	179 (7)
None	548 (100)	0 (0)	548 (20)
Year of HCT			
2010	1 (<1)	181 (8)	182 (7)
2011	6 (1)	142 (7)	148 (6)
2012	7 (1)	135 (6)	142 (5)
2013	13 (2)	274 (13)	287 (11)
2014	19 (3)	305 (14)	324 (12)
2015	51 (9)	305 (14)	356 (13)
2016	66 (12)	268 (13)	334 (12)
2017	85 (16)	196 (9)	281 (10)
2018	121 (22)	164 (8)	285 (11)
2019	101 (18)	128 (6)	229 (9)
2020	78 (14)	38 (2)	116 (4)
Median follow-up of survivors (range), months	25 (2-97)	58 (0-125)	48 (0-125)

Study Title: Comparative analysis of the incidence of graft versus host disease by age group in pediatric hematopoietic stem cell transplant recipients and impact on non-relapse mortality.

Research Question:

How does the incidence of acute and chronic graft versus host disease (GVHD) compare between pediatric hematopoietic stem cell transplant (HCT) recipients of different age groups, and has the impact of GVHD on non-relapse mortality (NRM) for these groups evolved over the past two decades?

Research Hypothesis:

1. The incidence and severity of GVHD in pediatric patients undergoing first HCT has decreased over the last two decades despite the expanded use of alternate donor grafts.
2. Acute and chronic GVHD in infants and toddlers occurs less frequently than in older children, and there are risk factors unique to this population for patients transplanted for malignant and nonmalignant disorders.
3. Patients who develop severe GVHD will have higher NRM than patients without GVHD.

Primary Objective:

1. To compare the incidence, severity, and risk factors for acute and chronic graft versus host disease in infant/toddler (<3 years), school-aged (3-10 years), and adolescent (11-17 years) patients undergoing HCT for malignant and nonmalignant conditions during two eras: 2002-2011 to 2012-2021.

Secondary Objectives:

1. To describe the impact of donor type and GVHD prophylaxis on both acute and chronic GVHD risk, and to identify any differences in risk factor by age group.

2. To compare overall survival (OS) and NRM among patients with and without acute and chronic GVHD.

SCIENTIFIC IMPACT:

The potential impact of this project is substantial. To our knowledge, there have been no recent publications on the incidence of GVHD and its impact on transplant-related mortality in children. The literature on GVHD and its role in morbidity/mortality and development of late effects in the younger pediatric population (i.e., infants and toddlers) is particularly lacking. Donor options and GVHD prophylaxis approaches expanding, with increase in the use of alternate donor transplantations. In particular, haploidentical transplants now account for 15% of allogeneic transplants in pediatric patients over the past 5 years [1, 2]. Evidence on the efficacy of recently developed GVHD therapeutic options has largely been extrapolated from adult data to pediatric groups. To better understand the risk for developing GVHD in current practice and the impact of development of GVHD on NRM among children in the current era, we will retrospectively analyze patient, transplant, and acute and chronic GVHD-related variables from a large

international database. Understanding more of the long-term impact of GVHD in these different age groups on their overall morbidity has the potential to help providers build a clinical care model around their specific needs.

STUDY POPULATION

Inclusion Criteria:

Pediatric patients aged 0 to <3 years, 3 to 10 years, and 11 to <18 years who received first allogeneic stem cell transplant for malignant or nonmalignant conditions between years 2002 – 2011 and 2012 – 2021.

Exclusion Criteria:

Patients receiving a second or greater number of transplants. Patients receiving autologous stem cell transplant, syngeneic stem cell transplant.

OUTCOMES:

- Incidence and severity of acute and chronic GVHD
- Non-relapse mortality, defined as death in the absence of recurrence of the primary malignancy or disease. Patients will be censored at last follow up. The event will be summarized by the cumulative incidence estimate with disease recurrence as a competing risk.
- Overall Survival, defined as the length of time from HCT that patients are still alive. There are no competing risks.

VARIABLES TO BE ANALYZED:

Patient-related:

- Age at transplant (continuous)
- Sex: Male, Female
- Race: Caucasian, African-American, Asian/Pacific Islander, Hispanic, Other, Unknown
- Performance Status at HCT: Karnofsky/Lansky performance scale: 90-100 vs < 90
- HCT CI: 0-2 versus $\geq$3
- Time from diagnosis to transplant
- CMV serostatus: seropositive versus seronegative

Disease-related:

- Malignant versus non-malignant
- Primary diagnosis:
    - Leukemia/myelodysplastic syndrome (MDS)
    - Lymphoma
    - Hemoglobinopathies
    - BM failure

  - Immunodeficiency
  - Hemophagocytic disorders
  - Metabolic syndromes
  - Other
- Pediatric disease risk index classification: low-risk, standard-risk, high-risk

Donor-related:

- Donor age, years: median (range)
- Sex: Male, Female
- Donor-recipient CMV status match: +/+, +/-, -/+, -/-
- Donor match: matched-related donor, well-matched unrelated donor, mismatched unrelated donor, haploidentical donor (<7/8 HLA match)
- Grace source: Bone marrow, peripheral blood (PBSC), manipulated PBSC (CD34-selected, alpha/beta T cell depletion, other manipulations), umbilical cord blood (UCB)
- Donor-recipient sex match: M/M, M/F, F/M, F/F

Transplant-related:

- Year of transplant: 2002 – 2011 versus 2012 – 2021
- Conditioning intensity: myeloablative, non-myeloablative, reduced intensity
- Conditioning regimen: TBI-based versus no TBI
- ABO mismatch
- GvHD prophylaxis:
  - Methotrexate with calcineurin inhibitor
  - Mycophenolate mofetil with calcineurin inhibitor
  - Other
- In vivo T-cell depletion (ATG or alemtuzumab): No, Yes

GvHD Severity:

- Acute GVHD organ involvement: skin, lower GI, upper GI, liver, other
- Acute GVHD grade I and II versus grade III and IV
- Acute GVHD grade 0-1 versus II-IV
- Chronic GVHD organ involvement: skin, lower GI, upper GI, liver, lung, other
- Chronic GVHD maximum grade: mild, moderate, severe, unknown
- Current chronic GVHD status (at time of last visit or at time of death): Yes, No

Cause of Death:

- GVHD-related
- Relapse/Disease Recurrence
- Infection
- Graft-failure
- Other
- Unknown

STUDY DESIGN:

In a univariate analysis, descriptive statistics will be used to summarize patient characteristics, donor, disease, and transplant-related factors as well as acute and chronic GVHD features. For discrete variables, the number of cases and their respective percentages will be calculated – with one table representing years 2002 – 2011 and another for 2012 – 2021. Probabilities for overall survival at fixed time points will be calculated using the Kaplan-Meier method. Comparison of survival curves will be done using the log-rank test. Estimates of NRM, OS, and disease relapse will be calculated according to the cumulative incidence. Multivariate analysis will be used to determine the impact of acute and chronic GVHD on disease relapse, NRM, and OS, while controlling for other risk factors, on the cause-specific hazards of using Cox proportional hazard models.

Table 1. Characteristics of patients age < 18 receiving first alloHCT in 2002-2020, CRF track

Characteristic	2002-2011	2012-2020	Total
No. of patients	8437	5797	14234
No. of centers	227	151	257
Age at HCT, years			
Median (range)	7 (0-18)	7 (0-18)	7 (0-18)
< 3	2275 (27)	1578 (27)	3853 (27)
3-10	3389 (40)	2483 (43)	5872 (41)
11-17	2773 (33)	1736 (30)	4509 (32)
Recipient sex			
Male	5038 (60)	3452 (60)	8490 (60)
Female	3399 (40)	2345 (40)	5744 (40)
Disease			
AML	1623 (19)	833 (14)	2456 (17)
ALL	2012 (24)	900 (16)	2912 (20)
OL	38 (<1)	1 (<1)	39 (<1)
CML	277 (3)	39 (1)	316 (2)
MDS	543 (6)	194 (3)	737 (5)
OAL	146 (2)	56 (1)	202 (1)
NHL	172 (2)	83 (1)	255 (2)
HD	32 (<1)	30 (1)	62 (<1)
PCD	0 (0)	1 (<1)	1 (<1)
ST	40 (<1)	9 (<1)	49 (<1)
SAA	736 (9)	662 (11)	1398 (10)
IEA	926 (11)	1508 (26)	2434 (17)
IIS	918 (11)	948 (16)	1866 (13)
IPA	50 (1)	24 (<1)	74 (1)
IMD	535 (6)	301 (5)	836 (6)
HIS	335 (4)	170 (3)	505 (4)
AI	12 (<1)	9 (<1)	21 (<1)
Other	31 (<1)	14 (<1)	45 (<1)
MPN	11 (<1)	15 (<1)	26 (<1)
Donor type			
HLA-identical sibling	2085 (25)	1496 (26)	3581 (25)
Other related	417 (5)	1207 (21)	1624 (11)
Well-matched unrelated (8/8)	1713 (20)	926 (16)	2639 (19)
Partially-matched unrelated (7/8)	816 (10)	339 (6)	1155 (8)
Mis-matched unrelated (<= 6/8)	299 (4)	22 (<1)	321 (2)
Multi-donor	16 (<1)	10 (<1)	26 (<1)
Unrelated (matching TBD)	62 (1)	177 (3)	239 (2)
Cord blood	3029 (36)	1620 (28)	4649 (33)

Characteristic	2002-2011	2012-2020	Total
Graft type			
Bone marrow	3958 (47)	3069 (53)	7027 (49)
Peripheral blood	1450 (17)	1108 (19)	2558 (18)
Cord blood	3029 (36)	1620 (28)	4649 (33)
Conditioning regimen intensity			
MAC	6254 (74)	3639 (63)	9893 (70)
RIC	774 (9)	692 (12)	1466 (10)
NMA	901 (11)	800 (14)	1701 (12)
TBD	168 (2)	403 (7)	571 (4)
Missing	340 (4)	263 (5)	603 (4)
GVHD prophylaxis			
Ex-vivo T-cell depletion	405 (5)	194 (3)	599 (4)
CD34 selection	217 (3)	218 (4)	435 (3)
Post-CY + other(s)	39 (<1)	603 (10)	642 (5)
Post-CY alone	1 (<1)	2 (<1)	3 (<1)
TAC + MMF +- other(s) (except post-CY)	417 (5)	636 (11)	1053 (7)
TAC + MTX +- other(s) (except MMF, post-CY)	948 (11)	798 (14)	1746 (12)
TAC + other(s) (except MMF, MTX, post-CY)	233 (3)	95 (2)	328 (2)
TAC alone	88 (1)	49 (1)	137 (1)
CSA + MMF +- other(s) (except post-CY)	1096 (13)	1133 (20)	2229 (16)
CSA + MTX +- other(s) (except MMF, post-CY)	2774 (33)	1062 (18)	3836 (27)
CSA + other(s) (except MMF, MTX, post-CY)	1386 (16)	298 (5)	1684 (12)
CSA alone	372 (4)	169 (3)	541 (4)
Other(s)	87 (1)	124 (2)	211 (1)
Missing	374 (4)	416 (7)	790 (6)
In-vivo T-cell depletion (ATG/alemtuzumab)			
No	3526 (42)	1997 (34)	5523 (39)
Yes	4623 (55)	3528 (61)	8151 (57)
Missing	288 (3)	272 (5)	560 (4)
Year of HCT			
2002-2003	1966 (23)	0 (0)	1966 (14)
2004-2005	2115 (25)	0 (0)	2115 (15)
2006-2007	1895 (22)	0 (0)	1895 (13)
2008-2009	1655 (20)	0 (0)	1655 (12)
2010-2011	806 (10)	0 (0)	806 (6)
2012-2013	0 (0)	958 (17)	958 (7)
2014-2015	0 (0)	1714 (30)	1714 (12)
2016-2017	0 (0)	1525 (26)	1525 (11)
2018-2020	0 (0)	1600 (28)	1600 (11)
Median follow-up of survivors (range), months	116 (0-228)	37 (0-104)	64 (0-228)

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

Chronic GVHD Risk Index: A clinical risk assessment score for development of moderate-severe chronic graft-versus-host disease (GVHD) after hematopoietic cell transplantation (HCT)

Q2. Key Words

chronic GVHD, clinical risk assessment score

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Annie Im, MD
Email address:	imap@upmc.edu
Institution name:	University of Pittsburgh
Academic rank:	Associate Professor

Q30. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q29. Do you identify as an underrepresented/minority?

- No

Q28. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Steven Pavletic, MD MS
Email address:	pavletis@mail.nih.gov
Institution name:	National Cancer Institute
Academic rank:	Senior Clinician

Q27. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q26. Do you identify as an underrepresented/minority?

- No

Q31. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

Annie Im

Q4. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: *A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:* *https://www.cibmtr.org/Studies/Observational/StudyManagement/p*

Q6. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

None current (have worked on projects that have been published)

Q7. PROPOSED WORKING COMMITTEE:

- Graft vs Host Disease

Q8. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- Yes

Q9. If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

Mukta Arora, MD MS

Q10. RESEARCH QUESTION:

Can development of moderate-severe chronic GVHD after HCT be predicted by baseline clinical and transplant factors?

Q11. RESEARCH HYPOTHESIS:

Patient and transplant clinical factors can be used to develop a risk score that predicts the development of moderate-severe chronic GVHD after HCT.

Q12. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

- To develop a risk score based on weighted clinical factors to predict the likelihood of developing moderate-severe chronic GVHD (requiring systemic therapy)
- To validate the risk score using a subset of the CIBMTR dataset

Q13. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

The development of a risk score that gives weight to clinical factors (patient and transplant-related) to predict the risk of chronic GVHD for a patient would provide essential data that could ultimately guide prevention trials and implementation of patient-tailored preventive measures in patients after HCT. While clinical risk factors for chronic GVHD are known, it is not known how these factors interact with each other, nor what the quantitative risk of each factor relative to others is.

Q14. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

Clinical risk factors for the development of chronic GVHD after transplant are well described, as well as strategies that decrease the risk of chronic GVHD. Despite this, there are a lack of risk scores or biomarkers that can predict the likelihood of developing chronic GVHD in a patient and assist assignment to the specific prevention therapy. Incredible progress has been made in this field in recent years, much in part due to the efforts of the NIH Chronic GVHD Consensus Project. Recently, there has been an emphasis on focusing efforts in the area of prevention of chronic GVHD as one of highest priorities for the field (1). The 2020 NIH Chronic GVHD Consensus conference will be publishing recommendations that focus on prevention specifically, and researchers in the field have been tasked with developing ways to identify patients who are at high enough risk of chronic GVHD to warrant prevention, given that prevention strategies may carry risks of major complications such as graft failure, infection, or malignancy relapse. Although effective strategies for chronic GVHD prevention exist (T-cell depletion, ATG, PTCy), none have been shown to improve survival in comparative trials. The main downside of prevention approaches is that all subjects receive intervention irrespectively if they would benefit from such intervention or not, so some patients end up being over treated and some under treated. Development of a risk score for chronic GVHD would provide essential data for research in this area, clinical trials assignment and may ultimately impact management of patients.
There already exist successful risk scores in HCT which led to substantial progress in conduct of clinical trials and clinical management. These include the Hematopoietic Cell Transplantation comorbidity index (HCT-CI) that predicts non-relapse mortality and overall survival based on existing comorbidities, Disease Risk Index (DRI) that predicts the risk of relapse of the underlying hematologic malignancy based on disease factors, and the CIBMTR Chronic GVHD risk score that predicts mortality in patients with chronic GVHD (2-4). These are both risk scores based on clinical factors whose use has been established in HCT patients. In chronic GVHD, some of the clinical factors that increase risk (e.g., peripheral blood stem cells, HLA-mismatch, patient and donor age, female to male transplants) and decrease risk (e.g., use of post-transplant cyclophosphamide (PTCY), use of ATG, naïve T-cell depletion) are well known (5-8). However, how these factors interact with each other and the quantitative risk of each factor relative to others are unknown.
Ideally, biomarkers will be developed that could be ultimately incorporated with clinical factors to have a comprehensive risk assessment for chronic GVHD and further increase the predictive value of such a scoring system. First, the development of a clinical risk score is essential to move the field forward in prevention efforts. The timing of the risk score is aimed to be at the time of HCT, so post-HCT factors will not be included unless planned ahead of transplant (such as GVHD prophylaxis).
This is a retrospective CIBMTR-based study that will evaluate a large cohort of patients who underwent allogeneic transplant from 2010-2019 for the development of moderate-severe chronic GVHD (requiring systemic therapy). Clinical factors that can be assessed at the time of transplant will be evaluated in a univariate analysis, followed by a multivariable analysis, with moderate-severe chronic GVHD (requiring systemic therapy) as the outcome of interest. Based on the results of the multivariable analysis, variable-specific risk scores will be assigned based on the relative risk of each category in the variable. From this, a risk scale will be developed, where higher scores predict for a higher likelihood of developing chronic GVHD (and potentially a threshold score can be determined above which the risk of chronic GVHD is significantly higher than scores below). Ideally, a subset of the data set can be used to develop the scale, and another can be used to validate the scale (a training cohort and a validation cohort). A major secondary endpoint in this analysis will be moderate-severe chronic GVHD-free survival, and a prognostic scoring system will be developed for both endpoints. We will also determine dynamic positive and negative predictive value as an exploratory endpoint driven by varying severity scores.

Q16. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

We will aim to analyze all patients in the CIBMTR database who underwent allogeneic HCT from 2010-2019, in order to capture all clinical factors.
• Allogeneic HCT in 2010-2019, excluding syngeneic (at least 1 year of follow up data to capture chronic GVHD)

Q17. Does this study include pediatric patients?

- Yes

Q19. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

Patient:
- Age at HCT
- Gender
- Diagnosis (individual diagnoses and malignant vs non-malignant)
- Karnofsky Performance score
- Race
- HCT-CI
- CMV status
- Time from diagnosis to transplant
- DRI
- Presence of MRD (if available)
- Baseline lymphocyte count
- Fungal infection prior to HCT

Donor:
- Type (matched sibling, matched unrelated, haploidentical, cord blood, mismatched related or unrelated)
- Age
- Gender
- CMV status
- Stem cell source

Transplant:
- HLA-match
- CD34-selected/T-cell depletion
- Conditioning regimen intensity
- GVHD prophylaxis (including use of PTCy)
- Use of ATG
- Use of TBI and dose

Q20. **PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.**

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

N/A

Q21. **SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.**

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

N/A

Q22. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

N/A

Q23. REFERENCES:

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Q24. **CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:**

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- No, I do not have any conflicts of interest pertinent to this proposal

Q32. **If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.**

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Table 1. Characteristics of patients receiving first alloHCT in 2010-2019, CRF track

Characteristic	N (%)
No. of patients	25457
No. of centers	267
Age at HCT, years	
Median (range)	50 (0-88)
<10	3763 (15)
10-17	1941 (8)
18-29	2468 (10)
30-39	1923 (8)
40-49	2674 (11)
50-59	4723 (19)
60-69	6379 (25)
≥70	1586 (6)
Recipient sex	
Male	15015 (59)
Female	10442 (41)
Primary disease for HCT	
AML	7646 (30)
ALL	3042 (12)
OL	552 (2)
CML	574 (2)
MDS	5371 (21)
OAL	226 (1)
NHL	1393 (5)
HD	296 (1)
PCD	228 (1)
ST	15 (<1)
SAA	1345 (5)
IEA	1611 (6)
IIS	1000 (4)
IPA	26 (<1)
IMD	336 (1)
HIS	212 (1)
AI	14 (<1)
Other	26 (<1)
MPN	1544 (6)
Donor type	
HLA-identical sibling	6132 (24)
Other related	4318 (17)
Well-matched unrelated (8/8)	8648 (34)
Partially-matched unrelated (7/8)	1698 (7)
Mis-matched unrelated (<= 6/8)	103 (<1)
Multi-donor	29 (<1)
Unrelated (matching TBD)	106 (<1)
Cord blood	4423 (17)
Graft type	
Bone marrow	5905 (23)
Peripheral blood	15129 (59)
Cord blood	4423 (17)

Characteristic	**N (%)**
Conditioning intensity	
MAC	10559 (41)
RIC	6706 (26)
NMA	2723 (11)
TBD	399 (2)
Missing	5070 (20)
GVHD prophylaxis	
Ex-vivo T-cell depletion	269 (1)
CD34 selection	698 (3)
Post-CY + other(s)	4514 (18)
Post-CY alone	82 (<1)
TAC + MMF +- other(s) (except post-CY)	3369 (13)
TAC + MTX +- other(s) (except MMF, post-CY)	7945 (31)
TAC + other(s) (except MMF, MTX, post-CY)	1175 (5)
TAC alone	420 (2)
CSA + MMF +- other(s) (except post-CY)	2976 (12)
CSA + MTX +- other(s) (except MMF, post-CY)	2162 (8)
CSA + other(s) (except MMF, MTX, post-CY)	444 (2)
CSA alone	266 (1)
Other(s)	344 (1)
Missing	793 (3)
In-vivo T-cell depletion (ATG/alemtuzumab)	
No	16295 (64)
Yes	9157 (36)
Missing	5 (<1)
Year of HCT	
2010	1910 (8)
2011	1358 (5)
2012	1388 (5)
2013	2689 (11)
2014	3386 (13)
2015	3368 (13)
2016	3210 (13)
2017	3007 (12)
2018	2886 (11)
2019	2255 (9)
Median follow-up of survivors (range), months	49 (12-132)

CIBMTR Study Proposal

Study Title:
A Risk-Score for Bronchiolitis Obliterans Syndrome after Allogeneic Hematopoietic Cell Transplantation

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Research Hypothesis:
We hypothesize that risk factors for the development of bronchiolitis obliterans syndrome (BOS) after allogeneic hematopoietic cell transplantation (alloHCT) include acute and chronic graft-versus-host-disease (GVHD), conditioning regimens containing busulfan and/or total body irradiation (TBI), peripheral blood stem cell source (PBSC), mismatched donor status, pre-HCT lung disease, and antecedent infectious and non-infectious pulmonary toxicities (NIPT). A novel risk score can help identify those at highest risk of this complication. In addition, we will assess the incidence and mortality of BOS in the modern era as it compares to a historical cohort.

Specific Aims:
Primary Aim:
1. Identify risk factors for the development of BOS after alloHCT to create a novel scoring system

Secondary Aims:
2. Assess the incidence, severity, and mortality of BOS after alloHCT
3. Evaluate the association of BOS occurring within 1-, 2-, and 3-years post-HCT on relapse, non-relapse mortality (NRM), disease-free survival (DFS), and overall survival (OS)
4. Evaluate change in pre/post-HCT DLCO/FEV1
5. Assess the incidence of BOS in patients who develop respiratory viral infections post-HCT
6. Cumulative incidence of chronic GVHD at 1-, 2- and 3-years post HCT
7. Cumulative incidence density of infections at 1-, 2- and 3-years post HCT
8. Causes of death

Scientific Impact:
Allogeneic HCT is a potentially curative treatment for a variety of malignant diseases, however it is limited by significant morbidity and mortality. Efforts to mitigate late effects such as chronic GVHD have been a primary focus in improving outcomes. NIPTs remain a challenging entity to prevent, diagnose, and treat as they are associated with a high mortality rate after HCT.[1] Despite advances in GVHD treatment and supportive care practices, pulmonary manifestations of chronic GVHD confer a poor prognosis.[2,3] Previously, a diagnosis of BOS conferred high mortality in part due to a lack of consensus on

diagnostic criteria, incomplete knowledge of disease pathogenesis, and few studies investigating therapeutic strategies.[4] While small scale studies have been conducted, a large registry-based analysis is needed.[5-7] However, gains remain modest with 5-year survival from BOS ranging from 40% to 50%.[5] Given the lack of efficacious treatment options for BOS, prevention is crucial. This study is critically important to provide a clinically relevant tool to better predict and risk stratify those who might develop BOS. Finding potentially modifiable factors might allow better transplant optimization with the hopes of preventing this complication.

Scientific Justification:

Chronic GVHD of the lung or BOS results from an immune-mediated attack of the small airways. This leads to fibrotic occlusion and obliteration. Diagnostic criteria for BOS includes: (1) FEV1 <75% predicted and an irreversible ≥10% decline in <2 years, (2) FEV1-to-vital capacity (VC) ratio <0.7, (3) absence of infection, and (4) either: (a) preexisting diagnosis of chronic GVHD, (b) air trapping by expiratory CT, or (c) air trapping on PFTs by residual volume (RV) >120%.[8,9] Infection must be excluded to diagnose BOS. In addition, other diagnoses such as idiopathic pneumonia syndrome, cryptogenic-organizing pneumonia (COP), pulmonary fibrosis, late radiation effects, and chronic obstructive pulmonary disease (COPD) need to be excluded as well. Workup typically includes bronchoalveolar lavage and rarely lung biopsy.

BOS begins as an asymptomatic, insidious process occurring with a median onset of 1.5 years after HCT.[4,10] As BOS progresses results in chronic respiratory failure, poor quality of life, and eventually death.[11] This toxicity confers an increased risk of mortality as these patients are more likely to develop infections or respiratory failure. Many of the studies seeking to identify the risk factors for BOS are limited by sample size unfortunately. Evident from this work includes the observation that those with chronic GVHD have double the incidence of BOS compared to other transplant recipients.[12] Previously suggested risk factors for BOS include conditioning regimens containing busulfan and/or total body irradiation (TBI), PBSC source, pre-HCT lung disease, history of significant acute GVHD, and ABO incompatibility.[13] Modern era transplant trends have made increasing use of mismatched donor sources, PBSC grafts, and PTCY as GVHD prophylaxis, but it remains unknown the impact of these changes on BOS incidence and outcomes.

Management includes treatment of any underlying co-habiting infection (bacterial, fungal, or viral). This is important as infections may upregulate cytokines and accelerate BOS progression.[14] Other adjunct therapies include management of acid reflux, nutrition optimization, use of β-agonists, and pulmonary rehabilitation.[15,16] The backbone of BOS therapy includes systemic steroids, calcineurin inhibitors, and combination therapy (fluticasone, azithromycin, montelukast).[17] In addition, extracorporeal photopheresis has shown activity as well.[18] Unfortunately, treatment options remain generally supportive in nature with limited efficacy. A novel risk-scoring system would assist in the prevention of BOS.

Patient Eligibility Population:

Inclusion Criteria:

- Adult or pediatric patients receiving an allogeneic HCT between 2007-2019 (with historical cohort from 1997 to 2006)
- Malignant or non-malignant diseases
- All disease stages
- HLA-identical sibling, matched related, haploidentical, mis-matched/partially/well-matched unrelated, cord blood
- Myeloablative or non-myeloablative/reduced intensity conditioning intensities

- Peripheral blood, bone marrow grafts, or umbilical cord blood graft sources

Exclusion Criteria:

- Ex-vivo T-cell depletion or CD34+ selected grafts

Data Requirements:

This study will use an expanded cohort from the RT18-03 dataset. Data to be analyzed will be from data collected in the CIBMTR Report forms. Supplemental data will be required from external datasets for national CRVI trends. Patient, disease, and transplant variables to collect as below.

Required Forms:

- Pre-TED (Form 2400)
- Post-TED (Form 2450)
- Post-HCT Follow-up Data (Form 2100)

Patient characteristics:

- Age/Gender/Ethnicity
- Karnofsky performance status
- Co-morbidity index (HCT-CI)
- RFI risk category
- History of asthma, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, asbestosis, or other chronic lung conditions
- History of CAD, HF, or PulmHTN
- Smoking history
- History of marijuana smoking
- History of pulmonary infections
- History of mechanical ventilation pre-HCT
- Pre-HCT DLCO and FEV1
- ABO blood type

Disease characteristics:

- Disease
- Date of disease diagnosis
- Disease stage
- Cytogenetic studies
- Molecular studies
- Dates of pre-transplant chemotherapy
- Pre-transplant chemotherapy regimen
- Number of cycles of chemotherapy
- Total number of lines of chemotherapy
- PB blast count pre-HCT (≤1% vs. >1%)
- Remission status at transplant

Transplant characteristics:

- Date of transplant
- Donor relationship
- Graft source
- HLA matching status
- Conditioning regimen agents/intensity
- TBI vs non-TBI regimens (including dose)
- CD34, T cell dose
- GVHD immunosuppressive regimen (TAC/MMF, TAC/MTX, CSA/MMF, CSA/MTX, Post-cy)
- Engraftment syndrome
- Donor age/gender
- Donor-recipient CMV status
- Transplant hospitalization length of stay
- History of donor lymphocyte infusions
- History of IVIG
- History of respiratory viral infections
- History of mechanical ventilation after HCT: yes vs. no
- Number of ICU admissions
- History of thrombotic microangiopathy
- Duration of systemic GVHD ppx
- BOS:
    - Method of diagnosis: (BAL, transbronchial biopsy, VATs biopsy, autopsy, other)
    - Organisms isolated from sputum, BAL, or aspirate (yes vs no)
    - Type of organism: fungal, bacterial, viral
    - Use of multiplex PCR to rule out infection: yes vs. no
    - Any preceding infections 1 month prior to dx of BOS and occurring during 1 month after
    - Presence of sepsis or ARDS

- Post-HCT DLCO and FEV1 at day 100

Outcomes:

- Time to BOS
- Pre/Post-HCT DLCO/FEV1
- Time to neutrophil, platelet, hemoglobin recovery
- Incidence and timing of graft failure
- Incidence and severity of acute and chronic GVHD
- Relapse
- Status at last follow-up
- Time to and cause of death
- WBC, ALC counts at day 100
- CD3, CD4, CD8, CD56 counts at day 100, 180

Sample Requirements:

None

Study Design:

This is a retrospective analysis to describe the incidence, severity, and mortality from the development of BOS after alloHCT. Using this information, we will develop a novel risk score to predict the risk of BOS. We will adjust for any possible center effect. Cumulative incidence of BOS will be computed using a competing risk function. The temporal relationship of chronic GVHD and BOS development will be explored. We will also examine preceding infections occurring 1 month prior to the development of BOS and concurrently. In addition, will evaluate pre/post-HCT changes in pulmonary function tests. The full cohort will be randomly divided into a training and a validation set. Prognostic factors for BOS will be identified using logistic regression with stepwise elimination on the training set. Assessment of risk factors for outcomes of interest will be evaluated in multivariate analyses using Cox proportional hazards regression or logistic regression where applicable. Risk factors will include patient-, disease-, and transplant-related characteristics. If the proportional hazards assumption is violated, it will be added as time-dependent covariate. Risk factors with a p-value ≤ 0.05 will be considered significant. Once the final model is built, the risk score and predicted probability of developing BOS will be calculated using stratified risk groups using maximum likelihood estimates. Finally, we will compare outcomes to a historical cohort to evaluate how BOS outcomes have changed over time.

Non-CIBMTR Data Source:

None

Conflicts of Interest:

No relevant disclosures

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indicators of disease severity and prognosis. *Biol Blood Marrow Transplant*. Apr 2013;19(4):632-9. doi:10.1016/j.bbmt.2013.01.013
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Table 1. Characteristics of patients receiving first alloHCT in 1996-2019, CRF track

Characteristic	1997-2007	2008-2019	Total
No. of patients	38621	33817	72438
No. of centers	430	293	489
Age at HCT, years			
Median (range)	35 (0-83)	48 (0-88)	40 (0-88)
<10	6238 (16)	5026 (15)	11264 (16)
10-17	4170 (11)	2555 (8)	6725 (9)
18-29	6292 (16)	3437 (10)	9729 (13)
30-39	5919 (15)	2752 (8)	8671 (12)
40-49	7151 (19)	3912 (12)	11063 (15)
50-59	6375 (17)	6532 (19)	12907 (18)
60-69	2345 (6)	7837 (23)	10182 (14)
≥70	131 (<1)	1766 (5)	1897 (3)
Recipient sex			
Male	22634 (59)	19899 (59)	42533 (59)
Female	15987 (41)	13918 (41)	29905 (41)
Disease			
AML	10581 (27)	10333 (31)	20914 (29)
ALL	6194 (16)	4153 (12)	10347 (14)
OL	1147 (3)	863 (3)	2010 (3)
CML	5483 (14)	885 (3)	6368 (9)
MDS	3591 (9)	6432 (19)	10023 (14)
OAL	358 (1)	330 (1)	688 (1)
NHL	3364 (9)	2170 (6)	5534 (8)
HD	574 (1)	630 (2)	1204 (2)
PCD	1011 (3)	341 (1)	1352 (2)
ST	355 (1)	18 (<1)	373 (1)
BC	63 (<1)	0 (0)	63 (<1)
SAA	2284 (6)	1821 (5)	4105 (6)
IEA	1562 (4)	1951 (6)	3513 (5)
IIS	876 (2)	1153 (3)	2029 (3)
IPA	47 (<1)	39 (<1)	86 (<1)
IMD	540 (1)	495 (1)	1035 (1)
HIS	303 (1)	308 (1)	611 (1)
AI	22 (<1)	20 (<1)	42 (<1)
Other	35 (<1)	31 (<1)	66 (<1)
MPN	231 (1)	1844 (5)	2075 (3)
Donor type			
HLA-identical sibling	16388 (42)	8549 (25)	24937 (34)
Other related	912 (2)	4911 (15)	5823 (8)

Characteristic	1997-2007	2008-2019	Total
Well-matched unrelated (8/8)	10080 (26)	11014 (33)	21094 (29)
Partially-matched unrelated (7/8)	5333 (14)	2397 (7)	7730 (11)
Mis-matched unrelated (<= 6/8)	2264 (6)	178 (1)	2442 (3)
Multi-donor	119 (<1)	100 (<1)	219 (<1)
Unrelated (matching TBD)	348 (1)	678 (2)	1026 (1)
Cord blood	3177 (8)	5990 (18)	9167 (13)
Graft type			
Bone marrow	18543 (48)	8005 (24)	26548 (37)
Peripheral blood	16901 (44)	19822 (59)	36723 (51)
Cord blood	3177 (8)	5990 (18)	9167 (13)
Conditioning regimen intensity			
MAC	27089 (70)	16699 (49)	43788 (60)
RIC	5017 (13)	9677 (29)	14694 (20)
NMA	3967 (10)	5761 (17)	9728 (13)
TBD	1091 (3)	859 (3)	1950 (3)
Missing	1457 (4)	821 (2)	2278 (3)
GVHD prophylaxis			
Post-CY + other(s)	227 (1)	4631 (14)	4858 (7)
Post-CY alone	6 (<1)	93 (<1)	99 (<1)
TAC + MMF +- other(s) (except post-CY)	2321 (6)	5040 (15)	7361 (10)
TAC + MTX +- other(s) (except MMF, post-CY)	6950 (18)	10845 (32)	17795 (25)
TAC + other(s) (except MMF, MTX, post-CY)	824 (2)	1651 (5)	2475 (3)
TAC alone	607 (2)	637 (2)	1244 (2)
CSA + MMF +- other(s) (except post-CY)	2899 (8)	4364 (13)	7263 (10)
CSA + MTX +- other(s) (except MMF, post-CY)	18179 (47)	3349 (10)	21528 (30)
CSA + other(s) (except MMF, MTX, post-CY)	2903 (8)	847 (3)	3750 (5)
CSA alone	2015 (5)	496 (1)	2511 (3)
Other(s)	340 (1)	545 (2)	885 (1)
Missing	1350 (3)	1319 (4)	2669 (4)
In-vivo T-cell depletion (ATG/alemtuzumab)			
No	25535 (66)	21092 (62)	46627 (64)
Yes	11653 (30)	11718 (35)	23371 (32)
Missing	1433 (4)	1007 (3)	2440 (3)
Year of HCT			
1996-1997	5985 (15)	0 (0)	5985 (8)
1998-1999	5357 (14)	0 (0)	5357 (7)
2000-2001	5897 (15)	0 (0)	5897 (8)
2002-2003	6418 (17)	0 (0)	6418 (9)
2004-2005	7658 (20)	0 (0)	7658 (11)
2006-2007	7306 (19)	0 (0)	7306 (10)
2008-2009	0 (0)	6457 (19)	6457 (9)

Characteristic	1997-2007	2008-2019	Total
2010-2011	0 (0)	3354 (10)	3354 (5)
2012-2013	0 (0)	4186 (12)	4186 (6)
2014-2015	0 (0)	7185 (21)	7185 (10)
2016-2017	0 (0)	6582 (19)	6582 (9)
2018-2020	0 (0)	6053 (18)	6053 (8)
Median follow-up of survivors (range), months	138 (0-299)	54 (0-158)	73 (0-299)
Post-transplant variables			
Bronchiolitis obliterans (cGVHD related)			
Yes	1389 (4)	1150 (3)	2539 (4)
No	10757 (28)	11853 (35)	22610 (31)
No cGVHD	24715 (64)	20445 (60)	45160 (62)
Missing	1760 (5)	369 (1)	2129 (3)
Other cGVHD related lung involvement			
Yes	1347 (3)	1926 (6)	3273 (5)
No	10801 (28)	11071 (33)	21872 (30)
No cGVHD	24715 (64)	20445 (60)	45160 (62)
Missing	1758 (5)	375 (1)	2133 (3)
Bronchiolitis obliterans (reported outside cGVHD)			
No	34858 (90)	32378 (96)	67236 (93)
Yes	1438 (4)	998 (3)	2436 (3)
Missing	2325 (6)	441 (1)	2766 (4)

Table 2. Cross-tabulation of BOS reported under cGVHD vs. pulmonary abnormality

	BOS (reported outside cGVHD)		
	No	Yes	Missing
BOS (cGVHD related)			
Yes	901 (1)	1617 (66)	21 (1)
No	22176 (33)	297 (12)	137 (5)
No cGVHD	43051 (64)	432 (18)	1677 (61)
Missing	1108 (2)	90 (4)	931 (34)

CIBMTR Study Proposal

Study Title:
Incidence and Risk Factors for thromboembolism in patients with Chronic Graft-versus-Host Disease

1st PI Information:
PI Name (First, Middle, Last): Najla El Jurdi
Degree(s): MD
Academic Rank: Assistant Professor of Medicine
Junior Investigator (yes/no), *if applicable*: yes
Junior Investigator Status (# years from fellowship), *if applicable*: 2
Email Address: neljurdi@umn.edu
Institution Name: University of Minnesota

2nd PI Information:
PI Name (First, Middle, Last): Mukta Arora
Degree(s): MD
Academic Rank: Professor of Medicine
Email Address: arora005@umn.edu
Institution Name: University of Minnesota

Research Hypothesis:
Graft-versus-Host Disease (GVHD) is a risk factor for thromboembolic events (TTE) after allogeneic hematopoietic cell transplantation (HCT), including venous thromboembolism (VTE) and pulmonary embolism (PE), with higher risk in those with severe cGVHD and non-O donor-recipient blood group matching.

Specific Aims:

1) **Evaluate impact of GVHD (acute and chronic) and ABO mismatch on incidence and risk factors for TEE in patients undergoing allogeneic HCT for acute leukemia**
2) **In patients with chronic GVHD, evaluate incidence and chronic GVHD specific risk factors for TEE in in patients undergoing allogeneic HCT for acute leukemia**
3) **Evaluate impact of TEE on NRM after allogeneic HCT for acute leukemia**

Multivariate analysis including covariates examined for possible associations with TEE including: gender, age, BMI (<30 or ≥30), donor type, conditioning intensity (MAC vs RIC), GVHD prophylaxis, disease risk index for malignant disorders (DRI) , HCT comorbidity index (HCT-CI), type of cGVHD at onset (de-novo, quiescent or progressive), severity of cGVHD at onset (mild, moderate or severe), platelets at cGVHD diagnosis (<100,000, ≥100,000), donor-recipient ABO match, and cGVHD organ involvement (skin, eyes, mouth, joints, lung, gastrointestinal, genitourinary, liver). We will additionally examine the effect of traditional TEE risk factors including smoking history, diabetes mellitus (DM), hyperlipidemia (HLD), hypertension (HTN), cerebrovascular accident (CVA), congestive heart failure (CHF), coronary artery disease (CAD), family history of TEE, and personal history of TEE prior to cGVHD diagnosis.

Scientific Impact:

Identifying a subgroup of allogeneic HCT recipients at a high risk for TEE prior to the development of the event, could inform early thromboprophylaxis and other supportive care strategies for prevention of TEE.

Scientific Justification:

cGVHD is a multisystem syndrome involving dysregulated immunity, tissue inflammation and injury, with endothelial dysfunction often resembling processes seen in autoimmune diseases and possibly leading to permanent organ damage[1–4].

Venous and arterial thromboembolism is pathologic formation of thrombi in organs, often associated with inflammation. Individuals with other chronic autoimmune disorders are known to be at risk for TEE[5].

Endothelial dysfunction and decreased thrombomodulin- dependent generation of activated protein C have been implicated in GVHD pathogenesis, partially contributing to a procoagulant state[6–9]. Limited studies have reported a wide range of thromboembolism incidence among allogeneic HCT recipients[10–13], with higher risk observed in patients developing GVHD[12,13].

Here, we aim to assess the incidence and risk factors for thromboembolic events (TEE) among patients developing cGVHD after allogeneic HCT and examine the impact of TEE on clinical outcomes after cGVHD.

Patient Eligibility Population:

Adults ≥18, undergoing first allogeneic HCT for acute leukemia (AML and ALL) in remission from 2008-2019, regardless of donor source, graft source, conditioning regimen or GVHD prophylaxis.

Data Requirements:

- Patient-related:
  - Age at HCT
  - Gender
  - ABO group
  - Karnofsky performance status at HCT and cGVHD onset
  - Hematopoietic Cell Transplantation- comorbidity index at HCT
  - BMI
  - Past medical history from HCT-CI score/ baseline form: smoking history, diabetes mellitus (DM), hypertension (HTN), cerebrovascular accident (CVA), congestive heart failure (CHF), coronary artery disease (CAD).

- Donor-related:
  - Donor source
  - Graft source
  - ABO group
  - Degree of HLA-match
  - Graft source (BM and PBSC)
  - Conditioning intensity
  - GVHD prophylaxis

- Disease-related:
  - Time from diagnosis to HCT
  - Time from HCT to cGVHD
  - Disease and disease risk index (DRI: low risk, intermediate risk, high/very risk)
  - Relapse: yes/no and date (if before or after cGVHD and TEE)
  - cGVHD NIH severity at onset
  - cGVHD organ involvement
  - cGVHD therapy: systemic treatment: yes/ no
  - cGVHD therapy: amongst those needing systemic therapy: duration of therapy

- TEE Outcome:
  - Vascular TEE: Deep vein thrombosis (DVT) and pulmonary embolus (PE)- date of diagnosis and if catheter related yes/no
  - Coronary artery disease: yes/no, date of diagnosis
  - Myocardial infarction/Unstable angina: yes/no, date of diagnosis
  - Neurologic- Stroke: yes/no, date of diagnosis

Study Design:

Retrospective observational study of patients reported to CIBMTR. Cumulative incidence of TEE after allogeneic HCT will be compared between those with and without GVHD (groups for comparison: no GVHD, grade 2-4 acute GVHD, acute GVHD + chronic GVHD, only chronic GVHD)
Risk factors for TEE will be evaluated considering patient, disease and transplant factors (including GVHD groups)
Amongst patients with chronic GVHD, cumulative incidence of TEE will be evaluated. Risk factors for TEE will be evaluated considering patient, disease and transplant factors and chronic GVHD specific factors (CGVHD onset, severity, organ involvement, platelet count at onset, and duration of systemic therapy).
Impact of TEE on NRM after TCT will be evaluated
Causes of death will be compared between those with TEE and no TEE

References:

1. MacDonald KPA, Blazar BR, Hill GR. Cytokine mediators of chronic graft-versus-host disease. *J. Clin. Invest.* 2017;127(7):2452–2463.

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13. Kekre N, Kim HT, Ho VT, et al. Venous thromboembolism is associated with graft-versus-host disease and increased non-relapse mortality after allogeneic hematopoietic stem cell transplantation. *Haematologica*. 2017;102(7):1185–1191.

Conflicts of Interest:

☐ Yes

X No

Proposal submission: E-mail your observational study proposal to: proposals.cibmtr@mcw.edu

Table 1. Characteristics of adult patients receiving first alloHCT for AML/ALL in CR in 2008-2019, CRF track

Characteristic	N (%)
No. of patients	9650
No. of centers	247
Age at HCT, years	
Median (range)	51 (18-81)
18-29	1603 (17)
30-39	1300 (13)
40-49	1769 (18)
50-59	2405 (25)
60-69	2168 (22)
≥ 70	405 (4)
Recipient sex	
Male	5216 (54)
Female	4434 (46)
Primary disease for HCT	
AML	7141 (74)
ALL	2509 (26)
Donor type	
HLA-identical sibling	2357 (24)
Other related	1585 (16)
Well-matched unrelated (8/8)	3153 (33)
Partially-matched unrelated (7/8)	737 (8)
Mis-matched unrelated (<= 6/8)	51 (1)
Multi-donor	8 (<1)
Unrelated (matching TBD)	51 (1)
Cord blood	1708 (18)
Donor/recipient ABO match	
Both type O	2468 (26)
Other matched	2363 (24)
Minor mismatch	1934 (20)
Major mismatch	1746 (18)
Bidirectional	521 (5)
Missing	618 (6)
Graft type	

Characteristic	N (%)
Bone marrow	1450 (15)
Peripheral blood	6492 (67)
Cord blood	1708 (18)
Conditioning intensity	
MAC	5724 (59)
RIC	2260 (23)
NMA	1329 (14)
TBD	139 (1)
Missing	198 (2)
GVHD prophylaxis	
Ex-vivo T-cell depletion	87 (1)
CD34 selection	255 (3)
Post-CY + other(s)	1636 (17)
Post-CY alone	60 (1)
TAC + MMF +- other(s) (except post-CY)	1293 (13)
TAC + MTX +- other(s) (except MMF, post-CY)	3381 (35)
TAC + other(s) (except MMF, MTX, post-CY)	463 (5)
TAC alone	178 (2)
CSA + MMF +- other(s) (except post-CY)	1132 (12)
CSA + MTX +- other(s) (except MMF, post-CY)	738 (8)
CSA + other(s) (except MMF, MTX, post-CY)	47 (<1)
CSA alone	71 (1)
Other(s)	92 (1)
Missing	217 (2)
In-vivo T-cell depletion (ATG/alemtuzumab)	
No	7344 (76)
Yes	2306 (24)
Year of HCT	
2008	1069 (11)
2009	917 (10)
2010	705 (7)
2011	410 (4)
2012	377 (4)
2013	854 (9)
2014	1058 (11)
2015	1033 (11)

Characteristic	N (%)
2016	1002 (10)
2017	790 (8)
2018	754 (8)
2019	681 (7)
Median follow-up of survivors (range), months	60 (0-157)
Post-transplant variables	
Chronic GVHD	
No	5409 (56)
Yes	4214 (44)
Missing	27 (<1)
Thromboembolic event	
No	8820 (91)
Yes	697 (7)
Coronary artery disease	29 (<1)
Deep vein thrombosis	257 (3)
Myocardial infarction	119 (1)
Stroke	257 (3)
More than one type	35 (<1)
Missing	133 (1)

Chronic GVHD	Thromboembolic event			
Frequency Row Pct Col Pct	No	Yes	Missing	Total
Missing	13 48.15 0.15	1 3.70 0.14	13 48.15 9.77	27
No	5006 92.55 56.76	345 6.38 49.50	58 1.07 43.61	5409
Yes	3801 90.20 43.10	351 8.33 50.36	62 1.47 46.62	4214
Total	8820	697	133	9650

aGVHD II-IV	Thromboembolic event			
Frequency Row Pct Col Pct	No	Yes	Missing	Total
Missing	80 38.10 0.91	6 2.86 0.86	124 59.05 93.23	210
No	5368 93.83 60.86	349 6.10 50.07	4 0.07 3.01	5721
Yes	3372 90.67 38.23	342 9.20 49.07	5 0.13 3.76	3719
Total	8820	697	133	9650

Chronic GVHD	Thromboembolic event					
Frequency Row Pct Col Pct	Coronary artery disease	Deep vein thrombosis	Myocardial infarction	Stroke	More than one type	Total
Missing	0 0.00 0.00	0 0.00 0.00	1 100.00 0.84	0 0.00 0.00	0 0.00 0.00	1
No	11 3.19 37.93	117 33.91 45.53	60 17.39 50.42	143 41.45 55.64	14 4.06 40.00	345
Yes	18 5.13 62.07	140 39.89 54.47	58 16.52 48.74	114 32.48 44.36	21 5.98 60.00	351
Total	29	257	119	257	35	697

aGVHD II-IV	Thromboembolic event					
Frequency Row Pct Col Pct	Coronary artery disease	Deep vein thrombosis	Myocardial infarction	Stroke	More than one type	Total
Missing	0 0.00 0.00	2 33.33 0.78	3 50.00 2.52	1 16.67 0.39	0 0.00 0.00	6
No	21 6.02 72.41	123 35.24 47.86	70 20.06 58.82	119 34.10 46.30	16 4.58 45.71	349
Yes	8 2.34 27.59	132 38.60 51.36	46 13.45 38.66	137 40.06 53.31	19 5.56 54.29	342
Total	29	257	119	257	35	697

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

Does race/ethnicity or socio-economic status impact the outcomes of patients with acute GVHD?

Q2. Key Words

Acute GVHD, hematopoietic stem cell transplant, socioeconomic status, race/ethnicity

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Nahid Rashid, MD
Email address:	narash@uw.edu
Institution name:	University of Washington
Academic rank:	hematology/oncology fellow

Q4. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- Yes

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Nosha Farhadfar, MD
Email address:	nosha.fardhadfar@medicine.ufl.edu
Institution name:	University of Florida
Academic rank:	Assistant Professor

Q7. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q8. Do you identify as an underrepresented/minority?

- No

Q9. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

Nahid Rashid

Q10. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: *A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:* *https://www.cibmtr.org/Studies/Observational/StudyManagement/p*

Q12. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

I am not currently involved with any projects with the CIBMTR.

Q13. PROPOSED WORKING COMMITTEE:

- Graft vs Host Disease

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- No

Q15. RESEARCH QUESTION:

Does race/ethnicity or socio-economic status (SES) predict outcomes of patients who develop grade II-IV acute graft versus host disease (aGVHD)?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that racial/ethnic minority status and lower SES will be associated with worse short-term and long-term outcomes in patients with grade II-IV aGVHD after allogeneic hematopoietic stem cell transplant (allo-HCT) compared to non-Hispanic White and higher SES patients.

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

Primary objective

o To characterize long-term outcomes including survival, non-relapse mortality and chronic GVHD following onset of aGVHD in patients based on differing races/ethnicities and SES.

Secondary objective

o To characterize short-term outcomes following the onset of aGVHD in patients based on differing races/ethnicities and SES. The short-term outcomes we will evaluate will be:

Maximum grade of aGVHD

Steroid refractoriness

Days alive outside of the hospital during the first 100 days of transplant

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

This project will expand our understanding about what factors influence outcomes of patients who have developed aGVHD. Although many factors are associated with increased risk of developing aGVHD, a deeper understanding of which characteristics lead to steroid refractoriness, increased morbidity/mortality, late effects, and cGVHD following the development of aGVHD is lacking. This knowledge could help providers identify which patients are at higher risk of worse outcomes following aGVHD. Patients known to have worse outcomes may benefit from different therapeutic approaches or increased supportive care.

Q19. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

Acute GVHD remains a major cause of morbidity/mortality following hematopoietic cell transplantation (HCT) [1]. Race/ethnicity and socio-economic status (SES) have been associated with outcomes in various diseases, including survival in hematologic malignancies and after HCT [2-6]. Genetic differences among race/ethnicities could lead to varying immune responses. Studies have shown that certain race/ethnicities have a genetic predisposition associated with increased rates of inflammatory diseases[7,8]. Social factors such as nutrition, stress and environment may also have a profound impact on development of aGVHD posttransplant. Previous studies have shown increased levels of inflammatory markers in patients of lower SES [9]. Whether outcomes following development of aGVHD are different based on race/ethnicity and SES has not been extensively studied.

One study in Brazil with 201 patients studied the association of SES with the development of aGVHD. The authors categorized patients into 5 groups based on wealth. The patients placed in the lowest 2 wealth groups had significantly increased rates of both aGVHD and cGVHD [10]. Another study in Britain including 251 patients examined the role of race/ethnicity in the development of GVHD. Non-Caucasian patients had a significantly higher risk of developing aGVHD [11] possibly because graft sources may be different as it is more difficult to find an HLA-matched donor in non-Caucasian patients [12].

While race/ethnicity and SES were seen to be associated with the diagnosis of GVHD in the studies mentioned above [10,11], less is known about how these factors may influence outcomes once GVHD is established. By starting the clock at the time of aGVHD diagnosis, we can best determine whether race/ethnicity and SES are associated with successful treatment, survival and long-term outcomes.

A larger study using a multi-center database can obtain a more in-depth analysis and characterization of the role of race/ethnicity and SES on aGVHD outcomes.

If we identify differences in outcomes after development of aGVHD in certain race/ethnicities or SES, further studies could be pursued to evaluate what underlying factors lead to these differences so they can be mitigated. Increasing our knowledge about any factors that lead to worse outcomes with aGVHD could guide both therapeutic approaches and supportive care decisions during the peri and posttransplant period.

Q19a. SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF)

N/A

Q20. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

Patient Inclusion Criteria
• First allogeneic HCT recipients
• Diagnosis of grade II-IV aGVHD
• Diagnosis of Acute Myelogenous Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), or Myelodysplastic Syndrome (MDS) who received first allogeneic HCT between 2008-2019
• Transplant in a US center
• All graft and donor sources- Donor and graft source can be driven by race/ethnicity.
Exclusion Criteria
• Missing racial/ethnicity or outcome data will be excluded from analysis.
• Patients who received grafts from multiple donors

Q21. Does this study include pediatric patients?

- Yes

Q22. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

- Patient/donor characteristics
  - Patient race/ethnicity
  - Patient zip code
  - Median annual household income based on zip code
  - Patient and donor age at time of transplantation
  - Patient and donor sex
  - Patient and donor CMV status
  - Patient Karnofsky performance status
  - Year of transplant
  - Disease at transplant
  - Disease risk index (DRI)
  - HCT-CI
  - HLA- matching status
- Transplant characteristics
  - Donor type
  - Graft source
  - Conditioning intensity
  - GVHD prophylaxis
  - In vivo T cell depletion
  - Acute GVHD grade – II, III, IV
  - Organ stages - skin, liver, GI – 1, 2, 3, 4
  - Agents used to treat acute GVHD (corticosteroids +/- cyclosporine or tacrolimus; mycophenolate mofetil or sirolimus; all other names agents)
- Longer-term Outcomes in patients diagnosed with aGVHD II-IV
  - Chronic GVHD – requiring immunosuppressive treatment or moderate-severe
  - Time from acute GVHD diagnosis to death (survival)
  - Time from acute GVHD diagnosis to relapse or death (disease-free survival)
  - Non-relapse mortality

Q23. **PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.**

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

N/A

Q24. **SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.**

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

N/A

Q25. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

N/A

Q26. REFERENCES:

1. Zeiser R, Blazar BR. Acute graft-versus-host disease: Biologic process, prevention, and therapy. N Engl J Med. 2017;377:2167-2179.
2. Patel MI, Ma Y, Mitchell BS, Rhoads KF. Understanding disparities in leukemia: a national study. Cancer Causes Control. 2012;23(11):1831-1837.
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5. Baker KS, Davies SM, Majhail NS, et al. . Race and socioeconomic status influence outcomes of unrelated donor hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2009;15(12):1543-1554.
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9. Muscatell K, Brosso S, Humphreys K. Socioeconomic status and inflammation: a meta-analysis. Mol Psychiatry. 2020; 25(9):2189-2199
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Q27. **CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:**

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- No, I do not have any conflicts of interest pertinent to this proposal

Q27a. **If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.**

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Table 1. Characteristics of patients receiving first alloHCT for AML, ALL, MDS in the United States in 2008-2019, who developed acute GVHD, CRF track

Characteristic	Non-Hispanic white	Non-Hispanic black	Hispanic	Asian	Other[a]	Total
No. of patients	5343	548	706	318	123	7038
No. of centers	157	113	117	84	55	165
Age at HCT, years						
Median (range)	58 (0-83)	42 (1-77)	31 (1-74)	45 (1-74)	33 (0-70)	55 (0-83)
<10	199 (4)	52 (9)	120 (17)	23 (7)	24 (20)	418 (6)
10-17	167 (3)	45 (8)	92 (13)	13 (4)	19 (15)	336 (5)
18-29	375 (7)	76 (14)	136 (19)	48 (15)	17 (14)	652 (9)
30-39	376 (7)	79 (14)	88 (12)	49 (15)	12 (10)	604 (9)
40-49	644 (12)	91 (17)	82 (12)	49 (15)	15 (12)	881 (13)
50-59	1258 (24)	106 (19)	87 (12)	66 (21)	16 (13)	1533 (22)
60-69	1840 (34)	79 (14)	90 (13)	54 (17)	20 (16)	2083 (30)
≥70	484 (9)	20 (4)	11 (2)	16 (5)	0 (0)	531 (8)
Recipient sex						
Male	3095 (58)	272 (50)	374 (53)	170 (53)	67 (54)	3978 (57)
Female	2248 (42)	276 (50)	332 (47)	148 (47)	56 (46)	3060 (43)
Marital status						
Single	572 (11)	154 (28)	141 (20)	49 (15)	21 (17)	937 (13)
Married	3619 (68)	224 (41)	273 (39)	185 (58)	47 (38)	4348 (62)
Separated	54 (1)	8 (1)	11 (2)	1 (<1)	1 (1)	75 (1)
Divorced	440 (8)	40 (7)	40 (6)	14 (4)	9 (7)	543 (8)
Widowed	144 (3)	8 (1)	12 (2)	6 (2)	1 (1)	171 (2)
Missing	514 (10)	114 (21)	229 (32)	63 (20)	44 (36)	964 (14)
Current or most recent work status prior to illness						
Full time	1352 (25)	157 (29)	179 (25)	80 (25)	25 (20)	1793 (25)
Part time	252 (5)	17 (3)	25 (4)	11 (3)	8 (7)	313 (4)
Unemployed	555 (10)	73 (13)	153 (22)	49 (15)	26 (21)	856 (12)
Medical disability	961 (18)	128 (23)	98 (14)	53 (17)	22 (18)	1262 (18)
Retired	1552 (29)	62 (11)	57 (8)	43 (14)	12 (10)	1726 (25)
Missing	671 (13)	111 (20)	194 (27)	82 (26)	30 (24)	1088 (15)
Health insurance type						
No insurance	30 (1)	5 (1)	18 (3)	8 (3)	2 (2)	63 (1)
Disability insurance +/- others	110 (2)	17 (3)	6 (1)	7 (2)	2 (2)	142 (2)
Private health insurance +/- others	2998 (56)	250 (46)	279 (40)	179 (56)	61 (50)	3767 (54)
Medicaid +/-others	627 (12)	172 (31)	301 (43)	61 (19)	46 (37)	1207 (17)
Medicare +/-others	1368 (26)	68 (12)	62 (9)	35 (11)	9 (7)	1542 (22)
Other	156 (3)	26 (5)	29 (4)	14 (4)	2 (2)	227 (3)
Missing	54 (1)	10 (2)	11 (2)	14 (4)	1 (1)	90 (1)

Characteristic	Non-Hispanic white	Non-Hispanic black	Hispanic	Asian	Other[a]	Total
Highest level of education completed						
No primary	102 (2)	23 (4)	49 (7)	10 (3)	11 (9)	195 (3)
Less than primary	61 (1)	10 (2)	41 (6)	7 (2)	11 (9)	130 (2)
Primary	67 (1)	28 (5)	54 (8)	13 (4)	4 (3)	166 (2)
Lower secondary	157 (3)	35 (6)	70 (10)	13 (4)	17 (14)	292 (4)
Upper secondary	1257 (24)	163 (30)	189 (27)	53 (17)	31 (25)	1693 (24)
Post-secondary (vocational)	428 (8)	45 (8)	40 (6)	17 (5)	8 (7)	538 (8)
Tertiary (4-year degree)	1292 (24)	79 (14)	70 (10)	80 (25)	11 (9)	1532 (22)
Tertiary (2-year degree)	289 (5)	23 (4)	26 (4)	11 (3)	6 (5)	355 (5)
Advanced research degree	225 (4)	15 (3)	14 (2)	32 (10)	2 (2)	288 (4)
Missing	1465 (27)	127 (23)	153 (22)	82 (26)	22 (18)	1849 (26)
ZIP code available						
No	25 (<1)	2 (<1)	11 (2)	4 (1)	2 (2)	44 (1)
Yes	5318 (100)	546 (100)	695 (98)	314 (99)	121 (98)	6994 (99)
Primary disease for HCT						
AML	2588 (48)	310 (57)	291 (41)	181 (57)	57 (46)	3427 (49)
ALL	675 (13)	139 (25)	310 (44)	81 (25)	45 (37)	1250 (18)
MDS	2080 (39)	99 (18)	105 (15)	56 (18)	21 (17)	2361 (34)
Donor type						
HLA-identical sibling	1018 (19)	68 (12)	128 (18)	61 (19)	13 (11)	1288 (18)
Haploidentical	468 (9)	119 (22)	104 (15)	28 (9)	14 (11)	733 (10)
Other related	45 (1)	4 (1)	4 (1)	4 (1)	1 (1)	58 (1)
Well-matched unrelated (8/8)	2585 (48)	86 (16)	135 (19)	90 (28)	29 (24)	2925 (42)
Partially-matched unrelated (7/8)	480 (9)	79 (14)	83 (12)	28 (9)	16 (13)	686 (10)
Mis-matched unrelated (<= 6/8)	19 (<1)	9 (2)	8 (1)	0 (0)	3 (2)	39 (1)
Unrelated (matching TBD)	8 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	9 (<1)
Cord blood	720 (13)	183 (33)	244 (35)	106 (33)	47 (38)	1300 (18)
Graft type						
Bone marrow	782 (15)	92 (17)	103 (15)	43 (14)	25 (20)	1045 (15)
Peripheral blood	3841 (72)	273 (50)	359 (51)	169 (53)	51 (41)	4693 (67)
Cord blood	720 (13)	183 (33)	244 (35)	106 (33)	47 (38)	1300 (18)
Conditioning intensity						
MAC	2911 (54)	375 (68)	532 (75)	203 (64)	90 (73)	4111 (58)
RIC	1721 (32)	106 (19)	108 (15)	65 (20)	19 (15)	2019 (29)
NMA	590 (11)	53 (10)	52 (7)	36 (11)	10 (8)	741 (11)
TBD	103 (2)	11 (2)	11 (2)	10 (3)	3 (2)	138 (2)
Missing	18 (<1)	3 (1)	3 (<1)	4 (1)	1 (1)	29 (<1)
GVHD prophylaxis						

Characteristic	Non-Hispanic white	Non-Hispanic black	Hispanic	Asian	Other[a]	Total
Ex-vivo T-cell depletion	39 (1)	9 (2)	8 (1)	3 (1)	2 (2)	61 (1)
CD34 selection	79 (1)	15 (3)	9 (1)	5 (2)	0 (0)	108 (2)
Post-CY + other(s)	583 (11)	130 (24)	106 (15)	38 (12)	16 (13)	873 (12)
Post-CY alone	27 (1)	1 (<1)	1 (<1)	0 (0)	0 (0)	29 (<1)
TAC + MMF +- other(s) (except post-CY)	956 (18)	116 (21)	99 (14)	48 (15)	17 (14)	1236 (18)
TAC + MTX +- other(s) (except MMF, post-CY)	2378 (45)	146 (27)	226 (32)	104 (33)	44 (36)	2898 (41)
TAC + other(s) (except MMF, MTX, post-CY)	285 (5)	14 (3)	43 (6)	17 (5)	3 (2)	362 (5)
TAC alone	74 (1)	6 (1)	7 (1)	3 (1)	3 (2)	93 (1)
CSA + MMF +- other(s) (except post-CY)	625 (12)	84 (15)	160 (23)	84 (26)	34 (28)	987 (14)
CSA + MTX +- other(s) (except MMF, post-CY)	187 (3)	12 (2)	24 (3)	7 (2)	2 (2)	232 (3)
CSA + other(s) (except MMF, MTX, post-CY)	28 (1)	10 (2)	16 (2)	1 (<1)	0 (0)	55 (1)
CSA alone	20 (<1)	1 (<1)	5 (1)	1 (<1)	1 (1)	28 (<1)
Other(s)	52 (1)	1 (<1)	2 (<1)	4 (1)	0 (0)	59 (1)
Missing	10 (<1)	3 (1)	0 (0)	3 (1)	1 (1)	17 (<1)
In-vivo T-cell depletion (ATG/alemtuzumab)						
No	4041 (76)	417 (76)	545 (77)	272 (86)	99 (80)	5374 (76)
Yes	1299 (24)	131 (24)	161 (23)	46 (14)	24 (20)	1661 (24)
Missing	3 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)
Year of HCT						
2008	534 (10)	45 (8)	85 (12)	18 (6)	18 (15)	700 (10)
2009	548 (10)	31 (6)	78 (11)	26 (8)	13 (11)	696 (10)
2010	393 (7)	35 (6)	66 (9)	22 (7)	9 (7)	525 (7)
2011	276 (5)	23 (4)	46 (7)	15 (5)	3 (2)	363 (5)
2012	278 (5)	21 (4)	44 (6)	10 (3)	4 (3)	357 (5)
2013	529 (10)	40 (7)	61 (9)	30 (9)	16 (13)	676 (10)
2014	607 (11)	61 (11)	67 (9)	23 (7)	8 (7)	766 (11)
2015	598 (11)	76 (14)	55 (8)	41 (13)	12 (10)	782 (11)
2016	529 (10)	60 (11)	61 (9)	37 (12)	12 (10)	699 (10)
2017	392 (7)	44 (8)	61 (9)	29 (9)	8 (7)	534 (8)
2018	375 (7)	57 (10)	47 (7)	41 (13)	10 (8)	530 (8)
2019	284 (5)	55 (10)	35 (5)	26 (8)	10 (8)	410 (6)
Median follow-up of survivors (range), months	70 (3-157)	49 (6-144)	62 (3-146)	53 (7-141)	60 (9-144)	67 (3-157)

[a] Includes Native Hawaiian/Pacific Islander (N=23), American Indian/Alaska Native (N=41), more than one race (N=77)