Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR REGIMEN-RELATED TOXICITY AND SUPPORTIVE CARE
Salt Lake City, UT
Sunday April 24, 2022, 6:45 AM – 8:15 AM

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1. **Introduction**
   a. Minutes from February 2021 TCT meeting (Attachment 1)

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

3. **Presentations, published or submitted papers**
   a. **RT17-01** Farhadfar N, Dias A, Wang T, Fretham C, Chhabra S, Murthy HS, Broglie L, D'Souza A, Gadalla SM, Gale RP, Hashmi S, Al-Homsi AS, Hildebrandt GC, Hematti P, Rizzieri D, Chee L, Lazarus HM, Bredeson C, Jaimes EA, Beitinjaneh A, Bashey A, Prestidge T, Krem MM, Marks DI, Benoit S, Yared JA, Nishihori T, Olsson RF, Freytes CO, Stadtmauer E, Savani BN, Sorror ML, Ganguly S, Wingard JR, Pasquini M. Impact of pretransplantation renal dysfunction on outcomes after allogeneic hematopoietic cell transplantation. ***Transplantation and Cellular Therapy. 2021 May 1; 27(5):410-422. doi:10.1016/j.jtct.2021.02.030. Epub 2021 Feb 26. PMCID:PMC8168834.***
   b. **RT18-02** Abou-Ismail MY, Fraser R, Allbee-Johnson M, Metheny III L, Ravi G, Ahn KW, Bhatt NS, Lazarus HM, de Lima M, El Jurdy N, Hematti P, Beitinjaneh AM, Nishihori T, Badawy SM, Sharma A, Pasquini MC, Savani BN, Sorror ML, Stadtmauer E, Chhabra S. Does recipient body mass index inform donor selection for allogeneic haematopoietic cell transplantation? ***British Journal of Haematology. doi:10.1111/bjh.18108. Epub 2022 Mar 14.***

c. **RT18-03** Patel SS, Ahn KW, Khanal M, Bupp C, Allbee-Johnson M, Majhail NS, Hamilton BK, Rotz SJ, Hashem H, Beitinjaneh A, Lazarus HM, Krem MM, Prestidge T, Bhatt NS, Sharma A, Gadalla SM, Murthy HS, Broglie L, Nishihori T, Freytes CO, Hildebrandt GC, Gergis U, Seo S, Wirk B, Pasquini MC, Savani BN, Sorror ML, Stadtmauer EA, Chhabra S. Non-infectious pulmonary toxicity after allogeneic hematopoietic cell transplantation. ***Transplantation and Cellular Therapy. doi:10.1016/j.jtct.2022.03.015. Epub 2022 Mar 18.***

d. **RT18-01a** Expanded Definitions in the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) Better Classifies Comorbidity in Children and Young Adults with Non-Malignant Diseases. (L Broglie/B Friend/G Schiller/M Thakar /M Sorror) ***Submitted.***

e. **RT18-01b** Adapting the HCT-CI Applicability for Children, Adolescents, and Young Adults with Hematologic Malignancies Undergoing Allogeneic Stem Cell Transplantation. (B Friend/L Broglie/G Schiller/M Thakar/M Sorror) ***Submitted.***

f. **RT18-S1** Differential use of the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) among adult and pediatric HCT physicians. (L Broglie/B Friend) ***Submitted****.*

4. Studies in progress (Attachment 3)

a. **RT19-01** Analysis of comorbidity-associated toxicity at a regimen-based level (R Shouval/ B Savani/ A Nagler) **Analysis**

b. **RT19-02** Hemorrhagic cystitis as a complication of hematopoietic stem cell transplantation in the post-transplant cyclophosphamide graft-versus-host disease prophylaxis era compared to other allogeneic stem cell transplants (K Adekola/ N Ali/ O Frankfurt/ L Metheny/ J Moreira/ M de Lima) **Datafile prep**

c. **RT20-01** Toxicities of older adults receiving allogeneic hematopoietic cell transplant compared to younger patients. (R Jayani/H Murff) **Protocol development**

5. Proposals

Future/proposed studies

a. **PROP 2109-09/ PROP 2110-02/ PROP 2110-257** Validating the HCT-CI score and exploring additional prognostic factors in patients undergoing second allogeneic transplants (S Ghanem/P Kebriaei/S Kharbanda/C Dvorak/A Alarcon Tomas/R Tamari) (Attachment 4)

b. **PROP 2109-25** Correlation of melphalan dose with regimen-related toxicity in multiple myeloma patients undergoing autologous transplant (M Krem/C Wagner) (Attachment 5)

c. **PROP 2110-23** Allogeneic hematopoietic cell transplantation (HCT) in patients 75 years and older-utilization and outcomes (A Artz/R Nakamura) (Attachment 6)

d. **PROP 2110-51** Trends of major organ injuries amongst children and young adults following allogeneic hematopoietic cell transplantation for hematologic malignancies (H Rangarajan/P Satwani) (Attachment 7)

e. **PROP 2110-80/ PROP 2110-244/ PROP 2110-315** Incidence, risk factors and outcomes of acute cardiac complications after post-transplant cyclophosphamide based GVHD prophylaxis; A Retrospective Analysis from CIBMTR Database (K Poonsombudlert/C Strouse/H Rangarajan/P Satwani/D Modi) (Attachment 8)

Dropped proposed studies

a. **PROP 2108-05** Evaluating the impact of post-transplant cachexia on allogeneic hematopoietic stem cell transplantation outcomes (A Mishra/J Pidala) *Dropped due to feasibility concerns*

b. **PROP 2109-05** Impact Of Non-Infectious Encephalopathy (PRES) On Outcomes Post Allogeneic Hematopoietic Stem Cell Transplant In Children. (H Rangarajan/P Satwani) *Dropped due to small sample size*

c. **PROP 2110-52** Rates and Severity of Idiopathic Pneumonia Syndrome During the Novel Coronavirus Pandemic (J Reagan/A Pelcovits) *Dropped due to overlap with study RT18-03*
d. **PROP 2110-199** Impact of Pegaspargase Therapy on Risk of Hepatic Veno-occlusive Disease After Allogeneic Hematopoietic Cell Transplantation (D Barth/S Patel) *Dropped due to small sample size*
e. **PROP 2110-239** Incidence and risk factors of engraftment syndrome in autologous hematopoietic cell transplant recipients and its impact on outcomes (M Bilal Abid/S Chhabra) *Dropped due to low scientific impact*
f. **PROP 2110-249** Quantifying Risk and Survival Benefit in Children Undergoing Liver Transplant for Hepatic Veno-occlusive Disease after Hematopoietic Stem Cell Transplantation (E King) *Dropped due to small sample size*
g. **PROP 2110-283** Veno-oclussive disease in Hispanic patients with B-cell acute lymphoblastic leukemia (ALL) undertaking allogeneic stem cell transplant compared to non-Hispanic patients in Era of novel agents. (A Ladha/G Yaghmour) *Dropped due to overlap with study SC17-10*

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?

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

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	44543	15903	8657
Source of data			
CRF	24072 (54)	6924 (44)	4451 (51)
TED	20471 (46)	8979 (56)	4206 (49)
Number of centers	258	232	351
Disease at transplant			
AML	15294 (34)	5896 (37)	2918 (34)
ALL	6535 (15)	2123 (13)	1370 (16)
Other leukemia	1408 (3)	385 (2)	249 (3)
CML	3509 (8)	1045 (7)	695 (8)
MDS	6346 (14)	2568 (16)	1072 (12)
Other acute leukemia	462 (1)	185 (1)	106 (1)
NHL	4032 (9)	1194 (8)	710 (8)
Hodgkin Lymphoma	917 (2)	220 (1)	160 (2)
Plasma Cell Disorders, MM	892 (2)	270 (2)	159 (2)
Other malignancies	59 (<1)	13 (<1)	18 (<1)
Breast cancer	7 (<1)	3 (<1)	1 (<1)
SAA	1428 (3)	485 (3)	344 (4)
Inherited abnormalities erythrocyte diff fxn	727 (2)	251 (2)	157 (2)
Inherited bone marrow failure syndromes	9 (<1)	9 (<1)	11 (<1)
Hemoglobinopathies	8 (<1)	6 (<1)	4 (<1)
Paroxysmal nocturnal hemoglobinuria	1 (<1)	4 (<1)	0
SCIDs	780 (2)	280 (2)	253 (3)
Inherited abnormalities of platelets	40 (<1)	14 (<1)	11 (<1)
Inherited disorders of metabolism	292 (1)	79 (<1)	95 (1)
Histiocytic disorders	376 (1)	107 (1)	94 (1)
Autoimmune disorders	22 (<1)	12 (<1)	5 (<1)
Other	51 (<1)	21 (<1)	19 (<1)
MPN	1347 (3)	733 (5)	204 (2)
Disease missing	1 (N/A)	0 (N/A)	2 (N/A)
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)
MDS Disease status at transplant			

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Early	1380 (22)	488 (19)	256 (24)
Advanced	4003 (63)	1854 (72)	592 (55)
Missing	963 (15)	226 (9)	224 (21)
NHL Disease status at transplant			
CR1	556 (14)	205 (17)	90 (13)
CR2	741 (18)	223 (19)	117 (17)
CR3+	345 (9)	102 (9)	66 (9)
PR	439 (11)	110 (9)	76 (11)
Advanced	1866 (47)	531 (45)	346 (49)
Missing	65 (2)	15 (1)	12 (2)
Recipient age at transplant			
0-9 years	3829 (9)	1110 (7)	1068 (12)
10-19 years	3937 (9)	1138 (7)	978 (11)
20-29 years	4617 (10)	1454 (9)	981 (11)
30-39 years	5099 (11)	1604 (10)	1015 (12)
40-49 years	6813 (15)	2184 (14)	1294 (15)
50-59 years	9175 (21)	3138 (20)	1573 (18)
60-69 years	9168 (21)	4145 (26)	1465 (17)
70+ years	1905 (4)	1130 (7)	283 (3)
Median (Range)	47 (0-84)	52 (0-82)	43 (0-81)
Recipient race/ethnicity			
Caucasian, non-Hispanic	36965 (83)	13172 (83)	6184 (71)
African-American, non-Hispanic	2018 (5)	651 (4)	388 (4)
Asian, non-Hispanic	1027 (2)	498 (3)	331 (4)
Pacific islander, non-Hispanic	55 (<1)	25 (<1)	23 (<1)
Native American, non-Hispanic	168 (<1)	66 (<1)	33 (<1)
Hispanic	2662 (6)	861 (5)	468 (5)
Missing	1648 (4)	630 (4)	1230 (14)
Recipient sex			
Male	25968 (58)	9313 (59)	5132 (59)
Female	18575 (42)	6590 (41)	3525 (41)
Karnofsky score			
10-80	15260 (34)	5968 (38)	2755 (32)
90-100	27634 (62)	9412 (59)	5408 (62)
Missing	1649 (4)	523 (3)	494 (6)
HLA-A B DRB1 groups - low resolution			
<=3/6	28 (<1)	37 (<1)	3 (<1)
4/6	235 (1)	102 (1)	45 (1)
5/6	6059 (14)	1819 (13)	1217 (15)
6/6	37443 (86)	12508 (86)	6817 (84)
Unknown	778 (N/A)	1437 (N/A)	575 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	884 (2)	102 (1)	45 (1)
6/8	1724 (4)	139 (1)	152 (3)
7/8	8420 (20)	1863 (16)	1254 (22)
8/8	31783 (74)	9524 (82)	4335 (75)
Unknown	1732 (N/A)	4275 (N/A)	2871 (N/A)
HLA-DPB1 Match			
Double allele mismatch	10933 (29)	1275 (23)	590 (26)
Single allele mismatch	20128 (54)	2834 (51)	1199 (52)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Full allele matched	6179 (17)	1427 (26)	512 (22)
Unknown	7303 (N/A)	10367 (N/A)	6356 (N/A)
High resolution release score			
No	9149 (21)	15838 (>99)	8450 (98)
Yes	35394 (79)	65 (<1)	207 (2)
KIR typing available			
No	30764 (69)	15880 (>99)	8609 (99)
Yes	13779 (31)	23 (<1)	48 (1)
Graft type			
Marrow	16082 (36)	4740 (30)	3436 (40)
PBSC	28404 (64)	11007 (69)	5187 (60)
BM+PBSC	11 (<1)	7 (<1)	3 (<1)
PBSC+UCB	27 (<1)	137 (1)	5 (<1)
Others	19 (<1)	12 (<1)	26 (<1)
Conditioning regimen			
Myeloablative	27651 (62)	8835 (56)	5389 (62)
RIC/Nonmyeloablative	16685 (37)	7019 (44)	3146 (36)
TBD	207 (<1)	49 (<1)	122 (1)
Donor age at donation			
To Be Determined/NA	410 (1)	1434 (9)	126 (1)
0-9 years	8 (<1)	36 (<1)	3 (<1)
10-19 years	1223 (3)	550 (3)	184 (2)
20-29 years	20165 (45)	7124 (45)	3529 (41)
30-39 years	12640 (28)	3985 (25)	2591 (30)
40-49 years	7729 (17)	2111 (13)	1682 (19)
50+ years	2368 (5)	663 (4)	542 (6)
Median (Range)	30 (0-69)	29 (0-109)	32 (0-67)
Donor/Recipient CMV serostatus			
+/+	11076 (25)	4431 (28)	2157 (25)
+/-	5279 (12)	2016 (13)	1101 (13)
-/+	14617 (33)	4780 (30)	2679 (31)
-/-	12957 (29)	4204 (26)	2327 (27)
CB - recipient +	3 (<1)	17 (<1)	0
CB - recipient -	1 (<1)	8 (<1)	0
CB - recipient CMV unknown	0	1 (<1)	0
Missing	610 (1)	446 (3)	393 (5)
GvHD Prophylaxis			
No GvHD Prophylaxis	146 (<1)	65 (<1)	45 (1)
TDEPLETION alone	100 (<1)	31 (<1)	31 (<1)
TDEPLETION +- other	1068 (2)	278 (2)	261 (3)
CD34 select alone	272 (1)	129 (1)	62 (1)
CD34 select +- other	881 (2)	628 (4)	194 (2)
Cyclophosphamide alone	785 (2)	676 (4)	226 (3)
Cyclophosphamide +- others	2016 (5)	1404 (9)	426 (5)
FK506 + MMF +- others	4990 (11)	1515 (10)	694 (8)
FK506 + MTX +- others(not MMF)	18673 (42)	6475 (41)	2380 (27)
FK506 +- others(not MMF,MTX)	2264 (5)	958 (6)	320 (4)
FK506 alone	1019 (2)	361 (2)	147 (2)
CSA + MMF +- others(not FK506)	2904 (7)	746 (5)	700 (8)
CSA + MTX +- others(not MMF,FK506)	6888 (15)	1819 (11)	2318 (27)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
CSA +- others(not FK506,MMF,MTX)	1112 (2)	333 (2)	299 (3)
CSA alone	448 (1)	121 (1)	292 (3)
Other GVHD Prophylaxis	735 (2)	250 (2)	145 (2)
Missing	242 (1)	114 (1)	117 (1)
Donor/Recipient sex match			
Male-Male	18261 (41)	6197 (39)	3395 (39)
Male-Female	11147 (25)	3783 (24)	1963 (23)
Female-Male	7474 (17)	2729 (17)	1655 (19)
Female-Female	7249 (16)	2505 (16)	1506 (17)
CB - recipient M	13 (<1)	78 (<1)	0
CB - recipient F	14 (<1)	67 (<1)	6 (<1)
Missing	385 (1)	544 (3)	132 (2)
Year of transplant			
1986-1990	383 (1)	49 (<1)	53 (1)
1991-1995	1959 (4)	460 (3)	503 (6)
1996-2000	3363 (8)	1200 (8)	823 (10)
2001-2005	5238 (12)	1036 (7)	1553 (18)
2006-2010	9426 (21)	1872 (12)	1486 (17)
2011-2015	13159 (30)	3524 (22)	1900 (22)
2016-2020	10087 (23)	6869 (43)	2066 (24)
2021	928 (2)	893 (6)	273 (3)
Follow-up among survivors, Months			
N Eval	18378	7541	3603
Median (Range)	63 (0-385)	36 (0-362)	47 (0-365)

Unrelated Cord 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

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	5894	1566	1557
Source of data			
CRF	4361 (74)	1124 (72)	947 (61)
TED	1533 (26)	442 (28)	610 (39)
Number of centers	152	138	201
Disease at transplant			
AML	2221 (38)	529 (34)	505 (32)
ALL	1222 (21)	344 (22)	347 (22)
Other leukemia	93 (2)	30 (2)	27 (2)
CML	128 (2)	35 (2)	38 (2)
MDS	523 (9)	151 (10)	119 (8)
Other acute leukemia	93 (2)	26 (2)	28 (2)
NHL	394 (7)	89 (6)	100 (6)
Hodgkin Lymphoma	97 (2)	27 (2)	27 (2)
Plasma Cell Disorders, MM	37 (1)	12 (1)	11 (1)
Other malignancies	11 (<1)	1 (<1)	1 (<1)
SAA	93 (2)	31 (2)	27 (2)
Inherited abnormalities erythrocyte diff fxn	165 (3)	50 (3)	33 (2)
Inherited bone marrow failure syndromes	2 (<1)	2 (<1)	1 (<1)
Hemoglobinopathies	1 (<1)	0	0
SCIDs	262 (4)	87 (6)	122 (8)
Inherited abnormalities of platelets	20 (<1)	5 (<1)	7 (<1)
Inherited disorders of metabolism	361 (6)	105 (7)	105 (7)
Histiocytic disorders	105 (2)	27 (2)	38 (2)
Autoimmune disorders	9 (<1)	0	2 (<1)
Other	11 (<1)	2 (<1)	5 (<1)
MPN	46 (1)	13 (1)	14 (1)
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
MDS Disease status at transplant			
Early	163 (31)	41 (27)	52 (44)
Advanced	315 (60)	95 (63)	48 (40)
Missing	45 (9)	15 (10)	19 (16)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
NHL Disease status at transplant			
CR1	60 (15)	6 (7)	18 (18)
CR2	74 (19)	20 (22)	31 (31)
CR3+	44 (11)	10 (11)	9 (9)
PR	67 (17)	12 (13)	11 (11)
Advanced	146 (37)	40 (45)	28 (28)
Missing	0	1 (1)	2 (2)
Recipient age at transplant			
0-9 years	1776 (30)	580 (37)	578 (37)
10-19 years	776 (13)	175 (11)	211 (14)
20-29 years	556 (9)	110 (7)	131 (8)
30-39 years	569 (10)	141 (9)	153 (10)
40-49 years	623 (11)	154 (10)	144 (9)
50-59 years	803 (14)	190 (12)	184 (12)
60-69 years	683 (12)	188 (12)	145 (9)
70+ years	108 (2)	28 (2)	11 (1)
Median (Range)	27 (0-83)	22 (0-76)	19 (0-78)
Recipient race/ethnicity			
Caucasian, non-Hispanic	3254 (55)	917 (59)	834 (54)
African-American, non-Hispanic	841 (14)	204 (13)	176 (11)
Asian, non-Hispanic	340 (6)	107 (7)	105 (7)
Pacific islander, non-Hispanic	30 (1)	3 (<1)	16 (1)
Native American, non-Hispanic	42 (1)	9 (1)	18 (1)
Hispanic	1054 (18)	229 (15)	209 (13)
Missing	333 (6)	97 (6)	199 (13)
Recipient sex			
Male	3249 (55)	892 (57)	879 (56)
Female	2645 (45)	674 (43)	678 (44)
Karnofsky score			
10-80	1563 (27)	400 (26)	391 (25)
90-100	4149 (70)	1075 (69)	1056 (68)
Missing	182 (3)	91 (6)	110 (7)
HLA-A B DRB1 groups - low resolution			
<=3/6	97 (2)	38 (3)	12 (1)
4/6	2341 (41)	537 (40)	555 (39)
5/6	2550 (45)	566 (42)	647 (46)
6/6	718 (13)	191 (14)	202 (14)
Unknown	188 (N/A)	234 (N/A)	141 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	2777 (55)	537 (56)	609 (54)
6/8	1193 (24)	228 (24)	279 (25)
7/8	701 (14)	129 (13)	166 (15)
8/8	333 (7)	70 (7)	79 (7)
Unknown	890 (N/A)	602 (N/A)	424 (N/A)
HLA-DPB1 Match			
Double allele mismatch	815 (39)	97 (43)	109 (39)
Single allele mismatch	1065 (51)	108 (48)	145 (51)
Full allele matched	199 (10)	21 (9)	28 (10)
Unknown	3815 (N/A)	1340 (N/A)	1275 (N/A)
High resolution release score			

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
No	4378 (74)	1500 (96)	1539 (99)
Yes	1516 (26)	66 (4)	18 (1)
KIR typing available			
No	4634 (79)	1560 (>99)	1545 (99)
Yes	1260 (21)	6 (<1)	12 (1)
Graft type			
UCB	5557 (94)	1429 (91)	1472 (95)
BM+UCB	1 (<1)	0	0
PBSC+UCB	307 (5)	137 (9)	78 (5)
Others	29 (<1)	0	7 (<1)
Number of cord units			
1	4944 (84)	0	1310 (84)
2	946 (16)	0	247 (16)
3	2 (<1)	0	0
Unknown	2 (N/A)	1566 (N/A)	0 (N/A)
Conditioning regimen			
Myeloablative	3852 (65)	1008 (64)	978 (63)
RIC/Nonmyeloablative	2029 (34)	554 (35)	570 (37)
TBD	13 (<1)	4 (<1)	9 (1)
Donor age at donation			
To Be Determined/NA	209 (4)	113 (7)	120 (8)
0-9 years	5183 (88)	1205 (77)	1316 (85)
10-19 years	296 (5)	141 (9)	70 (4)
20-29 years	65 (1)	35 (2)	11 (1)
30-39 years	56 (1)	34 (2)	18 (1)
40-49 years	39 (1)	17 (1)	8 (1)
50+ years	46 (1)	21 (1)	14 (1)
Median (Range)	3 (0-72)	5 (0-73)	3 (0-69)
Donor/Recipient CMV serostatus			
+/+	1338 (23)	309 (20)	307 (20)
+/-	573 (10)	148 (9)	145 (9)
-/+	1084 (18)	283 (18)	267 (17)
-/-	724 (12)	195 (12)	201 (13)
CB - recipient +	1253 (21)	336 (21)	339 (22)
CB - recipient -	828 (14)	238 (15)	238 (15)
CB - recipient CMV unknown	94 (2)	57 (4)	60 (4)
GvHD Prophylaxis			
No GvHD Prophylaxis	21 (<1)	8 (1)	9 (1)
TDEPLETION alone	1 (<1)	0	0
TDEPLETION +- other	27 (<1)	9 (1)	5 (<1)
CD34 select alone	0	2 (<1)	2 (<1)
CD34 select +- other	287 (5)	136 (9)	84 (5)
Cyclophosphamide alone	0	0	2 (<1)
Cyclophosphamide +- others	47 (1)	27 (2)	53 (3)
FK506 + MMF +- others	1622 (28)	415 (27)	260 (17)
FK506 + MTX +- others(not MMF)	214 (4)	56 (4)	71 (5)
FK506 +- others(not MMF,MTX)	221 (4)	63 (4)	65 (4)
FK506 alone	139 (2)	43 (3)	23 (1)
CSA + MMF +- others(not FK506)	2689 (46)	610 (39)	707 (45)
CSA + MTX +- others(not MMF,FK506)	99 (2)	33 (2)	41 (3)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
CSA +- others(not FK506,MMF,MTX)	333 (6)	124 (8)	151 (10)
CSA alone	50 (1)	18 (1)	50 (3)
Other GVHD Prophylaxis	132 (2)	19 (1)	25 (2)
Missing	12 (<1)	3 (<1)	9 (1)
Donor/Recipient sex match			
CB - recipient M	3249 (55)	892 (57)	878 (56)
CB - recipient F	2645 (45)	674 (43)	678 (43)
CB - recipient sex unknown	0	0	1 (<1)
Year of transplant			
1996-2000	1 (<1)	2 (<1)	5 (<1)
2001-2005	115 (2)	108 (7)	27 (2)
2006-2010	1811 (31)	413 (26)	492 (32)
2011-2015	2613 (44)	501 (32)	608 (39)
2016-2020	1300 (22)	506 (32)	389 (25)
2021	54 (1)	36 (2)	36 (2)
Follow-up among survivors, Months			
N Eval	2805	808	788
Median (Range)	66 (1-196)	56 (3-213)	52 (1-240)

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 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

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	9695	1555	646
Source of data			
CRF	3455 (36)	446 (29)	245 (38)
TED	6240 (64)	1109 (71)	401 (62)
Number of centers	90	72	59
Disease at transplant			
AML	3214 (33)	506 (33)	206 (32)
ALL	1578 (16)	299 (19)	124 (19)
Other leukemia	189 (2)	35 (2)	14 (2)
CML	314 (3)	36 (2)	20 (3)
MDS	1277 (13)	191 (12)	92 (14)
Other acute leukemia	133 (1)	29 (2)	7 (1)
NHL	856 (9)	141 (9)	61 (9)
Hodgkin Lymphoma	188 (2)	37 (2)	17 (3)
Plasma Cell Disorders, MM	254 (3)	40 (3)	18 (3)
Other malignancies	24 (<1)	0	0
Breast cancer	1 (<1)	0	0
SAA	442 (5)	62 (4)	20 (3)
Inherited abnormalities erythrocyte diff fxn	484 (5)	69 (4)	20 (3)
Inherited bone marrow failure syndromes	7 (<1)	1 (<1)	0
Hemoglobinopathies	35 (<1)	7 (<1)	2 (<1)
Paroxysmal nocturnal hemoglobinuria	2 (<1)	0	0
SCIDs	201 (2)	33 (2)	11 (2)
Inherited abnormalities of platelets	10 (<1)	0	0
Inherited disorders of metabolism	14 (<1)	3 (<1)	2 (<1)
Histiocytic disorders	57 (1)	6 (<1)	3 (<1)
Autoimmune disorders	11 (<1)	0	1 (<1)
Other	11 (<1)	3 (<1)	1 (<1)
MPN	393 (4)	57 (4)	27 (4)
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
MDS Disease status at transplant			
Early	209 (16)	26 (14)	18 (20)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Advanced	1026 (80)	154 (81)	69 (75)
Missing	42 (3)	11 (6)	5 (5)
NHL Disease status at transplant			
CR1	154 (18)	32 (23)	11 (18)
CR2	162 (19)	31 (22)	8 (13)
CR3+	93 (11)	15 (11)	2 (3)
PR	67 (8)	13 (9)	5 (8)
Advanced	371 (44)	49 (35)	34 (56)
Missing	5 (1)	0	1 (2)
Recipient age at transplant			
0-9 years	961 (10)	137 (9)	48 (7)
10-19 years	1139 (12)	139 (9)	56 (9)
20-29 years	829 (9)	169 (11)	51 (8)
30-39 years	763 (8)	137 (9)	66 (10)
40-49 years	1226 (13)	196 (13)	77 (12)
50-59 years	2129 (22)	350 (23)	133 (21)
60-69 years	2254 (23)	369 (24)	190 (29)
70+ years	394 (4)	58 (4)	25 (4)
Median (Range)	50 (0-82)	50 (0-76)	52 (0-83)
Recipient race/ethnicity			
Caucasian, non-Hispanic	6077 (63)	825 (53)	421 (65)
African-American, non-Hispanic	1174 (12)	188 (12)	55 (9)
Asian, non-Hispanic	438 (5)	116 (7)	31 (5)
Pacific islander, non-Hispanic	30 (<1)	3 (<1)	1 (<1)
Native American, non-Hispanic	37 (<1)	4 (<1)	2 (<1)
Hispanic	1434 (15)	298 (19)	102 (16)
Missing	505 (5)	121 (8)	34 (5)
Recipient sex			
Male	5676 (59)	917 (59)	380 (59)
Female	4019 (41)	638 (41)	266 (41)
Karnofsky score			
10-80	3458 (36)	625 (40)	284 (44)
90-100	5979 (62)	887 (57)	338 (52)
Missing	258 (3)	43 (3)	24 (4)
Graft type			
Marrow	2780 (29)	348 (22)	168 (26)
PBSC	6834 (70)	1181 (76)	464 (72)
UCB (related)	2 (<1)	10 (1)	0
BM+PBSC	8 (<1)	4 (<1)	1 (<1)
BM+UCB	38 (<1)	11 (1)	2 (<1)
PBSC+UCB	0	0	11 (2)
Others	33 (<1)	1 (<1)	0
Conditioning regimen			
Myeloablative	5411 (56)	862 (55)	327 (51)
RIC/Nonmyeloablative	4233 (44)	683 (44)	307 (48)
TBD	51 (1)	10 (1)	12 (2)
Donor age at donation			
To Be Determined/NA	16 (<1)	10 (1)	1 (<1)
0-9 years	659 (7)	89 (6)	28 (4)
10-19 years	983 (10)	140 (9)	56 (9)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
20-29 years	1354 (14)	231 (15)	97 (15)
30-39 years	1382 (14)	246 (16)	121 (19)
40-49 years	1574 (16)	258 (17)	88 (14)
50+ years	3727 (38)	581 (37)	255 (39)
Median (Range)	43 (0-82)	43 (0-79)	43 (1-76)
Donor/Recipient CMV serostatus			
+/+	3949 (41)	706 (45)	248 (38)
+/-	1079 (11)	127 (8)	60 (9)
-/+	2411 (25)	368 (24)	163 (25)
-/-	2115 (22)	325 (21)	151 (23)
CB - recipient +	0	3 (<1)	0
CB - recipient -	0	0	3 (<1)
Missing	141 (1)	26 (2)	21 (3)
GvHD Prophylaxis			
No GvHD Prophylaxis	103 (1)	14 (1)	6 (1)
TDEPLETION alone	40 (<1)	17 (1)	4 (1)
TDEPLETION +- other	63 (1)	19 (1)	7 (1)
CD34 select alone	77 (1)	20 (1)	6 (1)
CD34 select +- other	371 (4)	86 (6)	47 (7)
Cyclophosphamide alone	261 (3)	50 (3)	24 (4)
Cyclophosphamide +- others	2500 (26)	360 (23)	176 (27)
FK506 + MMF +- others	690 (7)	73 (5)	19 (3)
FK506 + MTX +- others(not MMF)	3524 (36)	478 (31)	233 (36)
FK506 +- others(not MMF,MTX)	713 (7)	253 (16)	49 (8)
FK506 alone	67 (1)	9 (1)	3 (<1)
CSA + MMF +- others(not FK506)	223 (2)	33 (2)	12 (2)
CSA + MTX +- others(not MMF,FK506)	666 (7)	83 (5)	33 (5)
CSA +- others(not FK506,MMF,MTX)	80 (1)	10 (1)	1 (<1)
CSA alone	76 (1)	9 (1)	3 (<1)
Other GVHD Prophylaxis	136 (1)	16 (1)	12 (2)
Missing	105 (1)	25 (2)	11 (2)
Donor/Recipient sex match			
Male-Male	3212 (33)	546 (35)	222 (34)
Male-Female	2068 (21)	313 (20)	136 (21)
Female-Male	2436 (25)	350 (23)	150 (23)
Female-Female	1934 (20)	317 (20)	125 (19)
CB - recipient M	24 (<1)	15 (1)	8 (1)
CB - recipient F	16 (<1)	6 (<1)	5 (1)
Missing	5 (<1)	8 (1)	0
Year of transplant			
2006-2010	604 (6)	72 (5)	38 (6)
2011-2015	3665 (38)	491 (32)	181 (28)
2016-2020	4930 (51)	874 (56)	361 (56)
2021	496 (5)	118 (8)	66 (10)
Follow-up among survivors, Months			
N Eval	5758	893	368
Median (Range)	37 (1-150)	29 (0-124)	27 (2-143)

HLA Mis-Matched Related Donor with Post-Transplant Cyclophosphamide 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

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	2163	306	152
Source of data			
CRF	1103 (51)	138 (45)	92 (61)
TED	1060 (49)	168 (55)	60 (39)
Number of centers	70	41	31
Disease at transplant			
AML	813 (38)	115 (38)	53 (35)
ALL	375 (17)	64 (21)	33 (22)
Other leukemia	29 (1)	5 (2)	4 (3)
CML	89 (4)	10 (3)	3 (2)
MDS	307 (14)	38 (12)	22 (14)
Other acute leukemia	30 (1)	5 (2)	2 (1)
NHL	165 (8)	24 (8)	13 (9)
Hodgkins Lymphoma	57 (3)	11 (4)	4 (3)
Plasma Cell Disorders, MM	37 (2)	4 (1)	3 (2)
Other malignancies	8 (<1)	0	0
SAA	77 (4)	8 (3)	2 (1)
Inherited abnormalities erythrocyte diff fxn	62 (3)	10 (3)	3 (2)
SCIDs	15 (1)	1 (<1)	1 (1)
Inherited abnormalities of platelets	1 (<1)	0	0
Inherited disorders of metabolism	2 (<1)	0	0
Histiocytic disorders	12 (1)	1 (<1)	1 (1)
Autoimmune disorders	2 (<1)	0	0
Other	1 (<1)	1 (<1)	0
MPN	81 (4)	9 (3)	8 (5)
AML Disease status at transplant			
CR1	482 (59)	71 (62)	32 (60)
CR2	136 (17)	20 (17)	8 (15)
CR3+	13 (1)	3 (3)	1 (2)
Advanced or active disease	181 (22)	20 (17)	12 (23)
Missing	1 (<1)	1 (<1)	0
ALL Disease status at transplant			
CR1	225 (60)	40 (63)	20 (61)
CR2	104 (28)	18 (28)	9 (27)
CR3+	27 (7)	4 (6)	2 (6)
Advanced or active disease	19 (5)	2 (3)	2 (6)
Missing	0	0	0
MDS Disease status at transplant			
Early	43 (14)	5 (13)	2 (9)
Advanced	253 (82)	31 (82)	18 (82)
Missing	11 (4)	2 (5)	2 (9)
NHL Disease status at transplant			
CR1	38 (23)	6 (25)	3 (23)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
CR2	38 (23)	6 (25)	2 (15)
CR3+	14 (8)	6 (25)	1 (8)
PR	4 (2)	0	0
Advanced	68 (41)	5 (21)	6 (46)
Missing	3 (2)	1 (4)	1 (8)
Recipient age at transplant			
0-9 years	127 (6)	11 (4)	6 (4)
10-19 years	200 (9)	18 (6)	10 (7)
20-29 years	260 (12)	39 (13)	16 (11)
30-39 years	202 (9)	29 (9)	19 (13)
40-49 years	286 (13)	45 (15)	16 (11)
50-59 years	422 (20)	64 (21)	27 (18)
60-69 years	523 (24)	89 (29)	50 (33)
70+ years	143 (7)	11 (4)	8 (5)
Median (Range)	50 (0-82)	52 (0-76)	54 (2-77)
Recipient race/ethnicity			
Caucasian, non-Hispanic	1113 (51)	125 (41)	96 (63)
African-American, non-Hispanic	415 (19)	61 (20)	17 (11)
Asian, non-Hispanic	107 (5)	25 (8)	7 (5)
Pacific islander, non-Hispanic	4 (<1)	1 (<1)	1 (1)
Native American, non-Hispanic	7 (<1)	0	2 (1)
Hispanic	374 (17)	70 (23)	17 (11)
Missing	143 (7)	24 (8)	12 (8)
Recipient sex			
Male	1281 (59)	195 (64)	102 (67)
Female	882 (41)	111 (36)	50 (33)
Karnofsky score			
10-80	929 (43)	135 (44)	83 (55)
90-100	1191 (55)	164 (54)	62 (41)
Missing	43 (2)	7 (2)	7 (5)
Graft type			
Marrow	949 (44)	106 (35)	69 (45)
PBSC	1211 (56)	199 (65)	83 (55)
BM+PBSC	3 (<1)	1 (<1)	0
Conditioning regimen			
Myeloablative	979 (45)	137 (45)	58 (38)
RIC/Nonmyeloablative	1184 (55)	169 (55)	94 (62)
Donor age at donation			
0-9 years	23 (1)	2 (1)	1 (1)
10-19 years	176 (8)	27 (9)	13 (9)
20-29 years	552 (26)	91 (30)	35 (23)
30-39 years	597 (28)	88 (29)	53 (35)
40-49 years	470 (22)	59 (19)	29 (19)
50+ years	345 (16)	39 (13)	21 (14)
Median (Range)	36 (2-77)	34 (1-70)	34 (10-74)
Donor/Recipient CMV serostatus			
+/+	919 (42)	159 (52)	54 (36)
+/-	245 (11)	18 (6)	16 (11)
-/+	569 (26)	75 (25)	38 (25)
-/-	412 (19)	53 (17)	38 (25)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Missing	18 (1)	1 (<1)	6 (4)
GvHD Prophylaxis			
Cyclophosphamide alone	12 (1)	3 (1)	0
Cyclophosphamide +- others	2151 (99)	303 (99)	152 (100)
Donor/Recipient sex match			
Male-Male	826 (38)	140 (46)	63 (41)
Male-Female	476 (22)	67 (22)	24 (16)
Female-Male	455 (21)	55 (18)	39 (26)
Female-Female	406 (19)	44 (14)	26 (17)
Year of transplant			
2006-2010	16 (1)	1 (<1)	1 (1)
2011-2015	456 (21)	55 (18)	23 (15)
2016-2020	1675 (77)	244 (80)	126 (83)
2021	16 (1)	6 (2)	2 (1)
Follow-up among survivors, Months			
N Eval	1336	185	100
Median (Range)	25 (1-133)	24 (3-82)	23 (2-100)

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Regimen-Related Toxicity and Supportive Care Working Committee Members

FROM: Saurabh Chhabra, MD, MS; Scientific Director for the Regimen-Related Toxicity and Supportive Care Working Committee

RE: Studies in Progress Summary

RT 19-01: Analysis of comorbidity-associated toxicity at a regimen-based level (R Shouval/ B Savani/ A Nagler). The study aims to 1) evaluate the comorbidity-specific risk of non-relapse mortality and overall mortality within patients receiving pre-defined conditioning regimens, and 2) within patients stratified by conditioning intensity groups (myeloablative, reduced-intensity, and non-myeloablative, and 3) explore toxicities associated with specific conditioning regimen stratified by preexisting comorbidities. The study is in analysis, and the goal to move to manuscript preparation by April 2022.

RT 19-02: Hemorrhagic cystitis (HC) as a complication of hematopoietic cell transplantation with post-transplant cyclophosphamide (PTCy)-based graft-versus-host disease prophylaxis compared to other allogeneic transplants (K Adekola/ N Ali/ O Frankfurt/ L Metheny/ J Moreira/ M de Lima). The study aims to determine the incidence and severity of HC in patients who received PTCy as part of GVHD prophylaxis, 2) to describe disease characteristics and pre-transplant regimens in patients that developed HC after receiving PTCy-based GVHD prophylaxis and 3) to evaluate survival outcomes in PTCy patients with HC. The study is in data file preparation with the goal to move to analysis by May 2022.

RT 20-01: Toxicities of older adults receiving allogeneic hematopoietic cell transplant compared to younger patients. (R Jayani/H Murff). The study aims to determine the incidence of organ toxicities in older and younger adult allo transplants for hematologic malignancies, 2) to describe comorbid conditions in this population and 3) to evaluate survival, progression-free survival, and non-relapse mortality outcome. The study is in protocol development with the goal to move to analysis by June 2022.

CIBMTR Combined study Proposal

Study Title:

"Validating the HCT-CI score and exploring additional prognostic factors in patients undergoing second allogeneic transplants."

Keywords:
Second allogeneic transplantation
Risk Score prediction
Non-relapse mortality
Comorbidities
HCT CI
Children

Principal investigators

Name (First, Middle, Last): Sassine Ghanem Degree(s): MD Academic Rank: Fellow Institution: UT MD Anderson Cancer Center Email Address: sghanem@mdanderson.org	Name (First, Middle, Last): Partow Kebriaei Degree(s): MD, Academic Rank: Professor Institution: UT MD Anderson Cancer Center Email Address: pkebriae@mdanderson.org
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Name (First, Middle, Last): Ana Alarcon Tomas Degree(s): MD Academic Rank: 2nd Year Research Fellowship. Institution: Memorial Sloan Kettering Cancer Center, NY Email Address: alarcona@mskcc.org	Name (First, Middle, Last): Roni Tamari Degree(s): MD, Academic Rank: Assistant Attending Institution: Memorial Sloan Kettering Cancer Center, NY Email Address: tamarir@mskcc.org

Research question:

Does HCT CI predict NRM and OS in second allogeneic transplants? Which other variables can predict outcomes in this setting?

Research hypothesis:

HCT-CI still predicts NRM and OS following second allogeneic transplantation in pediatric and adult patients. However, factors post first allogeneic transplantation are not included in this

predictive model and are hypothesized to impact the outcomes after second allogeneic transplant.

Specific objectives/outcomes to be investigated (Include Primary, Secondary, etc.)

Primary endpoint

1. To validate HCT-CI as a predictor of NRM in patients that underwent second allogeneic transplantation
   a) In adult population
   b) In pediatric population

Secondary endpoints

1. To validate HCT-CI as a predictor of OS in patients that underwent second allogeneic transplantation
2. To identify and evaluate additional prognostic comorbidities post the first allo-HCT that are predictive of NRM in second allo-HCT

Scientific impact

Second allogeneic transplants are being performed more routinely in adult and pediatric populations since the second transplant is often the only curative option for disease relapse or graft failure post allogeneic hematopoietic stem cell transplantation (allo-HCT). Nevertheless, data about predictive of outcomes in patients who underwent a second allo-HCTare lacking.

The HCT-CI score is routinely used in clinical practice and has been extensively validated as a robust predictor of nonrelapse mortality and survival in many transplant scenarios and patient populations, including pediatric patients. However, its utility in the setting of a second transplant has not been studied or reported to date. Without validation, one can't assume that the non-relapse mortality after a second transplant is similar to that post first transplant and that the HCT-CI retains its prognostic implication. Evaluation of the prognostic impact of each component of the HCT-CI and other pretransplant clinical factors and comorbidities will help evaluate whether a novel or modified HCT-CI is needed for patients undergoing a second transplant.

It is critical to determine objective measures to predict post-transplant morbidity and mortality to maximize SCT outcomes and counsel patients appropriately. Additionally, this will guide transplant physicians in assessing risk versus benefit and the appropriateness of conditioning intensity given the patients' HCT-CI score, especially in the modern era of precision medicine with the improvement of activity of novel agents in the relapsed setting.

This study will provide us with novel information regarding the features driving NRM following second allo-HCT. Furthermore, it could guide how to identify high-risk patients

Scientific justification

Second allo-HCT has been demonstrated to be effective therapy providing long-term survival in adult and pediatric populations. In the last years, an increasing number of patients have been considered for a second allogeneic stem cell transplant [1]. CIBMTR data shows that since 2013 the number of allogeneic transplants in adult patients has been increased 0.5-1% per year, with a total of 3669-second allogeneic transplants performed from 2013 to date (Figure A). However,

there are limited predictive models for outcomes after a second allogeneic stem cell transplant[2,3,4].

Comorbidities prior to transplant correlate with worsening morbidity and mortality throughout and following the transplant process [5]. The HCT Comorbidity Index (HCT-CI), a composite score of 17 weighted comorbidities, has been validated in many transplant scenarios and patient populations[6-15], including pediatric patients[16,17], and shown to discriminate risk of nonrelapse and overall mortality following HCT. Overall, all the studies reported so far have investigated the utility of HCT-CI in predicting outcomes following first allogeneic HCT, and no studies to date have explored the utility of predicting TRM and OS in patients undergoing second allogeneic HCT.

In a retrospective study of patients undergoing their second allogeneic transplant for AML at MD Anderson CancerCenter, chronic graft-versus-host disease (GVHD) after the first HCT and an HCT-CI score of greater than two on univariate analysis were associated with lower overall survival progression-free survival. However, the only significant factor on univariate analysis associated with higher non-relapse mortality was age older than 60 [4]. This study has several limitations. However, this data highlights the importance of validating the HCT-CI risk score and independently validating each component to evaluate whether a modified risk score is needed. Previous analysis by the EBMT on 2632 patients with relapsed hematological malignancies who received second allo-HCT showed that high non-relapse mortality (NRM) and disease relapse are significant challenges [2]. In this study, factors that significantly predicted the risk of NRM in univariate and multivariate analysis were age, duration of remission after the first transplantation, the interval between the transplantations, occurrence of acute or chronic GvHD after the first transplantation, EBMT risk score, type of donor and disease burden. However, other available clinical tools as HCT-CI or CIBMTR risk score were not assessed to that population. Furthermore, the studies only included patients that received a second allogeneic transplant up to 2009.

A retrospective analysis of pediatric patients (N=59) undergoing second allogeneic HCT in the University of California studied the role of HCT-CI in predicting outcomes (Figure B). In univariable and multivariable analysis, HCT-CI is the predominant factor that impacts TRM and OS, and it may be used as a predictor of outcomes of second allogeneic transplant. Additionally, HCT-CI to be strongly correlated with PFS in both malignant and nonmalignant disease subgroups.

Preliminary analysis at MSKCC of 46 patients who underwent second allogeneic transplantation could not find any association of HCT-CI and NRM or OS. However, the numbers are small, and conclusions can not be made (Figure C).

Due to the small numbers by centers, a registry study is the only way to address this question.

Participation selection criteria

INCLUSION CRITERIA:

1. Pediatric and adult patients who have undergone second allogeneic transplantation with HCT-CI scores are available
2. Any disease or reason (relapse or graft failure) from unrelated/related matched/mismatched/haploidentical/cord donors with MAC or RIC conditioning regimens.
3. Non-hematologic indication for Allogeneic Transplant
4. December 1st 2007 to December 2021

EXCLUSION CRITERIA:

- Unconditioned stem cell boosts will not be included
- Allogeneic transplantation after autologous transplantation

Data requirements. Participation selection criteria. Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

No supplementary data are required for this proposal.

All the data are already collected in the CIBMTR forms.

Data for 1st allogeneic stem cell transplant	*Data for 2nd allogeneic stem celltransplant*
Date of birth	
Gender	
Race	
Diagnosis	Reason for 2nd Allo: graft failure or relapse
Date first allogeneic	Date of second allogeneic transplant
Disease status at transplant.	Disease status at second transplant.
HCT-CI. Hematopoietic Cell Transplant Comorbidity Index	HCT-CI. Hematopoietic Cell Transplant Comorbidity Index at 2nd Allo
Comorbidities for HCT CI score	Comorbidities for HCT CI score
Number of prior lines of treatments	Number of treatments btw first and 2nd Allo
Karnofsky Performance Status	Karnofsky Performance Status
HLA compatibility: Matched, Mismatched, haploidentical.	HLA compatibility: Matched, Mismatched, haploidentical.
Stem cell source: Peripheral blood, Bone Marrow, cord blood	Stem cell source: Peripheral blood, Bone Marrow, cord blood.
Sibling, Related, Unrelated, cord.	Sibling, Related, Unrelated, cord.
Donor gender.	Same donor than 1st Allo
CMV status	CMV status
Conditioning regimen NMA, MA, RIC	Conditioning regimen NMA, MA, RIC
Type of conditioning regimen.	Type of conditioning regimen.
T cell depletion	T cell depletion
TIB based. Yes no.	TIB based. Yes no.
GVHD prophylaxis.	GVHD prophylaxis.
Acute GVHD assessment (grade)	Acute GVHD assessment (grade)
Treatment for Acute GVHD.	Treatment for Acute GVHD.
Chronic GVHD assessment grade	Chronic GVHD assessment grade
Treatment for chronic GVHD.	Treatment for chronic GVHD.
Disease relapse or progression and date	Disease relapse or progression and date
Graft failure	Graft failure
	Last contact
	Status at contact.
	Live/Death Status at last contact.
	Cause of death
Ferritin, Albumin and CRP	Ferritin, Albumin and CRP

Patient-reported Outcome (PRO)

N/A

Sample requirements

N/A

Non-CIBMTR Source

N/A

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Conflict of interest

No conflict of interest pertinent to this proposal for any of the principal investigators.

Characteristics of patients who underwent second allo HCT for any disease reported to the CIBMTR 2008-2019

Characteristic	N (%)
No. of patients	4982
No. of centers	187
Age at HCT - no. (%)	
<10	1313 (26)
18-29	644 (13)
30-39	522 (10)
40-49	616 (12)
50-59	902 (18)
60-69	853 (17)
>=70	132 (3)
HCT-CI Score Current TX - no. (%)	
0	1185 (24)
1	605 (12)
2	501 (10)
3+	1809 (36)
TBD	22 (0)
Not Reported	860 (17)
HCT-CI Score First Transplant - no. (%)	
0	1796 (36)
1	640 (13)
2	534 (11)
3+	1408 (28)
TBD	15 (0)
Not Reported	589 (12)
Primary disease for HCT - no. (%)	
AML	2134 (43)
ALL	707 (14)
Other leukemia	112 (2)
CML	136 (3)
MDS	589 (12)
MPN	187 (4)
Other acute leukemia	75 (2)
NHL	202 (4)
HD	62 (1)
PCD	69 (1)
SAA	250 (5)
IEA	259 (5)
IIS	7 (0)

Characteristic	**N (%)**
IPA	78 (2)
HIS	100 (2)
Other	15 (0)
Graft Source - no. (%)	
Bone marrow	758 (15)
Peripheral blood	3676 (74)
Umbilical cord blood	548 (11)
Indicator of HCT cases in CRF retrieval - no. (%)	
No	2523 (51)
Yes*	2459 (49)
Year of Transplant - no. (%)	
2008 - 2013	2228 (45)
2014 - 2019	2754 (55)
Follow-up - median (range)	60 (3-156)

*2013-2019 CRF cases n=1441

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

Correlation of melphalan dose with regimen-related toxicity in multiple myeloma patients undergoing autologous transplant

Q2. Key Words

Toxicity, mucositis, non-relapse mortality, melphalan, multiple myeloma

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Maxwell M Krem, MD, PhD
Email address:	mkrem@uw.edu
Institution name:	Kansas City VA Medical Center
Academic rank:	Assistant Professor

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

- No

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Charlotte B Wagner, PharmD
Email address:	charlotte.wagner@hci.utah.edu
Institution name:	University of Utah Huntsman Cancer Institute
Academic rank:	N/A

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

- Yes

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:

Maxwell M. Krem

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.

- LK19-02 (Evolving significance of Ph-positive status on ALL post-transplant outcomes in the TKI era): principal investigator.
- I am on the protocol development or writing committees for numerous other CIBMTR projects.

Q13. PROPOSED WORKING COMMITTEE:

- Regimen-Related Toxicity and Supportive Care

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

- Yes

Q14a. If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

Bipin Savani, MBBS

Q15. RESEARCH QUESTION:

Does melphalan dose reduction in autologous transplant for multiple myeloma reduce toxicity measures but also correlate with frailty measures for all age groups?

Q16. RESEARCH HYPOTHESIS:

Reduced-dose melphalan (140 mg/m2, MEL140) compared to standard dose (200 mg/m2, MEL200) prior to autologous hematopoietic stem cell transplantation (auto-HCT) for multiple myeloma (MM) reduces toxicity outcomes but also correlates with frailty, demonstrated by higher pre-transplant comorbidity indices, lower Karnofsky performance status, and higher non-relapse mortality (NRM), regardless of age. However, long-term disease-control outcomes, particularly rate of relapse, are not dependent on melphalan dose.

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

Suggested word limit of 200 words:

To compare pre- and post-auto-HCT complication measures for MM patients who received reduced dose MEL140 or standard dose MEL200 from 2012 – 2020.

• Primary aim: Compare NRM, regimen-related toxicities, infections, HCT-CI, and KPS for MEL200 versus MEL140 for patients undergoing auto-HCT for treatment of MM.

• Secondary aims: Compare progression free survival (PFS), response rates, early relapse, and overall survival (OS) for MEL200 versus MEL140 for patients undergoing auto-HCT for treatment of MM

Primary outcome:

• Non-relapse mortality

Secondary outcomes:

• Mucositis requiring therapy
• Infections
• Development of grade 3 or higher infection
• Hepatotoxicity
• Other organ impairment (cardiac, pulmonary, etc.)
• Progression-free survival
• Overall survival
• Best response (including overall and VGPR or better)
• Early relapse (<24 months)
• Development of second malignancy
• Cause of death (descriptive)

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.

High-dose melphalan followed by auto-HCT is superior to conventional chemotherapy and is standard-of-care consolidation for MM.1,2 The typical dose is MEL200; however, in practice, it is often dose-reduced to MEL140 due to concerns for tolerability based on age, performance status, and organ dysfunction. Based on preliminary and previously published data, we believe that dose reduction of melphalan reduces peri-transplant non-hematologic toxicities without impairing disease response. and that OS and PFS concerns about MEL140 actually stem from higher NRM, higher HCT-CI scores, and lower KPS. This knowledge would have significant impact on clinicians' decision-making when determining which patient factors are important when taking a MM patient to auto-HCT and the impact of melphalan dose selection on patient outcomes.

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.

High-dose melphalan followed by auto-HCT has been shown to improve response and survival outcomes in patients with MM compared to conventional chemotherapy1.2 .
The most common dose for auto-HCT is MEL2003. This dosing scheme was first described at the University of Arkansas4. It has been compared to both lower and higher doses of MEL. MEL200 was compared to 100 mg/m2. PFS and time to progression was superior in the patients who received MEL200. When the dose was escalated to 220 mg/m2, this larger dose was associated with higher rates of mucositis and cardiac arrhythmias6. Based on these data, MEL200 has been the standard. In current practice, clinicians often dose reduce to MEL140 in patients they deem unlikely to tolerate the higher dose. This practice is supported by retrospective studies from single institutions7,8,9. Two reported no difference in post-transplant outcomes with MEL1407,8. The largest study had 103 patients who received MEL1409. Multi-institution retrospectives in patients with renal insufficiency10 or general populations11 have established the efficacy of MEL140 in auto-HCT for MM, with survival possibly favoring MEL140 in patients who achieve very good partial response (VGPR) or better11. Notably, these studies did not focus on toxicity outcomes.
A recently published CIBMTR analysis (MM18-03 assessed outcomes in younger versus elderly MM patients undergoing auto-HCT for MM12. In a subset of elderly patients ≥ 70 years of age who received auto-HCT, the day 100 NRM was higher and OS was decreased in those who received MEL140. However, relapse was not statistically different for reduced and standard dose melphalan cohorts. Nevertheless, the purpose of MM18-03 was not to assess outcomes differences for patients based on melphalan dose.
A preliminary dataset from two institutions, including just over 200 patients, found that mucositis, grade ≥3 mucositis, diarrhea, and mean number of grade ≥3 toxicities were lower in patients who received MEL140 versus MEL20013.
A multi-institutional analysis examining the interplay of toxicity and melphalan dose in auto-HCT has not yet been performed in a large population of MM patients. This would help to define the correlation between MEL140 use and toxicity outcomes in patients undergoing auto-HCT and provide additional information and justification to guide decisions about MEL dose adjustment in melphalan auto-HCT.

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.

Inclusion criteria:
• Adults ≥ 18 years at time of MEL auto-HCT between 2012 - 2018
• Diagnosis of MM
• Recipients of auto-HCT
• Received induction therapy with PI, IMiD, or both
• Received single-agent MEL conditioning
Exclusion criteria:
• Patients who did not consent to research
• Received a dose other than MEL200 or MEL140
• Tandem transplant recipients
• Patients with primary amyloidosis or plasma cell leukemia

Q21. Does this study include pediatric patients?

- No

Q21a. If this study does not include pediatric patients, please provide justification:

Multiple myeloma is extremely rare among pediatric patients.

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.

We will collect data from standard CIBMTR forms including the following:
• Recipient baseline data (Forms 2000 and 2400)
• Post-HCT follow-up data (Form 2100)
• Multiple myeloma/plasma cell leukemia pre-HCT data (Form 2016)
• Multiple myeloma/plasma cell leukemia post-HCT data (Form 2116)
Variables to be described (bolded items to be considered in multivariate analysis):
Patient-related:
• Age
• Gender (M, F)
• Race (Caucasian, African-American, Asian, Pacific Islander, Native American, other)
• Karnofsky score (<90, ≥90)
• Renal function (SCr, eGFR)
• HCT-CI score (0,1,2,3+)
Disease-related:
• ISS and ISS-R stage
• Response per IMWG criteria prior to transplant
• Presence of high risk cytogenetics
• Involved M protein
• Involved light chains
Treatment/transplant-related:
• Main effect: Dose of melphalan (reduced- versus standard-dose)
• Pre-transplant treatment history (PI, IMiD, or both)
• 1st or 2nd auto-HCT
• Time from diagnosis to transplant
• Receipt of maintenance therapy after transplant
• Development of severe mucositis (CTCAE grade III – IV)

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. Attal M, et al. "A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma." New England Journal of Medicine 335.2 (1996): 91-7.
2. Child JA, et al. "High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma." New England Journal of Medicine 348.19 (2003): 1875-83.
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10. Mahindra A, et al. Autologous hematopoietic cell transplantation for multiple myeloma patients with renal insufficiency: a Center for International Blood and Marrow Transplant Research Analysis. Bone Marrow Transplant 2017; 52: 1616-1622
11. Auner HW, et al. Melphalan 140 mg/m2 or 200 mg/m2 for autologous transplantation in myeloma: results from the Collaboration to Collect Autologous Transplant Outcomes in Lymphoma and Myeloma (CALM) study. A report by the EBMT Chronic Malignancies Working Party. Haematologica 2018; 103: 514-521
12. Munshi PN., et al. "Age no bar: A CIBMTR analysis of elderly patients undergoing autologous hematopoietic cell transplantation for multiple myeloma." Cancer (2020).
13. Krem MM, et al. Reduced-dose melphalan (140 or 100 mg/m2) maintains efficacy and reduces toxicity for myeloma patients undergoing autologous transplant. Manuscript in preparation, 2021

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

Characteristics of patients who underwent auto HCT for any Multiple Myeloma reported to the CIBMTR 2008-2019

Characteristic	MEL 140	MEL 200	P Value
No. of patients	1019	6014	
No. of centers	97	131	
Age at HCT - no. (%)			<.01[a]
18-29	0 (0)	13 (0)	
30-39	15 (1)	175 (3)	
40-49	54 (5)	836 (14)	
50-59	182 (18)	2094 (35)	
60-69	407 (40)	2567 (43)	
>=70	361 (35)	329 (5)	
Karnofsky score prior to HCT - no. (%)			<.01[a]
90-100%	347 (34)	3187 (53)	
< 90%	625 (61)	2635 (44)	
Not reported	47 (5)	192 (3)	
HCT-CI Score - no. (%)			<.01[a]
0-2	394 (39)	3605 (60)	
3+	607 (60)	2167 (36)	
TBD	4 (0)	22 (0)	
Ethnicity - no. (%)	14 (1)	220 (4)	
Hispanic or Latino			0.72[a]
Non Hispanic or non-Latino	59 (6)	395 (7)	
Non-resident of the U.S.	928 (91)	5439 (90)	
Not reported	14 (1)	90 (1)	
Race - no. (%)			
White	541 (53)	3641 (61)	<.01[a]
Black or African American	402 (39)	1886 (31)	
Asian	41 (4)	195 (3)	
Native Hawaiian or other Pacific Islander	2 (0)	15 (0)	
American Indian or Alaska Native	9 (1)	57 (1)	
More than one race	1 (0)	38 (1)	
Not reported	23 (2)	182 (3)	
ISS stage at diagnosis (MM) - no. (%)			
Stage I	213 (21)	1974 (33)	<.01[a]
Stage II	236 (23)	1656 (28)	
Stage III	311 (31)	1028 (17)	
Not reported	259 (25)	1356 (23)	
Cytogenetic risk (MM) - no. (%)			
Standard risk	685 (67)	3892 (65)	0.12[a]
High risk	238 (23)	1432 (24)	

Characteristic	MEL 140	MEL 200	P Value
Test not done/unknown/ No metaphases	96 (9)	690 (11)	
Interval between diagnosis and transplant - no. (%)			
<6 months	209 (21)	1724 (29)	<.01[a]
6-12 months	468 (46)	2671 (44)	
12+ months	342 (34)	1618 (27)	
Not reported	0	1 (0)	
Indicator of HCT cases in CRF retrieval - no. (%)			0.39[a]
No	8 (1)	65 (1)	
Yes	1011 (99)	5949 (99)	
Year of Transplant - no. (%)			<.01[a]
2008-2013	300 (29)	2381 (40)	
2014 - 2019	719 (71)	3633 (60)	
Follow-up - median (range)	49 (3-149)	60 (3-157)	

Hypothesis testing: [a] Pearson chi-square test

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

Allogeneic hematopoietic cell transplantation (HCT) in patients 75 years and older-utilization and outcomes

Q2. Key Words

Older adults, Allogeneic hematopoietic cell transplantation, non-relapse mortality, outcomes, AML, MDS, reduced intensity conditioning

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Andrew Artz, MD, MS
Email address:	aartz@coh.org
Institution name:	City of Hope
Academic rank:	Professor

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

- No

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Ryo Nakamura, MD
Email address:	RNakamura@coh.org
Institution name:	City of Hope
Academic rank:	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:

Andrew Artz

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.

None

Q13. PROPOSED WORKING COMMITTEE:

- Regimen-Related Toxicity and Supportive Care

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

- Yes

Q14a. If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

All Committee Chairs by Email. M. Sorror, B. Sivana, and Scientific Office responded.

Q15. RESEARCH QUESTION:

Is allogeneic HCT safe and feasible for patients ≥ 75 years

Q16. RESEARCH HYPOTHESIS:

We hypothesize the transplant field has broken through the age barrier evidenced by rising transplant utilization among patients ≥ 75 years with acceptable rates of NRM

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

Suggested word limit of 200 words:

Primary Objective:
To compare HCT utilization among patients ≥ 75 years and older over time (two time periods of 2008-2013, 2014-2020)
Secondary Objectives:
To review drivers of transplant utilization in this age group (e.g., more centers, donor type composition, clinical trials, etc)
To summarize non-relapse mortality at 1 and 2 years in these patients by time period
To benchmark HCT outcomes among patients ≥ 75 years by describing overall survival (OS), leukemia-free survival (LFS), acute and chronic GVHD incidence

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 study will for the first-time report on outcomes in patients ≥ 75 years for which the field lacks prospective or comparative data. Descriptive findings of utilization over time, center diffusion, and subsets by race, sex, ethnicity, age ≥ 80 years will be invaluable. The study further will benchmark outcomes, especially for non-relapse mortality, for future study and counseling of patients. The findings partner exceptionally well with BMT CTN 1704 "CHARM" to develop a composite health assessment risk model for NRM among older adults employing geriatric assessments, comorbidity and biomarkers. (clinicaltrials.gov/ct2/show/NCT03992352) We anticipate CTN 1704 when published will further accelerate interest in the oldest patients.

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.

Age and Hematologic Malignancies. Hematologic malignancies are more common and often more fatal in older patients.1 Table 1 summaries recent disease registry estimates for hematologic malignancies for ≥ 75 years and older with available data.
Table 1. Registry estimates of age at diagnosis
Disease Proportion ≥ 75 years
AML (seer.cancer.gov) 33.8%
ALL (seer.cancer.gov) 6%
MDS 2
55.9%
CMML 3
≈50%
Although the proportion of patients diagnosed ≥ 75 years for myeloproliferative disorders can't be readily estimated, the median age of diagnosis for myelofibrosis hovers around 70 years. 4 Older age confers worse outcomes due to a variety of factors including adverse disease biology, undertreatment (which may include lack of HCT), and late diagnosis.
New treatment options. The therapeutic landscape has been reshaped by novel treatment options for hematologic malignancy patients; a higher number of successfully treated patients may further promote alloHCT consideration. For example, a seminal study by DiNardo reported for newly diagnosed AML ≥ 75 years or unfit for standard therapy, impressive composite complete response rates of 66.4% for hypomethylating agent with the BCL-2 inhibitor, venetoclax, compared 28.3% with hypomethylating therapy alone. 5 Although limited to patients 60-75 years of age, CPX-351 bested standard induction therapy for secondary AML, with particularly favorable outcomes among those consolidating CPX-351 responses by alloHCT.6 As well, the therapeutic landscape has widened for MDS, ALL and other hematologic malignancies. 7,8
HCT in Older Age. As a procedure with considerable toxicity such as non-relapse mortality (NRM), alloHCT has

generally been restricted to more fit and/or younger patients. Data for older adult alloHCT outcomes, nearly as a rule, stops at age 75 years.9 Likewise, comparative studies of alloHCT to non-HCT approaches confirming a benefit in older adults with AML and MDS, capped the upper age at 75 years.10-13 AlloHCT also likely affords a survival benefit for less common indications such as myelofibrosis and ALL in older adults as well.7,14

Registry studies uncovered the broadening application of alloHCT in patients in their eighth decade. Muffly's CIBMTR analysis among alloHCT patients at least 70 years of age for all diseases through 2013 found 1106 patients; however, only 115(10%) were 75-79 years and 8 (1) were ≥aart80 years. 15 Atalah described outcomes from a prospective registry for older MDS patients through the CIBMTR-among 688 patients ≥ 65 years; 14 (2%) were 75-79 years, and none ≥ 80 years.16 In the EBMTR experience for AML among 713 patients with AML ≥ 70 years of age, Ringden reported a median age of 72(70-79) without further age breakdown.17 Further, we have no data for those in their ninth decade. The European registry described no allografts in those ≥80 years for MDS and AML through 2013-2014.17,18

We believe the age barrier of 75 years is artificial, primarily driven by physician choices and policies of institutions, insurers or governments. Older age constitutes the most significant barrier for referral for alloHCT.19 Nevertheless, a recent physician survey sheds light on extension of the upper age limit of alloHCT. Mishra and colleagues surveyed HCT physicians and found most physicians reported an upper age limit between 70 and 80 years for reduced intensity conditioning (RIC) alloHCT; 17.7% described no upper age limit for RIC HCT.20 In fact, preliminary data provided by the CIBMTR reveal emerging use of alloHCT in the oldest patients. Specifically, for patients 76 years of age, 203 patients received first allografts compared to 34 in the 2008-2013 period (covered by the Muffly CIBMTR analysis)-a six fold increase and rising quickly. The marked change over several years suggests rather than marked advances in the field, HCT physician and center willingness has expanded.

Ongoing studies and need for TED level data. CIBMTR study LK-20-04, evaluated AML CR1 outcomes using case report forms (CRF) among patients ≥ 60 years of age by age cohort (60-64, 65-69, 70+). However, among the 197 patients in their eighth decade, the median age was 71.86 (range 10.02-77.69)(Maakaron J, ASH 2020 Abstract 1536) In another approved study, RT20-02, evaluating toxicities by age, the output will require CRF data, limiting information on actual utilization over time and primarily overlapping with LK20-04 as AML represents the most common indication.

Non-relapse mortality as a toxicity marker. Although transplant morbidity and quality of life are critical patient centered outcomes, NRM has emerged as the most objective and reproducible tool for serious transplant toxicity. In "real-world" registry data of patients 70 years and older, 1 and 2 year NRM was estimated at 25% and 33% in the 2008-2013 period. In an EBMT series of MDS or secondary AML in patients ≥ 70 years, NRM at 1 year was 32%. 18 The EBMT experience of the same age group with AML undergoing alloHCT had a median age of 72(70-79) without further age breakdown; 2 year NRM was 34% 17 In CIBMTR LK20-04 of AML in CR1, the authors reported 3 year NRM of 29.5% (p=0.035) for those in their eight decade. (Maakaron J, ASH 2020 Abstract 1536) Single institutional studies of matched donors or haploidentical donors described 2 year NRM of 17% and 27%, respectively. 21,22

Conditioning regimens. Most older adults receive reduced intensity conditioning regimens. 15,23 It is now well-established even among RIC regimens, regimens such as fludarabine-melphalan achieve better disease control but higher early NRM relative to lower intensity fludarabine and low dose busulfan, at least for AML.24 It remains to be established whether in this oldest age group selected for HCT will require non-ablative regimens or if intermediate intensity RIC may be associated with acceptable NRM. Toxicity must be balanced against the association of older age to higher-risk disease. 25,26

Strengths. This will be the first major study in this population newly being offered alloHCT, filling a major void in the field. Such data require the breadth of the registry to generate an adequate sample but more importantly to understand utilization trends. The study leverages Transplant Essential Data rather than overlap with studies employing CRF level data.

Weakness. The most significant limitation, as with most registry studies, is the lack of a non-HCT control group. By studying all diseases, we limit comparisons, but this is critical to understand utilization broadly. However, subset analysis of AML in remission may be prudent. Specific toxicity details will be unavailable as we the study requires TED data to capture the largest denominator possible. We are not proposing to compare to younger patients as this may create a false dichotomy-younger patients also do better without HCT but may be less selected. We will not have geriatric assessment data but will collect HCT-CI scores, and KPS.

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.

Inclusion criteria:
• Adults ≥ 75 years at time of first allo-HCT between 2008-2020
• Diagnosis of hematologic malignancy
Exclusion criteria:
• Recipients of second or later allo-HCT
• Patients who did not consent to research

Q21. Does this study include pediatric patients?

- No

Q21a. If this study does not include pediatric patients, please provide justification:

Objectives exclusive to older adults

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.

The primary analyses will be descriptive and univariate with the fields below.
MVA will apply forward selection based on 2 year NRM and include
Age 75-79, 80+, sex, KPS, HCT-CI, donor type, RIC vs NMA, disease, DRI, and disease response.
• Main effect: Time period 2008-2013 vs 2014-2020
Patient-related:
• Age: cutoff to be decided in multivariate analyses
• Sex: M, F
• Race: Caucasian, African-American, Asian, Pacific Islander, Native American, other
• Karnofsky score: <90, ≥90
• HCT-CI: 0, 1-2, 3+ (captured 2008 and later)
• Albumin (when available)
• Zip Code for USA recipients
Disease-related:
• Disease
• Revised disease risk index
• MRD status before transplant: positive, negative
Transplant-related:
• Participation in clinical trial Yes/ no (question 18)
• Study sponsor of trial
• Conditioning regimen intensity: MAC RIC, NMA
• Conditioning regimen- flu-bu, flu-mel, flu-cy +/- TBI, flu-TBI, other
• Donor type: MRD, other related, MUD, mismatched unrelated, UCB
• Donor/recipient sex match: M/M, M/F, F/M, F/F
• Donor/recipient CMV status: +/+, +/-, -/+, -/-
• Graft type: BM, PB, UCB
• GVHD prophylaxis: PT-Cy, TAC-based, CSA-based, other
• In-vivo T-cell depletion with ATG or alemtuzumab: yes, no
• Year of transplant: 2008-2013, 2014-2020
• Center
-

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

None

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

None

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.

None

Q26. REFERENCES:

1. Wildes TM, Artz AS: Characterize, Optimize, and Harmonize: Caring for Older Adults With Hematologic Malignancies. Am Soc Clin Oncol Educ Book 41:1-9, 2021
2. Ma X, Does M, Raza A, et al: Myelodysplastic syndromes: incidence and survival in the United States. Cancer 109:1536-42, 2007
3. Guru Murthy GS, Dhakal I, Mehta P: Incidence and survival outcomes of chronic myelomonocytic leukemia in the United States. Leuk Lymphoma 58:1648-1654, 2017
4. Srour SA, Devesa SS, Morton LM, et al: Incidence and patient survival of myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms in the United States, 2001-12. Br J Haematol 174:382-96, 2016
5. DiNardo CD, Jonas BA, Pullarkat V, et al: Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med 383:617-629, 2020
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7. Aldoss I, Forman SJ, Pullarkat V: Acute Lymphoblastic Leukemia in the Older Adult. J Oncol Pract 15:67-75, 2019
8. Platzbecker U, Kubasch AS, Homer-Bouthiette C, et al: Current challenges and unmet medical needs in myelodysplastic syndromes. Leukemia 35:2182-2198, 2021
9. Sorror ML, Sandmaier BM, Storer BE, et al: Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. JAMA 306:1874-83, 2011
10. Ustun C, Le-Rademacher J, Wang HL, et al: Allogeneic hematopoietic cell transplantation compared to chemotherapy consolidation in older acute myeloid leukemia (AML) patients 60-75 years in first complete remission (CR1): an alliance (A151509), SWOG, ECOG-ACRIN, and CIBMTR study. Leukemia 33:2599-2609, 2019
11. Versluis J, Hazenberg CL, Passweg JR, et al: Post-remission treatment with allogeneic stem cell transplantation in patients aged 60 years and older with acute myeloid leukaemia: a time-dependent analysis. Lancet Haematol 2:e427-36, 2015
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13. Kroger N, Sockel K, Wolschke C, et al: Comparison Between 5-Azacytidine Treatment and Allogeneic Stem-Cell Transplantation in Elderly Patients With Advanced MDS According to Donor Availability (VidazaAllo Study). J Clin Oncol:JCO2002724, 2021
14. Hernandez-Boluda JC, Pereira A, Kroger N, et al: Allogeneic hematopoietic cell transplantation in older myelofibrosis patients: A study of the chronic malignancies working party of EBMT and the Spanish Myelofibrosis Registry. Am J Hematol 96:1186-1194, 2021
15. Muffly L, Pasquini MC, Martens M, et al: Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States. Blood 130:1156-1164, 2017
16. Atallah E, Logan B, Chen M, et al: Comparison of Patient Age Groups in Transplantation for Myelodysplastic Syndrome: The Medicare Coverage With Evidence Development Study. JAMA Oncol 6:486-493, 2020
17. Ringden O, Boumendil A, Labopin M, et al: Outcome of Allogeneic Hematopoietic Stem Cell Transplantation in Patients Age >69 Years with Acute Myelogenous Leukemia: On Behalf of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 25:1975-1983, 2019
18. Heidenreich S, Ziagkos D, de Wreede LC, et al: Allogeneic Stem Cell Transplantation for Patients Age >/= 70 Years with Myelodysplastic Syndrome: A Retrospective Study of the MDS Subcommittee of the Chronic Malignancies Working Party of the EBMT. Biol Blood Marrow Transplant 23:44-52, 2017
19. Flannelly C, Tan BE, Tan JL, et al: Barriers to Hematopoietic Cell Transplantation for Adults in the United States: A Systematic Review with a Focus on Age. Biol Blood Marrow Transplant 26:2335-2345, 2020
20. Mishra A, Preussler JM, Al-Mansour Z, et al: Transplant Physicians' Attitudes on Candidacy for Allogeneic Hematopoietic Cell Transplantation (HCT) in Older Patients: The Need for a Standardized Geriatric Assessment (GA) Tool. Biology of Blood and Marrow Transplantation 26:S45-S46, 2020
21. Al Malki MM, Nathwani N, Yang D, et al: Melphalan-Based Reduced-Intensity Conditioning is Associated with Favorable Disease Control and Acceptable Toxicities in Patients Older Than 70 with Hematologic Malignancies Undergoing Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant 24:1828-1835, 2018
22. Imus PH, Tsai HL, Luznik L, et al: Haploidentical transplantation using posttransplant cyclophosphamide as GVHD prophylaxis in patients over age 70. Blood Adv 3:2608-2616, 2019
23. Mishra A, Preussler JM, Bhatt VR, et al: Breaking the Age Barrier: Physicians' Perceptions of Candidacy for Allogeneic Hematopoietic Cell Transplantation in Older Adults. Transplant Cell Ther 27:617 e1-617 e7, 2021
24. Zhou Z, Nath R, Cerny J, et al: Reduced intensity conditioning for acute myeloid leukemia using melphalan- vs busulfan-based regimens: a CIBMTR report. Blood Adv 4:3180-3190, 2020
25. Herold T, Rothenberg-Thurley M, Grunwald VV, et al: Validation and refinement of the revised 2017 European LeukemiaNet genetic risk stratification of acute myeloid leukemia. Leukemia 34:3161-3172, 2020
26. Kantarjian H, O'Brien S, Ravandi F, et al: Proposal for a new risk model in myelodysplastic syndrome that accounts for events not considered in the original International Prognostic Scoring System. Cancer 113:1351-61, 2008

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

Characteristics of patients 75 and older who underwent allo HCT for any disease reported to the CIBMTR 2008-2019

Characteristic	N (%)
No. of patients	392
No. of centers	78
Age at HCT - median (min-max)	76 (75-88)
HCT-CI Score - no. (%)	
0-2	176 (45)
3+	206 (53)
TBD	9 (2)
Not Reported	1 (0)
Ethnicity - no. (%)	
Hispanic or Latino	12 (3)
Non-Hispanic or non-Latino	363 (93)
Non-resident of the U.S.	2 (1)
Missing	15 (4)
Race - no. (%)	
White	372 (95)
Black or African American	5 (1)
Asian	7 (2)
Missing	8 (2)
Primary disease for HCT - no. (%)	
AML	201 (51)
ALL	9 (2)
Other leukemia	8 (2)
CML	2 (1)
MDS	137 (35)
Other acute leukemia	4 (1)
NHL	16 (4)
MPN	15 (4)
Donor type - no. (%)	
HLA-identical sibling	39 (10)
Other related	76 (19)
Well-matched unrelated (8/8)	238 (61)
Partially-matched unrelated (7/8)	29 (7)
Unrelated (matching TBD)	3 (1)
Cord blood	7 (2)
Reported planned conditioning regimen - no. (%)	
MAC	
TBI/Cy/Flu/TT	2 (1)
TBI/Flu	2 (1)
Bu/Mel	1 (0)
Flu/Bu	17 (4)
Flu/Mel/TT	16 (4)

Characteristic	N (%)
Mel/other(s)	1 (0)
RIC	
TBI/Cy/Flu	5 (1)
TBI/Mel	3 (1)
TBI/Flu	43 (11)
Flu/Bu	107 (27)
Flu/Mel	68 (17)
BEAM	1 (0)
NMA	
TBI/Cy	1 (0)
TBI/Cy/Flu	66 (17)
TBI/Flu	36 (9)
Flu/Bu	2 (1)
Cy/Flu	4 (1)
Cy alone	1 (0)
TLI	8 (2)
Other(s)	1 (0)
Not reported intensity	
TBI/Flu	1 (0)
Flu/Mel/TT	1 (0)
Mel alone	1 (0)
TLI	1 (0)
Other(s)	1 (0)
Not reported	2 (0)
Planned GVHD prophylaxis - no. (%)	
CD34 select ± other	3 (1)
Cyclophosphamide alone	1 (0)
Cyclophosphamide ± others	112 (29)
FK506 + MMF ± others	73 (19)
FK506 + MTX ± others	109 (28)
FK506 ± others	31 (8)
FK506 alone	12 (3)
CSA + MMF ± others	42 (11)
CSA + MTX ± others	1 (0)
CSA ± others	2 (1)
Other GVHD Prophylaxis	3 (1)
Missing	3 (1)
Graft Source - no. (%)	
Bone marrow	54 (14)
Peripheral blood	331 (84)
Umbilical cord blood	7 (2)
Prior auto-HCT - no. (%)	
No	381 (97)

Characteristic	N (%)
Yes	11 (3)
Indicator of HCT cases in CRF retrieval - no. (%)	
No	219 (56)
Yes	173 (44)
Year of Transplant - no. (%)	
2008 - 2013	62 (16)
2014 - 2019	330 (84)
Follow-up - median (range)	36 (9-120)

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

Trends of major organ injuries amongst children and young adults following allogeneic hematopoietic cell transplantation for hematologic malignancies

Q2. Key Words

Major organ injuries, alloHCT, Children and young adults

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Hemalatha Rangarajan MD
Email address:	Hemalatha.Rangarajan@nationwidechildrens.org
Institution name:	Nationwide Children's Hospital
Academic rank:	Clinical Assistant Professor of Pediatrics

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

- No

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Prakash Satwani, MD
Email address:	ps2087@columbia.edu
Institution name:	Columbia University Medical Center, New York
Academic rank:	Associate Professor of Pediatrics

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?

- Yes

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:

N/A

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 have completed the following study with CIBMTR
IB17-02: Outcomes of Pediatric patients with JMML following unrelated donor transplant: The impact of Donor KIR Gene Content and KIR Ligand Matching
Manuscript Published. Transplantation and Cellular Therapy. PMID: 34407489. Role : Principal investigator
The following proposals that I have submitted have been accepted and are at varying stages of development. I am one of the co-principal investigators on all these protocols.
1. IN20-01: Incidence, Risk Factors, and Outcomes of Infections post CD19 CAR T therapies. February 2020. Data analysis is ongoing.
2. CT20-02: Resource utilization in patients receiving CAR-T Therapy. February 2020. Protocol development is in progress.
3. PC19-03: Outcomes of allogeneic hematopoietic cell transplantation in pediatric patients with AML and CNS involvement. February 2019. Data analysis is ongoing.

Q13. PROPOSED WORKING COMMITTEE:

- Regimen-Related Toxicity and Supportive Care

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

- No

Q15. RESEARCH QUESTION:

What is the trends of major organ injuries amongst children and young adults following allogeneic hematopoietic cell transplantation for hematologic malignancies?

Q16. RESEARCH HYPOTHESIS:

Major organ injuries during first 100 days, amongst children and young adults (CAYA) who underwent allogeneic hematopoietic cell transplantation (alloHCT) for hematologic malignancies has significantly decreased over time, which has resulted in decreased early transplanted related mortality.

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

Suggested word limit of 200 words:

Primary Aim
- To evaluate trends of major organ injuries during 2000-2019 among CAYA with hematologic malignancies during first 100 days post-alloHCT. Major organ injury will be categorized under 5 systems as follows: pulmonary (mechanical ventilation), renal (need for dialysis), neurological (stroke or hemorrhage), liver (veno-occlusive disease) and cardiac (congestive heart failure).

Secondary Aim:
The following outcomes will be compared between patients with and without (controls) major organ injuries during the first 100 days post alloHCT
- Incidence of non-relapse mortality (NRM) at days +100, +180, 1 years & 2 years
- Overall survival (OS) at 1 and 2 years
- Evaluate trends of acute graft-versus-host disease(aGVHD) during 2000-2019

Exploratory aim
- To study risk factors associated with major organ injuries

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.

Major advances in the field of hematopoietic cell transplantation may have translated into a decreased risk of organ injuries in recipients of allogeneic HCT in the current era. To date there have been no large registry-based studies analyzing the trends of this post-transplant complication in a systematic fashion. Therefore, we propose to study the trends and impact of organ injuries in a large contemporary cohort of CAYA allogeneic HCT recipients. The findings of this study may provide further understanding of impact of recent advances on NRM and OS. It may also provide insight into identify potential modifiable risk factors that could be pursued prospectively in future studies.

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.

Allogeneic hematopoietic cell transplantation (alloHCT) is a curative treatment for high risk malignancies in children and young adults (CAYA) [1]. Refinement of HLA typing in late 90's and early 2000's had resulted in a major improvement in clinical outcomes following AlloHCT [2]. Other major changes in last 2 decades have been improved molecular diagnosis for viral, bacterial and fungal infections, availability of newer antibiotics for prophylaxis and treatment of infections, availability of defibrotide, increased use of haplo-identical transplants and availability of viral specific T-cells[3]. All these advances may have potentially decreased the organ injuries post-alloHCT and ultimately reduction in TRM in the most recent era.

At our center we have studied early organ toxicities (8 organ systems including GI tract, mucosal, bladder) and its association with TRM in a cohort of 164 alloHCT recipients [4].We observed that for a given patient the risk of TRM increased proportionally with increasing number of organ toxicities: 0.14% vs 29.6% vs 80% in patients with 0-2 vs 3-6 vs > 6 organ toxicities. In a more recent study of 240 patients, from our center we demonstrated that in recent time period, 2013-16 as compared to 2009-2012 and 2005-2008, patients had a significant decrease in pulmonary injury (30% vs 40% vs 50% p=0.01), kidney injury (66% vs 78% vs 86%; p=0.01) and a lower incidence of liver injury (31% vs 43% vs 45% p=0.20). Decrease in the incidence of organ injury was associated with decrease health care utilization and cost associated with alloHCT and improvement in survival [5]. Single center studies are important for the field but are not generalizable. Only multicenter or large database studies like CIBMTR can provide generalizable information regarding decrease in organ toxicities in the most recent era which can corroborate the impact of advances in the field of alloHCT on organ injuries and TRM. Therefore, in our proposed study we plan to utilize data extracted from the CIBMTR to study the incidence, trends of organ injuries in the current era and their impact on early transplant morality.

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.

Inclusion Criteria
- Age 0-39 years at time of alloHCT with 2 years of follow-up
- Transplant date: 2000-2019
- Transplant type – first alloHCT
- HCT Indication – ALL and AML
- Stem cell source – bone marrow, peripheral blood, umbilical cord blood.
- Received myeloablative and reduced intensity conditioning

Exclusion Criteria
- Non-consent patients
- Recipients of non-myeloablative conditioning
- Missing day 100 baseline form

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 related
- Age at transplant (0-2y vs 2-10y v 10-21y v 21-39y)
- Ethnicity (Caucasian vs African American v other)
- Gender (male vs female)
- Indication for transplant (ALL, AML)
- Disease Status at time of Transplant (CR1, CR2, ≥CR3)
- Performance Status (90-100 vs < others)
- Donor- Recipient CMV match
- HCT-CI (0-2 vs≥ 3)

Transplant related
- Donor source: Bone marrow, PBSC, UCB
- Donor and Graft Source (Matched Related BM v Matched Related PBSC v Matched Related Cord v Matched Unrelated BM v Matched Unrelated PBSC v Matched Unrelated Cord v. Mismatched Related BM v Mismatched Related PBSC v Mismatched Related Cord v Mismatched Unrelated BM v Mismatched Unrelated PBSC v Mismatched Unrelated Cord)
- TBI (Y/N)
- TBI >800cGy (Y/N)
- GVHD prophylaxis (ex-vivo T-cell depletion, CNI+MMF, CNI+MTX, CNI alone, other)
- In vivo T-cell depletion (ATG/Campath v none)
- Conditioning regimen (myeloablative/reduced intensity)
- Year of transplant (2000-2010 vs. 2011-2019)

Post-transplant variables during first 100 days.
- aGVHD (Y/N)
- aGVHD (grade II-IV vs grade I v none)
- Gut aGVHD: grade II-IV.
- Pulmonary injury: Need for BAL (Y/N), need for mechanical ventilation (Y/N)
- Liver dysfunction: VOD (Y/N), bilirubin >2mg/dl (Y/N)
- Renal failure severe enough to warrant dialysis post-HCT (Y/N)
- Congestive Heart Failure (Y/N)
- CNS: hemorrhage and/or stroke (Y/N)
- Bacterial infection (Gram +ve and Gram negative) (Y/N)
- Fungal infection (Y/N)

Study Design

This will be a retrospective cohort study evaluating the trends of major organ toxicities among CAYA population over 20-year period from 2000 to 2019. Using CRF level data, organ injury specific mortality will be assessed in each treatment era (2000-2006 vs 2007-2014 vs. 2015-2019). Descriptive statistics will be used to summarize patient demographics and transplant characteristics. Counts and percentages for categorical variables and mean, range will be described for continuous variables. The primary outcome for analysis will be incidence of major organ toxicities and it impact on short term mortality. The change in organ injury-specific mortality over time will also be compared between each treatment era .Outcomes (primary and secondary) will be compared between patients with any organ injury (1-5) vs without. We will further analyze impact of increasing organ injury on outcomes i.e. 0-1 vs 2-3 vs 4-5. Cox regression analysis will be performed to identify risk factors of early mortality in pediatric and young adult patients using a stepwise multivariable Cox regression analysis. A $p < 0.05$ will be considered significant. For survival analyses, events will be defined as disease relapse, death without relapse, death from disease relapse or death from any cause. NRM was defined as death from any cause other than relapse. The Kaplan-Meier method will be used to estimate the 2-year OS, and the cumulative incidence function will be used to estimate the 2-year TRM.

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

Not applicable

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

Not applicable

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.

Not applicable

Q26. REFERENCES:

1. Satwani P, Kahn J, Jin Z. Making strides and meeting challenges in pediatric allogeneic hematopoietic cell transplantation clinical trials in the United States: Past, present and future. Contemp Clin Trials. 2015 Nov;45(Pt A):84-92.
2. Ringdén O. Allogeneic bone marrow transplantation for hematological malignancies--controversies and recent advances. Acta Oncol. 1997;36(6):549-64.
3. Harris KM, Davila BJ, Bollard CM, Keller MD. Virus-Specific T Cells: Current and Future Use in Primary Immunodeficiency Disorders. J Allergy Clin Immunol Pract. 2019 Mar;7(3):809-818.
4. Al Mulla N, Kahn JM, Jin Z, Qureshi M, Karamehmet E, Yoon-Jeong Kim G, Levinson AL, Bhatia M, Garvin JH, George D, Kung AL, Satwani P. Survival Impact of Early Post-Transplant Toxicities in Pediatric and Adolescent Patients Undergoing Allogeneic Hematopoietic Cell Transplantation for Malignant and Nonmalignant Diseases: Recognizing Risks and Optimizing Outcomes. Biol Blood Marrow Transplant. 2016 Aug;22(8):1525-1530.
5. Ricci A, Jin Z, Bourgeois W, Broglie L, Bhatia M, Davis L, George D, Garvin JH, Hall M, Ruiz J, Satwani P. Financial impact of post-transplant complications among children undergoing allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2020 Jul;55(7):1421-1429.

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

Characteristics of patients 39 and younger who underwent first allo HCT for AML or ALL reported to the CIBMTR 2008-2019

Characteristic	N (%)
No. of patients	6210
No. of centers	130
Age at HCT - no. (%)	
<10	3089 (50)
10-17	2747 (44)
18-29	374 (6)
HCT-CI Score - no. (%)	
0-2	5093 (82)
3+	1078 (17)
TBD	14 (0)
Not Reported	25 (0)
Primary disease for HCT - no. (%)	
AML	2852 (46)
ALL	3358 (54)
Donor type (%dnrinfo() macro) - no. (%)	
HLA-identical sibling	1490 (24)
Twin	6 (0)
Other related	747 (12)
Well-matched unrelated (8/8)	1612 (26)
Partially-matched unrelated (7/8)	633 (10)
Mis-matched unrelated (<= 6/8)	44 (1)
Multi-donor	3 (0)
Unrelated (matching TBD)	72 (1)
Cord blood	1603 (26)
Computed planned conditioning intensity - no. (%)	
MAC	5838 (94)
RIC	154 (2)
NMA	70 (1)
TBD	131 (2)
Not reported	17 (0)
Planned GVHD prophylaxis - no. (%)	
No GvHD Prophylaxis	60 (1)
TDEPLETION alone	108 (2)
TDEPLETION ± other	130 (2)
CD34 select alone	99 (2)
CD34 select ± other	93 (1)
Cyclophosphamide alone	14 (0)
Cyclophosphamide ± others	368 (6)

Characteristic	**N (%)**
FK506 + MMF ± others	522 (8)
FK506 + MTX ± others	1757 (28)
FK506 ± others	82 (1)
FK506 alone	61 (1)
CSA + MMF ± others	1197 (19)
CSA + MTX ± others	1351 (22)
CSA ± others	180 (3)
CSA alone	99 (2)
Other GVHD Prophylaxis	77 (1)
Identical twin donor	4 (0)
Not reported	8 (0)
Graft Source - no. (%)	
Bone marrow	3388 (55)
Peripheral blood	1219 (20)
Umbilical cord blood	1603 (26)
Indicator of HCT cases in CRF retrieval - no. (%)	
No	3817 (61)
Yes	2393 (39)
Year of Transplant - no. (%)	
2008 - 2013	3009 (48)
2014 - 2019	3201 (52)
Follow-up - median (range)	60 (3-159)

Combined CIBMTR Proposal

Q1. Study Title

Incidence, risk factors and outcomes of acute cardiac complications after post-transplant cyclophosphamide based GVHD prophylaxis; A Retrospective Analysis from CIBMTR Database

Q2. Keywords

Adverse cardiac complications, Post-transplant Cyclophosphamide, Organ toxicity, Incidence, Risk factors and Outcomes

Q3. PI Information

Kittika Poonsombudlert
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Clinical Fellow
University of Iowa Hospital and Clinics, Hematology-Oncology and Blood and Marrow Transplantation

Christopher Strouse, MD
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Associate Professor
University of Iowa Hospital and Clinics, Hematology-Oncology and Blood and Marrow Transplantation

Hemalatha Rangarajan, MD
hemalatha.Rangarajan@nationwidechildrens.org
Clinical Assistant Professor of Pediatrics
Nationwide Children's Hospital, Columbus, Ohio

Prakash Satwani, MD
ps2087@columbia.edu
Associate Professor of Pediatrics
Columbia University Medical Center, NY

Dipenkumar Modi, MD
modid@karmanos.org
Assistant Professor
Karmanos Cancer Institute, Wayne State University

Q4. Junior Investigator Status

Yes

Q5. Do you identify as an underrepresented/minority?

No?

Q12. Current Ongoing Work with CIBMTR

Dr. Rangarajan:

I have completed the following study with CIBMTR
IB17-02: Outcomes of Pediatric patients with JMML following unrelated donor transplant: The impact of Donor KIR Gene Content and KIR Ligand Matching
Manuscript Published. Transplantation and Cellular Therapy. PMID: 34407489. Role: Principal investigator
The following proposals that I have submitted have been accepted and are at varying stages of development. I am one of the co-principal investigators on all these protocols.
1. IN20-01: Incidence, Risk Factors, and Outcomes of Infections post CD19 CAR T therapies. February 2020. Data analysis is ongoing.
2. CT20-02: Resource utilization in patients receiving CAR-T Therapy. February 2020. Protocol development is in progress.
3. PC19-03: Outcomes of allogeneic hematopoietic cell transplantation in pediatric patients with AML and CNS
involvement. February 2019. Data analysis is ongoing

Dr. Modi:

Impact of Conditioning Regimen Intensity on the Outcomes of Mature T-cell Lymphomas Undergoing Allogeneic Transplant- Contributed in results review and provided critical feedback on manuscript

Q13. Proposed Working Committee

- Regimen Related Toxicity and Supportive Care

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

Dr. Rangarajan: Yes

Dr. Modi: No

Q14a. If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

Dr. Rangarajan:

Dr. Bipin Savani. I briefly emailed Dr. Savani, to ask if this proposal/concept would be feasible, especially utilizing the existing dataset of IN18-01 and IN-19-01 to answer the study question. Dr. Savani replied positively and encouraged me to put forth the proposal for consider

Q15. Research Questions

<u>Primary questions:</u>

- What is the cumulative incidence of acute cardiac complications after the use of Post-Transplant Cyclophosphamide (PT-Cy) compared to non-PT-Cy based graft-versus-host disease (GVHD) prophylaxis?
- What pre-transplant risk factors are associated with development of cardiac complications?

<u>Secondary Questions:</u>

- How is the development of early post-transplant cardiac complications associated with other clinical outcomes, such as overall survival, disease free survival and non-relapse mortality?

(If deemed feasible and acceptable by CIBMTR)

- What is the incidence of other organ toxicities (including: neurological, mucositis, pulmonary, renal, and hepatic) following the use of PT-Cy compared to non-PT-Cy based GVHD prophylaxis?

IV. Research Hypothesis (Scientific question that is the basis for the study)

- Use of PT-Cy is associated with increased risk of cardiac complications compared to other types of GVHD prophylaxis.
- Patients who develop cardiac complications following PT-Cy are at risk for inferior short- and long-term outcomes compared to those who did not.
- (If deemed feasible and acceptable by CIBMTR) Use of PT-Cy is associated with increased risk of other non-cardiac organ toxicities compared to other types of GVHD prophylaxis.

V. Specific Objectives/Outcomes to be Investigated (Include Primary, Secondary, etc.)

Primary Objective:

1) To evaluate the incidence and risk factors for development of an acute cardiac event (ACE) as a composite endpoint

   ACE as defined per institution definition:

   - Development of acute heart failure
   - Cardiac arrhythmia (including de novo arrythmia and aggravated pre-existing arrhythmia)
   - Acute Coronary Syndrome
   - Cardiogenic shock
   - Pericarditis
   - Pericardial effusion

2) Perform multivariate analysis of pre-transplant variables for association with development of ACE. Variables to be considered:
   - Age
   - Sex
   - History of cardiac disease (defined by HCT-CI cardiac score: would include details if available)
   - Conditioning regimen intensity (MAC vs NMAC vs RIC)
   - GVHD prophylaxis (PT-Cy vs non-PT-Cy regimens)

Secondary Objectives:

1) To assess the
   - 1-year overall survival (OS)
   - 1-year disease free survival (DFS)
   - 100- day and 1-year non-relapse mortality (NRM) in patients who developed ACE compared to those who did not

2) (If feasible and acceptable to CIBMTR we also propose evaluating the following non-cardiac organ toxicities following use of PT-Cy)

Specific organ toxicities to be considered:

- Composite neurological events: ischemic or hemorrhagic stroke, posterior reversible encephalopathy syndrome (PRES), Seizure, acute metabolic encephalopathy
- Mucositis: symptomatic disease requiring treatment
- Composite pulmonary events: non-infectious pneumonia/pneumonitis, diffuse alveolar hemorrhage
- Composite renal events: thrombotic microangiopathy (TMA), acute kidney injury (AKI) requiring dialysis
- Composite hepatic events: veno-occlusive disease (VOD)

VI. Scientific Impact

Incorporation of haploidentical donor (haplo) transplant has greatly expanded the donor pool for patients in need of life saving allogeneic stem cell transplant [1]. Use of PT-Cy based GVHD prophylaxis has been instrumental in making these donors feasible options [2]. The current understanding of incidence and risk factors for cardiovascular complications and other non-cardiac organ toxicities remains limited as previous study are performed mainly at single institutions [3-5] limiting the generalizability of the data. Therefore, we anticipate that the findings from this large CIBMTR database will assist in identifying high risk population in the pre-transplant counselling phase, inform post-transplant monitoring practices and direct survivorship needs. The risk factors identified from this study may also guide future studies aiming at development of cardiovascular complication and non-cardiac organ toxicity mitigation strategies.

VII. Scientific Justification

For some hematologic conditions, alloHSCT remains the only curative treatment option. Because of the substantial rate of non-relapse mortality associated with this treatment modality, studies are needed to better identify high risk population and pre-emptively optimize these patients. With better supportive care, this life saving procedure are now being offered to more patients with advanced age. Most recently, PT-Cy has been incorporated into the post-transplant setting to suppress alloreactive T cells stemming from less stringent HLA matching and to prevent acute graft-versus-host disease (aGVHD), especially in the context of haplo transplant [6, 7].

Potentially, one of the most serious adverse events in the early post-transplant period are cardiac complications, estimated to occur in 4.5% of patients undergoing alloHSCT [8]. Data regarding incidence and risk factors for acute cardiovascular complications specifically following PT-Cy has to date been limited to retrospective single institution studies. The studies from Lin et al [5], Dulery et al [3], Benfield et al [10] and Modi et al [4] each reporting high incidence of AEC in patients receiving PT-Cy (21.9%,19%, 15.7% and 14.3% respectively) but with varied risk ratios in comparison to patients not treated with PT-Cy (1.2, p=0.33; 2.7, p=0.002; not reported; 1.4, p=0.34 respectively). These analyses may have had insufficient power to detect a clinically meaningful effect of PT-Cy on NRM, OS and DFS, and each may have reflected individualized practices at each center. Therefore, we propose this study to better define the incidence, risk factors and outcomes of acute cardiovascular events associated with PT-Cy use.

Modi et al [4] additionally reported an increased risk of other non-cardiac organ toxicities associated with PT-Cy use, including mucositis, hypoxia, hypotension and hemorrhagic cystitis. An increased incidence of VOD [9, 10] and TMA [11] following PT-Cy use have also been reported following use of PT-Cy. Therefore, we will explore the incidence of other non-cardiac organ toxicities using the CIBMTR database.

Collaboratively, we hope that the information gathered through this study will assist in identifying patients at risk for acute cardiac events and other non-cardiac organ toxicities in attempt to better select the optimal transplant candidate and provide guidance on the post-transplant surveillance protocol.

VIII. Participant Selection Criteria

Inclusion Criteria

- Patients of all age
- Patients undergoing first allogeneic stem cell transplant (alloHCT)
- Indications for transplant: all hematologic malignancies
- Transplant performed between 2008-2020
- Patients receiving either bone marrow stem cells (BM) and mobilized peripheral blood stem cells (PBSC) will be included
- All types of conditioning regimen: myeloablative (MAC), non-myeloablative (NMAC) and reduced intensity (RIC) will be included
- Patients with pre-existing cardiac conditions will also be included in our study
- Study population: haplo related transplant with PT-Cy as GVHD ppx
- Control population (we can be flexible based on CIBMTR recommendations): match related or match unrelated donor with non-PT-Cy as GVHD ppx matched for age, sex, conditioning regimen intensity and graft source
- (Alternatively, if preferable to CIBMTR) 2 control groups consisting of match related donor with PT-Cy as GVHD ppx vs match related donor with non-PT-Cy as GVHD ppx

Exclusion Criteria

- Patients who received umbilical cord blood stem cell transplant (UCBT)
- Mismatch unrelated donor transplant

IX. Does this Study Include Pediatric Patients

Yes

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

N/A

XI. Data Requirements

Patient related factors:

- Age at transplant
- Gender

- Race/Ethnicity
- Pre-transplant comorbidities
    - Hypertension requiring treatment
    - Dyslipidemia requiring treatment
    - Diabetes mellitus requiring insulin
    - Coronary artery disease
    - Chronic kidney disease
    - Baseline LVEF
    - Diastolic dysfunction at baseline
    - Peripheral vascular disease
- Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI)
- Karnofsky performance status scale

Disease related factors:

- Indication for transplant
- Cytogenetic risk group for each hematologic malignancy and revised international prognostic score (R-IPSS) for MDS
- Disease status at transplant

Donor related factors

- Donor age
- Donor/recipient gender
- Degree of donor/recipient HLA match
- Donor/recipient cytomegalovirus (CMV) serostatus

Treatment related factors and outcomes

- Conditioning regimen (regimen and intensity)
- Use of total body irradiation (TBI) in the conditioning regimen (yes vs no)
- Graft source (PBSC vs BM stem cell)
- GVHD ppx (PT-Cy vs non-PTCy regimen)
- Development of post-transplant cytokine release syndrome (CRS)
- aGVHD (yes vs no) with grade
- cGVHD (yes vs no) with grade

Outcomes:

Cardiac outcomes of interest

1) Cardiac complication
- Early post-transplant cardiac complication (up to day +100)
    - Development of acute heart failure
    - Cardiac arrhythmia (including de novo arrythmia and aggravated pre-existing arrhythmia)
    - Acute Coronary Syndrome
    - Cardiogenic shock
    - Pericarditis

- Pericardial effusion

- Late post-transplant cardiac complication (after day +100)
  - Development of acute heart failure
  - Cardiac arrhythmia (including de novo arrythmia and aggravated pre-existing arrhythmia)
  - Acute Coronary Syndrome
  - Cardiogenic shock
  - Pericarditis
  - Pericardial effusion

2) Other outcomes:
   - Survival status
   - Recovery from cardiac complication (if available)
   - Cause of non-relapse mortality
   - Time of death from HCT

(Based on feasibility and acceptability as determined by CIBMTR)

3) Adverse non-cardiac organ toxicity (occurring within day +100):

- Incidence of ischemic or hemorrhagic stroke, PRES
- Incidence of mucositis requiring treatment
- Incidence of non-infectious pneumonia/pneumonitis, diffuse alveolar hemorrhage
- Incidence of TMA or AKI requiring dialysis
- Incidence of VOD

XII. Patient Reported Outcome (PRO) Requirement

N/A

XIII. Sample Requirements (if study will use biologic samples from the NMDP Research Sample Repository)

Not required

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Characteristics of patients who underwent allo HCT for any malignant disease with PTCY reported to the CIBMTR 2017-2019

	PT-Cy Use	
Characteristic	**No**	**Yes**
No. of patients	3472	2089
No. of centers	140	122
Age at HCT - no. (%)		
18-29	330 (10)	224 (11)
30-39	307 (9)	189 (9)
40-49	408 (12)	262 (13)
50-59	690 (20)	457 (22)
60-69	1271 (37)	737 (35)
>=70	466 (13)	220 (11)
Primary disease for HCT - no. (%)		
AML	1083 (31)	789 (38)
ALL	436 (13)	301 (14)
Other leukemia	77 (2)	54 (3)
CML	62 (2)	46 (2)
MDS	1329 (38)	563 (27)
Other acute leukemia	28 (1)	27 (1)
NHL	245 (7)	153 (7)
HD	108 (3)	120 (6)
PCD	104 (3)	36 (2)
Donor type (%dnrinfo() macro) - no. (%)		
HLA-identical sibling	829 (24)	112 (5)
Other related	162 (5)	1468 (70)
Well-matched unrelated (8/8)	1799 (52)	299 (14)
Partially-matched unrelated (7/8)	161 (5)	157 (8)
Mis-matched unrelated (<= 6/8)	11 (0)	49 (2)
Unrelated (matching TBD)	2 (0)	1 (0)
Cord blood	508 (15)	3 (0)
Graft Source - no. (%)		
Bone marrow	362 (10)	545 (26)
Peripheral blood	2602 (75)	1541 (74)
Umbilical cord blood	508 (15)	3 (0)
Indicator of HCT cases in CRF retrieval - no. (%)		
Yes	3472 (100)	2089 (100)
Year of HCT - no. (%)		
2017	1383 (40)	628 (30)
2018	1193 (34)	730 (35)
2019	896 (26)	731 (35)

	PT-Cy Use	
Characteristic	**No**	**Yes**
Follow-up - median (range)	25 (3-52)	24 (3-51)

Characteristics of patients who underwent allo HCT for any malignant disease with PTCY reported to the CIBMTR 2017-2019

	PT-Cy Use	
Characteristic	**No**	**Yes**
No. of patients	3472	2089
Congestive heart failure (CHF) (CRF track) - no. (%)		
Censoring	3340 (96)	1991 (95)
Event	82 (2)	74 (4)
Missing	50 (1)	24 (1)
Arrhythmia (CRF track) - no. (%)		
Censoring	3100 (89)	1796 (86)
Event	253 (7)	178 (9)
Missing	119 (3)	115 (6)
Coronary artery disease (CAD) (CRF track) - no. (%)		
Censoring	3328 (96)	1966 (94)
Event	25 (1)	8 (0)
Missing	119 (3)	115 (6)
Myocardial infarction (MI) (CRF track) - no. (%)		
Censoring	3380 (97)	2036 (97)
Event	41 (1)	30 (1)
Missing	51 (1)	23 (1)