Not for publication or presentation

2021 STATUS REPORT
GRAFT SOURCES AND MANIPULATION WORKING COMMITTEE

Working Committee Leadership	
Co-Chair:	Ian McNiece; CellMED Consulting; aussiflier@aol.com
Co-Chair:	Claudio Brunstein; University of Minnesota; bruns072@umn.edu
Co-Chair:	Filippo Milano; Fred Hutchinson Cancer Research Center; fmilano@fredhutch.org
Scientific Director:	Mary Eapen; CIBMTR Statistical Center; meapen@mcw.edu
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Statistician:	Molly Johnson; CIBMTR Statistical Center; mhjohnson@mcw.edu

INTRODUCTION

a. Minutes and overview plan from 2020 TCT meeting (Attachment 1)

PROPOSALS MOVING FORWARD FOR SCORING (click here to cast your score)

a. PROP 2010-67 Optimal GVHD prevention strategy in older, robust patients with acute leukemias and myeloid malignancies undergoing myeloablative, matched donor hematopoietic cell transplantation (Rich
J. Lin/ Sergio A. Giralt). (Attachment 2)

b. PROP 2010-215 Post-transplant cyclophosphamide (PTCy) vs. anti-thymocyte globulin (ATG) in patients with acute leukemia receiving HLA-mismatched unrelated donor (MMUD) hematopoietic cell transplant (HCT) (Antonio Martin Jimenez/ Trent Peng Wang/ Krishna Komanduri/ Marcos de Lima). (Attachment 3)

PROPOSALS DROPPED BECAUSE THEY OVERLAP WITH EXISTING STUDIES OR ARE NOT FEASIBLE DUE TO LIMITATIONS OF AVAILABLE PATIENTS OR DATA

a. PROP 2006-03 An analysis of the impact of donor characteristics on overall survival of recipients of haploidentical hematopoietic stem cell transplants (Sophia R. Balderman/ Theresa E. Hahn/ Philip L. McCarthy).

b. PROP 2008-02 Comparison of haploidentical HSCT with post-transplant cyclophosphamide (PTCy) and of HLA matched unrelated donor (MUD) HSCT for children, adolescents and young adults with hematologic malignancies (Malika Kapadia/ John T. Horan).

c. PROP 2010-40 Single day salvage conditioning for second haploidentical transplant following graft failure after allogeneic hematopoietic cell transplantation (Emmanuel Katsanis).

d. PROP 2010-45 Non-first-degree related donor haploidentical transplants using posttransplant cyclophosphamide – curtailing degrees of separation (Pashna N. Munshi/ Scott D. Rowley/ Medhi Hamadani).

e. PROP 2010-93 Outcomes after haploidentical allogeneic hematopoietic cell transplantation using post-transplant cyclophosphamide as compared to matched sibling donor and other alternative donor transplantation in pediatrics patients with acute leukemia and myelodysplastic syndrome (Hemalatha Rangarajan/ Prakash Satwani).

f. PROP 2010-141 Comparison of bone marrow versus peripheral blood in haploidentical transplantation using post-transplant cyclophosphamide (Nidhi Sharma/ Yvonne Efebera).

g. PROP 2010-152 Outcomes of patients undergoing haploidentical, matched and mismatched unrelated peripheral blood stem cells (PBSC) transplant for acute myeloid leukemia and myelodysplastic syndrome with PTCy for GvHD prophylaxis (Monzr M. Al Malki/ Shukaib Arslan/ Filippo Milano).

h. PROP 2010-156 A comparison of post-transplant cyclophosphamide (PTCY) platforms: HLA-mismatched unrelated donor (MMUD) hematopoietic cell transplant (HCT) versus haploidentical HCT (Trent Peng Wang/ Antonio Martin Jimenez/ Krishna V. Komanduri).

i. PROP 2010-183 Comparison of outcomes after unmanipulated haploidentical transplantation, cord blood transplantation and unrelated donor transplantation in children with hematologic malignancies (Rabi Hanna/ Seth J. Rotz).

j. PROP 2010-196 Comparing outcomes between young HLA-haploidentical and old HLA-matched related donor allogeneic transplants in hematologic malignancies (Shatha Farhan).

k. PROP 2010-198 Comparing outcomes between HLA-haploidentical and HLA-matched unrelated donor allogeneic transplants in patients with MPN (Shatha Farhan).

l. PROP 2010-204 Comparison of haploidentical donor allogeneic hematopoietic cell transplant (HCT) with post- transplant cyclophosphamide to matched donor HCT for myeloproliferative neoplasms and myelodysplastic Syndrome/myeloproliferative neoplasm overlap syndromes (Hany Elmariah/ Nelli Bejanyan/ Taiga Nishihori).

m. PROP 2010-217 Haploidentical allogeneic stem cell transplant may have better overall survival, leukemia free survival and GVHD free relapse free survival (GRFS) than umbilical cord blood transplant in acute lymphoblastic leukemia patients (Ankur Varma/ Sunita Nathan/ Mohammad Junaid Hussain).

n. PROP 2010-239 Outcomes of allogeneic hematopoietic cell transplantation for older patients with hematological malignancies: A comparison between older matched related donor vs. younger matched unrelated donor vs. younger haploidentical donor (Guru Subramanian Guru Murthy/ Mehdi Hamadani).

o. PROP 2010-262 Effect of alternative donors choice in the outcomes of second transplant for disease relapse after first transplant (Evandro Bezerra/ William J. Hogan/ Mary E. Flowers/ Mark R. Litzow).

p. PROP 2010-273 T cell replete vs T cell deplete approaches for haploidentical transplant in patients with hematological malignancies (Hemalatha Rangarajan/ Prakash Satwani).

q. PROP 2010-274 Impact of donor and recipient ABO incompatibility on outcomes post allogeneic stem cell transplantation for non-malignant disorders in children (Hemlatha Rangarajan/ Prakash Satwani).

r. PROP 2010-291 Comparison of post-transplant cyclophosphamide and alpha-beta T-cell depletion in pediatric haploidentical hematopoietic stem cell transplant (Amanda M. Li/ Jacob Rozmus/ Kirk R. Schultz).

s. PROP 2010-302 Defining a safe and effective donor CD3 T-cell dose in T-cell replete haploidentical hematopoietic stem cell transplant with post-transplant cyclophosphamide (Antonio Di Stasi/ Ayman Saad/ Omer Jamy/ Susan Bal/ Donna Salzman/ Daniel Peavey/ Ameenah Tannehill).

t. PROP 2010-310 Graft source for salvage or rescue hematopoietic stem cell transplantation after primary graft Failure (Naveed Ali/ Leland Metheny/ Marcos de Lima).

u. PROP 2010-330 Outcomes for haploidentical transplantation with first- and second-degree relatives (Sayeef Mirza/ Lohith Gowda/ Stuart Seropian).

PROPOSALS NOT ACCEPTED FOR CONSIDERATION AT THIS TIME DUE TO RELATIVE SCIENTIFIC IMPACT COMPARED TO ONGOING STUDIES AND/OR OTHER PROPOSALS

a. PROP 2009-03 Comparing the efficacy of various donor sources in relapsed acute leukemias (AML and ALL) requiring a second allogeneic hematopoietic cell transplant (Mohamed A. Kharfan-Dabaja/ Hemant Murthy/ Madiha Iqbal/ Farah Yassine).

b. PROP 2010-121 Impact of CD34+ cell dose on outcomes after matched sibling and unrelated donor peripheral blood stem cell transplantation (Muhammad U. Mushtaq/ Sunil Abhyankar/ Joseph P. McGuirk).

c. PROP 2010-139 Impact of the various in vivo T-cell depletion agents (rabbit vs. equine ATG) on GVHD-free, relapse-free survival (GRFS) in patients with hematologic malignancies (Vanessa A. Fabrizio/ Kristin Page/ Jaap J. Boelens).

STUDIES IN PROGRESS

a. **GS18-01** Outcomes after haploidentical relative and matched unrelated donor transplants using PT-Cy containing GVHD prophylaxis. The aim of this study is to compare outcomes following haploidentical donor and matched unrelated donor transplantation in the setting of GVHD prophylaxis with post-transplant cyclophosphamide for both donor types. Presented at the 2020 Annual meeting of the American Society of Hematology. Status: Manuscript.

b. **GS19-02** Graft failure in MDS and acute leukemia patients after allogeneic stem cell transplantation receiving post-transplant cyclophosphamide (PT-Cy). The aim of this study is to examine outcomes of haploidentical HCT with PT-Cy, matched donor HCT with PT-Cy and matched donor HCT without PT-Cy GVHD prophylaxis. Status: Protocol Development.

c. **GS19-03a** Impact of granulocyte colony-stimulating factor on in-vivo T-cell depleted allogeneic hematopoietic cell transplantation. The aim of this study is to compare outcomes following T-cell depleted allo HCT with or without planned G-CSF. Status: Manuscript.

d. **GS20-01** Reduced intensity conditioning and transplantation of double unrelated umbilical cord blood versus human leukocyte antigen-haploidentical related bone marrow for acute leukemias. The aim of this study is a comparison of survival and other outcomes from the randomized clinical trial (BMT CTN 1101) with outcomes from a contemporaneous cohort from the CIBMTR to 1) generalizability of the findings of the clinical trial and 2) comparison of outcomes beyond 2 years. Status: Analysis.

PUBLICATIONS, SUBMITTED PAPERS, PRESENTATIONS

a. **GS19-03b** George G, Martin AS, Chhabra S, Eapen M. The effect of G-CSF use on hospital length of stay after an allogeneic hematopoietic cell transplantation: A retrospective multicenter cohort study. Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation. doi:10.1016/j.bbmt.2020.08.013. Epub 2020 Aug 18.

b. **GS18-02** Solomon SR, St Martin A, Zhang M-J, Ballen K, Bashey A, Battiwalla M, Baxter-Lowe LA, Brunstein C, Chhabra S, Perez MAD, Fuchs EJ, Ganguly S, Hardy N, Hematti P, McGuirk J, Peres E, Ringden O, Rizzieri D, Romee R, Solh M, Szwajcer D, van der Poel M, Waller E, William BM, Eapen M. Optimal donor for African Americans with hematologic malignancy: HLA-haploidentical relative or umbilical cord blood transplant. Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation. 2020 Oct 1; 26(10):1930-1936. doi:10.1016/j.bbmt.2020.06.029. Epub 2020 Jul 7. PMC7530013.

c. **GS18-03** Fatobene G, Rocha V, St Martin A, Hamadani M, Robinson S, Bashey A, Boumendil A, Brunstein C, Castagna L, Dominietto A, Finel H, Chalandon Y, Kenzey C, Kharfan-Dabaja M, Labussière-Wallet H, Moraleda JM, Pastano R, Perales M-A, El Ayoubi HR, Ruggeri A, Sureda A, Volt F, Yakoub-Agha I, Zhang M-J, Gluckman E, Montoto S, Eapen M. Nonmyeloablative alternative donor transplantation for Hodgkin and non-Hodgkin lymphoma: From the LWP-EBMT, Eurocord, and CIBMTR. Journal of Clinical Oncology. 2020 May 10; 38(14):1518-1526. doi:10.1200/JCO.19.02408. Epub 2020 Feb 7. PMC7213591.

d. **GS18-01** Comparison of myeloablative haploidentical or umbilical cord blood transplantation for pediatric and adult patients with acute leukemia. *Oral presentation at the ASH 2020 Annual Meeting.*

e. **GS18-04** Alternative donor transplantation for myelodysplastic syndromes: haploidentical relative and matched unrelated donors. *Submitted.*

f. **GS19-01** Comparison of myeloablative haploidentical or umbilical cord blood transplantation. *Submitted.*

A G E N D A
CIBMTR WORKING COMMITTEE FOR GRAFT SOURCES & MANIPULATION
Orlando, FL
Thursday, February 20, 2020, 2:45 – 5:15 pm

Co-Chair:	**Asad Bashey, MD, PhD, Northside Hospital, Atlanta, GA** **Telephone: 404-255-1930; E-mail: abashey@bmtga.com**
Co-Chair:	**Ian McNiece, PhD, CellMED Consulting, Miami, FL** **Telephone: 305-510-7057; E-mail: aussiflier@aol.com**
Co-Chair	**Claudio Brunstein, MD, PhD, University of Minnesota, Minneapolis, MN;** **Telephone: 612-625-3918 , E-mail: bruns072@umn.edu**
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Statistical Director:	**Mei-Jie Zhang, PhD, CIBMTR Statistical Center, Milwaukee, WI;** **Telephone: 414-456-8375; E-mail: meijie@mcw.edu**
Statistician:	**Molly Johnson, MPH, CIBMTR Statistical Center, Milwaukee, WI;** **Telephone: 414-805-2258, E-mail: mhjohnson@mcw.edu**

1. Introduction

Dr. Brunstein opened the meeting at 2:45 pm by welcoming the working committee members for attending the Graft Sources and Manipulation Working Committee (GSWC) meeting. He disclosed the funding and conflict of interest information for the CIBMTR. He introduced the GSWC's leadership, welcomed the incoming chair Dr. Milano and thanked Dr. Bashey for his contributions to the committee over the years. Dr. Brunstein asked for and received approval of 2019 meeting minutes. He then discussed working committee membership, goals, proposal selection, voting and rules of authors. Dr. Brunstein described the differences in data sources at the CIBMTR, trends in donor types in the United States, and the Advisory Committee metrics. Dr. Brunstein invited Dr. Bashey to the podium.

2. Published/ submitted papers and studies in progress

a. Dr. Bashey invited Dr. Fatobene to present GS18-03: *Comparison of outcomes of reduced intensity transplantation in lymphoma patients using haploidentical related donors vs unrelated cord blood* (*Journal of Clinical Oncology.* In Press). Dr. Bashey then invited Dr. Grunwald to present GS18-04: *Comparison of Outcomes with Haploidentical and Matched Unrelated Donors for Hematopoietic Stem Cell Transplantation in Myelodysplastic Syndromes* (Poster at ASH 2019, manuscript preparation). Dr. Bashey recommended committee members stop by the Graft Sources Poster Session on Saturday evening to see the poster for GS19-01: *Comparison of myeloablative haploidentical or umbilical cord blood transplantation for pediatric and adult patients with acute leukemia*. Dr. Bashey invited Dr. McNiece to introduce proposals.

3. Future/proposed studies

a. **PROP 1910-10** This proposal was seeking to compare outcomes between bone marrow and peripheral blood grafts and cell dose in myelofibrosis cases in matched related donors and matched unrelated donors. Dr. Salas presented the proposal.
The CIBMTR identified 621 cases of adults with myelofibrosis who received a peripheral blood transplant from a matched related or unrelated donor between 2008 and 2018. There was CD3+ infusion information available for 511 of these cases.
The primary objective of this proposal is to compare efficacy of graft sources. Due to low numbers of bone marrow grafts available and the proposal aimed to include a descriptive analysis of these cases only. The secondary aim of this study is to explore the optimal cell dose in each graft source. This became the primary aim as the proposal was limited to peripheral blood cases.
There was discussion on the importance of splenectomy and spleen size in outcomes of myelofibrosis cases. There was a recommendation to include the CD3 and TNC dose. There was a comment that pre-transplant management, specifically the Jakafi inhibitor and maintenance would be an important factor to consider and if we collect this information. Andrew informed the committee that we collect splenectomy and Jakafi inhibitor information. Dr. Bashey recommended we remove donor types with small numbers if the proposal is accepted to decrease heterogeneity in the study population.

b. **PROP 1911-06** This proposal was seeking to create primary graft failure (PGF) scoring systems for UCB and haploidentical with PTCY for adults with hematologic malignancies. Dr. Nathan presented the proposal.
The CIBMTR identified 1753 cases first allo transplants for adults with a hematologic malignancy (n=1435 haploidentical with PT-Cy, n=61 UCB, and n=257 dUCB) between 2014 and 2019.
The primary aim of the study is to create scoring systems for PGF for each graft source. The secondary aims are to predict PGF following transplant of Haploidentical with PT-Cy and UCB.
There was some discussion of donor specific antibodies. There was discussion if it would be important to add secondary graft failure to the study and the differences in determinants of primary and secondary graft failure. There was a question about how PGF was defined and Dr. Nathan responded that PGF is achieving counts greater than 500 for three consecutive days and by donor chimerism decreasing after initial engraftment. Dr. Brunstein asked if this study would be helpful if chimerism was not available. Andrew St. Martin commented that chimerism data is not consistent by cell type or time point. Dr. Bashey commented specific cell types. There was discussion on how many graft scoring systems would be necessary in this proposal, by graft source or donor type. There was a comment that chimerism is essential to the study and it does not have to be consistent information to be valid.

c. **PROP 1911-13** This proposal was seeking to compare all donor types, graft sources, DRI and conditioning regimens to identify the ideal donor for each transplant after identifying the "optimal goal" for each adult patient eligible for transplant for AML/MDS and ALL. Dr. Varma presented the proposal.
The CIBMTR identified 7065 cases who underwent their first allo transplant for AML, ALL, or MDS between 2012 and 2018 (3832 MAC, 3233 RIC/NMA).
The primary aim of the study was to look at non-relapse mortality, relapse, disease-free survival, overall survival, secondary malignancy at 5 years and GRFS. The secondary aim was to stratify the above outcomes by conditioning intensity for each donor type.
A comment was made about the nuance of donor selection, conditioning, GVHD prophylaxis and that it may need to be further stratified by conditioning regimen. A comment was made about other factors of importance, in order to individualize selection a large cohort would be necessary. A comment was made regarding the importance of mMUD and identifying PT-Cy cases as a separate group entirely. There was a question regarding the feasibility of the study and commented on the need to account for all factors. Dr. Varma responded that it is important to start somewhere, to identify donors and stratify by HCT-CI and conditioning.

d. **PROP 1911-170** This proposal was seeking to compare outcomes after a primary graft failure and associated salvage transplant for adults with hematologic malignancies. Dr. Ali presented the proposal.
The CIBMTR identified 631 adults with AML, ALL or MDS with primary graft failure after the first allogeneic transplant between 2008 and 2019, 147 of these cases went on to a second transplant.
The primary aim of this proposal was to examine 100-day and 1-year overall survival following salvage transplant by graft source. Secondary aims were to compare time to second transplant, relapse, and non-relapse mortality after primary graft failure and conditioning regimens for salvage transplant.
There was discussion about the inclusion of non-malignant diseases and myelofibrosis cases in the study. There was a comment that inclusion of non-malignant cases would introduce more heterogeneity to the study and the primary outcomes are related to relapse. A comment was made regarding the evaluation of early deaths which are not considered graft failure. Dr. Bashey commented on the second more cases being necessary. With 147 cases of salvage transplant, would there be sufficient cases to adjust for donor types and graft sources. There was a question regarding descriptive analysis instead of multivariate analysis. Additionally, the inclusion of lymphoid cases might be important although the disease matters. There was a recommendation to use EBMT and European cases to support the study.

e. **PROP 1911-20** The proposal seeks to compare outcomes of dUCB and HLA-Mismatched unrelated donors with PT-Cy for adults with hematologic malignancies. Dr. Farhadfar presented the proposal.
The CIBMTR identified 402 cases of adults with malignant disease (72 mMUD with PT-Cy, 15 dUCB 6/6 HLA match, 110 dUCB 5/6 HLA match, 205 dUCB ≤4/6 HLA match) transplanted between 2016-2018).
The primary aim of the study is to compare overall survival. The secondary aims include relapse free survival, transplant related mortality, time to engraftment, acute and chronic GVHD, and rates of early infections.
Dr. Soiffer commented that there was a small and heterogeneous population with short follow-up. Dr. Farhadfar recommended the years be increased. There was a comment that Hopkins has a large study ongoing and that the TED level might be an appropriate change. There was a comment on the low median follow-up of mMUD and noted a similar study was accepted 2 years ago. There was also a comment that PT-Cy and mMUD is a recent phenomenon and that may limit the available years.

f. **PROP 1911-39** This proposal seeks to compare outcomes from the CTN 1101 clinical trial cohort to a contemporaneous CIBMTR registry cohort. Dr. Brunstein presented this proposal.
The CIBMTR identified 875 adults transplanted for AML (CR 1), ALL (CR1), Non-Hodgkin Lymphoma or Hodgkin Lymphoma with TBI/Cy/Flu conditioning regimen (319 BM, 409 PBSC, 147 dUCB) between 6/19/2012 and 6/30/2018.
The primary aim of this study is to compare overall survival at 2 years post-transplant. Secondary aims include hematopoietic recovery, graft failure, acute and chronic GVHD, relapse, non-relapse mortality and progression-free survival.
There was discussion on the importance of including cord blood as it is less used. Dr. Brunstein recommended inclusion in the study as it was the contemporaneous nature of the registry cohort. There was a comment questioning the bias and graft type preference of centers.

g. **PROP 1911-19 / PROP 1911-210** This proposal seeks to compare the impact of cell dose for adults with hematologic malignancies who received a peripheral blood graft from a haploidentical donor. Dr. Farhadfar presented this proposal.
The CIBMTR identified 742 cases of adults who received a haploidentical transplant with PT-Cy with a peripheral blood graft for lymphoma/leukemia between 2013 and 2018.
The primary aim was to examine overall survival. The secondary aims include time to engraftment, acute and chronic GVHD, non-relapse mortality and relapse-free survival.
Dr. Bashey commented that there may be center issues when examining cell dose and haploidentical transplants as many centers may cap/limit the dose infused. A comment was made that all CIBMTR studies check for a center effect. A comment was made regarding the collection of CRS which is not

collected at this time. A comment was made on the importance of the CD3 dose and the conditioning intensity. A comment was made that high cell dose has issues as does low cell dose- different issues potentially.

Meeting adjourned at 4:45 pm.

Working Committee Overview Plan for 2020-2021

Study number and title	Current status	Goal with date	Total hours to complete	Total hours to goal - July 2021	Hours allocated to 6/30/2020	Hours allocated 7/1/2020-6/30/2021	Total Hours allocated
GS18-01: Comparison of outcomes after HCT from haploidentical donor with PT-Cy, MUD with PT-Cy, and MUD with CNI	Datafile prep	Manuscript prep – June 2020 Submitted – July 2021	160	160	90	70	160
GS18-02: Impact of race on relapse after haploidentical with PT-Cy vs cord blood	Submitted	Submitted – April 2020 Published – July 2021	0	0	0	0	0
GS18-04: Haploidentical donor with PT-Cy vs MUD for MDS	Manuscript preparation	Published – July 2021	10	20	10	10	20
GS19-01: Comparison of myeloablative haplo or CB in Acute Leukemia	Manuscript preparation	Published – July 2021	10	20	10	10	20
GS19-02: Graft Failure in MDS and Acute Leukemia with PT-Cy	Protocol pending	Data file preparation – July 2020	330	260	100	160	260

		Analysis- October 2020 Manuscript prep – July 2021					
GS19-03: Impact of G-CSF on in-vivo T-cell depleted Allogeneic Hematopoietic Cell Transplantation	Data file preparation	Manuscript preparation – July 2020 Submit – October 2020	170	170	100	70	170
GS20-01: RIC dUCB and haplo CTN 1101 cohort compared to CIBMTR contemporaneous registry cohort	Protocol pending	Protocol development preparation – July 2020 Manuscript prep – July 2021	330	260	0	260	260
GS20-02: Impact of PBSC cell dose on haplo with PT-Cy	Protocol pending	Protocol development – July 2020 Manuscript prep – July 2021	330	260	0	260	260

Oversight Assignments for Working Committee Leadership (March 2020)

Ian McNiece	**GS18-01:** Comparison of outcomes after HCT from haploidentical donor with PT-Cy, MUD with PT-Cy, and MUD with CNI.
	GS18-04: Haploidentical donor with PT-Cy vs MUD for MDS.
Claudio Brunstein	**GS19-01:** Comparison of myeloablative haplo or CB in Acute Leukemia
	GS19-02: Graft Failure in MDS and Acute Leukemia with PT-Cy
Ian McNiece	**GS19-03:** Impact of G-CSF on in-vivo T-cell depleted Allogeneic Hematopoietic Cell Transplantation
Filippo Milano	**GS20-01:** RIC dUCB and haplo CTN 1101 cohort compared to CIBMTR contemporaneous registry cohort
	GS20-02: Impact of PBSC cell dose on haplo with PT-Cy

Proposal: 2010-67

Title:
Optimal GVHD Prevention Strategy in Older, Robust Patients with Acute Leukemias and Myeloid Malignancies Undergoing Myeloablative, Matched Donor Hematopoietic Cell Transplantation

Richard J. Lin, MD, PhD, linr@mskcc.org, Memorial Sloan Kettering Cancer Center (Junior investigator)
Sergio A. Giralt, MD, giralts@mskcc.org, Memorial Sloan Kettering Cancer

Research hypothesis:
GVHD prophylaxis using either ex vivo TCD/CD34+ selection or PTCy-based, as compared to Tac/MTX, is associated with superior moderate to severe chronic GVHD-free, relapse free survival (CRFS) among older recipients (≥ 60yo) of myeloablative conditioned, allogeneic hematopoietic cell transplantation.

Specific aims:
The specific aims are:

- To compare CRFS among patients ≥ 60yo undergoing myeloablative conditioned, allogeneic hematopoietic cell transplantation with following GVHD prophylaxis in 2 matched-pair analysis:
  - **PTCy-based versus Tac/MTX**
  - **Ex vivo TCD/CD34+ selection versus Tac/MTX**
- To compare other transplant outcomes in the above 2 matched-pair analysis
  - OS
  - RFS/DFS
  - Cumulative incidence of relapse/disease progression
  - Cumulative incidence of NRM
  - 180-day cumulative incidence of acute GVHD (II-IV and III-IV)
  - 2-year cumulative incidence of chronic GVHD
  - 180-day cumulative incidence of infections

Scientific impact:
The study has the potential to establish the preferred GVHD prevention strategy among older patients with acute leukemias and myeloid malignancies who are candidates for myeloablative conditioning, as related to CRFS, infections, and relevant transplant outcomes. **Importantly, given the positive survival impact of myeloablation on MRD positive patients pre-transplant, there will be a significant population of older patients who could potentially benefit from myeloablative conditioning.**

Scientific justification:
Allogeneic hematopoietic cell transplantation (allo-HCT) is increasingly utilized in older patients with advanced hematologic malignancies because of advances in reduced intensity conditioning regimens, improved supportive care, and better selection of appropriate candidates (1). Little is known, however, about how allo-HCT affects the function, cognition, and quality of life of older recipients (2, 3). Moreover, given the significantly increased relapse risk associated with reduced intensity conditioning for acute leukemias and myeloid malignancies, older, robust patients must be strongly considered for myeloablative conditioning prior to allo-HCT (4,5). This is especially true for patients with MRD+ disease prior to transplantation based on recent NGS-based studies (6,7). For this selected, fit group of older patients who likely benefit from myeloablative conditioning regimen, it remains unclear what is the best GVHD prevention strategy. Ex-vivo TCD/CD34+ selection as well as PTCy-based regimen reduce risk of

acute and chronic GVHD but have been associated with delayed immune reconstitution and increased viral reaction, as compared to conventional, CNI-based GVHD prevention strategy (8,9). The recently completed BMT-CTN 1301 (Progress II) randomized trial compared these three strategies in mostly younger patients, and we early await the result (10). **Our study complements but does not directly compete with the BMT-CTN 1301 (PROGRESS II) study since: 1) BMT-CTN 1301 enrolled younger patients (<65 yo); 2) BMT-CTN 1301 results are expected to be published well before data analysis for the proposed study; and 3) Our proposed study incorporated real world situation where the PBSC graft is commonly utilized. In addition, the BMT/CTN 1703/1801 Progress 3 trial comparing PTCy and CNI-based GVHD prevention strategy, only enrolled patients suitable for the RIC regimen.**
Recently, we compared two GVHD prevention strategies in older patients (≥ 60 yo) who were transplanted at our center (11, 12). We examined the prevalence of key geriatric syndromes and compared their long-term functional outcomes. We found that ex-vivo TCD/CD34+ selection is associated with long-term reduced incidence of functional impairment, which is likely driven by reduced incidence of acute and chronic GVHD (Figure 1, 12). Based on these preliminary findings, we aim to examine our hypothesis in older, robust patients using myeloablative condition with CIBMTR database.

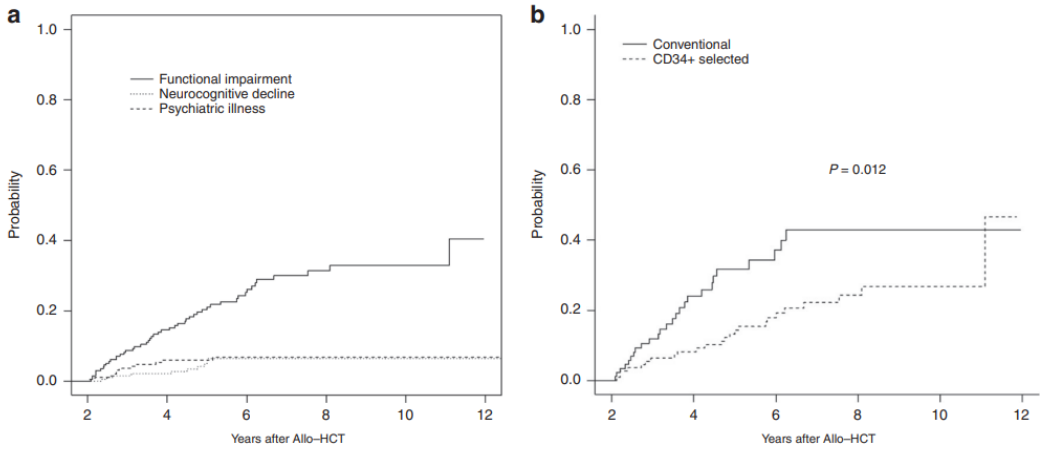

Fig. 1 Cumulative incidences of new geriatric syndromes. **a** Cumulative incidences of new functional impairment (FI, solid line); neurocognitive decline (dotted line); and psychiatric impairment (interrupted line). **b** Cumulative incidence of new FI for 2-year survivors of older allo-HCT recipients on either CD34+ selected platform (dotted line) or conventional GVHD prophylaxis (solid line).

Patient eligibility population:
This study will include adult patients ≥ 60 years old with acute leukemias (AML and ALL) and chronic myeloid malignancies (MDS, MPD, CMML, MDS/MPD overlaps) who received a first allogeneic transplantation using myeloablative conditioning and 8/8 matched-related or unrelated donor between 01/01/2010 and 12/30/2019.

Inclusion criteria:
- first allo-HCT between 2010 and 2019
- Age ≥ 60 yo at the time of HCT
- Any myeloablative conditioning defined by CIBMTR
- 8/8 matched related or unrelated donor only
- GVHD prophylaxis (ex-vivo TCD/CD34+ selection versus PTCy-based versus Tac/MTX)

Exclusion criteria:

- TBI containing regimen

Data requirements:

Utilizing data collected by CIBMTR from pre and post HCT, which includes pre-transplant essential data form #2400, post-transplant essential data form #2450, and post-HSCT data form #2100. The parameters to be assessed are outlined in table 1 below.

Table 1 data requirements:

Type of data	Data point	Specific data
Patient Specific	Patient specific characteristics	• Age at transplant (Date of birth) • Gender • Race • Primary disease type (AML, ALL, MDS, MPD etc) • Disease risk (high risk or standard) • Remission status (CR1, CR2, etc) • HCT-CI (0-2, ≥3) • KPS <90 vs 90-100
Transplant Specific	Transplant date	• Transplant date
	Preparative regimen	• Type of MAC
	GVHD prophylaxis	• Ex-vivo TCD/CD34+ selection • PTCy-based • Tac/MTX
	Graft characteristic	• Related versus unrelated • BM versus PBSC
Outcome Measures	Engraftment	• Time to absolute neutrophil count ≥500 cells/mm^3 • Time to unsupported platelets ≥20 x 10^9 cells/L • Graft failure (primary and secondary)

	GVHD	• Acute GVHD (aGVHD) by day 180
		  ○ Incidence of grade II-IV acute GVHD (aGVHD) (subset evaluating grade III-IV aGVHD)
		  ○ Time to aGVHD
		• GVHD after day 180
		  ○ Incidence of chronic GVHD (cGVHD)
		  ○ Date and maximal severity of cGVHD

	Mortality	• Time to death • Day 100, 6 months, 1-year, and 2-year mortality (both overall and non-relapse related) • Cause of mortality
	Disease relapse	• Incidence of disease relapse (include relapse defined by MRD status) • Time to disease relapse
	Infection (180-day)	• Overall cumulative incidence of viral infection • Overall cumulative incidence of bacterial infection • Overall cumulative incidence of fungal infection

Sample requirements:
None

Study design:
This is a retrospective study conducted utilizing CIBMTR data from patients transplanted from 01/01/2014 to 12/31/2019. Demographic data will be tabulated and compared among the two paired groups of interests: Ex-vivo TCD/CD34+ selection versus Tac/MTX; PTCy-based versus Tac/MTX.

Transplant outcomes to be compared among these two groups:
- Primary outcome is CRFS, defined as the first event among moderate or extensive chronic GVHD, relapse, and death.
- Secondary outcomes are:
  - OS, RFS/DFS, cumulative incidence of NRM and relapse/disease progression
  - Cumulative incidence of aGVHD
  - Cumulative incidence of cGVHD
  - Engraftment kinetics
  - 180d cumulative incidence of viral, bacterial, and fungal infections

Statistical analysis:
The Chi-square or Fisher's exact test will be used for categorical variables and the Wilcoxon rank-sum or Kruskal–Wallis test for continuous variables to compare patient, disease, and transplant related characteristics between these two GVHD prophylaxis groups. Other variables to be analyzed are included in Table 1. The Kaplan-Meier method will be used to estimate all survival measures. Differences in survival between different conditioning regimen groups will be assessed using the log-rank test. Associations between survival outcomes and potential prognostic factors will be determined using univariable and multivariable Cox proportional hazards regression models. The cumulative incidence function with the competing risks method will be used to estimate the endpoints of viral reactivation, relapse, NRM, acute GVHD, and chronic GVHD. The competing risk will be included for NRM is relapse, and the competing risk included for relapse is death. For GVHD, the competing risks included are relapse and death. Differences in cumulative incidence between subgroups will be assessed using Fine and Gray's test. For all multivariable analysis, covariates for inclusion within the model will be selected from those that are significant in the univariate analysis. Type of GVHD prophy will be included in all analysis as the main effect.

Non-CIBMTR data source:
None

Conflicts of interest:
None

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Characteristics of patients over sixty years old who underwent myeloablative allo HCT for AML, ALL or MDS with matched donor reported to the CIBMTR 2014-2019

Characteristic	CD34 select/T Cell Depleted	PT-Cy ± others	FK506 + MTX
No. of patients	80	97	1124
No. of centers	9	28	82
Patient Related			
Age at HCT - no. (%)			
Median (min-max)	64 (60-73)	64 (60-76)	64 (60-77)
60-64	50 (63)	60 (62)	669 (60)
65-69	25 (31)	30 (31)	371 (33)
70-74	5 (6)	5 (5)	72 (6)
75-80	0 (0)	2 (2)	12 (1)
Recipient sex - no. (%)			
Male	47 (59)	64 (66)	669 (60)
Female	33 (41)	33 (34)	455 (40)
Disease Related			
Primary disease for HCT - no. (%)			
AML	44 (55)	42 (43)	668 (59)
ALL	6 (8)	11 (11)	88 (8)
MDS	30 (38)	44 (45)	368 (33)
MRD at time of HCT (AML/ALL) - no. (%)			
MRD Negative	25 (50)	25 (47)	390 (52)
MRD Positive	22 (44)	26 (49)	323 (43)
Missing	3 (6)	2 (4)	43 (6)
MDS Group - no. (%)			
RA/RARS/RCMD	12 (40)	9 (21)	99 (27)
RAEB-1/RAEB-2	15 (50)	23 (52)	200 (54)
5-q	1 (3)	3 (7)	11 (30)
CMMoL	2 (7)	9 (21)	58 (16)
Donor Related			
Donor type - no. (%)			
Matched Sibling	22 (28)	26 (27)	393 (35)
Matched Unrelated	58 (73)	71 (73)	731 (65)
Transplant Related			
Graft type - no. (%)			
Bone marrow	0	2 (2)	180 (16)

Characteristic	CD34 select/T Cell Depleted	PT-Cy ± others	FK506 + MTX
Peripheral blood	80	95 (98)	944 (84)

Proposal: 2010-215

Title:
Post-Transplant Cyclophosphamide (PTCy) vs. Anti-Thymocyte Globulin (ATG) in Patients with Acute Leukemia receiving HLA-Mismatched Unrelated Donor (MMUD) Hematopoietic Cell Transplant (HCT)

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Research hypothesis:
When compared to anti-thymocyte globulin (ATG), *in vivo* graft manipulation with post-transplant cyclophosphamide (PTCy) is associated with improved clinical outcomes in Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL) patients undergoing HLA-mismatched unrelated donor (MMUD) transplantation.

Specific aims:
We propose to evaluate the impact of *in vivo* graft manipulation strategy (ATG vs. PTCy) on clinical outcomes following MMUD HCT for patients with AML and ALL. To achieve this objective, we will:

- **Aim 1.**: Identify differences in post-transplant outcomes (overall survival, leukemia-free survival, GVHD-free, relapse free survival [GRFS], non-relapse mortality, relapse and acute and chronic GVHD) in AML/ALL patients receiving *in vivo* graft manipulation with PTCy versus ATG, following MMUD HCT.
- **Aim 2.:** Evaluate differences in post-transplant outcomes for AML/ALL patients receiving graft manipulation with PTCy versus ATG based on graft source, degree of mismatch (7/8 vs $\leq$6/8) and conditioning intensity.

Scientific justification:
Allogeneic Hematopoietic Cell Transplant (alloHCT) continues to be the preferred consolidation strategy for many patients with acute leukemias, but unfortunately, several patients are unable to find an HLA-matched donor[1].
Mismatched unrelated donor (MMUD) grafts are frequently the sole source of stem cells for patients without matched or other alternative donor options. Historically, MMUD HCT has been associated with poor outcomes given increased rates of GvHD, graft failure and infection, all resulting in high non-relapse mortality (NRM)[2,3]. The post-transplant cyclophosphamide (PTCy) platform has successfully overcome barriers related to HLA-mismatching in the haploidentical donor setting and is being increasingly recognized as a suitable strategy for MMUD transplants[4-7].
PTCy-based GvHD prophylaxis in the MMUD HCT setting has shown to be safe and feasible in single institution studies.[4-6] A recent prospective phase-II, multicenter NMDP® trial (15-MMUD) demonstrated the effectiveness of PTCy in a cohort of 80 patients with hematologic malignancies (68% with a diagnosis of acute leukemias) receiving a MMUD bone marrow HCT, with one-year OS of 76% and satisfactory rates of NRM, RFS, GRFS and GVHD[7].
We retrospectively evaluated the outcomes of 73 adult patients (60% with a diagnosis of acute leukemias) who received a MMUD ($\geq$1 mismatch at -A, -B, -C, -DRB1 alleles) at the University of Miami[8].

Patients were stratified on the basis of graft manipulation strategy, conditioning intensity, graft source, and degree of mismatch. PTCy prophylaxis resulted in superior OS (73.6% *vs.* 36.9%, P=0.002) RFS, GRFS and lower NRM compared to ATG-based T-cell depletion. A large multicenter, retrospective study evaluating the role of alternative donor HCT (including 9/10 MMUD recipients, N=125) for ALL in CR2[9], demonstrated no differences in post-HCT outcomes among all different donor sources. Recent data from the Acute Leukemia Working Party of the EBMT, demonstrated superior outcomes for PTCy recipients (vs. ATG) in a cohort of 272 patients with AML, following a single-antigen (9/10) MMUD HCT[10]. Cohort included patients with DQ mismatched grafts, and various GVHD prophylactic regimens following transplantation.

We propose a retrospective cohort study to evaluate differences in post-HCT outcomes for acute leukemia (AML/ALL) patients receiving graft manipulation with PTCy versus ATG following a ≤7/8 MMUD HCT. To our knowledge, no large, multi-center studies addressing this important question have been conducted to date.

Patient eligibility population:

Inclusion criteria:

- Patients with a diagnosis of AML and ALL in CR
- Ages 18 and older
- Recipients of a MMUD graft (>1 mismatch at -A, -B, -C, -DRB1 alleles) between 2010-2019, receiving GVHD prophylaxis with CNI+MTX (ATG cohort) or CNI+MMF (PTCy cohort)

Exclusion criteria:

- In vivo graft manipulation other than ATG or PTCy
- Ex vivo TCD
- Recipients of a single-antigen DQ mismatch graft

Study outcomes:

- Overall survival (OS): time to death. Death from any cause will be considered an event. Surviving patients are censored at time of last follow-up.
- Relapse-free survival (RFS): Will be defined as time to relapse or death from any cause. Patients are censored at last follow-up.
- GVHD-free, relapse-free survival (RFS): Will be defined as time to development of grade 3-4 acute GVHD, systemic therapy-requiring chronic GVHD, relapse, or death from any cause. Patients are censored at last follow-up.
- Non-relapse mortality (NRM): Cumulative incidence of NRM. NRM is defined as death without preceding disease relapse/progression. Relapse is competing event.
- Relapse/Progression: Cumulative incidence of disease relapse/progression, with NRM as competing event.
- Incidence of acute and chronic GVHD: Cumulative incidence of acute and chronic GVHD, with death as competing risk. Patients are censored at subsequent HCT or last follow-up.

Variables to be described:

- Study main effect: Choice of *in vivo* graft manipulation (PTCy vs. ATG) following MMUD HCT.

Patient-related:

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

Disease-related:

- Blast percentage at diagnosis
- CR status: CR1 vs >CR2
- Time to achieve CR
- MRD prior to transplant
- CRi prior to transplant
- Extramedullary disease

AML patients:

- Clinical onset of AML: de novo vs. transformed from MDS/MPN vs. therapy related
- ELN genetic stratification
- White blood count at diagnosis: <10 vs. 10-100 vs. >100 x109/L

ALL patients:

- Genetic stratification
- Lineage: B-cell vs T-cell
- Hyperleukocytosis at diagnosis (>30,000 for B-ALL, >100,000 for T-ALL)
- Ph+ status

Transplant-related:

- Conditioning intensity: Myeloablative conditioning (MAC) vs. reduced-intensity /non-myeloablative conditioning (RIC/NMA)
- Graft source: bone marrow vs. peripheral blood
- Degree of HLA mismatch (7/8 or <6/8)
- Donor age
- Donor-recipient sex match
- Donor-recipient CMV status
- Time from diagnosis to HSCT
- Year of transplant

Study design:
This is a retrospective cohort analysis to evaluate the impact of choice of *in vivo* graft manipulation strategy on transplantation outcomes for AML/ALL patients undergoing MMUD HCT.
Continuous variables will be described as median and ranges and categorical variables will be reported as absolute numbers and percentage. The primary endpoint is OS. The secondary endpoints are RFS, GRFS, NRM, relapse and acute and chronic GVHD. All outcomes will be measured from time of transplant.
Univariate analysis will be performed using Kaplan-Meier Method and will be compared using log-rank test for OS, RFS and GRFS while NRM, GVHD and relapse will be calculated using the cumulative incidence method considering competing risks, with comparisons performed using Gray's method.
Multivariate analysis will also be performed using Cox proportional hazard model for OS, RFS, GRFS, NRM GVHD and relapse. The assumption of proportional hazards for each factor in the Cox model will be tested by adding time-dependent covariates. When the test indicated differential effects over time (non-proportional hazards), models will be constructed breaking the post-transplant time course into two periods, using the maximized partial likelihood method to find the most appropriate breakpoint. The proportionality assumptions will be further tested. A backward stepwise model selection approach will be used to identify all significant risk factors. Factors which are significant at a 5% level will be kept in the final model. Potential interaction between main effect and significant co-variates will be tested.
Adjusted probabilities of LFS and OS and adjusted cumulative incidence functions of NRM and relapse will be calculated using the multivariate models, stratified on main effect and weighted by the pooled sample proportion value for each prognostic factor. These adjusted probabilities estimate likelihood of outcomes in populations with similar prognostic factors.

Conflicts of interest:
Krishna Komanduri
- Ad hoc consultant to: Kite/Gilead, Novartis, Celgene, Atara, Takeda, Autolus, Kiadis, Gamida Cell, Incyte, Kadmon, Genentech.

Marcos de Lima
- Ad hoc consultant to: Pfizer – BMS.

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Characteristics of patients who underwent a mismatched unrelated donor transplant for AML or ALL using ATG or PTCY for *in vivo* graft manipulation

Characteristic	ATG	PTCy
No. of patients	257	133
No. of centers	52	39
Patient age at transplant - no. (%)		
Median (min-max)	49 (18-69)	54 (20-70)
18-29 yrs	56 (22)	10 (8)
30-39 yrs	34 (13)	21 (16)
40-49 yrs	47 (18)	18 (14)
50-59 yrs	77 (30)	40 (30)
60-69 yrs	43 (17)	44 (33)
Disease - no. (%)		
AML	178 (69)	91 (68)
ALL	79 (31)	42 (32)
Graft (Product) type - no. (%)		
Bone marrow	40 (16)	20 (15)
Peripheral blood	217 (84)	113 (85)
Conditioning regimen intensity - no. (%)		
MAC	207 (81)	74 (56)
RIC	50 (19)	59 (44)
GVHD Prophylaxis - no. (%)		
CNI + MMF	0	133 (100)
CNI + MTX	257 (100)	0
Year of Transplant		
2014-2016	170 (66)	29 (22)
2017-2019	87 (34)	104 (78)