2021 STATUS REPORT
PEDIATRIC CANCER WORKING COMMITTEE

Working Committee Leadership	
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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 2010-271 Impact of graft versus host disease following allogeneic hematopoietic cell transplantation on leukemia free survival in hematologic malignancies within the pediatric disease risk index risk stratification (Andrea Bauchat/ Muna Qayed/ John T. Horan). (Attachment 2)

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

a. PROP 2002-01 Comparison of BuMel vs Tandem conditioning for autologous hematopoietic stem cell transplantation (auto-HSCT) of high-risk neuroblastoma (Pierre Teira).

b. PROP 2002-02 Impact of sorafenib after allo-HSCT as prevention of AML relapse in children. (Pierre Teira).

c. PROP 2008-04 Clinical outcomes of pediatric patients who undergo a second transplant for relapsed leukemic disease after first transplant (Asmaa Ferdjallah/ Heather Stefanski).

d. PROP 2010-97 Survival and toxicities of autologous transplantation in children with neuroblastoma: Comparison of tandem transplant and a single transplant using busulfan and melphalan preparative regimen (Brian Stover/ Howard Katzenstein/ Biljana Horn).

e. PROP 2010-108 Evaluation of outcomes following allogeneic hematopoietic cell transplantation in pediatric patients with high-risk acute myeloid leukemia: A CIBMTR-EBMT joint study (Akshay Sharma/ Neel S. Bhatt/ Senthil V Bhoopalan).

f. PROP 2010-233 Linking CIBMTR to a children's oncology group (COG) cohort to evaluate access, outcomes, and toxicities after hematopoietic cell transplantation (HCT) in pediatric and adolescent patients with relapsed/refractory classical hodgkin lymphoma (cHL) (Sharon M. Castellino/ Justine Kahn/ Theresa Hahn).

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

a. PROP 2009-10 Real world outcomes following high dose chemotherapy with autologous stem cell transplant for newly diagnosed medulloblastoma in infants and younger children. (Michael A. Huang).

b. PROP 2010-59 Is there an optimal myeloablative TBI-containing conditioning regimen prior to allogeneic hematopoietic cell transplantation for pediatric acute lymphoblastic leukemia? (Sanam Shahid/ Jaap J. Boelens).

c. PROP 2010-295 Brentuximab vedotin as a maintenance therapy post-autologous HSCT in high-risk relapsed/refractory hodgkin lymphoma: A CIBMTR analysis of outcomes in children and adolescent and young adult patients (Ibrahim N. Muhsen/ Brian D. Friend).

STUDIES IN PROGRESS

a. **PC19-02** Does mixed peripheral blood T cell chimerism predict relapse?
Status: Protocol Development. The first draft study protocol has been written. Revision of the study protocol is currently in progress. The goal is to complete the final protocol and complete data file preparation to proceed to the analysis stage by July 2021.

b. **PC19-03** The impact of pre-transplant extramedullary disease on the outcome of allogeneic hematopoietic cell transplantation for acute myeloid leukemia in children: A combined CIBMTR and EBMT analysis.
Status: Data File Preparation. Preparation of the data file is currently in progress. The goal is to transfer study file to EBMT February 2021.

c. **PC20-01** Autologous graft cell dose and post-transplant granulocyte colony stimulating factor in post-transplant outcomes among pediatric patients undergoing autologous hematopoietic stem cell transplantation.
Status: Data File Preparation. Preparation of the data file is in progress – pending resolution of CD34 cell counts for a subset of eligible patients. The goal is to have the data file completed and the analysis completed by July 2021.

d. **PC20-02** Germline genetics of pediatric myelodysplastic syndromes.
Status: Sample confirmation and material transfer agreement. Upon execution of material transfer agreement, samples will be transferred to University of Minnesota.

PUBLICATIONS, SUBMITTED PAPERS, PRESENTATIONS

a. **PC18-01** Dandoy CE, Davies SM, Ahn KW, He Y, Kolb AE, Bo-Subait S, Abdel-Azim H, Bhatt N, Chewing J, Gadalla S, Gloude N, Hayashi R, Lalefar NR, Law J, MacMillan M, O'Brien T, Prestidge T, Sharma A, Shaw P, Eapen M, Levine J. Comparison of Total body irradiation versus non- Total body irradiation containing regimens for de novo acute myeloid leukemia in children. Haematologica. doi:10.3324/haematol.2020.249458. Epub 2020 Jun 18.

b. **PC19-01** Qayed M, Ahn KW, Kitko CL, Johnson MH, Shah NN, Dvorak CC, Mellgren KM, Friend BD, Verneris MR, Leung W, Toporski J, Levine JE, Chewning JH, Wayne AS, Kapoor U, Triplett BM, Schultz KR, Yanik GA, Eapen M. A validated pediatric disease risk index for allogeneic hematopoietic cell transplantation. Blood. doi:10.1182/blood.2020009342. Epub 2020 Nov 18. *Oral presentation at 2020 annual ASH meeting.*

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR PEDIATRIC CANCER
Orlando, Florida
Friday, February 21, 2020, 12:15pm – 2:15pm

Co-Chair:	**Gregory Yanik, MD, The University of Michigan, Ann Arbor, MI;** **E-mail: gyanik@med.umich.edu**
Co-Chair:	**Muna Qayed, MD, Emory University, Atlanta, GA;** **E-mail: mqayed@emory.edu**
Co-Chair:	**Angela Smith, MD, University of Minnesota, Minneapolis, MN;** **E-mail: smith719@umn.edu**
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1. Introduction

The CIBMTR Working Committee for Pediatric Cancer met on Friday, February 21st, 2020 at 12:15pm. Dr. Gregory Yanik welcomed the audience and introduced the working committee leadership. Dr. Kirk Schultz was introduced as the new incoming committee chair, and recognized for his considerable experience in the field that he will bring to the committee leadership. Dr. Angela Smith was thanked for her contributions to the committee as chair as her term as committee chair concluded with this meeting. Dr. Yanik proceeded to take the attendees through the committee's goals, expectations, and limitations. Dr. Yanik then took the attendees through the CIBMTR Advisory Committee metrics for committee performance. The Pediatric Cancer working committee had all active studies advance at least one stage in the prior year, and had no manuscripts in progress for over a year. One out of two papers reached their submission goals, with the other paper set for submission shortly after this meeting. Dr. Yanik then walked through the rules for authorship on committee studies, before explaining to the attendees the differences between TED and CRF level data. There was a motion to approve the 2019 working committee meeting minutes, and a second. The motion passed.

2. Accrual summary

Dr. Yanik directed the attendees' attention to the accrual summaries included in the meeting materials and provided a concise summary of the numbers of pediatric patients available in the database.

3. Presentations, published or submitted papers

Dr. Yanik directed the audience to the working committee materials for information regarding the two committee publications from 2019.

a. **PC18-01** Comparison of TBI vs Non-TBI based regimens for pediatric AML in the modern era (C Dandoy) **Submitted**

Dr. Yanik delivered a brief overview of the findings from this study, which aimed to compare TBI versus non-TBI regimens for pediatric AML HCT. The findings included no difference in overall survival or leukemia-free survival, higher non-relapse mortality with TBI, higher GVHD with TBI, and lower relapse rates with TBI.

4. Studies in progress

Dr. Yanik provided a brief overview of the committee's portfolio of active studies. PC19-01 has analysis results completed and a manuscript in progress. PC19-03 has a completed North American dataset, and will await completion of a corresponding European dataset before merging these datasets together for analysis. PC19-02 will be the next on the committee's list of priorities.

Dr. Muna Qayed presented the results of PC19-01, which is a study aimed at creating a new pediatric disease risk index by stratifying patients into groups based on disease-free survival outcomes following HCT for AML and ALL. Based on the multivariate analysis results, the study team was able to separate AML cases into four disease risk groups (Good, Intermediate, High, and Very High risks) based on age, disease status, and cytogenetic risk. ALL patients were broken into three risk groups (Good, Intermediate, and High) based on age and disease status. Individual cases are assigned "scores" based on their respective group for each of these prognostic factors, with higher "scores" indicating higher risk. The final disease risk assignment for each case is decided based score cutoffs for the sum of the scores across all of the aforementioned risk factors that were significant in the final models. The findings demonstrated comparable disease-free survival within each of the final disease risk groups, with statistically significant differences existing across the groups. The upcoming paper associated with this study will include concise summary tables that outline which final disease risk assignments correspond to different combinations of the included prognostic factors.

The full list of active committee studies is below:

a. **PC19-01** Validation of the disease risk index in children undergoing alloHCT (M Qayed/C Kitko) **Manuscript Preparation**
b. **PC19-02** Does mixed peripheral blood T cell chimerism predict relapse? (S Prcokp/J Boelens/ K Peggs) **Protocol Development**
c. **PC19-03** The impact of pre-transplant extramedullary disease on the outcome of allogeneic hematopoietic cell transplantation for Acute Myeloid Leukemia in Children- A combined CIBMTR and EBMT analysis (H Rangarajan/P Satwani/K Rao/D Chellapandian/B Savani/Juliana Silva) **CIBMTR – Data File Completed; EBMT - Pending**

5. Future/proposed studies

Dr. Smith outlined the voting process for the attendees, explaining that voting should be based both on scientific impact and on feasibility using the CIBMTR data.

a. **PROP1911-01** Long-Term Outcomes among Survivors of Primary Central Nervous System Tumors Undergoing Autologous Hematopoietic Cell Transplantation (Seth J. Rotz; Rabi Hanna; Navneet Majhail)

   Dr. Rotz presented the proposal. The objectives of the study would be to examine late effects and conditional survival of patients surviving autologous HCT for central nervous system tumors.

   The CIBMTR identified 295 pediatric and young adult patients on the CRF-level data collection track, and 1,708 patients with TED-level data that underwent autologous HCT for CNS tumors in the United States between 2000 and 2016. About half of these transplants were done for Medulloblastoma, while the other half were done for other central nervous system tumors.

   The question of supplemental data was raised, and Dr. Rotz replied that while he does think that the collection of supplemental data would enhance the study, it would be possible to

perform the study focusing only on data already in the database. A couple of attendees expressed enthusiasm for the study, but cautioned against trying to collect the supplemental data, as it would be difficult and with uncertain benefit and quality of data. When asked what the key toxicities to capture as part of the study would be, given that the data may be limiting, Dr. Rotz replied that the most important toxicities would be endocrinopathies, subsequent therapy-related neoplasms, and strokes. One attendee remarked that if it is decided that a full registry study isn't feasible for this idea, then perhaps a better approach might be to pursue this effort with a small group of dedicated transplant centers with data from a lot of cases.

b. **PROP 1911-14** Autologous graft cell dose and post-transplant granulocyte colony stimulating factor in post-transplant outcomes among pediatric patients undergoing autologous hematopoietic stem cell transplantation (Tristan Knight; Donna A. Wall; Kanhatai Chiengthong)
Dr. Knight presented the proposal. The objective of the study would be to analyze the effect of the usage of different dosing levels of CD34+ cells for pediatric autologous HCT. Given that children are generally excellent mobilizers, the research question is whether using higher doses of CD34+ cells has any benefit, or even has a detrimental effect on outcomes. The study proposes to do this examination of CD34+ cell doses in children while factoring in the use or non-use of G-CSF post-transplant.
The CIBMTR identified 555 patients on the CRF data track who received autologous HCT for malignancies in the United States from 2008 to 2018, with G-CSF used post-transplant. The vast majority of these cases, roughly 94%, had CD34+ cell dose information available. An attendee asked for a clarification on whether tandem transplants would be excluded. Dr. Knight responded that since a majority of these transplants were for various central nervous system tumors, many of these would be tandem transplants and they would need to be kept. Several attendees, along with the committee leadership, suggested that if the study were to move forward, it would be prudent to limit the inclusion to Neuroblastoma, Medulloblastoma, and other central nervous system tumors, as these diseases make up the majority of cases (~73%). This would significantly reduce disease heterogeneity to strengthen the study.

c. **PROP 1911-200** Outcomes of Adolescents and Young Adults after Allogeneic Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia at Pediatric Versus Adult Centers (Regina M. Myers; Martin S. Tallman)
Dr. Myers presented the proposal. The objective of the study would be to compare the outcomes of adolescent and young adult patients undergoing allogeneic HCT for AML or ALL between those treated at adult centers versus those treated at pediatric transplant centers. Another objective would be to attempt to compare and contrast standard clinical practice guidelines utilized for adolescent and young adult patients transplanted at adult versus pediatric centers to describe how these cases are handled.
The CIBMTR identified 3,000 patients from adult centers and 608 patients from pediatric centers transplanted for AML and with TED-level data. There were 1,322 patients from adult centers and 267 patients from pediatric centers transplanted for AML and with CRF-level data. The CIBMTR also identified 2,611 patients from adult centers and 650 patients from pediatric centers transplanted for ALL and with TED-level data. There were 989 patients from adult centers and 252 patients from pediatric centers transplanted for ALL and with CRF-level data. The first clarification made was that TED-level data would likely not be sufficient to capture all of the important disease-related data that would be necessary for this study to be a strong one. A few attendees expressed enthusiasm for the idea of the study. However, many attendees cautioned that huge obstacle to performing this study would be that there are many centers that transplant both adult and pediatric patients at the same center and report all of their data to the CIBMTR under the same center code. This could introduce substantial noise into any

results, and confidently separating these cases into adult or pediatric centers could be very challenging.

d. **PROP 1911-57/Prop 1911-58** Evaluation of Outcomes following Allogeneic Hematopoietic Cell Transplantation in pediatric patients with high-risk cytogenetic/molecular features in AML: A CIBMTR Analysis (Senthil Velan Bhoopalan; Neel Bhatt; Akshay Sharma)
Dr. Bhoopalan presented the proposal. The objective of the study would be to examine the clinical characteristics and outcomes of patients undergoing allogeneic HCT for high-risk AML, and to quantify the difference in post-transplant outcomes as compared to those AML patients without high-risk characteristics. An additional objective would be to identify any prognostic factors of importance impacting outcomes for the high-risk AML cases.
The CIBMTR identified 211 pediatric patients on the CRF track and 527 pediatric patients on the TED track that were transplanted for AML between 2014 and 2018 in the United States, and that had one of the selected cytogenetic or molecular high-risk features. A handful of additional cases could be considered to be added to this number for patients transplanted with therapy-related AML or who underwent transplant outside of first or second complete remission. The main critique of the study raised by several attendees was that while the study could quantify the outcomes for high-risk AML as compared to other AML cases, the numbers of any one specific abnormality would be far too low to have sufficient statistical power to identify the specific abnormalities causing the worst outcomes. The possibility was raised of inquiring whether it would be possible to combine data with EBMT to boost the numbers, but many felt that even doing that would leave nearly all of the groups too small.

e. **PROP 1911-68** Central nervous system monitoring and prophylaxis post transplantation for pediatric leukemia: avoiding toxicities without compromising outcomes (Ellen Fraint; David Loeb; Lisa Wray)
Dr. Fraint presented the proposal. The objectives of this study would be to describe the current landscape of clinical practice in the United States regarding central nervous system monitoring and prophylaxis following transplant for leukemia in pediatric patients. An additional objective would be to assess the impact of post-transplant prophylactic intrathecal treatment on CNS relapse rates.
The CIBMTR identified 1,314 patients undergoing allogeneic HCT for ALL in the United States on the CRF track between 2008 and 2018. Among these, only 156 received post-transplant intrathecal chemotherapy for reasons other than relapse. Dr. Fraint clarified that she proposes to send surveys to centers to ask about their current CNS prophylaxis practice guidelines. An attendee pointed out that there was a similar proposal in recent years, and that most centers have moved away from post-transplant CNS prophylactic therapies, and are instead using pre-transplant measures. Multiple commenters cautioned that for this kind of effort, response rates for surveys like this are often very bad. Multiple attendees worried that among the small number of patients receiving post-transplant CNS prophylaxis, most or all of them would have had a pre-existing risk factor that led to the use of this post-transplant preventative measure. If this were so, this could heavily bias results, and damage the confidence in any findings.

f. **PROP 1911-124** Germline genetics of pediatric myelodysplastic syndromes (MDS) (Jenny Poynter; Logan Spector)
Dr. Angela Smith presented the proposal on behalf of the group of proponents, who were unable to attend the meeting. The objectives of the study would be to use samples from the NMDP Sample Repository to identify genetic susceptibility variants for pediatric MDS. The study would include all recipients of a transplant for MDS between the ages of 0 and 19 at diagnosis of MDS that have an available sample in the repository.

One attendee expressed concern that this effort would be duplicative, as a similar study has already been done by a separate group within the past couple of years. Upon investigating this after the meeting, the committee leadership determined that while the previous study in question did involve genetic typing for MDS transplant patients, that study focused on outcomes following transplant, whereas this effort would be focused primarily on evaluating genetic susceptibility to pediatric hematologic malignancy, as the transplant component of a larger ongoing effort.

6. Dropped proposed studies

The committee received the following additional study proposal, but this proposal was not selected for presentation at the TCT meeting, for the reason outlined below.

a. **PROP 1910-19** Outcomes after Transplant for Children with Advanced Phase CML
Dropped due to low sample size

7. Concluding Notes

a. Meeting adjourned at 2:03pm.

b. Voting on proposals.
After the new proposals were presented, each participant in the meeting had an opportunity to rate each proposal using paper ballots. Based on the voting results, current scientific merit, available number of relevant cases, and the impact of the study on the field, the following two studies were accepted to move forward to be added to the committee's active studies:
PROP 1911-14 Autologous graft cell dose and post-transplant granulocyte colony stimulating factor in post-transplant outcomes among pediatric patients undergoing autologous hematopoietic stem cell transplantation (Tristan Knight; Donna A. Wall; Kanhatai Chiengthong)
PROP 1911-124 Germline genetics of pediatric myelodysplastic syndromes (MDS) (Jenny Poynter; Logan Spector)

c. The following proposals were not accepted as studies:
PROP 1911-01 Long-Term Outcomes among Survivors of Primary Central Nervous System Tumors Undergoing Autologous Hematopoietic Cell Transplantation
PROP 1911-200 Outcomes of Adolescents and Young Adults after Allogeneic Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia at Pediatric Versus Adult Centers
PROP 1911-57/Prop 1911-58 Evaluation of Outcomes following Allogeneic Hematopoietic Cell Transplantation in pediatric patients with high-risk cytogenetic/molecular features in AML: A CIBMTR Analysis
PROP 1911-68 Central nervous system monitoring and prophylaxis post transplantation for pediatric leukemia: avoiding toxicities without compromising outcomes

Working Committee Overview Plan for 2020 - 2021							
Study number and title	**Current status**	**Goal with date**	**Total hours to complete**	**Total hours to 2021 goal**	**Hours allocated to 6/30/20**	**Hours allocated 7/1/20-6/30/21**	**Total Hours allocated**
PC18-01: Comparison of TBI vs. Non-TBI based regimens for pediatric acute myeloid leukemia in the modern era	Submitted	Published – July 2020	10	**10**	10	0	10
PC19-01: Validation of the disease risk index in children undergoing alloHCT	Manuscript Preparation	Submitted – July 2020 Published – July 2021	80	**80**	70	10	80
PC19-02: Does mixed peripheral blood T cell chimerism predict relapse?	Protocol Development	Analysis – July 2020 Manuscript Preparation – July 2021	330	**260**	180	80	260
PC19-03: The impact of pre-transplant extramedullary disease on the outcome of allogeneic hematopoietic cell transplantation for Acute Myeloid Leukemia in Children- A combined CIBMTR and EBMT analysis.	Data File Preparation	Analysis – July 2020 Submitted – July 2021	200	**200**	50	150	200
PC20-01: Autologous graft cell dose and post-transplant granulocyte colony stimulating factor in post-transplant outcomes among pediatric patients undergoing autologous hematopoietic stem cell transplantation	Protocol Pending	Draft protocol received – July 2020 Manuscript Preparation – July 2021	330	**260**	0	260	260
PC20-02: Germline genetics of pediatric myelodysplastic syndromes (MDS)	Protocol Pending	Draft protocol received – July 2020 Sample typing – July 2021	340	**10**	0	10	10

Oversight Assignments for Working Committee Leadership (March 2020)		
Muna Qayed	**PC18-01**	Comparison of TBI vs Non-TBI based regimens for pediatric AML in the modern era
	PC19-03	The impact of pre-transplant extramedullary disease on the outcome of allogeneic hematopoietic cell transplantation for Acute Myeloid Leukemia in Children- A combined CIBMTR and EBMT analysis
Kirk Schultz	**PC19-01**	Validation of the disease risk index in children undergoing alloHCT
	PC20-02	Germline genetics of pediatric myelodysplastic syndromes (MDS)
Gregory Yanik	**PC19-02**	Does mixed peripheral blood T cell chimerism predict relapse?
	PC20-01	Autologous graft cell dose and post-transplant granulocyte colony stimulating factor in post-transplant outcomes among pediatric patients undergoing autologous hematopoietic stem cell transplantation

Proposal: 2010-271

Title:
Impact of Graft Versus Host Disease Following Allogeneic Hematopoietic Cell Transplantation on Leukemia Free survival in Hematologic Malignancies within the Pediatric Disease Risk Index Risk Stratification

Andrea Bauchat, DO, andrea.bauchat@emory.edu, Emory University
Muna Qayed, MD, MSc, mqayed@emory.edu, Emory University
John T. Horan, MD, MPH, john_horan@dfci.harvard.edu, Dana-Farber Cancer Institute, Boston Children

Hypothesis:
Mild to moderate acute graft versus host disease following hematopoietic stem cell transplant is associated with improved leukemia-free survival in children with favorite risk disease by pediatric DRI classification.

Objectives:
- To determine the impact of development of grade I and II acute graft versus host disease (aGVHD) on relapse and leukemia-free survival in children undergoing hematopoietic cell transplant (HCT) for ALL and AML
- To assess the impact of development of severe (grade III-IV) aGVHD on relapse and LFS in children undergoing HCT for ALL and AML
- To determine whether the impact of GVHD on relapse and LFS is influenced by disease risk prior to HCT

Scientific justification:
Relapse of disease remains one of the main etiologies of mortality in pediatric patients after HCT for hematologic malignancies. Predictors of leukemia-free survival (LFS) outcomes post-HCT include disease status prior to HCT, disease characteristics, and cytogenetics.[1,2] A recent analysis by Qayed et al validated the disease risk index (DRI) tool for pediatrics to categorize patients with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) based on risk factors for prognostication. This report evaluated 1228 ALL patients and 1135 AML patients identifying 3 and 4 risk groups, respectively, with the primary outcome focus on LFS. The 3 risk groups for ALL include good, intermediate, and high risk whereas the 4 risk groups of AML were good, intermediate, high, and very high risk.[3]
An additional variable to consider in risk stratification is the presence or absence of GVHD post-HCT. GVHD has been reported as protective against relapse in hematologic malignancies since it has been associated with an increased graft versus leukemia (GVL) effect.[4-7] The biology of this phenomenon consists of the donor T cells recognizing histocompatibility antigens on recipient leukemia cells resulting in one of the therapeutic benefits of HCT in this disease group.[4] Current literature suggests that development of acute GVHD grades I-II decreases relapse risk and improves overall survival. In a CIBMTR registry study reported by Yeshurun et al, 5215 patients with ALL were evaluated in 3 cohorts based on disease stratifications to determine the effects of GVHD on disease-free survival (DFS), non-relapse mortality (NRM), and overall survival (OS). Development of GVHD in children or adults with ALL in CR1/CR2 was associated with an improved DFS compared to those without GVHD. Specifically, patients in CR1/CR2 had significantly improved DFS with isolated grades I and II compared to no GVHD with HR 0.74 for adults (95% CI, 0.61-0.89) and HR 0.74 (95% CI, 0.61-0.89) for pediatrics.[8] The development of grade I-II aGVHD without cGVHD was associated with improved OS compared to those without any form of GVHD with 17-24% lower risk of overall mortality. Although relapse was decreased in patients who

developed aGVHD grades III or IV, non-relapse mortality was higher resulting in inferior OS regardless of cohort group.[8] In this analysis, patients in CR1 and CR2 were grouped together whereas our study will control for difference by utilizing the PDRI for risk stratification. Another study by Bader et al evaluated peri-HCT risk factors in pediatric and young adult patients with ALL. aGVHD was associated with decreased incidence regardless of pre-transplant MRD status with a threefold decrease in relapse.[9] Similar relapse rates were noted in patients with post-HCT MRD who developed aGVHD and MRD negative patients who did not develop aGVHD.[9]

In another study, Pulsipher et al (PBMTC ONC051) examined the association of risk factors including aGVHD on the risk of relapse in pediatric patients transplanted for ALL on the Children's Oncology Group (COG) ASWCT0431 Trial. The study was conducted from 2007–2011 and results were presented after multivariate analysis. A marked difference was noted in relapse rate of patients who had pre-HCT MRD <0.1% and developed aGVHD compared to those without aGVHD (13% vs. 40%; p= 0.008). Patients with pre-HCT MRD < 0.1% and aGVHD by day +55 had a decrease rate of relapse with improved event free survival compared to those with pre-HCT MRD ≥ 0.1% in the absence of aGVHD (CI of relapse 73% vs 13%; p=<0.0001; 2yr EFS 71 vs. 18%; p=0.001).[10] Furthermore, a notable difference in 2 year OS in these two groups was statistically significant at 74% versus 46% respectively (p=0.04). [10] There was no statistical differences between those with pre-HCT MRD ≥ 0.1% with aGVHD and any other group potentially due to the low patient numbers (n=5). Grade IV aGVHD decreased disease relapse, however, as noted in similar studies, the OS was decreased due to transplant related mortality.[10] Notably, these analyses focus solely on ALL without AML.

Currently, there is paucity of data evaluating GVHD impacts on patients with AML. Kato et al examined GVHD in both ALL (n=1030) and AML (n=496) pediatric patients in CR1/CR2. Between both leukemia groups, aGVHD grades II-IV demonstrated decreased relapse compared to patients with aGVHD grades 0-I at 3 years post-HCT. Specifically in ALL, developing grade II aGVHD was associated with a decreased relapse risk of 18.2% (95% CI 13.9–23.6) compared to 26.0% (95% CI 21.3–31.5) in grade 0 and 26.2% (95% CI 21.1–32.3) in grade I. Regarding AML, relapse risk reduction between grade I and grade II aGVHD was not significant at 20.7% (95% CI 14.6–28.9) and 20.5% (95% CI 14.1–29.3) respectively. OS was comparable in all patients with aGVHD grade 0-I at 79.0% and 79.5%, respectively and similar to patients with grade II GVHD (76.3%). Although those with grade III-IV aGVHD demonstrated lower relapse rate, the OS was significantly inferior at 66.9% and 42.5% respectively.[11] cGVHD decreased risk of relapse more in the patients with AML compared to the ALL disease group where results were not significant. Relapse risk in AML patients without cGVHD was 24.0% (95% CI 19.5–29.2; p = 0.02) compared to 11.0% (95% CI 6.8–17.6) in those with cGVHD. Although cGVHD provided some reductive effect on relapse, no survival advantage was observed.[11] Neudorf et all reported on the effects of GVL in DFS for AML pediatric patients in the Children's Cancer Group (CCG) study 2891. The data illustrated that grade I and 2 aGVHD were associated with improved DFS of 65% (95% CI 49-78%) compared to those without at 58% (95% CI, 46-68%).[12]

In this study, we will test the hypothesis that development of aGVHD grades I and II has a favorable impact on LFS in a subset of children undergoing HCT for hematologic malignancy. This focus is significant as current methods of immunosuppression impedes the effects of GVL, which could potentially increase the risk of disease relapse. The results of this protocol may provide objective support to further tailor GVHD prophylaxis to balance allowance of GVL and GVHD to improve LFS.

Study population:

We propose using the existing dataset from protocol PC19-01 for this analysis.

- Children < 18 years who received first HCT for ALL and AML receiving first allogeneic transplantation
- Transplant period: 2008-2017

- OUTCOME:
- Leukemia-free survival (LFS): LFS is defined as survival without relapse or progression. Disease relapse/progression and death are treated as events. Surviving patients will be censored at last follow up.
- Relapse: This is defined as recurrence of the ALL or AML that was the indication for HCT. Patients will be censored at last follow up.
- Non-relapse Mortality (NRM): This event is defined as death in the absence of recurrence of the primary malignancy. Patients will be censored at last follow up.
- Overall Survival (OS): This is defined as the length of time from HCT that patients are still alive.

Variables to be analyzed:

Patient:

- Age at transplant: included in PDRI
- Sex: Male, Female
- Karnofsky/Lansky performance score: 90 – 100 versus < 90
- HCT CI 0-2 versus ≥ 3
- Recipient CMV serostatus: seropositive versus seronegative

Disease:

- Primary diagnosis: ALL, AML
- Pediatric disease risk index classification: ALL (good, intermediate, and high risk), AML (good, intermediate, high, and very high risk)
- Cytogenetic risk (ALL): Good versus intermediate versus poor/high risk, AML included in PDRI
- Disease status: first CR MRD negative versus first CR MRD positive versus first CR MRD unknown versus second CR MRD negative versus second CR MRD positive versus second CR MRD unknown versus relapse/primary induction failure

Donor:

- HLA matched sibling versus Mismatched relative versus unrelated donor

Graft versus host disease:

- Acute GVHD grade I and II versus grade III and IV versus no aGVHD
- Chronic GVHD mild versus cGVHD moderate-severe (limited versus extensive depending on available data)
- aGVHD and cGVHD versus aGVHD alone versus cGVHD alone

Study design:

Data analysis will be performed separately for patients with ALL and patients with AML. Patient characteristics, disease related factors, and donor features will be described in univariate analysis and *data will be extracted from the existing data set utilized in the pediatric DRI validation study*. Cumulative incidence will be used to calculate the estimates of aGVHD, cGVHD, relapse, and NRM. Multivariate analysis will be used to determine the impact of GVHD on LFS, relapse, NRM, and OS. The Cox proportional hazards models will examine the effects of GVHD on the outcomes of LFS, relapse, NRM, and OS while controlling for PDRI - will assess the interaction of disease risk and GVHD in these models. Kaplan-Meier method will depict the overall survival and LFS at fixed times points. Comparison among survival curves will be performed with log-rank test.

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Table 1 and Table 2 describe the cohort used for PC19-01 analysis (without inclusion of GVHD data)

Table 1. Acute lymphoblastic leukemia: Patient, Disease and Transplant Characteristics

Variable	
Number	1345
Age at transplant	
<2 years	68 (5%)
≥2 years	1277 (95%)
Sex	
Male	835 (62%)
Female	510 (38%)
Hematopoietic co-morbidity index score	
≤2	1121 (83%)
≥3	223 (17%)
Not reported	1 (<1%)
Performance Score	
90-100	1116 (83%)
≤80	208 (15%)
Not reported	21 (2%)
Cytomegalovirus serostatus	
Negative	512 (38%)
Positive	821 (61%)
Not reported	12 (1%)
Cytogenetic risk	
Intermediate	770 (57%)
Poor	497 (37%)
Not reported	78 (6%)
Disease status	
1st complete remission MRD (+)	171 (13%)
1st complete remission MRD (-)	338 (25%)
1st complete remission	21 (2%)
2nd complete remission MRD (+)	156 (12%)
3rd complete remission MRD (+)	33 (2**%)
2nd complete remission MRD (-)	435 (32%)
3rd complete remission MRD (-)	94 (7%)
≥2nd complete remission	44 (3%)
Not in remission	53 (4%)
Donor	
HLA-matched sibling	255 (19%)

HLA-mismatched relative	117 (9%)
HLA-matched unrelated	335 (25%)
1-locus mismatched unrelated	133 (10%)
6-8/8 HLA-matched cord blood	297 (22%)
≤5/8 HLA-matched cord blood	208 (15%)
Conditioning regimen	
TBI/cyclophosphamide	478 (36%)
TBI/cyclophosphamide/fludarabine	334 (25%)
TBI/cyclophosphamide + other	330 (25%)
TBI + other	126 (9%)
Busulfan/cyclophosphamide	26 (2%)
Busulfan/melphalan	18 (1%)
Fludarabine/busulfan/thiotepa	33 (2%)
GVHD prophylaxis	
Ex vivo T-cell depletion/CD34 selection	75 (6%)
Post-CY ± other(s)	57 (4%)
Calcineurin inhibitor + mycophenolate	485 (36%)
Calcineurin inhibitor + methotrexate	610 (45%)
Calcineurin inhibitor ± other	93 (7%)
Other	25 (2%)
Transplant period	
2008-2012	381 (28%)
2013-2017	964 (72%)
Disease Risk Index Group	
Low	465 (34%)
Intermediate	743 (55%)
High	72 (5%)

Abbreviation: MRD = minimal residual disease; TBI = total body irradiation

*Cytogenetic risk: poor ((t9;22), iAMP21, abnormal 17p, loss of 13q, 11q23 (infant); intermediate (all others)

Table 2. Acute myeloid leukemia: Patient, Disease and Transplant characteristics

Variable	
Number	1224
Age at transplant	
<3 years	325 (26%)
≥3 years	909 (74%)
Sex	
Male	649 (53%)
Female	575 (47%)
Hematopoietic co-morbidity index score	
≤2	1012 (83%)
≥3	210 (17%)
Not reported	2 (<1%)
Performance Score	
90-100	1044 (85%)
≤80	169 (14%)
Not reported	11 (1%)
Cytomegalovirus serostatus	
Negative	446 (36%)
Positive	760 (62%)
Not reported	18 (2%)
Cytogenetic risk*	
Favorable	100 (8%)
Intermediate	778 (64%)
Poor	317 (26%)
Not reported	29 (2%)
Disease status	
1st complete remission MRD (+)	175 (14%)
1st complete remission MRD (-)	428 (35%)
1st complete remission	48 (4%)
2nd complete remission MRD (+)	84 (7%)
2nd complete remission MRD (-)	269 (22%)
2nd complete remission	28 (2%)
Not in remission	188 (15%)
Donor	
HLA-matched sibling	257 (21%)
HLA-mismatched relative	89 (7%)
HLA-matched unrelated	344 (28%)
1-locus mismatched unrelated	126 (10%)

6-8/8 HLA-matched cord blood	238 (19%)
≤5/8 HLA-matched cord blood	170 (14%)
Conditioning regimen	
TBI/cyclophosphamide	92 (8%)
TBI/cyclophosphamide/fludarabine	143 (12%)
TBI/cyclophosphamide + other	46 (4%)
TBI + other	53 (4%)
Busulfan/cyclophosphamide	537 (44%)
Busulfan/melphalan	75 (6%)
Fludarabine/busulfan/thiotepa	278 (23%)
GVHD prophylaxis	
Ex vivo T-cell depletion/CD34 selection	66 (5%)
Post-CY ± other(s)	51 (4%)
Calcineurin inhibitor + mycophenolate	427 (35%)
Calcineurin inhibitor + methotrexate	549 (45%)
Calcineurin inhibitor ± other	100 (8%)
Other	31 (3%)
Transplant period	
2008-2012	444 (36%)
2013-2017	780 (64%)
Disease Risk Index Group	
Low	63 (5%)
Intermediate	599 (49%)
High	282 (23%)
Very high	185 (15%)

Abbreviation: MRD = minimal residual disease; TBI = total body irradiation

*Cytogenetic risk: favorable (inv(16), t(16;16), t(15;17), t(8;21) without complex abnormality; poor (-5/5q, -7/7q, FLT3 ITD with high allelic ratio, t(6;9), 3q); intermediate (all others)