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A G E N D A
CIBMTR WORKING COMMITTEE FOR PEDIATRIC CANCER
Houston, TX
Saturday, February 23, 2019, 12:15 – 2:15 pm

Co-Chair:	**Parinda Mehta, MD, Cincinnati's Children's Hospital Medical Center, Cincinnati, OH; Telephone: 513-636-5917; E-mail: parinda.mehta@cchmc.org**
Co-Chair:	**Angela Smith, MD, MS; University of Minnesota Medical Center, Fairview; Telephone: 612-626-2778; Email: smith719@umn.edu**
Co-Chair:	**Gregory Yanik, MD, MS; University of Michigan, Ann Arbor, MI ; Telephone: 734-764-8630; Email: gyanik@umich.edu**
Scientific Director:	**Mary Eapen, MD, MS, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0700; E-mail: meapen@mcw.edu**
Statistical Director:	**Kwang Woo Ahn, PhD; CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-955-7387; E-mail: kwooahn@mcw.edu**
Statistician:	**TBD**

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1. **Introduction**
   a. Minutes and Overview Plan from February 2018 meeting (Attachment 1)
   b. Introduction of incoming Co-Chair: Muna Qayed, MD; Children's Healthcare of Atlanta at Egleston, Atlanta, GA; Email: muna.qayed@choa.org; Telephone: 404-785-1112

2. **Accrual summary** (Attachment 2)

3. **Presentations, published or submitted papers**
   a. **PC16-01** Lund TC, Ahn KW, Tecca HR, Hilgers MV, Abdel-Azim H, Abraham A, Diaz MA, Badawy SM, Broglie L, Brown V, Dvorak CC, Gonzalez-Vicent M, Hashem H, Hayashi RJ, Jacobsohn DA, Kent MW, Li C-K, Margossian SP, Martin PL, Mehta P, Myers K, Olsson R, Page K, Pulsipher MA, Shaw PJ, Smith AR, Triplett BM, Verneris MR, Eapen M. Outcomes after second hematopoietic cell transplant for children and young adults with relapsed acute leukemia. Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation.
   doi:10.1016/j.bbmt.2018.09.016. Epub 2018 Sep 19.

4. **Studies in progress** (Attachment 3)
   a. **PC18-01** Comparison of TBI vs. Non-TBI based regimens for pediatric acute myeloid leukemia in the modern era (C Dandoy/M Eapen/S Davies/T Cooper/E Kolb/J Horan/J Levine). **Analysis (**Attachment 4)

5. **Future/proposed studies**
   a. **PROP 1811-69** Variation of the disease risk index in children undergoing alloHCT (M Qayed/C Kitko) (Attachment 5)
   b. **PROP 1811-71** Does mixed peripheral blood T cell chimerism predict relapse? (S Prcokp/J Boelens/ K Peggs) (Attachment 6)

c. **PROP 1811-100** Outcomes of allogeneic hematopoietic cell transplantation in pediatric patients with acute myeloid leukemia and central nervous system involvement. (H Rangarajan/P Satwani)
PROP 1811-112 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 (K Rao/D Chellapandian/B Savani) (Attachment 7)
d. **PROP 1811-125** Outcomes post-hematopoietic stem cell transplant for Non-Hodgkin's lymphoma in children and adolescents: Analysis of a contemporary cohort (H Rangarajan/ M Verneris/P Satwani) (Attachment 8)
e. **PROP 1811-174** Determination of the Incidence and Functional Consequences of Clonal Hematopoiesis of Indeterminate Potential (CHIP) in Pediatric Allogeneic Stem Cell Transplant Recipients (E Obeng) (Attachment 9)

Dropped proposed studies

c. **PROP 1811-78** Outcomes after transplant with minimal residual disease. *Dropped due to due to feasibility.*
d. **PROP 1811-81** Clinical outcomes of children and young adults with eqings/PNET sarcoma undergoing high dose chemotherapy and auto HSCT. *Dropped due to feasibility.*
e. **PROP 1811-105** Comparison of Pediatric Allogeneic Transplant Outcomes Following Chemotherapy vs Immunotherapy Based Remissions. *Dropped due to feasibility.*
f. **PROP 1811-126** Outcomes and Late Effects of patients undergoing allogeneic hematopoietic cell transplantation for Immune Deficiency or Myelodysplasia from GATA2 mutations. *Dropped due to feasibility.*

6. Other Business

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR PEDIATRIC CANCER
Salt Lake City, UT
Friday, February 23, 2018, 12:15 – 2:15 pm

Co-Chair:	**Gregory Hale, MD, All Children's Hospital, St. Petersburg, FL** **Telephone: 727-767-5681; E-mail: haleg@allkids.org**
Co-Chair:	**Parinda Mehta, MD, Cincinnati's Children's Hospital Medical Center, Cincinnati, OH;** **Telephone: 513-636-5917; E-mail: parinda.mehta@cchmc.org**
Co-Chair:	**Angela Smith, MD, MS; University of Minnesota Medical Center, Fairview;** **Telephone: 612-626-2778; Email: smith719@umn.edu**
Scientific Director:	**Mary Eapen, MD, MS, CIBMTR Statistical Center, Milwaukee, WI;** **Telephone: 414-805-0700; E-mail: meapen@mcw.edu**
Statistical Director:	**Kwang Woo Ahn, PhD; CIBMTR Statistical Center, Milwaukee, WI;** **Telephone: 414-955-7387; E-mail: kwooahn@mcw.edu**
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1. Introduction

The CIBMTR Pediatric Cancer Working Committee (PCWC) meeting was called to order at 12:15pm on Friday, February 23, 2018, by Dr. Parinda Mehta. She also introduced the current working committee leadership and introduced the incoming chair, Dr. Gregory Yanik. The leadership thanked Dr. Gregory Hale for his service to the PCWC, although he was unable to attend the meeting. The processes of participating in the working committee, voting guidance, and rules of authorship were described. Dr. Angela Smith listed the 3 studies published in the past year and the one study currently in progress. She also presented the pediatric biorepository accruals and explained the process for proposing a biorepository study.

a. Minutes and Overview Plan from February 2017 meeting (Attachment 1)
Minutes from February 2017 were approved by the PCWC.

b. Introduction of incoming Co-Chair: **Gregory Yanik, MD**; University of Michigan;
Email: gyanik@umich.edu; Telephone: 734-764-8630

2. Accrual summary (Attachment 2)

3. Presentations, published or submitted papers

a. **PC14-01** Malogolowkin MH, Hemmer MT, Le-Rademacher J, Hale GA, Mehta PA, Smith AR, Kitko C, Abraham A, Abdel-Azim H, Dandoy C, Angel Diaz M, Gale RP, Guilcher G, Hayashi R, Jodele S, Kasow KA, MacMillian ML, Thakar M, Wirk BM, Woolfrey A, Thiel EL. Outcomes following autologous hematopoietic stem cell transplant for patients with relapsed Wilms' tumor: a CIBMTR retrospective analysis. ***BMT 2017 Nov; 52(11): 1549-1555.***

b. **PC14-02** Khandelwal P, Millard HR, Thiel E, Abdel-Azim H, Abraham AA, Auletta JJ, Boulad F, Brown VI, Camitta BM, Chan KW, Chaudhury S, Cowan MJ, Angel-Diaz M, Gadalla SM, Gale RP, Hale G, Kasow KA, Keating AK, Kitko CL, MacMillan ML, Olsson RF, Page KM, Seber A, Smith AR, Warwick AB, Wirk B, Mehta PA. Hematopoietic Stem Cell Transplantation Activity in Pediatric Cancer between

2008 and 2014 in the United States: A Center for International Blood and Marrow Transplant Research Report. ***BBMT 2017 Aug; 23(8): 1342-1349.***

c. **PC14-03** Bitan M, Ahn KW, Millard HR, Pulsipher MA, Abdel-Azim H, Auletta JJ, Brown V, Chan KW, Diaz MA, Dietz A, Vincent MG, Guilcher G, Hale GA, Hayashi RJ, Keating A, Mehta P, Myers K, Page K, Prestidge T, Shah NN, Smith AR, Woolfrey A, Thiel E, Davies SM, Eapen M. Personalized Prognostic Risk Score for Long-Term Survival for Children with Acute Leukemia after Allogeneic Transplantation. ***BBMT 2017 Sep; 23(9): 1523-1530.***

4. Studies in progress (Attachment 3)

a. **PC16-01** Outcomes after second HCT for relapsed malignancy in pediatric patients (T Lund/M Eapen). **Manuscript preparation**

5. Future/proposed studies

a. **PROP 1711-29** Comparison of TBI vs. Non-TBI based regimens for pediatric acute myeloid leukemia in the modern era (Dandoy) (Attachment 4)
Dr. Christopher Dandoy presented this proposal. The aim of this proposal is to compare outcomes between pediatric AML patients who received TBI based conditioning regimens vs. non-TBI based regimens. Preliminary data pulls showed 538 patients available for the non-TBI cohort and 317 available for the TBI cohort. Comments were received on how to handle the patients that received cord blood, the number of centers completing TBI transplants for these patients, and CRF variables available. It was noted that we do not have MRD data for many of these patients. Comments were also received on the differences in non-TBI regimens and including GVHD free survival in the outcomes.

b. **PROP 1711-59** Development of a Prognostic Scoring System for Pediatric Patients Undergoing HSCT for Myelodysplastic Syndrome (Hofmann/Locatelli/Eapen/Ruggeri) (Attachment 5)
This proposal was presented by Dr. Mary Eapen as a discussion to gauge interest and need for a pediatric MDS scoring system. In earlier discussion with EWOG-MDS there was interest in proceeding but the question that came up were: 1) definition of MDS and study inclusion criteria. RAEB-1 and RAEB-2 in pediatric population are similar to AML and there isn't much to learn from a prognostic scoring system in this group. Approximately 60 – 65% of pediatric MDS transplants are for RA/RARS/RCMD. The committee members were near unanimous in that children with RA/RARS/RCMD are worked up for transplant and offered this treatment with the best available donor. So the consensus was that there isn't much we would learn beyond what is already known. That said we would need >600-700 transplant recipients to develop a risk score – these children have few events after transplants. It is highly unlikely these numbers are available even with the collaboration with International Registries.

There is interest to study the biology of the disease (i.e., RA, RARS. RCMD) and the CIBMTR has recipient samples in its repository. But this requires submission of an application for supplemental funds. The committee members were encouraged to submit a grant application and the CIBMTR would support their application.

Dropped proposed studies

c. **PROP 1711-11** Late relapse and mortality for pediatric and young adult patients undergoing Hematopoietic Cell Transplantation for Hodgkin and Non-Hodgkin Lymphoma. *Dropped due to overlap with LE15-01.*

d. **PROP 1711-88** Comparing Transplant Outcomes for AYA Patients with ALL and AML Undergoing HSCT at Pediatric Centers versus Adult Centers. *Dropped due to feasibility and overlap with HS10-01.*
e. **PROP 1711-121** Hematopoietic Stem Cell Transplantation for Pediatric Mature T- and NK-cell Malignancies. *Dropped due to feasibility.*
f. **PROP 1711-154** Outcomes of pediatric patients with primary and secondary myelodysplastic syndrome after allogenic hematopoietic stem cell transplantation. *Dropped due to overlap with several CIBMTR publications.*

6. Other Business
The meeting concluded at 12:55pm.

Working Committee Overview Plan for 2018-2019

a. **PC16-01** Outcomes after second HCT for relapsed malignancy. We anticipate manuscript submission by May 2018.
b. **PC18-01** Comparison of TBI vs. Non-TBI based regimens for pediatric acute myeloid leukemia in the modern era. We anticipate submitting an abstract for ASH 2018 and submitting the manuscript by June 2019.

Oversight Assignments for Working Committee Leadership (March 2018)

Parinda Mehta	**PC16-01** Outcomes after second HCT for relapsed malignancy
Angela Smith	**PC18-01** Comparison of TBI vs. Non-TBI based regimens for pediatric acute myeloid leukemia in the modern era
Gregory Yanik	

Accrual Summary for the Pediatric Cancer Working Committee

Characteristics of patients aged ≤18 years with acute and chronic leukemia, myelodysplastic syndrome and lymphoma reported to the CIBMTR between 2000 - 2018*

HLA-identical sibling HCT	Registration, N (%)	Research, N (%)
Acute myeloid leukemia	2538	580
Bone Marrow	1763 (69)	399 (69)
Peripheral blood	730 (29)	165 (28)
Cord Blood	45 (2)	16 (3)
Acute lymphoblastic leukemia	3256	630
Bone Marrow	2335 (72)	394 (63)
Peripheral blood	829 (25)	201 (32)
Cord Blood	92 (3)	35 (6)
Chronic myeloid leukemia	455	135
Bone Marrow	293 (64)	91 (67)
Peripheral blood	154 (34)	42 (31)
Cord Blood	8 (2)	2 (1)
Myelodysplastic Syndrome	524	128
Bone Marrow	400 (76)	98 (77)
Peripheral blood	113 (22)	25 (20)
Cord Blood	11 (2)	5 (4)
Hodgkin lymphoma	45	10
Bone Marrow	18 (40)	3 (30)
Peripheral blood	27 (60)	7 (70)
Non-Hodgkin lymphoma	294	67
Bone Marrow	192 (65)	39 (58)
Peripheral blood	97 (33)	26 (39)
Cord Blood	5 (2)	2 (3)

* Cases in 2018 continue to be reported

Characteristics of patients aged ≤18 years with acute and chronic leukemia, myelodysplastic syndrome and lymphoma reported to the CIBMTR between 2000 and 2018*

Other related donor HCT	Registration, N (%)	Research, N (%)
Acute myeloid leukemia	766	280
Bone Marrow	343 (45)	142 (51)
Peripheral blood	408 (53)	133 (48)
Cord Blood	15 (2)	5 (2)
Acute lymphoblastic leukemia	923	317
Bone Marrow	441 (48)	149 (47)
Peripheral blood	464 (50)	159 (50)
Cord Blood	18 (2)	9 (3)
Chronic myeloid leukemia	100	48
Bone Marrow	55 (55)	29 (60)
Peripheral blood	44 (44)	18 (38)
Cord Blood	1 (1)	1 (2)
Myelodysplastic Syndrome	177	67
Bone Marrow	84 (47)	38 (57)
Peripheral blood	89 (50)	28 (42)
Cord Blood	4 (2)	1 (1)
Hodgkin lymphoma	21	8
Bone Marrow	10 (48)	4 (50)
Peripheral blood	11 (52)	4 (50)
Non-Hodgkin lymphoma	90	39
Bone Marrow	39 (43)	14 (36)
Peripheral blood	48 (53)	25 (64)
Cord Blood	3 (3)	0

* Cases in 2018 continue to be reported

Characteristics of patients aged ≤18 years with acute and chronic leukemia, myelodysplastic syndrome and lymphoma reported to the CIBMTR between 2000 and 2018*

Unrelated donor HCT	Registration, N (%)	Research, N (%)
Acute myeloid leukemia	3785	1911
Bone Marrow	1575 (42)	679 (36)
Peripheral blood	789 (21)	285 (15)
Cord Blood	1421 (38)	947 (50)
Acute lymphoblastic leukemia	5224	2468
Bone Marrow	2277 (44)	910 (37)
Peripheral blood	1054 (20)	356 (14)
Cord Blood	1893 (36)	1202 (49)
Chronic myeloid leukemia	525	282
Bone Marrow	319 (61)	177 (63)
Peripheral blood	111 (21)	51 (18)
Cord Blood	95 (18)	54 (19)
Myelodysplastic Syndrome	1335	647
Bone Marrow	643 (48)	255 (39)
Peripheral blood	226 (17)	86 (13)
Cord Blood	466 (35)	306 (47)
Hodgkin lymphoma	39	15
Bone Marrow	21 (54)	8 (53)
Peripheral blood	15 (38)	4 (27)
Cord Blood	3 (8)	3 (20)
Non-Hodgkin lymphoma	363	173
Bone Marrow	164 (45)	66 (38)
Peripheral blood	88 (24)	35 (20)
Cord Blood	111 (31)	72 (42)

* Cases in 2018 continue to be reported

Characteristics of patients aged ≤18 years with acute leukemia and lymphoma reported to the CIBMTR between 2000 and 2018*

Autologous HCT	Registration, N (%)	Research, N (%)
Acute myeloid leukemia	304	37
Bone Marrow	57 (19)	2 (5)
Peripheral blood	246 (81)	35 (95)
Cord Blood	1 (<1)	0
Acute lymphoblastic leukemia	67	5
Bone Marrow	5 (7)	0
Peripheral blood	60 (90)	5 (100)
Cord Blood	2 (3)	0
Chronic myeloid leukemia	3	1
Bone Marrow	0	0
Peripheral blood	2 (67)	1(100)
Cord Blood	1 (33)	0
Myelodysplastic Syndrome	4	1
Bone Marrow	0	0
Peripheral blood	4(100)	1(100)
Cord Blood	0	0
Hodgkin lymphoma	1567	151
Bone Marrow	71 (5)	4 (3)
Peripheral blood	1496 (95)	147 (97)
Non-Hodgkin lymphoma	605	74
Bone Marrow	54 (9)	2 (3)
Peripheral blood	551 (91)	72 (97)

* Cases in 2018 continue to be reported

Number of patients aged ≤18 years with solid tumor reported to the CIBMTR between 2000 and 2018*

	Autologous		Allogeneic	
	Registration	Research	Registration	Research
Testicular	68	9	1	1
Bone sarcoma(No Ewing sarcoma)	136	27	6	4
Central nervous system tumors	909	179	1	0
Wilms Tumor	247	29	6	2
Neuroblastoma	4290	607	50	18
Retinoblastoma	112	13	1	1
Ewing sarcoma	488	66	25	6
Extragonadal germ cell tumor	229	25	2	0
Medulloblastoma	1202	185	1	1
PNET	41	11	30	5
Rhabdomyosarcoma	106	13	1	1

* Cases in 2018 continue to be reported

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TO: Pediatric Cancer Working Committee Members

FROM: Mary Eapen, MBBS, MS; Scientific Director for the Pediatric Cancer Working Committee

RE: Studies in Progress Summary

PC18-01: 01 Comparison of TBI vs. Non-TBI based regimens for pediatric acute myeloid leukemia in the modern era (C Dandoy/M Eapen/S Davies/T Cooper/E Kolb/J Horan/J Levine).
The object of this study are to compare OS, LFS and NRM between pediatric patients who receive TBI based regimens vs. Non-TBI based regimens for de novo acute myeloid leukemia in the modern era; to compare transplant related toxicities between patients who receive TBI based regimens vs. Non-TBI based regimens for de novo acute myeloid leukemia in the modern era.
This study is currently in final analysis and we expect to submit by June 2018.

CIBMTR PC18-01

COMPARISON OF TBI VS. NON-TBI BASED REGIMENS FOR PEDIATRIC ACUTE MYELOID LEUKEMIA IN THE MODERN ERA

INITIAL PROTOCOL

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1.0 HYPOTHESIS

In pediatric patients receiving myeloablative conditioning for de novo acute myeloid leukemia (AML), we hypothesize non-TBI (total body irradiation) based regimens are associated with improved leukemia free survival (LFS), overall survival (OS), and non-relapse mortality (NRM) in the modern era (2008 to 2015).

2.0 OBJECTIVES

- Compare OS, LFS and NRM between pediatric patients who receive TBI based regimens vs. Non-TBI based regimens for de novo acute myeloid leukemia in the modern era.
- Compare transplant related toxicities between patients who receive TBI based regimens vs. Non-TBI based regimens for de novo acute myeloid leukemia in the modern era.

3.0 SCIENTIFIC JUSTIFICATION

Myeloablative preparative regimens are designed to eradicate the leukemia and provide sufficient immunosuppression to prevent graft rejection. TBI or busulfan (Bu) based myeloablative conditioning regimens are commonly used to treat patients with AML.[1,2] In 1992, a randomized control trial showed superior outcomes with cyclophosphamide (Cy) – TBI compared with Bu-Cy using oral busulfan formulation which was available at that time.[3] Intravenous busulfan has subsequently been developed, which provides more consistent pharmacokinetics and reliable dosing.[4] Further, pharmacokinetic targeting of intravenous busulfan dosing reduces treatment related toxicity.[5]

In the modern era, intravenous busulfan based conditioning has been shown to be associated with improved overall survival, non-relapse mortality, and disease-free survival in adults.[6,7] In pediatrics, the data is limited. In retrospective review of allogeneic HSCT recipients who received myeloablative conditioning regimens in Japan from 2006 to 2011 (n=220), NRM and OS were similar between patients receiving a busulfan based regimen versus those who received a TBI based regimen. Recently, an analysis of myeloablative AML conditioning regimens used in pediatric AML patients in CR1 were evaluated through a retrospective analysis by the European Group for Blood and Marrow Transplantation. Patients underwent transplant between 2000 and 2010 (n=631). Bu-Cy-Mel (n=133) conditioning regimen was superior (lower 5-year relapse, NRM and increased OS) than TBI-Cy (n=109) and Bu-Cy (n=389) conditioning regimens. However, the majority of patients included in the analysis received oral and not intravenous busulfan (199 of 346, 58%).

As TBI based regimens are associated with significant toxicity in pediatric patients,[8] and many centers continue to use TBI based regimens for AML in pediatric patients, it is important to compare outcomes of patients receiving TBI versus non-TBI regimens for AML.

4.0 STUDY POPULATION

The study population will consist of all pediatric and adolescent HSCT recipients who underwent allogeneic HSCT using myeloablative conditioning for de novo AML.

- First allogeneic HSCT for de novo AML
- Age ≤ 21
- Myeloablative conditioning only (TBI vs. non-TBI). TBI conditioning regimens limited to TBI-Cy, TBI-Cy-Flu, and TBI-Other. Non-TBI regiments limited to Bu-Cy and Bu-Flu.
- Undergoing allogeneic HSCT between 2008 and 2016

- Stem cell source including bone marrow, peripheral or cord blood
- Source including matched related, matched or mismatched unrelated donors, or cord blood
- Exclusion: Antecedent hematologic disorder at diagnosis
- Exclusion: Mismatched related donors
- Exclusion: Non-CNI-based GVHD prophylaxis regimens
- Exclusion: CR3 or greater
- Exclusion: Secondary leukemias

5.0 OUTCOMES

5.1 Primary:

- Overall Survival (OS): Defined as death by any cause; living patients are censored at last follow up. Causes of death according to what is reported by the transplant center will be described within this outcome.

5.2 Secondary:

- Non-relapse mortality (NRM): Time to death without evidence of disease relapse. This event will be summarized by the cumulative incidence estimate with relapse as the competing risk.
- Disease relapse: Disease relapse will be reported as defined by the transplant center either as morphologic/clinical or cytogenetic relapse.
- Leukemia-free survival (LFS): LFS is defined as death or recurrence of the disease for which the patient received the allogeneic transplant. Living patients are censored at last follow up.
- Acute GVHD II-IV: Time to development of grade II-IV acute GVHD. The event will be summarized by the cumulative incidence estimate, where death without grade II-IV acute GVHD will be treated as a competing risk. Patients will be censored at second transplant or date of last follow-up.
- Chronic GVHD: Time to the development of limited or extensive chronic GVHD. The event will be summarized by the cumulative incidence estimate, where death without chronic GVHD will be treated as a competing risk. Patients will be censored at second transplant or date of last follow-up.
- Veno-occlusive disease (VOD) by day +100: VOD is captured in CIBMTR form. Death is competing risks for this event.
- Incidence of bloodstream infections (bacterial and fungal) in the first 100 days: This will be assessed as the cumulative incidence function with death and relapse as competing risks.
- Timing of neutrophil engraftment: Neutrophil engraftment will be defined as granulocyte count $>.5 \times 10^9/L$ for 3 consecutive days after HSCT.

6.0 VARIABLES TO BE DESCRIBED

6.1 Patient-related

- Age at transplant: continuous; ≤10 vs 11-21
- Gender: male vs female
- Race: Caucasian vs African-American vs Asian vs Pacific islander vs Native American

- Karnofsky score: ≥90% v. <90%
- HCT – CI: 0-2 vs ≥3

6.2 Disease-related

- Disease status at HSCT: CR1 vs CR2 vs relapse/PIF
- Cytogenetic score: favorable vs intermediate vs poor
- Sites at diagnosis: BM only vs BM + CNS vs BM + other sites (not CNS)

6.3 Transplant-related

- Donor type
- Graft type: bone marrow vs peripheral blood vs cord blood
- GVHD prophylaxis
- Conditioning regimen
- Busulfan route, if given: oral vs IV
- Pharmacokinetics performed for busulfan dose, if given: yes vs no
- Use of ATG: yes vs no
- Year of transplant
- Median follow-up of survivors

7.0 STUDY DESIGN

Patients meeting the eligibility criteria will be extracted from the registry and divided into two groups: those who receive TBI based regimens vs. those who received non-TBI based regimens. Groups will be compared on donor/recipient characteristics (e.g. age, graft source, HLA-match, etc.). Outcomes and toxicity profiles will be compared between the two groups.

Patient-related, disease-related, and transplant-related outcomes will be compared between patients in the 2 conditioning-regimen groups using Mann-Whitney tests (continuous variables) and Fisher's exact test/chi-square analyses (categorical variables). A p-value of <0.05 will be considered statistically significant. The main analysis will be conducted using the pooled cohort and will focus on OS, NRM and LFS. Additionally, we will analyze differences in infection rates, GVHD, timing of engraftment, VOD and infections. Survival outcomes will be computed using Kaplan Meier and comparison will be done with log-rank tests. For relapse, NRM and GVHD outcomes, VOD and infection incidences, cumulative incidence will be used to describe outcomes after accounting for competing risks. Cox regression models will be built for OS, LFS, NRM, relapse, and acute/chronic GVHD using the whole cohort. The main effect will be forced in all models, and other covariates will remain in the final model if they meet a significance level of <0.05. Forward stepwise selection will be used to identify significant covariates. The interaction between the main effect and significant covariates will be examined. Assessment of the proportional hazards assumption will be done using graphical approaches and time-dependent covariates.

As many children under two receive non-TBI based conditioning, we will analyze outcomes with those <2 years of age included in the analysis and not included.

8.0 REFERENCES

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Table 1. Characteristics of first alloHCT from an HLA-identical sibling, unrelated donor, or cord blood donor for de novo AML in patients aged ≤ 21, years 2008-2016

Characteristic	TBI	Non-TBI
Number of patients	244	496
Patient related		
Median age at transplant (range), years	13 (<1-22)	9 (<1-22)
Age group		
≤10	103 (42)	269 (54)
11-21	141 (58)	227 (46)
Sex		
Male	128 (52)	253 (51)
Female	116 (48)	243 (49)
Race		
Caucasian	189 (77)	371 (75)
African-American	20 (8)	46 (9)
Asian	12 (5)	29 (6)
Pacific islander	1 (<1)	6 (1)
Native American	5 (2)	2 (<1)
Unknown	17 (7)	42 (8)
Karnofsky score		
90-100	201 (82)	435 (88)
< 90	37 (15)	57 (11)
Missing	6 (2)	4 (<1)
HCT-CI		
0-2	211 (86)	432 (87)
3+	31 (13)	54 (11)
Missing	2 (<1)	10 (2)
Disease related		
Disease status		
CR1	114 (47)	280 (56)
CR2	96 (39)	157 (32)
Relapse/PIF	34 (14)	59 (12)
Cytogenetic score		
Favorable	30 (12)	43 (9)
Intermediate	150 (61)	322 (65)
Poor	56 (23)	110 (22)
Not tested/Missing	8 (3)	21 (4)
Sites at diagnosis		
BM only	167 (68)	351 (71)
BM + CNS[a]	61 (25)	97 (20)
BM + other sites (not CNS)	13 (5)	30 (6)

Characteristic	TBI	Non-TBI
Missing	3 (1)	18 (4)
Transplant related		
Donor type		
HLA-identical sibling	21 (9)	136 (27)
Matched unrelated	44 (18)	131 (26)
Mis-matched unrelated	18 (7)	40 (8)
Matched unrelated CB	23 (9)	36 (7)
Mis-matched unrelated CB	123 (50)	116 (23)
CB, match unknown	15 (6)	37 (7)
Graft type		
Bone marrow	39 (16)	227 (46)
Peripheral blood	44 (18)	78 (16)
Umbilical cord blood	161 (66)	191 (39)
GVHD prophylaxis		
TAC + MMF	12 (5)	45 (9)
TAC + MTX	50 (20)	162 (33)
TAC alone	5 (2)	11 (2)
CSA + MMF	140 (57)	92 (19)
CSA + MTX	24 (10)	132 (27)
CSA alone	13 (5)	54 (11)
Conditioning regimen		
TBI + Cy	92 (38)	0
TBI + Cy + Flu	141 (58)	0
TBI + Other	11 (5)	0
Bu + Cy	0	381 (77)
Bu + Flu	0	115 (23)
Busulfan administration, if given (N=500)		
Oral	0	18 (4)
IV	11	471 (96)
Pharmacokinetics performed for busulfan dosing, if given (N=500)		
No	0	1 (<1)
Yes	10 (91)	383 (78)
Not answered	1 (9)	105 (21)
ATG use		
Yes	38 (16)	247 (50)
No	204 (84)	226 (46)
Missing	2 (<1)	23 (5)
Year of transplant		
2008	39 (16)	68 (14)
2009	43 (18)	83 (17)

Characteristic	TBI	Non-TBI
2010	55 (23)	67 (14)
2011	25 (10)	20 (4)
2012	15 (6)	44 (9)
2013	19 (8)	43 (9)
2014	14 (6)	69 (14)
2015	17 (7)	54 (11)
2016	17 (7)	48 (10)
Median follow-up of survivors (range), months	66 (3-122)	51 (3-122)

[a] N=9 from TBI group, and N=5 from non-TBI group received planned intrathecal therapy post-transplant

Table 2. TBI use by center

	TBI only	TBI or non-TBI	non-TBI only
Number of centers	15	106	64

Table 3. Patients only from centers that use both TBI and non-TBI regimens

Characteristic	TBI	Non-TBI
Number of patients	197	264
Median age at transplant (range), years	12 (<1-22)	8 (<1-22)
Age group		
≤ 10	87 (44)	152 (58)
11-21	110 (56)	112 (42)
Disease status		
CR1	89 (45)	159 (60)
CR2	80 (41)	80 (30)
Relapse/PIF	28 (14)	25 (9)
Sites at diagnosis		
BM only	127 (64)	185 (70)
BM + CNS	55 (28)	50 (19)
BM + other sites (not CNS)	13 (7)	18 (7)
Missing	2 (1)	11 (4)
Graft type		
Bone marrow	35 (18)	127 (48)
Peripheral blood	33 (17)	33 (13)
Umbilical cord blood	129 (65)	104 (39)
Donor type		
HLA-identical sibling	14 (7)	70 (27)
Matched unrelated	38 (19)	68 (26)
Mis-matched unrelated	16 (8)	24 (9)
Matched unrelated CB	21 (11)	20 (8)
Mis-matched unrelated CB	96 (49)	66 (25)
CB, match unknown	12 (6)	16 (6)

Time (set date: 05/01/18)	TBI (N = 244), %	Non-TBI (N = 496), %	Overall, %
1-year	99	99	99
2-year	97	97	97
3-year	95	95	95
4-year	94	92	93
5-year	92	90	91

Data source: November 2018 CRF Retrieval

Proposal: 1811-69

Title:
Validation of the Disease Risk Index in Children Undergoing Allogeneic Hematopoietic Cell Transplantation

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Hypothesis:
Disease risk index will stratify pediatric patients undergoing HCT for hematologic malignancies by relapse risk.

Objectives:

- To examine the impact of disease risk index (DRI) on relapse and disease free survival (DFS) in children undergoing hematopoietic cell transplant (HCT) for hematologic malignancies
- To compare the impact of DRI on DFS within major disease categories (ALL, AML, MDS)
- To refine the DRI for as needed for pediatric patients
- To derive the DRI categorization for juvenile myelomonocytic leukemia

Scientific justification:
Disease relapse remains the major cause of failure after HCT. Disease characteristics such as primary diagnosis, disease status and cytogenetic abnormalities impact the risk of relapse, and subsequently survival outcomes after HCT. In adults, these disease attributes were used to derive the disease risk index (DRI), a tool that can be used to categorize patients into four distinct risk strata for OS: low risk (LR), intermediate risk (IR), high risk (HR), and very high risk (VHR), .[1, 2] The strata are not evenly sized: LR includes 12% of patients, IR 64%, HR 23%, and, only 1% of patients are classified as VHR. In small sized analyses, HR and VHR are often combined. Since its original publication, DRI strata are increasingly used in clinical trial design as an eligibility criteria or to develop risk strata.
The application of DRI has not been validated for children. It is possible that disease characteristics that determine outcomes in adults may differ in children. In analysis of HCT outcomes for AML, DFS differed by age group, with better outcomes for children and young adults, compared to older adults.[3] In pediatric ALL, the majority of patients are cured with chemotherapy alone. As a result the indication for transplant differs substantially from adult patients. Only children with very high risk disease (hypodiploidy, induction failure) proceed to HCT in CR1, but the existing DRI schema may underestimate the risk for relapse in this setting as all patients with ALL in CR1 are categorized as *intermediate* risk. Other examples where the current DRI classification may underestimate risk are T-cell ALL and infant ALL.[4, 5] Well-known differences in survival between children and adults may also require refinement of the DRI for use in pediatrics. For example, the 3- year probability of survival following HLA-matched sibling transplant for ALL for children is consistently better than for adults when stratifying patients by CIBMTR definition for early (73%±2% vs 59%±1%), intermediate (58%±2% vs 39% ± 2%), or advanced disease (40%±5% vs 28%±2%).[6] It is likely that outcomes for DRI categories in children will substantially differ from adults, at least for some diseases. Furthermore, the DRI cannot be calculated for some pediatric diseases like juvenile myelomonocytic leukemia (JMML).

We have explored the utility of DRI classification in pediatric patients undergoing HCT for hematologic malignancies (Abstract Submitted to TCT 2019). We calculated the DRI for 280 pediatric patients participating in the Mount Sinai Acute GVHD International Consortium (MAGIC) observational trial. The distribution of patients into risk strata was different for children compared to adults; LR (n=12, 4%), IR (n=128, 46%), HR (n=108, 39%), and VHR (n=32, 11%) and. This finding can be partly explained by differences in the most common indications for HCT. In children ALL (51%) was the most common indication, followed by AML (31%), MDS (10%), and JMML (4%). DRI cannot be calculated for JMML. In our study, we were not able to adequately evaluate the LR strata due to small numbers and therefore we used IR as the reference group. Despite these limitations, we found that adult version of the DRI effectively stratified pediatric patients into distinct strata for relapse (p=0.001) and disease-free survival (p<0.001). Children with HR DRI were significantly more likely to relapse (HR 2.1, 95% CI 1.2-3.7) and have worse DFS (HR 1.6, 95% CI 1.0-2.5) compared to IR DRI. The risks for relapse and worse DFS were even greater for children with VHR DRI (relapse, HR 3.4, 95% CI 1.6-7.3; DFS 3.59, 95% CI 2.0-6.5). The adult version of DRI did not distinguish for differences in overall survival for all risk strata when applied to children. Although VHR pts had significantly worse 2y OS (HR 3.2, 95% CI 1.6-6.4), HR pts were not significantly different than IR pts (HR 1.3, 95% CI 0.7-2.2). In a preliminary analysis, survival for JMML was most similar to the VHR strata, but the confidence intervals for these patients is wide. In summary, despite a modest sample size, we found that the adult version of DRI risk stratifies children for long-term outcomes such as relapse, DFS, and OS. A larger sample size is needed to adequately study and refine the DRI for pediatric patients.

In this study, we will test the hypothesis that the DRI can categorize pediatric hematologic malignancies by relapse and DFS. We will also determine how to categorize malignancies that develop primarily in children, such as JMML, whenever a sufficient number of patients is available. If our hypothesis is correct, the DRI can be used in pediatric trials and retrospective analyses, to stratify for risk of relapse.

Study population:

- Children <18 years who received first HCT, excluding autologous and syngeneic transplantations, for hematologic malignancy.
- Disease categories with <1% frequency will be excluded.
- From Armand et al, published in 2014, there were 1731 pediatric (age < 18 years) that were excluded from the CIBMTR adult-focused analysis. The years included in that analysis were patients transplanted in 2008 - 2010. In order to form a larger pediatric cohort, we would recommend expanding the years from 2008 – 2013.

Outcomes:

Primary:

- Disease-free survival (DFS): This event is defined as survival without recurrence of primary disease. Events are in the form of either death or relapse. This event is summarized by a survival curve or the sum of the cumulative incidence estimates. Patients are censored at the time of last follow-up. There are no competing risks.

Secondary:

- Relapse: This event is defined as recurrence of the underlying malignancy for which the HCT was performed. Patients are censored at date of last follow-up. This will be summarized by the cumulative incidence estimate with non-relapse mortality (NRM) as a competing risk.

- Overall survival (OS): This event is defined as death from any cause. The event will be summarized by a survival curve. There are no competing risks.
- Non-relapse mortality (NRM): This event is defined as time to death without evidence of recurrence of hematological malignancy. Patients are censored at the date of last follow-up. The event will be summarized by the cumulative incidence estimate with relapse as a competing risk.

Variables to be described:

Patient-related:

- Age at transplant: continuous
- Gender: male, female
- Karnofsky/Lansky performance score: < 90%, ≥ 90%, missing
- Race: Caucasian, African-American, Asian/Pacific Islander, Hispanic, other, missing
- Disease
    - Primary diagnosis
    - CR status/ disease status at transplant
    - Cytogenetics
- Time from diagnosis to transplant

Donor-related:

- Donor age, years: median (range)
- Donor match: matched related, well-matched unrelated, mismatched unrelated, haploidentical donor
- Graft source: Bone marrow, peripheral blood, umbilical cord
- Donor-recipient sex match: M/M, M/F, F/M, F/F, missing
- Donor-recipient CMV status match: +/+, +/-, -/+, -/-, missing

Transplant-related:

- Total nucleated cell (TNC) pre-cryo dose, x 10^8/kg: median (range)
- TNC pre-cryo dose, x 10^8/kg: < 2, 2-<5, 5-<8, ≥ 8, missing
- CD34 dose, x 10^6/kg
- ABO mismatch
- Conditioning regimen
- GVHD prophylaxis
- Year of transplant

Variables to be analyzed:

Patient-related

- Race: Caucasian vs. Non-Caucasian
- Disease
    - Primary diagnosis: ALL, AML, MDS, MPAL, CML, other
    - CR status
    - Cytogenetics
    - Disease status at time of transplant

Donor-related

- Donor Match
- Graft source
- Donor-recipient sex match: M/M vs. M/F vs. F/M vs. F/F
- Donor-recipient CMV status match: +/+ vs. +/- vs. -/+ vs. -/-

Transplant-related:

- Conditioning regimen: myeloablative vs reduced intensity
- GVHD prophylaxis
- Year of transplant

Study design:

In univariate analysis, patient characteristics will be summarized through descriptive tables of patient, disease, donor, and transplant related factors. For discrete variables, the number of cases and their respective percentages will be calculated. For continuous variables, the median and ranges will be calculated. Probabilities for overall survival at fixed time points will be calculated using the Kaplan-Meier method. Comparison of survival curves will be done using the log-rank test. Estimates of NRM, DFS and relapse will be calculated according to the cumulative incidence. For OS, DFS and relapse, multivariate analyses will examine the impact of DRI, while controlling for other risk factors, on the cause-specific hazards of using Cox proportional hazard models. We propose to divide the entire cohort into separate test (2/3) and validation (1/3) cohorts to determine the best stratification. This will include testing if the adult patient validated DRI categorizations are the best discriminators within a pediatric population. In addition, other stratifications can be tested, such as redefining ALL risk groups (transplant in CR1 for hypodiploid maybe more high risk than for MRD+ at the end of consolidation, as one example). We would also propose reanalyzing each disease type-disease status combinations. For example, previous data from the CIBMTR has shown worse survival when patients with ALL and AML are transplanted in CR1 vs CR2 or greater.[6] This method will also allow for testing of pediatric specific diseases such as JMML to determine level of risk associated with these diseases. Once the best stratification is determined, we can test the performance of the refined classifications in the test cohort.

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Characteristics of patients under 18 years old who underwent 1st allo-HCT from 2008-2016

Characteristic	TED	CRF
Number of patients	5484	2428
Age at HCT, median(range), yrs	9 (<1-18)	8 (<1-18)
Age at HCT, yrs		
<10	2932 (53)	1410 (58)
10-18	2552 (47)	1018 (42)
Disease		
ALL	2465 (45)	983 (40)
AML	1927 (35)	973 (40)
RA, RARS, RCMD, RCC	119 (2)	53 (2)
RAEB1, RAEB2	103 (2)	40 (2)
JMML	178 (3)	102 (4)
MDS, NOS	164 (3)	79 (3)
CML	148 (3)	53 (2)
Non-Hodgkin lymphoma	188 (3)	68 (3)
Hodgkin lymphoma	29 (<1)	9 (<1)
Biphenotypic, bilineage or hybrid leukemia	163 (3)	68 (3)
Type of donor		
HLA-identical sibling	1400 (26)	313 (13)
Other related	435 (8)	155 (6)
Unrelated donor	1957 (36)	598 (25)
Cord blood	1692 (31)	1362 (56)
Graft source		
Bone marrow	2917 (53)	802 (33)
Peripheral blood	875 (16)	264 (11)
Cord blood	1692 (31)	1362 (56)
Conditioning regimen		
MAC	5265 (96)	2338 (96)
TBI/Cy/other	2799	1213
TBI/other	409	152
Bu/Cy	1157	566
Bu/Mel/other	330	164
Bu/Flu/other	457	193
Mel/Flu/other	69	33
BEAM	7	2
Mel/other	37	15
RIC/NMA	219 (4)	90 (4)
TBI/Cy/Flu	60	29
TBI/Flu	33	8
Flu/Bu	57	29

Characteristic	TED	CRF
Flu/Mel	69	24
Year of HCT		
2008-2011	2477 (45)	1246 (51)
2012-2016	3007 (55)	1182 (49)
Median follow-up of survivors (range), months	52 (2-127)	56 (3-127)

Proposal: 1811-71

Title:
Does mixed peripheral blood T cell chimerism predict relapse?.

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Specific aims:

- What is the incidence of persistence of host T cells after transplant for non-T cell malignant disease in pediatric patients at Day 100, 1 year and 2 years.
- Is the incidence of relapse higher in patients with persistence of host T cell populations at these time points?
- Does reactivation of CMV in patients who were CMV seropositive prior to transplant influence the incidence of host T cells after transplant?

Scientific justification:
Relapse of disease remains a clear medical need after allogeneic hematopoietic cell transplantation. Recent data has increased our concern that harbingers of relapse after transplant include not only the depth of remission at the time of transplant but the incidence of minimal residual disease and mixed chimerism in the early post-transplant period. Concern that mixed chimerism increases the risk that a patient will suffer either a relapse or rejection has led to interventions after finding mixed chimerism[1-7]. However, the concern that mixed chimerism portends subsequent relapse is largely extrapolated from studies evaluating mixed chimerism in both total and lineage specific populations in specific populations of adult [8-10] and pediatric transplant recipients[11,12] and has not been a consistent finding in these populations or when extrapolated to recipients of T cell depleted or reduced intensity based transplant [7,13,14]

Mixed chimerism in the myeloid compartment likely results from and leads to different events than mixed chimerism in the lymphoid compartment and more specifically the T vs B vs NK cell compartments. Importantly, after T cell depleted transplantation, mixed chimerism in the T cell compartment can be the result of the persistence and expansion of host viral specific T cells.[15]
This study will attempt to evaluate the role of CMV in mixed T cell chimerism. The presence of recipient T cell chimerism in patients at risk for CMV reactivation will be compared to that in those not at risk for CMV reactivation. As many factors can affect the incidence of post-transplant mixed chimerism, patients in this analysis will be stratified by the intensity of conditioning and the stem cell source (conventional BM or PBSC, in vitro or in vivo T cell depleted or cord blood). Patients will be stratified by whether they received serotherapy with ATG or alemtuzumab, were transplanted for ALL or AML and the level of HLA identity, TBI vs chemotherapy-based conditioning, GvHD prophylaxis and recipient CMV serostatus. The analysis with not extend to recipients of non-myeloablative conditioning.

Scientific impact:
We believe that it is particularly relevant to determine the transplant settings in which persistence of host T cells is an independent predictor of relapse. Further evaluation is needed to define the specific predictors associated with mixed chimerism. Identifying patients for whom reversing mixed chimerism - with the risk of DLI induced GvHD or elimination of protective populations of T cells- is not justified by an increased risk of relapse is important. There is enthusiasm to answer this question within the pediatric transplant community.

The analysis required includes evaluation of both bulk and lineage specific chimerism which is now being collected on comprehensive long track CRFs as well as on all recipients of cord blood transplant.
Patient Eligibility Population:
Pediatric patients transplanted for malignant diseases excluding T cell leukemia and lymphoma: thus B-ALL (in CR), AML (in CR) and MDS who received myelo-ablative conditioning. No limitation for cell sources or in vivo / ex vivo T cell depletion will apply.

Data requirements:
No supplemental data is required. We anticipate that there are likely too few recipients of non-myeloablative or reduced intensity condition in the pediatric cohort to include in this analysis but we would like to confirm that.

Sample requirements:
No biologic sample requirements from the NMDP repository

Study design:
All patients (0-21) reported to CIBMTR by CRF reporting centers, transplanted for an acute leukemia (B-ALL, AML in CR, MDS) between 2005 and 2016, transplanted with a first transplant will be included. This analysis of the correlation between persistence of host T cells and relapse will also include an analysis of some potential triggers for persistent host T cells by evaluating the role of CMV reactivation in this event. Predictor analysis will be performed taking the following donor, recipient and transplant variables into account: indication, donor source (PB, BM, CB), age, co-mobidity score, gender, conditioning (chemo-bases, TBI), ex-vivo T cell depletion, ATG/campath (timing of serotherapy), GvHD prophylaxes. Statistical analysis will be done under the guidance of the CIBMTR Working Committee Statistician as well as medical director. Cox proportional hazard analyses and fine – gray competing risk analyses will be used for analyses.

<u>The study protocol will include:</u>
Assessment of persistence of host T cells after transplant for malignant disease (excluding T cell leukemia and lymphoma). Incidence of mixed T cell chimerism in transplants after cord blood, conventional marrow or PBSC or T cell depleted transplant
Role of infectious complications will be an exploratory endpoint.

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Conflicts of interest:
None

Characteristics of patients under 21 years old who underwent 1st allo-HCT for ALL/AML/MDS with MAC regimen and with post-HCT chimerism studies performed using peripheral blood and T-cell, 2014-2017.

Characteristic	N (%)
Number of patients	186
Age at HCT, median(range), yrs	10 (<1-21)
Age at transplant, yrs	
<10	92 (49)
10-21	94 (51)
Disease	
B-cell ALL (CR)	75 (40)
AML (CR)	105 (56)
Therapy related	4
Antecedent hematologic disorder	8
MDS (RA, RARS, RAEB1, RAEB2)	6 (3)
Donor type	
HLA-identical sibling	32 (17)
Other related	30 (16)
Unrelated donor	124 (67)
Graft source	
Bone marrow	73 (39)
Peripheral blood	45 (24)
Cord blood	67 (36)
Others	1 (<1)
Relapse	
No	148 (80)
Yes	37 (20)
Missing	1 (<1)
Year of HCT	
2014	6 (3)
2015	65 (35)
2016	68 (37)
2017	47 (25)

Proposal: 1811-112

Title:
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

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Hypothesis:
Does the presence of extramedullary disease in pediatric patients with AML at any time prior to transplant (with or without associated bone marrow disease) have an impact on survival and disease-free survival after allogeneic hematopoietic cell transplantation?

Specific aim:
To describe the clinical characteristics and outcomes (OS, DFS, NRM, relapse incidence) of pediatric patients with AML presenting with EMD and identify prognostic factors associated with improved outcome.

Scientific justification:
Extramedullary disease (EMD) is a rare form of presentation in acute myeloid leukemia (AML) and includes most frequently central nervous system (CNS) disease and myeloid sarcoma. There are very few studies analysing the impact of the presence of EMD in AML on the outcomes of allogeneic hematopoietic cell transplantation (allo-HCT).
Previous studies did not observe any impact of pre-transplant EMD associated with AML on the transplant outcome among adults (1). However, only a few studies reviewed the prognostic significance of EMD in pediatric AML in general with no specific transplant data. A Japanese group found that EMD with high white cell count (≥ 100x109/L) had lower event free survival (EFS) as compared with their counterparts with high counts and no EMD (24% vs 64 % p=0.035) (2); while absence of EMD improved EFS in a study from Pediatric Oncology Group (hazard ratio 0.522 p=0.037) (3). On the other hand, CNS involvement in children with AML increased relapse risk in a recent study with no effect on overall survival (CNS 3 vs CNS 2 and CNS 1, 18%, 12%, 4 % p<0.001) (4). Overall survival was affected in a Nordic study due to early induction death among children with EMD (8% vs 1 % p=0.002) (5). None of these reports presented segregated results for the transplanted patients.
We aim to analyse the impact of EMD in children with AML at any time prior to allo-HCT with or without associated bone marrow disease on overall and disease-free survival following transplantation. The period of the analysis will be between 2000 and 2017 to avoid bias due to the changes in chemotherapy treatment and supportive care and in order to have optimal data on disease cytogenetics. The study will answer the important question of the need (or not) for therapy adjustment prior to allo-HCT in patients with EMD.

Patient eligibility population:
Inclusion criteria:

All patients ≤18 years of age who are affected by extramedullary disease associated with AML any time prior to transplantation with or without bone marrow involvement and who underwent an allo-HCT between 2000 and 2017.

Exclusion criteria:
Promyelocytic leukemia (M3 AML), Down Syndrome and therapy-related AML.
Data Requirements
This proposed study will require data that is included in the CIBMTR collection forms for pre-HCT and post-HCT acute myelogenous leukemia. The CIBMTR Data will be combined with EBMT data using similar data collection forms with the same inclusion and exclusion criteria.

Sample requirements:
Registry Data from CIBMTR and EBMT

Study design (scientific plan):
This study is a retrospective registry analysis of all patients who received an allo-HCT for AML between 2000 and 2017. The study will involve a pilot phase where a matched-pair study will be conducted to analyze the transplant outcome in children with acute myeloid leukemia presenting with and without extra medullary disease and a sample size will be determined prior to the undertaking the larger study. Baseline characteristics and known prognostic variables will be collected from CIBMTR database forms. These characteristics will include: age, sex, Karnofsky performance status, presence of EMD at diagnosis (including CNS), WBC at diagnosis, immune-phenotype at diagnosis, number of prior chemotherapy regimens, time from diagnosis to transplant, remission status at transplant (first remission, second remission, progressive/refractory disease), conditioning therapy (chemotherapy-based or total body irradiation based, including chemotherapy type and TBI dose), GvHD prophylactic regimen, use of anti-thymocyte globulin, T-cell depletion of the graft, presence of minimal residual disease prior to transplant (molecular data or flow cytometry data), donor source (peripheral blood, cord, bone marrow), transplant type (haploidentical, 1 or 2 HLA-antigen mismatch, MUD, sibling donor, cord blood), hematopoietic cell transplantation-co-morbidity index, and cytogenetics at diagnosis.
Transplant outcomes (OS, DFS, cumulative incidence NRM, and CI Relapse) will be evaluated for patients with EMD. Additionally, cumulative incidence of relapse will be evaluated for patients based on type of EMD (CNS, skin, lymph nodes and other organ involvement).
Median overall survival, and progression-free survival will be calculated utilizing Kaplan-Meier analysis and compared utilizing the log-rank test. Cumulative incidences of NRM, relapse, and GvHD (chronic and acute) will be performed utilizing the cumulative incidence procedure to account for competing risks, and comparison will be performed utilizing the Fine-Gray test. Differences between groups will be evaluated utilizing the Chi-squared test or Fisher's exact test for categorical variables, two-sample test for proportions, or the Wilcoxon rank sum test for medians. For cumulative incidence, the Fine-Gray analysis will be utilized to compare variables with competing risks.

Conflicts of interest:
None

Timeline:
Expected start date: March 2019
Expected end date: September 2019

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Proposal: 1811-100

Title:
Outcomes of allogeneic hematopoietic cell transplantation in pediatric patients with acute myeloid leukemia and central nervous system involvement.

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Background and scientific justification
Central nervous system (CNS) involvement in acute myeloid leukemia (AML) occurs in 6-29% of pediatric patients at diagnosis (1, 2). The outcome of patients with AML and CNS involvement has been earlier reported to be worse than those without CNS disease in some studies (3, 4) but improved in others (1, 5).
In a COG study (1) of 1459 patients with AML and CNS involvement, although the overall survival (OS) of patients with CNS 3 disease [> 5 white blood cells (WBCs) with blasts in cytospin or with clinical or radiographic signs of CNS leukemia] was similar to patients with CNS1 (< 5 WBC but without blasts) or CNS 2 (< 5 WBC but with blasts on cytospin) involvement, patients with CNS3 had an increased risk of isolated CNS relapse (1). In a more recent multivariate analysis (5) of 1344 patients with CNS involvement, the same authors showed that presence of CNS 2 and CNS 3 disease adversely affected disease free survival (DFS) and relapse rate (RR) but not OS (CNS1: DFS: 58.9% RR: 34.1% OS: 69.3%; CNS2: DFS 53.2%, RR 40.9%, OS 74.7% and CNS3: DFS 45.2%, RR: 48.4%, OS: 60.8%, p=0.06, p< 0.01, p=0.045 respectively) . Many of these children undergo allogeneic hematopoietic cell transplantation (HCT) for relapse of AML in CNS and/or bone marrow. Optimal conditioning regimen for patients with history of CNS involvement is not well described in children. In some instances, such as in patients with history of CNS3 disease, a decision may be made by the treating physician to incorporate total body irradiation (TBI) as part of the conditioning regimen. However, study in adults (6) with AML with CNS involvement prior to allogeneic HCT, the authors observed that use of high dose TBI or cranial irradiation as part of transplant conditioning regimen did not affect time to relapse, leukemia free survival and overall survival. From this analysis, the authors concluded that history of prior CNS disease when treated, is not an independent factor in determining survival after HCT.
In a Japanese study of pediatric AML (7), the 2 year relapse free survival (RFS) in patients who received busulfan based myeloablative condition regimen (Bu-MAC) (n=69) vs TBI based myeloablative conditioning (TBI-MAC) regimens (n=151) was similar (71% vs 67% p=0.36). Extra medullary involvement was seen in 24 (13 with CNS only) patients in the Bu-MAC arm vs 23 patients (13 only CNS only) in TBI-MAC arm. RFS for the small cohort of patients CNS disease was similar after Bu-MAC vs TBI-MAC regimens (2 year RFS 77% vs 64% p=0.54).
It is interesting to note that in a recent CIBMTR study of trends in HCT for pediatric cancer from 2008-2014, 1516 patients underwent allogeneic HCT for AML (8). In this cohort, 544 (35%) patients with AML received TBI as part of the conditioning regimen. Although this report was not designed to analyze the indication for TBI in children with AML, it is possible that a history of CNS disease may have influenced the decision to use TBI as a part of the conditioning regimen.
It is intriguing that pediatric transplant community continues to use TBI for children with AML despite well-known increased risk of second malignancies (9), severe late effects (10) and non-inferiority of busulfan based conditioning regimen for AML (7, 11-13). Since radiation therapy is well established modality of treatment in children with CNS acute

lymphoblastic leukemia (ALL), it is plausible that pediatric transplant physicians have adopted radiation therapy from ALL experience due to lack of established guidelines for treating children with CNS-AML. Without large data it is unlikely that pediatric transplant physicians will change their practice. Hence, large CIBMTR studies are needed to compare outcome of CNS-AML patients post chemotherapy vs. TBI based MAC HCTs, to provide meaningful practice changing data.

Hypothesis:
We hypothesize that in pediatric patients with AML and history of CNS involvement, outcomes post chemotherapy based MAC regimens will be comparable to TBI based MAC regimens.

Primary objectives:
Compare outcomes of pediatric patients with AML with CNS involvement stratified by basis of conditioning regimens received: TBI based vs non-TBI based MAC regimens.

- 2 year leukemia free survival (LFS)
- 2 year overall survival

Secondary objectives:

- 100 days and 1 year non relapse mortality (NRM) following allogeneic HCT
- Timing and location of relapse post allogeneic HCT in both cohorts

Study population:
Inclusion criteria:

- Diagnosis: AML with history of CNS involvement at any point of time pre-HCT
- Age ≤ 21 years at the time of allogeneic HCT
- Therapy: Received allogeneic HCT in CR1 or beyond CR1 with either TBI based or non-TBI based regimens.
- Years: 2000-2018

Exclusion criteria:

- Therapy related AML
- Patients with Downs syndrome
- Patients who underwent autologous HCT
- Recipients of ≥ 2nd allogeneic HCT
- Recipients of reduced intensity conditioning regimens

Variables to be collected:
Patient:

- **Age at transplant**: continuous and <3, 4-12 and 13-21 years
- Age at last follow up
- **Sex**: male vs. female
- Karnofsky/Lansky performance score: ≥90% vs. <90%
- Donor/recipient CMV status: negative vs. positive
- Infused total nucleated cell count (if available, CD34+ cell dose and CD3 dose)

Disease related:

- Cytogenetics
- Bone marrow at end of induction, end of therapy and pre-allogeneic HCT
- Number of chemotherapy cycles prior to allogeneic HCT.
- Patient received Intrathecal therapy prior to allogeneic HCT Y/N

- Did patient received radiation therapy prior to allogeneic HCT if Y, specify type site of radiation therapy and dose if available
- Pre allogeneic-HCT: Active leukemia prior to start of preparatory regimen Y/ N if Y specify site: BM, CNS, Skin, Testes, others (specify)

Transplant related:

- Year of Transplant
- Disease and CR status at time of transplant
- Time from diagnosis to transplant
- **Graft source**: bone marrow vs. peripheral blood vs. cord blood
- **Donor**: HLA-identical sibling vs unrelated donor vs cord blood vs haploidentical donor
- Conditioning regimen: TBI based: Total dose of TBI /dose per fraction
- Non TBI based regimens: details of preparative regimen
- Was additional radiation given to other sites within 14 days of pre HCT preparative regimen Y/N If Yes specify radiation filed and total dose.
- **GVHD prophylaxis**: No GVHD prophylaxis, Ex-vivo T-cell depletion, TAC + MMF +- other(s), TAC + MTX +- other(s), TAC +- other(s), CSA + MMF +- other(s), CSA + MTX +- other(s), CSA + other(s), CSA alone, Others
- **ATG/Campath**: yes vs. no
- **Year of allogeneic HCT**: 2000-2009 vs. 2010-2018

Post-transplant

- Days to neutrophil and platelet engraftment
- Acute GvHD
- Max grade of aGvHD
- Site of aGvHD
- Chronic GvHD
- Max grade of cGvHD: none vs. limited vs. extensive
- If patient relapsed post-HCT
    - Time to relapse
    - Site of relapse BM only vs BM + EM involvement (specify)/EM only (specify site)
      Was CNS irradiation given post-Transplant Y/N
    - Was intrathecal therapy given post-Transplant Y/N

Study design:
Allogeneic HCT with Chemotherapy based MAC (cases) regimens will be matched with 1 control of TBI based MAC regimens. Matching criteria would be based on age, donor type, cytogenetics and year of allogeneic HCT.

Study risk factors associated with relapse:
Age of patient, donor, gender of patient, ethnicity, year of allogeneic HCT, CR1 vs. CR2 vs. other disease status indications, MSD vs. MUD vs. unrelated cord blood donor, stem cell source BM vs PBSC , TBI vs. chemotherapy based conditioning regimens, cranial/craniospinal radiotherapy as part of conditioning regimen, acute GVHD, chronic GVHD, .

Statistical consideration:
The continuous variables were summarized by mean and standard deviation; the categorical variables were summarized by percentage. To compare EFS and OS between TBI vs. non-TBI

MAC regimens, Kaplan-Meir curves will be generated. Univariate and multivariate analysis will be performed for risk factors associated with relapse and TRM.

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Characteristics of pediatric patients who underwent 1st allo-HCT for AML with MAC regimen, 2008-2016

Characteristic	BM only	BM + CNS	BM + other sites
Number of patients	660	221	56
Age at HCT, median(range), yrs	9 (<1-18)	8 (<1-18)	4 (<1-16)
Age at HCT, yrs			
<10	364 (55)	132 (60)	46 (82)
10-18	296 (45)	89 (40)	10 (18)
Disease status			
Primary induction failure	56 (8)	15 (7)	3 (5)
1st complete remission	369 (56)	108 (49)	28 (50)
2nd complete remission	190 (29)	86 (39)	22 (39)
1st relapse	45 (7)	12 (5)	3 (5)
Donor type			
HLA-identical sibling / Twin	134 (20)	40 (18)	10 (18)
Other related	33 (5)	6 (3)	3 (5)
Unrelated donor	493 (75)	175 (79)	43 (77)
Graft source			
Bone marrow	252 (38)	82 (37)	23 (41)
Peripheral blood	84 (13)	23 (10)	7 (13)
Cord blood	322 (49)	115 (52)	26 (46)
Others	2 (<1)	1 (<1)	0
Post-HCT therapy planned			
No	596 (90)	176 (80)	46 (82)
Yes	63 (10)	45 (20)	10 (18)
CNS irradiation	6	2	0
Intrathecal therapy	13	30	4
Systemic therapy	43	14	6
Azacytidine (Vidaza)	11	2	1
All-trans retinoic acid (Tretinoin)	1	0	1
Decitabine (Dacogen)	1	1	1
Midostaurin	1	0	0
Sorafenib	16	9	3
Other systemic therapy	15	1	1
Cellular therapy	2	0	0
Missing	1 (<1)	0	0
Year of HCT			
2008-2011	332 (50)	107 (48)	28 (50)
2012-2016	328 (50)	114 (52)	28 (50)

Proposal: 1811-125

Title:
Outcomes post-hematopoietic stem cell transplant for Non-Hodgkin's lymphoma in children and adolescents: Analysis of a contemporary cohort.

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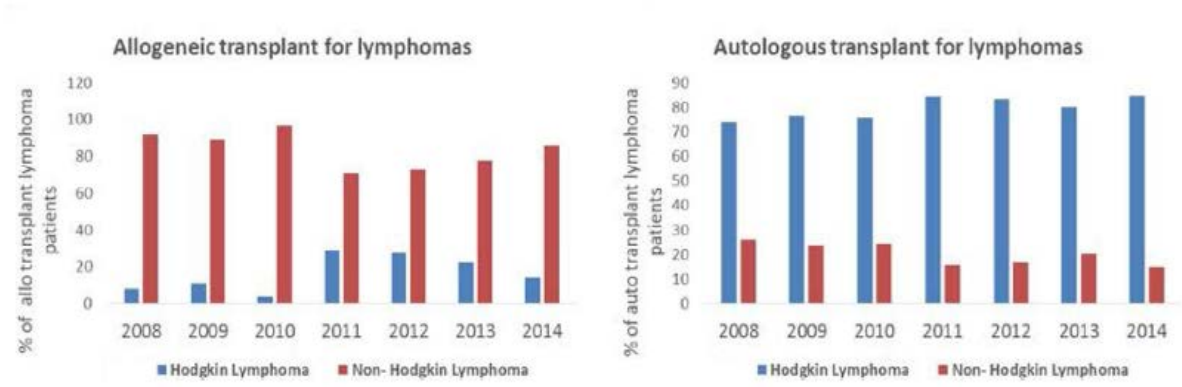
Background and scientific justification:
Pediatric Non-Hodgkin lymphomas are heterogeneous group of diseases with 800 new cases diagnosed annually (1, 2). Unlike adults where low grade indolent NHL predominate, most pediatric NHL cases are high grade and have an aggressive clinical behavior. Use of upfront intensive multi-agent chemotherapy has led to considerable improvements in survival of pediatric (≤ 18 year) NHL patients with an event free survival (EFS) of 60-90% depending on the histological sub-type of NHL (3). Increasing newer targeted therapies, such as rituximab, ALK inhibitors, anti-CD30 (brentuximab) are also being incorporated in upfront chemotherapy regimens. Relapsed/refractory NHL, on the other hand has been historically associated with a poor prognosis with the exception of anaplastic large cell lymphoma (ALCL). The EFS in R/R ALCL is round 60% but is around 10-20% in sub-types such as Burkitt lymphoma (BL) and diffuse large B Cell lymphoma (DLBCL) (4-6).
HCT is no longer being used as a consolidative treatment of choice in CR1. However it continues to be used as treatment strategy in pediatric patients with R/R NHL. In the absence of clear guideline or conclusive data, choice regarding type of transplant in R/R cases i.e. autologous vs allogenic is often dependent on individual physician/center preference, availability of donors, timing of transplant and intent to utilize the benefit of a possible graft versus lymphoma effect. In order to study the role of autologous (auto) vs allogenic (allo) HCT in CR2 or in recurrent NHL, a large analysis of pediatric patients with NHL who under HCT from 1990 to 2005 (n=182) was performed by CIBMTR (3). This study showed that in patients ≤18 year, EFS was similar after allogeneic (n=92) and autologous HCT (n=90) for patients with DLBL, Burkitt's and ALCL. However, in patients with lymphoblastic lymphoma (LL) EFS was better in recipient of allo-HCT vs auto-HCT (40% vs 4% p <0.01). In this study all alloHCT recipients received myeloablative (MA) regimens. Recurrent or progressive disease was a more frequent cause of death in autoHCT recipient (70% of deaths) vs alloHCT recipients (58% of all deaths). Deaths from transplant related complications however were more common in alloHCTs. Due to fewer numbers in other rare sub-types of NHL (such as PTL, Mantle zone lymphoma e.t.c), were not included in the analysis. Other large scale studies have also been limited to single center or registry studies with limited numbers.
In a recent Japanese registry study (7) of 99 pediatric patients with mature B cell NHL, OS was worse in alloHCT recipients (n=36) vs auto-HCT recipients (n=73) (57% vs 82% p=0.004) due to a high TRM (17% vs 1.4% vs p<0.001). There was no difference in relapse rates was noted between the two cohorts. In a single center study of 36 consecutive pediatric patients from 1982 to 2004, once again a similar disease free survival (DFS) was observed in both in autoHCT and alloHCT recipients at 53%. DFS in R/R disease was worse at 25% compared to 61% in patients with chemo-sensitive disease (8).
In the above studies, autologous HCTs were performed in earlier years and mostly in patients with chemo sensitive disease or in CR1. Incidence of relapse or progression of disease post HCT was similar post alloHCT and autoHCT, thereby showing no effect of donor choice (auto vs allo) on outcomes. Disease status at time of transplant was a consistent predictor of outcome with patients not in CR at

time of HCT faring poorly. Additionally, increased TRM post alloHCT led to decreased OS compared to autoHCT in these patients.
Despite evidence not showing superiority of alloHCT over autoHCT in this setting, there continues to be increasing use of alloHCT in pediatric NHL. Some reasons for continued use of allogeneic HCT in NHL could be decreased TRM in alloHCT recipients (9) due to improved supportive care. Moreover, in current era of intensive upfront chemotherapy and use of biological targeted agents, R/R NHL patients are harder to treat; indicative of chemotherapy resistance. Therefore, allogeneic HCT may be preferred in order to harness the graft versus lymphoma effect.
In a recent report by CIBMTR (10) on trends in transplant for pediatric cancer over a 6 year period from 2008-2014, 5% (n=217) of all allogeneic HCTs (n=4,408) during this period were performed for lymphomas with 85% (n=184) being performed for NHL. Interestingly, auto HSCT for NHL (total n= 105) showed a decline from 2008 to 2014 from 26% in 2008 to 15% in 2014, whereas allogeneic HCT for NHL demonstrated a decline in 2011 followed by an increase annually thereafter (Figure 1). It is possible that some of these alloHCT recipients received reduced intensity conditioning regimens (RIC) in the recent years.

Figure 1- Temporal trends of HCT for lymphomas in pediatric patients



Another area of interest in R/R NHL has been the influence of NK cell function and alloreactivity in the post-transplant setting and its impact on relapse free survival. In myeloid malignancies several factors indicative of increased NK cell function and alloreactivity in the post-transplant setting have been associated with improved survival and RFS. These include increased number of NK cells in stem cell graft, rapid recovery of NK cells in the early post-HCT period and alloreactivity of NK cell in the GvH direction predicted by KIR Ligand (HLA mismatch), more refined measure of mismatch that include KIR genotyping, activating KIR gene content, assigned KIR genotypes and presence or absence of specific KIR genes (11-13). More recently, in a CIBMTR study (14), Bachanova et al investigated the impact of KIR donor genotype in a cohort of 614 adult patients with NHL receiving unrelated donor T replete marrow or PBSC transplants. Using a multivariate analysis they were able to demonstrate that use of a KIR B/x donors was associated with significantly reduced relapse risk and PFS (14). To our knowledge the impact of donor NK cell determinants in pediatric patients with NHL has not performed to date.
To conclude, despite lack of supporting alloHCT over auto-HCT in pediatric patients with R/R NHL and comparable EFS in both instances, allogenic HCT continues to be increasingly employed in these

patients. Over the last decade not much has changed in the field of autologous HCT. However, in the filed allogeneic HCT field TRM has potentially decreased due to advances in supportive care, better molecular testing for infections and utilization of RIC regimens(9). Contrary to the old data, contemporary analysis may provide evidence that alloHCT is superior to autoHCT. CIBMTR database might be able to demonstrate superiority of alloHCT and might change the practice.
Therefore, we propose to analyze outcomes post autologous vs allogenic HCT in a contemporary cohort of pediatric NHL patients. Additionally, if feasible (depending on availability of donor-recipient samples) we also propose to look the impact of donor KIR B content score on outcomes in this subset of patients. An analysis of this nature is only possible by utilizing a large database such as that of the CIBMTR. Results obtained from this proposed study will provide the practicing physician contemporary data on outcomes of HCT in pediatric NHL. It may also provide guidance regarding choice of donors as determined by donor KIR genotype in order to optimize outcomes, especially in patients with R/R disease, who have historically had a dismal prognosis.

Hypothesis.
We hypothesize that in the contemporary era, the outcomes of children with NHL will be superior following allogeneic HCT compared to patients who have undergone autologous HCT.

Aim:
To analyze outcomes post-HCT for pediatric non Hodgkin lymphomas stratified by type of HCT i.e. autologous vs allogenic.

Primary objective:

- Compare 2 year OS and DFS between allogenic vs autologous HCT recipients with NHL

Secondary objective:

- Compare outcomes of this cohort with the previously published historical CIBMTR cohort of R/R NHL (3)
- Compare 100 day, 1 year and 2 year transplant related mortality between allogenic vs autologous HCT recipients with R/R NHL
- Analyze impact of KIR gene content on relapse and disease free survival in recipients of allogenic HCT.

Primary Endpoints:

- 2 year OS in patients who received allogenic HCT vs Autologous HCT for R/R NHL
- 2 year DFS in patients who received allogenic vs Autologous HCT for R/R NHL

Secondary Endpoints

- 100 day and 1 and 2 year mortality
- In allogeneic HCT recipients
    - Acute GVHD
    - Chronic GVHD
    - In matched unrelated transplants (depending on feasibility as determined by sample size), KIR gene content and impact on outcomes namely 2 year DFS, OS, aGVHD, 100 day and 1 year TRM using the following KIR models
        - KIR Bx vs A/A
        - KIR B gene content
        - KIR composite score (Tel A/A, Cen B)
        - KIR ligand matching

Study population:

Inclusion criteria

- All patients ≤ 18 years of age with NHL
- **CR1 (it is likely that number of patients in CR1 and undergoing HCT will be few in number and such patients may more likely to be recipients of auto-HCT)**
- Refractory cases
- Relapsed cases in CR2 or subsequent CR (complete disapperance of all known disease for ≥ 4 weeks)
- Recipient of autologus or allogenic HCT
- Year of HCT 2006-2016
- With atleats 2 years of follow up

Exclusion criteria

- Patients missing baseline of day 100 form
- Exclude patients that received grafts from multiple donors
- Exclude non-consented patients
- Exclude patients who underwent autologous followed by allogeneic transplant

Study design:

This will be a retrospective cohort study investigating transplant outcomes in patients

Variables to be collected:

Patient related:

- **Age at transplant**: continuous and <10 vs 11-21 years.
- **Sex**: male vs. female
- Performance Score: Karnofsky/Lansky performance score: ≥90% vs. <90%
- Year of HSCT 2006-2010, 2010-2016
- Age at last follow up
- Co-morbidity index 0-2 vs ≥ 3

Patient and donor related:

- Donor/recipient CMV status: negative vs. positive
- In allogeneic HCTs only Donor KIR genotype/Recipient KIR genotype

Disease-related:

- Histological type
- Number of therapies prior to Transplant
- Time to relapse
- Chemo sensitive vs. chemo refractory disease.
- Duration of CR
- CR status at time of Transplant CR Y/N
- Disease status (CR1, CR2 or >CR2 vs not in remission)

Treatment-related:

- **Autoglous HCT Recipients**
  - Conditioning regimen
  - Time from diagnosis to transplant
  - Year of HCT
  - Cell dose TNC and CD34+ /kg of recipient body weight
  - Graft type: bone marrow (BM) vs peripheral blood stem cells (PBSC)
- **Allogenic HCT Recipients**
  - **Conditioning regimen**: Myeloablative versus reduced intensity vs NMA
  - Time from diagnosis to transplant
  - **Graft source**: BM vs PBSC v umbilical cord blood
  - **Cell dose** (TNC, CD34+, CD3 content of graft per recipient body weight)
  - **Use of Serotherapy:** ATG/Campath/vs none
  - **Donor**: HLA-identical sibling vs unrelated donor vs cord blood vs haploidentical donor
  - **GVHD prophylaxis**: No GVHD prophylaxis, Ex-vivo T-cell depletion, TAC + MMF +- other(s), TAC + MTX +- other(s), TAC +- other(s), CSA + MMF +- other(s), CSA + MTX +- other(s), CSA + other(s), CSA alone, Others

Post-transplant (all recipients):

- Neutrophil engraftment
- Platelet engraftment
- TRM (Deaths occurring in CR defined as TRM) at 100 days and 1 year
- Progression of Disease Y/N
- Recurrent disease Y/N if Y details (time from transplant)
- Cause of death progressive disease/recurrent disease/infections/GVHD/ organ toxicity/others

Allo-HCT recipients only:

- Acute GVHD (details, maximum grade, staging)
- Incidence of chronic GVHD (limited or extensive)

Statistical analysis:

The continuous variables will be summarized by mean and standard deviation; the categorical variables were summarized by percentage. 2 year DFS and OS will be calculated by using Kaplan Meier Estimates. Univariate and multivariate analysis will be performed for risk factors including donor KIR B content score with specified outcomes (2 year DFS, RFS, aGvHD and cGvHD).

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Characteristics of patients under 29 years old who underwent auto/allo-transplant for NHL, 2008-2017

Characteristic	Auto only	1st allo	Auto+Allo
Number of patients	83	191	27
Age at HCT, median(range), yrs	23 (7-29)	18 (<1-29)	22 (7-29)
Age at HCT, yrs			
<10	3 (4)	38 (20)	3 (11)
10-18	20 (24)	54 (28)	8 (30)
18-29	60 (72)	99 (52)	16 (59)
Sub-disease			
ALL Aggressive NK-cell Lk	0	6 (3)	0
NHL follicular, predominantly small cleaved cell	0	2 (1)	0
NHL follicular, mixed, small cleaved and large cell	0	1 (<1)	0
NHL follicular, predominantly large cell	1 (1)	1 (<1)	0
NHL diffuse, large B-cell	34 (41)	21 (11)	11 (41)
Burkitt lym/Burkitt cell leukemia	18 (22)	20 (10)	6 (22)
Primary CNS lymphoma	2 (2)	0	0
T-cell / histiocytic rich large B-cell lymphoma	3 (4)	3 (2)	1 (4)
NHL small lymphoplasmacytic	0	2 (1)	0
Primary mediastinal large B-cell (095CORE)	4 (5)	3 (2)	1 (4)
Large granular lymphocytic leukemia	0	2 (1)	0
Other B-cell, spec	3 (4)	12 (6)	0
Peripheral T-cell lymphoma, NOS	4 (5)	18 (9)	1 (4)
Angioimmunoblastic T-cell lymphoma	2 (2)	2 (1)	1 (4)
Enteropathy-type T-cell lymphoma	1 (1)	1 (<1)	0
Adult T-cell lymphoma/leukemia	0	3 (2)	0
High-grade B-cell lymphoma	1 (1)	1 (<1)	0
Extranodal NK-T-cell	2 (2)	3 (2)	0
Other T/NK-cell lymphoma, specify	0	32 (17)	1 (4)
B-cell unclass. between DLBCL and Burkitt	0	1 (<1)	0
Mycosis fungoides	0	2 (1)	0
Anaplastic large-cell lymphoma (ALCL), ALK positive	0	19 (10)	3 (11)
Anaplastic large-cell lymphoma (ALCL), ALK negative	1 (1)	1 (<1)	0
Hepatosplenic gamma-delta T-cell	2 (2)	14 (7)	0
Subcutaneous panniculitis T-cell	0	4 (2)	0
Anaplas LC,T/N cell, cutaneous	1 (1)	3 (2)	1 (4)
Anaplas LC,T/N cell, systemic	1 (1)	12 (6)	0
B-cell unclass. between DLBCL and hodgkin	3 (4)	1 (<1)	0
Follicular, predominantly large cell Grade IIIA (2400v4)	0	0	1 (4)
Follicular, predominantly large cell Grade IIIB (2400v4)	0	1 (<1)	0
Disease status at HCT			
PIF	25 (30)	55 (29)	9 (33)

Characteristic	Auto only	1st allo	Auto+Allo
CR1	25 (30)	52 (27)	3 (11)
Rel 1	8 (10)	17 (9)	3 (11)
CR2	22 (27)	56 (29)	6 (22)
Other/Unknown	3 (4)	11 (6)	6 (22)
Donor type			
HLA-identical sibling / Twin	0	54 (28)	10 (37)
Other related	0	21 (11)	2 (7)
Unrelated donor	0	116 (61)	15 (56)
Autologous	83	0	0
Graft source			
Bone marrow	2 (2)	58 (30)	7 (26)
Peripheral blood	81 (98)	74 (39)	12 (44)
Cord blood	0	58 (30)	7 (26)
Others	0	1 (<1)	1 (4)
Conditioning regimen			
MAC	15 (18)	143 (75)	7 (26)
TBI/other(s)	4	120	5
Bu/Cy	7	6	0
Bu/Mel	4	0	0
Flu/Bu/TT	0	1	2
Flu/Bu	0	8	0
Flu/Mel/TT	0	3	0
Mel/other(s)	0	3	0
Other(s)	0	2	0
RIC	15 (18)	143 (75)	7 (26)
TBI/other(s)	1	7	0
Flu/Bu	0	4	8
Flu/Mel	0	12	5
CBV	2	3	0
BEAM	65	9	1
NMA	0	13 (7)	6 (22)
TBI/other(s)	0	9	6
Cy/Flu	0	4	0
Year of HCT			
2008-2012	28 (34)	94 (49)	12 (44)
2013-2017	55 (66)	97 (51)	15 (56)

Proposal: 1811-174

Title:
Determination of the Incidence and Functional Consequences of Clonal Hematopoiesis of Indeterminate Potential (CHIP) in Pediatric Allogeneic Stem Cell Transplant Recipients

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Hypothesis:
We hypothesize that the replicative stress and altered microenvironment associated with hematopoietic stem cell transplant leads to the selection and expansion of stem cell clones with clonal hematopoiesis of indeterminate potential (CHIP) mutations in pediatric allogeneic BMT recipients and that the presence of CHIP clones is associated with adverse clinical outcomes.

Specific aims:
- Aim1: Test the hypothesis that increased donor age is associated with CHIP in pediatric allogeneic hematopoietic stem cell transplant (HSCT) recipients.
- Aim 2: Determine whether adverse clinical outcomes are associated with CHIP in pediatric allogeneic HSCT recipients.

Scientific impact:
Young children treated for cancer are eight times more likely to die from cardiovascular-related disease than the general population.[1] The incidence of developing leukemia after being treated for another cancer ranges from 2 – 8% in childhood cancer survivors.[2] Radiation and chemotherapy are known risk factors, but do not completely explain or predict morbidity development. Presently, childhood cancer survivors can only be closely monitored in the hopes of catching a secondary malignancy or cardiovascular event "early." A **critical barrier** to a more complete understanding of the causes of late effects in pediatric cancer survivors is the identification of genetic risk factors associated with adverse outcomes. Successful completion of the proposed studies will provide data in support of larger prospective clinical trials and lead to the identification of specific genetic lesions associated with an increased risk for cardiovascular disease or leukemia that can be followed with a simple blood test prior to symptom development.

Scientific justification:
The ability to detect potential pre-cancerous lesions in the blood, i.e. a clonal expansion of blood cells derived from a single hematopoietic stem cell (HSC), was first demonstrated by Dr. Garry Gilliland's group in 1996 when they detected skewing of the normally random inactivation of the maternal or paternal X chromosome in blood samples from older women (> 3:1 in 40% of women over age 60), but a normal 1:1 ratio in newborn girls.[3] Nearly 20 years later, two large studies leveraged target capture and whole exome sequencing to test for the presence of 65 – 160 leukemia-associated mutations in the blood of 12,000 to 17,000 presumably healthy adults.[4, 5] Clonal populations of blood cells with leukemiaassociated mutations were detected in blood samples at a variant allele frequency (VAF) as low as 2%. Consistent with the Gilliland studies, the incidence of CHIP was found to increase significantly with age (1 - 2% in people under age 40 and 10 - 15% in people over 70). Both groups demonstrated that CHIP was associated with a statistically significant increased risk of developing a hematological malignancy or cardiovascular disease. In 2017, Gibson and Ebert performed an 86 gene next generation sequencing (NGS) study on 401 bone marrow samples from relapsed lymphoma patients undergoing autologous HSCT.[6] They found that CHIP was higher in lymphoma patients (7.5 – 10% in patients ≤ 40) compared to "healthy adults" and that patients with CHIP had a higher risk of secondary leukemia and death from cardiovascular disease. A study

of 500 related allogeneic HSCT donor-recipient pairs identified CHIP in 16% of donors aged 55 to 79, and found that donor-CHIP was associated with an increased incidence of chronic graft-versus-host-disease (GVHD) and donor derived leukemia in recipients aged 26 to 75.[7] These studies suggest that the higher incidence of CHIP in younger patients undergoing cancer treatment/HSCT may be due to selection of HSCs with mutations that confer a growth advantage.

Although these findings suggest that conditions that cause HSC stress, such as chemotherapy, could cause CHIP in even younger patients, there are conflicting reports on the incidence of CHIP in children. Patients less than 20 were 1.4% of the 8,110 patients evaluated with a 341 to 410 NGS assay in 2017. CHIP was identified in 2 – 8% of patients younger than 20, however the clinical implications could not be assessed as these patients had many different types of aggressive solid tumors and had a median follow up of 16 months.[8] A smaller NGS evaluation for mutations in 14 genes in the blood of 84 childhood cancer survivors, with a median of 6 years after all planned cancer treatment, did not detect CHIP in any patients.[9] These two studies suggest that outcomes in a larger number of pediatric cancer survivors with a more uniform NGS evaluation need to be studied before any conclusions about the incidence and potential impact of CHIP in pediatrics can be made. We have recognized that there are certain populations of pediatric patients, namely allogeneic HSCT recipients, with a high risk of developing leukemia and/or cardiovascular complications, that may also have a high risk of developing CHIP. We will also consider donor age by limiting our evaluation to unrelated donors ≥ 30. Using these conceptual innovations, we will perform a comprehensive evaluation for previously unconsidered acquired risk factors for cardiovascular disease and leukemia that can be quantified and followed before these vulnerable populations suffer irreversible complications.

Patient eligibility population:

Inclusion criteria:

- Pediatric (age <18 at HCT) patients who underwent allogeneic HCT for malignant and nonmalignant conditions, reported to the CIBMTR
- Transplanted with unrelated donor aged ≥30 years at the time of the donation and donor sample stored
- Peripheral blood or bone marrow as stem cell source
- All conditioning regimens
- Underwent transplant between January 1, 1995 and December 31, 2008

Data Requirements: Variables to be described (those to be analyzed in bold)

Forms:

- 2000 Recipient Baseline Data
- 2006 Hematopoietic Stem Cell Transplant Infusion
- 2100, 2200, 2300 Post-HSCT Data

Patient-related:

- Age at HCT: continuous and 0-4, 5-9, 10-14, 15-17
- Sex: male vs female
- Race/ethnicity: Caucasian vs African American vs Asian/ pacific islander vs Hispanic vs others
- Karnofsky performance score: ≥90 vs <90 vs missing Disease-related:
- Disease diagnosis: ALL vs AML vs other hematologic malignancies vs non-malignant disorders
- Disease status prior to HCT (for malignant diseases only)
- Time from diagnosis to transplant Donor-related:
- Donor age: continuous and 30-39 vs 40-49 vs ≥50
- Donor/ recipient sex

- Donor race/ ethnicity
- Donor/ recipient CMV status
- Graft source: bone marrow vs peripheral blood
- Donor type: HLA-identical vs other related vs matched unrelated vs mismatched unrelated vs autologous

Transplant-related:

- Conditioning regimen: MAC vs RIC/ NMA as defined by CIBMTR
- TBI use: yes vs no
- TBI dose: MAC vs RIC/ NMA
- GVHD prophylaxis: calcineurin inhibitor + MTX vs calcineurin inhibitor + MMF vs others

Outcome:

- Primary: Cardiovascular disorder (Congestive heart failure, Myocardial infarction)
- Secondary: overall survival, acute GVHD, chronic GVHD, relapse, secondary malignancy, donor-derived leukemia

Sample requirements:
1.5 micrograms of genomic DNA.

Study design:
Aim1:
Test the hypothesis that increased donor age is associated with CHIP in pediatric allogeneic HSCT recipients. We hypothesize that the replicative stress after transplantation into a bone marrow microenvironment altered by cytotoxic chemotherapy influences the competitive fitness of transplanted HSCs and selects for HSCs with CHIP mutations. The genes associated with CHIP have been well annotated in previous studies.[4, 5] In collaboration with the Hartwell Genome Sequencing Center, we will use targeted deep sequencing of whole blood samples from adult donors to focus on genes known to cause CHIP. We have identified 2313 donors ≥ age 30 with recipients aged 0 to 19 years in the CIBMTR Sample Repository. 1.5 micrograms of genomic DNA will be enriched for target exons by liquid phase hybridization using an Agilent SureSelect custom kit designed for capturing all coding exons from 86 target genes, selected based on pathogenic involvement in CHIP or myeloid malignancies, [6] according to the manufacturer's protocol. Library preparation will be performed in my laboratory and sequencing performed at the Hartwell Genome Sequencing Center on the HiSeq2500. Sequencing reads will be aligned to the human genome reference (hg19) using Burrows-Wheeler Aligner with default parameter settings. Mutation calling will be performed using an established internal pipeline. Mutations with a VAF > 2% by amplicon sequencing will be considered positive.

Aim 2:
Determine whether adverse clinical outcomes are associated with CHIP in pediatric allogeneic HSCT recipients. Clinical outcome association analyses of demographic, primary diagnosis, treatment exposure, subsequent neoplasm, cardiovascular disease, and overall survival will be performed in collaboration with Dr. Pounds. Fisher exact test, Welch's two sample t-tests, Mann-Whitney U test and one-way analysis of variance will be used for group comparisons. Pearson correlation coefficients will be used to assess the linear relationship between two variables. Survival analysis will be performed for overall survival (time from transplant to all-cause mortality) using the Kaplan-Meier method. These studies will help define the incidence and impact of CHIP in childhood cancer survivors, and inform how they are followed to prevent adverse clinical outcomes.

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Conflicts of interest:

None

Characteristics of patients under 21 years old who underwent 1st allo-HCT with donor sample stored, 1995-2008

Characteristic	N (%)
Number of patients	1113
Age at HCT, median(range), yrs	12 (<1-21)
Age at HCT, yrs	
0-4	230 (21)
5-9	245 (22)
10-14	202 (18)
15-17	234 (21)
18-21	202 (18)
Disease	
ALL	464 (42)
AML	310 (28)
CML	112 (10)
JMML	16 (1)
MDS(RA)	21 (2)
MDS(RAEB)	16 (1)
Other MDS	2 (<1)
Severe aplastic anemia	63 (6)
Fanconi anemia	34 (3)
SCID/non-SCID	34 (3)
IEU	41 (4)
Donor type	
Well-matched unrelated	482 (43)
Partially-matched unrelated	381 (34)
Mis-matched unrelated	250 (22)
Donor's age	
30-39	593 (53)
40-49	403 (36)
50-59	117 (11)
Graft source	
Bone marrow	952 (86)
Peripheral blood	161 (14)
Conditioning regimen	
Malignant disease	
TBI/Cy/other	814 (73)
Bu/Cy	104 (9)
Bu/Mel	23 (2)
Non-malignant disease	
TBI/Cy/other	122 (11)
Bu/Cy	50 (4)
Year of HCT	

Characteristic	N (%)
1995-1998	348 (31)
1999-2002	348 (31)
2003-2006	289 (26)
2007-2010	128 (12)
Median follow-up of survivors (range), months	143 (12-264)