Not for publication or presentation

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

A G E N D A
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 Hospital, Atlanta, GA; E-mail: mqayed@emory.edu**
Co-Chair:	**Angela Smith, MD, University of Minnesota, Minneapolis, MN; E-mail: smith719@umn.edu**
Scientific Director:	**Mary Eapen, MBBS, MS, CIBMTR Statistical Center, Milwaukee, WI; E-mail: meapen@mcw.edu**
Statistical Director:	**Kwang Woo Ahn, PhD, CIBMTR Statistical Center, Milwaukee, WI; E-mail: kwooahn@mcw.edu**
Statistician:	**Kyle Hebert, MS, CIBMTR Statistical Center, Milwaukee, WI; E-mail: khebert@mcw.edu**

---

1. **Introduction**
   a. Minutes and Overview Plan from February 2019 meeting (Attachment 1)
   b. Introduction of incoming Co-Chair:
   Kirk Schultz, MD; British Columbia Children's Hospital; Vancouver, BC, Canada;
   E-mail: kschultz@mail.ubc.ca

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

3. **Presentations, published or submitted papers**
   a. **PC18-01** Comparison of TBI vs Non-TBI based regimens for pediatric AML in the modern era (C Dandoy) **Submitted**

4. **Studies in progress** (Attachment 3)
   a. **PC19-01** Variation 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

a. **Prop 1911-01** Long-Term Outcomes among Survivors of Primary Central Nervous System Tumors Undergoing Autologous Hematopoietic Cell Transplantation (Seth J. Rotz; Rabi Hanna; Navneet Majhail) (Attachment 4)
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) (Attachment 5)
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) (Attachment 6)
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) (Attachment 7)
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) (Attachment 8)
f. **Prop 1911-124** Germline genetics of pediatric myelodysplastic syndromes (MDS) (Jenny Poynter; Logan Spector) (Attachment 9)

6. Dropped proposed studies

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

MINUTES AND OVERVIEW PLAN
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**

---

1. **Introduction**
   The CIBMTR Pediatric Cancer Working Committee (PCWC) meeting was called to order at 12:15pm on Saturday, February 23, 2019, by Dr. Angela Smith. She also introduced the current working committee leadership and introduced the incoming chair, Dr. Muna Qayed. The leadership thanked Dr. Parinda Mehta for her service to the PCWC. The CIBMTR COI policy and processes of participating in the working committee, voting guidance, and rules of authorship were described. She also presented the PCWC advisory committee metric dashboard. Minutes from February 2018 were approved by the PCWC.

2. **Accrual summary**
   The accrual summary of registration and research cases between 2000 and 2018 were not presented to the committee but were available as part of the Working Committee attachments.

3. **Presentations, published or submitted papers**
   Dr. Parinda Mehta announced that PC16-01 was published and thanked Dr. Troy Lund for his work on this study.
   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)
   Dr. Parinda Mehta invited Dr. Christopher Dandoy to present an update on PC18-01.

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)

Dr. Christopher Dandoy presented an update on this study, which aims to compare overall survival, leukemia-free survival, and non-relapse mortality between pediatric patients who receive TBI based regimens vs non-TBI regimens for de novo acute myeloid leukemia in the modern era. The population included 199 TBI, and 425 non-TBI patients transplanted between 2008 and 2016. There was no statistically significant difference in disease-free survival, chronic GVHD, or overall survival. Grade II-IV acute GVHD, and treatment-related mortality were found to be lower in the non-TBI cohort, and relapse was higher in the non-TBI cohort. It is planned to add GVHD-free, leukemia-free survival.
Comments:

- *Relapse is higher in the patients that received busulfan + fludarabine compared to TBI regimens.*
- *Differentiate between Q6 hour and Q24 hour dosing for the busulfan and look for differences either in toxicity and/or relapse.*
- *The predominant population in the TBI group are recipients of unrelated cord blood transplants*
- *Describe severity of chronic GVHD and treatment received, if available*

5. Future/proposed studies

Dr. Gregory Yanik reported that 10 proposals were received this year and 6 will be presented.

a. **PROP 1811-69** Validation of the disease risk index in children undergoing alloHCT (M Qayed/C Kitko) (Attachment 5)

Dr. Muna Qayed presented this proposal, which aims to examine the impact of DRI on relapse and disease-free survival, compare the impact of DRI on disease-free survival within ALL/AML/MDS, refine the DRI as needed for pediatric patients, and derive the DRI categorization for JMML. The eligible population is pediatric patients with first HCT (excluding autologous and syngeneic) for hematologic malignancy in 2008-2013. Preliminary population selection identified 5485 TED, and 2428 CRF patients eligible for this study.
Comments:

- *DRI is best to classify in the patient's level*
- *DRI of pediatric and adult population may different*
- *The current published study of DRI is for adults and for overall survival only, this study will be an independent study and will not be a validate for an adult study*
- *Consequently, in the proposed study we will also consider validation of pediatric risk score*
- *Use a combination of CRF and TED-level data after 2013 (2014-2017)*
- *Limiting diseases in ALL, AML, RA, RARS, RCMD, RCC, RAEB1, RAEB2, JMML and MDS(NOS)*
- *When available, consider MRD status pre-transplant which is available at the CRF level data collection Form. Acknowledge the limitation that the response to the question is based on institutional practice and not defined by the CIBMTR*

b. **PROP 1811-71** Does mixed peripheral blood T cell chimerism predict relapse? (S Prcokp/J Boelens/ K Peggs) (Attachment 6)

Dr. Susan Prockop presented this proposal, which aims to determine the incidence of persistence of T cells after transplant for non-T cell malignant disease in pediatric patients at day 100, 1 year, and 2 years; determine if the incidence of relapse is higher in patients with persistence of host T cell population at these time points; and determine of reactivation of CMV in patients who were CMV

seropositive prior to transplant influence the incidence of host T cells after transplant. Preliminary population selection identified 186 patients eligible for this study.
Comments:

- *Concern about selection bias: who is selected for testing, is it an institutional practice, so suggest adjusting for differences in centers. Generally "sorted chimerism" tests are driven by institutional preference*
- *Chimerism is not fixed, it will go up and down based on interventions, and cautioned that chimerism will not behave the same in matched versus mismatched transplants.*
- *Sensitivity of test of chimerism is not collected*
- *It was noted that patients who received DLI or other manipulation can be excluded from this study.*
- *Non-myeloablative conditioning may skew probability for mixed chimerism*
- *It was asked if in myeloablative definition if RIC is separated from other regimens.*
- *Increase upper age limit to 25 years*

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)
Dr. Deepak Chellapandian presented a joint proposal (resulting from the merged of two separate proposals) aiming to Compare clinical characteristics and outcomes (2-yr OS, LFS, NRM, relapse rate) of pediatric AML patients presenting with and without EMD, and to assess the impact of radiation and non-radiation based conditioning regimens on outcomes of pediatric AML with EMD. The population included pediatric patients (age<=18) underwent all allogeneic HCT for AML CR1 or beyond using radiation or non-radiation based preparative regimen in 2008-2016. M3 AML, Down syndrome, previous autologous HCT and recipients of ≥ 2nd allogeneic HCT have been excluded. Preliminary population selection identified 837 patients available for this study.
Comments:

- *Adding EMBT patients will be more meaningful. The dataset for this proposal would use the dataset for PC 18-01*
- *Consider a matched-pair analysis with AML patients without extramedullary disease.*
- *It would be interesting to compare CNS involvement or not, if feasible.*
- *The importance of accounting for differences by center in post-transplant therapy regimens*

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)
Dr. Hemalatha Rangarajan presented this proposal which aims to compare 2 year OS and DFS between allogenic vs autologous HCT recipients with NHL; compare 100 day, 1 yr and 2 yr TRM and RR between auto and allo HCT recipients; and compare outcomes of this cohort with previously published historical CIBMTR cohorts. The elicitable patients are all patients <=29 years with NHL, CR1 or greater, refractory cases for autologous and allogenic HCT, 2006-2016 with at least 2 years of follow up. If the patients with multiple donors or underwent autologous followed by allogeneic transplant have been excluded. Preliminary population selection identified 301 patients available for this study; 83 auto, 191 allo, and 27 auto + allo.

Comments:

- *The statistical power to detect difference is low*
- *May consider include patients reported at the TED-level but the details such as prior chemotherapy is not available. In an earlier study by the CIBMTR that was a major criticism from the reviewers.*

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)
Dr. Esther Obeng presented this proposal which aims to test the hypothesis that increased donor age is associated with CHIP in pediatric allogeneic HSCT recipients and determine whether adverse cardiac clinical outcomes are associated with CHIP in pediatric allogeneic HSCT recipients. The primary outcomes is prevalence of CHIP in adult donors. The secondary outcomes are overall survival, cardiovascular disorder, secondary malignancy and relapse. Preliminary population selection identified 1113 patients available for this study.
Comments:

- *The incidence of cardiovascular complications based on a recent publication through CIBMTR-RCIBMT that involved prospective data collection was very low. With a very low expected incidence of CHIP (~n=40 in a sample size of 1000 donors) both scientific merit / feasibility were of concern*
- *Another major concern was the timing of cardiovascular complications which tend to occur 20-30 years after transplant. In the current population (~1000 patients) we can confirm that transplant centers provided ~10 years of follow-up for 85% of transplant at their center. Considering these complications occur 20-30 years late, we have a much smaller patient pool.*
- *Another concern was the analytic method proposed (i.e., CHIP)*
- *Noted that the prevalence of CHIP in an older population (sample size with thousands of adults) is published (from the BROAD Institute) and the question was asked as to whether the investigators could justify determining the prevalence in as substantially smaller cohort of patients (in this case volunteer donors). Do they expect to record differences?*

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

Dr. Parinda Mehta invited members to start thinking about ideas for proposals to submit next year.
The meeting concluded at 1:40pm.

Working Committee Overview Plan for 2019-2020							
Study number and title	**Current status**	**Goal with date**	**Total hours to complete**	**Total hours to goal**	**Hours allocated to 6/30/2019**	**Hours allocated 7/1/2019-6/30/2020**	**Total Hours allocated**
PC18-01 *Comparison of TBI vs. Non-TBI based regimens for pediatric acute myeloid leukemia in the modern era*	*Manuscript Preparation*	*Published - June 2020*	*55*	***55***	*50*	*5*	***55***
PC19-01 *Validation of the disease risk index in children undergoing alloHCT*	*Protocol Pending*	*Manuscript – July 2020*	*330*	***0***	*0*	*260*	***260***
PC19-02 *Does mixed peripheral blood T cell chimerism predict relapse?*	*Protocol Pending*	*Analysis - July 2020*	*330*	***200***	*0*	*200*	***200***
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.*	*Protocol Pending*	*Data file Preparation -July 2020*	*200*	***50***	*0*	*50*	***50***

Oversight Assignments for Working Committee Leadership (March 2019)	
Angela Smith	***PC18-01*** *Comparison of TBI vs. Non-TBI based regimens for pediatric acute myeloid leukemia in the modern era*
Angela Smith	***PC19-01*** *Validation of the disease risk index in children undergoing alloHCT*
Gregory Yanik	***PC19-02*** *Does mixed peripheral blood T cell chimerism predict relapse?*
Muna Qayed	***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*

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 - 2019*

HLA-identical sibling HCT	Registration, N (%)	Research, N (%)
Acute myeloid leukemia	2619	642
Bone Marrow	1819 (69.5)	444 (69.2)
Peripheral blood	755 (28.8)	178 (27.7)
Cord Blood	45 (1.7)	20 (3.1)
Acute lymphoblastic leukemia	3365	705
Bone Marrow	2410 (71.6)	454 (64.4)
Peripheral blood	858 (25.5)	212 (30.1)
Cord Blood	97 (2.9)	39 (5.5)
Chronic myeloid leukemia	459	139
Bone Marrow	298 (64.9)	95 (68.3)
Peripheral blood	153 (33.3)	42 (30.2)
Cord Blood	8 (1.7)	2 (1.4)
Myelodysplastic Syndrome	546	138
Bone Marrow	416 (76.2)	108 (78.3)
Peripheral blood	118 (21.6)	25 (18.1)
Cord Blood	12 (2.2)	5 (3.6)
Hodgkin lymphoma	45	10
Bone Marrow	18 (40)	3 (30)
Peripheral blood	27 (60)	7 (70)
Non-Hodgkin lymphoma	303	74
Bone Marrow	199 (65.7)	43 (58.1)
Peripheral blood	99 (32.7)	29 (39.2)
Cord Blood	5 (1.7)	2 (2.7)

* Cases in 2019 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 2019*

Other related donor HCT	Registration, N (%)	Research, N (%)
Acute myeloid leukemia	876	332
Bone Marrow	395 (45.1)	167 (50.3)
Peripheral blood	466 (53.2)	160 (48.2)
Cord Blood	15 (1.7)	5 (1.5)
Acute lymphoblastic leukemia	1042	383
Bone Marrow	497 (47.7)	189 (49.3)
Peripheral blood	528 (50.7)	184 (48)
Cord Blood	17 (1.6)	10 (2.6)
Chronic myeloid leukemia	105	51
Bone Marrow	56 (53.3)	31 (60.8)
Peripheral blood	48 (45.7)	19 (37.3)
Cord Blood	1 (1)	1 (2)
Myelodysplastic Syndrome	197	78
Bone Marrow	87 (44.2)	39 (50)
Peripheral blood	106 (53.8)	38 (48.7)
Cord Blood	4 (2)	1 (1.3)
Hodgkin lymphoma	22	10
Bone Marrow	10 (45.5)	5 (50)
Peripheral blood	12 (54.5)	5 (50)
Non-Hodgkin lymphoma	101	49
Bone Marrow	45 (44.6)	19 (38.8)
Peripheral blood	53 (52.5)	30 (61.2)
Cord Blood	3 (3)	0

* Cases in 2019 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 2019*

Unrelated donor HCT	Registration, N (%)	Research, N (%)
Acute myeloid leukemia	3965	2048
Bone Marrow	1679 (42.3)	716 (35)
Peripheral blood	818 (20.6)	296 (14.5)
Cord Blood	1468 (37)	1036 (50.6)
Acute lymphoblastic leukemia	5428	2618
Bone Marrow	2392 (44.1)	948 (36.2)
Peripheral blood	1097 (20.2)	373 (14.2)
Cord Blood	1939 (35.7)	1297 (49.5)
Chronic myeloid leukemia	541	291
Bone Marrow	331 (61.2)	181 (62.2)
Peripheral blood	115 (21.3)	52 (17.9)
Cord Blood	95 (17.6)	58 (19.9)
Myelodysplastic Syndrome	1400	702
Bone Marrow	687 (49.1)	267 (38)
Peripheral blood	238 (17)	89 (12.7)
Cord Blood	475 (33.9)	346 (49.3)
Hodgkin lymphoma	41	18
Bone Marrow	23 (56.1)	11 (61.1)
Peripheral blood	15 (36.6)	4 (22.2)
Cord Blood	3 (7.3)	3 (16.7)
Non-Hodgkin lymphoma	377	184
Bone Marrow	173 (45.9)	71 (38.6)
Peripheral blood	90 (23.9)	36 (19.6)
Cord Blood	114 (30.2)	77 (41.8)

* Cases in 2019 continue to be reported

Characteristics of patients aged ≤18 years with acute leukemia and lymphoma reported to the CIBMTR between 2000 and 2019*

Autologous HCT	Registration, N (%)	Research, N (%)
Acute myeloid leukemia	307	54
Bone Marrow	57 (18.6)	4 (7.4)
Peripheral blood	249 (81.1)	50 (92.6)
Cord Blood	1 (0.3)	0
Acute lymphoblastic leukemia	69	6
Bone Marrow	5 (7.2)	1 (16.7)
Peripheral blood	62 (89.9)	5 (83.3)
Cord Blood	2 (2.9)	0
Chronic myeloid leukemia	3	1
Peripheral blood	2 (66.7)	1
Cord Blood	1 (33.3)	0
Myelodysplastic Syndrome	4	2
Peripheral blood	4	2
Hodgkin lymphoma	1661	200
Bone Marrow	73 (4.4)	5 (2.5)
Peripheral blood	1588 (95.6)	195 (97.5)
Non-Hodgkin lymphoma	626	98
Bone Marrow	56 (8.9)	4 (4.1)
Peripheral blood	570 (91.1)	94 (95.9)

* Cases in 2019 continue to be reported

Number of patients aged ≤18 years with solid tumor reported to the CIBMTR between 2000 and 2019*

	Autologous		Allogeneic	
	Registration	Research	Registration	Research
Testicular	70	10	1	1
Bone sarcoma(No Ewing sarcoma)	139	28	6	4
Central nervous system tumors	965	189	1	0
Wilms Tumor	257	29	6	2
Neuroblastoma	4560	678	53	18
Retinoblastoma	124	18	1	1
Ewing sarcoma	503	71	27	7
Extragonadal germ cell tumor	246	26	0	0
Medulloblastoma	1270	206	2	0
PNET	41	12	1	1
Rhabdomyosarcoma	107	14	31	6

* Cases in 2019 continue to be reported

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Pediatric Cancer Working Committee Members

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

RE: Studies in Progress Summary

PC19-01: Variation of the disease risk index in children undergoing alloHCT (M Qayed/C Kitko)
The objective of this study is to stratify children and adolescents undergoing HCT for hematologic malignancy into risk groups based on leukemia-free survival to create a pediatric disease risk index (PDRI).
The analysis has been completed, and preparation of the manuscript is underway. The goal of the study is to submit the final manuscript by June 2020.

PC19-02: Does mixed peripheral blood T cell chimerism predict relapse? (S Prcokp/J Boelens/ K Peggs)
The objectives of this study include determining the incidence of persistence of host T cells after transplant for non-T cell malignant diseases in pediatric patients. Other study objectives include exploring whether the incidence of relapse is higher in patients with persistence of host T cell populations, and determining whether reactivation of CMV in patients who were CMV seropositive prior to transplant influence the incidence of host T cells after transplant.
The study protocol is being developed. The goal is to finalize the study protocol by June 2020.

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)
The objective of this study is to determine whether the presence of extramedullary disease in pediatric patients with AML prior to transplant impacts post-transplant outcomes, including overall survival and disease-free survival.
Preparation of the CIBMTR data is complete. Merging with EBMT data is pending. The goal is to complete preparation of the data file and begin analysis prior to June 2020.

Proposal: 1911-01

Title:
Long-Term Outcomes among Survivors of Primary Central Nervous System Tumors Undergoing Autologous Hematopoietic Cell Transplantation.

Seth J Rotz, MD, rotzs@ccf.org, Cleveland Clinic Foundation
Rabi Hanna, MD, hanna2@ccf.org, Cleveland Clinic Foundation
Navneet Majhail, MD, majhain@ccf.org, Cleveland Clinic Foundation

Hypothesis:
We hypothesize that long-term survivors of autologous hematopoietic cell transplantation (HCT) for primary central nervous system (CNS) tumors will have an increased risk of mortality compared to the general US population. Further, we hypothesize that survivors who do not require radiotherapy will have a decreased burden of late effects and secondary malignancies compared to those patients who required subsequent radiotherapy.

Specific aims:
- Determine the standardized mortality ratio compared to the general US population, for patients who have undergone HCT for primary CNS malignancies.
- Determine the conditional survival for patients undergoing HCT for primary CNS malignancies (1-, 3-, 5-year survivors). Determine the conditional survival for the subset of patients who undergo HCT for primary CNS disease and require radiotherapy for relapse post-HCT.
- Describe the burden of CIBMTR captured late effects in patients who undergo HCT for primary CNS malignancy. Among those who have and have not received radiotherapy, compare the cumulative incidence of late effects and examine differences in performance score.
- Estimate the cumulative incidence of second malignant neoplasms in patients who undergo HCT for primary CNS neoplasm.

Scientific impact:
Autologous HCT is an effective treatment for many CNS malignancies.[1] The main indication for autologous HCT in pediatrics is to obviate or delay the need for CNS radiation, however, the long-term outcomes of this treatment strategy remain unclear. This study would provide useful information to clinicians and patients in several areas. First the estimated overall survival and standardized mortality ratio compared to the US general population for survivors of HCT for primary CNS malignancies is unknown. Second, although the spectrum of late effects in patients who received CNS radiation therapy is well characterized, little is known about the late effects burden in those that received autologous HCT without radiotherapy. Finally, although there is a significant risk of secondary malignancies in children with brain tumors who receive radiotherapy, it is unknown what the incidence of malignancy is in those who are treated with autologous HCT.

Scientific justification:
Historically, late morbidity and mortality is common in survivors of CNS tumors treated with conventional chemotherapy and CNS radiation.[2,3] The Headstart series of clinical trials has demonstrated the efficacy of high dose chemotherapy with stem cell rescue for young children with primary CNS malignancies, particularly meduloblastoma.[4-7] With the success of these trials, additional studies have examined autologous HCT across various primary CNS histologies,[8,9] and clinical indications have expanded.[1]

A retrospective case series has demonstrated fewer endocrine late effects in children who have received radiation sparing regimens.[10] However, the frequency of non-endocrine late effects and endocrine late effects across a larger cohort of patients has not been thoroughly studied. The CIBMTR reported between 2008 and 2014 in children ≤ 18 years of age, 389 autologous HCTs performed for medulloblastoma and 409 for other CNS tumors.[11] To date, long-term outcomes in in children and young adults with primary CNS malignancies have not been examined by the CIBMTR.

Patient eligibility population:

Age:	<40 years (at the time of HCT)
Race/Ethnicity:	Any
Disease:	Primary CNS malignancies
Disease stage/status at transplant:	Non-relapsed at the time of transplant
Year of Transplant:	2000-2016
Transplant Type:	Autologous
Prior Treatments/Specific Regimens:	First transplant recipients only, patients requiring subsequent unplanned HCT prior to one year will be excluded.

Data requirements:

TED, Form 2100 (Post- HCT follow-up), Form 2025 (CNS Tumor Pre- HSCT Data), Form 2125 (CNS Tumor Post-HSCT Data)

<u>Outcome variables:</u>

- Overall Survival
- Treatment related mortality
- Relapse
- Secondary Malignancy
    - If sufficient patient numbers available, subtypes of second cancers (at least MDS/AML vs. solid tumors)
- Late Effects Including:
    - Chronic Kidney Disease
    - Congestive Heart Failure
    - Neurologic Disorders including CNS hemorrhage, Encephalopathy (non-infectious) Neuropathy, Seizures, and Stroke
    - Endocronopathies including: Diabetes, Growth Hormone deficiency, hypothyroidism, gonadal dysfunction requiring hormone replacement
    - Psychiatric Issues including: Depression and Anxiety requiring therapy, and PTSD
    - Cataracts
- Performance status

<u>Variables to be described:</u>

Patient Variables

- Patient age – continuous
- Patient sex: male vs. female

Disease-related

- Disease: specific diagnosis/ histology
- Disease status prior to transplant

- CNS Radiation post-HCT
- Pre-HCT performance score

Transplant-related
- Conditioning regimen (for each HCT if multiple)
- Number of HCT (if multiple)

Sample requirements:
n/a

Study design:
For aim one, we will determine the standardized mortality ratio compared to the general US population for patients who have undergone HCT for primary CNS malignancies. Estimates of standardized mortality will be performed as described by Andersen and Vaeth, taking into account differences among patients with regard to age, sex, and ethnicity as previously performed by the CIBMTR.[12,13] If sufficient numbers allow, we will compute separate ratios for histology, disease status prior to HCT, and pre- and post-HCT radiotherapy. *Note, data for pre- and post-HCT radiation is available from form 2025 and 2125 starting in 2007.*
For study aim two, conditional survival at five and ten years post-HCT will be calculated using the Kaplan-Meier method for patients surviving and in remission at one, three, and five years post-HCT. A subset analysis will be performed for patients who have data available and required subsequent radiotherapy. If sufficient numbers allow, multivariate cox models will be produced to determine hazard ratio for conditional survival based on age at diagnosis, sex, pre-HCT performance status, disease histology, conditioning regimen, disease status prior to HCT, pre-HCT performance score, and pre-HCT radiotherapy.
For aim three, we will describe the cumulative incidence of late effects in patients who underwent HCT for primary CNS malignancy. Late effects will include chronic kidney disease, congestive heart failure, CNS hemorrhage, encephalopathy (non-infectious) neuropathy, seizures, stroke, diabetes growth hormone deficiency, hypothyroidism, gonadal dysfunction requiring hormone replacement, depression and anxiety requiring therapy, post-traumatic stress disorder, and cataracts. If sufficient patient numbers are available, the cumulative incidence of late effects and performance score will be compared between those who received radiotherapy and those that did not.
Finally we will described the cumulative incidence of secondary malignancy in patients who underwent HCT for primary CNS malignancy. If sufficient patient numbers are available, the cumulative incidence of late effects will be compared between those who received radiotherapy and those that did not. As well, if sufficient patient numbers available, subtypes of second cancers (i.e. tMDS/ AML vs. solid tumors) will be compared

Non-CIBMTR data source:
Estimates of relative mortality for the general US population taking into account differences among patients with regard to age, sex, ethnicity as previously performed by CIBMTR.[12,13]
Note, if the concept is of interest, but the percent of patients who have forms 2100, 2025, and 2125 is small, our institution may have a funding mechanism available that could provide funding for a subset of centers to retrospectively fill out these forms.

Conflicts of interest:
The study team reports no pertinent conflicts of interest.

References:

1. Marachelian A, Butturini A, Finlay J. Myeloablative chemotherapy with autologous hematopoietic progenitor cell rescue for childhood central nervous system tumors. *Bone Marrow Transplant*. 2008;41(2):167-172.
2. Armstrong GT. Long-term survivors of childhood central nervous system malignancies: the experience of the Childhood Cancer Survivor Study. *Eur J Paediatr Neurol*. 2010;14(4):298-303.
3. Salloum R, Chen Y, Yasui Y, et al. Late Morbidity and Mortality Among Medulloblastoma Survivors Diagnosed Across Three Decades: A Report From the Childhood Cancer Survivor Study. *J Clin Oncol*. 2019;37(9):731-740.
4. Zaky W, Dhall G, Ji L, et al. Intensive induction chemotherapy followed by myeloablative chemotherapy with autologous hematopoietic progenitor cell rescue for young children newly-diagnosed with central nervous system atypical teratoid/rhabdoid tumors: the Head Start III experience. *Pediatr Blood Cancer*. 2014;61(1):95-101.
5. Venkatramani R, Ji L, Lasky J, et al. Outcome of infants and young children with newly diagnosed ependymoma treated on the "Head Start" III prospective clinical trial. *J Neurooncol*. 2013;113(2):285-291.
6. Fangusaro J, Finlay J, Sposto R, et al. Intensive chemotherapy followed by consolidative myeloablative chemotherapy with autologous hematopoietic cell rescue (AuHCR) in young children with newly diagnosed supratentorial primitive neuroectodermal tumors (sPNETs): report of the Head Start I and II experience. *Pediatr Blood Cancer*. 2008;50(2):312-318.
7. Dhall G, Grodman H, Ji L, et al. Outcome of children less than three years old at diagnosis with non-metastatic medulloblastoma treated with chemotherapy on the "Head Start" I and II protocols. *Pediatr Blood Cancer*. 2008;50(6):1169-1175.
8. Cohen BH, Geyer JR, Miller DC, et al. Pilot Study of Intensive Chemotherapy With Peripheral Hematopoietic Cell Support for Children Less Than 3 Years of Age With Malignant Brain Tumors, the CCG-99703 Phase I/II Study. A Report From the Children's Oncology Group. *Pediatr Neurol*. 2015;53(1):31-46.
9. Bode U, Zimmermann M, Moser O, et al. Treatment of recurrent primitive neuroectodermal tumors (PNET) in children and adolescents with high-dose chemotherapy (HDC) and stem cell support: results of the HITREZ 97 multicentre trial. *J Neurooncol*. 2014;120(3):635-642.
10. Cochrane AM, Cheung C, Rangan K, et al. Long-term follow-up of endocrine function among young children with newly diagnosed malignant central nervous system tumors treated with irradiation-avoiding regimens. *Pediatr Blood Cancer*. 2017;64(11).
11. Khandelwal P, Millard HR, Thiel E, et al. 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. *Biol Blood Marrow Transplant*. 2017;23(8):1342-1349.
12. Andersen PK, Vaeth M. Simple parametric and nonparametric models for excess and relative mortality. *Biometrics*. 1989:523-535.
13. Wingard JR, Majhail NS, Brazauskas R, et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. *Journal of Clinical Oncology*. 2011;29(16):2230.

Characteristics of patients undergoing first autologous HCT for CNS tumors in the United States

Characteristic	CRF	TED
No. of patients	**295**	**1708**
Age at transplant, years - no. (%)		
≤ 5	167 (56.6)	990 (58)
6 to 10	67 (22.7)	315 (18.4)
11 to 18	38 (12.9)	231 (13.5)
19 to 29	12 (4.1)	103 (6)
30 to 39	11 (3.7)	69 (4)
Type of CNS tumor - no. (%)		
Medulloblastoma	145 (49.2)	955 (55.9)
Other Central nervous system tumors, including CNS PNET	150 (50.8)	753 (44.1)
Graft (Product) type - no. (%)		
Bone marrow	17 (5.8)	149 (8.7)
Peripheral blood	278 (94.2)	1559 (91.3)
Year of transplant - no. (%)		
2000-2006	112 (38)	578 (33.8)
2007-2012	112 (38)	662 (38.8)
2013-2016	71 (24.1)	468 (27.4)
Follow-up - median (min-max)	117.2 (5.07-219.18)	72.63 (0.23-219.18)

Overall survival estimates of patients undergoing first autologous HCT for CNS tumors in the United States

		CRF		TED
Outcomes	**N**	**Prob (95% CI)**	**N**	**Prob (95% CI)**
Overall survival	295		1708	
1-year		83.2 (78.6-87.2)%		83.2 (81.4-85)%
5-year		57.5 (51.4-63.4)%		57 (54.4-59.5)%
10-year		50.8 (44.4-57.1)%		51.5 (48.6-54.4)%

Proposal: 1911-14

Title:
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, MD, tristan.knight@sickkids.ca, The Hospital for Sick Children (SickKids)
Donna A. Wall, MD, donna.wall@sickkids.ca, The Hospital for Sick Children (SickKids)
Kanhatai Chiengthong, MD, kanhatai.chiengthong@sickkids.ca, The Hospital for Sick Children (SickKids)

Research hypothesis:
Is more always better in pediatric autologous hematopoietic stem cell transplant (HSCT)? Children are often excellent mobilizers and there are frequently large numbers of hematopoietic progenitors available for cell infusions. Does infusing larger cell numbers, with or without post-transplant granulocyte colony stimulating factor (G-CSF) improve or possibly even negatively impact early outcome and ultimately disease-free survival?

Specific aims:
We propose to analyze hematopoietic recovery, disease response, and survival in pediatric patients who have undergone autologous HSCT focusing on patients who have received doses of CD34+ cells in their grafts with or without filgrastim. We hypothesize that there is limited utility and perhaps a detrimental effect to utilizing higher cell doses and/or filgrastim post-transplant. This proposal is specifically intended to assess these factors in a pediatric population given the uniquely pediatric disorders that make up a majority of pediatric autologous transplants, and that children tend to be robust mobilizers. (Karrow et al 2019, Rhodes et al 2008).

Scientific impact:
Administration of post-transplant G-CSF is currently delivered on an ad-hoc or per-protocol basis – with an anticipated decrease in neutropenia by 24-36 hours and delay in platelet recovery. While a graft $CD34^+$ count of 2-5x10^6/kg is targeted, practice is variable and institution-dependent when larger cell doses are collected – is there a maximum dose? Given the appreciation of the potential for graft resident young myeloid and lymphoid cells to function in the post-transplant inflamed milieu, it is possible that higher cells doses may either benefit or be detrimental to tumor control. If an association between these variables is identified, it may inform clinical practice as to G-CSF administration and cell doses infused and lead directly to further studies of the hematopoietic graft as part of the therapy in pediatric autologous transplant. There is sufficient clinical equipoise regarding these variables to warrant study of the CIBMTR registry experience.

Scientific justification:
Auto transplant – not just rescue therapy, but a therapy itself
Autologous HSCT involves treatment with tumor-toxic chemotherapy at doses sufficient to induce marrow aplasia, with the patient's own previously collected hematopoietic stem cells (HSCs) then being infused to reconstitute hematopoiesis (Barriga et al 2012). Key gaps remain in our understanding of this process. One of these is the role of the graft itself in the treatment's efficacy - this type of transplant is regularly referred to as a 'stem cell rescue' with the haematopoietic stem cell graft being conceptualized as playing a necessary but ultimately supportive role, secondary in importance to the high dose chemotherapy. Beyond the CD34 cell content we know little about the content of the autologous HSC graft, nor do we understand the role these non-HSC components may play therapeutically. HSCs

themselves, as conventionally defined by $CD34^+$ expression, make up only 1-3% of a graft, with the role and specific phenotype of the remaining 99-97% of non-HSCs comprising an autologous HSCT not being well characterized – it appears however that the graft includes a large proportion of immune effector cells and is heterogeneous between individuals (Saraceni et al 2015, Impola 2016). A small but growing body of evidence therefore exists to suggest that both cell dose and graft composition may play a role in a patient's response to treatment.

What evidence is there that cell dose matters?

A $CD34^+$ count of 2-5x10^6/kg is generally used as a target cell dose in autologous transplant. Higher doses of cells present in an autologous HSCT graft (e.g. above approximately 4-5x10^6/kg) has been shown to correlate with improved speed to neutrophil engraftment, as well as reduced needs for supportive care e.g. antibiotic/antifungal use and transfusion support (Hyder et al 2018, Schulman et al 1999). However, doses below 2x10^6 CD 34/kg are still well above the range needed to ensure count recovery, albeit with mildly delayed platelet recovery (Bai et al 2014, Bender et al 1992). Whether or not an upper threshold exists, above which a higher cell dose is deleterious, is not clear. Beyond the 5x10^6/kg dose range, a point of diminishing returns appears to exist in autologous transplant where prompt neutrophil engraftment is achieved and beyond-which further escalation of cell dose makes a minimal or no impact on neutrophil engraftment (Bai et al 2014). At standard $CD34^+$ cell doses, this time may be as little as 230 minutes per additional 1x10(6)/kg CD34+ cells (Nath et al 2018). An inverse correlation also may exist between escalating $CD34^+$ doses and time to platelet engraftment (Stiff et al 2011), but this has not been seen consistently (Harris et al 2011). Perhaps most interestingly - and even counter-intuitively - the presence of higher $CD34^+$ and/or TNC doses present in an autologous graft above and beyond a threshold of 5x10(6)/kg do not necessarily correlate with improved survival or superior outcomes (Carlsten et al 2019, Sorigue et al 2017). Considerable heterogeneity and an important knowledge gap therefore coexist in the literature as to whether survival and disease response vary as a function of cell dose received during autologous HSCT, and there is sufficient equipoise in this area so as to warrant further investigation. This is a particularly relevant concern among pediatric transplant centers, for whom higher collected cell doses are more common than in their adult counterparts (Karrow et al 2019, Rhodes et al 2008).

Is there any evidence for post-auto anti-tumor effect?

Response to allogeneic HSCT is in large part mediated by activity of donor lymphocytes against malignant disease – the 'graft versus tumor' (GVT) or 'graft versus leukemia' (GVL) effect (Gill 2013). Less well understood is the presence of a GVT effect following autologous HSCT. A mounting body of evidence suggests that autologous GVT affects patient outcomes in a clinically relevant and potentially evaluable fashion (Porrata 2016, Dong 2018) – therefore suggesting that, as in allogeneic HSCT, measures to optimize and preserve the autologous GVT effect are warranted. An elevated peripheral blood absolute lymphocyte count (ALC) to absolute monocyte count (AMC); (ALC/AMC) ratio has been shown to be predictive of outcome in pediatric patients undergoing autologous HSCT for Hodgkin Lymphoma (Silva et al, 2017). Early lymphocyte recovery is correlated with prolonged OS and PFS follow autologous HSCT for multiple myeloma and non-Hodgkin lymphoma, with the ALC 15 days post-transplant being and independent prognosticator for OS and PFS (Porrata, 2016). Conversely, the presence of increased monocytes in the autologous graft as evidenced by AMC recovery appears to be a negative prognosticator (Porrata et al 2016). For reasons which are not well understood, an increased absolute monocyte count (AMC) correlates with reduced PFS and OS (Porrata et al, 2011). Although the specific monocytic phenotype has not been elucidated, it has been theorized that monocytic myeloid-derived suppressor cells (MDSCs) may potentially suppress a lymphocytic GVT effect (Porrata 2016).

Certainly, MDSCs have been shown to inhibit T-cell proliferation and NK cytotoxicity (Betsch A et al 2018).

What is known about the constituents of an auto-graft?

As described previously, CD34+ HSCs make up only 1-3% of the autologous graft – the vast majority of a graft is therefore not well characterized, though some evidence does exist for the presence of immune effector cells. As noted above, early lymphocyte recovery is correlated with clinical outcomes. It appears that the dose of lymphocytes present in the graft itself, rather than the dose of HSCs correlates with day 15 ALC, and that the dose of such lymphocytes impacts upon OS and PFS (Porrata et al 2004, Porrrata et al 2004, Hiwase et al 2008). This relationship has been borne out in clinical trials as well, with patients with non-Hodgkin Lymphoma whom received an autograft containing an ALC of more than 0.5x109 lymphocytes/kg experiencing superior OS and PFS (Porrata et al 2016). Additional immune effector cells present in the autologous graft, which have been associated with superior OS and PFS, include CD4+ T-cells and NK cells (Porrata et al 2016) while, conversely, the presence of immune effector cells which are suppressive in their phenotype such as myeloid-derived suppressor cell (MDSC) is associated with an inferior outcome in adult patients (Lee et al 2019). Evidence such as this provide further support for the concept of autologous GVT as a clinically important and desirable feature of autologous HSCT, and lends credence to the concept that manipulation of certain graft constituents (e.g. graft manipulation) either in-vivo or ex-vivo could potentially influence clinical patient outcomes – and that the impact of autologous GVT should be taken into account when considering post-transplant supportive measures.

What does G-CSF actually do?

The most common peri-transplant means by which in-vivo graft manipulation occurs is via the use of granulocyte-colony stimulating factor (G-CSF). G-CSF is a lineage-specific hematopoietic growth factor, and acts upon the G-CSF receptor (CD114; G-CSF-R), which is particularly strongly expressed on neutrophils and their myeloid progenitor precursor cells, but is also present on monocytes, dendritic cells, and lymphocytes (Morikawa et al 2002, Sivakumar et al 2015). In the instance of myeloid progenitor cells, it acts to promote the survival and proliferation of these cells, and their terminal differentiation into mature neutrophils. Among lymphocytes, expression of G-CSF-R is constitutive on B-cells and inducible on T-cells (Morikawa et al 2002). G-CSF also demonstrates immunomodulatory functions, altering cytokine production to polarize T lymphocytes from a Th1 to a Th2 phenotype via IL-4 and IL-10 secretion, as well as reducing T-cell cytotoxicity and mitogen response (Sivakumar et al 2015, Pan et al 1995, Sloand et al 2000, Franzke et al 2003). Post-GCSF treatment, T-lymphocytes appear to secrete increased anti-inflammatory cytokines such as IL-4 and decreased pro-inflammatory cytokines such as IL-2, IL-12, tumor necrosis factor alpha, and interferon gamma (Pan 1995, Hartung et al 1995, Hartung et al 1999). The production of regulatory T-cells have also been shown to be enhanced via G-CSF exposure (Rutella et al 2002). Critically, there is also evidence that the number and function of immunosuppressive myeloid-derived suppressor cells (MDSC) is enhanced and demonstrate increased suppressive abilities/anti-proliferative abilities against T cells and increased regulatory T-cell promotion following G-CSF exposure (Wang et al 2019, Betsch A et al 2018). To put the preceding data into another, simpler context: exogenously administered G-CSF, though conceptualized as a straightforward way to boost neutrophil engraftment and minimize neutropenia, appears capable of exerting an array of immunomodulatory effects. Whether these effects are clinically relevant in the setting of post-autologous HSCT is not known, however. We therefore aim to assess whether the presence or absence of exogenous G-CSF is associated with disease response, with the hypothesis that the suppressive immunophenotype driven via G-CSF use negatively impacts upon outcome, due to a theorized inhibition of the autologous GVT effect.

Patient eligibility population:

- Inclusion criteria: All pediatric patients (e.g. below 18 years of age) who have undergone at least one autologous HSCT for a malignant disease indication, between the years of 2006-2016 (inclusive), and for whom data exists regarding:
    - Cell dose in the autologous graft, as defined by: total number of cells present in the product, including either total nucleated cells AND/OR CD34+ cells
    - Weight (to allow calculation of per kilogram dosing).
    - Disease assessment at 2 years post-transplant.
- Exclusion criteria: Patients who do not meet the above criteria, and/or patients who have undergone autologous HSCT for non-malignant indications (e.g. inflammatory/autoimmune conditions)
- Administration of G-CSF shall not be an inclusion criteria, nor shall non-administration be an exclusion criteria.

Data requirements:

The proposed study will not require the collection of supplemental data, nor will it require combining CIBMTR data with data from another group. As provided on CIBMTR, we propose to utilize the following forms/collected variables contained there-in (as available at: https://www.cibmtr.org/DataManagement/DataCollectionForms/Pages/index.aspx)

- CIBMTR Form 2000 (Recipient Baseline Data)
    - To identify autologous transplant recipients, including weight (for subsequent calculation of per-kilogram cell doses) (Q. 105 and 106) and age under 18 (Q. 248), and to specifically select for pediatric recipients of autologous HSCT.
- And/OR CIBMTR 2400 (Pre-Transplant Essential Data)
    - To identify basic characteristics of transplant recipients, specifically weight (Q.157) (for subsequent calculation of per-kilogram cell doses), autologous transplant status (Q.31) to specifically select for pediatric recipients of autologous HSCT.
- CIBMTR Form 2006 (Hematopoietic Stem Cell Transplant (HCT) Infusion)
    - To identify autologous grafts (Q.1), and the cell counts within those grafts in as much detail as is available (Q.161-Q176), and to ensure that the entire product was infused (Q.204 and, in this instance Q.160 to determine percentage of infused vs non-infused product),
- CIBMTR Form 2100 (Post-HSCT Data)
    - To identify whether G-CSF was administered in the post-transplant setting (Q.19-Q25.)
- CIBMTR Form 2402 (Pre-Transplant Essential Data: Disease Classification)
    - To identify diagnose, and select for malignant indications for autologous transplant only (Q.2; Hodgkin lymphoma ->Q.268, Q2; Non-Hodgkin lymphoma -> Q.268), Q.2; Solid Tumors -> Q.318).
- Outcomes data (disease assessment and best response) for patients with applicable diagnoses who underwent autologous HSCT:
    - CIBMTR Form 2450 (Post-Transplant Essential Data): Determination of patient survival (Q.2) and if not, primary (Q.3) and contributing cause of death (Q.5) for recurrence, persistence, or progression of primary disease for which HSCT was performed.
    - CIBMTR Form 2118 (Hodgkin and Non-Hodgkin Lymphoma Post-HCT Data): Disease assessment at time of best response (Q.1, Q.4), including disease relapse/progression (Q.36) and disease status at time of reporting period (Q.87-Q.90)

- CIBMTR Form 2124 (Sarcoma Post-HSCT Data): Disease assessment at time of best response (Q.1), including disease relapse/progression (Q.6) and disease status at time of reporting period (Q.63)
- CIBMTR Form 2125 (Central Nervous System Tumor Post-HSCT Data): Disease assessment at time of best response (Q.1), including disease relapse/progression (Q.3) and disease status at time of reporting period (Q.101)
- CIBMTR Form 2126 (Neuroblastoma Post-HSCT Data): Disease assessment at time of best response (Q.1), including disease relapse/progression (Q.77) and disease status at time of reporting period (Q.158)

Sample requirements:
The proposed study does not require biologic samples; not applicable.

Study design:
$CD34^+$ cell dose in autologous grafts will be stratified in intervals of $<1x10^6$/kg ("super-low dose"), 1-$1.99x10^6$/kg ("low dose"), 2-5 $x10^6$/kg ("standard dose"), 5.01-$10x10^6$/kg ("high dose") and $>10x10^6$/kg ("super-high dose"), to achieve a high degree of granularity. Total nucleated cell dose in the graft will be stratified in similar intervals where reported, $<1x10^8$/kg ("super-low dose"), 1-$1.99x10^8$/kg ("low dose"), 2-5 $x10^8$/kg ("standard dose"), 5.01-$10x10^8$/kg ("high dose") and $>10x10^8$/kg ("super-high dose"). G-CSF administration will be a categorical variable. Univariate and multivariate Cox regressions will be carried out to determine the impact of cell dose and G-CSF administration upon best disease response at the 100 day, 1 year, and 2-year post-transplant disease assessment; study population will include a 10-year period of transplants performed from 2007-2016 (so-as to allow 2-year follow up visits to have been completed for all surviving patients).

Non-CIBMTR data source:
The proposed study does not require non-CIBMTR data; not applicable

Conflicts of interest:
No real or perceived conflicts of interest exist for any investigators of this proposal, regarding any of: employment (such as an independent contractor, consultant or providing expert testimony), relationships, ownership, transactions, or legal.

References:
1. Bai L, Xia W, Wong K, et al. Factors predicting haematopoietic recovery in patients undergoing autologous transplantation: 11-year experience from a single centre. Ann Hematol. 2014:93;1655-1664
2. Barriga F, Ramírez P, Wietstruck A, Rojas N. Hematopoietic stem cell transplantation: clinical use and perspectives. Biol Res. 2012;45(3):307-16.
3. Bender JG, To LB, Williams S, et al. Defining a therapeutic dose of peripheral blood stem cells.
4. J Hematother. 1992;1:329–341
5. Betsch A, Rutggerts O, Fever S et al. The role of myeloid-derived suppressor cells in autologous hematopoietic stem cell transplantation. European Journal of Cancer. 2018:92(S1);S10
6. Carlsten M, Jadersten M, Hellstrom A, et al. The Karolinska experience of autologous stem-cell transplantation for lymphoma: a population-based study of all 433 patients 1994–2016. Experimental Hematology and Oncology. 2019;8(7).
7. Dong S, Ghobrial IM. Autologous graft versus myeloma: it's not a myth. J Clin Invest. 2019;129(1):48-50

8. Franzke A, Piao W, Lauber J, Gatzlaff P, Könecke C, et al. G-CSF as immune regulator in T cells expressing the G-CSF receptor: implications for transplantation and autoimmune diseases. Blood. 2003; 102:734-739.
9. Gill S., Porter D. L. Reduced-intensity hematopoietic stem cell transplants for malignancies: harnessing the graft-versus-tumor effect. Annual Review of Medicine. 2013;64:101–117. doi: 10.1146/annurev-med-121411-103452
10. Harris RE, Termuhlen AM, Smith LM. Autologous Peripheral Blood Stem Cell Transplantation in Children with Refractory or Relapsed Lymphoma: Results of Children's Oncology Group Study A5962. Biology of Blood and Marrow Transplantation. 2011;17(22): 249-258.
11. Hartung T, Döcke WD, Gantner F, Krieger G, Sauer A, et al. Effect of granulocyte colony-stimulating factor treatment on ex vivo blood cytokine response in human volunteers. Blood. 1995;85: 2482-2489.
12. Hartung T, Doecke WD, Bundschuh D, Foote MA, Gantner F, et al. Effect of filgrastim treatment on inflammatory cytokines and lymphocyte functions. Clin Pharmacol Ther. 1999;66: 415-424
13. Hiwase DK, Hiwase S, Bailey M, Bollard G, Schwarer AP. Higher infused lymphocyte dose predicts higher lymphocyte recovery, which in turn, predicts superior overall survival following autologous hematopoietic stem cell transplantation for multiple myeloma. Biology of Blood and Marrow Transplantation. 2008;14(1):116–124. doi: 10.1016/j.bbmt.2007.08.051.
14. Hyder MA, et al. Low CD34+ Cell Doses Are Associated with Increased Cost and Worse Outcome after Tandem Autologous Stem Cell Transplantation in Patients with Relapsed or Refractory Germ Cell Tumors. Biol Blood Marrow Transplant. 2018 Jul;24(7):1497-1504. doi: 10.1016/j.bbmt.2018.01.032. Epub 2018 Feb 2.
15. Impola U, Larjo A, Salmenniemi U, Putkonen M, Itälä-Remes M, Partanen J. Graft Immune Cell Composition Associates with Clinical Outcome of Allogeneic Hematopoietic Stem Cell Transplantation in Patients with AML. Front Immunol. 2016;7:523. Published 2016 Nov 21. doi:10.3389/fimmu.2016.00523
16. Karrow A, Wilhem A, Ammann RA, et al. Peripheral blood progenitor cell collection in pediatric patients optimized by high pre-apheresis count of circulating CD34+ cells and high blood flow. Bone Marrow Transplant. 2019;54(6):885-893.
17. Lee SE, Lim JY, Kim TW, et al. Different role of circulating myeloid-derived suppressor cells in patients with multiple myeloma undergoing autologous stem cell transplantation. J Immunother Cancer. 2019;7(1):35.
18. Morikawa K, Morikawa S, Nakamura M, Miyawaki T. Characterization of granulocyte colony-stimulating factor receptor expressed on human lymphocytes. Br J Haematol (2002) 118:296–304.
19. Nath K, Boles R, McCutchan A. The relationship between CD34+ stem cell dose and time to neutrophil recovery in autologous haematopoietic stem cell recipients—A single centre experience. Transfusion and Apheresis Science. 2018;57(4): 532-536.
20. Pan L, Delmonte J, Jalonen CK, Ferrara JLM (1995) Pretreatment of donor mice with granulocyte colony-stimulating factor polarizes donor T lymphocytes toward type-2 cytokine production and reduces severity of experimental graft-versus-host disease. Blood. 1995;86: 4422-4429.
21. Porrata L. F., Lotzow M. R., Inwards D. J., et al. Infused peripheral blood autograft absolute lymphocyte count correlates with day 15 absolute lymphocyte count and clinical outcome after autologous peripheral hematopoietic stem cell transplantation in non-Hodgkin's lymphoma. Bone Marrow Transplantation. 2004;33(3):291–298. doi: 10.1038/sj.bmt.1704355.
22. Porrata L. F., Gertz M. A., Geyer S. M., et al. The dose of infused lymphocytes in the autograft directly correlates with clinical outcome after autologous peripheral blood hematopoietic stem cell transplantation in multiple myeloma. Leukemia. 2004;18(6):1085–1092. doi: 10.1038/sj.leu.2403341.

23. Porrata L. F., Inwards D. J., Ansell S. M., et al. Early lymphocyte recovery predicts superior survival after autologous stem cell transplantation in non-hodgkin lymphoma: a prospective study. Biology of Blood and Marrow Transplantation. 2008;14(7):807–816. doi: 10.1016/j.bbmt.2008.04.013.
24. Porrata L. F., Inwards D. J., Ansell S. M., Micallef I. N. Day 15 peripheral blood lymphocyte/monocyte ratio post-autologous peripheral hematopoietic stem cell transplantation and survival in diffuse large B-cell lymphoma. Journal of Stem Cell Research & Therapy. 2011;1, article 103
25. Porrata LF. Autologous Graft-versus-Tumor Effect: Reality or Fiction? Adv Hematol.2016:5385972. doi: 10.1155/2016/5385972.
26. Porrata L. F., Burgstaler E. A., Winters J. L., et al. Immunologic autograft engineering and survival in non-Hodgkin lymphoma. Biology of Blood and Marrow Transplantation. 2016;22(6):1017–1023. doi: 10.1016/j.bbmt.2016.01.024.
27. Rhodes B, Anderlini P. Allogeneic Peripheral Blood Stem Cell Collection as of 2008. Transfus Apher Sci. 2008; 38(3): 219–227.
28. Rutella S, Pierelli L, Bonanno G, et al. Role for granulocyte colony-stimulating factor in the generation of human T regulatory type 1 cells. Blood. 2002;100(7):2562-71.
29. Saraceni F, Shem-Tov N, Olivieri A, Nagler A. Mobilized peripheral blood grafts include more than hematopoietic stem cells: the immunological perspective. Bone Marrow Transplant. 2015;50(7):886-891.
30. Schulman R, Birch R, Zhen B, Pania N, Weaver CH. Effect of CD34(+) cell dose on resource utilization in patients after high-dose chemotherapy with peripheral-blood stem-cell support. J Clin Oncol, 17 (1999), p. 1227
31. Silva JG, Maher OM, Park M, et al. Analysis of the prognostic effect of peripheral blood lymphocyte and monocyte count after autologous hematopoietic stem cell transplant in refractory/relapsed Hodgkin's lymphoma in a pediatric, adolescent, and young adult population. Biol Blood Marrow Transplant, 22 (2017), pp. S219-S220
32. Sivakumar R, Atkinson MA, Mathews CE, Morel L. G-CSF: a friend or foe? Immunome Res (2015) S2:007.
33. Sloand EM, Kim S, Maciejewski JP, Van Rhee F, Chaudhuri A, et al. Pharmacologic doses of granulocyte colony-stimulating factor affect cytokine production by lymphocytes in vitro and in vivo. Blood. 2000; 95:2269-2274.
34. Sorigue M, Sancho JM, Morgades M et al. Relapse risk after autologous stem cell transplantation in patients with lymphoma based on CD34+ cell dose. Leuk Lymphoma. 2017;58(4):916-922.
35. Stiff PJ, Micallef I, Nademanee AP, et al. Transplanted CD34(+) cell dose is associated with long-term platelet count recovery following autologous peripheral blood stem cell transplant in patients with non-Hodgkin lymphoma or multiple myeloma. Biol Blood Marrow Transplant. 2011:17; 1146-1153
36. Wang K, Lv M, Cang YJ, et al. Early myeloid-derived suppressor cells (HLA-DR−/lowCD33+CD16−) expanded by granulocyte colony-stimulating factor prevent acute graft-versus-host disease (GVHD) in humanized mouse and might contribute to lower GVHD in patients post allo-HSCT. Journal of Hematology and Oncology. 2019;12:31

Characteristics of pediatric patients undergoing first autologous HCT for a malignancy in the United States, with G-CSF used post-transplant, CRF track only

Characteristic	Total
No. of patients	**555**
Age at transplant, years - no. (%)	
Median (min-max)	4.47 (0.5-17.99)
≤ 5	337 (60.7)
6 to 10	103 (18.6)
11 to 18	115 (20.7)
Disease - no. (%)	
NHL	33 (5.9)
HD	45 (8.1)
Solid tumors	477 (85.9)
Head and neck	1
Testicular	2
Ovary (epithelial)	3
Central nervous system tumors	79
Wilm Tumor	8
Neuroblastoma	245
Retinoblastoma	6
Germ cell tumor, Extragonadal	13
Medulloblastoma	80
Rhabdomyosarcoma	4
Other solid tumor	23
Soft tissure sarcoma	2
Ewing family tumors of bone	9
Ewing family tumors, extraosseous	2
Graft type - no. (%)	
Peripheral blood	555
CD34+ cell dose available - no. (%)	
No	34 (6.1)
Yes	521 (93.9)
CD34+ cell dose (x 10^6)	
Median (Inter-quartile range)	109.12 (57.98 – 256.00)
Year of transplant - no. (%)	
2008-2012	232 (41.8)
2013-2018	323 (58.2)
Follow-up - median (min-max)	49.38 (1.38-132.14)

Proposal: 1911-200

Title:
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, MD, myersrm@email.chop.edu, Children's Hospital of Philadelphia
Martin S. Tallman, MD, tallmanm@mskcc.org, Memorial Sloan Kettering Cancer Center/Weill Cornell Medical College

Research hypothesis:
For adolescents and young adults (AYA) who receive an allogeneic hematopoietic cell transplant (alloHCT) for acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML), we hypothesize that transplant practices will vary significantly by center type: adult versus pediatric. We also hypothesize that outcomes may be different by center type.

Specific aims:
Aim 1:
To compare transplant practices between adult and pediatric centers for AYAs who received an alloHCT for ALL or AML.

Aim 2:
To compare disease-free survival, overall survival, non-relapse mortality, and relapse between AYAs transplanted for ALL or AML at adult versus pediatric centers.

Scientific justification and impact:
In general, adolescents and young adults (AYAs) with cancer have experienced less improvements in survival compared with children or older adults.[1] Furthermore, AYAs with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) have significantly worse survival than children.[2] The survival differences are likely multifactorial, but in the upfront treatment setting, there is data to suggest that some AYAs with cancer have better outcomes when treated in pediatric centers or on pediatric-inspired protocols.[3,4] For ALL, in particular, multiple studies have demonstrated improved survival for AYAs treated at pediatric instead of adult centers.[5,6] For AML, survival differences for AYAs by pediatric versus adult center type have not been as significant or consistent as for ALL.[7] This is likely, at least in part, due to fewer differences between pediatric and adult AML treatment protocols. However, it has been shown that treatment at a designated NCI Comprehensive Cancer Center or Children's Oncology Group is associated with better survival compared with treatment at other centers.
In the alloHCT setting, AYAs with ALL and AML also have inferior survival compared to children. For AYAs with AML transplanted using a matched sibling donor between 1998-2005, 5-year adjusted survival was 42% compared to 53% for children. For unrelated donor transplants, survival was 28% compared to 37% for children.[8] In a single center study of patients who underwent alloHCT for B-ALL, the hazard ratio for 5-year overall survival was 1.74 (95% CI, 1.04-2.95) for AYAs compared with children.[9] Over the past few decades, however, survival after alloHCT for AYAs with both AML and ALL has improved, and rates of improvement have paralleled children and older adults.[8,10] Interestingly, it has been found that survival improvements are largely due to decreased transplant-related mortality as opposed to decreases in relapse rates.

Although it is known that AYAs have inferior survival to children after alloHCT and that AYAs may have better outcomes when treated in pediatric centers or on pediatric protocols in the upfront setting, it is not known whether center type impacts outcomes after alloHCT. There is only one available report of AYA outcomes after alloHCT that assessed center type.[10] The analysis, which used CIBMTR data, included a subgroup of AYAs ages 15-25 years who received a myeloablative alloHCT for ALL. The study found differences in transplant practices, including conditioning regimen and GVHD prophylaxis, but did not find differences in outcomes. However, the analysis was limited by a small sample size (222 patients) and a less contemporary sample (alloHCT 2002-2007). Given the inclusion criteria for the current proposal, we expect to have a much larger and more contemporary sample.
The proposed project aims to evaluate differences in transplant practices and survival outcomes for AYAs with ALL and AML based on center type. Given that AYAs with leukemia are a vulnerable population with survival disparities, it is critical to assess the range of factors that may influence outcomes. In addition, differences in outcomes by center type in the upfront treatment setting makes this question an important one to answer in the alloHCT setting. Furthermore, as discussed above, differences in transplant practices for ALL between pediatric and adult centers have been observed.[10] It is possible these differences may influence relapse risk or risk of transplant-related morbidity and mortality.
This analysis is particularly relevant in the current era because many immunotherapy and other clinical trials at pediatric centers are allowing patients up to age 29 years to enroll. This may translate into additional AYA patients then pursuing subsequent transplants at pediatric centers – or at least, questioning whether they should receive an alloHCT at a pediatric or an adult center. Thus, the study results will provide important guidance to patients, their families and clinicians.

Patient eligibility population:
Inclusion criteria:

- AYAs ages 15-29 years at time of alloHCT
- Patients who received their first alloHCT for ALL or AML
- AlloHCT between 2002 and 2017
- AlloHCT at a United States transplant center
- Any donor type
- Any graft source
- Any conditioning regimen

Exclusion criteria:

- Patients with acute promyelocytic leukemia
- Prior alloHCT

Data requirements:
We propose to use data available on the pre- and post-TED forms:

- Pre-TED forms (2400): demographic information, donor type, product type, product manipulation, Karnofsky/Lansky score at time of transplant, history of complications prior to transplant (including mechanical ventilation, fungal infections, and other organ impairments), cytogenetic data, preparative regimen (including intensity, specific chemotherapeutic agents, and radiation), and GVHD prophylaxis.
- Post-TED forms (2450) at days 100, six months and one, two and three years: survival status, remission status, cause of death, subsequent HCT, hematopoietic recovery, platelet recovery, late graft failure, VOD, and GVHD (including organ and grade).

- We will also include data from the following CRF forms:
- AML pre-infusion (2010) and ALL pre-infusion (2011): date of diagnosis, disease assessment at diagnosis, pre-HCT therapy including cellular therapy, relapse history, disease status at time of infusion, date of CR1
- AML post-infusion (2110) and ALL post-infusion (2111): cytogenetics, disease status, post-infusion therapy

Sample requirements:
N/A

Study design:
This will be a retrospective cohort study of AYAs who received an alloHCT between 2002-2017.

Outcomes:
For Aim 1, the primary outcomes are specific transplant practices, including:
- Conditioning regimen
- Donor type
- Graft source
- Product manipulation
- GVHD prophylaxis

For Aim 2, the primary outcomes are survival outcomes up to 3-year post-alloHCT, including:
- Disease-free survival
- Overall survival
- Non-relapse mortality
- Relapse

Exposure:
The primary exposure of interest is center type: adult versus pediatric.

Co-variates*:* Co-variates captured from CIBMTR data will include:
- Diagnosis: AML vs ALL
- Cytogenetics, including cytogenetic risk group
- Age at alloHCT
- Age at diagnosis
- Prior treatment history
- Time from diagnosis to CR1
- Disease status at time of transplant
- Time from diagnosis to alloHCT
- HLA match
- Performance score at alloHCT

In addition, the primary outcomes for Aim 1 will be used as co-variates in Aim 2.

Statistical considerations:
Aim 1: Unadjusted point estimates of the primary outcomes (specific transplant practices) will be calculated separately for ALL and AML. The point estimates will be compared by center type: pediatric vs

adult. Chi-squared and logistic regression analyses will be used to identify univariate factors associated with transplant practices. Multivariate modeling adjusting for significant factors by univariate analysis will be used to estimate adjusted estimates of the primary outcomes.

Aim 2: Univariate probabilities of overall survival and disease-free survival up to 3-years after alloHCT will be estimated separately for ALL and AML using the Kaplan-Meier method. Probabilities of relapse and transplanted-related mortality, separately for ALL and AML, will be estimated using the cumulative incidence function method. Cox proportional hazards analysis will then be used to estimate survival probabilities based on selected sets of covariates (e.g. donor type, graft source).

Non-CIBMTR data source:
N/A

Conflicts of interest:
None

References:
1. Bleyer WA. Cancer in older adolescents and young adults: Epidemiology, diagnosis, treatment, survival, and importance of clinical trials. *Med Pediatr Oncol*. 2002;38(1):1-10. doi:10.1002/mpo.1257
2. Wolfson J, Sun CL, Wyatt L, Stock W, Bhatia S. Adolescents and young adults with acute lymphoblastic leukemia and acute myeloid leukemia: Impact of care at specialized cancer centers on survival outcome. *Cancer Epidemiol Biomarkers Prev*. 2017;26(3):312-320. doi:10.1158/1055-9965.EPI-16-0722
3. Boissel N, Baruchel A. Acute lymphoblastic leukemia in adolescent and young adults: Treat as adults or as children? *Blood*. 2018;132(4):351-361. doi:10.1182/blood-2018-02-778530
4. Seftel MD, Neuberg D, Zhang MJ, et al. Pediatric-inspired therapy compared to allografting for Philadelphia chromosome-negative adult ALL in first complete remission. *Am J Hematol*. 2016. doi:10.1002/ajh.24285
5. Gupta S, Pole JD, Lau C, et al. Superior survival in adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL) treated in pediatric vs. adult centers is only partially attributable to inadequate adoption of pediatric protocols: A population-based IMPACT Cohort study. *J Clin Oncol*. 2018;36(15_suppl):6564-6564. doi:10.1200/jco.2018.36.15_suppl.6564
6. Ram R, Wolach O, Vidal L, Gafter-Gvili A, Shpilberg O, Raanani P. Adolescents and young adults with acute lymphoblastic leukemia have a better outcome when treated with pediatric-inspired regimens: Systematic review and meta-analysis. *Am J Hematol*. 2012;87(5):472-478. doi:10.1002/ajh.23149
7. Creutzig U, Kutny MA, Barr R, Schlenk RF, Ribeiro RC. Acute myelogenous leukemia in adolescents and young adults. *Pediatr Blood Cancer*. 2018;65(9). doi:10.1002/pbc.27089
8. Majhail NS, Brazauskas R, Hassebroek A, et al. Outcomes of Allogeneic Hematopoietic Cell Transplantation for Adolescent and Young Adults Compared with Children and Older Adults with Acute Myeloid Leukemia. *Biol Blood Marrow Transplant*. 2012;18(6):861-873. doi:10.1016/j.bbmt.2011.10.031
9. Burke MJ, Gossai N, Wagner JE, et al. Survival differences between adolescents/young adults and children with B precursor acute lymphoblastic leukemia after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2013;19(1):138-142. doi:10.1016/j.bbmt.2012.08.020
10. Wood WA, Lee SJ, Brazauskas R, et al. Survival improvements in adolescents and young adults after

myeloablative allogeneic transplantation for acute lymphoblastic Leukemia. *Biol Blood Marrow Transplant*. 2014;20(6):829-836. doi:10.1016/j.bbmt.2014.02.021

Characteristics of adolescent and young adult patients undergoing first allogeneic HCT for AML in the United States

	TED		CRF	
Characteristic	**Adult center**	**Pediatric center**	**Adult center**	**Pediatric center**
No. of patients	**3000**	**608**	**1322**	**267**
Age at transplant, years - no. (%)				
Median (min-max)	24 (15-30)	17.33 (15.02-29.84)	23.91 (15-29.99)	17.21 (15.02-29.84)
15 to 19	571 (19)	524 (86.2)	258 (19.5)	227 (85)
20 to 24	1156 (38.5)	71 (11.7)	528 (39.9)	33 (12.4)
25 to 29	1273 (42.4)	13 (2.1)	536 (40.5)	7 (2.6)
Disease status - no. (%)				
Primary induction failure	377 (12.6)	26 (4.3)	155 (11.7)	11 (4.1)
1st complete remission	1556 (51.9)	356 (58.6)	628 (47.5)	146 (54.7)
2nd complete remission	710 (23.7)	173 (28.5)	356 (26.9)	82 (30.7)
1st relapse	263 (8.8)	43 (7.1)	131 (9.9)	22 (8.2)
2nd relapse	94 (3.1)	10 (1.6)	52 (3.9)	6 (2.2)
Donor type - no. (%)				
HLA-identical sibling	1007 (33.6)	169 (27.8)	266 (20.1)	37 (13.9)
Unrelated donor	1993 (66.4)	439 (72.2)	1056 (79.9)	230 (86.1)
Year of transplant - no. (%)				
2000-2004	622 (20.7)	121 (19.9)	343 (25.9)	70 (26.2)
2005-2009	819 (27.3)	139 (22.9)	527 (39.9)	86 (32.2)
2010-2014	888 (29.6)	215 (35.4)	298 (22.5)	82 (30.7)
2015-2018	671 (22.4)	133 (21.9)	154 (11.6)	29 (10.9)
Follow-up - median (min-max)	65.82 (1.74-217.96)	59.8 (3.39-219.57)	94.14 (3.13-217.96)	62.66 (3.39-217.57)

Characteristics of adolescent and young adult patients undergoing first allogeneic HCT for ALL in the United States

	TED		CRF	
Characteristic	**Adult center**	**Pediatric center**	**Adult center**	**Pediatric center**
No. of patients	**2611**	**650**	**989**	**252**
Age at transplant, years - no. (%)				
Median (min-max)	23.5 (15.01-30)	17.88 (15.02-29.67)	23.58 (15.1-30)	17.58 (15.07-29.67)
15 to 19	556 (21.3)	502 (77.2)	212 (21.4)	202 (80.2)
20 to 24	1087 (41.6)	130 (20)	398 (40.2)	44 (17.5)
25 to 29	968 (37.1)	18 (2.8)	379 (38.3)	6 (2.4)
Disease status - no. (%)				
Primary induction failure	116 (4.4)	14 (2.2)	46 (4.7)	5 (2)
1st complete remission	1276 (48.9)	271 (41.7)	412 (41.7)	108 (42.9)
2nd complete remission	903 (34.6)	344 (52.9)	367 (37.1)	128 (50.8)
1st relapse	202 (7.7)	13 (2)	93 (9.4)	7 (2.8)
2nd relapse	114 (4.4)	8 (1.2)	71 (7.2)	4 (1.6)
Donor type - no. (%)				
HLA-identical sibling	987 (37.8)	216 (33.2)	214 (21.6)	38 (15.1)
Unrelated donor	1624 (62.2)	434 (66.8)	775 (78.4)	214 (84.9)
Year of transplant - no. (%)				
2000-2004	490 (18.8)	125 (19.2)	310 (31.3)	78 (31)
2005-2009	676 (25.9)	157 (24.2)	358 (36.2)	89 (35.3)
2010-2014	828 (31.7)	205 (31.5)	191 (19.3)	47 (18.7)
2015-2018	617 (23.6)	163 (25.1)	130 (13.1)	38 (15.1)
Follow-up - median (min-max)	61.48 (1.35-220.53)	60.26 (3.22-220.49)	73.68 (2.8-215.95)	75.89 (3.22-195.49)

Combined Proposal: 1911-57 / 1911-58

Title:
Evaluation of Outcomes following Allogeneic Hematopoietic Cell Transplantation in Pediatric Patients with High-Risk Acute Myeloid Leukemia: A CIBMTR Analysis.

Senthil Velan Bhoopalan, MBBS, PhD, Senthil.Bhoopalan@STJUDE.ORG, St. Jude Children's Research Hospital
Neel Bhatt, MBBS, NBhatt@FREDHUTCH.ORG, Fred Hutchinson Cancer Research Center
Akshay Sharma, MBBS, Akshay.Sharma@STJUDE.ORG, St. Jude Children's Research Hospital

Research hypothesis:
Pediatric patients with acute myeloid leukemia associated with high-risk cytogenetic and molecular features (HR-AML) who undergo allogeneic hematopoietic cell transplantation (HCT) have a higher mortality and higher relapse rate than those pediatric patients with AML not associated with high-risk features.

Specific aims:
- To describe the clinical characteristics and outcomes (overall survival, progression-free survival, non-relapse mortality, relapse incidence) of pediatric patients with HR-AML who undergo allogeneic hematopoietic cell transplantation (HCT) and identify prognostic factors associated with improved outcomes within this subgroup of patients.
- To describe the impact of cytogenetic and molecular aberrations associated with HR-AML on stratifing patients to predict post-transplant outcomes.

Scientific impact:
Acute myeloid leukemia is an aggressive disease with poor outcome in children (1). Outcomes are determined by the genetic features of the malignancy and response to induction therapy. While outcomes for AML in children have been continually improving over the last 3 decades, overall survival is still at around 70%. For HR-AML, which accounts for ~15% of all AML diagnoses in children, outcomes are worse with OS of less than 50% (2). However, variations in definition of HR-AML make it difficult to compare OS across the different trials. In addition, the relatively small number of pediatric AML patients that undergo HCT at any one center make it difficult to identify the role of HCT for AML associated with specific cytogenetic and molecular aberrations (3). There is limited data to suggest that HCT improves outcomes in AML associated with some of the mutations such as *FLTR-ITD* with high allelic ratio, monosomy 7 and certain MLL rearrangements (4-8). Role of HCT for the rest of the cytogenetic and molecular features are not well understood. The poor outcomes in HR-AML and the heterogeneity of the cytogenetic/molecular features of this disease makes it imperative to study outcomes following HCT and identify prognostic factors that improve outcomes (7, 9).

Scientific justification:
Outcomes for children with HR-AML are dismal in spite of chemotherapy intensification, advances in supportive care and HCT. Additionally, the outcomes vary depending on the high-risk feature. The following mutations have been associated with adverse outcomes: -5/-5q, 7/-7q, FLT3 ITD with high allelic ratio, NUP98-NSD1 or WT mutation associated with FLT3 ITD, treatment-related AML, abnormalities of 3q, DEK-NUP214 [t(6;9)], KAT6A-CREBBP [t(8;16)], RUNX1-CBFA2T3 [t(16;21)], CBFA2T3-GLIS2, [inv(16)(p13.3q24.3)], NUP98-KDM5A [t(11;12)(p15;p13)], ETV6-HLXB[t(7;12)(q36;p13)], NUP98-HOXA9, [t(7;11)(p15.4;p15)], NUP98-NSD1, t(6;11)(q27;q23), t(10;11)(p11.2;q23),

t(10;11)(p12;q23), t(11;19)(q23;p13.3), t(4;11)(q21;q23) and complex karyotype defined as three or more cytogenetic abnormalities. Minimal residual disease (MRD) has been a particularly useful tool for prognostication. MRD > 1% after induction 1 and > 0.01% after induction 2 have been associated with poor overall survival (2, 9). But is it not known whether MRD based prognostication is independent of the cytogenetic risk factors. In other words, do patients with HR-AML with MRD negative disease prior to undergoing an HCT have better outcoes irrespective of their underlying cytogenetic risk factors is not known.

A recent restrospective study by Doherty *et al* showed that HR-AML patients had comparable outcomes with matched related donor and matched unrelated donor transplant, with 3-year OS of 52% (95% CI: 41-62%) (10). A larger combined analysis from two successive pediatric trials in France showed a 10-year OS of 74.4+/-3.6% and EFS at 10 years was 65.9+/-3.6% (11). While the HR-AML children treated on the first trial had poor OS compared to intermediate-risk AML (50+/-14.4% vs 90.6+/-5.2%), the following trial included in the analysis had comparable results for the two groups (71.3+/-6% vs 80.9+/-6%). However, a retrospective analysis of patients treated from 1989 to 2006, with data collected from COG and CIBMTR, did not show any benefit for HCT over chemotherapy alone in HR-AML (12). However, HR-AML in this study was limited to monosomy 7, deletion of 7q (del(7q)), monosomy 5, deletions of 5q, abnormalities of 3q, t(6;9)(p23;q34), and complex karyotype: defined as five or more cytogenetic abnormalities (which is different from the current internationally accepted definition of complex karyotype). While the role of MRD and certain molecular features such as *FLT3-ITD* have been shown to benefit from HCT (6), the role of HCT for other cytogenetic and molecular aberrations needs to be resolved further.

Only 11-29% of pediatric patients with AML undergo HCT (3). This makes it difficult to do a thorough subgroup analysis for HR-AML patients without large collaborative studies. However, this is likely possible using a well annotated and large pooled database such as CIBMTR. This would be an important study to fill the knowledge gap, to aid in development of better treatment strategies and to counsel patients undergoing HCT. Furthermore, as transplant methods and outcomes in general have improved in the past decade, this analysis will target a more contemporary cohort of patients for analysis to reflect current practices.

Patient eligibility population:

All patients 18 years of age or younger who underwent HCT for AML registered with CIBMTR between years 2014 and 2018. The study will focus on HR-AML and compare their outcomes to other AML patients.

Data requirements:

This proposed study will require no supplemental data to be collected. The current data is included in the CIBMTR collection forms for Pre-HCT and Post-HCT Acute Myelogenous Leukemia (Forms 2010 and 2110).

<u>Variables to be analyzed:</u>

- Age
- Sex of patient
- Lanksy/Karnofsky performance status
- Presence of extramedullary site at diagnosis
- CNS status at diagnosis
- WBC at diagnosis
- Immunophenotype at diagnosis
- Cytogenetics and molecular pathology at diagnosis

- Time from diagnosis to transplant
- Remission status at time of transplant (CR1 vs CR2)
- If progressed, time to progression after previous CR
- Year of transplant
- Secondary AML or de novo AML
- Antecedent disease leading to secondary AML (MDS, ALL, Ewing sarcoma etc)
- Presence of minimal residual disease (MRD) status prior to transplant
- Sex of donor
- CMV status of patient/donor
- Type of donor (haploidentical, 1 or 2 HLA-antigen mismatch, MUD, sibling donor, cord blood)
- Source of stem cells (peripheral blood, cord, bone marrow)
- AML treatment regimen(s)
- Conditioning regimen
- Graft manipulation
- T cell depletion
- Time to neutrophil recovery
- Time to platelet recovery
- GVHD prophylactic regimen
- Acute GVHD
- Chronic GVHD
- Post-transplant relapse chemoprophylaxis (if used)

Desired outcome variables include:

- Overall survival
- Progression-free survival
- Relapse incidence
- Non-relapse mortality

Sample requirements:
No biological samples are required for this study.

Study design:
This study is a retrospective registry analysis of all pediatric patients who received HCT for AML between 2014 and 2018.

Specific aim:

- Aim 1: To describe the clinical characteristics and outcomes (overall survival, progression-free survival, non-relapse mortality, relapse incidence) of pediatric patients with HR-AML who undergo allogeneic hematopoietic cell transplantation (HCT) and identify prognostic factors associated with improved outcomes within this subgroup of patients.
- Aim 2: To describe the impact of cytogenetic and molecular aberrations associated with HR-AML on stratifing patients to predict post-transplant outcomes.

Study design:
We will determine overall survival (time from allogeneic HCT to death from any cause), progression-free survival (survival without any evidence of relapse or progression), non-relapse mortality (death without any evidence of relapse or progression) and relapse incidence (>5% blasts in the bone marrow and/or

chloroma). These endpoints will be determined for each patient and the data will be aggregated utilizing Kaplan-Meier analysis and compared using log-rank test. Outcomes will be compared between patients in CR1, CR2+ and refractory disease, TBI-based conditioning will be compared to non-TBI conditioning regimens, between different remission statuses (CR with positive MRD or CR with negative MRD), between the different sources of stem cells and the different types of donors (haploidentical, 1 or 2 HLA-antigen mismatch, MUD, matched sibling donor, cord blood). 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. Studies from adult population with MLLr AML has also suggested that some of the fusion partners with KMT2A are associated with poor outcome (t(10;11), t(6;11)) after allogeneic HCT. We will explore if the impact of the individual cytogenetics and molecular aberrations on OS, PFS, NRM and relapse after allogeneic HCT utilizing univariate analysis and multivariate analysis by cox proportional hazards analysis.

Conflicts of interest:
No

References:

1. Woods WG. Curing childhood acute myeloid leukemia (AML) at the half-way point: Promises to keep and miles to go before we sleep. Pediatric blood & cancer. 2006;46(5):565-9.
2. Rubnitz JE. Current Management of Childhood Acute Myeloid Leukemia. Paediatr Drugs. 2017;19(1):1-10.
3. Hasle H. A critical review of which children with acute myeloid leukaemia need stem cell procedures. British journal of haematology. 2014;166(1):23-33.
4. Horan JT, Alonzo TA, Lyman GH, Gerbing RB, Lange BJ, Ravindranath Y, et al. Impact of disease risk on efficacy of matched related bone marrow transplantation for pediatric acute myeloid leukemia: the Children's Oncology Group. J Clin Oncol. 2008;26(35):5797-801.
5. Trobaugh-Lotrario AD, Kletzel M, Quinones RR, McGavran L, Proytcheva MA, Hunger SP, et al. Monosomy 7 associated with pediatric acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS): successful management by allogeneic hematopoietic stem cell transplant (HSCT). Bone Marrow Transplant. 2005;35(2):143-9.
6. Meshinchi S, Arceci RJ, Sanders JE, Smith FO, Woods WB, Radich JP, et al. Role of allogeneic stem cell transplantation in FLT3/ITD-positive AML. Blood. 2006;108(1):400-1.
7. Balgobind BV, Raimondi SC, Harbott J, Zimmermann M, Alonzo TA, Auvrignon A, et al. Novel prognostic subgroups in childhood 11q23/MLL-rearranged acute myeloid leukemia: results of an international retrospective study. Blood. 2009;114(12):2489-96.
8. Ciurea SO. Allogeneic stem cell transplantation for FLT3 mutated acute myeloid leukemia in first complete remission: does age really matter? Haematologica. 2018;103(2):191-3.
9. Rubnitz JE, Razzouk BI, Lensing S, Pounds S, Pui CH, Ribeiro RC. Prognostic factors and outcome of recurrence in childhood acute myeloid leukemia. Cancer. 2007;109(1):157-63.
10. Doherty EE, Redell M, Sasa G, Yassine K, John TD, Craddock J, et al. Outcomes after Allogeneic Hematopoietic Stem Cell Transplantation for Pediatric Acute Myeloid Leukemia in the Contemporary Era. American Society of Hematology Washington, DC; 2019.
11. Alloin A, Leverger G, Dalle J, Galambrun C, Bertrand Y, Baruchel A, et al. Cytogenetics and outcome of allogeneic transplantation in first remission of acute myeloid leukemia: the French pediatric experience. Bone marrow transplantation. 2017;52(4):516.

12. Kelly MJ, Horan JT, Alonzo TA, Eapen M, Gerbing RB, He W, et al. Comparable survival for pediatric acute myeloid leukemia with poor-risk cytogenetics following chemotherapy, matched related donor, or unrelated donor transplantation. Pediatric blood & cancer. 2014;61(2):269-75.

Number of pediatric patients undergoing first allogeneic HCT for AML in the United States between 2014 and 2018 with selected high-risk cytogenetic and molecular abnormalities

Characteristic	CRF	TED
No. of patients	**211**	**527**
High-risk cytogenetic abnormalities - no. (%)		
Monosomy 5	0	1 (0.2)
Monosomy 7	10 (4.7)	29 (5.5)
Monosomy 17	1 (0.5)	2 (0.4)
Trisomy 4	3 (1.4)	8 (1.5)
Trisomy 8	16 (7.6)	37 (7)
Trisomy 11	0	1 (0.2)
Trisomy 13	0	2 (0.4)
Trisomy 22	0	2 (0.4)
t(3;3)	1 (0.5)	2 (0.4)
t(6;9)	11 (5.2)	22 (4.2)
t(9;11)	11 (5.2)	24 (4.6)
t(16;16)	1 (0.5)	1 (0.2)
Del 3q	2 (0.9)	4 (0.8)
Del 5q	5 (2.4)	15 (2.8)
Del 7q	7 (3.3)	13 (2.5)
Del 11q	2 (0.9)	2 (0.4)
Del 16q	2 (0.9)	4 (0.8)
Del 17q	0	1 (0.2)
Del 20q	1 (0.5)	3 (0.6)
Inv(16)	8 (3.8)	26 (4.9)
11q23	43 (20.4)	93 (17.6)
12p abnormality	6 (2.8)	8 (1.5)
Complex karyotype	57 (27)	157 (29.8)
None of the above listed	24 (11.4)	70 (13.3)
High-risk molecular abnormalities - no. (%)		
FLT3-D835	3 (1.4)	13 (2.5)
FLT3-ITD	33 (15.6)	94 (17.8)
None of the above listed	175 (82.9)	420 (79.7)

Proposal: 1911-68

Title:
Central nervous system monitoring and prophylaxis post transplantation for pediatric leukemia: avoiding toxicities without compromising outcomes

Ellen Fraint, MD, efraint@montefiore.org, Children's Hospital at Montefiore
David Loeb, MD PhD, dloeb@montefiore.org, Children's Hospital at Montefiore
Lisa Wray, MD, wrayl@email.chop.edu, Children's Hospital of Philadelphia

Hypothesis:
- Consensus is lacking regarding post transplant CNS monitoring and prophylaxis best practices, as evidenced by heterogeneous approaches across pediatric transplant centers.
- Prophylactic CNS treatment post transplantation for pediatric leukemia decreases the rate of CNS relapse by at least 20%.

Objects:
- To describe the current landscape of clinical practice in the USA regarding CNS monitoring and prophylaxis post transplant for pediatric leukemia.
- To assess whether prophylactic intrathecal treatment post transplant for pediatric leukemia decreases the risk of CNS relapse, and if so to what extent.

Scientific justification:
Pediatric transplant centers vary in their post-transplant central nervous system (CNS) prophylaxis approaches, partly because the risk of post-transplant CNS relapse is not known in the modern era where CNS prophylaxis is a critical component of upfront leukemia therapy. In order to determine the most effective approach to post-transplant CNS treatment and monitoring, we need to determine the actual risk of CNS relapse post-transplant and consider this in context with the risks inherent in administering intrathecal chemotherapy. The potential impact of this study is enormous, as it could help determine, for the first time, the most effective way to treat or monitor the CNS post-transplant for patients with leukemia. This will clear the way for consensus guidelines to be drafted and implemented, harmonizing practices across centers.

Before the role for universal CNS prophylaxis was realized in the treatment paradigm for acute leukemias, a large percentage of the patients who were able to achieve a remission would eventually experience a CNS relapse. Intrathecal prophylaxis is now a universally accepted and critical component of leukemia therapy to prevent CNS relapse, both in pediatrics and adults (1). Consensus is lacking, however, on CNS prophylaxis approaches after hematopoietic stem cell transplant (HSCT). Published reports on CNS prophylaxis practices in adults differ widely between centers, and there are no publications describing the current range of practice patterns in pediatrics (2, 3). Since the goal of definitive treatment with HSCT requires the prevention of relapse while avoiding untoward toxicities, it is critical that as a community we develop a more rigorous understanding of the risks and benefits of post transplant CNS prophylaxis. The necessary first step in this process is to understand what is currently being practiced.

The practice variation between pediatric transplant centers is partially explained by the fact that the efficacy of post transplant intrathecal prophylaxis in preventing CNS relapse has not been established, with no prospective and very few retrospective studies addressing this question (1). In retrospective analyses of adults, reports are conflicting in their conclusions about whether CNS prophylaxis decreases the risk of CNS relapse (1). Moreover, it is not well understood what the actual current risk of post transplant CNS relapse is, either in adults or children, since many of the published retrospective studies include patients transplanted before CNS prophylaxis became a universal component of standard leukemia treatment (1).

Certainly, if post transplant CNS prophylaxis provides a clinically relevant decrease in the risk of CNS relapse, universal adoption of this approach would be warranted.
Any consideration of whether to perform post transplant CNS prophylaxis must balance the yet-unknown benefit of such treatment against the well-known risks of toxicities and adverse events inherent in intrathecal chemotherapy administration. For example, acute toxicities of intrathecal methotrexate include seizures, leukoencephalopathy, electrolyte derangements, and headaches, while long-term toxicities in children include learning difficulties and loss of IQ points (4). In order to determine whether there is a scientific rationale to expose patients to the risks inherent in these treatments, it is critical to understand how important post transplant CNS prophylaxis is in decreasing the risk of CNS relapse.

Study population:
Inclusion criteria:
- Patients aged 0-30
- HSCT for treatment of acute leukemia (ALL or AML)

Exclusion criteria:
- Age >30
- Transplant for diagnosis other than ALL or AML
- Patient with CNS status information unavailable

Outcomes:
Primary:
CNS relapse post-transplant

Secondary:
- Overall survival for patients who received post-transplant CNS prophylaxis and for patients who did not
- Event free survival for patients who received post-transplant CNS prophylaxis and for patients who did not
- Adverse events of post-transplant CNS prophylaxis

Variables to be described:
- Patient age (0-30 years)
- Gender (male or female)
- Race (Caucasian, African American, Asian, Pacific Islander, Native American)
- Year of transplant
- Diagnosis (ALL or AML)
- CNS status (I-IV) at diagnosis
- CNS status (I-IV) at last evaluation pre-transplant
- Conditioning regimen
- Post-transplant therapies given (CNS irradiation, intrathecal chemotherapy)
- CNS relapse post-transplant (yes/no)

Study design:
An electronic questionnaire will be sent to all pediatric transplant centers registered with the CIBMTR in the USA. We will ask questions regarding their institutional practices, including “do you routinely perform monitoring of the CNS post transplant with diagnostic lumbar punctures” and “do you routinely administer post transplant intrathecal prophylaxis?” Each question will be asked in the context of patients with acute lymphoblastic leukemia, patients with acute myeloid leukemia, patients with a

history of prior CNS disease, and patients with no prior history of CNS disease. As this component of the project is meant to merely be descriptive to explore the degree of heterogeneity in practice across the USA, power calculations will not be necessary.
The survey will be performed via SurveyMonkey.com and will utilize our institutional resources. An email with the survey link will be sent to both the director of the transplant program, as well as the transplant coordinator, for each pediatric transplant center in the USA registered with the CIBMTR. Reminder emails will be sent weekly for 3 weeks. Responses will be anonymous. IRB approval will be obtained prior to dissemination of the survey.
A retrospective study will also be performed to estimate the overall risk of CNS relapse post transplant, as well as to compare the risk in patients who received post transplant prophylaxis versus those who did not. The CIBMTR database will be queried for all patients between the ages of 0-30 years who received a transplant for acute lymphoid or acute myeloid leukemia (ALL and AML). Data to be collected will include age, year of transplant, type of leukemia, stage of prior CNS disease, utilization of pre-transplant CNS treatment in the form of intrathecal chemotherapy and/or craniospinal radiation, type of conditioning regimen, use of post transplant CNS prophylaxis, and the presence or absence of CNS relapse post-transplant.
Primary and secondary outcomes will be calculated separately for patients with ALL and for patients with AML, comparing outcomes in each category for patients who received post-HSCT CNS prophylaxis compared with those who did not.

Conflicts of interest:
None

References:
1. Sauter CS, DeFilipp Z, Inamoto Y, Johnston L, Nagler A, Savani BN, Carpenter PA, Perales MA. ASBMT Statement on Routine Prophylaxis for Central Nervous System Recurrence of Acute Lymphoblastic Leukemia following Allogeneic Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant. 2018. Epub 2018/12/28. doi: 10.1016/j.bbmt.2018.12.757. PubMed PMID: 30590125.
2. Ruutu T, Corradini P, Gratwohl A, Holler E, Apperley J, Dini G, Rocha V, Schmitz N, Socie G, Niederwieser D. Use of intrathecal prophylaxis in allogeneic haematopoietic stem cell transplantation for malignant blood diseases: a survey of the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant. 2005;35(2):121-4. Epub 2004/11/16. doi: 10.1038/sj.bmt.1704727. PubMed PMID: 15543201.
3. Hamdi A, Mawad R, Bassett R, di Stasi A, Ferro R, Afrough A, Ram R, Dabaja B, Rondon G, Champlin R, Sandmaier BM, Doney K, Bar M, Kebriaei P. Central nervous system relapse in adults with acute lymphoblastic leukemia after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2014;20(11):1767-71. Epub 2014/07/16. doi: 10.1016/j.bbmt.2014.07.005. PubMed PMID: 25017763; PMCID: PMC4346133.
4. Duffner PK, Armstrong FD, Chen L, Helton KJ, Brecher ML, Bell B, Chauvenet AR. Neurocognitive and neuroradiologic central nervous system late effects in children treated on Pediatric Oncology Group (POG) P9605 (standard risk) and P9201 (lesser risk) acute lymphoblastic leukemia protocols (ACCL0131): a methotrexate consequence? A report from the Children's Oncology Group. J Pediatr Hematol Oncol. 2014;36(1):8-15. Epub 2013/12/19. doi: 10.1097/MPH.0000000000000000. PubMed PMID: 24345882; PMCID: PMC4465396.

Characteristics of pediatric patients undergoing first allogeneic HCT for ALL in the United States, CRF track

Characteristic	Post-transplant Remission	Post-transplant Relapse
No. of patients	**1006**	**308**
Age at transplant, years - no. (%)		
Median (min-max)	14.85 (0.05-29.99)	14.72 (0.3-29.8)
≤ 5	177 (17.6)	62 (20.1)
6 to 10	197 (19.6)	66 (21.4)
11 to 18	279 (27.7)	58 (18.8)
19 to 29	353 (35.1)	122 (39.6)
Disease status at transplant - no. (%)		
1st complete remission	564 (56.1)	117 (38)
2nd complete remission	442 (43.9)	191 (62)
Sites of disease at diagnosis - no. (%)		
BM alone	793 (78.8)	226 (73.4)
BM + CNS	152 (15.1)	52 (16.9)
BM + others	61 (6.1)	30 (9.7)
Post-transplant CNS therapy (for reasons other than relapse) - no. (%)		
CNS irradiation	5 (0.5)	3 (1)
Intrathecal chemotherapy	110 (10.9)	46 (14.9)
None	891 (88.6)	259 (84.1)
Year of transplant - no. (%)		
2008-2013	486 (48.3)	189 (61.4)
2014-2018	520 (51.7)	119 (38.6)
Follow-up - median (min-max)	47.7 (2.8-124.54)	60.2 (3.29-120.03)

Post-transplant CNS therapy by sites of disease at diagnosis - patients in post-transplant remission only

Characteristic	BM alone	BM + CNS	BM + others
Post-transplant CNS therapy (for reasons other than relapse) - no. (%)			
None	711 (89.7)	125 (82.2)	55 (90.2)
CNS irradiation	4 (0.5)	1 (0.7)	0
Intrathecal chemotherapy	78 (9.8)	26 (17.1)	6 (9.8)

Post-transplant CNS therapy by sites of disease at diagnosis - patients relapsing post-transplant only

Characteristic	BM alone	BM + CNS	BM + others
Post-transplant CNS therapy (for reasons other than relapse) - no. (%)			
None	192 (85)	40 (76.9)	27 (90)
CNS irradiation	3 (1.3)	0	0
Intrathecal chemotherapy	31 (13.7)	12 (23.1)	3 (10)

Proposal: 1911-124

Title:
Germline genetics of pediatric myelodysplastic syndromes (MDS)

Jenny N Poynter Degree(s): PhD, MPH, poynt006@umn.edu, University of Minnesota
Logan G Spector Degree(s): PhD, spector@umn.edu, University of Minnesota

Research hypothesis:
We hypothesize that we will identify genetic variants that predict MDS risk

Specific aims:
To identify genetic susceptibility variants for pediatric MDS in an unselected cohort of pediatric patients from the Center for International Blood & Marrow Transplant Research (CIBMTR). Genotyping will be conducted using the Illumina Global Screening array and controls will include >2000 DNA samples that have been genotyped for other childhood cancer studies. To improve power, we will focus on regions of the genome expressed in myeloid cells as determined by ATAC-seq in primary MDS cell cultures.

Scientific impact:
Little is known about the germline genetics of pediatric MDS, partly due to the lack of available germline DNA for evaluation. We are proposing to utilize T cells isolated from peripheral blood mononuclear cells, which has been demonstrated to be a valid source of germline DNA in patients with myeloid malignancy.[1] This will be the first evaluation of common genetic variation in pediatric MDS. The data generated in this proposal will be used as pilot data to expand our investigation of the genetics of pediatric MDS, including new recruitment of MDS patients from the Children's Oncology Group. In future studies, we will pursue whole exome sequencing in paired germline and disease tissue to identify rare mutations that may suggest new directions for clinical therapy. We will also compare the germline genomics of pediatric and adult MDS, using data from our NIH funded study of adult MDS (NIH R01 CA142714; PI Poynter).

Scientific justification:
MDS are a group of clonal hematologic disorders that result in dysplastic and ineffective hematopoiesis.[2] MDS is typically a disease of the elderly, with the majority of cases diagnosed after age 60 years[3]; however, MDS also occurs in children, adolescents and young adults. In recent years, it has becoming increasingly recognized that the biology of MDS differs in children and adults, with distinct morphologic features, cytogenetic abnormalities, prognostic factors and therapeutic strategies.
Recent evidence suggests that the role of germline genetic variation in hematopoietic malignancy has been underappreciated to date.[4] Analyses of families with multiple affected individuals have identified a number of MDS/AML predisposition syndromes with high penetrance, including cases associated with germline mutation in *RUNX1*, *CEBPA*, *GATA2*, *ETV6*, *ATG2B*, and *GSKIP.*[1, 5-7] Inherited predisposition also occurs in the context of bone marrow failure syndromes such as dyskeratosis congenita, severe congenital neutropenia and Fanconi anemia.[7] A recent sequencing study identified mutations in 13.6% of pediatric MDS,[8] with mutations in GATA2 representing the most common alteration.[1, 8] Notably, family history of hematologic malignancy was not predictive of mutation status.
In addition to sequencing studies that have demonstrated a higher than expected prevalence of high risk cancer susceptibility genes in childhood cancer patients,[9, 10] GWAS have been successfully conducted in multiple types of childhood cancer.[11-15] These studies have identified susceptibility loci and provided clues to disease biology despite modest samples sizes.[16] These findings provide evidence that germline variation is associated with risk outside the context of rare high penetrance syndromes. Germline

susceptibility has not been evaluated in an agnostic fashion in MDS.

Patient eligibility population:
Recipients of a transplant for MDS between the ages of 0 and 19 years at MDS diagnosis with an available DNA sample.

Data requirements:
We would like the following variables for each recipient with a DNA sample:
Date of HSCT; Demographics: sex, ethnicity, race, date of birth; Primary disease: disease subtype, therapy-related including alkylating agent/topo II; History of other malignancy

Sample requirements:
We are requesting DNA samples for individuals who were diagnosed with MDS between the ages of 0 and 19 years. If available, our preference would be for DNA samples isolated from T cells to avoid myeloid contamination. If this is not possible, we would still be interested in DNA from available samples. We would plan to exclude regions of the genome with known somatic mutations in MDS and AML from our analysis. We would require 500ng DNA from each case. A detailed description of the genotyping procedure is included below in the Study Design section.
Dr. Poynter and Dr. Spector are both experienced at conducting genomic studies of childhood and adult cancers. Dr. Poynter is the PI of a case-parent triad study of pediatric germ cell tumors where DNA samples were collected and genotyped for 867 cases and their biological parents (NIH R01 CA151284).[17, 18] She is also the PI of a case control study of adult MDS with array genotyping data for > 2,000 individuals (R01 CA142714). Similarly, Dr. Spector is PI of NIH funded studies of hepatoblastoma, osteosarcoma, Ewing sarcoma and ALL that have included genomewide genotyping or whole genome sequencing for thousands of samples.[12] See attached biosketches for Drs. Poynter and Spector demonstrating funding history and publications resulting from previous genomic studies.

Study design:
We will utilize a case control study design to identify genetic variants that are enriched in pediatric MDS compared with controls. These samples will contribute to a larger project to evaluate genetic susceptibility to pediatric hematologic malignancy funded by the Children's Cancer Research Fund. The overall project will include 102 MDS cases, 197 AML cases, 2600 ALL cases and >2000 population controls. In addition to comparing genetic variation in MDS cases and controls, we will also evaluate genetic variation that increases risk of hematologic malignancy overall and risk of myeloid malignancy (MDS and AML).
ATAC Seq Historically, GWAS have identified variants that are in deoxynuclease I (DNase I) hypersensitivity sites (DHSs),[19] which are characterized by altered chromatin structure that increases the availability of DNA to transcriptional activity.[20] Measuring DHSs via DNase-seq requires large numbers of cells that may not be feasible to obtain in primary human cultures[21]; however, chromatin accessibility can also be measured more reliably and in a much smaller number of cells using the assay of transposase-accessible chromatin (ATAC-seq).[22] We will identify regions of open chromatin in myeloid cells using ATAC-seq in primary human MDS cell cultures available in the laboratory of Dr. Jeff Miller. All cells will be cultured at a density of $1x10^6$ cells/ml in Modified Dulbecco's Medium with 20% FBS and penicillin antibiotics (1%) following standard tissue culture protocols. Cells will be prepared for ATAC-seq following the methods of Buenrostro et al.[22] with sequencing on the Illumina Hi-Seq2500 using 2x50 paired end reads in the University of Minnesota Genomics Center (UMGC). Each cell type will be run in duplicate.
Genotyping The University of Minnesota Genomics Center (UMGC) will perform genotyping using Illumina Global Screening Array (GSA) BeadChips (Illumina, San Diego) according to the manufacturer's specified

protocol. The GSA is a highly optimized array including a universal genome-wide backbone, hand-curated clinical research variants, and sample tracking content to determine ancestry. Allele cluster definitions for each variant will be determined using Illumina GenomeStudio Genotyping Module. The resulting cluster definition file will be used on all samples to determine genotype calls and quality scores. Blind duplicate samples will be distributed among the plates to assess genotyping concordance and to detect plate effects. Genvisis (http://www.genvisis.org) will be used to identify samples with sex aneuploidy. Samples having genotypes for at least 98% of the variants will be included in analyses.
Statistical Analysis Logistic regression will be used to derive risk estimates and 95% confidence intervals for variants using an additive genetic model. All analyses will be performed stratified by ancestral population using an additive genetic model with matching on age and sex and population-specific PCs to account for ancestry. The rare functional variants that are present on this array will be further evaluated using burden tests using the seqMeta package (https://cran.r-project.org/web/packages/seqMeta/). The rationale is that individual rare risk variants in a gene may not have statistical power to be detected but multiple such variants in the same gene can be pooled together to reach a cumulative minor allele count (MAC) that can reach statistical significance.

Non-CIBMTR data source:
N/A

Conflicts of interest:
None

References:

1. Wlodarski MW, Hirabayashi S, Pastor V, et al. Prevalence, clinical characteristics, and prognosis of GATA2-related myelodysplastic syndromes in children and adolescents. Blood. 2016;127: 1387-1397.
2. Tefferi A, Vardiman JW. Myelodysplastic syndromes. N Engl J Med. 2009;361: 1872-1885.
3. Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. . Available from URL: http://seer.cancer.gov/csr/1975_2010/ </csr/1975_2009_pops09/>, based on November 2012 SEER data submission, posted to the SEER web site, April 2013.
4. Furutani E, Shimamura A. Germline Genetic Predisposition to Hematologic Malignancy. J Clin Oncol. 2017;35: 1018-1028.
5. Saliba J, Saint-Martin C, Di Stefano A, et al. Germline duplication of ATG2B and GSKIP predisposes to familial myeloid malignancies. Nat Genet. 2015;47: 1131-1140.
6. Churpek JE, Pyrtel K, Kanchi KL, et al. Genomic analysis of germ line and somatic variants in familial myelodysplasia/acute myeloid leukemia. Blood. 2015;126: 2484-2490.
7. Godley LA. Inherited predisposition to acute myeloid leukemia. Semin Hematol. 2014;51: 306-321.
8. Keel SB, Scott A, Sanchez-Bonilla M, et al. Genetic features of myelodysplastic syndrome and aplastic anemia in pediatric and young adult patients. Haematologica. 2016;101: 1343-1350.
9. Zhang J, Walsh MF, Wu G, et al. Germline Mutations in Predisposition Genes in Pediatric Cancer. N Engl J Med. 2015;373: 2336-2346.
10. Parsons DW, Roy A, Yang Y, et al. Diagnostic Yield of Clinical Tumor and Germline Whole-Exome Sequencing for Children With Solid Tumors. JAMA Oncol. 2016.
11. Trevino LR, Yang W, French D, et al. Germline genomic variants associated with childhood acute lymphoblastic leukemia. Nat Genet. 2009;41: 1001-1005.
12. Savage SA, Mirabello L, Wang Z, et al. Genome-wide association study identifies two susceptibility loci for osteosarcoma. Nat Genet. 2013;45: 799-803.
13. Postel-Vinay S, Veron AS, Tirode F, et al. Common variants near TARDBP and EGR2 are associated with susceptibility to Ewing sarcoma. Nat Genet. 2012;44: 323-327.

14. Maris JM, Mosse YP, Bradfield JP, et al. Chromosome 6p22 locus associated with clinically aggressive neuroblastoma. N Engl J Med. 2008;358: 2585-2593.
15. Turnbull C, Perdeaux ER, Pernet D, et al. A genome-wide association study identifies susceptibility loci for Wilms tumor. Nat Genet. 2012;44: 681-684.
16. Raynor LA, Pankratz N, Spector LG. An analysis of measures of effect size by age of onset in cancer genomewide association studies. Genes Chromosomes Cancer. 2013;52: 855-859.
17. Marcotte EL, Pankratz N, Amatruda JF, et al. Variants in BAK1, SPRY4, and GAB2 are associated with pediatric germ cell tumors: A report from the children's oncology group. Genes Chromosomes Cancer. 2017;56: 548-558.
18. Williams LA, Pankratz N, Lane J, et al. Klinefelter syndrome in males with germ cell tumors: A report from the Children's Oncology Group. Cancer. 2018;124: 3900-3908.
19. Maurano MT, Humbert R, Rynes E, et al. Systematic localization of common disease-associated variation in regulatory DNA. Science. 2012;337: 1190-1195.
20. Thurman RE, Rynes E, Humbert R, et al. The accessible chromatin landscape of the human genome. Nature. 2012;489: 75-82.
21. Song L, Crawford GE. DNase-seq: a high-resolution technique for mapping active gene regulatory elements across the genome from mammalian cells. Cold Spring Harb Protoc. 2010;2010: pdb prot5384.
22. Buenrostro JD, Wu B, Chang HY, Greenleaf WJ. ATAC-seq: A Method for Assaying Chromatin Accessibility Genome-Wide. Curr Protoc Mol Biol. 2015;109: 21 29 21-29.

Characteristics of pediatric patients undergoing first allogeneic HCT for MDS in the United States, with recipient samples available in the sample repository

Characteristic	CRF	TED
No. of patients	**112**	**282**
Age at transplant, years - no. (%)		
Median (min-max)	11.62 (0.45-17.92)	10.85 (0.45-17.96)
< 1	1 (0.9)	2 (0.7)
1 to 5	26 (23.2)	74 (26.2)
6 to 10	22 (19.6)	68 (24.1)
11 to 18	63 (56.3)	138 (48.9)
MDS type - no. (%)		
MDS, not otherwise specified	53 (47.3)	136 (48.2)
RA - Refractory anemia	14 (12.5)	34 (12.1)
RARS	3 (2.7)	5 (1.8)
RAEB-1	14 (12.5)	42 (14.9)
RAEB-2	15 (13.4)	36 (12.8)
RCMD	10 (8.9)	23 (8.2)
RCMD / RS	1 (0.9)	2 (0.7)
5q-syndrome	2 (1.8)	4 (1.4)
Follow-up - median (min-max)	62.83 (11.71-123.36)	62.83 (8.75-124.7)