Not for publication or presentation

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR PEDIATRIC CANCER
Orlando, Florida
Friday, February 17th, 2023, 12 pm – 2 pm

Co-Chair:	**Gregory Yanik, MD, The University of Michigan**
	Phone: (734) 647-8902; E-mail: gyanik@med.umich.edu.
Co-Chair:	**Kirk Schultz, MD, The University of British Columbia**
	Phone: (604)875-3168; E-mail: kschultz@mail.ubc.ca.
Co-Chair:	**Muna Qayed, MD, MSc, Emory University School of Medicine**
	Telephone: (404)785-1112; Email: muna.qayed@choa.org
Scientific Director:	**Larisa Broglie, MD, MS, CIBMTR Statistical Center**
	Telephone: (414)805-0574; Email: lbroglie@mcw.edu
Statistical Director:	**Kwang Woo Ahn, PhD, CIBMTR Statistical Center**
	Phone: (414)955-7387; Email: kwooahn@mcw.edu
Statistician:	**Rasha Atshan, MS, CIBMTR Statistical Center**
	Telephone: (414)805-0705; Email: ratshan@mcw.edu

---

1. **Introduction**

   The Pediatric Cancer Working Committee (PCWC) meeting was called at 12:05 pm on Friday, February 17, 2023, by Dr. Larisa Broglie. The chairs, scientific director, and statistical team were present at the meeting. Attendees were asked to have their name badges scanned at the front gate for attendance purposes and to maintain the committee membership roster. Virtual attendees were reminded that they are part of the committee membership roster as well.

   Dr. Broglie welcomed the attendees on behalf of the working committee leadership and introduced the current WC leadership. Dr. Broglie thanked the leaving chair, Dr. Gregory Yanik, for his contribution to the PCWC and she welcomed Dr. Akshay Sharma as incoming chair. Dr. Broglie proceeded to take the attendees through the committee's goals, expectations, and limitations. She described the CIBMTR COI policy. Then she provided an overview of CIBMTR, data availability & retrievals, publicly available datasets, and Early Career Investigators opportunities. Dr. Broglie introduced Dr. Yanik as the next speaker to provide an overview of PCWC and Accruals report summary.

2. **Accrual summary**

   Dr. Yanik introduced himself to the attendees and reminded them about WC participation, membership, and rules of authorship. Then he directed the attendees' attention to the accrual summaries included in the meeting materials. Dr. Yanik provided a concise summary of the numbers of pediatric patients available in the CIBMTR database.

3. **Presentations, Published or Submitted Papers**

   Dr. Broglie announced that PC20-01 was accepted by TCT and she thanked the PCWC members for their contributions. Then, Dr. Broglie gave an overview of fellowship study SC21-08 and she introduced the study investigator Nicole Liberio. Nicole introduced herself and provided an overview of the study and the corresponding findings.

a. **PC20-01:** Autologous graft cell dose and post-transplant granulocyte colony stimulating factor in post-transplant outcomes among pediatric patients undergoing Autologous Hematopoietic Stem Cell Transplantation. (Knight T/ Wall D/ Chiengthong K), **Submitted.**
b. **SC21-08:** Optimizing Haploidentical Donor Selection for Pediatric HCT. (Liberio N/ Broglie L), **Manuscript in preparation.**
   Comments from discussion:

   i. A question was asked if there was a difference between PBSCS and Marrow in the GVHD evaluation. Nicole replied that graft source was significant for aGVHD outcome in the univariate analysis, but this finding was adjusted in the multivariable analysis.
   ii. Another question was asked about the severity and extent of cGVHD outcomes. Nicole replied that the details of such an outcome could be evaluated in future analysis.
   iii. Another question about the ability to break down graft manipulation to CD34 selection, Alpha Beta, vs. others. Nicole replied that CIBMTR data forms didn't provide graft manipulation data. Dr. Broglie added that the CIBMTR forms changed over time. She added CIBMTR collected CD34 selection or T-Cell depletion but in recent years the graft manipulation questions were moved to CRF retrieval adding Alpha Beta T-Cell depletion.
   iv. A question was asked about data collection forms for siblings and half siblings. Nicole replied that half siblings were included in the study population if they were categorized as Haploidentical donors without knowing if they are full sibling or not. Dr. Broglie added that the study didn't distinguish full sibling Haploidentical from half sibling Haploidentical donors. The attendees clarified if they study distinguish between sibling donors and other donors, and Nicole replied confirmed that the study does.
   v. A follow-up comment about the insight of graft manipulation (T-Cell depletion) data into the study findings.
   vi. A question about considering compounding variables like multiparity and age with the outcomes. Nicole replied that parity is being considered for future analysis.
   vii. Another question about considering Nima and Nepa in the analysis. The attendee added that Nima is the non-inherited maternal antigen while Nepa is the non-inherited paternal antigen. Nicole replied that it isn't part of the study, but it is something to consider evaluating in future analysis.
   viii. Another question about considering specific HLA-mismatches and correlation with the outcomes. Dr. Broglie replied that this was discussed previously and was excluded from the study, and she added that this should be considered in future analysis.
   ix. Dr. Yanik asked about the age of the youngest donor in the registry for this study and how many donors were younger than ten years old. Nicole replied that wasn't certain at the time of how many donors were younger than ten years old. She added that she is considering categorizing the age groups for father, mother, and sibling donors who are younger than ten years old. She added that the sample size of these donor and age groups needs to be evaluated to check if analysis results will have enough statical power to support the findings.

4. Studies in Progress

Dr. Schultz introduced himself to the attendees and he provided an overview of the WC portfolio of the active studies.

a. **PC19-02:** Does mixed peripheral blood T Cell Chimerism predict relapse? (Prockop S/Boelens J/Peggs K), **Protocol Development/ Data file preparation.**
b. **PC19-03:** The impact of pre-transplant extramedullary disease on the outcome of Allogeneic Hematopoietic Cell Transplantation for Acute Myeloid Leukemia in Children. (Rangarajan H/ Satwani P/Chellapandian D), **Protocol Development/ Data file preparation.**

c. **PC20-02:** Germline genetics of pediatric Myelodysplastic Syndromes (MDS). (Poynter J/ Spector L), **Sample Typing/ Data file preparation.**
d. **PC22-01:** Impact of graft versus host disease following allogeneic hematopoietic cell transplantation on leukemia free survival in hematologic malignancies within the pediatric disease risk index risk stratification. (Bauchat A/Qayed M), **Protocol Development.**
e. **PC22-02:** Evaluating predictors of access and outcomes with hematopoietic cell transplantation in pediatric and adolescent patients with relapsed/refractory classical Hodgkin lymphoma after treatment on an initial cooperative group clinical trial. (Castellino S/Kahn J), **Protocol Development.**
Comments from discussion:

i. A question about the range of years that will be included in this study. Dr. Broglie replied that the initial protocol is looking for those cases of patients enrolled on the early COG relapse refractory studies and the hope is to expand the study as early as 2000.

f. **SC21-08:** Optimizing Haploidentical Donor Selection for Pediatric HCT. (Liberio N/ Broglie L), **Manuscript in preparation.**

5. Future/Proposed Studies

Dr. Muna Qayed reminded the attendees of the proposals scoring logistics. She also reminded the presenters that each presentation duration is five minutes followed by five minutes for the Questions & Answers session. Dr. Qayed announced the collaborative session where PCWC proposal will be presented, then she added the Collaborative Session date, time, and location. Dr. Qayed introduced each proposal title and the presenters to the audience in the following order.

a. **PROP 2210-104:** Post-transplant Cyclophosphamide vs. TCR αβ/CD19+ deplete approaches for Haploidentical Transplant in pediatric patients with Acute Leukemias and Myelodysplastic Syndrome: A CIBMTR/EBMT collaborative study. (Li A/Rangarajan H/Satwani P).
Dr. Li presented the proposal on behalf of the group. The proposal hypothesizes that outcomes in pediatric patients with Acute Leukemias and Myelodysplastic syndrome undergoing haploidentical. hematopoietic stem cell transplants (haplo HCT) will be comparable between alpha-beta T-cell receptor deplete (TCR αβ/CD19+) and post-transplant cyclophosphamide (PTCY) transplant approaches.
Comments from discussion:

i. A Comment regarding the limited number of centers that use TCR αβ, the attendee added the patients with positive MRD had poor outcomes after HCT, and he added the value of using Disease Risk Index to categorization. He also added that CIBMTR should consider data linkage for this study with COG for example. Dr. Broglie replied that the goal is to collaborate with EBMT to complete this study.
ii. A comment about COG prospective study initially investigates TCR αβ vs PTCY vs CB. Since CB is used less in HCT and the statistical power issues of comparing three cohort, the investigators decided to exclude CB. The attendees suggested using CB in this study since the retrospective data is available. He states that there is a lack of pediatrics data in comparison to adults' data.
iii. Another attendee emphasized the center effect on the analysis, he added that this effect needs to be addressed and explained. He also added the ethics principles in a bias study and that researchers can investigate any scientific questions.
iv. An attendee asked the COG faculty about the statistical power issues in the COG prospective study that investigated TCR αβ vs PTCY vs CB. An Attendee replied that it was difficult to consider the statical power.

v. Dr. Schultz added that the bias in the COG study is a consideration, but waiting for five years to answer the question doesn't seem reasonable when there is rich and retrospective data available. As for the center biased effect, Europe will be biased towards TCR αβ data in compared to PTCY.
vi. A question about the volume of TCR αβ in European database. Dr. Broglie replied that EBMT database has more TCR αβ data than CIBMTR database. Dr. Broglie stated that she wasn't certain of the EBMT data volume at the time.
vii. A question about including GVHD, relapse free survival outcomes. Dr. Li replied that these outcomes are being investigated in the study.
viii. An attendee from Spain emphasized that their center is willing to collaborate by sharing the TCR αβ data with CIBMTR to complete this study.
ix. An attendee added that this is an important question regardless of the fact that this data belongs to a prospective trial. She added that the centers that are using TCR αβ think it is more effective for HCT with haploidentical donors. Then, she added that not every center is able to use TCR αβ, also from statistical standpoint if there is enough sample size to use matched pair analysis, using heterogeneous groups by disease, by DR, by MRD, to compare TCR αβ vs PTCY. She also added that the investigators should consider factors like cost analysis and policies & procedures for initial hospitalization within 100 days.
x. Dr. Li commented that coming from an institution with a limited budget for TCR αβ, this study will contribute to patients' treatment if it shows how TCR αβ is optimal for specific population and not others than these findings.
xi. Dr. Schultz asked the audience about adding CB as a third cohort to this study. The audience were in favor of adding CB cohort.
xii. A question about fertility data collection on CRF forms, Dr. Broglie replied that this data isn't collected at the time.
xiii. Dr. Yanik asked about considering the variation between sites in terms of methodology and infused cell dose when using TCR αβ in stem cell transplant. An attendee confirmed that methodology and infused cell dose are considered.

b. **PROP 2210-120:** Comparison of myeloablative conditioning regimens for acute myeloid leukemia in children and young adults. (Pfeiffer T/Shenoy S).
Dr. Pfeiffer presented the proposal virtually on behalf of the group. The proposal hypothesizes that the optimal conditioning regimen for children with AML undergoing allogeneic hematopoietic cell transplantation (allo-HCT) is subject of ongoing debate. Clinical trials prospectively evaluating different conditioning regimens are lacking. Registry data suggest similar non-relapse mortality (NRM), overall (OS) and relapse-free survival (RFS) for pediatric AML patients receiving busulfan either with cyclophosphamide (Bu/Cy) or fludarabine (Bu/Flu) (1). Total body irradiation (TBI) based regimens were recently shown to result in similar outcomes despite increased toxicity (2). Further improvement of disease control may be achieved through the addition of melphalan and the resultant increase in (leukemic) stem cell toxicity. Indeed, recent European data demonstrate superior outcomes with Bu/Cy/Mel conditioning compared to Bu/Flu and Bu/Cy (3). Additional validation of these data is now needed. We hypothesize that OS and RFS rates may be improved with Bu/Cy/Mel conditioning compared to other Busulfan based myeloablative regimens.
<u>Comments from discussion:</u>

i. A comment about considering the morbidity at 100 days and remembering the effect of Alkylators being high in the analysis. Dr. Pfeiffer thanked the attendee and added that it is a good suggestion to investigate such outcomes, but the data collection forms need to be reviewed to check the availability of this data.

ii. An attendee added that each centers combine the drugs differently and he asked if the data forms collect the time the drug was gives to a patient. Dr. Broglie replied that the data forms collect the drug combination but not the time a drug was given. The attendee added that this is a limitation to the study but not a big limitation.
iii. Dr. Yanik asked if the database contains information like Flu/Bu2 vs Flu/Bu4. Dr. Broglie replied that the database provides information on the intended dose and the target.
iv. Dr. Pfeiffer added that is a limitation to the study as it relates to toxicity, and the effect on the analysis.
v. Dr. Broglie asked about considering toxicity between regimens like VOD. Dr. Pfeiffer replied that toxicity is an important outcome to consider and one of the hesitations in deducting this study was toxicity vs Leukemia control and there is not a particular answer to this question, and he added that VOD and other toxicity is something the study team is curious about analyzing.

c. **PROP 2210-217:** Outcomes of children who receive an allogeneic hematopoietic cell transplantation for Juvenile Myelomonocytic Leukemia. (Sharma A/Bhatt N).
Dr. Sharma presented the proposal virtually on behalf of the group. The proposal hypothesizes that the overall and disease-free survival of patients with JMML who undergo allogeneic HCT, especially with HLA-matched sibling donor and myeloablative conditioning with busulfan, cyclophosphamide, and melphalan has improved over time. However, the burden of short-term toxicities and late effects among HCT recipients remains high due to the conditioning intensity.
<u>Comments from discussion:</u>

i. A comment about the population number for JMML is the biggest population the attendee had seen for this disease. He added that the study is too broad for example TBI isn't used for these patients and he wonder if it will be useful to publish such a study in this era. He added that JMML is a rare disease, and it is several different diseases are classified as JMML based on patients' genetic profile; for example, KRAS mutation is easy to transplant while a disease with multiple mutations has dismal outcomes. The attendee added that he doesn't think this data is collected on CIBMTR forms. He referred to Elliot Stevens publication about JMML patients don't go to HCT with pre-transplant remission by molecular basis but the patients that reach remission have better outcomes. Dr. Sharma agreed with attendee that nobody is using TBI these days; and he added that the population can be divided into two cohort by decade. Dr. Sharma addressed the molecular data question, since 47% of the patients have CRF level data and molecular data might by captured by CIBMTR. Then Dr. Sharma asked Dr. Broglie to clarify the data availability, Dr. Broglie replied that CIBMTR database has disease status not MRD status data.
ii. Dr. Schultz asked if the molecular data is available. Dr. Broglie replied that this data is available but may not be consistent. Dr. Schultz also asked the attendee about TBI era vs not TBI era, is that a 10-year range. The attendee confirmed with yes.
iii. Dr. Qayed asked if patients who received TBI should be excluded or divided the population into TBI vs non-TBI. She also asked what the least bias would be.
iv. A comment about published studies did not monitor therapeutic drugs expect for the Japanese study and population numbers were low.
The attendee also recommended that the investigators look at TBI vs non-TBI and the therapeutical drugs monitoring were available or not since that is an effect in morbidity associate with the treatment. His second comment regarding the pre-transplant chemotherapy treatment; he added that the data isn't collected on CIBMTR data forms. He also added that people in the field agree that this is an important factor in the treatment to decrease the size of the disease before transplant. He recommended including such data in the analysis. Dr. Sharma replied that CIBMTR collects the pre-

transplant chemotherapy data; CRF forms collect BCR ABL, KRAS and NRAS, PTPN 11 mutations, that data is collect for at 47% of population.

v. Another comment about including post-transplant drugs in the analysis. Dr. Sharma replied that the team is interested in acute short-terms and late effects outcomes.

vi. Dr. Yanik asked what is the follow up time for late effects. Dr. Sharma replied that analyzing late effect outcomes at 2 years seems reasonable based on pervious CIBMTR studies.

Future/proposed studies to be presented at the CIBMTR Collaborative Working Committee Study Proposals Session

Dr. Qayed reminded the attendees that proposal "**PROP 2210-276**: Comparison of bone marrow and peripheral blood stem cells as graft source in Children undergoing Allogeneic Hematopoietic Stem Cell Transplantation for Hematological malignancies with unmanipulated haploidentical grafts utilizing post-transplant Cyclophosphamide as GvHD prophylaxis. (Srinivasan A/ Krueger J)." was selected to be presented at the Collaborative Session. She also reminded the attendees of the voting logistics.

6. Dropped proposed studies

The committee received the following additional studies proposal, but these proposals were not selected for presentation at the Tandem meeting, for the reason outlined below.

a. **Prop 2209-10:** Feasibility and Outcomes of Third Allogeneic Hematopoietic Cell Transplantation in Individuals with Relapsed or Refractory Acute Leukemia. *Dropped due to overlap with ongoing study.*
b. **PROP 2210-47:** Outcomes of Allogeneic Hematopoietic Cell Transplantation (Allo-HCT) after Blinatumomab Salvage Therapy in Pediatric Patients with Relapsed/Refractory B-cell Lineage Acute Lymphoblastic Leukemia (BL-ALL). *Dropped due to overlap with an ongoing corporate study.*
c. **PROP 2210-102:** Determinants of Outcome for Children with Acute Leukemia or MDS Who Receive a Third or Subsequent Allogeneic Hematopoietic Cell Transplant. *Dropped due to overlap with ongoing study.*
d. **PROP 2210-144:** Determining the Optimal CD34+ Cell Dose and TNC Content in Pediatric Allogeneic Hematopoietic Cell Transplantation Performed for Malignant Diseases. *Dropped due to heterogeneous population.*
e. **PROP 2210-166:** Post-Transplant Clinical Outcomes and Neoplastic Risk in Fanconi Anemia. *Dropped due to overlap with ongoing study.*
f. **PROP 2210-167:** Impact of Epstein Barr virus (EBV) infection on outcomes of allogenic hematopoietic cell transplantation (HCT) for hematologic malignancies. *Dropped due to feasibility, data not collected by CIBMTR.*
g. **PROP 2210-216:** Prognostic Impact of Cytogenetic and Molecular Risk Classification in AML after Hematopoietic Stem Cell Transplant in Pediatrics, Adolescents, and Young Adults. *Dropped due to overlap with a published study.*
h. **PROP 2210-243:** Impact of Sorafenib after Allo-HSCT as prevention of AML relapse in children. *Dropped due to feasibility, data not reliably reported to CIBMTR.*
i. **PROP 2210-281:** Comparison of umbilical cord blood transplants and unmanipulated haploidentical stem cell transplants in children undergoing allogeneic transplant for hematological malignancies. *Dropped due to Overlap with a published study.*

7. Concluding Notes

The meeting was adjourned at 1:35 p.m. After the new proposals were presented, each attendee had the opportunity to vote using the Tandem mobile application or Tandem website. Based on the voting results, current scientific merit, and impact of the studies on the field, the PCWC leadership will determine which studies will move forward as the committee's research portfolio for the upcoming year.

Not for publication or presentation

Working Committee Overview Plan 2023-2024		
Study number and title	**Status**	**Chairs priority**
PC19-02: Does mixed peripheral blood T cell chimerism predict relapse?	Protocol development/ Data file preparation	4
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 development/ Data file preparation	2
PC20-01: Autologous graft cell dose and post-transplant granulocyte colony stimulating factor in post-transplant outcomes among pediatric patients undergoing autologous hematopoietic stem cell transplantation.	Manuscript preparation	1
PC20-02: Germline genetics of pediatric myelodysplastic syndromes.	Sample Typing/ Data file preparation	3
PC22-01: Impact of Graft Versus Host Disease following Allogeneic Hematopoietic Cell Transplantation on Leukemia free survival in Hematologic Malignancies within the pediatric disease Risk Index Risk Stratification.	Protocol development	5
PC22-02: Evaluating predictors of access and outcomes with Hematopoietic Cell Transplantation (HCT) in pediatric and adolescent patients with relapsed/refractory classical Hodgkin Lymphoma (cHL) after treatment on an initial cooperative group clinical trial.	Protocol development	8
PC23-01: Post-transplant Cyclophosphamide vs. TCR αβ/CD19+ deplete approaches for Haploidentical Transplant in pediatric patients with Acute Leukemias and Myelodysplastic Syndrome: A CIBMTR/EBMT collaborative study.	Protocol pending	6
PC23-02: Comparison of bone marrow and peripheral blood stem cells as graft source in Children undergoing Allogeneic Hematopoietic Stem Cell Transplantation for Hematological malignancies with unmanipulated haploidentical grafts utilizing post-transplant Cyclophosphamide as GvHD prophylaxis.	Protocol pending	7