*Not for publication or presentation*

**MINUTES AND OVERVIEW PLAN**
**CIBMTR WORKING COMMITTEE FOR PEDIATRIC CANCER**
**Houston, TX**
**Saturday, February 23, 2019, 12:15 – 2:15 pm**


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


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1. **Introduction**
   *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.*

***Not for publication or presentation***

| 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)** | |
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| *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* |