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

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1. **Introduction**

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

2. **Accrual summary**

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

3. **Presentations, published or submitted papers**

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

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

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

4. Studies in progress

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

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

The full list of active committee studies is below:

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

5. Future/proposed studies

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

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

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

   The CIBMTR identified 295 pediatric and young adult patients on the CRF-level data collection track, and 1,708 patients with TED-level data that underwent autologous HCT for CNS tumors in

the United States between 2000 and 2016. About half of these transplants were done for Medulloblastoma, while the other half were done for other central nervous system tumors. The question of supplemental data was raised, and Dr. Rotz replied that while he does think that the collection of supplemental data would enhance the study, it would be possible to perform the study focusing only on data already in the database. A couple of attendees expressed enthusiasm for the study, but cautioned against trying to collect the supplemental data, as it would be difficult and with uncertain benefit and quality of data. When asked what the key toxicities to capture as part of the study would be, given that the data may be limiting, Dr. Rotz replied that the most important toxicities would be endocrinopathies, subsequent therapy-related neoplasms, and strokes. One attendee remarked that if it is decided that a full registry study isn't feasible for this idea, then perhaps a better approach might be to pursue this effort with a small group of dedicated transplant centers with data from a lot of cases.

b. **PROP 1911-14** Autologous graft cell dose and post-transplant granulocyte colony stimulating factor in post-transplant outcomes among pediatric patients undergoing autologous hematopoietic stem cell transplantation (Tristan Knight; Donna A. Wall; Kanhatai Chiengthong)

Dr. Knight presented the proposal. The objective of the study would be to analyze the effect of the usage of different dosing levels of CD34+ cells for pediatric autologous HCT. Given that children are generally excellent mobilizers, the research question is whether using higher doses of CD34+ cells has any benefit, or even has a detrimental effect on outcomes. The study proposes to do this examination of CD34+ cell doses in children while factoring in the use or non-use of G-CSF post-transplant.

The CIBMTR identified 555 patients on the CRF data track who received autologous HCT for malignancies in the United States from 2008 to 2018, with G-CSF used post-transplant. The vast majority of these cases, roughly 94%, had CD34+ cell dose information available. An attendee asked for a clarification on whether tandem transplants would be excluded. Dr. Knight responded that since a majority of these transplants were for various central nervous system tumors, many of these would be tandem transplants and they would need to be kept. Several attendees, along with the committee leadership, suggested that if the study were to move forward, it would be prudent to limit the inclusion to Neuroblastoma, Medulloblastoma, and other central nervous system tumors, as these diseases make up the majority of cases (~73%). This would significantly reduce disease heterogeneity to strengthen the study.

c. **PROP 1911-200** Outcomes of Adolescents and Young Adults after Allogeneic Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia at Pediatric Versus Adult Centers (Regina M. Myers; Martin S. Tallman)

Dr. Myers presented the proposal. The objective of the study would be to compare the outcomes of adolescent and young adult patients undergoing allogeneic HCT for AML or ALL between those treated at adult centers versus those treated at pediatric transplant centers. Another objective would be to attempt to compare and contrast standard clinical practice guidelines utilized for adolescent and young adult patients transplanted at adult versus pediatric centers to describe how these cases are handled.

The CIBMTR identified 3,000 patients from adult centers and 608 patients from pediatric centers transplanted for AML and with TED-level data. There were 1,322 patients from adult centers and 267 patients from pediatric centers transplanted for AML and with CRF-level data. The CIBMTR also identified 2,611 patients from adult centers and 650 patients from pediatric

centers transplanted for ALL and with TED-level data. There were 989 patients from adult centers and 252 patients from pediatric centers transplanted for ALL and with CRF-level data. The first clarification made was that TED-level data would likely not be sufficient to capture all of the important disease-related data that would be necessary for this study to be a strong one. A few attendees expressed enthusiasm for the idea of the study. However, many attendees cautioned that huge obstacle to performing this study would be that there are many centers that transplant both adult and pediatric patients at the same center and report all of their data to the CIBMTR under the same center code. This could introduce substantial noise into any results, and confidently separating these cases into adult or pediatric centers could be very challenging.

d. **PROP 1911-57/Prop 1911-58** Evaluation of Outcomes following Allogeneic Hematopoietic Cell Transplantation in pediatric patients with high-risk cytogenetic/molecular features in AML: A CIBMTR Analysis (Senthil Velan Bhoopalan; Neel Bhatt; Akshay Sharma)

   Dr. Bhoopalan presented the proposal. The objective of the study would be to examine the clinical characteristics and outcomes of patients undergoing allogeneic HCT for high-risk AML, and to quantify the difference in post-transplant outcomes as compared to those AML patients without high-risk characteristics. An additional objective would be to identify any prognostic factors of importance impacting outcomes for the high-risk AML cases.

   The CIBMTR identified 211 pediatric patients on the CRF track and 527 pediatric patients on the TED track that were transplanted for AML between 2014 and 2018 in the United States, and that had one of the selected cytogenetic or molecular high-risk features. A handful of additional cases could be considered to be added to this number for patients transplanted with therapy-related AML or who underwent transplant outside of first or second complete remission. The main critique of the study raised by several attendees was that while the study could quantify the outcomes for high-risk AML as compared to other AML cases, the numbers of any one specific abnormality would be far too low to have sufficient statistical power to identify the specific abnormalities causing the worst outcomes. The possibility was raised of inquiring whether it would be possible to combine data with EBMT to boost the numbers, but many felt that even doing that would leave nearly all of the groups too small.

e. **PROP 1911-68** Central nervous system monitoring and prophylaxis post transplantation for pediatric leukemia: avoiding toxicities without compromising outcomes (Ellen Fraint; David Loeb; Lisa Wray)

   Dr. Fraint presented the proposal. The objectives of this study would be to describe the current landscape of clinical practice in the United States regarding central nervous system monitoring and prophylaxis following transplant for leukemia in pediatric patients. An additional objective would be to assess the impact of post-transplant prophylactic intrathecal treatment on CNS relapse rates.

   The CIBMTR identified 1,314 patients undergoing allogeneic HCT for ALL in the United States on the CRF track between 2008 and 2018. Among these, only 156 received post-transplant intrathecal chemotherapy for reasons other than relapse. Dr. Fraint clarified that she proposes to send surveys to centers to ask about their current CNS prophylaxis practice guidelines. An attendee pointed out that there was a similar proposal in recent years, and that most centers have moved away from post-transplant CNS prophylactic therapies, and are instead using pre-transplant measures. Multiple commenters cautioned that for this kind of effort, response

rates for surveys like this are often very bad. Multiple attendees worried that among the small number of patients receiving post-transplant CNS prophylaxis, most or all of them would have had a pre-existing risk factor that led to the use of this post-transplant preventative measure. If this were so, this could heavily bias results, and damage the confidence in any findings.

f. **PROP 1911-124** Germline genetics of pediatric myelodysplastic syndromes (MDS) (Jenny Poynter; Logan Spector)

Dr. Angela Smith presented the proposal on behalf of the group of proponents, who were unable to attend the meeting. The objectives of the study would be to use samples from the NMDP Sample Repository to identify genetic susceptibility variants for pediatric MDS. The study would include all recipients of a transplant for MDS between the ages of 0 and 19 at diagnosis of MDS that have an available sample in the repository.

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

6. Dropped proposed studies

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

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

7. Concluding Notes

a. Meeting adjourned at 2:03pm.
b. Voting on proposals.

After the new proposals were presented, each participant in the meeting had an opportunity to rate each proposal using paper ballots. Based on the voting results, current scientific merit, available number of relevant cases, and the impact of the study on the field, the following two studies were accepted to move forward to be added to the committee's active studies:

PROP 1911-14 Autologous graft cell dose and post-transplant granulocyte colony stimulating factor in post-transplant outcomes among pediatric patients undergoing autologous hematopoietic stem cell transplantation (Tristan Knight; Donna A. Wall; Kanhatai Chiengthong)

PROP 1911-124 Germline genetics of pediatric myelodysplastic syndromes (MDS) (Jenny Poynter; Logan Spector)

c. The following proposals were not accepted as studies:

PROP 1911-01 Long-Term Outcomes among Survivors of Primary Central Nervous System Tumors Undergoing Autologous Hematopoietic Cell Transplantation

PROP 1911-200 Outcomes of Adolescents and Young Adults after Allogeneic Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia at Pediatric Versus Adult Centers

PROP 1911-57/Prop 1911-58 Evaluation of Outcomes following Allogeneic Hematopoietic Cell Transplantation in pediatric patients with high-risk cytogenetic/molecular features in AML: A CIBMTR Analysis

PROP 1911-68 Central nervous system monitoring and prophylaxis post transplantation for pediatric leukemia: avoiding toxicities without compromising outcomes

Working Committee Overview Plan for 2020 - 2021							
Study number and title	**Current status**	**Goal with date**	**Total hours to complete**	**Total hours to 2021 goal**	**Hours allocated to 6/30/2020**	**Hours allocated 7/1/2020-6/30/2021**	**Total Hours allocated**
PC18-01: Comparison of TBI vs. Non-TBI based regimens for pediatric acute myeloid leukemia in the modern era	Submitted	Published – July 2020	10	**10**	10	0	10
PC19-01: Validation of the disease risk index in children undergoing alloHCT	Manuscript Preparation	Submitted – July 2020 Published – July 2021	80	**80**	70	10	80
PC19-02: Does mixed peripheral blood T cell chimerism predict relapse?	Protocol Development	Analysis – July 2020 Manuscript Preparation – July 2021	330	**260**	180	80	260
PC19-03: The impact of pre-transplant extramedullary disease on the outcome of allogeneic hematopoietic cell transplantation for Acute Myeloid Leukemia in Children- A combined CIBMTR and EBMT analysis.	Data File Preparation	Analysis – July 2020 Submitted – July 2021	200	**200**	50	150	200

PC20-01: Autologous graft cell dose and post-transplant granulocyte colony stimulating factor in post-transplant outcomes among pediatric patients undergoing autologous hematopoietic stem cell transplantation	Protocol Pending	Draft protocol received – July 2020 Manuscript Preparation – July 2021	330	**260**	0	260	260
PC20-02: Germline genetics of pediatric myelodysplastic syndromes (MDS)	Protocol Pending	Draft protocol received – July 2020 Sample typing – July 2021	340	**10**	0	10	10

Oversight Assignments for Working Committee Leadership (March 2020)

Muna Qayed	**PC18-01**	Comparison of TBI vs Non-TBI based regimens for pediatric AML in the modern era
Kirk Schultz	**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
Gregory Yanik	**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
Kirk Schultz	**PC20-02**	Germline genetics of pediatric myelodysplastic syndromes (MDS)