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MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR NON-MALIGNANT DISEASES
San Antonio, TX
Friday, February 23, 2024, 1:00 – 3:00 PM CT

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Co-Chair:	**George Georges, MD; Fred Hutchinson Cancer Research Center, Seattle, WA; E-mail: ggeorges@fredhutch.org**
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1. Introduction

The Non-Malignant Disease Working Committee (NMWC) met on Friday, February 23, 2024, at 1:05 p.m. Attendees were asked to have their name badges scanned at the front gate for attendance purposes and members attending the meeting virtually will be part of the committee membership roster.
As scientific director of the NMWC, Dr. Kristen Page called the meeting to order and welcomed the attendees on behalf of the working committee leadership.
Dr. Page started the welcome presentation by introducing each member of the working committee leadership. Dr. Page introduced new leadership members of the non-malignant working committee, including incoming chairs Ashish Gupta and Carmen Bonfim. The committee also acknowledged the contributions of outgoing members, George and Andy, who have been with the committee for five years.
Dr. Page also introduced the working committee's new statistician, Yongzi Yu.

Dr. Brian Ball, then walked the audience through the sources of data and the difference between TED and CRF data. Additionally, cellular therapy data is collected and available.
Dr. Ball talked about the CIBMTR's Patient-Reported Outcome (PRO) data collection effort. It collects survey data from HCT/CT patients who have agreed to be contacted by CIBMTR. We are currently collecting data from adult patients at 17 partnering centers, with plans to expand to pediatric patients in the future.

Dr. Page shared that there are publicly available datasets for secondary analysis on the organization's website, including those specifically from the Non-Malignant Diseases Working Committee, and highlighted the website as a resource for additional information on the committee. Dr. Page then shared with the audience the new initiative called CIBMTR Working Committee Training and Leadership (CTL)

Program. The program is offered to early career investigators who are interested in expanding their observational research skills as well as gaining exposure to CIBMTR and its Working Committee study portfolios.

Dr. George Georges shared the goals, limitations, and expectations of the committee, the rules for working committee membership and the rules of authorship. Dr. Georges emphasized all in person attendees that had the name badges scanned at the front gate for attendance purposes and members attending the meeting virtually will be part of the committee membership roster.

2. Accrual summary

Dr. Andrew Gennery presented the accruals summary. In non-malignant diseases, the highest accrual is in acquired aplastic anemia, followed by primary immune deficiencies, hemoglobinopathies, and bone marrow failure syndrome. Most patients with inherited bone marrow are under Fanconi Anemia, with half of the patients having CRF data available. Sickle Cell Anemia, Thalassemia, and Beta Thalassemia comprised the majority of patients with hemoglobinopathies. In metabolic diseases, Hurler Syndrome, Osteopetrosis, MLD, and ALD have the highest proportions with high percentages on the CRF track. Among histiocytic diseases, the highest accrual is familial HLH. In Immune Deficiencies, the highest proportions are in SCID and CGD.

3. Presentations, Published or Submitted Papers

Dr. George Georges provided updates on the committee. The two committee publications from 2023 are below:

a. **NM16-03b:** Gale RP, Hinterberger W, Young NS, Gennery AR, Dvorak CC, Hebert KM, Heim M, Broglie L, Eapen M. What causes aplastic anaemia? ***Leukemia. 2023 Jun 1; 37(6):1191-1193. doi:10.1038/s41375-023-01892-2. Epub 2023 Apr 27. PMC10353698.***

b. **NM19-01:** Nakamura R, Patel BA, Kim S, Wong FL, Armenian SH, Groarke EM, Kessler DA, Hebert KM, Heim M, Eapen M, Young NS. Conditional survival and standardized mortality ratios of patients with severe aplastic anemia surviving at least one year after hematopoietic cell transplantation or immunosuppressive therapy. ***Haematologica. 2023 Dec 1; 108(12):3298-3307. doi:10.3324/haematol.2023.282781. Epub 2023 Jun 1. PMC10690917.***

4. Studies in progress

Dr. George Georges shared the studies in progress including two manuscripts in progress and other ongoing studies in protocol development. The following is the full list of the current status of the active committee studies:

a. **NM15-01:** Outcome of Allogeneic Hematopoietic Cell Transplant in Erythropoietic Porphyria (A Saad/ H Abdel-Azim/ J Bloomer) **Manuscript Preparation.**
b. **NM17-01:** Late effects after hematopoietic stem cell transplantation in patients with HLH (A Horne/ KS Baker/ K Beutel) **Protocol Development.**
c. **NM18-01:** Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease (A Prakash/ D Wall/ K Paulson) **Protocol Development.**
d. **NM20-01:** Hematopoietic stem cell transplantation for Fanconi anemia (S Rotz/ H Eissa) **Manuscript Preparation.**
e. **AC18-02:** Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis (G Georges/ K Sullivan) **Manuscript Preparation.**

f. **NM22-01:** Outcomes after second or greater allogeneic stem cell transplants in patients with severe aplastic anemia: A contemporary analysis. **Protocol Development.**

g. **NM23-01:** Impact of conditioning intensity and donor type on outcomes in patients with severe aplastic anemia undergoing upfront or salvage hematopoietic stem cell transplant. **Protocol Development.**

5. Future/proposed studies

Dr. Kasiani Myers introduced the five proposals that were presented. Dr. Myers emphasized that each proposal had 5 minutes for presentation and ~10 minutes for discussion. Dr. Myers outlined the voting process for the attendees, explaining that voting should be based both on scientific impact and feasibility using the CIBMTR data.

a. **PROP 2309-09:** Outcomes of second allogeneic-HSCT for graft failure in patients with inherited bone marrow failure syndromes (J Koo/ A Sabulski)
The proposal was presented by Dr. Anthony Sabulski. The objective is to evaluate outcomes of children or adults with IBMFS who completed second allogeneic HSCT for primary or secondary graft failure.
   1. *A question was made that DKC and FA are 2/3 of the patients, how to divide the patients? Those questions highlighted the suggestion to consider dividing the data into two manuscripts, DKC and FA, and rest of other disease. However, there are comments made that we need to be cautious in these disorders because it is FA and approaches in Europe and US are different.*
   2. *A comment was made that if we want to have a good data, we need to join the EBMT and CIBMTR. There was a second transplant outcome in FA patients and published the data. There was a good paper about cause of death in the patients who underwent a second transplant was another graft failure event.*
   3. *A comment was made that CIBMTR does not have data on donor-specific antibodies. Dr. Page commented that she does not believe so for this disease, but we do collect it for other diseases.*

b. **PROP 2309-12:** A comparative study of the use of myeloablative or reduced-intensity/non-myeloablative conditioning regimens in hematopoietic stem cell transplant outcomes for the treatment of Telomere Biology Disorders (J Koo/ K Myers)
The proposal was presented by Dr. Jane Koo. The objective is to describe and evaluate outcomes of children and adults with TBD undergoing HSCT (OS, EFS, GVHD) comparing myeloablative and reduced intensity/non-myeloablative regimens.
   1. *A question was made that there are 60 patients had received their transplant with myeloablative conditioning. It speculated that these patients could be older. Dr. Georges explained that 68% of myeloablative patients were between 2010 and 2021 and they may be the MDS AML patients.*
   2. *A recommendation was made to look at chimerism as an outcome since we do not know the implications of having mixed chimerism in the long term. Dr. Page added that chimerism data will be restricted to CRF so there is only a subset of patients with chimerism.*
   3. *Does CIBMTR collect the gene defects data from 2000 to 2010? Dr. Page commented that we rely on center to report data correctly. We can send query to center to ask for more information about genetic testing to show the mutation. But it requires some time and not fully sure we can get the center of data.*

4. *How to define TBD for this study? Dr. Koo explained that there are some specific questions on CRF forms, such as do they have a genetically defined mutation? And questions like telomere length.*
5. *Why there are few numbers of patients in accruals for DC? Dr. Page explained that because Dr. Broglie and statistician added patients from other specify category for DKC patients.*
6. *A comment was made that the conditioning regimen classification should be reconsidered like separate RIC and non-myeloablative. Dr. Page added that CIBMTR will clean the date and make sure the assignment is appropriate for the study in terms of conditioning regimen.*

c. **PROP 2310-143:** Outcomes of allogeneic stem cell transplant for Hurler's syndrome in a contemporary era: Analyzing the Impact of conditioning regimens (H Rangarajan/ RA Arja/ J Kurtzberg/ P Satwani)

The proposal was presented by Hema Rangarajan. The objective is to estimate the 2-year OS of patients with HS who have received BuCY vs BuFlu-based conditioning regimens for allogeneic HCT.

1. *A comment was made that it should restrict the population to 2010 onwards and combing with European data.*
2. *Does CIBMTR collect PK data because it can make a difference related to graft failure? Dr. Rangarajan replied that there are some data but not sure about the amount of it.*
3. *Does the study collect enzyme data? Dr. Page commented that CIBMTR do collect the patient enzyme level, but only half of the patients have those CRF data.*
4. *Can CIBMTR provide some guides for regiments? Dr. Page responded that CIBMTR will have the planned conditioning regimen. But we will not make too many changes. We may not define a conditioning regimen that has the outcome of optimal enzyme or chimerism since it requires too much registry data.*
5. *A comment was made that newborn younger than 6 months should be selected.*

d. **PROP 2310-205:** Impact of somatic mutations in aplastic anemia (AA) after allogeneic stem cell transplantation (B Ball)

The proposal was presented by Dr. Brian Ball. The objective is to determine the impact of CH, CH variant allele fraction ≥ 10%, and CH number of mutations on OS after alloHCT in adult patients with AA and determine the impact of AA unfavorable mutations on OS after alloHCT in adult patients with AA.

1. *Does the study have any funding? Dr. Brian and his collaborators replied that yes they have funding support with several organizations such as AAMDSIF, Leukemia Research Foundation, NHLBI.*
2. *A comment was made that concerns about the challenges of interpreting data from patients dating back to 2000 due to changes in diagnosis methods.*
3. *A suggestion was made that considering collaboration with the NIH, which has a larger patient population and longitudinal data.*

e. **PROP 2310-213/2310-255:** Comparison of Haploidentical Donor transplantation using post-transplant cyclophosphamide platform versus Matched Unrelated Donor transplantation in Severe Aplastic Anemia patients who lack a Matched Sibling Donor (Revision 1) / Assess impact of Post Transplant Cyclophosphamide as GVHD prophylaxis in aplastic anemia (N Khaire/ R Kumar/L Gowda/ S Mirza)
The *proposal was presented by Dr. Niranjan Carey. The research team wants to answer those research questions: Outcomes of PTCY based SCT across donor types in real world setting (Haplo, MUD, MMUD)? Does PTCY make Haplo donor comparable to MUD? Does PTCY make MUD and MMUD SCT even safer that conventional SCT?*

1. *A question was asked about PTCY and non PTCY for haplo in table since the overall percentage is over 100%. Dr. Niranjan replied that that the percentage should be 73.7% instead of 83.1%.*
2. *A question was asked about whether to make a comparison for the earlier versus later since the tbi dosing is now recommended to 400? Dr. Niranjan replied that current table don't have the exact breakdown of the conditioning.*
3. *A question was asked about are you planning to report whether they were transplanted for relapsed versus refractory? Dr. Niranjan replied that yes, 25% of more than 40 years will be refractory, so we hope that data is available.*

6. Dropped proposed studies

a. **PROP 2309-06:** The impact of Transplant Conditioning Intensity (TCI) score on the prognosis of allogeneic hematopoietic cell transplantation for aplastic anemia and Fanconi anemia in children. *Dropped due to overlap with current ongoing study (NM 23-01).*

b. **PROP 2310-26:** Second transplantations for severe aplastic anemia. *Dropped due to overlap with current ongoing study (NM 22-01).*

c. **PROP 2310-90:** HSCT for DADA2 - Real World Experience from the CIBMTR. *Dropped due to low sample size.*

d. **PROP 2310-88:** Allogeneic Hematopoietic Stem Cell Transplant in non-SCID Rare Inborn Errors of Immunity: Leukocyte Adhesion Deficiency (LAD) Type I and III and Cartilage Hair Hypoplasia (CHH).
Dropped due to recent EBMT publication of LAD.

e. **PROP 2310-109:** Outcomes following Allogeneic Hematopoietic Stem Cell Transplant in patients with hemophagocytic lymphohistiocytosis (HLH) and oculocutaneous manifestations (Chediak Higashi Syndrome and Griscelli syndrome). *Dropped due to low sample size.*

f. **PROP 2310-126:** Pain and Physical Function post-HCT for SCD. *Dropped due to low sample size and only recent addition of questions to capture chronic pain on recent forms.*

7. Concluding Notes

a. Meeting adjourned at 2:20pm.

b. After the new proposals were presented, each participant in the meeting had an opportunity to score each proposal electronically using the Tandem app or website. Based on the voting results, current scientific merit, available number of relevant cases, and the impact of the study on the field, the following proposal was accepted to move forward to be added to the committee's active studies:

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1. ***PROP 2310-213/2310-255 and PROP 2310-205:*** *The outcomes of PTCY based GVHD prophylaxis for allogeneic stem cell transplantation in patients with severe aplastic anemia patients who lack a HLA-matched sibling donor*
    a) *We had ranked this along with the other SAA study as 1a/1b. We discussed combining the two studies since the other one is dependent on funding.*
2. ***PROP 2309-12****: A comparative study of the use of myeloablative or reduced-intensity/non-myeloablative conditioning regimens in hematopoietic stem cell transplant outcomes for the treatment of Telomere Biology Disorders*
    b) *This we had tentatively ranked #2*

The following proposals were not accepted as studies:

3. ***PROP 2309-09:*** *Outcomes of second allogeneic-HSCT for graft failure in patients with inherited bone marrow failure syndromes*
4. ***PROP 2309-143:*** *Outcomes of allogeneic stem cell transplant for Hurler's syndrome in a contemporary era: Analyzing the impact of conditioning regimens.*

Working Committee Overview Plan 2024-2025		
Study Number and Title	**Current Status**	**Chairs Priority**
NM15-01: Outcome of allogeneic Hematopoietic CellTransplant (HCT) in Erythropoietic Porphyria	Manuscript Preparation	**3**
NM17-01: Late effects after hematopoietic stem celltransplantation in patients with HLH	Protocol Development	**3**
NM18-01: Impact of choice of serotherapy in pediatricstem cell transplantation for non-malignant disease	Protocol Development	**2**
AC18-02: Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for SystemicSclerosis	Manuscript Preparation	**1**
NM20-01: Hematopoietic Stem Cell Transplantation forFanconi anemia	Manuscript Preparation	**2**
NM22-01: Outcomes After Second or Greater AllogeneicStem Cell Transplants in Patients with Severe Aplastic Anemia: A Contemporary Analysis	Protocol Development	**2**
NM23-01: Impact of conditioning intensity and donor type on outcomes in patients with severe aplastic anemia undergoing upfront or salvage hematopoietic stem cell transplant	Protocol Development	**3**