Not for publication or presentation

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR NON-MALIGNANT DISEASES
Orlando, Florida
Wednesday, February 15, 2023, 1:00 p.m. – 3:00 p.m. (EST)

Co-Chair:	**Christopher Dvorak, MD, University of California San Francisco Medical Center, San Francisco, CA;** **E-mail: christopher.dvorak@ucsf.edu**
Co-Chair:	**George Georges, MD, Fred Hutchinson Cancer Research Center, Seattle, WA;** **E-mail: ggeorges@fredhutch.org**
Co-Chair:	**Andrew Gennery, MD, Newcastle General Hospital / The Royal Victoria Infirmary, Newcastle, UK;** **E-mail: andrew.gennery@newcastle.ac.uk**
Scientific Director:	**Larisa Broglie, MD, MS, CIBMTR Statistical Center, Milwaukee, WI;** **E-mail: lbroglie@mcw.edu**
Statistical Director:	**Soyoung Kim, PhD, CIBMTR Statistical Center, Milwaukee, WI;** **E-mail: skim@mcw.edu**
Statistician:	**Charimar Santiago Parilla, MPH, CIBMTR Statistical Center, Milwaukee, WI;** **E-mail: csantiago@mcw.edu**

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1. Introduction

a. ***Minutes from February 2022 TCT Working Committee Session*** *(Attachment 1)*

The Non-Malignant Disease Working Committee (NMWC) met on Wednesday, February 15, 2023, at 1:03 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. Larisa Broglie called the meeting to order and welcomed the attendees on behalf of the working committee leadership.

Dr. Broglie started the welcome presentation by introducing each member of the working committee leadership. Dr. Broglie also introduced the working committee's new statistician, Charimar Santiago, and the other working committee leadership, which have not changed since last year. Dr. Broglie acknowledged Dr. Christopher Dvorak for all his effort during the past years as Co-Chair and introduced Dr. Kasiani Myers as the newly appointed Chair for the Working Committee starting March 1, 2023.

Dr. Broglie, 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. Broglie 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. Larisa Broglie 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. Broglie 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 (Attachment 2)

Dr. Georges 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. Others have low numbers such as autoimmune diseases. It is expected that in the following years, this number will grow. Among patients with aplastic anemia, a large number have CRF forms completed, thus more granular data is available. Most patients with inherited bone marrow are under Fanconi Anemia, with half of the patients having CRF data available. Sickle Cell Anemia, 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, with a smaller contribution of the other causes. In Immune Deficiencies, the highest proportions are in SCID and CGD. Dr. Georges then turned the floor over to Dr. Andrew Gennery who explained the process for new working committee leadership.

3. Presentations, Published or Submitted Papers

Dr. Gennery provided updates on the committee. The two committee publications from 2021 and two submitted papers are listed below:

a. **NM16-03** Results of transplants from genetically-identical twin donors in persons with aplastic anemia (RP Gale) ***Submitted*.**
b. **NM19-01** Conditional and cause-specific mortality of patients with severe aplastic anemia surviving at least one year after alloHCT or immunosuppressive therapy (R Nakamura/FL Wong/S Armenian) ***Submitted.***
c. **NM19-02** Marsh RA, Hebert K, Kim S, Dvorak CC, Aquino V, Baker KS, Chellapandian D, Saldana BD, Duncan C, Eckrich MJ, Georges GE, Olson TS, Pulsipher MA, Shenoy S, Stenger E, Lugt MV, Yu LC, Gennery A, Eapen M. A comparison of hematopoietic cell transplant conditioning regimens for hemophagocytic lymphohistiocytosis disorders. ***Journal of Allergy and Clinical Immunology. doi:10.1016/j.jaci.2021.07.031. Epub 2021 Aug 7.***
d. **NM19-03** Cancio M, Hebert K, Kim S, Aljurf M, Olson T, Anderson E, Burroughs L, Vatsayan A, Myers K, Hashem H, Hanna R, Horn B, Prestidge T, Boelens JJ, Boulad F, Eapen M. Outcomes in hematopoietic stem cell transplantation for congenital amegakaryocytic thrombocytopenia. ***Transplantation and Cellular Therapy. doi:10.1016/j.jtct.2021.10.009. Epub 2021 Oct 17.***

4. Studies in progress (Attachment 3)

Dr. Gennery shared the studies in progress including two manuscripts in progress and other ongoing studies in protocol development or data file preparation. 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) **Data File Preparation.**
d. **NM20-01** Hematopoietic stem cell transplantation for Fanconi anemia (S Rotz/ H Eissa) **Data File 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 (H Rangarajan/P Satwani) **Protocol Development.**

5. Future/proposed studies

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

a. **2205-02** Allogeneic Bone Marrow Transplantation for Metachromatic Leukodystrophy (MLD) (E Ayala) (Attachment 4)

The proposal was presented by Dr. Ernesto Ayala. The objective of this study is to examine the results of AlloHCT in the treatment of MLD in a modern cohort. The CIBMTR identified 87 patients who underwent an HCT for Metachromatic Leukodystrophy (MLD) 2008-*2019. The following questions were answered during the Q&A:*

I. *A comment was made that there's a center that has a group focusing on MLD, it's crucial to have that neurological outcome data. This center does extensive neuro-psych testing, both before and after transplant. And just having survival really won't be that impactful in the field. These are very challenging patients to transplant. There are three types, and they can present with different degrees of neurological decline before the transplant. Would this study lend to the body of information that's already known about an MLD?*
II. *Dr. Broglie commented that there are a few questions on the forms about MRI findings and certain neurologic testing that has been done and didn't know how reliably these questions have been answered. These questions are on the CRF forms, and we have only 41 patients that would potentially have that information available.*
III. *A comment was made that this study may be important because gene therapy will be coming for these diseases. CIBMTR might be able to provide what has happened so far and how does it compare with upcoming gene therapy options. The commenter thought it would be doable from a neurological standpoint, and it may form a platform for comparison later.*
IV. *Dr. Gennery commented that Gene therapy is here. This is a rare condition and there were probably not many centers that are looking after these patients. It's worth thinking about talking to EBMT, because there'll be a population of patients in Europe*

as well. And that will just give you more patients and therefore, a greater chance of being able to answer the questions you're asking.

V. *I think this is an example of a study that is worst done by CIBMTR in that we don't have the detail that you want to give a meaningful report of whether the intervention was successful or not. You can put two or three centers together and get the best report in a totally way.*

VI. *Dr. Broglie added that if there are any centers that see a lot of these patients and partnering with them to obtain more neurologic data might be a better option than to using the CIBMTR data that is currently available. CIBMTR can always try to supplement information, each transplant center can request data on their own patients back to them. This might be an alternative especially if there's a lot of concern from the group about the neurologic outcomes.*

b. **2210-19/2210-60** Impact of RBC Factors (prior allo-immunization and donor-recipient ABO mismatch) on Outcomes Post-Allogeneic Hematopoietic Stem Cell Transplant in Patients with Hemoglobinopathies (E Elsabbagh / C McKinney /N Shah/H Rangarajan/) (Attachment 5)

The proposal was presented by Dr. Erman Elsabbagh. The primary objective of this study is to determine and compare 2-year EFS based on the presence of RBC alloimmunization and ABO matching between donor and recipient. The CIBMTR identified 1451 patients who underwent an HCT for SCD and TDT between 2008-2019. The following questions were answered during the Q&A:

I. *How will you define the events? Dr.* Elsabbagh responded that the study will use any graft vs host disease or any graft failures as events.

II. *How will the missing alloimmunization data will be handled? Dr. Broglie replied to the number of missing data needs to be considered when choosing the study. The CIBMTR has asked the question for patients but is not always answered on the forms. If the group decide that we want to move the study forward, then CIBMTR will try to go back to the centers to ask them to fill out that form, this process will take time and potentially the N will increase but we anticipate that there's still going to be missing data that we will have to consider in the analysis.*

III. *Is this a CRF data study? Dr. Broglie confirmed this is a CRF-level study.*

IV. *Do the forms collect information about the treatments for alloimmunization? Dr. Broglie replied that CIBMTR does not collect this type of information.*

c. **2210-110/2210-183** Impact of conditioning intensity and donor type on outcomes in patients with severe aplastic anemia undergoing upfront or salvage hematopoietic stem cell transplant (A Rayes/ S Otoukesh/R Nakamura/M Pulsipher) (Attachment 6)

The proposal was presented by Dr. Ahmad Rayes. The principal objective of this study is to examine the 24-month cumulative incidence (CI) of GF and autoimmune cytopenia. 24 month of OS and EFS. The CIBMTR identified 957patients who underwent an HCT for Aplastic Anemia between 2008-2019, The following questions were answered during the Q&A:

I. *Does this study overlap with a previous study published in Blood Advances in 2019? The current proposal is a subset of the patients that were published in 2019. The study proposal presented has a new question but most of the questions that are being asked*

including 8/8 vs 7 /8 mismatched were already published. Dr. Rayes responded that it is true, and that what hasn't been published is an overlook to see if all these centers doing different regimens, how are they comparing to each other in a longer time, and then dissecting early versus modern or contemporary regimens, which happened after 2015.

II. *A comment was made that it's difficult to select patients based on no therapy at all. The proposal has patients that have received cyclosporine, others who have received no ATG, etc. How are you going to select patients without any kind of therapy? What will be the definition of an upfront transplant? Dr. Broglie responded that a way we would have to do it's to look at the three main questions. Was therapy given prior to transplant? Did they receive ATG? And the treatment with cyclosporine? The study will only include patients that said 'no' to each of those questions.*

d. **2210-131** Outcomes of allogeneic hematopoietic stem cell transplant for severe congenital neutropenia (N Gibson/J Oved) (Attachment 7)

The proposal was presented by Dr. Nora Gibson. The objective of this study is to examine how outcomes of HSCT for SCN are impacted by age, donor source, and graft source. The CIBMTR identified 87 patients who underwent an HCT for Kostmann Syndrome between 2008-2019.The following questions were answered during the Q&A:

I. *Dr. Broglie shared additional data of the conditioning regimens: 26 patients received Bu/Cy, 36 received Flu/Bu and other regimens that had less than 10 patients in each.*

II. *Do all these patients presumably not have MDS and AML? Dr. Gibson responded that their understanding of the preliminary data for the 87 patients, their primary indication for transplant was not MDS or AML but SCN.*

III. *A question was made based on the numbers that Dr. Broglie shared. The patients that received Flu/Bu, were they defined as myeloablative? Dr. Broglie replied that the committee did not get a chance to review these numbers and there's probably a mixture within there of myeloablative and reduced intensity. Another question was made, what was the cut-off for Bu/Cy that the study will use for myeloablative vs nonmyeloablative? Dr. Dvorak responded that there's a standard CIBMTR definition for Bu/Cy dose that has been worked through well and CIBMTR knows what the doses are. Dr. Broglie added that CIBMTR should have what will be the planned therapy or their Bu/Cy dosing. The data will have to be reviewed and categorized.*

IV. *A comment was made that there might be an opportunity to collaborate with the severe congenital neutropenia registry because of what one of the things the study would like to conclude is that the transplant would protect from the malignancy risk over the long term.*

V. *Do we collect data on the underlying genetic abnormalities in these patients? Dr. Broglie responded that CIBMTR does not collect information on the mutation leading to severe congenital neutropenia if it is written in the 'other specified' field CIBMTR may have it, but it's not consistent. CIBMTR do have in the instructions that if a patient has MDS or AML, even with this underlying disorder, they fill out the indication for transplant as MDS or AML. These should be non-MDS or AML patients with SCN.*

VI. *Why not include the category of those patients who have or who had evidence of AML or MDS as a variable to see if the outcome is different? Dr. Gibson replied that this could make sense and that the study is primarily looking at SCN.*

VII. *A suggestion was made to have the Flu/Bu separated one way or another from the Bu/Cy, because they're going to end up falling together in the same subcategory.*

e. **2210-236/2210-283** Alternative Donor Choices for Hematopoietic Stem Cell Transplantation (HCT) in Children and Young Adults with Hemophagocytic Lymphohistiocytosis (HLH) and other Immune Dysregulatory Disorders, Non-SCID Primary Immunodeficiency Diseases, and Inherited Bone Marrow Failure disorders (M Lakkaraja/ L Burroughs/ K Scott Baker/ M Pereda/ C Mckinney/ M Verneris) (Attachment 8)

The proposal was presented by Dr. Maria Pereda and Dr. Madhavi Lakkaraja. The objective of this study is to examine Overall Survival at 1-year post-HCT. The CIBMTR identified 612 patients who underwent an HCT for Bone marrow failure syndromes, 439 for Immune dysregulation and HLH and 401 for Non-SCID primary immune deficiencies between 2008-2019. The following questions were answered during the Q&A:

I. *On the first slide, you showed a survey and people voted that they slightly preferred ex vivo T cell depletion Haplo over PTCy Haplo, why are you excluding them? Dr. Broglie replied that CIBMTR doesn't have enough data about alpha beta T cell depletion but has T cell depletion. The alpha beta information was not added until more recent years and the numbers are small.*

II. *A comment was made regarding the heterogeneity of the study. The diseases are so different that one donor source might wash each other out and going up to age 30 doesn't add many numbers but adds a lot of heterogeneity. By the time you've got all the different diseases, all the different donors with potential things going in different directions, not sure this study is going to get a strong answer out of this bucket. Dr. Lakkaraja replied that given that there are such rare non-malignant disorders, maybe they could put them in a combined proposal and maybe have a subgroup analysis that could be informative.*

III. *A comment was made on another issue that could be that just looking at survival may not be enough when some of these diseases may not be fully corrected, by transplant. Do we have data on whether the disease itself and the manifestation of the disease is corrected? Dr. Broglie replied that CIBMTR does not have the data.*

IV. *A comment was received that it's not just the donor source as the GVHD prophylaxis and it's the preoperative therapy, there's been a lot of change in our community about how we're transplanting these patients. When you look at all these aspects, it'd be so noisy to get a measure of the impact of a certain factor.*

V. *A suggestion was made that Fanconi and DKC should be removed because you cannot give PT Cy for those graphs.*

VI. *A suggestion was made to narrow the scope of the study.*

6. Dropped Proposed Studies

a. **2205-01** Impact of Total Body Irradiation (TBI) Dose for Allogeneic Hematopoietic Stem Cell Transplantation in Severe Aplastic Anemia (SAA) *Dropped due to overlap with current BMT-CTN study.*

b. **2209-02** A comparative study of the use of reduced-intensity and myeloabative conditioning regimens in hematopoietic stem cell transplant outcomes for the treatment of Diamond-Blackfan Anemia (DBA) *Dropped due to low sample size.*

c. **2209-14** Trends of Early Mortality Within First Two Years Following Allogeneic Hematopoietic Cell Transplantation in Children and Adolescents with Non-Malignant Disorders. *Dropped due to heterogeneity of diseases.*
d. **2210-05** Sickle cell disease and CD34 positive cell for gene therapy. *Dropped as data not currently collected.*
e. **2210-16** Impact of Donor/Recipient CMV serological status on survival and outcomes post allogeneic hematopoietic cell transplant in patients with hemoglobinopathies. *Dropped due to overlap with recent published study* (*PMID: 31495699).*
f. **2210-122** Evaluation of Allogeneic Hematopoietic Stem Cell Transplantation Outcomes and Prognostic Factors in X-linked lymphoproliferative disease type 1 (XLP1): A CIBMTR Analysis *Dropped due to overlap with recent published study* (*PMID: 34375618).*
g. **2210-151** Identify optimal rabbit ATG (Thymoglobuline) dosing in reduced intensity conditioning HCT to minimize graft failure in severe aplastic anemia: Exposure-response analysis using an established population PK model for rabbit ATG *Dropped due to overlap with recent published study* (*PMID: 28341733).*
h. **2210-210** Outcomes of stem cell transplantation for leukocyte adhesion deficiency and other syndromes of defective neutrophil adhesion. *Dropped due to small sample size.*
i. **2210-221** Analysis of Graft Failure in Hematopoietic Stem Transplants for Sickle Cell Disease. *Dropped due to small sample size.*
j. **2210-239** Long Term Impact of Allogeneic Stem Cell Transplantation on Pulmonary Hypertension and Renal Outcomes in Patients with Sickle Cell Disease. *Dropped due to overlap with current Late Effects Working Committee study.*
k. **2210-240** Post-transplant cyclophosphamide vs. TCR αβ/CD19 deplete Haploidentical Transplant in Non-Malignant Diseases: A Comparative Analysis. *Dropped due to overlap with current EBMT study.*
l. **2210-280 Outcomes** of allogeneic hematopoietic cell transplantation in aplastic anemia with post transplantation cyclophosphamide. *Dropped due to overlap with recent published study* (*PMID: 35907408).*

7. Concluding Notes

a. Meeting adjourned at 2:24 pm.
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:
    a. **2210-110/2210-183** Impact of conditioning intensity and donor type on outcomes in patients with severe aplastic anemia undergoing upfront or salvage hematopoietic stem cell transplant (A Rayes/ S Otoukesh/R Nakamura/M Pulsipher)

c. The following proposals were not accepted as studies, for the reasons specified:
    a. **2205-02** Allogeneic Bone Marrow Transplantation for Metachromatic Leukodystrophy (MLD) (E Ayala). **Dropped due to feasibility and need for supplemental data.**
    b. 2210-19/2210-60 Impact of RBC Factors (prior allo-immunization and donor-recipient ABO mismatch) on Outcomes Post-Allogeneic Hematopoietic Stem Cell Transplant in Patients with Hemoglobinopathies (E Elsabbagh / C McKinney /N Shah/H Rangarajan/). **Dropped due supplemental/additional data needed.**
    c. 2210-131 Outcomes of allogeneic hematopoietic stem cell transplant for severe congenital neutropenia (N Gibson/J Oved). **Dropped due supplemental/additional data needed.**

d. **2210-236/2210-283** Alternative Donor Choices for Hematopoietic Stem Cell Transplantation (HCT) in Children and Young Adults with Hemophagocytic Lymphohistiocytosis (HLH) and other Immune Dysregulatory Disorders, Non-SCID Primary Immunodeficiency Diseases, and Inherited Bone Marrow Failure disorders (M Lakkaraja/ L Burroughs/ K Scott Baker/ M Pereda/ C Mckinney/ M Verneris). **Dropped due to heterogeneity of the population.**

Working Committee Overview Plan 2023-2024		
Study Number and Title	**Current Status**	**Chairs Priority**
NM15-01: Outcome of allogeneic Hematopoietic CellTransplant (HCT) in Erythropoietic Porphyria	Manuscript Preparation	**3**
NM16-03: Results of transplants from genetically- identical twin donors in persons with aplastic anemia	In Press	**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	Data file preparation	**2**
NM19-01: Conditional and cause-specific mortality of patients with severe aplastic anemia surviving at leastone year after alloHCT or immunosuppressive therapy	Submitted Manuscript	**1**
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	Protocol Development	**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 Pending	**3**