Not for publication or presentation

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR NON-MALIGNANT DISEASES
Salt Lake City, UT
Saturday, April 23rd, 2022, 12:15pm – 1:45pm MDT

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: a.r.gennery@ncl.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:	**Michael Heim, MS, CIBMTR Statistical Center, Milwaukee, WI;** **E-mail: miheim@mcw.edu**

---

1. Introduction

The CIBMTR Working Committee for Non-Malignant Diseases met on Saturday, April 23rd, 2022, at 12:15pm. Dr. Larisa Broglie called the meeting to order and welcomed the audience. She introduced herself as the new scientific director for the working committee and shared that Dr. Mary Eapen decided to step away as to focus on the Cure Sickle Cell Initiative. Dr. Broglie also introduced the working committee's new statistician, Michael Heim, and the other working committee leadership which have not changed since last year. Dr. Chris Dvorak then walked the audience through the difference between TED and CRF data. He then shared that there are research datasets available 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. Dvorak shared the goals, limitations, and expectations of the committee, and the rules for working committee membership and study authorship. Lastly, Dr. Dvorak explained the process for new working committee leadership before turning the floor over to Dr. Georges to share updates on accruals.

2. Accrual summary

Dr. Georges presented on the accruals. First, autoimmune diseases, of which the highest accrual is in multiple sclerosis, then scleroderma, and others which have low numbers. He also highlighted the number of cases with and without CRF data. In immune deficiencies the highest accrual is SCID with a high percentage on the CRF track. The rest are quite rare and have low accrual. In histiocytic disorders the highest accrual is FELH. In metabolic diseases each of the diseases is well-represented with high proportions having CRF data. Among all diseases, aplastic anemia has the highest number of cases as

well as a high proportion of CRF data. Red blood cell disorders including thalassemia, sickle cell disease, and Fanconi anemia all have high accrual.

3. Presentations, published or submitted papers

Dr. Larisa Broglie provided updates on the committee. The two committee publications from 2021 and one submitted paper are listed below:

a. **NM16-03:** Results of transplants from genetically-identical twin donors in persons with aplastic anemia (RP Gale) ***Submitted*.**

b. **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.***

c. **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

Dr. Broglie shared the studies in progress including three manuscripts in progress and other ongoing studies in protocol development or data file preparation. Dr. Broglie reminded the audience that collaborative studies with EBMT can take longer than other studies.

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) ***Data File Preparation.***

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. **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) ***Manuscript Preparation.***

e. **NM20-01:** Hematopoietic stem cell transplantation for Fanconi anemia (S Rotz/H Eissa) ***Protocol Development.***

f. **AC18-02:** Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis (G Georges/K Sullivan) ***Manuscript Preparation.***

5. Future/proposed studies

Dr. Larisa 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. **2106-02:** Curability of non-hematologic autoimmune diseases (AID) with allogeneic hematopoietic cell transplantation (HCT) / Outcomes of allogeneic hematopoietic cell translation (HCT) performed for an autoimmune disease (AID) – joint EBMT & CIBMTR study (J Storek)

The proposal was presented by Dr. Jan Storek. The objective of this study is to examine the relapse incidence rate, non-relapse mortality, relapse-free and overall survival of patients undergoing a first allo HCT for an AID. The CIBMTR identified 56 patients who underwent an HCT for AID between 1989-2019, and EBMT has approximately 95 patients that fit the criteria for this study. There has been a recent study published by EBMTR of 128 patients receiving an HCT purely for the AID that demonstrated the efficacy and toxicity of the HCT were both high. The follow questions were answered during the Q&A:

i. *Is there data on the age of disease onset rather than the age at transplant? Teenagers that were transplanted for an AID have likely been sick for awhile and very likely have an underlying monogenetic etiology even if it has not been established. Dr. Storek responded that this would be part of the supplemental data collection, and hopefully since most of the transplants have been done after 2000 genetic analysis will be available in most of the cases.*

ii. *What is the general plan for supplemental data collection, including in terms of funding? Dr. Storek responded that since most cases come from EBMT there is not a need for supplemental funding. Supplemental funding would only be needed for CIBMTR, a minority of cases, and hopefully a government/industry/charitable sponsor would be willing to fund the study.*

iii. *Will we be diluting the study by including many diseases with inadequate numbers for analysis? Also, might we want to narrow the number of questions/objectives as collecting too much data supplementally is difficult and burdensome? Dr. Storek responded that most cases come from their own center, so centers would only have to share a lot of information on a single patient.*

iv. *A suggestion to exclude the cases before 2000 as they are old, there are only a couple cases, and data may be hard to collect. Dr. Storek responded that though that is correct, if we were able to obtain data on these cases and they were still in remission this would be quite informative.*

v. *Are cases scored on their disease status pre-transplant? This is not collected as part of the CIBMTR but would be part of the supplemental data collection and would be important to have.*

vi. *Due to the heterogeneity of the disease cohort, the variety of conditioning regimens and donor sources it seems like it would be difficult to come to any meaningful conclusions.* Dr.

Storek responded that it is true that we would likely not be able to address the factors influencing outcomes for the individual diseases, but even addressing these for all AID would be helpful.

vii. *A suggestion to group the cytopenias as one subgroup.*

viii. *A comment that this study will take a lot of curating and it may be difficult as the patients may be very different. For example, the autoimmune hemolytic anemia cases may undergo multiple transplants. Dr. Storek responded that in general, these cases go to transplant because they are incredibly sick, and we are only taking a spectrum of these disorders. We will be focusing on first transplants.*

ix. *The presentation slides showed that there were 42 cases from EBMT categorized as "other", what are these? Dr. Storek responded that they could fit into the other defined disease categories, we would have to ask centers to share this information.*

x. *How is the preliminary discussion with EBMT, how is this study different from the study published 2-3 years ago? Dr. Storek responded that the prior study did not exclude monogenetic disorders, and this is probably why the study found 4x lower relapse in children versus adults. The two chairs of the EBMT working party have been supportive and there are ongoing discussions about moving forward with an EBMT study.*

b. **2109-15:** Outcomes after second or greater allogeneic hematopoietic stem cell transplant (HCT) in patients with severe aplastic anemia (SAA): a contemporary analysis (H Rangarajan/P Satwani)

Dr. Hemalatha Rangarajan presented the proposal. The objective of the study is to examine 2-year overall survival after a second or greater transplant for SAA. The secondary outcomes include examining neutrophil and platelet engraftment, incidence of graft failure, grades II-IV acute and chronic GVHD, non-relapse mortality, and GVHD-free survival. This would be a contemporary analysis that would include alternative donors as well as matched siblings (prior CIBMTR study included only matched siblings and HCTs were in an earlier era). The CIBMTR identified 492 patients undergoing a second or greater HCT for SAA between 2000-2019. The following questions were answered during the Q&A:

i. *Where do the haplo cases fall under the donor type? Dr. Rangarajan responded under the "other related" category.*

ii. *A suggestion that the hypothesis should be more bold; we should look to see if we should use a haplo donor for a second or greater HCT or use another unrelated. The hypothesis should be that haplos are the same as unrelated donors for a rescue HCT. Also, a recent study from the EBMT showed that BM is safer than PB for aplastic anemia patients, but does this still apply for rescue HCTs? Along these lines, if we increased the year range to 2021, we could capture more cases. Early rejections happen in the first 6 months and allow one year for follow-up.*

iii. *A comment that this is a burning question the community needs to know.*

iv. *Is it possible to look at those that don't go to second transplant, have the trends of using a second HCT in SAA increased in recent years with the use of haplos? Dr. Rangarajan responded maybe look at first HCT with graft failure and look at outcomes, do they go to second transplant, and have they changed in recent eras? Though, this could be a different study.*

v. *A haplo followed by another haplo is not useful? Dr. Rangarajan responded that we will look at the combination of donor for first HCT and donor for second HCT as a variable.*

vi. *Will this include PNH patients? Dr. Rangarajan responded that they are not included.*

vii. *Part of the hypothesis should be in the era of haplos the time to second transplant is quicker. This variable would be included.*

viii. *Is there data on the antibodies? If it is not available, then recipient gender and the relationship of the haplo can be predictive. Dr. Rangarajan responded that we will have to look to see if it is captured and how well it is captured, such as what time period.*

ix. *When there is acute rejection, most providers will intensify the therapy and often add radiation, but one of the challenges is late rejections when the first HCT did not ablate what is happening with aplastic anemia and partial chimerism occurs. If possible, the analysis should compare the first and the second transplant. Did they use the same regimen or intensify? Dr. Rangarajan responded that that is a great point.*

x. *Why are you only selecting patients that survive more than 1 or 2 years, this may not give a good picture of the outcomes as some patients may die before these times? Dr. Rangarajan responded that 2-years of follow up includes those that die before 2 years.*

xi. *Would you review TBI vs non-TBI conditioning? Dr. Rangarajan responded we would have to review the data; it can be looked into.*

c. **2110-118:** Pre-transplant factors associated with survival in older patients transplanted after 1st line of treatment for aplastic anemia (A Prabahran/D Ritchie)

The proposal was presented by Dr. Ashvind Prabahran. The objectives of the study are to evaluate the relationship between pre-transplant factors including recent or active infections, number of lines of prior therapies, use of mismatched donors, time from diagnosis to transplant, and inflammatory biomarkers EASIX and ferritin on overall survival. The CIBMTR identified 273 patients from 2009-2019. The following questions were answered during the Q&A:

i. *Would age be evaluated as discrete or continuous? Dr. Prabahran responded, I imagine discrete.*

ii. *Is there good data on prior immunosuppressive therapies? Please refer to the slides. Data has only been recently collected on eltrombopag.*

iii. *Would we examine just the number of lines of therapies or sequence? Dr. Prabahran responded that date of therapy is collected in some cases, so we could order first, second,*

third lines.

iv. *How will you collect the pre-transplant ferritin and the other measure? Dr. Prabahran responded that ferritin is captured on the CRF and EASIX can be calculated. These may have been added recently.*

v. *There may be patients that have received more than one type of a line of therapy, how will we separate these? It is also important to assess how the patient is coming into transplant, such as organ damage mainly in the ATG/cyclosporine group. Dr. Prabahran responded that we might have to just quantify the number of therapies rather than the types of therapy, and best response prior to transplant should be captured on the CRF. HCT-CI is also captured and can be a measure of comorbidity burden.*

vi. *Is there data on prior transfusions? We can analyze the number of lines of prior transfusions.*

vii. *How many of the subjects never receive therapy? Dr. Prabahran responded that a selection criteria is patients who have had at least one prior line of therapy.*

viii. *Is it worth comparing to those patients who did not have a prior therapy and went directly to HCT? Dr. Prabahran responded that it would be interesting, but we may not have the numbers in this age group.*

d. **2110-137:** Allogeneic hematopoietic cell transplantation for pure red cell aplasia (J Vaughn/B Shaffer)

Dr. John Vaughn presented the proposal virtually. The objectives of the study are to estimate the overall survival of patients receiving an allogeneic HCT for PRCA including a comparison between transplants before and after 2015, non-relapse mortality, and the cumulative incidence of primary engraftment failure, acute and chronic GVHD. The CIBMTR identified 243 congenital and acquired PRCA in the US and Canada from 2000-2019. There is a recent publication from EBMT in 2019 on the outcomes of acquired PRCA and in 2021 in Diamond-Blackfan anemia. The following questions were answered during the Q&A:

i. *Who are the patients with acquired PRCA? Are they post-transplant? Dr. Vaughn responded that those with acquired would not be those who had a prior transplant, they were acquired unrelated and then underwent an HCT.*

ii. *What can we find from the condition regimens used and the status/number of transfusions and iron load? Dr. Vaughn responded that we aren't sure yet as we only have preliminary tables so far, but these data would be good to examine. This granularity of the data is not available and may not be very reliable. It may be worth collecting this supplementally.*

iii. *A comment that in patients referred from outside the number of transfusions is not reliably available, maybe only above or below 50, though this should be good enough.*

6. Dropped proposed studies

The committee received the following additional study proposals, but these proposals were not selected for presentation at the Tandem meeting, for the reasons outlined below:

a. **2109-11:** 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. ***Dropped due to low sample size.***

b. **PROP 2110-09:** Outcomes of allogeneic hematopoietic cell transplantation (HCT) in patients with Histiocytic Disorders. ***Dropped due to low sample size and overlap with recent publications.***

c. **2110-12:** Outcomes of hematopoietic cell transplantation in aplastic anemia with posttransplantation cyclophosphamide. ***Dropped due to overlap with current study in progress BMT-CTN 1502.***

d. **2110-44:** Haploidentical Donor Transplantation for Severe Aplastic Anemia. ***Dropped due to overlap with current study in progress BMT-CTN 1502.***

e. **2110-111:** Impact Of Preexisting RBCs Allo-Antibodies on The Outcome of Hematopoietic Stem Cell Transplantation for Patients with Sickle Cell Disease. ***Dropped due to low sample size/feasibility.***

f. **2110-175:** Outcomes after autologous hematopoietic stem cell transplant with cyclophosphamide and anti-thymocyte globulin (ATG) compared with carmustine, etoposide, cytarabine, and melphalan (BEAM) and ATG conditioning for the treatment of Multiple Sclerosis. ***Dropped due to low sample size.***

g. **2110-198:** 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 study NM19-02.***

h. **2110-252:** 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.***

i. **2110-256:** Impact of Donor/Recipient CMV serological status on survival post allogeneic hematopoietic cell transplant in children with non-malignant disorders. ***Dropped due to heterogeneity of diseases.***

j. **2110-258** Impact of Donor and Recipient ABO incompatibility on Outcomes Post Allogeneic Stem Cell transplantation for Non-malignant Disorders in Children. ***Dropped due to heterogeneity of diseases.***

k. **2110-318:** Sickle cell disease-related symptom changes after allogeneic hematopoietic cell transplantation. ***Dropped due to overlap with recent studies and publications.***

7. Concluding Notes

a. Meeting adjourned at 1:30pm.

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:

2109-15: Outcomes after second or greater allogeneic hematopoietic stem cell transplant (HCT) in patients with severe aplastic anemia (SAA): a contemporary analysis (H Rangarajan/P Satwani)

c. The following proposals were not accepted as studies, for the reasons specified:

2106-02: Curability of non-hematologic autoimmune diseases (AID) with allogeneic hematopoietic cell transplantation (HCT) / Outcomes of allogeneic hematopoietic cell translation (HCT) performed for an autoimmune disease (AID) – joint EBMT & CIBMTR study (J Storek). ***Dropped due to feasibility.***

2110-118: Pre-transplant factors associated with survival in older patients transplanted after 1st line of treatment for aplastic anemia (A Prabahran/D Ritchie). ***Dropped due to feasibility, timing of lines is not well-collected and eltrombopag has only been collected recently.***

2110-137: Allogeneic hematopoietic cell transplantation for pure red cell aplasia (J Vaughn/B Shaffer). ***Dropped due to recent overlapping EBMT publications.***

Not for publication or presentation

Working Committee Overview Plan for 2022-2023		
Study Number and Title	**Current Status**	**Chairs Priority**
NM15-01: Outcome of allogeneic Hematopoietic Cell Transplant (HCT) in Erythropoietic Porphyria	Manuscript Preparation	**3**
NM16-03: Results of transplants from genetically-identical twin donors in persons with aplastic anaemia	Manuscript Preparation	**3**
NM17-01: Late effects after hematopoietic stem cell transplantation in patients with HLH	Protocol Development	**3**
NM18-01: Impact of choice of serotherapy in pediatric stem 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 least one year after alloHCT or immunosuppressive therapy	Manuscript Preparation	**1**
AC18-02: Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis	Manuscript Preparation	**1**
NM20-01: Hematopoietic Stem Cell Transplantation for Fanconi anemia	Protocol Development	**2**
NM22-01: Outcomes After Second or Greater Allogeneic Stem Cell Transplants in Patients with Severe Aplastic Anemia: A Contemporary Analysis	Protocol Pending	**2**

Not for publication or presentation

Working Assignments for Working Committee Leadership (May 2022)

George Georges	**NM16-03:**	Results of transplants from genetically-identical twin donors in persons with aplastic anaemia
	NM19-01:	Conditional and cause-specific mortality of patients with severe aplastic anemia surviving at least one year after alloHCT or immunosuppressive therapy
	AC18-02:	Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis
Christopher Dvorak	**NM15-01:**	Outcome of Allogeneic Hematopoietic Cell Transplant in Erythropoietic Porphyria
	NM17-01:	Late effects after hematopoietic stem cell transplantation in patients with HLH
	NM20-01:	Hematopoietic Stem Cell Transplantation for Fanconi anemia
Andrew Gennery	**NM18-01:**	Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease