Not for publication or presentation

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR PRIMARY IMMUNE DEFICIENCIES, INBORN ERRORS OF METABOLISM AND OTHER NON-MALIGNANT MARROW DISORDERS
Houston, Texas
Friday, February 22, 2019, 12:15pm – 2:15pm

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1. Introduction

The CIBMTR Working Committee for Primary Immune Deficiencies, Inborn Errors of Metabolism and other Non-Malignant Marrow Disorders met on Friday, February 22nd, 2019 at 12:15pm. Dr. Dvorak welcomed the audience and introduced the working committee leadership, reviewed the committee's goals, expectations, and limitations. Dr. Andrew Gennery and Dr. George Georges were introduced as the newest committee chairs. Dr. Jaap-Jan Boelens was thanked for his contributions to the committee as chair as his term as committee chair has concluded. There was a motion to approve the 2018 working committee meeting minutes, and a second. The motion passed. Dr. Dvorak then reviewed the CIBMTR guidelines for committee membership and rules for authorship of studies. The links to additional working committee related information were also provided. Dr. Dvorak also re-emphasized for the committee members that the CIBMTR data is collected on two tracks: the Transplant Essential Data (TED) and the Comprehensive Report Form (CRF), and that it is important to keep in mind that only CRF-level patients have detailed disease-specific data collected, which is often relevant to this committee that studies rare diseases.

Dr. Eapen then explained to the audience that the working committee would be absorbing autoimmune diseases and cellular therapies for non-malignant diseases. Additionally, the Primary Immune Deficiencies, Inborn Errors of Metabolism and other Non-Malignant Marrow Disorders Working Committee, with the addition of the autoimmune diseases, will be renamed the Non-Malignant Diseases Working Committee.

2. Accrual summary (Attachment 2)

The accrual tables were referenced for review but not formally presented in the interest of time.

3. Presentations, published or submitted papers

Dr. Dvorak directed the audience to the working committee materials for information regarding the two committee publications from 2018.

The two committee publications from 2018, 1 publication currently under review, and 2 papers ready for submission are listed below:

a. **NM16-01** Rice C, Eikema DJ, Marsh JCW, Knol C, Hebert K, Putter H, Peterson E, Deeg HJ, Halkes S, Pidala J, Anderlini P, Tischer J, Kroger N, McDonald A, Antin JH, Schaap NP, Hallek M, Einsele H, Mathews V, Kapoor N, Boelens JJ, Mufti GJ, Potter V, Pefault de la Tour R, Eapen M, Dufour C. Allogeneic Hematopoietic Cell Transplantation in Patients Aged 50 Years or Older with Severe Aplastic Anemia. ***Biology of Blood and Marrow Transplantation. 2018 Sep; doi: 10.1016/j.bbmt.2018.08.029. [Epub ahead of print]***

b. **NM16-02** Marsh RA, Hebert KM, Keesler D, Boelens JJ, Dvorak CC, Eckrich MJ, Kapoor N, Parikh S, Eapen M. Practice pattern changes and improvements in hematopoietic cell transplantation for primary immunodeficiencies. ***The Journal of Allergy and Clinical Immunology. 2018 Aug; doi: 10.1016/j.jaci.2018.08.010. [Epub ahead of print]***

c. **NM17-03** Impact of Age, Donor Type, and Conditioning Regimen Intensity on Allogeneic Transplant Outcome for Sickle Cell Disease (Eapen M) **Submitted**

d. **NM17-02** Related and Unrelated Donor Transplantation for β Thalassemia major: Results of an International Survey (C Li/ V Mathews) **Ready for submission**

e. **NM16-04** The effect of conditioning regimen on clinical outcomes of allogeneic hematopoietic cell transplantation in severe aplastic anemia (N Bejanyan/N Kekre/D Weisdorf/J Antin) **Ready for submission**

4. Studies in progress (Attachment 3)

Dr. Kasiani Myers presented the results of the ongoing active study entitled *Outcomes of allogeneic hematopoietic cell transplant in patients with Shwachman diamond syndrome*. One audience member asked whether all of the patients who died of AML following HCT for Schwachman-Diamond had AML prior to the transplant. Dr. Myers responded that they did.

Dr. Eapen presented the results of the ongoing active study entitled *Hematopoietic cell transplantation for congenital neutropenia/kostmann agranulocytosis*. One audience member asked whether the non-significant difference in survival between patients transplanted for primary severe combined neutropenia versus those with leukemia may have been a power issue due to low numbers. Dr. Eapen replied that this does not appear to be the case, as the survival estimates actually look quite similar. Another attendee asked whether there might be an interaction between recipient age and donor type. Dr. Eapen responded that interactions were tested for, and there was no such interaction. A concern was raised that it seemed strange to have grouped patients for analysis with the cutoff point of 4 years. The committee leadership clarified that this was merely a typo, and that the cut point used in the analysis had been 4 months. An attendee asked about the prevalence of graft failure in the cohort, and Dr. Eapen responded that in this population, it would have been the inverse of the survival, which would put graft rejection somewhere around 25%, with some patients going to a second transplant and others dying. An attendee asked whether we know if the patients who were transplanted for primary SCN were resistant to G-CSF and whether this was the reason for going to HCT. The response was that we do not have information on the reason the primary SCN patients proceeded to transplant. Another audience member asked whether starting neutrophil counts pre-transplant were available, however this information was not included in the data sent to CIBMTR by the European SCN registry. A committee member asked whether the mismatched unrelated donors in the population included cord bloods, to which Dr. Eapen clarified that they did include cord bloods, however graft type was not tested for survival differences because of heavy confounding with donor type.

Dr. Vikram Mathews presented the results of the upcoming committee paper entitled *Related and Unrelated Donor Transplantation for β Thalassemia major: Results of an International Survey.* One attendee noted that the related mismatched donors appeared to be performing worse even then the mismatched unrelated donors, and wondered whether the leadership believed this to be a genuine effect. Dr. Mathews replied that while this group was quite small in the current analysis and this effect cannot be definitively proven here, this was in fact consistent with his experience at his center and he suspects that there is something there. Dr. Mathews clarified that most of the mismatched related donors in the study population were parents of the recipients. Another attendee asked whether we know about if the parents who served as donors had previously given blood transfusions to the

recipients, to which the answer was that we do not have that data. Another audience member asked whether there was a clear winner among the conditioning regimens used to treat these patients in the study, and the leadership responded that it was too difficult to declare a winner in terms of regimen because of heavy confounding with recipient age and donor type.

Meeting attendees were directed to the committee materials for more complete details about all of the rest of the committee's current active studies.

The full list of active committee studies are listed below:

a. **AA13-02** Malignancies in patients with fanconi anemia (J Wagner) **Analysis**

b. **ID13-01** Hematopoietic cell transplantation for congenital neutropenia/kostmann agranulocytosis (C Zeidler/S Keogh/J Connelly) **Manuscript Preparation**

c. **NM14-02** Outcomes of allogeneic hematopoietic cell transplant in patients with Shwachman diamond syndrome (K Myers) **Manuscript Preparation**

d. **NM15-01** Outcome of Allogeneic Hematopoietic Cell Transplant in Erythropoietic Porphyria (A Saad/H Abdel-Azim/J Bloomer) **Analysis**

e. **NM16-03** Results of transplants from genetically-identical twin donors in persons with aplastic anemia (RP Gale) **Data File Preparation**

f. **NM17-01** Late effects after hematopoietic stem cell transplantation in patients with HLH (A Horne/KS Baker/K Beutel) **Protocol Development**

g. **NM18-01** Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease (A Prakash/ D Wall/ K Paulson) **Protocol Development**

5. Future/proposed studies

Dr. Boelens 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. **Prop 1811-110** Impact of Reduced Intensity Conditioning on Allogeneic HCT Outcomes for HLH (R Marsh) (Attachment 4)

Dr. Kasiani Myers presented the proposal on behalf of Dr. Rebecca Marsh. The goal of the study will be to compare patients transplanted for HLH using reduced intensity conditioning to those using myeloablative conditioning for any differences in outcomes.

The CIBMTR identified 431 patients transplanted for HLH with myeloablative conditioning, and 366 patients transplanted for HLH with reduced intensity since the year 2005. One attendee asked whether there is available data on the remission status of these patients. The leadership responded that this data would be available only for the subset of patients with CRF data collected, which includes pre-transplant disease status for this disease. Multiple commenters stressed the importance of carefu;lly defining what is meant by reduced intensity conditioning for this study. Dr. Dvorak pointed out that generally for CIBMTR studies, patients with conditioning regimens containing only a single alkylating agent are classified by the dose of the alkylating agent in mg/kg. A few audience members suggested that using exposure would make for a better analysis, and the leadership agreed that this should be considered. Another audience member suggested changing the primary outcome from overall survival to survival with sustained engraftment. A final question was whether these patients had chimerism data collected, to which Dr. Eapen replied that this would only be available in the CRF subset.

b. **Prop 1810-11** Outcomes of allogeneic hematopoietic stem cell transplant in adult patients with history of hemophagocytic lymphohistiocytosis (M Hegazi) (Attachment 5)

Dr. Hamza Hashmi presented the proposal on behalf of Dr. Hegazi's group. The goal of the study will be to examine the prognostic factors and determine the outcomes of adult patients transplanted for HLH.

The CIBMTR identified 119 adult patients transplanted for HLH since the year 2005, for which only 22 have detailed disease-specific data collected on the CRF track. A few attendees pointed out that this proposal covered the same disease as the previous proposal, and that perhaps this overlap meant that this study could simply be done as part of the previous one. However, others argued that the focus of the two studies were inherently different, with one seeking to explore conditioning regimen choices in the younger population of HLH patients and the other seeking to learn anything possible about older HLH patients. One attendee pointed out that with the proposed restriction to patients younger than age 30 in the regimen proposal, there really is only an overlap between patients aged 18-30 between the two proposals. Dr. Arjan Lankester, chair of the corresponding working party of the EBMT, provided an update that there was an active EBMT study already at the manuscript phase studying adult patients transplanted for HLH.

c. **Prop 1811-67** Does mixed chimerism after alloHCT in patients with Fanconi Anemia impact on the eventual outcome? (M Ayas) (Attachment 6)

Dr. Mouhab Ayas presented the proposal. Dr. Ayas explained that his group at King Faisal in Saudi Arabia studied approximately 50 patients transplanted for Fanconi Anemia with mixed chimerism post-transplant, and that the study found no significant difference in survival from fully engrafted patients. Dr. Ayas and his colleagues would be interested in confirming these findings on a broader scale.

The CIBMTR identified 43 patients transplanted for Fanconi Anemia who were confirmed to have mixed chimerism following transplant, since the year 2005. One commenter stated that she had been part of a group that had done a previous study on Fanconi Anemia patients, and that only a very small number of these patients had had mixed chimerism after transplant. As such, there was concern over the small number of mixed chimerism patients that would be available to compare to full donor chimerism patients. A few audience members, as well as the leadership, expressed concern that the chimerism data has a tendency to be inconsistently reported by centers, and that it would also be complicated to ensure that patients with mixed chimerism after transplant ultimately remained as sustained mixed chimerism, rather than failing the graft or recovering.

d. **Prop 1811-94** Conditional and cause-specific mortality of patients with severe aplastic anemia surviving at least one year after alloHCT or immunosuppressive therapy (R Nakamura/ L Wong/ S Armenian) (Attachment 7)

Dr. Nakamura presented the proposal. The goal of the study will be to examine the long-term survival of patients transplanted for severe aplastic anemia who survived at least one year following the transplant, and to compare the conditional survival beyond one year to a separate group of patients with severe aplastic anemia treated with immunosuppressive therapy. The immunosuppressive therapy group would come from the National Heart, Lung, and Blood Institute.

The CIBMTR identified 2,111 patients transplanted for severe aplastic anemia and surviving at least one year since the year 2000. One audience member asked how patients would be addressed who had undergone immunosuppressive therapy first, and then ultimately proceeded to transplant. Dr. Nakamura responded that he thinks that this is indeed the critical question for this study, and that the group would welcome input on this issue. Dr. Nakamura suggested that one possible way to handle this would be to censor patients in the immunosuppressive therapy group at the time of transplant. Others pointed out that a clean approach could be to restrict the study population to only transplant patients with matched sibling donors, as this would still leave a large enough sample size, and it would be reasonable to presume that nearly all of these patients would have gone to transplant as a first-line treatment. Another audience member asked whether time from diagnosis to transplant is captured on the forms, and the leadership confirmed that it is.

e. **Prop 1811-175** Outcomes after Allogeneic Hematopoietic Cell Transplantation in Patients with Griscelli syndrome (P Satwani) (Attachment 8)

Dr. Satwani presented the proposal. The goal of the study will be to examine prognostic factors and describe outcomes for patients undergoing allogeneic transplantation for Griscelli syndrome.

The CIBMTR identified 53 patients transplanted for Griscelli syndrome since the year 2000, of which 24 patients had detailed disease-specific data collected on the CRF track. Of these 53 patients, only 8 were transplanted in the United States. One audience member asked whether this could be a situation where since it is a small number of patients, we could go back and ask centers for CRF-level data if TED data had initially been collected. Dr. Eapen explained that while this could be helpful, it would impose a burden on the transplant centers and that centers are compensated for filling out CRF forms, so collecting this data would require funding. Dr. Lankester was asked whether he knew how many European patients EBMT might be able to contribute to this effort, and Dr. Lankester answered that he could look into that if the study were to proceed.

f. **Prop 1811-180** Hematopoietic Stem Cell Transplantation for Congenital Amegakaryocytic Thrombocytopenia (F Boulad/ M Cancio/ JJ Boelens) (Attachment 9)

Dr. Farid Boulad presented the proposal. The goal of the study will be to explore prognostic factors and describe outcomes in patients undergoing allogeneic transplantation for Congenital Amegakaryocytic Thrombocytopenia (CAMT).

The CIBMTR identified 66 patients transplanted for CAMT in the United States since the year 2000, of which 37 patients have had detailed disease-specific data collected on the CRF track. A few audience members wondered whether it would be possible to combine with EBMT or reach out to the centers to provide a few additional pieces of critical data. Dr. Eapen explained that it would be fairly easy to simply reach out to the centers who contributed patients and ask just a couple of important yes/no questions. One of these questions would be whether or not the diagnosis of CAMT was done via molecular means. The other question would be what was the bone marrow status prior to transplant, for patients who received bone marrow grafts. Another attendee suggested that it would be extremely valuable to include graft failure as an outcome in this study, and also to describe patients who went to a second transplant and their outcomes thereafter. Dr. Eapen confirmed that this was very much possible to add.

6. Dropped proposed studies

The committee received the following additional study proposals, but these proposals were not selected for presentation at the TCT Meeting, for the reasons outlined below.

a. **Prop 1811-14** Post-transplant cyclophosphamide as single agent for GVHD prophylaxis in patients with aplastic anemia undergoing matched-related stem cell transplantation: An observational study
Dropped due to feasibility

b. **Prop 1811-20** Outcomes of allogenic hematopoietic stem cell transplant in pediatric and adult patients with paroxysmal nocturnal hemoglobinuria
Dropped due to existing scientific literature

c. **Prop 1811-29** Outcomes in older patients undergoing HLA-identical sibling allogeneic stem cell transplantation as first line for severe aplastic anemia
Dropped due to overlap with NM16-01

d. **Prop 1811-38** Incidence of mixed chimerism and evaluation of the impact of donor lymphocyte infusion in patients post-transplant for hemoglobinopathies
Dropped due to low sample size

e. **Prop 1811-60** Long term outcome of mixed chimerism in children undergoing allogeneic stem cell transplantation for primary immunodeficiency disorders
Dropped due to overlap with ongoing PIDTC research

f. **Prop 1811-75** Haploidentical alloHCT in pediatric patients with beta thalassemia major; an observational study
Dropped due to overlap with NM17-02

g. **Prop 1811-83** Outcomes post-allogeneic hematopoietic stem cell transplantation in patients with congenital dyserythropoietic anemia
Dropped due to feasibility

h. **Prop 1811-118** Allogeneic hematopoietic stem cell transplantation outcomes for patients with deficiency of adenosine deaminase type 2
Dropped due to feasibility

i. **Prop 1811-127** Retrospective study of the prognostic significance of comorbidities in recipients of allogeneic hematopoietic cell transplantation (alloHCT) for primary immunodeficiency (PID)
Dropped due to overlap with Regimen-related toxicity published study RT07-01b

j. **Prop 1811-131** Impact of non-infectious encephalopathy on outcomes among children undergoing allogeneic hematopoietic stem cell transplant for non-malignant disorders
Dropped due to feasibility

k. **Prop 1811-162** Haplo-identical donor transplants for Thalassemia major
Dropped due to overlap with NM17-02

l. **Prop 1811-166** 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 Late Effects WC active study LE17-01

7 Other Business

a. Meeting adjourned at 1:55pm.

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 three studies were accepted to move forward to be added to the committee's active studies:

Prop 1811-110 Impact of Reduced Intensity Conditioning on Allogeneic HCT Outcomes for HLH (R Marsh)

Prop 1811-94 Conditional and cause-specific mortality of patients with severe aplastic anemia surviving at least one year after alloHCT or immunosuppressive therapy (R Nakamura/ L Wong/ S Armenian/ N Young)

Prop 1811-180 Hematopoietic Stem Cell Transplantation for Congenital Amegakaryocytic Thrombocytopenia (F Boulad/ M Cancio/ JJ Boelens)

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

Prop 1810-11 Outcomes of allogeneic hematopoietic stem cell transplant in adult patients with history of hemophagocytic lymphohistiocytosis
Dropped due to feasibility, as there are too few patients with CRF-level data needed to study this disease in this population in-depth. Also, direct overlap with EBMT completed study.

Prop 1811-67 Does mixed chimerism after alloHCT in patients with Fanconi Anemia impact on the eventual outcome?
Dropped due to feasibility, with too few patients available with mixed chimerism, and difficulty of confirming sustained mixed chimerism with the data that is available.

Prop 1811-175 Outcomes after Allogeneic Hematopoietic Cell Transplantation in Patients with Griscelli Syndrome
Dropped due to feasibility, as there are too few patients with CRF-level data needed to study this disease in this population in-depth.

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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**
AA13-02 Malignancies in patients with Fanconi Anemia	Manuscript preparation	Submission -June 2019	50	**50**	50	5	**55**
ID13-01 HCT for Congenital Neutropenia/Kostmann Agranulocytosis	Manuscript preparation	Submission -June 2019	10	**10**	10	5	**15**
NM14-02 Allo HCT for Shwachman Diamond Syndrome	Manuscript preparation	Submission -June 2019	20	**20**	20	5	**25**
NM15-01 Outcome of allogeneic Hematopoietic Cell Transplant (HCT) in Erythropoietic Porphyria	Analysis	Submission -June 2019	50	**50**	50	5	**55**
NM16-03 Results of transplants from genetically-identical twin donors in persons with aplastic anaemia	Data File Preparation	Analysis -June 2019	150	**40**	40	110	**150**
NM16-04 The effect of conditioning regimen on clinical outcomes of allogeneic transplantation in severe aplastic anemia	Manuscript Preparation	Submitted -April 2019	10	**10**	10	5	**15**
NM17-01 Late effects after hematopoietic stem cell transplantation in patients with HLH	Data collection/ Protocol Develop-ment	Analysis -June 2019	310	**160**	160	150	**310**
NM17-02 Outcomes of HCT for thalassemia major	Manuscript Preparation	Submitted -March 2019	10	**10**	10	5	**15**

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**
NM18-01 Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease	Protocol develop-ment	Data File Prepar-Ation -June 2019	310	**60**	60	250	**310**
NM19-01 Conditional and cause-specific mortality of patients with severe aplastic anemia surviving at least one year after alloHCT or immunosuppressive therapy	Protocol pending	Draft protocol received -June 2019	370	**0**	0	140	**140**
NM19-02 Impact of Reduced Intensity Conditioning on Allogeneic HCT Outcomes for HLH	Protocol pending	Draft protocol received -June 2019	330	**0**	0	100	**100**
NM19-03 Hematopoietic Stem Cell Transplantation for Congenital Amegakaryocytic Thrombocytopenia	Protocol pending	Draft protocol received -June 2019	330	**0**	0	100	**100**
AC18-02 Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis	Protocol pending	Draft protocol received -June 2019	380	**0**	0	150	**150**

Oversight Assignments for Working Committee Leadership (March 2019)

Vikram Mathews	**AA13-02**	Malignancies in patients with fanconi anemia
Andrew Gennery	**ID13-01**	Second and subsequent hematopoietic cell transplants for congenital neutropenia/kostmann agranulocytosis
Christopher Dvorak	**NM14-02**	Outcomes of allogeneic hematopoietic cell transplant in patients with Shwachman diamond syndrome
Andrew Gennery	**NM15-01**	Outcome of Allogeneic Hematopoietic Cell Transplant in Erythropoietic Porphyria
George Georges	**NM16-03**	Results of transplants from genetically-identical twin donors in persons with aplastic anaemia
Andrew Gennery	**NM17-01**	Late effects after hematopoietic stem cell transplantation in patients with HLH
Christopher Dvorak	**NM18-01**	Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease
George Georges	**NM19-01**	Conditional and cause-specific mortality of patients with severe aplastic anemia surviving at least one year after alloHCT or immunosuppressive therapy
Christopher Dvorak	**NM19-02**	Impact of reduced intensity conditioning on allogeneic HCT outcomes for HLH
Vikram Mathews	**NM19-03**	Hematopoietic stem cell transplantation for Congenital Amegakaryocytic Thrombocytopenia
George Georges	**AC18-02**	Prospective Cohort study of Recipients of Autologous Hematopoietic cell Transplant for Systemic Sclerosis