Not for publication or presentation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
Honolulu, Hawaii
Thursday, February 18, 2016, 12:15 – 2:15 pm

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1. Introduction

The CIBMTR Working Committee for Primary Immune Deficiencies, Inborn Errors of Metabolism and other Non-Malignant Disorders met on Thursday, February 18, 2016 at 12:15 pm. Dr. Kapoor welcomed the audience and introduced the working committee leadership and reviewed the committee's goals, expectations, and limitations. The minutes from the 2015 Tandem meeting were approved. Dr. Kapoor then reviewed the CIBMTR guidelines for assigning priority/scientific merit for study proposals, committee membership, and rules of authorship.

2. Accrual Summary

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

3. Presentations, published or submitted papers

The audience was directed to the working committee materials for information on presentations, published, or submitted papers. The committee had 3 publications and 1 submitted paper. These are listed below:

a **AA12-01** Ayas M, Eapen M, Le-Rademacher J, Carreras J, Abdel-Azim H, Alter BP, Anderlini P, Battiwalla M, Bierings M, Buchbinder DK, Bonfim C, Camitta BM, Fasth AL, Gale RP, Lee MA, Lund TC, Myers KC, Olsson RF, Page KM, Prestidge TD, Radhi M, Shah AJ, Schultz KR, Wirk B, Wagner JE, Deeg HJ. Second Allogeneic Hematopoietic Cell Transplantation for Patients with Fanconi Anemia and Bone Marrow Failure. ***Biol Blood Marrow Transplant 2015 Oct;21(10):1790-5***

b. **ID98-05** Orchard PJ, Fasth AL, Le Rademacher J, He W, Boelens JJ, Horwitz EM, Al-Seraihy A, Ayas M,Bonfim CM, Boulad F, Lund T, Buchbinder DK, Kapoor N, O'Brien TA, Perez MA, Veys PA,Eapen M. Hematopoietic stem cell transplantation for infantile osteopetrosis. ***Blood. 2015 Jul 9;126(2):270-6.***

c. **ID99-02** Veys PA, Nanduri V, Baker KS, He W, Bandini G, Biondi A, Dalissier A, Davis JH, Eames GM, Egeler RM, Filipovich AH, Fischer A, Jürgens H, Krance R, Lanino E, Leung WH, Matthes S, Michel G , Orchard PJ, Pieczonka A, Ringdén O, Schlegel PG, Sirvent A, Vettenranta K, Eapen M. Hematopoietic Stem Cell Transplantation for Refractory Langerhans Cell Histiocytosis: Outcome by Intensity of Conditioning. ***Br J Haematol. 2015 Jun;169(5):711-8.***

d. **ID10-02** Gennery A et. al. International study on outcomes of hematopoietic stem cell transplant for DNA DSB repair defects. ***Submitted***

4. Studies in progress

In the interest of time, the audience was directed to check the working committee packet for details on the studies in progress.

5. Future/proposed studies

a. PROP 1505-03/1511-25 Outcomes of allogeneic stem cell transplantation in patients (above 18 years of age or older) with paroxysmal nocturnal hemoglobinuria (PNH): A CIBMTR Analysis (S Ganguly/ P Mehta)

Dr. Parinda Mehta presented the proposal. This study will investigate post-eculizumab era HCT trends for PNH, including number of patients going to transplant, time from diagnosis to transplant, and indications for HCT. It is hypothesized that trends will be similar for other non-malignant disorders, and that HCT outcomes for PNH have improved over time. Additionally, it is hypothesized that prior treatment with eculizumab may play a role in overall outcomes in PNH transplant patients. The primary aim will be to report HCT trends and outcomes for PNH patients transplanted with matched sibling donors or unrelated donors, looking at overall survival, engraftment, and GVHD. The secondary aim will be to identify any covariates that may impact survival following HCT, possibly including age, indication, donor type, conditioning intensity, and treatment with eculizumab.

The CIBMTR identified 22 matched sibling and 49 unrelated donor cases for the transplant period of interest. There were several concerns regarding feasibility and scientific merit: 1) small sample size which will limit the ability to identify factors that may influence outcomes. Some discussion on reporting trends rather than a definitive analysis; 2) require supplemental data collection; 3) unable to distinguish cases of primary PNH (data not collected).

The proposal was not approved.

b. **PROP 1510-18** Outcomes for adults with hemophagocytic lymphohistiocytosis requiring HCT (B Tomlinson)
Dr. Tomlinson presented the proposal. This study will look at adults aged 18 and older with HLH

without clear secondary malignancy (eg. NK-cell and T-cell lymphoma) to describe outcomes following transplantation. It is hypothesized that allo stem cell transplant can be an effective therapy for adults with HLH. There are few studies evaluating outcomes of a specific therapy for HLH in adults, and this study could serve as a potential guide for HSCT as part of the treatment algorithm in adults. The primary aim will be investigating overall survival and disease-free survival in HLH adult patients following HCT, with a secondary aim of looking at treatment related mortality and identification of possible prognostic factors for overall and disease-free survival.

The CIBMTR identified 33 adult patients with HLH who underwent HCT. However, the majority of these cases do not have a disease-specific data collection Form. Further, it was suggested that to restrict the age to 30 years and older, as adults younger than 30 might be too similar to adolescent (15 – 17 years). By restricting age as such, the number of cases drops to 9. Another suggestion was to contact EBMT re: adults with HLH older than 30 years. Although this is an interesting idea, with only 9 patients it is impossible to draw any conclusion. Additionally disease-specific characteristics would require supplemental data collection.

This proposal was not approved.

c. **PROP 1511-09** Clinical course and outcome of allogeneic HCT in Glanzmann thrombasthemia (GT) (S Savasan)

Dr. Savasan presented the proposal. This study will investigate the use of HCT as therapy for GT. It is hypothesized that allogeneic HCT is a safe and successful therapeutic modality in the treatment of GT, even when alternative donors are used. Additionally, it is hypothesized that pre-transplant patient characteristics do not affect allogeneic HCT course and outcome. The primary aim of the study is to determine clinical course and outcomes following transplant in patients with GT. Secondarily, the investigator would like to review the frequency and effect of platelet alloimmunization on the course and outcome of allo HCT in GT patients.

The CIBMTR identified 30 GT cases from 2000-2013. The investigator would like supplemental data to be collected for: 1) type of GT, 2) platelet and PRBC transfusion,3) rFVIIa use, 4) ICU admissions prior to HCT, 5) platelet alloimmunization history, and 6) immunosuppression use before HCT. During the discussion it was recommended that in addition to the above mentioned factors it is important to collect data on the type of GT as HCT is often offered based on GT type.

Although an interesting concept it would require supplemental data collection and the type/quality of data needed may be readily available at the transplant center. Therefore the proposal was not approved.

d. **PROP 1511-13** Allogeneic HCT for primary immune deficiencies (PID): Current patterns of practice and change over the past 10 years (R Marsh)

Dr. Marsh presented the proposal. Since there are no large experiences published to detail outcomes of PID patients treated in the last 10 years in North America or describe possible practice pattern changes with regard to conditioning regimen choices, this study will describe HCT trends in the last 10 years for PID. It is hypothesized that allogeneic HCT practice patterns have changed for patients with PID and that outcomes have improved over the last 10 years. The primary aim will be to describe and compare the choice of conditioning regimen intensity for patients with PIDs treated in the last 10 years to previous decades and examine differences in choice of conditioning regimens among patients with different PIDs. The secondary aim will be to examine the covariates which may impact overall survival of patients with PID's considering disease categories, decade of transplant, conditioning intensity, age, donor/ donor-recipient HLA

match, graft source, GVHD prophylaxis.

The CIBMTR identified ~ 4500 patients with PIDs treated with HCT from 1980 to 2014. There is be variability in patient characteristics between the various PIDs, and that grouping the diseases into broad categories make for a more meaningful analysis.

The NMWC chairs decided to group the diseases as follows:

i. Classical SCID
    1. SCID ADA deficiency
    2. SCID absence of T and B cells
    3. SCID absence of T, normal B cell
    4. Reticular dysgenesis
ii. Leaky SCID
    1. Ommen syndrome
    2. Bare lymphocyte syndrome
    3. CD40 ligand deficiency
iii. Wiskott Aldrich syndrome
iv. Hemophagocytic lymphohistiocytosis
v. Chronic granulomatous disease

Other diseases were excluded due to low numbers.

This proposal was approved and prioritized.

e. **PROP 1511-44** Pulmonary complications of HCT in sickle cell disease (J Dill)

Dr. Eapen presented the proposal. This study will investigate HCT as a treatment modality for SCD, looking at the short and long term complications including pulmonary complications. It is hypothesized that pulmonary complications after HCT in SCD patients are higher with older age, with PFT abnormalities pre-transplant, and with a history of acute chest syndrome pre-transplant. The primary aim is to describe the types of pulmonary complications after HC in the first 100 days, at 1 year post-transplant, and at 2-years post-transplant. The secondary aim is to study the effect of age, pre-HCT PFT, and history of acute chest syndrome on the risk of post-transplant pulmonary complications in addition to known patient and transplant factors that may affect HCT outcomes.

The CIBMTR identified 170 SCD cases from 2002 to 2012 fitting the criteria. Among these patients, 4% developed IPS, 7% required intubation, 1% reported noninfectious pulmonary complications and 1% acute chest syndrome. By 1- and 2-years these complications occur at rate of 1% except for intubation/ventilation which occurred in 2-3%. CIBMTR rely on transplant centers to report data and there is always some concern that specific organ toxicity may be underreported if the event occurred/treated at a site other than the transplant center. Additionally CIBMTR does not collect pre- and post-transplant PFTS. There were discussions on how easy/difficult it would be to obtain PFTs and ascertain that all patients were followed up at the transplant center for the entire 2 years so we are confident all pulmonary events are captured. There was consensus that this is an important question but one best asked / data collected as part of a prospective study.

This proposal was not accepted.

f. **PROP 1511-71** The effect of conditioning regimen on clinical outcomes of allogeneic HCT in severe aplastic anemia (SAA) (N Bejanyan)

Dr. Bejanyan presented the proposal. This study will investigate the effect of conditioning regimen on outcomes of allogeneic HCT in SAA across patient age groups, donor type, and graft sources, as there are no uniformly accepted conditioning regimens. It was hypothesized that clinical outcomes of allogeneic HCT for SAA can be best informed by conditioning regimen. The primary aim will be to examine the effect of conditioning regimen on overall survival, while the secondary aim will be to examine the effect of conditioning regimen on neutrophil and platelet recovery, transplant related mortality, late complications of HCT, and acute and chronic GVHD.

The CIBMTR identified 855 SAA cases from matched related donors and 495 cases from unrelated donors from 2001-2013. Patients with SAA that progressed to MDS or AML prior to HCT were excluded. During discussion, it was suggested that this study be combined with another proposal looking at SAA (**PROP 1512-01)**, but NMWC leadership explained that PROP 1512-01 was limited to adults aged 50 years and older. Additionally, it was mentioned that the investigator should be careful about dose/type of ATG, as there are different types of ATG and may have different effects on survival. Dr. Bejanyan acknowledged this and said that ATG type would be considered when analyzing data. The lack of details on IST pre-HCT is a limitation – almost all URD transplant recipients have received IST but the date, response and # courses are not captured.

This proposal was approved and prioritized.

g. **PROP 1511-82** Second allogeneic HCT for hemoglobin disorders (NR Lalefar)

Dr. Lalefar presented the proposal. This study will investigate second transplants for patients with hemoglobin disorders. It is hypothesized that developing a uniform approach to graft rejection will optimize disease-free survival after HCT for hemoglobin disorders, and that reviewing raft rejection and second transplants in hemoglobin disorders might guide how to select an optimal donor and conditioning regimen for a second transplant. The aims of the study are to determine the rate of graft failure in patients with hemoglobin disorders in HLA identical sibling and alternate donor HCT, to describe pre-transplant and rescue/ second transplant characteristics associated with outcomes, and to evaluate survival, disease-free survival, and functional status.

The CIBMTR identified 26 patients with both first and second transplant information with hemoglobin disorders from 1994 to 2015. The main concern voiced during discussion about this proposal is that it will be hard to draw conclusions by describing 24 patients.

This proposal was not accepted.

h. **PROP 1511-101** Evaluation of the impact of changing clinical profile, transplant conditioning regimens, and stem cell source on clinical outcome in patients with Thalassemia major (V Mathews)

Dr. Mathews presented the proposal. Due to increasing changes in HCT for Thalassemia major over the past 10 years, this study will examine those changes and their impact on HCT outcomes. It is hypothesized that there have been significant changes in the demographic profile of patients with Thalassemia major who underwent an allogeneic HCT over the last 10 years with significant improvement in clinical outcomes related to changes in conditioning regimens and stem cell source and graft type. The primary aim is to describe the demographic profile of patients who underwent an allogeneic HCT over the last 10 years and compare with previously reported historical control, and to evaluate the impact of baseline demographic characteristics on clinical outcomes. The secondary aims are to evaluate the impact of variations in conditioning regimens on clinical outcome, especially impact of a treosulfan based vs conventional busulfan based regimen, and to evaluate the impact of different donor and graft types on clinical outcomes.

The CIBMTR does not have sufficient patient numbers to address the questions posed. Dr. Mathews is in discussion with collaborators in SE Asia so that data at his center and those centers in SE Asia (high volume for thalassemia HCTs) can collaborate. Dr. Mathews will take the lead on discussions and if feasible will submit a revised proposal (including data transfer to CIBMTR) in time for the next Tandem meeting.

i. **PROP 1511-131** Results of transplants from genetically identical twin donors in people with aplastic anemia (RP Gale)

Dr. Gale presented the proposal. This study will be looking at identical twin donors in the setting of aplastic anemia. It is hypothesized that about one-half of cases of aplastic anemia are caused by defective hematopoietic stem or progenitor cells. The primary aim will be to determine the proportion of people with aplastic anemia receiving an infusion of bone marrow or blood cells from a genetically identical twin recover normal bone marrow function after no pre-transplant conditioning, and if this fails, after pre-transplant conditioning. The results will estimate the proportion of cases of aplastic anemia resulting from absent or defective hematopoietic stem or progenitor cells vs other mechanisms such as immune dysfunction.

The CIBMTR identified 88 HCT from genetically identical twin donors. However most had received a conditioning regimen – requires verification re: donor type and whether these patients really received transplant conditioning as indicated. There were concerns from the committee that it may be difficult to tell in patients who received GVHD prophylaxis (cyclosporine) whether the effects are due to HCT or cyclosporine as immunosuppressive agent. Recovery of normal bone marrow function could be donor-derived or self. Additionally, some thought it might make the study more meaningful to add an HLA identical group for comparison of engraftment.

Despite these concerns the proposal received a priority score to proceed.

j. **PROP 1512-01** Combined EBMT/CIBMTR retrospective study of allogeneic stem cell transplant outcomes in older patients (age > 50 years) with severe aplastic anaemia (SAA) (J Marsh)

Dr. Eapen presented the proposal. Due to a lack of data for older patients with SAA, this study will investigate HCT as a treatment modality for older patients with SAA. It is hypothesized that evaluations of outcomes after HCT for SAA in older patients is likely to show improvements over time. The primary aim will be to use combined EMBT and CIBMTR databases to describe outcomes for SAA patients in two age groups (50-59 and ≥60) including survival, graft failure, and GVHD, considering the impact of HCT-CI, performance score, previous IST, donor type, graft source, and conditioning regimen on outcomes.

The CIBMTR identified 358 patients with HLA-matched sibling donors and 317 patients with unrelated donors eligible for the study. There was some confusion from the committee as to why a collaborative study was necessary, given the available numbers. Each registry contributed about 50% of the cases to each donor type and would make for a more robust analysis. Others viewed the study as interesting and relevant, as treatment for older patients with SAA is almost always done without published data and data generated from this study would be of value to BMT physicians.

This proposal was accepted.

k. **PROP 1512-05** Alternative donor HCT for Sickle Cell Disease: an analysis on behalf of Eurocord/Monacord/BMT/CIBMTR (E Gluckman)

Dr. Eapen presented the proposal. HLA-matched siblings are available for a limited number of patients with SCD, so this study will investigate outcomes after alternative donor HCT. It is hypothesized that CB and haploidentical transplants will have a higher frequency of graft failure, while unelated adult donor transplants will have higher GVHD. The primary aim is to compare overall survival for the different donor types. The secondary aim is to compare neutrophil and platelet recovery, graft rejection, GVHD, and disease-free survival between the donor types.

The CIBMTR identified 135 eligible patients, while Eurocord and Monacord identified 36 eligible patients. The major issue with this proposal voiced by the committee is the heterogeneity of donor types and conditioning regimens. Cord blood transplants were the commonest but that has been described including a recent CIBMTR/Eurocord report. As such studying cord blood transplants again was not novel. There were too few haplo-BMTs and techniques were driven by institutions. The unrelated donor transplants used a variety of transplant conditioning regimens and would be difficult to draw any conclusion from the descriptive report.

This proposal was not accepted.

Other business

The committee was interested in knowing when rare diseases will be increased to CRF level data collection. Dr. Eapen explained that due to funding and burden on the centers, there is an algorithmic approach to selecting which cases get CRF level collection. It was suggested that the NMWC create a task force to address the desire for additional data collection. The task force will work to develop a list of 5 to 10 specific diseases that the committee would like to have collected at the CRF level more frequently to help with the committee's studies. From there, Dr. Eapen will present that list to CIBMTR leadership, and if granted approval, the task force will work to develop the disease specific form questions for the newly added rare diseases. Approval from the CIBMTR leadership is not guaranteed. The task force will consist of all three NMWC co-chairs, as well as 3-4 other members of the committee. Those interested in being a part of the task force should email Dr. Eapen.

Adjourned at: 1:54pm

Working Committee Overview Plan for 2016 - 2017

a. **AA13-01** Correlation of levels of donor cell chimerism after alloHCT for hemoglobinopathy (A Abraham). Submit manuscript June 2016.

b. **AA13-02** Malignancies in patients with FA (J Wagner). Submit manuscript June 2016.

c. **ID12-01** Allo HCT for CID/CVID (G Cuvelier/G Guilcher/N Wright). Manuscript preparation by June 2017.

d. **ID13-01** HCT for Congenital Neutropenia/Kostmann Agranulocytosis (J Connelly). Completed date file preparation of transplant data and data integration with Congenital Neutropenia Registry. If the German registry joins study status will be data file preparation. Otherwise submit manuscript September 2016

e. **NM14-01** Outcomes of HCT in boys with X-ALD (R Wynn/J Boelens/P Orchard). Supplemental data collection.

f. **NM14-02** Allo HCT for Shwachman Diamond Syndrome (K Myers). No hours allocated.

g. **NM15-01** Outcome of allogeneic Hematopoietic Cell Transplant (HCT) in Erythropoietic Porphyria (A Saad). Manuscript submission June 2017.

h. **NM16-01** Combined EBMT/CIBMTR retrospective study of allogeneic stem cell transplant outcomes in older patients (age > 50 years) with severe aplastic anemia . Protocol development, data file prep, analysis by June 2017.

i. **NM16-02** Allogeneic transplantation for primary immune deficiencies: Current patterns of practice and change over the past 10 years. Protocol development, data file preparation by January 2017.

j. **NM16-03** Results of transplants from genetically-identical twin donors in persons with aplastic anaemia. Protocol development by June 2017

k. **NM16-04** The effect of conditioning regimen on clinical outcomes of allogeneic transplantation in severe aplastic anemia. Protocol development and data file preparation by June 2017

Oversight Assignments for Working Committee Leadership (March 2015)

Neena Kapoor	**AA13-01**	Correlation of levels of donor cell chimerism with hemoglobinopathy symptoms following allogeneic hematopoietic cell transplantation
Vikram Mathew	**AA13-02**	Malignancies in patients with fanconi anemia
Vikram Mathew	**ID12-01**	Allogeneic hematopoietic cell transplantation for combined immunodeficiency and common variable immunodeficiency
Mary Eapen	**ID13-01**	Second and subsequent hematopoietic cell transplants for congenital neutropenia/kostmann agranulocytosis
Jaap Boelens	**NM14-01**	An investigation of the long term neurological outcomes of Hematopoietic Stem Cell Transplant (HCT) in boys with X-linked Adrenoleukodystrophy
Paolo Anderlini	**NM14-02**	Outcomes of allogeneic hematopoietic cell transplant in patients with Shwachman diamond syndrome
Jaap Boelens	**NM15-01**	Outcome of Allogeneic Hematopoietic Cell Transplant in Erythropoietic Porphyria
Paolo Anderlini	**NM16-01**	Combined EBMT/CIBMTR retrospective study of allogeneic stem cell transplant outcomes in older patients (age > 50 years) with severe aplastic anemia
Neena Kapoor	**NM16-02**	Allogeneic Hematopoietic Cell Transplantation for Primary Immune Deficiencies: Current Patterns of Practice and Change over the last 10 years
Vikram Mathew	**NM16-03**	Results of transplants from genetically-identical twin donors in persons with aplastic anaemia
Jaap Boelens	**NM16-04**	The effect of Conditioning Regimen on Clinical Outcomes of Allogeneic Hematopoietic Cell Transplantation in Severe Aplastic Anemia