Not for publication or presentation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
San Diego, CA
Friday, February 13, 2015, 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 Friday, February 13, 2015 at 12:15 pm. Minutes from the 2014 Tandem meeting in Grapevine, TX were approved. Dr. Kapoor welcomed the audience and introduced the working committee leadership. Drs. Malech and Shenoy were acknowledged for their efforts for the past 5 years.

Dr. Malech reviewed the CIBMTR guidelines for assigning priority/scientific merit for study proposals, and rules of authorship.

2. Accrual Summary

The accrual tables were referenced for review but not formally presented.

3. Presentations, published or submitted papers

Publications for year 2014 were briefly reviewed. The committee had 3 publications and 1 manuscript is under review. These are listed below:

a. **AA10-02** Kim SY, Le Rademacher J, Antin JH, Anderlini P, Ayas M, Battiwalla M, Carreras J, Kurtzberg J, Nakamura R, Eapen M, Deeg HJ. Myelodysplastic syndrome evolving from aplastic anemia treated with immunosuppressive therapy: efficacy of hematopoietic stem cell transplantation. ***Haematologica 2014 Dec;99(12):1868-75.***

b. **ID11-02** Lund TC, Cathey SS, Miller WP, Eapen M, Andreansky M, Dvorak CC, Davis JH, Dalal JD, Devine SM, Eames GM, Ferguson WS, Giller RH, He W, Kurtzberg J, Krance R, Katsanis E, Lewis VA, Sahdev I, Orchard PJ. Outcomes after hematopoietic stem cell transplant for children with I-cell disease. ***Biol Blood Marrow Transplant 2014 Nov;20(11):1847-51.***

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. ***B J Haematol (In press; 2015).***

Presented at the 30th Annual Meeting of the Histiocyte Society, Toronto, Canada. October 2014. Awarded the President's prize (The Nesbit award) for the best clinical presentation.

d. **ID98-05** Orchard PJ, Fasth A, Le Rademacher J, He W, Horwitz E, Boelens JJ, Ayas MF, Al-Seraihy A, Buchbinder D, Bonfim C, Boulad F, O'Brien T, Kapoor N, Diaz Perez MD, Veys P, Eapen M. Hematopoietic stem cell transplantation for osteopetrosis. ***Submitted.***

4. Studies in progress

a. **ID10-02** Outcome of HCT for DNA repair disorders (A Gennery). This is a collaborative study with EBMT. It is in manuscript preparation and anticipated submission by June 2015.

b. **ID11-01** Allo HCT for adrenoleukodystrophy (P Orchard). Submission June 2015.

c. **AA12-01** Outcome of second allogeneic stem cell transplantation in patients with Fanconi anemia (M Ayas). Submission March 2015.

Data files are being prepared for the studies listed below:

d. **AA13-01** Correlation of levels of donor cell chimerism after alloHCT for hemoglobinopathy (A Abraham/M Hsieh/C Fitzhugh/J Tisdale/S Shenoy)

e. **AA13-02** Malignancies in patients with FA (J Wagner/B Alters)

f. **ID13-01** HCT for Congenital Neutropenia (S Keogh/P Shaw/J Levine/J Connelly)

The following two studies are in the stage of data collection.

g. **ID12-01** Allo HCT for CID/CVID (G Cuvelier/G Guilcher/N Wright). Dr. Malech will discuss with the investigators regarding supplemental data collection that was intended to confirm the diagnosis. However, diagnosis of CID/CVID are moving targets in that with better diagnostic tests these patients are now being assigned a proper diagnosis instead of common variable immune deficiency. Therefore It might be best to determine selection criteria based on some of the variables that have been collected by the CIBMTR for those patients for whom the indication for transplant was reported as CID or CVID.

h. **NM14-01** Outcomes of HCT in boys with X-ALD (R Wynn/J Boelens/P Orchard). Dr. Wynn presented a brief update of the study. The study aims to investigate the quality of life of long term survivors of HCT for X-ALD. There are 46 eligible patients from CIBMTR and 93 eligible patients from EBMT. Supplemental data collection form has been developed to study functional status of these patients as adults. Will follow up with Drs Wyn and Boelens regarding the logistics of data collection. Fortunately these transplants were performed at a few centers and most of these centers are motivated to better understand whether transplantation cures these patients to the extend they can function as independent adults.

There is no update for **NM14-02** Allo HCT for Shwachman Diamond Syndrome (K Myers).

5. Future/proposed studies

a. **PROP 1405-02** A decision analysis to determine the optimal timing of unrelated donor marrow transplantation for children, adolescents and young adults with severe aplastic anemia (S Arnold/M Bhatia/J Horan/P Scheinberg/D Townsley/N S Young)

Dr. Staci Arnold presented the proposal. This study will compare treatment strategies for children, adolescents and young adults with severe aplastic anemia and without a HLA-matched family donor, on the basis of discounted quality of life adjusted life expectancy. There will be 3 cohorts: transplantation at diagnosis, transplantation after having failed 1 course of IST and transplantation after having failed two courses of IST. The primary purpose of these analyses is to define the role of transplantation across the groups.

The CIBMTR (based on inclusion criteria per investigators) identified 91 patients; 5 patients proceeded to transplantation without prior IST, the remaining patients had had 1 or more courses of IST. The CIBMTR data collection form only asks whether patients received IST bit not the number of courses or dates of administration. Additional information on IST (number of courses) would require supplemental data collection and not always feasible.

Potential collaboration with NHLBI and the EBMT.

The NHLBI database has 240 patients who received IST for newly diagnosed SAA and 108 patients treated for recurrent or refractory SAA. Among the 108 patients treated with IST for recurrent or refractory SAA there were concerns re: ability to identify these patients in the CIBMTR database in the event some of these patients received transplant outside of the NHLBI. The CIBMTR is unable to share identifiers with others. There was no information available re: data sharing rules regarding the NHLBI database. Further, there was no information available with respect to description of population, timing of IST, duration of follow-up etc.

The investigators had contacted the EBMT and we were told about 20 patients in the EBMT database had received an unrelated donor transplant without prior IST. There was no additional information offered on potentially eligible patients from the EBMT.

Taken together, this proposal poses several challenges:

1. Given the very few numbers of patients who proceeded to unrelated donor transplant without IST, this group will have to be excluded from the analysis.
2. To perform a decision analysis on role of unrelated donor transplantation versus IST we would need a better description of the IST cohort, ability to identify duplicate cases in the

CIBMTR and NHLBI to allow us determine feasibility.
3. No information available on EBMT cases.

Therefore, this study was not approved to proceed to protocol development.

b. **PROP 1408-04** Outcome of allogeneic Hematopoietic Cell Transplant (HCT) in Erythropoietic Porphyria (A Saad)

Dr. Ayman Saad presented the proposal. The proposed study aims to describe the outcome of allogeneic HCT for erythropoietic porphyria (EP). There are 15 eligible patients in CIBMTR database. We will not be able to perform an analysis of prognostic factors as suggested by the investigator – this will be a descriptive study only and will require supplemental data collection: date of diagnosis, ferritin level (or other marker of iron overload), skin photosensitivity, hepatic involvement including pre-transplant liver function test, involvement of other organs, was the patient transfusin dependent, chelation prior to transplant and reason for HCT. Outcomes of interest include: VOD, transfusion dependence, immune suppression at last follow up and chimerism at last follow up. By describing 10-15 patients all we are trying to determine is whether the disease can be cured by transplantation. Of note, 15 patients were reported by 15 centers; 8 center representatives were in attendance at the meeting and eager to facilitate the study. Paul Veys has transplanted 2 cases and should have been reported to CIBMTR via EBMT. As there are delays in data transfer between the EBMT central office and CIBMTR, Dr. Veys will provide his cases separately to CIBMTR.

As this would be the first report on role of transplantation for EP, the proposal was approved to proceed to protocol development.

c. **PROP 1411-09** Risk factors for graft failure in patients with non-malignant conditions receiving alemtuzumab based conditioning regimens

Dr. Prakash Satwani presented the proposal. The study proposed to investigate the incidence of graft failure in pediatric patients who had HCT for non-malignant disorders receiving alemtuzumab based conditioning regimens.

There are 240 potentially eligible patients with a variety of non-malignant / immune / metabolic disorders. The committee members questioned the feasibility of the study based on the following:

1. There isn't a single disease with sufficient numbers; it would be challenging to interpret the results in a group of patients with heterogeneous diseases
2. Although the 240 transplants represent all donor sources, almost 80% are unrelated donors and could have limited the dataset to unrelated donor transplants if there had been at least 1 disease category with a large enough population to study.
3. The timing and alemtuzumab dose was not collected consistently across the time period of interest.

Therefore, this study proposal was not approved to proceed to protocol development.

d. **PROP 1411-16** Effect of recipient age on outcomes after allogeneic HCT in Patients with acquired or inherited bone marrow failure (S Gadalla/B P Alter)

Dr. Shahinaz Gadalla presented the proposal. The proposed study aims to examine the role of

recipient age in outcomes after allogeneic HCT in aplastic anemia with the hypothesis that outcomes after transplantation are age dependent and differ by disease subtypes. Of note, this may be of particular concern for patients with inherited bone marrow failure syndrome as patients with clinical features consistent with aplasia may be treated conservatively rather than referral for transplantation.

The CIBMTR has published a paper (Vikas Gupta et al, Haematologica 2010) on the effect of patient age on outcomes after HLA-matched sibling transplantation for aplastic anemia. A similar study was not undertaken in the setting of unrelated donor transplantation because the CIBMTR does not collect detailed information on number of IST treatments, dates and response to IST. For inherited marrow failure diseases such as Fanconi anemia, CIBMTR forms collect the date of diagnosis but not the date of onset of cytopenia / date of progression to pancytopenia. The CIBMTR forms collect clonal abnormality prior to transplant but not the date of onset of clonal abnormality – all of which makes it challenging to conduct this study without an exhaustive supplemental disease-specific data collection form.

Therefore, this study proposal was not approved to proceed to protocol development.

e. **PROP 1411-29** Outcome after unrelated donor hematopoietic cell transplantation for sickle cell disease (M Bhatia/M Walters/N Kamani)

Dr. Bhatia presented the proposal. The aim of the proposed study is to describe the outcome of unrelated donor HCT in patients with sickle cell disease. There are 31 unrelated bone marrow and 32 unrelated cord blood patients with comprehensive report forms eligible for the study. Reviewing the conditioning regimen for the 31 unrelated donor bone marrow transplants, the regimen is similar to that used for BMTCTN 0601, a 30-35 patient phase II, multi-center trial in the US conducted by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). We anticipate significant overlap with BMT CTN 0601. The results of BMT CTN 0601 will be available in the later half of 2015. Although there are 32 unrelated cord blood patients with comprehensive report forms, published reports suggest graft failure rates are high. The data presented at the working committee meeting suggest patients received two predominant conditioning regimens: busulafan + cyclophosphamide and melphalan + fludarabine. However, the relatively small sample size suggest this will be a descriptive report and unlikely to report anything beyond what is already known. Alternative donor transplantation for sickle cell disease is of great interest but will require several more transplants before one can conduct a study that can begin to address transplantation strategies for this disease.

Therefore, this study proposal was not approved to proceed to protocol development.

f. **PROP 1411-96** Outcome of allogeneic HCT using Busulfan, Fludarabine with or without in vivo T cell Depletion in pediatrics nonmalignant disease apart from immunodeficiency disorders (N Shah/J Dalal/A Pawlowska)

Dr. Niketa Shah presented the proposal. The study aims to evaluate the outcomes of allogeneic HCT in pediatrics using busulfan, fludarabine with or without thymoglobulin or alemtuzumab in nonmalignant diseases excluding immunodeficiency.

There are 115 eligible patients from 5 broad disease groups (N=15 aplastic anemia; N=3 Fanconi

anemia; N=34 thalassemia; N=15 sickle cell disease; N=48 Inborn errors of metabolism). As with PROP 1411-09, the study population is heterogeneous with respect to diseases, donor source and regimen intensity (about 60% received myeloablative doses and 40%, reduced intensity doses of busulfan). These raised concerns regarding feasibility.

Therefore, this study proposal was not approved to proceed to protocol development.

Working Committee Overview Plan for 2015 - 2016

a. **ID10-02** Outcome of HCT for DNA repair disorders (A Gennery). Submit manuscript for peer review June 2015
b. **ID11-01** Allo HCT for adrenoleukodystrophy (P Orchard). Submit manuscript for peer review June 2015
c. **AA12-01** Outcome of second allogeneic stem cell transplantation in patients with Fanconi anemia (M Ayas). Submit manuscript for peer review March 2015
d. **AA13-01** Correlation of levels of donor cell chimerism after alloHCT for hemoglobinopathy (A Abraham). Submit manuscript for peer review before June 2016.
e. **AA13-02** Malignancies in patients with FA (J Wagner). Submit manuscript for peer-review before June 2016.
f. **ID12-01** Allo HCT for CID/CVID (G Cuvelier/G Guilcher/N Wright). Manuscript preparation by Dec 2015.
g. **ID13-01** HCT for Congenital Neutropenia/Kostmann Agranulocytosis (S Keogh/P Shaw/J Levine/J Connelly). Completing date file preparation of transplant data and data integration with Congenital Neutropenia Registry by June 2015.
h. **NM14-01** Outcomes of HCT in boys with X-ALD (R Wynn/J Boelens/P Orchard) Supplemental data collection.
i. **NM14-02** Allo HCT for Shwachman Diamond Syndrome (K Myers). Completing protocol development and data file preparation by Dec 2015.
j. **NM15-01** Outcome of allogeneic Hematopoietic Cell Transplant (HCT) in Erythropoietic Porphyria (A Saad). Case ascertainment and supplemental data collection by June 2015, manuscript preparation by Dec 2015.

Oversight Assignments for Working Committee Leadership (March 2015)	
Mary Eapen	**ID11-01** Allo HCT for adrenoleukodystrophy
	AA13-02 Malignancies in patients with FA
	ID13-01 HCT for Congenital Neutropenia/Kostmann Agranulocytosis
	NM15-01 Outcome of allogeneic HCT in Erythropoietic Porphyria
Shalini Shenoy	**AA13-01** Correlation of levels of donor cell chimerism after alloHCT for hemoglobinopathy
Jaap J Boelens	**NM14-01** Long-term neurological outcomes of allogeneic transplantation for X-linked adrenoleukodystrophy
	ID10-02 Outcome of HCT for DNA repair disorders
Harry Malech	**ID12-01:** Hematopoietic cell transplantation for common variable immunodeficiency
Paolo Anderlini	**NM14-02** Allo HCT for Shwachman Diamond Syndrome