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A G E N D A
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

Co-Chair:	**Christopher Dvorak, MD, University of California San Francisco Medical Center, San Francisco, CA;** **Telephone: 415-476-2188; E-mail: christopher.dvorak@ucsf.edu**
Co-Chair:	**Jaap Jan Boelens, MD, PhD, Memorial Sloan Kettering Cancer Center, New York, NY;** **Telephone: 212-639-3641; E-mail: boelensj@mskcc.org**
Co-Chair:	**Vikram Mathews, MD, DM, MBBS, Christian Medical College Hospital, Vellore, India;** **Telephone: +011 91 416 228 2891; E-mail: vikram@cmcvellore.ac.in**
Scientific Director:	**Mary Eapen, MBBS, MS, CIBMTR Statistical Center, Milwaukee, WI;** **Telephone: 414-805-0700; E-mail: meapen@mcw.edu**
Statistical Director:	**Soyoung Kim, PhD, CIBMTR Statistical Center, Milwaukee, WI;** **Telephone: 414-955-8271; E-mail: skim@mcw.edu**
Statistician:	**Kyle Hebert, MS, CIBMTR Statistical Center, Milwaukee, WI;** **Telephone: 414-805-0673; E-mail: khebert@mcw.edu**

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1. **Introduction**
   a. Minutes and Overview Plan from February 2018 meeting (Attachment 1)
   b. Introduction of incoming Co-Chair:
   Andrew Gennery, MD; Newcastle General Hospital / The Royal Victoria Infirmary;
   Email: a.r.gennery@ncl.ac.uk

2. **Accrual summary** (Attachment 2)

3. **Presentations, published or submitted papers**
   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) **Submitted**

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) **Submitted**

4. Studies in progress (Attachment 3)

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) **Manuscript Preparation**
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

a. **Prop 1811-110** Impact of Reduced Intensity Conditioning on Allogeneic HCT Outcomes for HLH (R Marsh) (Attachment 4)
b. **Prop 1810-11** Outcomes of allogeneic hematopoietic stem cell transplant in adult patients with history of hemophagocytic lymphohistiocytosis (M Hegazi) (Attachment 5)
c. **Prop 1811-67** Does mixed chimerism after alloHCT in patients with Fanconi Anemia impact on the eventual outcome? (M Ayas) (Attachment 6)
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)
e. **Prop 1811-175** Outcomes after Allogeneic Hematopoietic Cell Transplantation in Patients with Griscelli syndrome (P Satwani) (Attachment 8)
f. **Prop 1811-180** Hematopoietic Stem Cell Transplantation for Congenital Amegakaryocytic Thrombocytopenia (F Boulad/ M Cancio/ JJ Boelens) (Attachment 9)

6. Dropped proposed studies

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

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR PRIMARY IMMUNE DEFICIENCIES, INBORN ERRORS OF METABOLISM AND OTHER NON-MALIGNANT MARROW DISORDERS
Salt Lake City, Utah
Saturday, February 24, 2018, 2:45pm – 4:45pm

Co-Chair:	**Paolo Anderlini, MD, MD Anderson Cancer Center, Houston, TX;** **Telephone: 713-745-4367; E-mail: panderli@mdanderson.org**
Co-Chair:	**Neena Kapoor, MD, Children's Hospital of Los Angeles, Los Angeles, CA;** **Telephone: 323-361-2546; E-mail: nkapoor@chla.usc.edu**
Co-Chair:	**Jaap Jan Boelens, MD, PhD, University Medical Center Utrecht, Utrecht, Netherlands;** **Telephone: +31 8875 54003; E-mail: j.j.boelens@umcutrecht.nl**
Co-Chair:	**Vikram Mathews, MD, DM, MBBS, Christian Medical College Hospital, Vellore, India;** **Telephone: +011 91 416 228 2891; E-mail: vikram@cmcvellore.ac.in**
Scientific Director:	**Mary Eapen, MBBS, MS, CIBMTR Statistical Center, Milwaukee, WI;** **Telephone: 414-805-0700; E-mail: meapen@mcw.edu**
Statistical Director:	**Soyoung Kim, PhD, CIBMTR Statistical Center, Milwaukee** **Telephone: 414-955-8271; E-mail: skim@mcw.edu**
Statistician:	**Kyle Hebert, MS, CIBMTR Statistical Center, Milwaukee** **Telephone: 414-805-0673; E-mail: khebert@mcw.edu**

1. Introduction

The CIBMTR Working Committee for Primary Immune Deficiencies, Inborn Errors of Metabolism and other Non-Malignant Marrow Disorders met on Saturday, February 24, 2018 at 2:45pm. Dr. Mathews welcomed the audience and introduced the working committee leadership, reviewed the committee's goals, expectations, and limitations. Dr. Christopher Dvorak was introduced as the newest committee Chair. Drs. Neena Kapoor and Paolo Anderlini were thanked for their contributions to the committee as chairs as their term as committee chairs has concluded. Note: Dr. Anderlini was not at the meeting. There was a motion to approve the 2017 working committee meeting minutes, and a second. The motion passed. Dr. Mathews 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. The number of samples available for non-malignant diseases in the NMDP Sample Repository was also shown. Dr. Mathews 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.

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. Boelens directed the audience to the working committee materials for information regarding the two committee publications from 2017.

The two committee publications from 2017 are listed below:

a. **SC14-01** Kekre N, Zhang Y, Zhang M, Carreras J, Anderlini P, Ahmed P, Atta EH, Ayas M, Boelens JJ, Bonfim C, Deeg HJ, Kapoor N, Lee JW, Nakamura R, Pulsipher M, Eapen M, Antin JH. Effect of antithymocyte globulin source on outcomes of bone marrow transplantation for severe aplastic anemia. ***Haematologica. 2017 Jul;102(7):1291-1298.***
b. **AA13-01** Abraham A, Hsieh M, Eapen M, Fitzhugh C, Carreras J, Keesler D, Guilcher G, Kamani N, Walters MC, Boelens JJ, Tisdale J, Shenoy S. Relationship between mixed donor-recipient chimerism and disease recurrence after hematopoietic cell transplantation for sickle cell disease. ***Biology of Blood and Marrow Transplantation. 2017 Dec;23(12):2178-2183.***

4. Studies in progress (Attachment 3)

Dr. Kapoor directed the audience to the working committee materials for the complete list of studies in progress and details regarding each study.

Dr. Eapen then presented the results of the upcoming committee publication entitled *Combined EBMT/CIBMTR retrospective study of allogeneic stem cell transplant outcomes in older patients (age > 50 years) with severe aplastic anemia*. Dr. Eapen informed the attendees that this paper had recently been submitted. There were no questions about the study upon completion of the presentation.

Dr. Nelli Bejanyan from the University of Minnesota presented an update on the background and preliminary analysis results for the active committee study entitled *The effect of conditioning regimen on clinical outcomes of allogeneic hematopoietic cell transplantation in severe aplastic anemia.* One attendee asked whether the dose of cyclophosphamide or number of red blood cell transfusions could be added to the analysis as adjustment factors. Dr. Eapen explained that number of red blood cell transfusions are not collected at the TED or CRF level; collection of RBC transfusions is challenging for Data Managers. Cyclophosphamide dose (unrelated donor transplant) was explored, but limited by sample size. Another attendee asked whether ATG dose had been explored. Dr. Bejanyan responded that it had not yet been checked. A final question was whether we were prepared to make a strong statement recommending the elimination of TBI use for aplastic anemia patients based on these results of lower chronic GVHD and better engraftment for sibling donors. Dr. Bejanyan replied that the results are preliminary, so no such definitive statement should be extracted yet. Note that the numbers of transplants especially in subgroups are limited, and it would be not be possible to make a definitive recommendation like elimination of TBI from conditioning regimens.

All of the working committee active studies are listed below:

a. **AA13-02** Malignancies in patients with fanconi anemia (J Wagner) **Analysis**
b. **ID12-01** Allogeneic hematopoietic cell transplantation for combined immunodeficiency and

common variable immunodeficiency (G Cuvelier/G Guilcher/N Wright) **Data File Preparation**

c. **ID13-01** Hematopoietic cell transplantation for congenital neutropenia/kostmann agranulocytosis (C Zeidler/S Keogh/J Connelly) **Analysis**
d. **NM14-02** Outcomes of allogeneic hematopoietic cell transplant in patients with Shwachman diamond syndrome (K Myers) **Data File Preparation**
e. **NM15-01** Outcome of Allogeneic Hematopoietic Cell Transplant in Erythropoietic Porphyria (A Saad/H Abdel-Azim/J Bloomer) **Data File Preparation**
f. **NM16-01** Combined EBMT/CIBMTR retrospective study of allogeneic stem cell transplant outcomes in older patients (age > 50 years) with severe aplastic anemia (C Rice/J Marsh/V Potter) **Manuscript Preparation**
g. **NM16-02** Allogeneic hematopoietic cell transplantation for primary immune deficiencies: current patterns of practice and change over the last 10 years (R Marsh) **Manuscript Preparation**
h. **NM16-03** Results of transplants from genetically-identical twin donors in persons with aplastic anemia (RP Gale) **Protocol Development**
i. **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) **Analysis**
j. **NM17-01** Late effects after hematopoietic stem cell transplantation in patients with HLH (A Horne/KS Baker/K Beutel) **Protocol Development**
k. **NM17-02** 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/S Hongeng/C Li) **Data Collection**

5. Future/proposed studies

Dr. Kapoor 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 1711-45** Retrospective analyses to identify predictors for immune cytopenia after transplantation for benign disorders (metabolic, PID and BMF syndromes) (J Boelens/C Lindemans/R Wynn) (Attachment 4)

Dr. Lindemans presented the proposal. The goal of the study will be to identify risk factors that are predictive of the development of autoimmune cytopenia post-transplant. Questions of particular importance include the impact of stem cell source or prior occurrence of GVHD on the incidence of autoimmune cytopenia. Also, the study would explore whether incidence of AIC is higher in benign disorders than malignancies. The study would also seek to determine whether AIC influences the probability of chronic GVHD, relapse-free-survival, and overall survival. The study population would consist of all patients aged 0-21 years with a T-cell replete graft transplanted for a non-malignant disorder, AML in complete remission, or MDS, during the years 2005-2017.

The CIBMTR identified 35 patients with autoimmune cytopenia (AIC) reported post-transplant. Of these, 19 were patients transplanted for benign disorders, and 16 were patients transplanted for malignancies. Multiple attendees cautioned that the definition of AIC is not uniform and difficult to standardize. There was the added concern of “under reporting” and

that the incidence of AIC is likely determined by the underlying disease. Dr. Eapen agreed and clarified that the big question for this proposal is that of whether there is sufficient interest in this to justify going back to centers to ask. Concern was raised that the amount of work required for this study because of this would be massive. Dr. Davies suggested that exploring development of AIC would be a beneficial undertaking, but that perhaps the best way to do so would be to pursue a study with a small group of centers dedicated to the effort as a prospective study, instead of a registry study that would be time-consuming and possibly have heterogeneous reporting. Later discussions with Dr. DiFronzo resulted in Drs. Eapen and Davies committed to applying for funds to pursue a prospective study the prevalence of AIC post-transplant for non-malignant diseases and identify risk factors predictive for AIC. Dr. Bolens will join this effort as a consultant (resides in the Netherlands and challenging to participate in an NIH funded study in the US).

b. **Prop 1711-50** Outcomes of second and subsequent hematopoietic stem cell transplants in patients with inborn errors of metabolism (A Gupta/W Miller/T Lund/P Orchard) (Attachment 5)

Dr. Gupta presented the proposal. The goal of the study will be to examine outcomes of patients undergoing a second (or more) transplant for inborn errors of metabolism, including overall survival, acute and chronic GVHD, and hematopoietic recovery. Justification for the impact of this study is that survival among those transplanted for inborn errors of metabolism are improving over time, and that graft failure is relatively common in this population usually necessitating a second transplant.

The CIBMTR identified 71 patients with research-level data that underwent a second allogeneic HCT for an inborn error of metabolism during the years 2000-2016. One attendee asked how many centers were represented by this data. Dr. Eapen explained that this was not provided to the proponents because this could essentially identify the centers involved as few centers performed these transplants. Concerns were raised about the heterogeneity of diseases – the role of second transplantation is most likely to differ amongst the various inborn errors of metabolism. One meeting attendee voiced that his center is already performing a study on second transplants for all non-malignant diseases and will not participate in the CIBMTR study in the event the proposal is approved. An attendee asked whether there is information available on patients who had graft failure after first allogeneic transplant but did *not* go to second transplant for comparison. Dr. Eapen responded that this data was not pulled for the presentation as the study question focused on those who underwent second transplant, but that this subgroup could be prepared if the proposal is to be accepted.

c. **Prop 1711-138** Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease (A Prakash/D Wall/K Paulson) (Attachment 6)

Dr. Prakash presented the proposal. The goal of the study will be to examine the impact of the specific choice of serotherapy 9ATG vs. alemtuzumab) on the post-transplant outcomes for non-malignant diseases in the pediatric setting. In particular, a comparison between patients receiving anti-thymocyte globulin (ATG) and patients receiving alemtuzumab will be done with the aim of helping to inform clinical decision-making in the future. The primary justification for the impact of this study is that serotherapy is very commonly used in the non-malignant setting to reduce risk of GVHD and improve engraftment, and no large-scale study has yet been done to explore the impact of serotherapy choice non-malignant diseases. The investigators

hypothesize that alemtuzumab -containing regimens will be associated with higher rates of overall survival than ATG-containing regimens.

The CIBMTR identified 1290 patients receiving ATG and 528 patients receiving alemtuzumab regimens between 2005 and 2015. Note that alemtuzumab use began after 2007 so the study period will be limited to 2008 and later years. One committee member asked if the study plans to look at timing of alemtuzumab. Dr. Prakash responded that the date of alemtuzumab given is collected on the forms, but that the completeness would need to be checked for this data field. Another question was whether source of ATG would be analyzed. Dr. Prakash responded that source of ATG is collected on the forms and that this could be done as a subgroup analysis. The next question was whether infection data would be available. Dr. Eapen explained that we would not have that data on patients reported at the TED level; collected at the CRF. As patients are not always followed at the transplant center, there may be incomplete data reporting beyond 1 year of transplant. Therefore, generally we limit to infections at 3 or 6 months and sometimes 1-year. A final clarification was made to the group. The table displayed for the meeting included aplastic anemia and several disease subsets with too few recipients of alemtuzumab-containing regimens. Therefore, if approved to proceed, we will make a careful determination of the diseases to be studied. Also, it was pointed out to the group that histiocytic disorders were mistakenly left out, but that these patients would be added if the proposal is selected to proceed.

d. **Prop 1711-155** Outcomes of congenital amegakaryocytic thrombocytopenia (CAMT) after allogeneic hematopoietic stem cell transplantation; effect of conditioning regimen and long-term toxicities (M Schoettler/C Duncan) (Attachment 7)

Dr. Duncan presented the proposal. The goal of the study will be to determine the number of transplants done since 1990 for the rare bone marrow failure syndrome congenital amegakaryotic thrombocytopenia (CAMT), and describe outcomes following transplant. Outcomes to be described will include overall survival, acute and chronic GVHD, and graft failure. Risk factors such as conditioning regimen, age at transplant, and HLA match. This would be the largest study for this indication for transplant yet to date.

The CIBMTR identified 42 total patients transplanted for CAMT during the years 1990 to 2016. There were no questions or comments from the group following the presentation of this proposal.

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. **Prop 1710-19** Outcomes of haploidentical hematopoietic cell transplant in patients with hemoglobinopathies and primary immunodeficiency
Dropped due to feasibility

b. **Prop 1711-33** Impact of donor and recipient ABO incompatability on outcomes post allogeneic stem cell transplantation for non-malignant disorders in children
Dropped due to overlap with DS13-02

c. **Prop 1711-40** Clinical course and outcome of allogeneic hematopoietic stem cell transplantation in glanzmann thrombasthenia
Dropped due to supplemental data required
d. **Prop 1711-55** Late effects and second neoplasms in severe combined immunodeficiency survivors treated with hematopoietic cell transplantation
Dropped due to overlap with LE16-02
e. **Prop 1711-60** Impact of donor/recipient CMV serological status on survival post allogeneic hematopoietic cell transplant in children with non-malignant disorders
Dropped due to overlap with previous publication
f. **Prop 1711-136** Outcomes of acquired severe aplastic anemia patients who developed graft failure after hematopoietic stem cell transplant
Dropped due to overlap with previous publication
g. **Prop 1711-140** Feasibility and efficacy of allogeneic hematopoietic stem cell transplantation in adults with histiocytic disorders, particularly adult-onset hemophagocytic lymphohistiocytosis
Dropped due to feasibility
h. **Prop 1711-142** Fludarabine-based conditioning for unrelated donor bone marrow transplantation for severe aplastic anemia
Dropped due to overlap with NM16-04
i. **Prop 1711-144** Comparative study of haploidentical versus other alternative donor transplants (MURD, MMURD, and UCB) in patients with hemoglobinopathies
Dropped due to feasibility (SCD) and overlap with NM17-02

7. Other Business

a. NM17-01: Late effects after hematopoietic stem cell transplantation in patients with HLH

Dr. K Scott Baker provided an update for this study. Dr. Baker explained that a data collection form has been nearly finalized to be ready for use to collect necessary supplemental data regarding late effects for patients transplanted for HLH. This form implements a modified criteria for grading late morbidity. There is grant funding to be used for collection of the supplemental data by EBMT. However, funding was not secured for American data collection, and it is unlikely that some of the funds allocated for the European patients can be transferred to the U.S. Dr. Baker asked the group if there would be volunteers to participate in the study without funding among centers who see a lot of HLH patients. Several of the centers with an interest in HLH will contribute supplemental data – summer 2018.

Meeting adjourned at 4:00pm.

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 study was accepted to move forward to be added to the committee's active studies:

Prop 1711-138 Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease (A Prakash/D Wall/K Paulson)

Working Committee Overview Plan for 2018 - 2019

a. **AA13-02** Malignancies in patients with Fanconi Anemia (J Wagner). Analysis is in progress. The goal is to submit the final manuscript by June 2018.

Statistical Hours allocated- Through June 2018: 70; To completion: 70

b. **ID12-01** Allo HCT for CID/CVID (G Cuvelier/G Guilcher/N Wright). Data file preparation is underway. The goal for the study is to submit the final manuscript by June 2019.

Statistical Hours allocated- Through June 2018: 150 ; To completion: 150

c. **ID13-01** HCT for Congenital Neutropenia/Kostmann Agranulocytosis (C Zeidler/J Connelly/S Keogh). U.S. data has been cleaned and prepared for presentation. The population will be expanded through collaboration with the German SCN registry. The goal for the study is to prepare the manuscript by June 2018.

Statistical Hours allocated- Through June 2018: 10; To completion: 80

d. **NM14-02** Allo HCT for Shwachman Diamond Syndrome (K Myers). Data for descriptive tables is complete. The goal is to submit the final manuscript by June 2019.

Statistical Hours allocated- Through June 2018:120; To completion: 190

e. **NM15-01** Outcome of allogeneic Hematopoietic Cell Transplant (HCT) in Erythropoietic Porphyria (A
Saad). The manuscript will be prepared following the completion of supplemental data collection for European patients. The goal is to submit the final manuscript by June 2019.

Statistical Hours allocated- Through June 2018:20; To completion: 50

f. **NM16-01** Combined EBMT/CIBMTR retrospective study of allogeneic stem cell transplant outcomes in older patients (age > 50 years) with severe aplastic anemia. (C Rice/J Marsh/V Potter) The final manuscript has been submitted.

Statistical Hours allocated- Through June 2017: 0; To completion: 0

g. **NM16-02** Allogeneic transplantation for primary immune deficiencies: Current patterns of practice and change over the past 10 years. (R Marsh) The final manuscript will be submitted in March 2018.

Statistical Hours allocated- Through June 2018: 0; To completion: 0

h. **NM16-03** Results of transplants from genetically-identical twin donors in persons with aplastic anaemia. (RP Gale) The goal is to submit the final manuscript by June 2019.

Statistical Hours allocated- Through June 2018:30; To completion: 220

i. **NM16-04** The effect of conditioning regimen on clinical outcomes of allogeneic transplantation in severe aplastic anemia. (N Bejanyan/N Kekre/D Weisdorf/J Antin) Analysis is complete. The goal is to submit the final manuscript by June 2018.

Statistical Hours allocated- Through June 2018: 80; To completion: 80

j. **NM17-01** Late effects after hematopoietic stem cell transplantation in patients with HLH (A Horne/KS Baker/K Beutel). Study protocol is being developed and supplemental data collection form is being finalized. The goal is to finalize the study protocol by June 2018.

Statistical Hours allocated- Through June 2018: 60; To completion: 310

k. **NM17-02** 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/C Li/S Hongeng). The study will include a large number of patients with disease-specific data from the United States, India, and China. Data collection is nearing completion. The goal is to complete final analysis by June 2018.

Statistical Hours allocated- Through June 2018: 140; To completion: 210

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

Oversight Assignments for Working Committee Leadership (March 2017)

Vikram Mathews	**AA13-02**	Malignancies in patients with fanconi anemia
Vikram Mathews	**ID12-01**	Allogeneic hematopoietic cell transplantation for combined immunodeficiency and common variable immunodeficiency
Jaap Boelens	**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
Jaap Boelens	**NM15-01**	Outcome of Allogeneic Hematopoietic Cell Transplant in Erythropoietic Porphyria
Vikram Mathews	**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
Jaap Boelens	**NM17-01**	Late effects after hematopoietic stem cell transplantation in patients with HLH
Vikram Mathews	**NM17-02**	Evaluation of the impact of changing clinical profile, conditioning regimens and stem cell source on clinical outcome in patients with Thalassemia major
Christopher Dvorak	**NM18-01**	Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease

Accrual Summary for the Primary Immune Deficiencies, Inborn Errors of Metabolism and Other Non-Malignant Marrow Disorders Working Committee

Allogeneic Transplants for Immune Deficiencies reported to the CIBMTR from 2000-2018

Characteristic	TED N	CRF N
Number of patients	5407	2683
Number of centers	272	182
Disease		
Immune Deficiencies (ID), NOS	92	23
SCID ADA deficiency	128	87
SCID absence of T and B cells	274	166
SCID absence of T, normal B cell SCID	326	225
Omenn syndrome	153	94
Reticular dysgenesis	14	11
Bare lymphocyte syndrome	104	40
SCID, NOS	235	136
SCID other, specify	431	306
Wiskott Aldrich syndrome	507	272
DiGeorge anomaly	14	8
Chronic granulomatous disease	463	219
Chediak-Higashi syndrome	89	31
Common variable immunodef	87	37
X-linked lymphoproliferative syndrome	145	67
Leukocyte adhesion deficiencies	88	49
Kostmann agranulocytosis	156	56
Cartilage hair hypoplasia	48	23
TED Immune deficiency plus neutropenia	1	0
CD40 ligand deficiency	86	26
Griscelli syndrome type 2	17	8
Combined immunodef dis (CID), NOS	12	7
CID other, specify	17	17
Other immunodeficiencies, specify	562	179
Histiocytic disorder, NOS	29	5
FELH Familial erythrohemophagocytic lymphohis	954	411
Langerhans Cell Histiocytosis	79	37
Hemophagocytosis	188	88
Malignant histiocytosis	15	3
Other histiocytic disord	93	52

*Only first transplants are included in this accrual.

Abbreviations: ADA = adenosine deaminase; NOS = not specified; SCID = severe combined immunodeficiency

Allogeneic Transplants for Inborn Errors of Metabolism reported to the CIBMTR from 2000-2018

Characteristic	TED N	CRF N
Number of patients	1770	975
Number of centers	191	122
Disease		
Inherited disorders of metabolism, NOS	23	2
Osteopetrosis	307	139
Lesch-Nyhan(HGPTR defic)	2	2
Neuronal ceroid lipofuscinosis	7	5
Other inherited metabolism disorders, specify	79	40
Mucopolysaccharidosis, NOS	15	6
Hurler syndrome	484	306
Scheie syndrome	1	1
Hunter syndrome	34	22
ISanfillippo	32	27
Maroteaux-Lamy	39	25
B-glucuronidase deficiency	2	1
Mucopolysaccharidosis	5	1
Other mucopolysaccharidosis	4	3
Mucolipidoses, NOS	4	3
Gaucher disease	14	4
Metachromatic leukodystrophy(MLD)	157	85
Adrenoleukodystrophy(ALD)	371	192
Globoid leukodystrophy/Krabbe disease	96	61
Neiman-Pick disease	22	11
I-cell disease	24	16
Wolman disease	11	6
Glucose storage disease	1	0
Other mucolipidoses	1	1
Aspartyl glucosaminuria	3	0
Fucosidosis	6	5
Mannosidosis	26	11

*Only first transplants are included in this accrual.

Allogeneic Transplants for non-malignant disorders reported to the CIBMTR from 2000-2018

Characteristic	TED N	CRF N
Number of patients	14788	6555
Number of centers	435	322
Disease		
Paroxysmal nocturnal hemoglobinuria	458	234
Severe aplastic anemia	7857	3298
Amegakaryocytosis	24	11
Shwachman-Diamond	68	34
Acquired Pure Red Cell Aplasia	75	24
Dyskeratosis congenita	63	34
Other acquired cytopenic syndrome, specify	257	125
Inherited abnormalities of erythrocyte differentiation, not otherwise specified	18	10
Fanconi anemia	1434	759
Diamond-Blackfan anemia	310	135
Other constitutional anemia	163	61
Thalassemia	2422	1021
Sickle cell disease	1639	809

*Only first transplants are included in this accrual.

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Primary Immune Deficiencies, Inborn Errors of Metabolism and Other Non-Malignant Marrow Disorders Working Committee Members

FROM: Mary Eapen, MBBS, MS; Scientific Director for the Primary Immune Deficiencies, Inborn Errors of Metabolism and Other Non-Malignant Marrow Disorders Working Committee

RE: Studies in Progress Summary

AA13-02: Malignancies in patients with Fanconi anemia (J Wagner) The aim of the study is to determine whether the risk of solid cancer is higher after allogeneic transplantation compared to non-transplanted patients with Fanconi anemia, and describe the types of solid cancer and the outcome. Analysis is in progress. The goal is to submit the final manuscript by June 2019.

ID13-01: HCT for congenital neutropenia/kostmann agranulocytosis (C Zeidler/S Keogh/J Connelly) The aim of the study is to describe the population of patients with severe congenital neutropenia who have undergone HCT, and examine the outcomes post-transplant. U.S. data has been cleaned and prepared for presentation. The population has been expanded through collaboration with the German SCN registry. Analysis has been completed and manuscript preparation is in progress. The goal for the study is to prepare the manuscript by June 2019.

NM14-02: Outcomes of allogeneic hematopoietic cell transplant in patients with Shwachman diamond syndrome (K Myers) The aim of the study is to describe the population of children or adults with Shwachman diamond syndrome who have undergone HCT, and examine the outcomes post-transplant. Descriptive analysis has been completed. Manuscript preparation is in progress. The goal is to submit the final manuscript by March 2019.

NM15-01: Outcome of allogeneic Hematopoietic Cell Transplant (HCT) in Erythropoietic Porphyria (A Saad/H Abdel-Azim/J Bloomer) The aim of the study is to describe the population of children or adults with Erythropoietic Porphyria who have undergone HCT, and examine the outcomes post-transplant. U.S. data has been cleaned and prepared for presentation. European supplemental data has been collected and cleaned. Analysis has been completed. Manuscript preparation is in progress. The goal is to submit the final manuscript by June 2019.

NM16-03: Results of transplants from genetically-identical twin donors in persons with aplastic anemia (R P Gale) The goal of this study is to determine the proportion of patients receiving transplant from genetically-identical twin donor for aplastic anemia that recover normal bone marrow function. In doing so, the objective is to estimate the proportion of aplastic anemia cases that result from absent/defective stem or progenitor cells, as opposed to immune-dysfunction. Descriptive analysis is in progress. The goal is to submit the final manuscript by June 2019.

NM17-01: Late effects after hematopoietic stem cell transplantation in patients with HLH (A Horne/KS Baker/K Beutel) The purpose of this study is to investigate the long-term outcomes and late effects of patients with hemophagocytic lymphohistiocytosis (HLH) who are survivors after hematopoietic cell transplantation (HCT). The main hypothesis is that HLH survivors will be at risk for significant long term

medical and neuropsychological late effects that will be dependent upon pre-transplant disease related factors and the intensity of the BMT conditioning regimen. Study protocol is being developed. Steps are being taken to ensure that both the CIBMTR and the EBMT will have sufficient data to address key objectives of the study. Supplemental data collection is ongoing.

NM18-01: Impact of choice of serotherapy in pediatric stem cell transplantation for non-malignant disease (A Prakash/ D Wall/ K Paulson) The purpose of this study is to compare outcomes following allogeneic HCT for pediatric patients with non-malignant disease based on the specific serotherapy used. Post-transplant outcomes, including overall survival, acute and chronic GVHD, graft failure, and graft-failure free survival will be compared between patients given alemtuzumab and patients given ATG. The focus will be on non-malignant diseases for which transplant is most commonly used as treatment to establish as much homogeneity as possible in the comparison. The available population has been identified and data file preparation is in progress. The goal is to perform the analysis and prepare a manuscript by June 2019.

Proposal: 1811-110

Title:
Impact of Reduced Intensity Conditioning on Allogeneic HCT Outcomes for HLH

Rebecca Marsh, MD, Rebecca.Marsh@cchmc.org, Cincinnati Children's Hospital

Hypothesis:
We hypothesize that allogeneic hematopoietic cell transplantation using reduced intensity conditioning (RIC) is associated with higher overall survival for patients with hemophagocytic lymphohistiocytosis (HLH) diseases compared with myeloablative conditioning (MAC) regimens despite increased need for subsequent hematopoietic cell product administrations.

Specific aims:
- Aim 1: To compare the overall survival of patients with HLH who are treated with RIC and MAC regimens.
- Aim 2: To compare the cumulative incidences of primary graft failure, secondary graft failure, mixed chimerism, DLI administration, stem cell boost administration, and second allogeneic HCT among patients with RIC and MAC regimens.
- Aim 3: To compare the event-free survival of patients with HLH who are treated with RIC and MAC regimens. An event will be defined as death, primary graft failure, secondary graft failure, administration of DLI, administration of stem cell boost, and second transplant.
- Aim 4: To examine the overall and event-free survival of the subset of RIC and MAC patients who develop mixed chimerism, describe donor chimerism over time, and compare outcomes of those who are treated with Donor Lymphocyte Infusions (DIL), CD34+ selected boost, and second allogeneic HCT including overall survival and incidence of grades II-IV and III-IV acute GVHD.
- Aim 5: To examine covariates which may impact overall and event free survival among patients treated with RIC and MAC regimens including age, HLA match, graft source, graft CD34+ selection/T cell depletion, choice of serotherapy, development of grades II-IV and III-IV acute GVHD, chronic GVHD, and HLH activity if known/collected.
- Aim 6: To compare the Lansky/Karnofsky scores at last follow up among patients treated with RIC versus MAC and examine chronic GVHD-free survival.

Scientific impact:
If this proposal is accepted, it will be the first large-scale comparison of RIC versus MAC outcomes for patients with HLH and will help guide current practices. There is a vital need to perform a large analysis comparing RIC versus MAC approaches for patients with HLH to determine if the complications of RIC are justified by superior overall survival.

Scientific justification:
There are no large studies of outcomes for patients with HLH treated with reduced intensity conditioning (RIC) allogeneic HCT. The majority of studies are small, single-center, retrospective reports which suggest that RIC is associated with superior outcomes in patients with HLH, but complicated by increased rates of mixed chimerism, secondary graft failure, and additional cell product administration. A recent small prospective multi-center study (n=34 patients with HLH) observed a 1 year overall survival rate of 80%, but an event-free survival rate of only 39% including primary and secondary graft failure and administration of additional cell products such as donor lymphocyte infusions (Allen et al,

2018). It is difficult to know if current RIC approaches are truly superior to MAC approaches given the increased incidence of failure.

VII. Patient Eligibility Population

- We have familiarized ourselves with existing CIBMTR data collection forms.
- We will include all patients with a diagnosis of HLH, XLP, Griscelli Syndrome, or Chediak-Higashi Syndrome transplanted at an age of 29 years or less and transplanted between 2006-2016. We will include all donor and graft types and transplant regimens that are either myeloablative or reduced intensity (minimal intensity and no conditioning regimens will be excluded).

Data requirements:

- Recipient Baseline Data
- Hematopoietic Stem Cell Transplant (HCT) Infusion
- X-Linked Lymphoproliferative Syndrome Pre-HCT Data
- Hemophagocytic Lymphohistiocytosis Pre-HCT Data
- 100 Day Post-HSCT Data
- Six Months to Two Years Post-HSCT Data
- Yearly Follow-Up for Greater than Two Years Post-HSCT Data
- Post-HSCT Data

Note that collection of additional data will extend the time for completion of your study by one year

Variables:

- Date of HCT
- Date of repeat HCT
- Diagnosis
- Genetic Diagnosis if reported
- Age
- HLA Match
- Relation
- Graft Source
- Graft modification (T cell depletion/CD34+ selection)
- Conditioning Regimen
- Choice of serotherapy
- GVHD Prophylaxis
- Engraftment (ANC and PLT)
- Survival/death, last follow up
- Cause of Death
- Acute GVHD grades II-IV and onset
- Acute GVHD grades III-IV and onset
- Chronic GVHD limited
- Chronic GVHD extensive
- History of mechanical ventilation prior to HCT (surrogate for significant illness)
- History of HLH prior to HCT (patients transplanted October 2013 and later)
- Active HLH or not at the time of HCT (patients transplanted October 2013 and later)
- Occurrence of Mixed chimerism (<95% donor cells) in whole blood and Date of Onset
- Reported Chimerism Studies in whole blood, subsets, dates
- Administration of DLI and Date
- Administration of Additional Stem Cell Boost and Date
- Occurrence of primary and secondary graft failure and date if known

Study design (scientific plan):
*****Reference specific aim

- **Aim 1:** Kaplan-Meier curves will be created and groups compared using the log-rank test. Depending on the number of various RIC conditioning regimens, we may additionally subset the analysis to compare melphalan, busulfan, and treosulfan based RIC regimens.
- **Aim 2:** Cumulative incidence curves will be generated and groups compared using Gray's test.
- **Aim 3:** Kaplan-Meier curves will be created and groups compared using the log-rank test. An event will be defined as death, primary graft failure, secondary graft failure, administration of DLI, administration of stem cell boost, and second transplant.
- **Aim 4:** We will subset RIC and MAC patients who develop mixed chimerism and create Kaplan-Meier Curves to examine overall survival. We will create box and whisker plots and compare chimerism in whole blood and subsets at last follow up using ANOVA or Kruskal-Wallis or other statistical method as appropriate. We will create cumulative incidence curves to compare the rates of grades II-IV and III-IV acute GVHD between interventions.
- **Aim 5:** We will use Cox Hazard Regression analysis to model overall and event-free survival including the above covariates using step-wise selection.
- **Aim 6:** We will compare the Lansky/Karnofsky score at last follow up in patients treated with RIC and MAC to estimate any differences, and create Kaplan-Meier curves to compare probabilities of chronic GVHD-free survival between RIC and MAC groups.

Data source:
CIBMTR Research Database Only

References:

I. Allen CE, Marsh R, Dawson P, et al. Reduced-intensity conditioning for hematopoietic cell transplant for HLH and primary immune deficiencies. *Blood*. 2018;132(13):1438-1451.

Patients undergoing first MAC or RIC allogeneic HCT for HLH between 2005-2018 reported to the CIBMTR

	TED-track		CRF-track	
Characteristic	**MAC N (%)**	**RIC N (%)**	**MAC N (%)**	**RIC N (%)**
Number of patients	**431**	**366**	**177**	**122**
Age at transplant, years				
< 18	412 (96)	290 (79)	177	109 (89)
18 – 30	11 (3)	44 (12)	0	10 (8)
31 – 50	5 (1)	23 (6)	0	3 (2)
51-70	3 (<1)	9 (2)	0	0
Conditioning regimen				
Bu/Cy	233 (54)	0	131 (74)	0
Flu/Bu/TT	20 (5)	0	11 (6)	0
Flu/Bu	62 (14)	46 (13)	10 (6)	9 (7)
Flu/Mel/TT	54 (13)	0	22 (12)	0
Flu/Mel	62 (14)	320 (87)	3 (2)	113 (93)
Donor				
HLA-identical sibling	96 (22)	73 (20)	14 (8)	18 (15)
Other relative	44 (10)	18 (5)	13 (7)	3 (2)
Unrelated	291 (68)	275 (75)	150 (85)	101 (83)
Graft type				
Bone marrow	212 (49)	264 (72)	52 (29)	81 (66)
Peripheral blood	57 (13)	69 (19)	14 (8)	12 (10)
Umbilical cord blood	162 (38)	33 (9)	111 (63)	29 (24)
Year of transplant				
2005 – 2008	153 (35)	20 (5)	82 (46)	32 (26)
2009 – 2012	118 (27)	155 (42)	48 (27)	38 (31)
2013 – 2018	160 (37)	191 (52)	47 (27)	52 (43)

Serotherapy versus conditioning regimen by conditioning intensity, TED-track

Myeloablative regimens

	Conditioning regimen				
Serotherapy	**Bu/Cy**	**Flu/Bu/TT**	**Flu/Bu**	**Flu/Mel/TT**	**Flu/Mel**
ATG	171	10	24	4	8
Alemtuzumab	5	1	13	45	41
None	57	9	25	5	13

Reduced intensity regimens

	Conditioning regimen				
Serotherapy	**Bu/Cy**	**Flu/Bu/TT**	**Flu/Bu**	**Flu/Mel/TT**	**Flu/Mel**
ATG	0	0	17	0	34
Alemtuzumab	0	0	8	0	264
None	0	0	21	0	22

Serotherapy versus conditioning regimen by conditioning intensity, CRF-track

Myeloablative regimens

	Conditioning regimen				
Serotherapy	**Bu/Cy**	**Flu/Bu/TT**	**Flu/Bu**	**Flu/Mel/TT**	**Flu/Mel**
ATG	106	6	6	2	1
Alemtuzumab	1	1	3	19	2
None	24	4	1	1	0

Reduced intensity regimens

	Conditioning regimen				
Serotherapy	**Bu/Cy**	**Flu/Bu/TT**	**Flu/Bu**	**Flu/Mel/TT**	**Flu/Mel**
ATG	0	0	6	0	7
Alemtuzumab	0	0	1	0	91
None	0	0	2	0	15

Proposal: 1810-11

Title:
Outcomes of Allogenic Hematopoietic Stem Cell Transplant (AHSCT) in adult patients with history of Hemophagocytic lymphohistiocytosis (HLH)

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Shruti Bhandari, MD, s0bhan04@louisville.edu, University of Louisville

Hypothesis:
This study aims to determine the outcomes of AHSCT in adult patients with history of Hemophagocytic lymphohistiocytosis. Patients who developed such a strong abnormal immune activation during or after diagnosis with a hematologic malignancy, are a unique population and should be studied in regard to outcomes after AHSCT. Such population might carry their own pattern in response to AHSCT. Something that urges for a retrospective review of outcomes.

Specific aims:
- Survival rates in patients with history of HLH after HSCT
- Determine if there are recipient or donor baseline characteristics that have prognostic value
- Impact of conditioning regimens on survival outcomes
- Impact of graft source on survival outcomes
- Incidence of Graft-versus-host disease in this population

Scientific impact:
This study will give insight into the outcomes of HSCT in patients with HLH and factors that have prognostic value.

Scientific justification:
HLH is a rare syndrome of excessive inflammation and tissue destruction due to abnormal immune activation. This disease can be familial or secondary triggered by an underlying infection, malignancy, or rheumatologic condition. HLH is a highly morbid condition; if left untreated, patients survive for only a few months because of progressive multisystem organ failure [1]. Current management in adults are mostly based on HLH-94 protocol that was studied in pediatric population [2]. HSCT is recommended in patients with lack of response to initial systemic treatment, central nervous system involvement, associated with hematologic malignancy and presence of homozygous or compound heterozygous HLH gene mutations. Due to rarity of the disease, there is paucity of data about outcomes of AHSCT in these patients.

Patient eligibility population:
- Age >= 18 years
- Diagnosed with HLH
- Received Allogenic Hematopoietic Stem Cell Transplant

Data requirements:

Baseline recipient data:

- Diagnosis
  - disease sub classification or histology
  - stage at transplant, cytogenetics
  - molecular markers
  - pre-HCT disease treatment
- Demographic
  - socioeconomic information
  - gender
  - age
  - race/ethnicity
- Transplant procedure
  - HLA typing
  - conditioning regimen
  - graft source
  - mobilization
  - T-cell depletion
  - other graft manipulation
- Clinical
  - coexisting diseases
  - pre-HCT infection
  - HCT history

Baseline donor data:

- Demographics
- HLA typing
- Infectious disease markers
- Pre-donation CBC and differential
- Pre-donation toxicities
- Filgrastim administration

Follow-up recipient data:

- Collected at 100 days, 6 months and annually after HCT

Transplant outcomes:

- Survival
- neutrophil and platelet engraftment
- acute and chronic GVHD, relapse
- GVHD prophylaxis
- Immune reconstitution
- Chimerism, Infection
- Organ function
- Subsequent HCT or DCI
- New malignancy
- Cause of death

Follow-up donor data

- Collected at 2 days, 1 week and weekly until donor reports full recovery
- Then at 1 month, 6 months and annually after donation

Donor outcomes:

- post-donation CBC and differential
- post-donation toxicities
- adverse events

Product analysis:

- cell counts
- viability
- volume

Study design:

The data mentioned above for the patients who meet the inclusion criteria will be requested from the Center for International Blood and Marrow Transplant Research (CIBMTR). The primary outcome of this study will be overall survival. The impact of both recipient and donor baseline characteristics on survival outcomes will analyzed. Subgroup analyses based on conditioning regimen and graft source will also be performed. Analyses will be done using SPSS software, version 25.

References:

1. Jordan, M.B., et al., *How I treat hemophagocytic lymphohistiocytosis.* Blood, 2011. **118**(15): p. 4041-52.
2. Henter, J.I., et al., *Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation.* Blood, 2002. **100**(7): p. 2367-73.

Conflict of interest:

None

Adult patients undergoing first allogeneic HCT for HLH between 2005-2018 reported to the CIBMTR

Characteristic	TED N (%)	CRF N (%)
Number of patients	**119**	**22**
Age at transplant, years		
18-30	65 (55)	13 (59)
31-50	40 (34)	8 (36)
51-70	14 (12)	1 (5)
Graft type		
Bone marrow	46 (39)	9 (41)
Peripheral blood	69 (58)	11 (50)
Umbilical cord blood	4 (3)	2 (9)
Donor		
HLA-identical sibling	34 (29)	3 (14)
Other relative	14 (12)	4 (18)
Unrelated	71 (60)	15 (68)
Conditioning regimen intensity		
Myeloablative	27 (23)	3 (14)
Reduced intensity	92 (77)	19 (86)
Year of transplant		
2005 – 2008	8 (7)	5 (23)
2009 – 2012	34 (29)	2 (9)
2013 – 2018	77 (65)	15 (68)

Proposal: 1811-67

Title:
Does Mixed Chimerism after Allogeneic Hematopoietic Cell Transplantation in Patients with Fanconi Anemia Impact on the Eventual Outcome?

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Hypothesis:
Fanconi anemia (FA) cells are characterized by genomic instability which places FA patients (pts) at risk for malignancies; leukemia and oropharyngeal/urogenital cancers. The risk of development of leukemia is hypothetically eliminated after hematopoietic cell transplantation (HCT). Mixed chimerism (MC) - Simultaneous presence of both host- and donor-derived cells in the recipient- is observed in a large proportion of patients after HCT with non-malignant disorders. In FA patients however, MC might have a unique implication and the persistent existence of FA cells post allogeneic HCT represents a management dilemma as the lingering FA cells may theoretically evolve into a malignant clone which predisposes the patient to leukemia.

Specific aims:
- To study the long-term consequences of mixed chimerism in patients with FA after allogeneic HCT.
- Specifically, the data will be reviewed to check FA patients with MC for
    - Overall survival (OS)
    - Incidence of graft failure, evidence of myelodysplasia, abnormal clones or leukemia after HCT in addition to the incidence of other secondary malignancies and compare that with same in FA patients who have full chimerism

Scientific impact:
The persistence of FA cells in FA patient post allogeneic HCT is a management dilemma; if indeed this study proves that such patients suffer from an increased incidence of malignancies (Hematological in particular) and/or lower survival, this might suggest that more aggressive management (even such as second HCT) for such patients may be warranted.

Scientific justification:
Allogeneic hematopoietic cell transplantation (HCT) is currently the only modality to restore normal hematopoiesis in FA patients. The persistence of some recipient's cells along the donor's cells post HCT in non-malignant hematological disorders is not uncommon and should not usually confer any poorer prognosis; in FA patients however, any lingering FA cells post HCT might –in theory at least- evolve into a malignant clone and consequently herald a more dismal outcome. This had not been addressed previously in the literature.
We at King Faisal Specialist Hospital & Research Center reviewed our data of 2.5 decades; 163 FA pts underwent allogeneic HCT at our center; chimerism data at last contact were available on 100 of them. Those 100 were the subject of a study that was submitted and accepted for poster presentation at ASH 2018.
We looked at chimerism data and evaluated patients with full and mixed chimerism for overall survival, incidence of graft failure, graft versus host (GVHD) and malignancy
Median follow up time was 67.2±14.6 months (95% CI: 38.7-95.7) from HCT date. Chimerism analysis at last follow up showed full chimerism (100%; Myeloid/lymphoid) in 46 pts; 54 had MC defined as the

presence of any residual recipient cells. No statistically significant association was noted between full and MC patients in the incidence of aGvHD (P-Value: 0.331). The 10-year cumulative probability of Overall Survival (OS) was 0.904±0.042. No significant difference was observed in OS between full and MC pts (0.954±0.032 vs. 0.883±0.059, P-value: 0.943) with 4 deaths in each group. New malignancy occurred in 4 patients; 2 in each group. In full Chimerism patients: Acute Mixed Lineage Leukemia and carcinoma and in MC patients: acute myeloid leukemia and acute lymphocytic leukemia, (P-Value=1.00). Graft failure occurred in 2 patients in the mixed chimerism group versus none in the full chimerism group (P-Value=1.0). So, in our study we showed that mixed chimerism in FA patients did not appear to have an adverse effect on outcome in our follow up period. Clearly longer follow up and larger number of patients are required to validate this statement. Data from CIBMTR could help shed a better light on this dilemma.

Patient eligibility population:
All FA patients who underwent allogeneic hematopoietic transplant with available chimerism data

Data requirements:

- We will use the Fanconi Anemia / Constitutional Anemia Post-HSCT Data (FAN): Form 2029.
- Include a list of variables from the existing CIBMTR data collection forms that need to be analyzed, and desired outcome variables.

Study design (scientific plan):

- Overall survival in patients with mixed chimerism will be evaluated. Mixed chimerism will be divided into relevant categories depending on available data: e.g. 10-30% donor; 31-60% donor; 61-99% donor. Survival will be estimated in the different groups and compared to survival in full chimerism patients.
- Incidence of graft failure, development of post-transplant myelodysplasia, abnormal clones and leukemia; development of post-transplant secondary non-hematological malignancies

Data source

- CIBMTR Research Database, CIBMTR Sample Repository.

Patients undergoing first allogeneic HCT for Fanconi Anemia between 2005-2018, with mixed chimerism, and reported to the CIBMTR, CRF-track

Characteristic	N (%)
Number of patients	**43**
Country	
United States	15 (35)
Other	28 (65)
Age at transplant, years	
< 18	39 (91)
18-30	3 (7)
31-50	1 (2)
Donor type	
HLA-identical sibling	19 (44)
Other relative	6 (14)
Unrelated	18 (42)
Graft type in merge	
Bone marrow	25 (58)
Peripheral blood	7 (16)
Umbilical cord blood	11 (26)
Year of transplant	
2005-2008	24 (56)
2009-2012	5 (12)
2013-2018	14 (33)

Proposal: 1811-94

Title:
Conditional and cause-specific mortality of patients with severe aplastic anemia surviving at least one year after allogeneic hematopoietic cell transplantation or immunosuppressive therapy

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Hypothesis:
Primary hypothesis: Among patients with severe aplastic anemia (SAA) who underwent an allogeneic hematopoietic cell transplant (HCT) AND survived at least 1 year, the projected 5-y survival rates improve conditional on time survived from alloHCT. However, the overall mortality remains greater than that of the general population even after surviving for 5-10 years.

Secondary hypothesis: The long-term conditional survival of SAA patients treated with immunosuppressive therapy (IST) differs from that of BMT survivors; the overall mortality (due to HCT-related late effects) is lower after IST, and the causes of death are more likely disease-related rather than non-disease related causes.

Specific aims:
- Determine conditional survival and cause-specific mortality (disease-related [DRM], non-disease-related [NDRM], and GvHD-related) after alloHCT in patients with SAA who received BMT and survived at least one year.
- Compare conditional survival and cause-specific mortality (disease-related [DRM], non-disease-related [NDRM], and GvHD-related) between HCT and IST survivors.

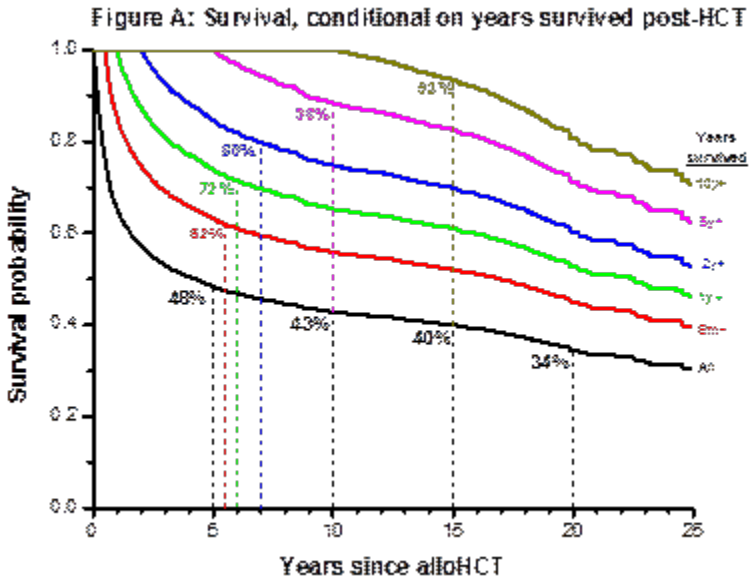
Scientific impact:
The proposed study will effectively define the conditional survival and cause-specific mortality (disease-related [DRM], non-disease-related [NDRM], and GvHD-related) after allogeneic HCT in patients with SAA who received BMT and survived at least one year. Since SAA is a non-malignant disease and often occurs in younger patients, understanding of the late effects and survival outcomes is critically important. While the late effects (morbidities) have been described by the CIBMTR earlier (1), there were no detailed mortality data available in that study, partly due to limited follow up (median ~ 5 years).
In addition, this study will explore the long-term survival data of SAA patients who received IST as their primary treatment, in collaboration with the NHLBI (Dr. Neal Young). The differences or similarities of long-term conditional survival would significantly improve our understanding of the natural history of SAA patients after surviving initial definitive therapy. The knowledge gained by the proposed study will help identify the areas of intervention that can be addressed to improve patients' longevity and quality of life. Importantly, the data obtained from this proposed study will help inform treating physicians and researchers in counseling newly diagnosed SAA patients about BMT and IST options.

Scientific justification:
Allogeneic HCT is offered with curative intent to patients with malignant as well as some nonmalignant hematologic diseases such as SAA. In particular, HCT has been used successfully to treat acquired severe aplastic anemia (SAA) for several decades both in matched sibling donor (MSD) and unrelated donor (URD) HCT (2-6).

Conventionally-computed survival estimates are offered for prognosticating outcomes. However, conventionally-computed survival and mortality risk estimates do not account for patients' elapsed survival time which, among other factors, could affect subsequent mortality. Conditional survival overcomes these limitations by calculating the probability of survival after having already survived a certain period of time – such data are unavailable for alloHCT recipients.

We have recently evaluated 4,315 consecutive patients who underwent alloHCT for hematologic diseases at a single institution (7). Among these, 198 patients (5%) were transplanted for SAA. Vital status and cause of death were determined using the National Death Index Plus and medical records. As of December 31, 2014, 1841 patients were still alive in whom the median follow-up was 8.5y (0.2-36.6). Conventionally-computed probabilities of survival at 5, 10, 15, and 20y after alloHCT were 48%, 43%, 40%, and 34%, respectively. For patients who had survived 6 mo, 1, 2, 5, 10y after alloHCT, 5-y conditional survival rates were 62%, 72%, 80%, 88% and 93%, respectively (**Figure A**). Overall, the cohort was at a 24-fold (Standardized Mortality Ratio [SMR]=24.1, 95%CI=23.1-25.0) risk of any death, compared to the general population; SMR and cause-specific conditional mortality rates by primary diagnosis are shown in the **Table**. For the overall cohort, after adjusting for primary diagnosis, relapse risk at allogeneic Hct, treatment era, and ethnicity, DRM was significantly lower for patients who developed acute GvHD (HR=0.78, 95%CI=0.66-0.93). Adjusted for the same factors, NDRM risk increased with older age at HCT (HR=1.02 per year, 95% CI=1.01-1.03), and for patients with acute GvHD (HR=1.9, 95%CI=1.6-2.2) and those exposed to Total Body Irradiation (TBI) (HR=1.4, 95%CI=1.2-1.8).

As discussed above, SAA is a unique population in which the long-term survival data are more relevant and important as this is a non-malignant disorder with generally good prognosis and the patients are often young. The limited number of cases in a single institution does not provide adequate power and the opportunity for detailed analysis without collaborating with the CIBMTR. In addition, the survivorship data are lacking in patients who received IST as their primary therapy and who survived for at least one year.



		All alloHCT (n=4315)		1 yr survivors (n=2828)		2 yr survivors (n=2349)		5 yr survivors (n=1627)		10 yr survivors (n=980)	
		5-y mortality (%)	SMR (95%CI)	5-y mortality (%)	SMR (95%CI)	5-y mortality (%)	SMR (95%CI)	5-y mortality (%)	SMR (95%CI)	5-y mortality (%)	SMR (95%CI)
All Patients	DRM	19.1	24.0 (23.1-25.0)	14.3	9.8 (9.2-10.4)	8.7	6.6 (6.1-7.1)	3.2	3.7 (3.3-4.1)	0.6	2.6 (2.2-3.0)
	GvHD	13.5		6.9		4.8		1.9		0.4	
	NDRM	25.0		12.6		9.3		5.2		2.6	
ALL (n=960)	DRM	25.6	48.8 (44.9-52.7)	20.7	21.1 (18.5-23.7)	13.1	13.2 (11.1-15.3)	4.3	6.6 (5.0-8.1)	0.7	5.2 (3.7-6.8)
	GvHD	14.7		8.8		6.1		1.4		0.0	
	NDRM	27.8		14.2		9.1		4.2		2.5	
AML (n=1382)	DRM	24.3	28.7 (26.7-30.6)	17.4	10.9 (9.6-12.1)	10.4	7.0 (6.0-8.0)	2.5	3.8 (3.0-4.6)	0.0	2.9 (2.0-3.8)
	GvHD	10.5		6.7		4.7		2.2		1.0	
	NDRM	22.2		12.2		10.0		6.1		4.6	
CML/CLL (n=742)	DRM	8.9	14.1 (12.7-15.4)	6.6	6.2 (5.3-7.2)	3.9	4.7 (4.0-5.5)	2.5	3.1 (2.4-3.7)	0.9	1.8 (1.3-2.4)
	GvHD	20.5		8.8		6.1		1.9		0.4	
	NDRM	31.5		15.2		11.5		4.7		1.6	
NHL/HL (n=467)	DRM	18.7	21.3 (18.7-23.9)	15.1	9.3 (7.5-11.0)	8.9	6.2 (4.7-7.6)	5.7	3.4 (2.2-4.6)	0.0	2.1 (0.8-3.4)
	GvHD	12.3		4.1		3.6		0.8		0.0	
	NDRM	22.4		11.4		8.9		4.7		2.6	
MDS (n=438)	DRM	14.9	17.8 (15.5-20.0)	13.2	6.6 (5.2-8.0)	9.9	4.6 (3.4-5.8)	4.7	2.6 (1.5-3.6)	0.0	1.8 (0.5-3.0)
	GvHD	12.7		4.5		3.6		4.6		0.0	
	NDRM	26.2		10.5		8.1		5.8		5.6	
SAA (n=198)	DRM	4.5	13.9 (10.1-17.6)	0.7	5.4 (3.1-7.7)	0.0	3.6 (1.7-5.6)	0.0	2.7 (1.0-4.3)	0.0	1.5 (0.2-2.9)
	GvHD	6.4		3.3		1.5		0.0		0.0	
	NDRM	11.1		5.3		2.2		0.0		0.0	

DRM=Disease-related mortality; NDRM=Non-disease-related mortality
ALL=Acute lymphoblastic leukemia; AML=Acute myeloid leukemia; CML=Chronic myeloid leukemia; CLL=Chronic lymphocytic leukemia
NHL=Non-Hodgkin lymphoma; HL=Hodgkin Lymphoma; MDS=Myelodysplasic syndrome; SAA=Severe aplastic anemia

Patient eligibility population:

- Patients with diagnosis of severe aplastic anemia (excluding congenital bone marrow failures)
- Transplanted between 2000 and 2014
- Any age/gender
- Use of bone marrow or peripheral blood grafts

Data requirements:

- Patient characteristics (Age, Gender, KPS, etc.)
- Disease-specific characteristics (Prior treatments, Time from diagnosis to BMT, Iron overload and ferritin levels, if available, CBC (ANC, Hb, platelets) at presentation and at BMT, Cytogenetic abnormalities)
- HCT-related variables:
  - Year of HCT
  - conditioning regimen including type of ATG
  - dose of CY in conditioning
  - GVHD prophylaxis
  - donor type (all MUD; 7/8 vs. 8/8) and age
  - graft source (bone marrow graft)
  - total nucleated cell dose/CD34+ cell dose (if available)
  - donor-recipient sex match (Female to Male vs. others)
  - donor-recipient CMV status
  - donor-recipient ABO blood group

- Outcome measures
  - Vital status
  - Causes of death
  - non-relapse mortality (NRM)
  - Graft failure (primary and secondary)
  - Graft-versus-host disease (GVHD): acute GVHD grade 2-4/3-4and onset data, chronic GVHD (limited/extensive or mild/moderate/severe and onset data, if available)

Study design:
The study will be a multi-center retrospective analysis of patients (registered at CIBMTR), who underwent alloHCT for SAA from 1995 and 2006 (n=1718 according to reference 1) with follow up through 12/31/2016. Descriptive analyses of patient-, disease- and donor-variables will be performed. Kaplan-Meier curves will be used to estimate OS. Cumulative incidence curves will be computed for NRM, graft failure, acute and chronic GVHD by accounting for competing risks. Probabilities of OS, NRM, graft failure, and GVHD at specified time points and their 95%CIs will be estimated from these curves.
The primary objective will be to derive the 5-year conditional survival rates for patients who survived 1, 2, 5, and 10y after BMT. Descriptive analysis will be performed for causes of death. Cumulative incidence curves will be used for cause-specific mortality. Multivariate analyses for OS will be performed using the Cox proportional hazards model. For cause-specific survival and other outcomes, the proportional sub-distribution hazards model accounting for competing risks and covariates will be employed.
The covariates to be evaluated will include patient-specific variables (age, gender, KPS, HCT-CI if available), disease-related variables (time from diagnosis to BMT, treatment before transplantation), and transplant-related variables (7/8 vs. 8/8 HLA match, source of graft [BM vs. PBSC], GVHD prophylaxis, donor-recipient sex match, donor-recipient CMV serostatus, year of transplantation). Potential correlations of outcomes among patients at the transplant center level will be adjusted using robust standard errors in the multivariable regression models (3).
Comparison of the outcomes between BMT and IST will be conducted by including the group indicator variable adjusted for demographic and clinical variables in multivariate regression methods. Recognizing that the two groups may vary in ways that cannot be totally adjusted by inclusion of covariates in the model, we will also employ propensity score analysis, applying the multivariate regression models within groups of individuals with similar propensity scores, to better equalize the two groups.
The survival rates at 1y, 2y, and 5y among 1718 SAA patients were 0.76, 0.73, and 0.70 respectively (ref 1). Hence, the sample size expected for 1y-, 2y-, and 5y-survivors are 1306, 1254, and 1203, respectively. Assuming the 5y survival rate in these patients to be 80%, these sample sizes will produce a 95% confidence intervals with a width of 0.045, or 0.78 to 0.82, for the 5-year survival rate for 1y-, 2y-, and 5y-survivors. For survival rates > 0.80, the width of the 95% CI will be less.
A cohort of patients from NHLBI will be analyzed similarly. The exact number of cases and data available are still pending at this time of submission, and will be updated as soon as the numbers become known to the study team. The observations for those who initially received IST, then, subsequently underwent HCT will be censored at the time of HCT.

Non-CIBMTR data source:
SAA cases treated at the National Heart, Lung, and Blood Institute (Dr. Neal Young).

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Characteristics of patients undergoing first allogeneic HCT for severe aplastic anemia with bone marrow graft and Fludarabine-containing regimen, and surviving at least one year post-HCT registered to the CIBMTR, TED-track

Characteristic	TED N (%)
Number of patients	**2111**
Age at transplant, years	
Median (range)	19 (2-76)
0-9	398 (19)
10-19	713 (34)
20-29	443 (21)
30-39	244 (12)
40-49	140 (7)
50-59	106 (5)
60+	67 (3)
Sex	
Male	1219 (58)
Female	892 (42)
Donor type	
HLA-identical sibling	1304 (62)
Unrelated	807 (38)
Graft type	
Bone marrow	1706 (81)
Peripheral blood	405 (19)
Conditioning intensity	
Myeloablative	567 (27)
TBI/Cy	253 (12)
TBI/Cy/Flu	102 (5)
TBI/Cy/TT	7 (<1)
TBI/Cy/VP	1 (<1)
TBI/Flu	4 (<1)
TBI/other(s)	3 (<1)
Bu/Cy	158 (7)
Bu/Mel	2 (<1)
Flu/Bu	19 (<1)
Flu/Mel/TT	9 (<1)
Flu/Mel	9 (<1)

Characteristic	TED N (%)
Reduced intensity	1544 (73)
TBI/Cy	64 (3)
TBI/Cy/Flu	144 (7)
TBI/Cy/Flu/TT	1 (<1)
TBI/Flu	18 (<1)
Flu/Bu	56 (3)
Flu/Mel	36 (2)
Cy/Flu	339 (16)
Cy alone	886 (42)
Year of transplant	
2000-2005	559 (26)
2006-2010	765 (36)
2011-2015	787 (37)
Median follow-up of survivors (range), months	71 (12-218)

Estimated conditional mortality of one-year, two-year, three-year, five-year, and seven-year survivors following allogeneic HCT for severe aplastic anemia

	1-year survivors (N=2111)	2-year survivors (N=1981)	3-year survivors (N=1797)	5-year survivors (N=1265)	7-year survivors (N=755)
Mortality over next 1 year (%)	2.5	1.8	1.0	1.0	1.0
Mortality over next 3 years (%)	5.3	3.5	2.7	3.0	3.5
Mortality over next 5 years (%)	6.9	5.4	4.7	5.4	4.8

Proposal: 1811-175

Title:
Outcomes after Allogeneic Hematopoietic Cell Transplantation in Patients with Griscelli syndrome

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Hypothesis:
Griscelli syndrome type 2 is an autosomal, recessively inherited disease. Phenotypically, it is associated with hypopigmentation (characterized by the silvery sheen of a patient's hair and eyelashes) and hemophagocytic lymphohistiocytosis (HLH), which is fatal if not treated.[1] Characteristic hypopigmentation is a common feature among individuals with GS1, GS2, and GS3.
GS1, caused by a myosin 5a-defect, mostly associates the hypopigmentation with a primary neurologic impairment presenting with muscular hypotonia at onset, mental retardation, or regressive neurologic processes,[2,3] while GS3, caused by a melanophilin-defect is restricted to hypopigmentation.[4] GS2 is caused by mutations in the gene encoding the small GTPase Rab27a.[5] Rab27a-deficiency causes defects in the exocytosis of cytotoxic granules from T cells and natural killer (NK) cells (accounting for an impaired cytotoxicity [6]) and melanosome exocytosis. In 2009, French group published data on 10 patients who received alloHCT for Griscelli syndrome type 2, 7 patients survived[7]. Since then 3 studies were published (Saudi Arabia, Turkey and Iran) with combined n of 21 patients [8-10]. Studies from large databases have never been published. We hypothesize that CIBMTR database will have enough number of patients to provide reasonable estimates of overall survival among children with Griscelli syndrome who have received alloHCT.

Specific aims:
To study 2 years' overall survival among patients undergoing alloHCT for Griscelli syndrome

Scientific impact:
Based on the communication with CIBMTR 45 patients between 2000-2017 have received AlloHCT for Griscelli syndrome with 66% overall survival at 2 years. This information will be important for pediatric alloHCT community and parents for counselling and prognostication. Potentially we can also understand risk factors associated with poor outcome.

Scientific justification:
Over last 20 years, 4 small single center retrospective studies were published, total number of patients included in those studies is 31. CIBMTR has data on 45 patients, this study if published will be largest ever and can potentially provide information regarding risk factors associated with poor outcomes.

Patient eligibility population:
- Diagnosis Griscelli syndrome
- Age < 21 years old
- Years 2000-2017

Data requirements:
- Age and gender of recipient
- Age and gender of donor

- Performance score
- History of hemophagocytic lymphohistiocytocis.
- Date of alloHCT
- Date of Diagnosis
- Time to alloHCT from original diagnosis
- CMV serological status of donor and recipient
- Donor type
- Stem cell source
- Degree of HLA match
- Conditioning regimen
- Use of ATG/alemtuzumab
- TNC/CD34 count of cells infused
- Date of ANC and platelet recovery
- Primary or secondary graft failure
- Incidence and grades of acute GVHD
- Incidence of limited or chronic GHVD
- Overall survival at 1, 2, and 3 years post HCT

Study design:

- Retrospective study
- The primary endpoint will be overall survival
- Other outcomes
- Time to neutrophil engraftment
- Platelet engraftment
- Incidence of acute graft-versus-host disease (GVHD), and chronic GVHD.
- Cause of death

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Characteristics of patients undergoing first allogeneic HCT for Griscelli syndrome in US registered to the CIBMTR

Characteristic		TED N (%)		CRF N (%)
Number of patients		**53**		**24**
Age at transplant, years				
Median (range)		1 (<1-15)		1 (<1-15)
0-9		49 (92)		22 (92)
10-19		4 (8)		2 (8)
Sex				
Male		29 (55)		11 (46)
Female		24 (45)		13 (54)
Donor type				
HLA-identical sibling		18 (34)		5 (21)
Other related		11 (21)		6 (25)
Unrelated		24 (45)		13 (54)
Graft type				
Bone marrow		28 (53)		12 (50)
Peripheral blood		8 (15)		4 (17)
Umbilical cord blood		17 (32)		8 (33)
Conditioning intensity				
Myeloablative	46 (87)		22 (92)	
Bu/Cy		32 (60)		17 (71)
Bu/Mel		1 (2)		1 (4)
Flu/Bu/TT		2 (4)		1 (4)
Flu/Bu		6 (11)		1 (4)
Flu/Mel		2 (4)		0
Treosulfan		2 (4)		2 (8)
Bu/Thio		1 (2)		0
Reduced intensity	7 (13)		2 (8)	
Flu/Bu		1 (2)		0
Flu/Mel/TT		1 (2)		0
Flu/Mel		4 (8)		1 (4)
Treosulfan		1 (2)		1 (4)
Year of transplant				
2000-2004		9 (17)		9 (38)
2005-2009		15 (28)		6 (25)
2010-2017		29 (55)		9 (38)

Proposal: 1811-180

Title:
Hematopoietic Stem Cell Transplantation for Congenital Amegakaryocytic Thrombocytopenia

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Hypothesis:
Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare inherited bone marrow (BM) failure syndrome characterized by severe thrombocytopenia with reduced or absent megakaryocytes in the BM, absence of physical anomalies and progression into aplastic anemia and secondary myeloid malignancies. It is caused by a mutation in the c-mpl gene, resulting in a complete loss or altered function of the TPO receptor (1).
CAMT is the rarest of the inherited marrow failure syndromes (IBMFS). Only 100 patients are included on the "Blanche Alter IBMFS table" (2). A PubMed search reveals only 113 publications.
A search for hematopoietic stem cell transplantation for CAMT reveals only 5 publications over the last 10 years, with a total of 13 patients, all of whom are alive post transplant (3-6). These include three patients transplanted at our institutions who are all three alive and disease free.
Clearly, several questions can be derived from this review and reports: (1) Are there patients with CAMT who were transplanted and did not well and therefore not published? Or What is the denominator of transplants for CAMT? A review of published reports was added to our report – See table 1. (2) There reports reveal different approaches for transplantation of these patients: umbilical cord blood grafts vs other grafts, unrelated donors vs mismatched related donors, reduced intensity vs myeloablative cytoreduction; would there be an approach that is associated with better results? (3) Is CAMT similar to other non-malignant hematological disorders in a way such, that younger patients do better than older patients or otherwise, does age at transplant matter? (4) What percentage of patients with CAMT proceeded to transplant with thrombocytopenia only, or aplastic anemia, or leukemia; what was the outcome of these different stages of disease?
A second aspect of this disease is important: Little is known of patients CAMT long term follow-up. Are there other aspects of these diseases that are not known because (1) there were too few patients and (2) these patients did not survive prior to the availability of HSCT. At least one of our three patients has significant developmental delay and one other patient has short stature.
Lastly, most of the IBMFS have one or more disease-specific databases / registries but there is none for this disease, which also contributes with the paucity of clinical information on the clinical aspects of this disease. A CAMT registry would be a very helpful tool to be able to better understand the clinical course of this disease

Table 1 Unrelated HSCT in patients with CAMT

Reference	*Age at SCT (months)*	*Donor HLA match SCT source*	*Conditioning*	*Cell dose Nucl cells/Kg*	*GVHD prophylaxis*	*Engraftment Neut/Plt*	*Acute GVHD grade*	*Chronic GVHD grade*	*Outcome*
Henter[3]	21	UD, 9/10 BM	ATG/CY/TBI	5.7×10^8	CSA/MTX	D14/D23	1 Skin	No	Alive 12 months
MacMillan[4]	49	MUD × 2 1st BM 2nd PBSCT	1st Cy/TBI 2nd CY	3×10^8 13.6×10^8	CSA/MTX ATG/MP/CSA	D21/NR D12/NR	1 Skin	NR	Alive 16 months
	80	1st UD CB, 5/6 2nd MSib, BM 3rd UD CB, 5/6	CY/TBI/MP/ATG CY/ATG/MP	0.35×10^8 3×10^8 0.48×10^8	NR	No No D40/NR	1, Gut 2, Skin	NR	Alive 7 months
Lackner[5]	22	MUD BM	BU/CY/ATG	4×10^8	CSA/MTX	D21/D31	2	No	Died of bronchiolitis obliterans
	12	MUD BM	BU/CY/ATG	13.1×10^8	CSA/MTX	No	1	No	Died of infection
Kudo[6]	28	MUD BM	ATG/CY/TBI	5.5×10^8	CSA/MTX	D16/D30	NR	NR	Died of pneumonia at 1-year post SCT
	5	MUD BM	ATG/CY/TBI	7×10^8	MTX/tacro	D14/D24	NR	NR	Alive 3 months
Steele[7]	87	MUD BM	Flu/CY/ATG	13.5×10^8	CSA/steroids	D10/D7	1 Skin/Gut	Limited chronic gut	Alive 21 months
Savoia (2007)[11]	78	UD CB, 5/6	Thio/Flu	NR	NR	NR	4 Skin	Extensive chronic skin	Alive 6 months
Frangoul (2010)[8]	8	MUD	BU/CY/ATG	4.94×10^8	CSA/MMF	D18/D12	2 Skin	Limited chronic gut	Alive 22 months
	25	MUD	CY/ATG/TBI	3.78×10^8	CSA/MTX	D23/D20	0	No	Alive 29 months

Abbreviations: ATG = anti-thymocyte globulin; CB = cord blood; Flu = fludarabine; MMF = mecophenolate mofetil; MP = methylprednisolone; MUD = matched-unrelated donor; NR = not reported; Tacro, tacrolimus; Thio = thiotepa; UD = Unrelated donor.

Specific aims:

- Describe the outcome of HSCT in all patients with Congenital amegakaryocytic thrombocytopenia as reported to CIBMTR. We could also reach out to EBMT for their interest in collaborating on this project

- Study the impact of the following prognostic factors
    - Age
    - Hematologic status – Thrombocytopenia – Aplastic anemia – MDS AML
    - Donor and grafts
    - Type of cytoreduction
    - GvHD prophylaxis

- Obtain information on late effets and long term follow up in patients with CAMT. We will develop a “simple” long term outcome questionnaire to be completed by the transplant centers involved in the CIBMTR data. Given the probable low patient number (15-25?) we anticipate that this will be a feasible effort.

Scientific impact:
Report the outcome of a very rare disease, which will provide us tools to develop guidelines and recommendations for the treatment of this disease.

Scientific justification:
Except for some case reports and small case series no registry report / analyses have been done for this rare condition yet. It is important to have ‘unbiased’ outcome data report on the outcome of this disease. This could help us develop guidelines and recommendations for the management of this disease.

Patient eligibility population:
All patients registered to CIBMTR (and possibly EBMT) database who received a hematopoietic stem cell transplant for congenital amegakaryocytic thrombocytopenia, without any restrictions. We assume this will not be a very large number ~ 15-30 patients?

Data requirements:
Optimally, we would prefer CRF data. If we only have access to TED data only, then we would like to reach out to the different center for more detailed information, especially for long term follow-up and late effects of transplantation. As mentioned above, given how rare this disease is, we would expect that it will be feasible to reach out to the centers and complete a database for this disease.

Study design:

- Obtain data on all patients with CAMT who received an HSCT and have been reported to CIBMTR.
- Consider doing the same for EBMT data
- Then:
    - Analyze data and study prognostic factors on outcome including age, Hematologic status, donor and grafts, type of cytoreduction, GVHD prophylaxis
    - Create short questionnaire on long term follow-up and late effects including constitutional and psychosocial aspects that are possibly inherent to this disease and those that are more specifically post-transplant.

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Characteristics of patients undergoing first allogeneic HCT for Congenital Amegakaryocytic Thrombocytopenia (CAMT) in US registered to the CIBMTR

Characteristic	TED N (%)	CRF N (%)
Number of patients	**66**	**37**
Age at transplant, years		
Median (range)	3 (<1-53)	2 (<1-53)
0-9	61 (92)	34 (92)
10-19	2 (3)	1 (3)
20-29	1 (2)	1 (3)
50-59	2 (3)	1 (3)
Sex		
Male	26 (39)	13 (35)
Female	40 (61)	24 (65)
Donor type		
HLA-identical sibling	11 (17)	3 (8)
Other related	3 (5)	3 (8)
Unrelated	52 (79)	31 (84)
Graft type		
Bone marrow	38 (58)	15 (41)
Peripheral blood	8 (12)	6 (16)
Umbilical cord blood	20 (30)	16 (43)
Conditioning intensity		
Myeloablative	47 (71)	30 (81)
TBI/Cy	4 (6)	4 (11)
TBI/Cy/Flu	2 (3)	1 (3)
TBI/Flu	1 (2)	1 (3)
Bu/Cy/Mel	1 (2)	0
Bu/Cy	30 (45)	21 (57)
Bu/Mel	2 (3)	2 (5)
Flu/Bu/TT	1 (2)	0
Flu/Bu	3 (5)	0
Flu/Mel/TT	2 (3)	1 (3)
Missing	1 (2)	0
Reduced intensity	19 (29)	7 (19)
Flu/Mel/TT	4 (6)	1 (2)
Flu/Mel	10 (15)	3 (7)
Cy/Flu	4 (6)	3 (7)
Cy alone	1 (2)	0

Characteristic	TED N (%)	CRF N (%)
Year of transplant		
2000-2004	12 (18)	10 (27)
2005-2009	17 (26)	14 (38)
2010-2014	21 (32)	5 (14)
2015-2018	16 (24)	8 (22)