MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR REGIMEN-RELATED TOXICITY AND SUPPORTIVE CARE
Orlando, FL
Friday, February 24, 2017, 12:15 – 2:15 pm

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1. Introduction
Dr. Artz announced the CIBMTR Regimen-Related Toxicity and Supportive Care Committee (RRTWC) meeting started at 12:15 pm on Friday, February 24, 2017. He introduced the RRTWC leadership, the goals, area of focus and limitation of the RRTWC. A brief comparison of Transplant Essential Data (TED) and Comprehensive Report Forms (CRF) was also explained to members to better understand the CIBMTR data sources.

2. Accrual summary (Attachment 2)

3. Presentations, published or submitted papers


4. **Studies in progress** (Attachment 3)
   a. **RT07-01b** Prospective validation of the impacts of the hematopoietic cell transplantation comorbidity index, alone and combined with aging on hematopoietic cell transplantation outcomes (M Sorror/M Thakar) **Analysis**
   b. **RT13-02** Safety of high-dose total body irradiation followed by an allogeneic hematopoietic cell transplant for hematologic malignancies (M Sabloff) **Manuscript preparation**
   c. **RT14-01** Trends and risk factors for infant mortality following allogeneic hematopoietic cell transplant: Case-Control study (P Satwani/S Parikh) **Data file preparation**
   d. **RT14-02** Endothelial injury complications after allogeneic hematopoietic cell transplantation (S Davies/ W Chinratanalab/S Jodele/M Ramanathan/B Laskin) **Protocol development**
   e. **RT14-03** Multicenter cohort identification of transplant-related risk factors for infection, organ failure, and mortality among pediatric hematopoietic stem cell transplant patients requiring intensive care unit admission (C Dvorak/M Zinter/A Sapru) **Data file preparation**
   f. **RT15-01** Comparison of outcomes for myeloablative conditioning regimens combining busulfan with either cyclophosphamide or fludarabine (A Harris/J Levine) **Manuscript preparation**
   g. **RT15-02** Association of anti-epileptic medication with outcomes after conditioning with targeted busulfan followed by cyclophosphamide before allogeneic hematopoietic cell transplantation (PJ Martin/ JS McCune) **Protocol development**
   h. **RT16-01** Effect of chemotherapy dose adjustments on the outcomes of autologous HCT in patients with lymphoma and multiple myeloma (C Brunstein/ J Rogosheske/ MA Perales) **Protocol development**
   i. **RT16-02** Evaluation of lung toxicity following allogeneic stem cell transplant with fludarabine/total body irradiation conditioning regimen (A Saad/ K Mingawa/ Y Kanda/ S Mineishi) **Protocol development**

5. **Future/proposed studies**
   a. **PROP 1610-05** Transplant outcomes of reduced intensity conditioning with Fludarabine, Melphalan and Alemtuzumab: A CIBMTR/ NMDP database analyses (MK Veeraputhiran/R Ravilla/S Arai) (Attachment 4)

Dr. Veeraputhiran presented the proposal. The hypothesis is that fludarabine melphalan (FMC)-alemtuzumab conditioning regimen has similar NRM and OS rate as fludarabine busulfan (FB) – ATG and fludarabine melphalan (FM) –ATG and reduce incidence of aGVHD and cGVHD. The proposal is to 1) analyze cumulative probability of overall survival and disease free survival at two years and 5 years with FMC conditioning compared to other 2 RIC regimens; 2) determine and compare non relapse mortality (NRM) and relapse rate (RR) at 100 days, 1 and 2 years and subset analyses with varying doses of Campath, HCT-CI scores and disease risk index; 3) determine incidence of acute GVHD grades II-IV with varying doses of Campath; 4) determine incidence of chronic GVHD grades (mild, moderate and severe) with varying doses of Campath.

The discussion raised the concern about the use of Campath which can reduce the incidence of aGVHD and cGVHD but might increase disease relapse. The other concern was the number of cases and heterogeneity of cases in the Flu-Mel –Campath group.

b. **PROP 1611-18** Prognostic analyses of the intensified myeloablative regimens for acute leukemia in adults (Y Arai) (Attachment 5)
Dr. Arai presented the proposal. The hypothesis from investigator is that intensified myeloablative regimens, such as high-dose cytarabine or etoposide added to the conventional CY/TBI or Bu/CY, can suppress the post-transplant relapse and improve the prognosis. The Aims of proposal are to 1) determine the precise type and frequency of intensified myeloablative regimens used in the conditionings for acute leukemia; 2) confirm the prognostic differences between the conventional and intensified myeloablative regimens in each disease status and donor source.

Shin commented that if adding intensified myeloablative regimens to CY/TBI or Bu/Cy the results might be worse than CY/TBI or Bu/Cy only.

c. **PROP 1611-19** The impact of pharmacokinetic dose escalation of “myeloablative busulfan” on patients with acute myeloid leukemia in complete remission undergoing HLA-matched allogeneic hematopoietic stem cell transplant (HCT) after fludarabine-based regimens (A Saad/M de Lima/S Mineishi) (Attachment 6)

Dr. Saad presented the proposal. The hypothesis is that among patients with acute myeloid leukemia (AML) in complete remission, escalation of “myeloablative” busulfan exposure (by pharmacokinetic AUC dosing) is associated with less relapse rate. However, increased non-relapse mortality may preclude overall survival benefit in these patients.

The proposal is to 1) compare the relapse rate at 1 year of patients with AML in CR who had different “myeloablative” busulfan exposure; 2) compare non-relapse mortality in the same patient groups; 3) compare the overall survival and disease-free survival in the same patient groups.

Marcelo clarified to committee members that the forms do capture intended Bu dose by PK, but it does not capture whether actual PK results. The question in this proposal is important but it will require supplemental data from reference labs in order to obtain details of Bu exposure.

d. **Prop 1611-67** Allogeneic hematopoietic stem cell transplant outcome for patients with end stage renal disease on dialysis (N Farhadfar/JR Wingard/H Murthy) (Attachment 7)

Dr. Farhadfar presented the proposal. The hypothesis is that allogeneic hematopoietic stem cell transplant in patients with end stage disease requiring dialysis is feasible with well-designed transplantation strategy and supportive care. The aims are: 1) the primary objective of the study is to determine the clinical outcomes of patient who underwent allogeneic hematopoietic cell transplant while on renal replacement therapy/ dialysis. Primary end point is overall survival; 2) secondary endpoints are median time to neutrophil engraftment, median time to platelet engraftment, non-relapse mortality, disease free survival, relapse rate, post-transplant infection rate, and cumulative incidences of acute and chronic graft versus host disease.

A member raised the question why there is not a study on allogeneic HCT for patients who require dialysis. The fact is that we did try to study in the past but it failed due to data quality. Now data collection is getting better. The CIBMTR has more HCT data for patients on
dialysis.

e. **Prop 1611-69** Impact of HCT-CI over time on outcomes of first allogeneic hematopoietic stem-cell transplantation, in patients with myeloid and lymphoid hematologic malignancies (M Gooptu/J Koreth) (Attachment 8)

Dr. Gooptu presented the proposal. The hypothesis is that patients with higher HCT-CI scores may have significantly improved NRM, and therefore survival outcomes, in the current era, indicating a need to re-evaluate the predictive value of the HCT-CI score and the cut-offs utilized for stratifying patient’s low or high-risk HCT-CI scores. The aims are to 1) evaluate NRM at 2 years in patients stratified by low (0-2) and high (>/=3) HCTCI scores, in patients undergoing first HSCT for myeloid and lymphoid malignancies from 2013-2015; 2) evaluate 2-year survival outcomes (overall survival or OS, disease-free survival or DFS) in patients stratified by low (0-2) and high (>/=3) HCTCI scores in patients undergoing first HSCT for myeloid and lymphoid malignancies from 2012-2015; 3) compare NRM as well as OS and DFS in these patients, stratified by HCT-CI score, over three distinct time periods namely 2006-2009, 2010-2012 and 2012-2015 to evaluate the change in survival outcomes with time; 4) descriptive analysis of change in outcomes over time for patients with lower and higher-risk disease in different HCT-CI categories, undergoing allogeneic stem-cell transplant; 5) re-evaluate the predictive power and cut-offs for HCT-CI scores, which define patients as low or higher-risk, during pre-transplant evaluation

HCT-CI score has become an important factor for center performance evaluation. This might be one reason to explain HCT-CI scoring improve over time. The other reason could be that Dr. Sorror who created HCT-CI published a follow-up paper that might impact centers how to HCT-CI.

f. **Prop 1611-110** Choice of Conditioning Regimen in Particular Total Body Irradiation affects patient outcomes in Acute leukemia with Skin Involvement (Leukemia Cutis) (K Adekola/J Gavin/J Altman) (Attachment 9)

Dr. Galvin presented the proposal. The hypothesis is that the use of total body irradiation (TBI) in the preparative (conditioning) regimen improves outcomes in patients with extramedullary leukemia involving the skin (leukemia cutis). The proposal is to 1) describe characteristics of patients greater than 18 years old with leukemia cutis who had a stem cell transplant most especially an allogeneic HSCT; 2) evaluate differences in survival and outcomes for patients with leukemia cutis who got TBI as part of their preparative (conditioning) regimen versus those who did not; 3) evaluate factors that affected and predicted for outcomes in patients with leukemia cutis who had an allogeneic HSCT

Some members concerned about the TBI dosing and certain body area boost radiation dosing because some centers might report as a part of total TBI dose.

g. **Prop 1611-74** Rates of Early Donor Chimerism in Patients with myeloid malignancies Undergoing Stem Cell Transplantation Using FluBu4 with and without Busulfan Pharmacokinetics versus BuCy (S Farhan/N Janakiraman/E Peres) (Attachment 10)

Dr. Farhan presented the proposal. The hypothesis is that patients with myeloid malignancies who get fludarabine and busulfan (FluBu4) with Bu kinetics has a trend for
higher early donor chimerism similar to busulfan with cyclophosphamide (BuCy). The aims are 1) to study the impact of BuCy vs FluBu4 with Bu Kinetics vs FluBu4 without Bu Kinetics on total and T lymphocyte chimerism evaluated between day d30 to d120 after transplantation in patients with myeloid disorders undergoing allogeneic HSCT; 2) Other endpoints of interest will be relapse, non-relapse mortality, disease free survival and graft-versus-host disease.

Marcelo clarified the availability of chimerism data in CIBMTR database, which has tremendous variability as certain practices vary. There are ways in order to address this variability. Based on past studies, availability of sorted chimerism is in a subset of patients.

h. **Prop 1611-148** Impact of early donor chimerism on relapse and survival after allogeneic hematopoietic stem cell transplantation (HSCT) (AC Hall/CR D’Angelo) (Attachment 11)

Dr. D’Angelo presented the proposal. The hypothesis is that multiple donor and transplant factors that have predictive value for outcomes post-allogeneic transplant have their benefit mediated by influencing the rate of early full donor T-cell chimerism, with patients who achieve early full donor T-cell chimerism having similar superior outcomes regardless of donor or transplant factors. The aims are to 1) investigate the impact of donor age, donor relationship, conditioning regimen, and pre-transplant lymphopenia on achievement of early (arbitrarily defined as at day +100) full donor T-cell chimerism following allogeneic HSCT for hematologic malignancies; 2) investigate the impact of the above variables on early full donor T-cell chimerism and on the risks of relapse, GVHD, NRM, and death following HSCT; 3) perform competing risk regression analysis to identify which of the factors identified are predictive of risks of relapse and death and univariate and multivariate analysis to determine which are independent predictors of the risks of relapse, non-relapse mortality, graft versus host disease, and death and determine if age, donor relationship, and cell dose have an impact independent of full donor T-cell chimerism.

Data for donor cell type chimerism is center specific. A past CIBMTR study indicated about 20% are T-cell chimerism. The investigator debated that although the trend of chimerism might be important they would like to focus on T-cell chimerism which might be the main factor for graft versus leukemia effect. The investigator tried to find what factors may affect the chimerism and how chimerism may affect post-transplant outcomes.

i. **Prop 1611-136** The Effect of Pre-Transplant Composite Comorbidity and Disease Risk Index (cDRI) on Survival after Allogeneic Hematopoietic Cell Transplantation (N Bejanyan/C Brunstein/D Weisdorf) (Attachment 12)

**Prop 1611-162** Integration of the hematopoietic cell transplantation comorbidity index (HCT-CI) and disease risk index (DRI) in estimation of transplant outcomes (Z DeFilipp/YB Chen) (Attachment 13)

Dr. Bejanyan presented the proposal for combined proposal 1611-136 and 1611-162. The hypothesis is that composite Comorbidity and Disease Risk Index (cDRI) is prognostic for overall survival (OS) after allogeneic hematopoietic cell transplantation (alloHCT) in patients with hematological malignancies. The aims are 1) primary endpoint: To study the effect of cDRI on OS of adult allograft recipients with hematological malignancies; 2) secondary endpoints: To study treatment-related mortality (TRM), relapse incidence and disease-free survival (DFS)
A study from the University of Minnesota using cDRI can distinguish risk group nicely for 2-year overall survival ranging from 34 – 74% on a small population. Therefore the investigator wants to approach CIBMTR for a large population for evaluate the findings. The advantage of DRI is able to divide small group well with fine resolution. The DRI is to summarize the disease risk groups. Whereas HCT-CI is to find the risk factors.

k. PROP 1610-10 Incidence and predictors of kidney dysfunction after allogeneic stem cell transplantation (HK Choe/S Lee) (Attachment 14)

Dr. Choe presented the proposal. The hypothesis is that post-transplant kidney failure is associated with acute and chronic GVHD and BKV infection. The proposal is to 1) identify risk factors associated with post-transplant kidney failure requiring renal replacement therapy (RRT). To identify non-modifiable risk factors (i.e., race, gender, age, comorbidities) and modifiable risk factors (i.e., conditioning regimen intensity, transplant type); 2) analyze the association of (1) acute GVHD, (2) chronic GVHD, and (3) BKV infection with subsequent requirement of RRT.

The variables of renal failure severe enough to warrant dialysis and receive dialysis are kind of new. We haven’t done a 2 by 2 table to exam how many patients with HCT-CI or renal dysfunction. This would be good opportunity to identify high risk factor.

Study Proposal Acceptance:

Prior to the meeting the CIBMTR Advisory Committee release recommendations for each committee with the numbers of proposals to be approved to proceed. The RRTWC was recommended to accept one proposal, given the number of study in progress and the total statistical hours allocated to the committee. The study RT17-01 (proposal 1611-67) was accepted based on voting scores, scientific impact in HCT community and feasibility.
a. **RT07-01b**: Prospective validation of the impacts of the hematopoietic cell transplantation co-morbidity index, alone and combined with aging on hematopoietic cell transplantation outcomes. We anticipate completing analysis in June 2017, preparing manuscript in July 2017, and submitting to peer-review journal by June 2018. (Total hour: 10; Allocated for the fiscal year: 10)

b. **RT13-02**: Safety of high-dose total body irradiation followed by an allogeneic hematopoietic cell transplant for hematologic malignancies. We anticipate completing manuscript in June 2017 and submitting to peer-review journal by July 2017. (Total hour: 10; Allocated for the fiscal year: 10)

c. **RT14-01**: Trends and risk factors for infant mortality following allogeneic hematopoietic cell transplant: Case-Control study. We will complete analysis in June 2016, prepare manuscript in July 2017, and submit to peer-review journal by June 2018. (Total hour: 70; Allocated for the fiscal year: 70)

d. **RT14-02**: Endothelial injury complications after allogeneic hematopoietic cell transplantation. We will complete data analysis by June 2017, prepare manuscript in July 2017 and submit manuscript by June 2018. (Total hour: 70; Allocated for the fiscal year: 70)

e. **RT14-03**: Multicenter cohort identification of transplant-related risk-factors for infection, organ failure, and mortality among pediatric hematopoietic stem cell transplant patients requiring intensive care unit admission. We will complete data analysis by June 2017, prepare manuscript in July 2017 and submit to peer-review journal by June 2018. (Total hour: 70; Allocated for the fiscal year: 70)

f. **RT15-01**: Comparison of outcomes for myeloablative conditioning regimens combining busulfan with either cyclophosphamide or fludarabine. The manuscript will be submitted to peer-review journal by June 2017. (Total hour: 10; Allocated for the fiscal year: 10)

g. **RT15-02**: Association of anti-epileptic medication with outcomes after conditioning with targeted busulfan followed by cyclophosphamide before allogeneic hematopoietic cell transplantation. Propose a survey to assess antiepileptic uses by centers to assess the feasibility of this study. We anticipate completing data file preparation in June 2017, completing analysis in July 2017 and preparing manuscript by June 2018. (Total hour: 100; Allocated for the fiscal year: 50)

h. **RT16-01**: Effect of BEAM dose adjustments on the outcomes of patients with lymphoma or multiple myeloma. We anticipate finalizing data file by June 2017, completing data analysis in July 2017 and preparing manuscript in June 2018. (Total hour: 100; Allocated for the fiscal year: 50)

i. **RT16-02**: Evaluation of lung toxicity following allogeneic stem cell transplant with fludarabine/total body irradiation conditioning regimen. We anticipate finalizing protocol, completing data file by June 2017, completing analysis in July 2017 and preparing manuscript by June 2018. (Total hour: 200; Allocated for the fiscal year: 150)
j. **RT17-01** (proposal 1611-67): Allogeneic hematopoietic stem cell transplant outcome for patients with end stage renal disease on dialysis. We anticipate to having a draft protocol by June 2017. (Total hour: 60; Allocated for the fiscal year: 60)

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### Oversight Assignments for Working Committee Leadership (March 2017)

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<th>Name</th>
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