MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR REGIMEN-RELATED TOXICITY AND SUPPORTIVE CARE
San Diego, CA
Saturday, February 14, 2015, 2:45 – 4:45 pm

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1. Introduction
Dr. Artz announced the CIBMTR Regimen-Related Toxicity and Supportive Care Committee (RRTWC) meeting started at 2:45 pm on Saturday, February 14th, 2015. He introduced the leadership of RRTWC. Dr. Shin Mineishi was welcomed to RRTWC as the incoming chair starting from March 2015. The outgoing chair Dr. Philip L. McCarthy was acknowledged for his services from the CIBMTR. Dr. Artz explained working committee’s membership to all attendees that CIBMTR working committees are open to any individual willing to take an active role in study development and completion. All members who attend the working committee meetings during the Tandem BMT meeting are automatically added to the working committee membership.

2. Dr. McCarthy updated the members on some studies recently submitted, published or presented.
   c. **RT11-01** Yi-Bin Chen, Andrew A. Lane Brent Logan, Xiaochun Zhu, Görgün Akpek, Mahmoud Aljurf, Andrew Artz, Christopher N. Bredeson, Kenneth R. Cooke, Vincent T. Ho, Hillard M. Lazarus, Richard Olsson, Wael Saber, Philip McCarthy, Marcelo C. Pasquini. Impact of Conditioning Regimen on
Outcomes for Patients with Lymphoma Undergoing High-Dose Therapy with Autologous Hematopoietic Cell Transplantation. Accepted by BBMT (2015) right before Tandem meeting.


3. Studies in progress

Dr. Pasquini briefly summarized the studies that were in progress but not presented. Due to several studies in manuscript stage, the activities during the second semester of 2014 were dedicated in submission and re-submission of all these manuscripts. Other studies in protocol or dataset stages were pushed for this semester.

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 (M Sorror/M Thakar). The current status is manuscript preparation.

b. **RT10-01** Pre-transplant C-reactive protein (CRP), ferritin and albumin as biomarkers to predict transplant related mortality (TRM) after allogeneic hematopoietic cell transplant (HCT) (A. Artz). Presentation at ASH 2014. PI is working on manuscript.

c. **RT12-03** Transplant in older adults: is it feasible in those 70 years and older? (L Muffly/A Artz). The current status is protocol development.

d. **RT13-01** In-hospital mortality among allogeneic hematopoietic cell transplant recipients that develop critical illness in the early post-transplantation period: a nationwide temporal trend analysis (1998 - 2010) (S Kadri/ S Hohmann). The protocol development was completed and activities were stalled during the dataset stage. This study requires data merge with UHC to obtain certain diagnosis or procedure codes that could help define a critical illness or ICU care. These data are collected by UHC. However, UHC is quality database and not necessarily built for research utilization as patients are not specifically consented. Thus after several discussions, UHC felt that they could not share this data directly with CIBMTR. One alternative is to the request through the centers directly as a supplemental data collection. The plan is to run this in two sites first in order to understand and verify this process.

e. **RT13-02** Safety of high-dose total body irradiation followed by an allogeneic hematopoietic cell transplant for hematologic malignancies (M Sabloff). The current status is protocol development.

f. **RT14-01** Trends and risk factors for infant mortality following allogeneic hematopoietic cell transplant: Case-Control study (P Satwani/S Parikh). The current status is protocol development.
g. **RT14-02** Endothelial injury complications after allogeneic hematopoietic cell transplantation (S Davies/ W Chirratanalab/S Jodele/M Ramanathan/B Laskin). The current status is protocol development.

h. **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). The current status is protocol development.

### 4. Future/Proposed studies

Drs. Loren and McCarthy led this section. The proposals were the following:

a. **PROP 1407-01** Association of anti-epileptic medication with outcomes after conditioning with targeted busulfan followed by cyclophosphamide before allogeneic hematopoietic cell transplantation. (PJ Martin/JS McCune)  
Dr. Martin presented the proposal. The proposal plans to evaluate the safety of using levetiracetam as a replacement for phenytoin in preventing seizures caused by busulfan when followed by CY 60 mg/kg on two successive days as the conditioning regimen before allogeneic hematopoietic cell transplantation. Safety will be evaluated primarily through measures of hepatic toxicity and secondarily through measures of non-relapse mortality, relapse or progression of malignant disease and overall survival. The study requires a center survey to determine anti-seizure prophylaxis practices and time windows. However, it would be important to understand if there are sufficient amount of centers that are still using phenytoin in order to make this study feasible. Additionally, the information related to PK as prescribed in the eligibility of this proposal might require additional information from centers. One alternative is to request PK results directly from centers. This proposal was approved by the committee.

b. **PROP 1410-02** Scoring system to predict major outcomes after hematopoietic cell transplantation in elderly population. (C Ustun/D Weisdorf) 
Dr. Ustun presented the proposal. The proposal is 1) to develop a scoring system (SS) to predict their major outcomes for older patients receiving alloHCT for hematologic malignancy (leukemias, lymphomas, myeloma); 2) to validate this SS (training on 2/3; validation on 1/3); 3) to develop a user-friendly web-based calculator (to be used by health care providers) to predict estimated outcomes for individual patients; 4) to evaluate the differences between 60-69yo and 70+ patients; 5) to evaluate survival, TRM, relapse, acute and chronic GVHD.  
The main concern was the age scoring system could not be easily distinguished from other scoring systems, e.g. HCT-CI, DRI. The proposal was not approved due to low impact score from committee members voting and input from the committee leadership.

c. **PROP 1411-11** Prediction of Allogeneic Hematopoietic Stem Cell Transplantation Outcomes: Development and Validation of Machine Learning Based Models. (R Shouval/A Nagler/B Savani) 
Dr. Shouval presented the proposal. The proposal is to 1) validate of the – Alternating Decision Tree (ADT) ML based prediction model for day 100 NRM. The model was developed on the registry of the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT); 2) develop ML based prediction models for long term allogeneic (allo) transplant related outcomes: NRM, overall survival (OS), leukemia free survival (LFS), Relapse incidence (RI); 3) establish a data driven decision support systems for allo-HSCT candidate selection, in patients with hematologic malignancies, eligible for transplantation; 4) Introduce the data mining approach as a tool for HSCT data analysis.
Dr. Shouval explained the basic concepts to all members. Main concerns were: 1) how much effort need to clean large number of missing data; 2) although random forest was chosen appropriately for this study, it is unclear whether how much more information related to predictors of TRM this approach would provide in comparison to current standard methods. The proposal was not approved due to low impact score from committee members.

d. **PROP 1411-21** A case control study of health care utilization associated with hepatic veno-occlusive disease in pediatric patients receiving hematopoietic cell transplant: a subanalysis of CIBMTR study RT14-02. (S Arnold/P Satwani)

Dr. Arnold presented the proposal. The proposal is 1) to identify outcomes of VOD management with and without defibrotide; 2) to determine HCU associated with VOD.

A member concerned that it is difficult to identify patients who got severe VOD. The proposal was not approved due to low impact score from committee members.

e. **PROP 1411-50** Body Mass Index and Reduced Intensity Conditioning Hematopoietic Cell Transplantation (HCT) Regimens for Acute Myeloid Leukemia (AML) (C Yuen/SA Hopp/JH Chakrabarty)

Dr. Yuen presented the proposal. The proposal is to compare differences in overall survival, nonrelapse mortality, relapse, progression, progression-free survival, acute and chronic graft-versus-host disease (GVHD) and transplant-related mortality (TRM) after hematopoietic cell transplantation with reduced-intensity conditioning regimens for Acute Myeloid Leukemia (AML) of differing weight groups. Dr. Pasquini commented the actual/adjusted weight and dosing/intend regimen intensity in the CIBMTR data collection forms. A member raised a question if the hypothesis is true how the result will change the practice of transplant. Dr. Yuen responded that either prior transplant intervention can be done by reducing body weight or alternative treatment can be considered for high risk group of patients. The proposal was not approved due to low impact score from committee members.

f. **PROP 1411-63** Comparison of outcomes for myeloablative conditioning regimens combining busulfan with either cyclophosphamide or fludarabine. (A Harris/JE Levine).

Dr. Harris presented the proposal. The primary aims of the proposal are: 1) to compare regimen-related toxicity (e.g., SOS, IPS, hemorrhagic cystitis) between children receiving myeloablative conditioning regimens consisting of fludarabine/busulfan and those receiving busulfan/cyclophosphamide; 2) to compare transplant-related complications (primary graft failure, acute GVHD, infections, chronic GVHD) between children receiving myeloablative conditioning regimens consisting of fludarabine/busulfan and those receiving busulfan/cyclophosphamide; 3) to compare overall outcomes (non-relapse mortality, overall survival) at 2 years post-transplant between children receiving myeloablative conditioning regimens consisting of fludarabine/busulfan and those receiving busulfan/cyclophosphamide. The second aim is to compare relapse rates for the subset of patients receiving HCT for AML in CR between children receiving myeloablative conditioning regimens consisting of fludarabine/busulfan and those receiving busulfan/cyclophosphamide.

Currently 80% of pediatric busulfan-based transplants use Bu/Cy conditioning regimen. A member pointed out that more practices in Europe recommend using Flu/Bu in pediatric. Another important issue was raised related to limit the analysis to malignant disease due to the heterogeneity of the nonmalignant disease and the conditioning regimens used in this setting. The PI agreed with that approach.

This proposal was approved by the committee.
Working Committee Overview Plan for 2015-2016

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. We anticipate finalizing manuscript, circulating to writing committee in April 2015, submitting to peer-review journal in June 2015.

b. **RT10-01** Pre-transplant C-reactive protein (CRP), ferritin and albumin as biomarkers to predict transplant related mortality (TRM) after allogeneic hematopoietic cell transplant (HCT). We anticipate finalizing manuscript, circulating to writing committee in April 2015, submitting to peer-review journal in June 2015.

c. **RT12-03** Transplant in older adults: is it feasible in those 70 years and older? We will finalized data analysis by March 2015 and prepare manuscript by June 2015.

d. **RT13-01** In-hospital mortality among allogeneic hematopoietic cell transplant recipients that develop critical illness in the early post-transplantation period: a nationwide temporal trend analysis (1998 - 2010). We will finalized data analysis by March 2015 and complete analysis by June 2015.

e. **RT13-02** Safety of high-dose total body irradiation followed by an allogeneic hematopoietic cell transplant for hematologic malignancies. We will finalized data analysis by March 2015 and complete analysis by June 2015.

f. **RT14-01** Trends and risk factors for infant mortality following allogeneic hematopoietic cell transplant: Case-Control study. We will finalize protocol April 2015 and start data file preparation by June 2015.

g. **RT14-02** Endothelial injury complications after allogeneic hematopoietic cell transplantation. We will finalize protocol April 2015 and data file by May 2015. Analysis will be in June 2015.

h. **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 finalize protocol April 2015 and start data file preparation by June 2015.

i. **RT15-01 (proposal 1411-63)** Comparison of outcomes for myeloablative conditioning regimens combining busulfan with either cyclophosphamide or fludarabine. We anticipate to have a draft protocol by June 2016.

j. **RT15-02 (proposal 1407-01)** 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 to have a draft protocol by June 2016.
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