1. Introduction

Dr. Loren announced the CIBMTR Regimen-Related Toxicity and Supportive Care Committee (RRTWC) meeting started at 2:45 pm on Friday, February 19th, 2016. She introduced the leadership of RRTWC. Dr. Loren 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. Loren updated the members on some studies recently submitted, published or presented.


American Society for Blood and Marrow Transplantation. 2015 Sep 1; 21(9):1679-1686.


3. Studies in progress

Dr. Pasquini briefly summarized the studies that were in progress but not presented.

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). This study are 1) to investigate the interaction between comorbidities, aging and the addition of age intervals to the HCT-CI to form composite scores using retrospective data collected from 6 collaborative academic institutions; 2) to validate the comorbidities ± aging scores on HCT outcomes using data from the Center for International Bone Marrow Transplantation Registry (CIBMTR). The current status is manuscript preparation.

b. **RT12-03** Transplant in older adults: is it feasible in those 70 years and older? (L Muffly/A Artz). This study are 1) to describe the baseline characteristics of patients 70 years and older receiving an allogeneic hematopoietic cell transplant (HCT) reported to the CIBMTR; 2) to detail the secular trend in absolute numbers and proportion of all transplanted patients for adults 70 years and older undergoing HCT from 2000 to 2013, describe 1 year mortality rates and incidence of graft failure over time; 3) first Subset Analysis: To examine factors associated with survival outcomes post transplant in patients older than 70y with malignant disease from 2008 to 2013; 4) second Subset analysis: To assess TRM, disease relapse or progression, OS, DFS and GVHD among patients with early and intermediate acute leukemia/MDS and chemotherapy sensitive NHL at time of transplant from 2008 to 2013. Analyze factors associated with TRM and overall mortality in this second subset. The current status is manuscript preparation.

c. **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 aims are 1) to determine and trend the annual proportion of adults that develop critical illness following Allogeneic Hematopoietic Stem Cell Transplantation (Allo-HSCT) on the same hospitalization between 1998 and 2012; 2) to determine and trend ICU, in-hospital, 100 day, 200 day and 1 year mortality and readmission rates for each year’s cohort between 1998 and 2012 and identify predictors of mortality and short and long term survival; 3) to determine the incidence (and grade) of Acute and Chronic Graft Versus Host Disease (GVHD) following critical illness that develops in the early post Allo-HSCT period; 4) to assess the impact of graft source, donor/HLA status, underlying disease and regimen intensity on the development of critical illness and on short and long term survival following critical illness; 5) to understand the importance of clinical data points in transplantation that reflect critical illness, critical care utilization and outcomes to allow potentially valuable additions to CIBMTR data record forms. The current status is data file preparation.

d. **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 specific aims are: 1) to identify transplant-related risk factors for PICU mortality through multivariate regression; 2) to identify transplant-related risk factors for life-threatening infections in the PICU, including sepsis, gram-positive and gram-negative bacterial infections, fungal infections, and viral infections; 3) to identify transplant-related risk factors for organ dysfunction and life-saving interventions both on PICU admission and throughout PICU stay. The current status is data file preparation.

e. **RT15-01** Comparison of outcomes for myeloablative conditioning regimens combining busulfan with either cyclophosphamide or fludarabine (A Harris/J Levine). The specific aims are 1) to compare regimen-related toxicity (e.g., SOS, IPS, hemorrhagic cystitis) between children receiving myeloablative conditioning regimens consisting of busulfan/fludarabine 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 busulfan/fludarabine and those receiving busulfan/cyclophosphamide; 3) to compare outcomes (non-relapse mortality, overall survival) post-transplant between children receiving myeloablative conditioning regimens consisting of busulfan/fludarabine and those receiving busulfan/cyclophosphamide; 4) to compare relapse rates for the subset of patients receiving HCT for AML in CR between children receiving myeloablative conditioning regimens consisting of busulfan/fludarabine and those receiving busulfan/cyclophosphamide. The current status is data file preparation.

d. RT13-02 Safety of high-dose total body irradiation followed by an allogeneic hematopoietic cell transplant for hematologic malignancies (M Sabloff). The specific aims are 1) To describe the toxicity profile of those patients receiving high dose TBI (>12Gy) compared to those who had a myeloablative transplant with TBI ≤12, with or without chemotherapy. To study if any pre BMT characteristics might have an influence on the type of toxicity in either group; 2) To compare the toxicity profile of those patients who received high dose TBI (>12Gy) with chemotherapy to those who received high dose TBI (>12Gy) without chemotherapy. To study if any pre BMT characteristics might have an influence on the type of toxicity in either group; 3) To describe the overall and progression free survival of those receiving high dose TBI (>12Gy) compared to patients who received a myeloablative transplant with TBI ≤12, with or without chemotherapy; 4) To describe the overall and progression free survival of those receiving high dose TBI (>12Gy) with chemotherapy to patients who received conditioning with high dose TBI (>12Gy), without chemotherapy. The current status is protocol development.

g. RT14-01 Trends and risk factors for infant mortality following allogeneic hematopoietic cell transplant: Case-Control study (P Satwani/S Parikh). The primary objectives are 1) to compare transplant related mortality in infants (<1 year old) following allogeneic hematopoietic stem cell transplant (AlloHCT) between the period of 2001-2005 and 2006-2011; 2) to compare the transplant related mortality in infants (<1 year old) vs. children >1-10 years old following AlloHCT between the period of 2001-2005 and 2006-2011. The secondary objectives are 1) to compare the incidence of day+30, +100 and 1 year TRM between two-time periods for patients <1 year at the time of start of conditioning. Measure the incidence of TRM in patients receiving AlloHCT for malignant (ALL, AML and MDS/MPS) and non-malignant diseases (SCID, HLH & other immune system disorders, metabolic disorders) between the period of 2001-2005 and 2006-2011; 2) to compare the incidence of day+30, +100 and 1 year TRM between patients <1 year vs. >1-10 years. Measure the incidence of TRM in patients receiving AlloHCT for malignant (ALL, AML and MDS/MPS) and non-malignant diseases (SCID, HLH & other immune system disorders, metabolic disorders) between the period of 2001-2005 and 2006-2011; 3) to calculate the incidence of acute and chronic graft versus host disease, incidence of veno-occlusive disease (VOD), pulmonary toxicity and graft failure; 4) to identify risk factors associated with transplant-related mortality in infants following AlloHCT. The current status is protocol development.

h. RT14-02 Endothelial injury complications after allogeneic hematopoietic cell transplantation (S Davies/ W Chinratanalab/S Jodele/M Ramanathan/B Laskin). The specific aims are 1) to report outcomes of children and adults who developed transplant-associated thrombotic microangiopathy (TA-TMA) after allogeneic and autologous HSCT in comparison to HCT patients without TMA; 2) to study the risk factors for VOD in the current era of reduced intensity conditioning regimens and reduced toxicity myeloablative conditioning regimens. The current status is protocol development.

i. 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). The specific aims is to evaluate the safety of using levetiracetam as a replacement
for phenytoin in preventing seizures caused by high-dose busulfan (BU) when followed by high-dose cyclophosphamide (CY) 60 mg/kg on two successive days as the conditioning regimen before allogeneic hematopoietic cell transplantation. Safety will be evaluated through measures of hepatic toxicity, interstitial pneumonia, renal failure requiring dialysis, non-relapse mortality, relapse or progression of malignant disease, and overall survival. The current status is protocol development.

4. Future/proposed studies

Drs. Mineishi, Loren and Artz led this section. The proposals were the following:

a. PROP 1510-07 Prediction of outcomes of patients undergoing T-cell replete haploidentical donor transplantation using post-transplant cyclophosphamide using the HCT-CI. (M Perales)

Dr. Perales presented the proposal. The proposal is to assess the ability of the HCT-CI and HCT-CI/age and predict outcomes in patients undergoing Haplo-post-HCT-CY conditioning regimen. There were more patients received RIC/NMA (76%). One of the main points is that in the HCT CI validation manuscript using the CIBMTR data, RIC recipients with HCT CI of 4 or greater experienced a greater impact on outcomes. Reduction in the intensity decreases up front toxicity, thus only patients with a greater number of cumulative comorbidities were required to observe an impact. The numbers here were much less than the validation study and it was felt that this would affect the interpretation of the results. Thus the proposal was not approved to proceed.

b. PROP 1511-89 Effect of BEAM dose adjustments on the outcomes of patients with lymphoma. (C Brunstein/ J Rogosheske/ M Perales)

Dr. Brunstein presented the proposal. The proposal is to 1) determine the incidence of regimen related toxicity stratified by dose adjustment practices using re-hospitalization/hospitalization, number of days hospitalized (day zero to day +30), need to TPN, prevalence of neutropenic fevers as surrogates; 2) determine the incidence of TRM stratified by dose adjustment practices; 3) determine overall survival at days +30, +100 and 1 yr, stratified by dose adjustment practices.

The CIBMTR form did not capture the reason of adjustment. It could be related to weight. If no dose adjustment obesity patients would have more toxicity. The dose adjustment can be figured out by the relation of actual body weight, dosing weight and the calculated ideal body weight. This study could also investigate melphalan because large number of autotransplants for multiple myeloma. This proposal was approved by the committee with recommendations: address the possibility of adding patients with multiple myeloma, limit to patients with BMI higher than 30 and explore the adjustment factor in relation to the difference between the actual and the dosing weight.


Dr. Saad presented the proposal. The proposal is to 1) identify the frequency of lung transplantation for non-infectious pulmonary complications after allogeneic stem cell transplant (allo HCT); evaluate the impact of lung transplantation on overall survival in these patients; 3) identify favorable factors associated with better survival after lung transplantation; 4) identify complications of lung transplantation (infections, secondary cancer, and recurrence of lung disease).

The CIBMTR does not collect lung transplant data. Therefore it is necessary to query data from United Network for Organ Sharing (UNOS). Although clinically relevant question, the voting of this proposal was low in priority. The proposal was not approved but there was a recommendation to contact UNOS and assess whether there would be interest in looking at this data in the future.
d. **PROP 1511-106** Evaluation of lung toxicity following allogeneic stem cell transplant with fludarabine/total body irradiation conditioning regimen. (A Saad/K Minagawa/Y Kanda/S Mineishi)

Dr. Saad presented the proposal. The proposal is to 1) identify the incidence of non-infectious lung toxicity in patients receiving allo HCT following myeloablative FLU/TBI regimen; 2) compare the risk of non-infectious lung toxicity in myeloablative FLU/TBI with a matched cohort who received other myeloablative or reduced intensity regimens (e.g. FLU/BU or BU/CY); 3) identify risk factors for development of non-infectious lung toxicity (recipient-, disease-, and transplant-related variables); 4) identification of the impact of non-infectious lung toxicity on non-relapse mortality; 5) identification of the impact of non-infectious lung toxicity on overall survival. The lung infection data need to be cleaned. A question regarding the sequence of fludarabine and TBI was raised up during discussion. The CIBMTR form collected dates of TBI and fludarabine given. The question to explore the association of a particular regimen and a toxicity can be done using the database. Based on the committee voting, the leadership decided to approved this proposal to move forward.

e. **Prop 1511-57 & 1509-03 (combined)** Reduced intensity conditioning compared with Myeloablative conditioning using Haploidentical Donor transplants with post-transplant Cyclophosphamide in patients with AML or MDS. (N Shah/M Kharfan-Dabaja/M Hamadani/P Hari)

Dr. Hari presented the proposal. The proposal is to 1) to compare outcomes of patients with AML/MDS undergoing either myeloablative or reduced intensity haploidentical transplant with post-transplant cyclophosphamide; 2) evaluate overall survival and progression-free survival; 3) evaluate NRM, incidence of acute and chronic graft versus host disease, infectious complications, rates of graft failure/rejection, and engraftment.

There was significant interest by the committee with this proposal as this is a timely question. The main issue is related to small number of cases in the CRF track. This affects the most common indication, AML, because there is no information about cytogenetic risk stratification. The proposal was not approved but given the interest by the committee, the PIs were encouraged to inquire again in one year.

<table>
<thead>
<tr>
<th>Working Committee Overview Plan for 2016-2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a. RT07-01b</strong> 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 May 2016, submitting to peer-review journal in June 2016.</td>
</tr>
<tr>
<td><strong>b. RT12-03</strong> Transplant in older adults: is it feasible in those 70 years and older? We anticipate finalizing manuscript, circulating to writing committee in May 2016, submitting to peer-review journal in June 2016.</td>
</tr>
<tr>
<td><strong>c. RT13-01</strong> 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 collection by June 2016 and complete analysis by June 2017.</td>
</tr>
<tr>
<td><strong>d. RT13-02</strong> Safety of high-dose total body irradiation followed by an allogeneic hematopoietic cell transplant for hematologic malignancies. We will complete analysis by June 2016, prepare manuscript and submit by June 2017.</td>
</tr>
</tbody>
</table>
e. **RT14-01** Trends and risk factors for infant mortality following allogeneic hematopoietic cell transplant: Case-Control study. We will complete file preparation by June 2016, complete analysis in July 2016, and prepare manuscript by June 2017.

f. **RT14-02** Endothelial injury complications after allogeneic hematopoietic cell transplantation. We will complete data analysis by June 2016, prepare manuscript in July 2016 and submit manuscript by June 2017.

g. **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 file by June 2016 and prepare manuscript by June 2017.

h. **RT15-01** Comparison of outcomes for myeloablative conditioning regimens combining busulfan with either cyclophosphamide or fludarabine. We will complete analysis by June 2016, start manuscript in July 2016, and submit manuscript by June 2017.

i. **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 will start protocol development in July 2016 and complete data file by June 2017.

j. **RT16-01** (proposal 1511-89) Effect of BEAM dose adjustments on the outcomes of patients with lymphoma or multiple myeloma. We anticipate to having a draft protocol by June 2017.

k. **RT16-02** (proposal 1511-106) Evaluation of lung toxicity following allogeneic stem cell transplant with fludarabine/total body irradiation conditioning regimen. We anticipate to having a draft protocol by June 2017.

**Study Proposal Acceptance Justification:**

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 accepted one proposal, given the number of study in progress and the total statistical hours allocated to the committee. The committee leadership discussed the proposals thoroughly and decided to accept two proposals. Both of the proposals received similar scores by the committee members. The RT16-01 study proposal came from the BMT CTN Pharmacy Task Force that was established to address dose adjustment and standardization of such adjustments. The Task Force conducted a survey to address adjustment practices across centers and concluded that these practices vary widely across centers, across chemotherapy agents and patient weight. Yet, the data on outcomes to justify such adjustment is scant. The Task Force recommended an analysis to compare adjustment vs. non adjustment to understand the magnitude of the impact on outcomes. The CIBMTR is best position to answer this question and the data on actual and dosing weight is collected. This study can inform this Task Force and the community and influence dosing practices. The second study was also considered important and along the lines of the objectives of this committee. In 2015 the committee publish data that informed the association between autologous regimens used for lymphoma and IPS, which confirmed the association with BCNU but also demonstrated that regimens with higher BCNU doses were associated
with more toxicity without significant impact on disease control. The RT16-02 study is along the same lines, but explores the impact of fludarabine and TBI on lung toxicity. The committee leadership recommended these two studies to proceed for their relevance to the committee scientific agenda, availability of data and interest by the committee.

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Assignment</th>
</tr>
</thead>
</table>
| Alison Loren     | **RT14-01** Trends and Risk Factors for Infant Mortality Following Allogeneic Hematopoietic Cell Transplant: Case-Control study.  
|                  | **RT14-02** Endothelial injury complication after allogeneic hematopoietic cell transplantation.  
|                  | **RT16-01** Effect of BEAM dose adjustments on the outcomes of patients with lymphoma or multiple myeloma. We anticipate to having a draft protocol by June 2017. |
| Andrew Artz      | **RT12-03** Transplant in older adults: is it feasible in those 70 years and older?  
|                  | **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  
|                  | **RT16-02** Evaluation of lung toxicity following allogeneic stem cell transplant with fludarabine/total body irradiation conditioning regimen. We anticipate to having a draft protocol by June 2017. |
| Shin Mineishi    | **RT13-02** Safety of high-dose total body irradiation followed by an allogeneic hematopoietic cell transplant for hematologic malignancies.  
|                  | **RT15-01** Comparison of outcomes for myeloablative conditioning regimens combining busulfan with either cyclophosphamide or fludarabine.  
|                  | **RT15-02** Association of anti-epileptic medication with outcomes after conditioning with targeted busulfan followed by cyclophosphamide before allogeneic hematopoietic cell transplantation. |
Marcelo Pasquini

**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.

**RT13-01:** In-hospital mortality among allogeneic hematopoietic stem cell transplant recipients that develop critical illness in the early post-transplantation period - a nationwide temporal trend analysis