1. Introduction

Dr. Marcie Riches moderated the introduction of the working committee followed by which all the attending co-chairs and the statisticians were introduced. She welcomed Krishna Komanduri, MD as the new chair for INWC starting March 1st 2015, and thanked Dr. Michael Boeckh for his excellent service to the INWC.

She reviewed the goal of the working committee is to publish high impact studies in a timely manner. The expectations of the meeting are to review the current status of ongoing studies and timelines and for the committee members to assess and select proposals that will have a high impact on the field.

The working committee Members were asked to vote on a level of scientific impact score, 1 is the highest impact and 9 is the lowest impact score for the new proposals based on the feasibility and impact on the transplant community. The minutes from the 2014 Tandem meeting held in Grapevine, TX were approved by committee members.

2. Future/proposed studies

a. **PROP 1411-18** An analysis of immune reconstitution and outcomes in acute leukemia patients receiving cord blood units compared to match-related, match-unrelated, and mismatched donor allogeneic transplant sources (M Tees, M Riches, M Kharfan-Dabaja)

Dr Michael T. Tees presented the proposal. The hypothesis of the proposal is that since immune reconstitution after a cord blood transplant lags in comparison to other non-haploidentical transplant sources, this is associated with an increased risk of transplant-related mortality. The specific aims are 1)To determine whether certain lymphocyte subsets repopulate at different rates when cord blood
units are utilized as a hematopoietic stem cell source compared to other non-haploidentical sources; 2) To assess whether any differences detected in lymphocyte recovery between the cord blood and non-cord blood donor groups, as well as within the donor groups, are associated with Incidences of bacterial, viral, and fungal infections; Incidences of acute and chronic graft-versus-host disease (GVHD); Transplant-related mortality; Relapse and the overall survival.

One recommendation from the committee is to consider acute GVHD as a time dependent covariate and not an outcome. Chronic GVHD may remain as an outcome. Dr. Riches suggested we use available cleaned dataset of IN10-01 for this study to reduce the statistical hours.


Dr. Zeina Al-Mansour presented the proposal. The hypothesis of the proposal is that stem cell source, conditioning regimens and GVHD prophylaxis regimens affect the kinetics of IR post allo-SCT. The specific aims are: 1) To evaluate kinetics of IR following allo-SCT; 2) To evaluate different factors affecting the kinetics of IR post allo-SCT; 3) To evaluate as to how kinetics of IR impact infectious complications, disease relapse and overall survival post allo-SCT.

Dr. Riches mentioned the limitation of immune reconstitution data over the years. This is the first time we have relatively large number of patients with IR data. The concerns from the group are: 1) Comparing to BM and PB, cords patients have different GVHD prophylaxis and conditioning regimen. Data is confounding significantly with disease and condition regimen. 2) The data reported differently by centers.

The recommendation from the group is to combine this proposal with PROP 1411-18.

c. PROP 1411-44 Infection burden and disease relapse following initial allogeneic hematopoietic cell transplantation for hematologic malignancies (J Auletta, M Ardura, M Riches) (Attachment 5)

Dr. Jeffery J. Auletta presented the proposal. The hypothesis is the cumulative amount of infection, defined herein as infection burden, influences the risk for hematologic malignant disease relapse in adult and pediatric patients receiving initial allogeneic hematopoietic cell transplant. The study primary objectives are 1) To quantify infection burden (cumulative bacterial, fungal and viral infections per patient days at risk) in adult and pediatric allogeneic hematopoietic transplant recipients with hematologic malignancies at 30 (D30), 100 (D100), 180 (D180), and 365 (D365) days after transplant. 2) To determine if post-transplant infection burden is associated with hematologic malignant disease relapse. The secondary objectives are: 1) To determine the cumulative incidence of bacterial bloodstream infections (BSI), invasive fungal infection (IFI), respiratory viral infection (RVl), and viral reactivation (VR). 2) To evaluate the effect of conditioning, graft source & cell dose, and use of growth factor on infection burden. 3) To evaluate the effect of conditioning, graft source & cell dose, and use of growth factor on infection burden.

One concern from the group is the accuracy of infection reported by center, particularly for infections beyond day 100 as well as lack of information regarding severity of the infection. Dr. Riches mentioned the data limitation of the infection data, we collecting organism and site of infection, but not collecting the severity of the infection. The suggestions from the group: 1) Focus on one type of infection. 2) Propose to a CTN study, using smaller sample but more accurate and detailed dataset.
d. **PROP 1411-45** CMV reactivation influences the incidence and severity of acute GvHD following initial allogeneic hematopoietic cell transplantation for hematologic malignancies (J Auletta, M Ardura, M Riches)

Dr. Jeffery J. Auletta presented the proposal. The hypothesis is CMV reactivation influences the incidence and severity of acute GvHD in patients receiving initial alloHCT for heme malignancy (ALL, AML, MDS). The study primary objectives are 1) To compare incidence and severity of acute GvHD between transplant patients with and without CMV reactivation (RA); To evaluate whether early CMV RA (≤D100) affects aGvHD; To evaluate whether aGvHD affects subsequent CMV RA; 2) To determine if CMV reactivation affects response to GvHD therapy; To compare incidence of steroid refractory acute GvHD between CMV RA+ and RA-; The secondary objectives are 1) To determine if early CMV reactivation (RA) increases the incidence of subsequent infection in alloHCT recipients, such as bacterial blood stream infection (BSI), Invasive fungal infection (IFI) and Respiratory viral infection (RVI) 2) To determine if age influences differences in infection and aGvHD severity, in general, and CMV RA, in particular 3) To compare rates of non-relapse mortality (NRM), infection-related mortality (IRM), overall survival (OS), and relapse among 4 patient groups: CMV RA-, no aGvHD vs. CMV RA+, no aGvHD vs. CMV RA-, yes aGvHD vs. CMV RA+, yes aGvHD.

Dr. Riches mentioned this study is related to current ongoing study IN12-01. If use cleaned dataset of IN12-01, may reduce the statistical hours.

One concern from the group is if there is a correlation between CMV and aGvHD, how we analyze the data. Dr. Riches suggested use aGVHD as a time dependent covariate.

One question from the group is CMV reactivation is not assessed in the same way by different centers. Do we have that information? The answer is no. Dr. Michael Beock suggested, perhaps we have to change how these data are reported to the CIBMTR.

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e. **PROP 1411-66** Impact of Epstein Barr virus (EBV) infection on outcomes of allogenic hematopoietic cell transplantation (HCT) for hematologic malignancies (P Teira)

Dr. Pierre Teira presented the proposal. The hypothesis is that the donor and recipient serostatus for Epstein Barr Virus (EBV) may impact the incidence of relapse for leukemia after hematopoietic stem cell transplantation. The specific aims are: 1) To assess the impact of donor and recipient EBV serostatus (+/+ vs +/- vs -/+ vs -/-) on PTLD, disease relapse, incidence of acute and chronic GVHD, NRM, EFS and OS after allo-HCT. 2) To assess the impact of EBV reactivation on the same outcomes and for the same population

Dr. Riches mentioned the EBV serostatus question was removed due to the form revision starting 2008, and has been added back in October 2013. That is why we have to limit the population to before 2008. A question is raised how representative will the data be with the missing years of reporting of donor serology for EBV. Dr. Michael Beock pointed out, the good side is we will have a longer follow up. He also mentioned, for the clinical endpoints this study is very doable and will give definitive answer for the impact of serostatus EBV; however, not EBV reactivation. One suggestion from the group is, NMDP consistently collect EBV serostatus information, and we may get the information from NMDP.

Dr. Krishna Komanduri mentioned this study may have a high impact fact, since if the study demonstrates EBV serostatus has no effect on clinical outcomes (such as mortality), we do not have to
check EBV serostatus anymore, thus potentially changing clinical practice.

One comment from the group is that it would be useful to assess EBV reactivation. EBV reactivation is reported differently and especially might be missing as it may occur quite late.

f. **PROP 1411-88** Real World Effectiveness analysis of vaccination for encapsulated organisms in Hematopoietic Stem Cell Transplant recipients- A Center for International Blood and Marrow Transplant Research Study (M Damlaj, S Hashmi, M Litzow)

Dr. Moussab Damlaj presented the proposal. The specific aims are: 1) Determine the incidence and timing of encapsulated organism infections (EOI) post hematopoietic stem cell transplant (HCT) and its impact on overall survival over different time periods. 2) Identify risk factors and outcomes of EOI. 3) Compare the incidence of EOI between autologous and allogeneic transplant recipients. 4) Determine impact of Graft vs. Host disease (GVHD) and immunosuppression (IST) on incidence of infection

The comments from the group are: 1) we do not know whether the center follows the vaccine guidelines and we do not know the incidence of encapsulated organism infections in the normal population. 2) We do not know if the patients were vaccinated. 3) We would not even know the policy of the reporting centers. There will still be patients that have transferred to their local oncologist by the time of vaccinations.

The suggestion is: we could identify some risk factors. We know time period of infection. It would define the burden of this infection in this population.

Dr. Michael Boeckh mentioned it would be a great proposal for a case control study.

3. Studies in progress

a. **IN07-01/IN11-01** Early Bacterial infection in patients undergoing allogeneic HCT (M Robien/G Papanicolaou/Celalettin Ustun/ JA Young) Early Bacterial infection in patients undergoing allogeneic HCT

Dr Genovefa Papanicolaou outlined that the hypotheses of the study are 1) Early (Day 0-45) bacterial infections in the bloodstream (BSI) or non-BSI have a negative impact on long-term survival (3, 6, 12 months post-transplant 2) BSI by vancomycin resistant Enterococci (VRE) negatively impacts long-term survival; and 3) Changes in clinical practices (donor sources, growth factors use) over the last decade are likely to affect the impact of early bacterial infections on survival. The objectives of this study are 1) To define the epidemiology of early bacterial infections during 2002-2011 and early VRE bacteremia (2008-2011); 2) To identify risk factors for early bacterial infections; 3) To evaluate the effect of early bacterial infection on outcomes (Overall survival at 3 months, 6 months, and 12 months and 2years); 4) Frequency of concomitant fungal and viral infections through day +100 post-transplant; and 5) Incidence of acute GVHD through day+100). Comparison between patients with and without early bacterial infection revealed differences in the following variables: Age, Performance status, Graft type (Cord/Peripheral blood/Bone Marrow), HLA match, conditioning regimen (myeloablative vs. others), Days to engraftment, GVHD prophylaxis. The same variables were significantly different across patients
with VRE, non VRE bacterial infection and without bacterial infection. No question or further discussion for this study.

The study is in data file preparation stage, we are expecting to finish the analysis by June 30, 2015 and manuscript published by June 30, 2016.

b. **IN13-01** Bacterial and fungal infections in patients undergoing allogeneic hematopoietic cell transplantation following non- myeloablative and myeloablative regimens (C Usten)

Dr. Celalettin Ustun updated the study. The primary objective is to compare the incidence of early (within 100 days after alloHCT) bacterial, viral, and fungal infections between NMAR alloHCT and MAR alloHCT. The secondary objectives are 1) To compare neutrophil engraftment (> 0.5 x 10^9/L for 3 consecutive days) between NMAR alloHCT and MAR alloHCT; and 2) To compare TRM in 100 days between MAR and NMAR. The population of this study is patients with AML in CR1 receiving alloHCT between January 2006 and December 2011, of any age (however patients ≤40 years will be separately evaluated) and receiving any graft source.

Dr. Riches mentioned that the study is in protocol development stage; we are planning to present it at stats meeting in April, 2015 and have the final protocol by June 30, 2015.

c. **IN14-01** Post allogeneic hematopoietic transplant Epstein Barr Virus related Lymphproliferative disorder following conditioning with Antithymocyte globulin or Alemtuzumab (S Naik, C Bachier, P Shaughnessy, P Hari, R Kamble)

Dr. Seema Naik updated the study. It was combined by two proposals, PROP 1303-03 and PROP1311-19. The specific aims of this study are: 1) To determine the incidence of post allogeneic hematopoietic transplant Epstein Barr virus related lymphproliferative disorder following myeloablative or reduced intensity conditioning including antithymocyte globulin or alemtuzumab as conditioning or GVHD prophylaxis. 2) To determine morbidity and outcomes associated with EBV-PTLD

This study is in protocol development stage; we are participating to have the final protocol by June 30, 2015, and a data file preparation by June 30, 2016

4. **Studies in manuscript preparation**

a. **IN05-02** Atypical mold infections in hematopoietic cell transplantation (HCT) patient (M Riches)

b. **IN10-01** Comparison of infection rates among alternative graft sources: single and double cord blood, matched unrelated donor and mismatched unrelated donor (K Ballen)

c. **IN06-01** Breakthrough PCP (P Jiroveci) as a function of prophylaxis regimen (K Williams)

d. **IN09-01** Allo HCT for patients with/without pre-existing fungal infx (R Maziarz/A Ciszewski)

e. **IN12-01a** CMV infection and relapse after HCTs(PB/BM) (Minoo Battiwalla/John Barrett/ Muthalagu Ramanathan/ Pierre Teira)

**IN12-01b** CMV infection and relapse after HCTs(Cord) (Minoo Battiwalla/John Barrett/ Muthalagu Ramanathan/ Pierre Teira)
5. Dropped study/proposal
   a. **PROP 1411-67** Temporal trends in the incidence, disease severity and mortality associated with invasive fungal infections in allogeneic stem cell transplant recipients from 2002-2014: Comparison of eras before and after the availability of voriconazole and posaconazole for antifungal prophylaxis (Maheen Z. Abidi, Anita D’Souza,, M. Rizwan Sohail, Randall C. Walker )
   b. **IN13-02** Incidence of early C. difficile infections after allogeneic hematopoietic cell transplantation over the last 12 years (C Usten)

6. Other Business
   After discussion the 6 proposals and the data limitation, one comment from the group is, the registry data is not strong enough to do some of the studies.
   Dr. Riches encouraged the group to propose adding/deleting questions and revise the collection forms.
Working Committee Overview Plan for 2015-2016

a. **IN06-01** Rate of breakthrough of pneumocystis jiroveci pneumonia as a function of prophylaxis regimens (K Wlliams/A Chen/A Agwu/T Walsh). We anticipate receiving the final manuscript by April 15, 2015 and manuscript submitted by May 1, 2015.

b. **IN09-01** Outcomes of allogeneic hematopoietic stem cell transplantation for patients with and without pre-existing fungal infections (R Miazirz/A Ciszewski). We anticipate receiving the final manuscript by May 1, 2015 and manuscript submitted by June 30, 2015.

c. **IN10-01** Comparison of Infectious rates among alternative graft sources: single and double cord blood, matched unrelated donor and mismatched unrelated donor (K Ballen). We anticipate receiving the final manuscript by June 1, 2015 and submitting the manuscript for peer-review by June 30, 2015.

d. **IN07-01/IN11-01** Early bacterial infection in patients undergoing allogeneic HCT (C Ustun /J-A Young/M Robien/G Papanicolaou). We anticipate finish the final analysis June 30, 2015 and manuscript published by June 30, 2016.

e. **IN12-01a** CMV infection and relapse after stem cell transplant (PB/ BM)(M Battiwalla /J Barrett /M Ramanathan/P Teira). The analysis has been done for ALL. We are expecting submit the papers by June 30, 2015.

f. **IN12-01b** CMV infection and relapse after stem cell transplant (Cord) (M Battiwalla /J Barrett /M Ramanathan/P Teira). The analysis has been done for ALL. We are expecting submit the papers by June 30, 2015.

g. **IN 13-01** Bacterial and fungal infections in patients undergoing allogeneic hematopoietic cell transplantation following nonmyeloablative and myeloablative regimens (C Usten). We anticipate finish the final analysis by June 30 2016.

h. **IN 14-01**: Post allogeneic hematopoietic transplant Ebstein Barr Virus related lymphproliferative disorder following conditioning with antithymocyte globulin or alemtuzumab (R Kamble/ P Hari/S Naik /C Bachier/P Shaughnessy). We anticipate a data file preparation by June 30, 2016.

i. **IN15-01**(PROP 14-66) Impact of Epstein Barr virus (EBV) infection on outcomes of allogenic hematopoietic cell transplantation (HCT) for hematologic malignancies(P Teira) We anticipate having the finalized protocol by June 30 2016.
### Oversight Assignments for Working Committee Leadership (March 2015)

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