MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR GRAFT-VERSUS-HOST DISEASE
Orlando, FL
Friday, February 24, 2017, 12:15 – 2:15 pm

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1. Introduction
   a. Minutes and Overview Plan from February 2016 meeting (Attachment 1)

      Dr. Amin Alousi began meeting at 12:15pm by introducing the GVWC leadership and reviewing the goals, expectations and limitations of the GVWC.

2. Accrual summary (Attachment 2)

   Dr. Alousi referenced that the Accrual Summary tables could be found online.

3. Presentations, published or submitted papers


Dr. Alousi also highlighted the 6 studies that have been presented, published or submitted for publication during the 2016 calendar year.

4. **Future/proposed studies**

Dr. Joseph Pidala introduced the proposal section of the meeting with some explanation on how the Voting Sheet works and a reminder to the presenters that they will each have 5 minutes to present and then allow for 5 minutes of questions and discussion.

a. **PROP 1611-04** Risk stratification by time to onset of acute GVHD. (H Choe/ S Lee) (Attachment 3)

Dr. Hannah Choe presented the proposal. Dr. Choe stated that the timing of aGVHD onset relative to neutrophil engraftment has not been examined yet utilizing the CIBMTR database. The hypothesis of the study is that early onset of aGVHD will indicate a higher risk of other outcomes, namely OS, NRM and cGVHD, and the analysis will aim to identify risk factors associated with the development of each time to onset category.

A question from the GVWC was asking why the study population was restricted to patients developing aGVHD within 100 days post-transplant. Dr. Choe suspected that aGVHD reported beyond 100 days post-transplant are not as reliable instances of aGVHD as those reported within 100 days, but would be open to considering them in the population if they’re thoroughly reviewed. Another question asked if the proposal would evaluate sample typing and the GVWC leadership answered that sample
typing data would only be available in a subset of the population. A concern was expressed that very early aGVHD could be an incorrect diagnosis.

b. **PROP 1611-05** Analysis of the risk factors for hepatic acute GVHD after allogeneic stem cell transplantation (Y Arai) (Attachment 4)

Dr. Yasuyuki Arai presented the proposal. Dr. Arai stated the exact incidence and impact of risk factors of hepatic aGVHD are still unknown and that the number of hepatic aGVHD patients found in the CIBMTR database would make the proposal statistically viable. This proposal could provide early therapeutic and diagnostic interventions in high-risk patients and the findings from this study could provide baseline data for future investigations.

A member of the GVWC noted that a prior publication showed that incidence of hepatic aGVHD has been decreasing in recent years. Another member of the GVWC asked why pediatric patients were excluded from the population and encouraged including them in the population. Dr. Arai clarified that hepatic aGVHD will include patients who experienced liver-based and/or other organ involvement in aGVHD. The CIBMTR does not collect timing of each organ involved in aGVHD, so the proposal cannot analyze timing of liver involvement relative to other organs. Another comment was to consider creating a score of some kind that can provide more weight for patients who have multiple aGVHD organs involved.

c. **PROP 1611-108** The cumulative incidence and risk factors for renal GVHD after allogeneic hematopoietic cell transplantation (A Alousi/ A Abudayyeh/ R Saliba) (Attachment 5)

Dr. Amin Alousi presented the proposal. Dr. Alousi emphasized that renal cGVHD is a very rare event, and the largest case study published had 12 patients included. The CIBMTR database allows the opportunity to investigate far more renal cGVHD cases than has been examined before. The hypothesis of the proposal is that renal cGVHD is associated with increased mortality and has discrete risk factors when compared to other manifestations of cGVHD.

The GVWC leadership clarified a comment that while there is no variable on the CIBMTR follow-up forms asking for kidney involvement in cGVHD, there was a variable for other organ involvement and the renal cGVHD cohort had indicated renal or kidney involvement in the other, specify field on the forms. Dr. Alousi agreed with a comment from the GVWC that renal involvement is underreported and answered that the CIBMTR forms do collect whether biopsies were obtained for the other organs (on which renal or kidney involvement was specified). A question was whether the CIBMTR collects treatment response, which the forms do not collect. A member of the GVWC expressed concern over the small number of patients (n=37) who indicated renal cGVHD and had biopsies available.

d. **PROP 1611-109** Impact of baseline renal sufficiency on the rate of acute GVHD following allogeneic HCT and a determination of risk factors on and the impact for decline in glomerular filtration rate post-HCT (A Alousi/ A Abudayyeh/ R Saliba) (Attachment 6)

Dr. Amin Alousi presented the proposal. Dr. Alousi cited several publications that show conflicting findings of baseline renal insufficiency and its impact on NRM. The goal of this proposal is to determine if there is a threshold of glomerular filtration rate (GFR) for increased risk for aGVHD and NRM.

A comment from the GVWC was that GFR decreases with age and that adding pediatric patients would add more interest to examining this variable. It was further suggested to consider adding a maximum age cut-off to the population. When a member of the GVWC expressed concern for how to account for decreased kidney function with increasing age, and how to handle confounding variables...
(especially conditioning intensity), Dr. Alousi responded that those concerns will be accounted for in the statistical analysis. Another comment was to consider different cut-off points for the GFR distribution, to which Dr. Alousi agreed that would be under consideration. Another comment was to examine conditioning regimen drugs and doses thoroughly to see if certain combinations arise with connections to GFR or study’s outcomes.

e. **PROP 1611-113 Investigating antibiotic exposure and risk of acute GVHD in children undergoing hematopoietic stem cell transplantation for acute leukemia (C Elgarten/ B Fisher/ R Aplenc)** (Attachment 7)

Dr. Caitlin Elgarten presented the proposal. The aims of the proposal are to determine the association of antibiotics commonly administered for neutropenic fever and the differential impact of antibiotic exposures before transplant with subsequent development of aGVHD among pediatric patients undergoing transplant for acute leukemia. The hypothesis is that exposure to antibiotics with activity against anaerobic commensal microorganisms in the peri-transplant period is associated with an increased risk of aGVHD. In order to obtain the detailed data required for this proposal, Dr. Elgarten proposes merging the patients fitting the population from CIBMTR registry with the Pediatric Health Information System (PHIS) database. Dr. Elgarten said this would be the first pediatric study to assess differential impact of broad spectrum antibiotics on GVHD.

A question was asked whether the CIBMTR forms can discern as to what purpose antibiotics were administered (whether for prophylaxis or treatment for active infection). While the CIBMTR forms do not collect the purpose for which the treatment was given, the investigators may be able to make assumptions based on the timing of the administration of the treatment. A question was asked whether infection data was collected by the CIBMTR, which it is, but the study will rely on the FISK database for those data. A member of the GVWC warned that there will likely be patients who have constantly escalating antibiotics and the exposure will be difficult to quantify. Another concern expressed was whether the proposal would be able to account for patients who were started on antibiotics for a different factor than infection, say GVHD, and Dr. Elgarten answered that yes, she will be able to account for those different instances of use of antibiotic use.

f. **PROP 1608-01 Evaluate the relationship between clostridium difficile colitis and subsequent gastrointestinal graft versus host disease in recipients of allogeneic stem cell transplantation (D Bhutani/ A Deol)** (Attachment 8)

Dr. Divaya Bhutani presented the proposal. The hypothesis of the proposal is that development of clostridium difficile infection (CDI) post-transplant increases the risk of subsequent development of gastrointestinal (GI) aGVHD. The incidence and major risk factors of CDI were covered by Dr. Bhutani. There are reports, including an analysis of 300 patients that Dr. Bhutani worked on, that demonstrated that patients who developed CDI had a statistically significantly higher chance of developing subsequent GI aGVHD. Dr. Bhutani is proposing to perform a similar analysis to compare the incidence of GI aGVHD in patients with a preceding history of CDI versus those with no CDI history in a much larger population, which the CIBMTR can provide.

A concern was expressed by the GVWC that different centers may have reported CDI differently based on different thresholds. Dr. Bhutani clarified that the time frame of this proposal predates the PCR test, which should result in more consistent reporting across centers. A GVWC member recommended to exclude patients with viruses that cause diarrhea, to create a more focused group on which to focus the analysis.

Dr. Pidala informed the GVWC that the remaining two proposals are each the results of separate
proposals of similar topics that were merged together, at the request of the GVWC leadership. All of the proponents were very respectful and collaborated successfully.

g. PROP 1610-08/1611-24 Risk factors for GVHD and outcomes in T-replete HLA-haploidentical HCT using post-transplant cyclophosphamide (A Im/ B Hamilton/ A Rashidi/ S Pavletic/ N Majhail/ D Weisdorf) (Attachment 9)

Dr. Annie Im presented the proposal, stating that she was a part of a team that presented this topic last year, but did not proceed due to small sample sizes that have since increased in the CIBMTR research database. Dr. Im stated that while studies in haploidentical transplantation (haploHCT) have become more common, there has yet to be a large analysis comparing myeloablative (MA) versus reduced intensity or non-myeloablative (RIC/NMA) conditioning intensity on aGVHD incidence following haploHCT with post-transplant cyclophosphamide (PTCy). This proposal will describe the incidence and identify risk factors for aGVHD and cGVHD after haploHCT using PTCy, separately for MA and RIC/NMA as well as BM and PB graft sources. The hypothesis is that there will be a low incidence of both aGVHD and cGVHD following haploHCT using PTCy, with MA and RIC/NMA having similar incidences of aGVHD while PB grafts may experience a higher incidence of cGVHD compared to BM grafts.

Clarifications were made that donor characteristics, TBI use and GVHD prophylaxis will be included in the analysis. There was a concern expressed that even though the numbers have increased since last year, that there might be too few events of severe aGVHD (Grade III-IV) but it’s expected that the RIC/NMA cohort (n=330 patients) would have sufficient numbers to evaluate aGVHD Grade II-IV.

h. PROP 1611-15/1611-131 Characteristics and outcomes of acute and chronic GVHD after haploidentical related donor allogeneic stem cell transplantation (R Saliba/ S Ciurea/ J Schriber) (Attachment 10)

Dr. Rima Saliba presented the proposal. The goal of the proposed study is to compare GVHD outcomes between patients receiving post-transplant Cyclophosphamide (PTCy)-based GVHD prophylaxis versus those receiving standard (Tacrolimus/Cyclosporine + MTX) GVHD prophylaxis. The hypothesis brought forward by Dr. Saliba is that PTCy-based GVHD prophylaxis is associated with lower incidence of severe aGVHD, severe cGVHD, and mortality among patients with GVHD, when compared to standard GVHD prophylaxis. Furthermore, Dr. Saliba speculates that this difference in mortality is more pronounced in patients 60 years or older at time of transplant.

It was further clarified that the analysis will compare haploidentical donors receiving PTCy-based GVHD prophylaxis versus matched unrelated donors who received standard calcineurin inhibitor-based GVHD prophylaxis. A GVWC member asked if the proposal will investigate HLA data for the haploidentical donors, but Steve Spellman expressed concern about the clarity of the HLA data on those patients. It was also further clarified that the analysis will perform a subset analysis to specifically examine the effect of donor type and GVHD prophylaxis among patients 60 years or older at transplant.

Dropped proposed studies

Dr. Mukta Arora introduced the proposals that were submitted to the GVWC but were determined by the GVWC leadership that they were not feasible for the specified reasons.

i. PROP 1611-28 Outcomes of acute and chronic GVHD treated with mesenchymal stromal cells. Small sample size and insufficient data on response to GVHD treatment.

k. PROP 1611-45 Impact of the use of ATG as prophylaxis of acute and chronic GVHD in patients undergoing allogeneic hematopoietic cell transplant. Insufficient data on ATG dose collected for GVHD prophylaxis.

l. PROP 1611-76 Combination of etanercept and photopheresis as treatment for steroid refractory GVHD of the lower GI tract following allogeneic hematopoietic stem cell transplantation. Small sample size and insufficient data on timing of GVHD treatment.

m. PROP 1611-78 Comparison of calcineurin inhibitors with post-transplant cyclophosphamide alone as GVHD prophylaxis in patients undergoing allogeneic hematopoietic cell transplant. Small sample size.

n. PROP 1611-123 Incidence and risk factors for severe aGVHD in the perfect HLA match setting. Overlapped with current study GV12-01.

o. PROP 1611-128 Risk of chronic GVHD with use of Rituximab-based regimen. Overlap with current study in the Lymphoma Working Committee LY16-05.

p. PROP 1611-129 Amphiregulin, the amphiregulin/epidermal growth factor ratio, and clinical outcomes after classic acute GVHD: A biomarker study of BMT CTN 0302 and 0802. Dropped with referral to BMT CTN.

q. PROP 1611-156 Incidence of chronic GVHD in myelofibrosis after prior Ruxolitinib therapy. Small sample size, due to pre-transplant Ruxolitinib not being reliably captured until 2013.

5. Studies in progress (Attachment 11)

Dr. Dan Couriel introduced our studies in progress by reviewing a slide summarizing the activity accomplished by the GVWC so far in the current academic year and what remained to be accomplished before July 2017.

a. GV15-02 Peripheral blood versus bone marrow from unrelated donors: Bone marrow grafts are best for survival and graft-versus-host disease, relapse-free survival (AM Alousi) Manuscript Preparation

b. GV 13-01 Unrelated male donors versus parous sibling female donors: Impact on transplant-related outcomes (AJ Kumar/ A Loren) Manuscript Preparation

c. GV14-02 Influence of age on acute and chronic GVHD in children receiving HLA-identical sibling BMT for acute leukemia: Implications for prophylaxis (M Qayed/ J Horan) Manuscript Preparation

d. GV15-01 Impact of donor obesity and inflammation on acute and chronic GVHD among HCT recipients (L Turcotte/ M Verneris/ J Knight) Manuscript Preparation

e. GV14-01 Comparison of mycophenolate versus methotrexate in combination with a calcineurin inhibitor for GVHD prophylaxis in allogeneic HCT (B Hamilton/ S Chhabra/ N Majhail/ L Costa/ R Stuart/ D Kim/ O Ringden) Analysis

f. GV16-01 GVHD-free relapse-free survival in alternative donor hematopoietic cell transplantation (Mehta R/ Holtan S/ Weisdorf D) Data File Preparation

g. GV16-02 The impact of the graft T cell dose on the outcome of allogeneic HLA-matched peripheral blood stem cell transplantation (Saad A/ Hashmi S/ Sharma M/ Lamb L) Data File Preparation

6. Other Business

Repository summary

Steve Spellman presented a summary slideshow on the repository, and encouraged GVWC members to utilize these data if they believe it will enhance their proposals or studies.

Hearing no other calls for business to discuss, Steve Spellman ended the meeting at 2:15pm.
a. **GV14-01** Comparison of MMF vs. MTX in combination with a CNI for GVHD prophylaxis in allogeneic HCT (B Hamilton / S Chhabra / N Majhail / L Costa / R Stuart / D Kim / O Ringden)

This study will compare the incidence of grade 2-4 aGVHD between patients receiving a GVHD prophylaxis regimen of a calcineurin inhibitor (CNI; cyclosporine or tacrolimus) with mycophenolate mofetil (MMF) versus methotrexate (MTX). Incidence of grade 3-4 aGVHD, cGVHD and rates of relapse, TRM, DFS, OS and hematopoietic recovery will also be evaluated.

We anticipate revising the initial draft of the manuscript by August 2017. We also anticipate submitting an abstract for ASH. After circulating to the Writing Committee for feedback, we expect to submit the final manuscript by November 2017. 70 statistical hours have been allocated to accomplish these goals.

b. **GV15-01** Impact of donor obesity and inflammatory cytokine levels on GVHD (L Turcotte / M Verneris / J Knight)

This study aims to evaluate the impact of donor inflammatory status as a function of donor serum inflammatory cytokine concentration on the development of GVHD in patients undergoing allogeneic HCT for AML, ALL, CML, MDS from an 8/8-matched unrelated donor.

We anticipate the samples and data file to be prepared for analysis by July 2017 and the analysis to be completed by September 2017. We further anticipate submitting an abstract for Tandem by October 2017 and receiving the initial draft of the manuscript by November 2017. The initial draft will be revised by December 2017 and circulated to the Writing Committee by January 2018. We finally expect to submit the final manuscript for publication by March 2018. 70 statistical hours have been allocated to accomplish these goals.

c. **GV16-01** GRFS in alternative donor HCT (R Mehta/ S Holtan/ D Weisdorf)

This study will compare GRFS at 1- and 2-years post-transplant among patients with hematological malignancies who underwent HCT in one of the following “alternative donor” categories – (a) UCB transplant (b) haploidentical donor (c) PB related/unrelated donor with 1-antigen HLA mismatch and (d) BM related/unrelated donor with 1-antigen HLA mismatch. The study will further describe the distribution of contributing events of GRFS at 1- and 2-years post-transplant. The study will also analyze OS and DFS at 1- and 2-years post-transplant.

We anticipate that the data file will be prepared for analysis by July 2017. We further anticipate that the analysis will be completed by August 2017, so that an ASH abstract can be submitted. We further anticipate an initial draft of the manuscript will be received by September 2017 and a final manuscript submitted for publication by January 2018. 150 statistical hours have been allocated to accomplish these goals.

d. **GV16-02** The impact of the graft T cell dose on the outcome of allogeneic HLA-matched peripheral blood stem cell transplantation (A Saad/ S Hashmi/ M Sharma/ L Lamb)

This study will test the hypothesis that the graft dose of CD3+, CD4+ and CD8+ T cells, and the CD4+/CD8+ ratio, will correlate with the incidence and grade of aGVHD and cGVHD after allogeneic PBSC transplantation. The study will also test the correlation of those graft doses with OS and DFS among allogeneic PBSC transplants.

We anticipate that the protocol will be finalized by July 2017. We further anticipate preparing the data file by January 2018 and have preliminary results from analysis by February 2018. 100 statistical hours have been allocated to accomplish these goals.
The top three proposals were selected based on priority scores provided by committee attendees, and post-meeting deliberation by the GVWC Chairs with attention to the proposals’ novelty, design, impact, and feasibility.
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