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1. Introduction
   a. 2013 Tandem Minutes & Overview Plan for approval
   b. Newly appointed chair: Amin Alousi, MD; MD Anderson Cancer Center, Houston, TX;
      Telephone: 1-713-745-8613; E-mail: aalousi@mdanderson.org; Focus on prevention and
      treatment of acute and chronic GVHD.

Dr. Dan Couriel began introductions by introducing himself and the incoming chair, Dr. Amin Alousi. The rest of the GVWC leadership introduced themselves to the committee with their names and affiliations.

2. Accrual summary
   Dr. Alvaro Urbano-Ispizua explained the Accrual summary tables could be found with the rest of the meeting’s materials online, and had been available for the past few weeks.

3. Presentations, published or submitted papers
   Dr. Urbano-Ispizua presented brief updates on these presentations made from the GVWC in the past year. One paper has been submitted and three have been presented as 2013 ASH oral abstracts.


The main take-away from GV04-02/05-03c was that GVHD had a protective effect on CML patients in terms of overall survival, but still led to higher rates of non-relapse mortality.


GV11-04 is a study to validate a risk score initially proposed by the CIBMTR several years ago. There were patients fulfilling 4 of the 6 risk groups defined in the initial study, but due to small sample sizes, risk group 3 and 4 were combined.


GV06-04 studied the change in cGVHD incidence over time. Year of transplant proved to be an important factor in determining cGVHD incidence, and it was observed that unrelated donors and peripheral blood stem cell grafts were used increasingly over time.


The main conclusion from the study was that there was a significant association of GVHD with a lower rate of relapse/progression post-transplant in patients with follicular lymphoma (FL) and mantle cell lymphoma (MCL) and this relationship also appeared to be more prominent in reduced intensity transplants. However, GVHD did not lead to improved rates of overall or progression-free survival in FL or MCL due to excess non-relapse mortality.

4. **Future/proposed studies**

Dr. Corey Cutler first thanked Dr. Urbano-Ispizua, who will be leaving the leadership as an outgoing chair, for his contributions towards the GVWC over the past 5 years.

Dr. Cutler then reminded the committee that everyone is encouraged to vote on the scientific impact each proposal would have on the field, with a score of 1 being most impactful and 9 being least impactful.

a. **PROP 1304-01** Influence of donor and recipient age on risk for acute and chronic graft versus host disease in children receiving HLA identical BMT (M Qayed/J Horan)

Dr. Muna Qayed presented this proposal, which wanted to explore influences that the age of the donor and recipient had on a protective effect against GVHD in pediatric patients that has been seen in previous literature, but there is room for a more detailed investigation in recipients younger than 10. Dr. Qayed’s proposal further wants to address the question if reducing the intensity of GVHD prophylaxis on these pediatric patients could be a solution to reducing post-
transplant relapse. While the initial population looked into recipients 10 years old or younger and HLA-identical sibling donors, the GVWC leadership recommended expanding the cohort to include recipients younger than 18 years old and from unrelated donors in an effort to increase sample size. There are 953 patients who are under 18 years old receiving their first myeloablative allogeneic transplant from an unrelated or HLA-identical sibling donor from a non T-cell depleted bone marrow graft source with calcineurin inhibitor-based GVHD prophylaxis from 2000-2011 for AML or ALL in 1st or 2nd complete remission (of the 953 total patients, 601 had an unrelated donor and 352 had an HLA-identical sibling donor). The outcomes on interest are acute and chronic GVHD.

There was concern expressed by members of the GVWC about the potential for low numbers of patients, specifically when dividing the patients into categories to analyze the effect of donor and recipient age (i.e. donor age < 5 & recipient age < 5 vs. donor age 5-10 & recipient < 5 vs. ...). Dr. Qayed acknowledged the numbers could become an issue, and the age categories described in her presentation (< 5, 5-9, 10-14, 15-18) were arbitrary and could be changed. There was an expressed interest in evaluating patients younger than 5 years old, as recipients this young typically do not experience GVHD, but have high rates of relapse. Another comment was whether it would be possible to seek collaboration with the EBMT in an effort to gather more patients. Dr. Cutler responded that that could be something we propose to the EBMT if the sample sizes prove to be prohibitive to an analysis with the CIBMTR’s data.

b. **PROP 1311-51 The impact of season on the incidence and severity of acute GVHD (A El-Jawahri/Y Chen)**

Dr. Areej El-Jawahri presented the proposal. Dr. El-Jawahri began by stating that viral infection at time of transplant could play a pivotal role in the outcomes of a transplant and hypothesized that there were specific times of the year when a transplant would be favorable compared to other times. Dr. El-Jawahri first addressed this question within the Dana Farber database by evaluating the incidence of grade III-IV acute GVHD for each month of transplant. Dr. El-Jawahri found that there was a statistically significant difference in the rates of grade III-IV acute GVHD between her defined “flu season” (of October – May) and “non-flu season” (June – September). Dr. El-Jawahri specified the aims of the proposal are to determine the impact of whether a transplant occurred within this flu season or not on the incidence and grade of acute GVHD, in addition to relapse, NRM, DFS and OS. There were 32188 patients 18 years old or older from 1995-2012 who had received their first allogeneic transplant from an HLA-identical sibling or unrelated donor for a hematologic malignancy (the table presented in the proposal was restricted to the 22586 patients from North America).

Comments from the GVWC were that the PIs were boxing themselves in by already defining a flu and non-flu season, and that line of thinking also assumes that the time points within flu season are equal (beginning or end of flu season could make a difference). It would be more beneficial to evaluate as narrow a period time as you can (months would probably be most practical). When asked if the CIBMTR could address the issue of pneumonitis, Dr. Mukta Arora said the only way the CIBMTR forms capture this information is on an “Other, specify” field for cause of death. Similarly, the CIBMTR forms do not capture whether a recipient had received a flu shot prior to transplant. When asked, Dr. El-Jawahri explained the clinical impact of this study would be to educate patients about the impact of viral infections, patients who are scheduling “non-urgent” transplants far ahead in advance could plan to avoid a time when they’re more likely to get the flu
and could start asking the question if patients in flu season should be managed differently (Dr. El-Jawahri acknowledged that this study alone won’t be able to answer that question, but could lead to a clinical trial).

c. **PROP 1310-22/1311-02/1311-26/1311-91** Comparison of mycophenolate versus methotrexate in combination with a calcineurin inhibitor for GVHD prophylaxis in allogeneic HCT

(B Hamilton/S Chhabra)

Dr. Betty Hamilton presented this proposal, which will compare outcomes of grade II-IV and grade III-IV acute GVHD, incidence and severity of chronic GVHD, hematopoietic recovery, graft failure, CMV viremia, infection, organ toxicities, relapse, TRM, LFS and OS between patients that receive mycophenolate mofetil (MMF) versus those who receive methotrexate (MTX) in a calcineurin inhibitor-based GVHD prophylaxis setting. Since the CIBMTR recently presented the results finding worse outcomes of acute and chronic GVHD in patients receiving MMF compared to MTX from unrelated donors in reduced intensity conditioning setting, this study will analyze conditioning intensities separately. Within the myeloablative setting, the analysis will evaluate potential interactions between donor type (unrelated vs. sibling), graft source (BM vs. PBSC) and type of calcineurin inhibitor (tacrolimus vs. cyclosporine). In the reduced intensity setting, the effects of graft source and calcineurin inhibitor will be assessed. In order to meet either population, the patient had to be 20 years old or older receiving their first allogeneic transplant from 2000-2012 with a calcineurin inhibitor plus either MMF or MTX for GVHD prophylaxis.

There were 5660 patients receiving their first myeloablative transplant for AML, ALL, CML or MDS from an HLA-identical sibling or unrelated donor with a BM or PBSC graft source.

There were 965 patients receiving their first reduced-intensity or non-myeloablative allogeneic transplant for AML, ALL, CML, MDS or NHL from an HLA-identical sibling donor with a PBSC graft source.

Comments from Dr. Alousi were that if the proposal wanted to evaluate aGVHD treatment, it would be very dependent on transplant center and the grade of acute GVHD (and grading can vary by center as well). Dr. Arora confirmed that dosing for GVHD prophylaxis is not collected on the CIBMTR forms. Tao Wang explained that there are 2 ways the analysis for this study could be implemented; (1) using Cox model to analyze the crude hazard of aGVHD or (2) using the pseudo-value approach to look at the cumulative aGVHD rate at certain fixed time points by treating death without aGVHD as a competing risk. The effect of transplant center could be adjusted by random effect models.

**DROPPED**

Dr. Arora presented several slides on each of the dropped proposals, detailing the intended aims, population and study design, as well as the reasons why the proposals weren’t feasible within the GVWC.

d. **PROP 1311-25** Refinement of risk factors for the development of sclerotic chronic GVHD and immunosuppressant cessation (D Kim/J Uhm)

*Dropped due to insufficient data collection on immunosuppressant duration, and sclerotic chronic GVHD on older forms.*

The CIBMTR forms aren’t designed to collect cGVHD information according to the NIH consensus
criteria. While there were a sufficient number of patients who identified as experiencing sclerotic cGVHD, there were an equivalent number of patients who could not be identified as having sclerotic cGVHD or not because this information was not collected by the CIBMTR for unrelated donors prior to 2008.

e. **PROP 1311-45** Survival after severe aGVHD: Are we making progress? (K Jamani/J Storek)  
*Dropped due to overlap with current study GV12-01.*

f. **PROP 1311-78** A CIBMTR retrospective study of incidence of sclerodermous cGVHD in patients with BCR-ABL-positive CML/ALL receiving tyrosine kinase inhibitors post alloHCT  
(A Salhotra/R Nakamura)  
*Dropped due to insufficient data collection on tyrosine kinase inhibitors post-transplant, and on sclerotic chronic GVHD on older forms.*

The concerns about sclerotic cGVHD mentioned above in **PROP 1311-25** apply to this proposal as well. Additionally, post-transplant TKI usage and dosage were not collected on the CIBMTR forms prior to 2008.

### 5. Studies in progress

In the interest of time, Dr. Couriel gave brief updates on the first 5 studies below.

a. **GV06-04** Current trends in chronic GVHD – updated report from the CIBMTR/NMDP (S Arai)  
*Manuscript Preparation*

b. **GV11-04** Validation of cGVHD CIBMTR risk score associated with major outcomes (M Flowers)  
*Manuscript Preparation*

c. **GV11-02** Acute and chronic GVHD after unrelated umbilical cord blood transplantation: Analysis of risk factors and outcomes (Y-B Chen/C Cutler)  
*Data File Preparation*

d. **GV11-03** Comparison of tacrolimus versus cyclosporine with methotrexate for immunosuppression after allogeneic HCT for severe aplastic anemia (Y Inamoto/P Martin/M Flowers/A Urbano-Ispizua)  
*Analysis*

e. **GV13-02** The impact of the combination and sequence of immunosuppressive treatments on outcomes of acute GVHD: A methodological exercise in modeling adaptive treatment strategies (E Krakow/E Moodie)  
*Analysis*

f. **GV12-01** Outcomes of grades 3-4 acute GVHD post-allogeneic HCT: How much progress was achieved? (HJ Khoury)

Dr. Khoury presented the update. The objectives of the study are to determine the change and prognostic factors in determining OS, DFS, TRM and relapse of adult allogeneic transplant recipients for AML, ALL, CML and MDS who developed severe (grade III-IV) aGVHD from 1995-2010.

Comments from the GVWC were to consider adding children to the study population.

g. **GV12-02** Prognostic implications of acute upper gastrointestinal GVHD in patients undergoing myeloablative HCT (S Nikiforow/C Cutler)  
*Protocol Development*

Dr. Cutler presented the update. The study's first objective is to determine the impact on prognosis and outcomes of OS, TRM, DFS and incidence of cGVHD between those patients who had isolated upper gastrointestinal (UGI) aGVHD vs those with no aGVHD vs those with aGVHD
The second objective is to determine within each individual grade of aGVHD, the impact on prognosis and outcomes that UGI involvement has. The study population consists of 7889 adult patients undergoing first non T-cell depleted myeloablative allogeneic transplant with an HLA-identical sibling donor or 8/8, 7/8, 6/8 unrelated donor with BM or PBSC graft sources and calcineurin inhibitor-based GVHD prophylaxis. This total number of patients will change to address each of the two objectives specified above.

Comments from the GVWC were clarifying that the Glucksberg aGVHD scale (I-IV) would be used to grade aGVHD. When asked if the IBMTR scale (A-D) should be used instead, Dr. Cutler said that that would be considered.

h. **GV13-01 Impact of donor parity and donor type on outcomes of allogeneic HCT (A Kumar/A Loren)**

Dr. Couriel presented this update on behalf of the PIs. The primary objective of the study is to compare acute and chronic GVHD and OS between transplant recipients with HLA-identical female parous donors versus 8/8-matched unrelated male donors, as well as to determine whether the relationship between donor type, parity, gender and GVHD is impacted by other transplant variables. The secondary objective is to compare these 2 cohorts in terms of LFS and TRM. The study population consists of 1869 adult patients receiving their first non T-cell depleted, myeloablative allogeneic HCT for AML or ALL from an HLA-identical sibling female parous donor or 8/8-matched unrelated male donor between 2000-2012.

Dr. Couriel confirmed that specific organ involvement of acute and chronic GVHD can be investigated via the CIBMTR forms.

6. **Other Business**

Hearing no items for other business, Dr. Couriel adjourned the meeting at 4:30 pm and reminded people to turn in their voting sheets and working committee evaluations.

a. **GV04-02/05-03c** Impact of cGVHD on late relapse, TRM and survival after allogeneic HCT for hematological malignancies.
   The manuscript is being revised to be submitted to *Clinical Cancer Research*. We anticipate the manuscript will be submitted by March 2014.

b. **GV06-04** Current trends in chronic GVHD - updated report from the CIBMTR/NMDP.
   The manuscript is undergoing revisions to be submitted to *Blood*. We anticipate the manuscript will be submitted by March 2014.

c. **GV11-04** Validation of cGVHD CIBMTR risk score associated with major outcomes.
   The initial draft of the manuscript is being prepared by Dr. Mukta Arora. We anticipate the manuscript will be submitted by July 2014.

d. **GV11-03** Comparison of tacrolimus versus cyclosporine with methotrexate for immunosuppression after allogeneic HCT for severe aplastic anemia.
   Analysis will begin shortly after Tandem and expected to be finished by April 2014. We plan on submitting the study as an abstract for ASH 2014 and submitting the manuscript by March 2015.

e. **GV11-02** Acute and chronic GVHD after unrelated umbilical cord blood transplantation: Analysis of risk factors and outcomes.
   We anticipate the protocol will be brought to the Stats Meeting for a second time by May 2014 and since a large portion of the data file has already been prepared, we plan to finish the analysis by July 2014. We plan on submitting the study as an abstract for ASH 2014 and submitting the manuscript by March 2015.

f. **GV12-01** Outcomes of grades 3-4 acute graft-versus-host disease post-allogeneic hematopoietic stem cell transplantation: how much progress was achieved?
   We anticipate the study will be in data file preparation by July 2014. After July, we anticipate preparing the data file and finishing the analysis by September 2014 so that the abstract may be submitted for Tandem 2015. We further anticipate submitting the manuscript by July 2015.

g. **GV12-02** Prognostic implications of acute upper gastrointestinal GVHD in patients undergoing myeloablative HCT.
   We anticipate the study will be in data file preparation by July 2014. After July, we anticipate preparing the data file, finalizing the analysis and having the manuscript in preparation by July 2015.

h. **GV13-01** Impact of donor parity and donor type on outcomes of allogeneic HCT.
   We anticipate the study will be in data file preparation by July 2015.

i. **GV13-02** The impact of the combination and sequence of immunosuppressive treatments on outcomes of acute graft-versus-host disease; A methodological exercise in modeling adaptive treatment strategies.
   The data file preparation and analysis is being completed by the PI as a part of her Master’s thesis project. We anticipate the analysis will be completed and the manuscript will be in preparation by December 2014.

j. **GV14-01** (PROP 1304-01) Influence of donor and recipient age on risk for acute and chronic graft versus host disease in children receiving HLA identical BMT.
   We anticipate finalizing the protocol after July 2014 and that the study will be in data file preparation by July 2015.
k. **GV14-02** (PROP 1310-22/1311-02/1311-26/1311-91) Comparison of mycophenolate versus methotrexate in combination with a calcineurin inhibitor for GVHD prophylaxis in allogeneic HCT.
   We anticipate finalizing the protocol after July 2014 and that the study will be in data file preparation by July 2015.
### Oversight Work Assignments for Working Committee Leadership (February 2014)

**Corey Cutler**
- **GV11-02**: Acute and chronic GVHD after unrelated umbilical cord blood transplantation: Analysis of risk factors and outcomes
- **GV11-04**: Validation of cGVHD CIBMTR risk score associated with major outcomes
- **GV12-01**: Outcomes of grades 3-4 acute graft-versus-host disease post-allogeneic hematopoietic stem cell transplantation: how much progress was achieved?
- **GV12-02**: Prognostic implications of acute upper gastrointestinal GVHD in patients undergoing myeloablative HCT

**Daniel Couriel**
- **GV04-02/05-03c**: Impact of cGVHD on late relapse, TRM and survival after allogeneic HCT for hematological malignancies
- **GV06-04**: Current trends in chronic GVHD - updated report from the CIBMTR/NMDP
- **GV11-03**: A retrospective comparison of tacrolimus versus cyclosporine with methotrexate for immunosuppression after allogeneic HCT according to graft and donor type
- **GV14-02**: Comparison of mycophenolate versus methotrexate in combination with a calcineurin inhibitor for GVHD prophylaxis in allogeneic HCT

**Amin Alousi**
- **GV13-01**: Impact of donor parity and donor type on outcomes of allogeneic HCT
- **GV13-02**: The impact of the combination and sequence of immunosuppressive treatments on outcomes of acute graft-versus-host disease: A methodological exercise in modeling adaptive treatment strategies
- **GV14-01**: Influence of donor and recipient age on risk for acute and chronic graft versus host disease in children receiving HLA identical BMT