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A G E N D A
CIBMTR WORKING COMMITTEE FOR GRAFT-VERSUS-HOST DISEASE
Houston, TX
Wednesday, February 20, 2019 12:15 – 2:15 PM

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1. **Introduction**
   The CIBMTR Graft-versus-Host Disease Working Committee (GVWC) was called to order at 12:15 pm by Dr. Amin Alousi. The GVWC Leadership was introduced to the GVWC members. Dr. Alousi introduced the new incoming GVWC Co-Chair, Dr. Margaret (Margy) MacMillan, who would be replacing Dr. Alousi, who had fulfilled his 5-year term as Co-Chair. Dr. Alousi reminded those in attendance that scanning their badges as they entered the conference room would include them in the GVWC email list, so they would receive invitations to participate in new studies seeking input. The voting sheet was explained and presenters were reminded they would be allowed 5 minutes to present, followed by approximately 5-10 minutes for discussion. Dr. Joseph Pidala thanked Dr. Alousi for his contributions to the GVWC and presented him with a gift.

2. **Accrual Summary** (Attachment 2)
   Dr. Mukta Arora presented an overview of the CIBMTR, BMT CTN and Chronic GVHD Consortium research repository collections, and encouraged prospective investigators to utilize this resource to further enhance their proposals or studies.

3. Presentations, published or submitted papers

Dr. Arora referenced the publications and submissions, noting that there was an omission in this section. Study **GV15-02**, led by Amin Alousi, which evaluated the composite endpoint of GVHD-free, relapse-free survival between matched unrelated donors with bone marrow versus peripheral blood stem cells.

a. **GV14-01a** Chhabra S, Liu Y, Hemmer MT, Costa L, Pidala JP, Couriel DR, Alousi AM, Majhail NS, Stuart RK, Kim D, Ringden O, Spellman SR, Arora M, Hamilton BK, et. al. ***Biology Blood Marrow Transplant.*** **2018 Aug 25.**

b. **GV14-01b** Hamilton BK, Liu Y, Hemmer MT, Costa L, Pidala JP, Couriel DR, Alousi AM, Majhail NS, Stuart RK, Kim D, Ringden O, Spellman SR, Arora M, Chhabra S, et. al. ***Submitted.***

c. **GV15-01b** Turcotte L, Wang T, Hemmer MT, Spellman SR, Arora M, Yingst A, Couriel DR, Alousi AM, Pidala J, Knight JM, Verneris MR. Proinflammatory cytokine and adipokine levels in adult unrelated marrow donors are not associated with hematopoietic cell transplantation outcomes. ***Biology Blood Marrow Transplant.*** **2018 Aug 23.**

d. **GV16-01a** Mehta R, Holtan S, Wang T, Hemmer MT, Arora M, Spellman SR, Alousi AM, Couriel DR, Pidala J, Weisdorf D. GVHD-free, relapse-free survival (GRFS) and chronic GVHD-free, relapse-free survival (CRFS) in alternative donor hematopoietic cell transplantation for adult patients with acute leukemia. ***Submitted.***

e. **GV16-01b** Mehta R, Holtan S, Wang T, Hemmer MT, Arora M, Spellman SR, Alousi AM, Couriel DR, Pidala J, Weisdorf D. GVHD-free, relapse-free survival (GRFS) and chronic GVHD-free, relapse-free survival (CRFS) in alternative donor hematopoietic cell transplantation for pediatric patients with acute leukemia. ***Submitted.***

f. **GV16-02** Saad A, Wang T, Hemmer MT, Spellman SR, Arora M, Lamb LS, Hashmi SK. Impact of T-cell dose on graft-versus-host disease risk after allogeneic HLA-matched peripheral blood stem cell transplantation. ***Poster presentation at ASH meeting in San Diego, CA, December 2018.***

g. **GV17-02** Im A, Wang T, Hemmer MT, Spellman SR, Arora M, Majhail NS, Pavletic SZ, Weisdorf DJ, Rashidi A, Hamilton BK. Risk factors of acute and chronic GVHD in haploidentical hematopoietic cell transplantation using post-transplant Cyclophosphamide. ***Poster presentation at TCT meeting in Houston, TX, February 2019.***

4. Future/proposed studies

a. **PROP 1803-03** Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients (N Gills/ E Padron/ A Lazaryan) (Attachment 3)

Dr. Nancy Gillis presented the proposal. The stated hypothesis is that donor-engrafted clonal hematopoiesis (CH) is associated with an increased risk of GVHD among adult allogeneic HCT recipients. The specific aims of the proposed study are to determine the prevalence of CH in matched sibling and unrelated allogeneic HCT, determine if allogeneic HCT from donors with CH is associated with an increased risk of acute and chronic GVHD, and whether CH mutations are present in donor-engrafted T-cells. This proposal could change pre-HCT donor screening, as well as disentangle the effect of donor age versus CH status on GVHD risk.

A member of the GVWC Leadership asked whether CHIP mutations have been analyzed in a post-transplant setting before, to which Dr. Gillis responded that they have not but feel they plan to use the same strategy used in their pre-transplant sequencing. A GVWC member asked if the proponents have secured funding for this study, as there seems to be a lot of sample analysis that will be required. The proponents have not secured funding, as of yet. Another member of the GVWC raised the issue that it may not be possible to make a conclusion of CHIP on GVHD, since CHIP mutations are typically myeloid while GVHD occurs from lymphoid T-cells. Dr. Gills mentioned that there is some data of fewer CHIP in lymphoid cells. Regarding assessment of CHIP in donor

engrafted T-cells, another member commented that since mostly allo-reactive T cells cause acute GVHD whereas auto-reactive T cells could cause CGVHD, this phenomenon may result in positive results for CGVHD but not acute GVHD. Dr. Gillis mentioned that the recent European publication, which documented an association between CHIP and chronic GVHD, illustrated that there are associations to be made. However, as another GVWC member stated, this phenomenon could be connected between CHIP and chronic GVHD but will likely prove impossible to analyze acute GVHD. It was confirmed that donors with these samples available have consented for research. These samples are coming from the NMDP Biorepository, whose donors and recipients have all consented for research.

b. **PROP 1810-08/1811-55** Determining the optimal ATG dosing in conditioning regimen in patients with hematologic malignancies (M Byrne/ L Metheny/ M de Lima) (Attachment 4)
Dr. Michael Byrne presented the proposal. The hypothesis of the proposal is that ATG dose and pre-HCT absolute lymphocyte count (ALC) will influence post-HCT outcomes, specifically incidence and severity of GVHD, NRM and OS. The scientific impact of this study is that such a large-scale analysis to identify an optimal dose of ATG has not been undertaken. The results of the analysis on these outcomes may inform future ATG dosing, and if the hypothesis is disproven, transplant providers will be encouraged to continue to dose ATG in their existing fashion.
A member of the GVWC stated that they worked on a study that evaluated the half life of rabbit ATG and that the timing of ATG administration made a difference in outcomes. At the meeting, the GVWC Leadership said that date of ATG administration was not captured, but in this population in the proposal, date of ATG administration would be collected. Another clarification from the GVWC was that source of ATG is collected by the CIBMTR. ATG source is collected, although the population described in the proposal has already been restricted to rabbit ATG. Another comment from the GVWC was to consider restricting the population to one disease type, specifically aplastic anemia was suggested, in an effort to make the study more homogenous with respect to disease.

c. **PROP 1811-34** Cyclosporine vs tacrolimus based GVHD prophylaxis in children undergoing allogeneic hematopoietic cell transplantation (L Broglie/ P Satwani/ L Davis) (Attachment 5)
Dr. Laurie Davis presented the proposal. The proposal's hypothesis is that cyclosporine-based GVHD prophylaxis in children is associated with a lower incidence of cGVHD compared to tacrolimus-based regimens. If this hypothesis is not disproven, it will encourage a change in practice in terms of GVHD prophylaxis treatment for pediatric patients, which would result in lower rates of cGVHD and long-term morbidity.
A member of the GVWC asked if the CIBMTR collects dose information on methotrexate used in GVHD prophylaxis, which unfortunately the CIBMTR forms do not collect. Another member of the GVWC asked if the proponents would evaluate MMF versus methotrexate, in addition to the stated goal of comparing cyclosporine versus tacrolimus.

d. **PROP 1811-163** Racial and ethnic differences in patients with chronic graft versus host disease (N Farhadfar/ J Wingard/ S Lee) (Attachment 6)
Dr. Nosha Farhadfar presented the proposal. Dr. Farhadfar stipulated that racial background on clinical outcomes of patients who develop post-HCT cGVHD has been addressed in several studies, but the true impact has not yet been adequately evaluated in a large-scale analysis. The proposal hypothesizes that there are racial differences in clinical manifestations, severity, treatment patterns and outcome of patients with cGVHD, and Dr. Farhadfar stated that this would be the first study to make such an investigation. If these characteristics do differ between racial groups, it may be possible to identify groups of patients with poor outcomes who should be considered for analysis in future clinical trials. This proposed study would also evaluate whether there is appropriate representation of minorities in clinical trials.

A member of the GVWC Leadership clarified that the CIBMTR did not collect NIH Global Severity of cGVHD to be able to be analyzed in this population proposed, but data are available on organ involvement, severity (mild, moderate, severe) and extent (limited, extensive) of cGVHD. A GVWC member asked if this proposal would restrict the population to 1 country, which it currently is not, and recommended restricting to 1 country to remove the heterogeneous factors of including multiple countries. Another GVWC member asked if donor race and ethnicity would be evaluated, and Dr. Farhadfar noted that none of the referenced publications evaluated donor race. Another GVWC member noted that there were no patients of the Hispanic race described in the population, and Dr. Farhadfar clarified that the patients' ethnicity is described in the proposal table. The next GVWC member noted that Hispanic ethnicity is not a race, and should not be treated as a category to compare against Caucasians, African-Americans and Asian/Pacific Islanders. This GVWC member also noted that some centers may have done single center studies examining this question, and perhaps this question could be better suited by a single (or several) center study. Another GVWC member noted that there is a big discrepancy in donor type between the different patient racial groups, and may prove difficult to analyze.

Dropped proposed studies

Dr. Arora explained that there were some proposals that were not presented at this meeting, due to factors related to data availability. Due to that, Dr. Arora briefly explained the difference between the CIBMTR's two tracks of data collection, Transplant Essential Data (TED) which collects more broad data on a wider population and Comprehensive Report Forms (CRF) which collects more detailed information on a subset of the patients completing TED forms. The main point relevant to the GVWC is that necessary post-HCT GVHD data has only been collected on the CRF forms. As of 2017, the TED follow-up forms began collecting more detailed GVHD data so it is possible to use TED patients to analyze GVHD in the detailed standard that GVWC studies require. Also, since 2017, data have been collected to calculate NIH Global Severity of cGVHD, so that is an outcome that can hopefully be evaluated soon in retrospective studies.

e. **PROP 1811-158** Role of post-allogeneic hematopoietic cell transplant hypomethylating agents on the incidence and severity of graft-versus-host disease in patients with myelodysplastic syndrome and acute myeloid leukemia. *Small sample size of patients with valid date available for post-HCT hypomethylating agents. Also, it was pointed out that dates of initiating hypomethylating agent were not collected, hence its trajectory with regards to GVHD (whether it was administered prior to development of acute GVHD or not) is unknown.*
f. **PROP 1812-08** The impact of recipient abnormal Stimulator of Interferon Genes (STING) genotypes on acute and chronic graft-versus-host disease after matched unrelated donor allogeneic HCT. *Withdrawn by proponents based on data provided to them evaluating a pre-existing dataset.*

5. Studies in progress (Attachment 7)

Dr. Arora presented a slide that illustrated the current status of the active studies.

a. **GV17-01** Investigating antibiotic exposure and risk of acute GVHD in children undergoing HCT for acute leukemia (C Elgarten/ B Fisher/ R Aplenc) **Protocol Development**
b. **GV17-03** Alterations in the characteristics and outcomes of GVHD following post-transplant Cy for haploidentical HCT and in patients over 60 at high risk for GVHD (R Saliba/ S Ciurea/ J Schriber) **Analysis**
c. **GV18-01** Comparison of late effects among allogeneic hematopoietic cell transplantation survivors with and without chronic graft-versus-host disease (Lee CJ/ Couriel DR) **Protocol Development**

b. **GV18-02** Comparison of antibacterial prophylaxis strategies and outcomes in allogeneic hematopoietic cell transplantation patients with acute graft-versus-host disease (Wallis W/ Alousi AM/ Gulbis A) **Data File Preparation**
b. **GV18-03** Impact of chronic graft-versus-host disease on non-relapse mortality and disease relapse in transplant recipients (Bhatt V/ Lee SJ) **Protocol Development**

6. Other Business

Dr. Arora reminded the GVWC members that the leadership would remain at the table for 10-15 minutes after the meeting if anyone had questions or comments. Hearing no other calls for business, Dr. Arora adjourned the meeting at 1:45 PM.

After the new proposals were presented, each participant in the meeting had the opportunity to rate each proposal using paper ballots. Based on the voting results, current scientific merit, available number or relevant cases and the impact of the study on the field, the following study will move forward as a part the committee's research portfolio for the upcoming year:

PROP 1803-03 Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients (N Gills/ E Padron/ A Lazaryan)

Working Committee Overview Plan for 2019 – 2020

a. **GV17-01** Investigating antibiotic exposure and risk of acute GVHD in children undergoing HCT for acute leukemia (C Elgarten / B Fisher / R Aplenc)

The aims of the study are to determine the association of antibiotics commonly administered for neutropenic fever with subsequent development of post-HCT aGVHD among pediatric patients undergoing HCT for acute leukemia. The hypothesis is that these patients who are exposed to antibiotics with activity against anaerobic commensal microorganisms are associated with an increased risk of aGVHD.

We anticipate the results will be finalized and an abstract for ASH submitted by August 2019. The initial manuscript is expected to be received by September 2019 and will be revised and circulated to the Writing Committee by November 2019. We finally expect to submit the final manuscript for publication by January 2020. 80 statistical hours have been allocated to accomplish these goals (PHIS statisticians will perform the multivariate analysis).

b. **GV17-03** Characteristics and outcomes of acute and chronic GVHD after haploidentical related donor allogeneic HCT (R Saliba / S Ciurea / J Schriber)

The aims of the study are to compare aGVHD, cGVHD, OS and TRM between patients receiving post-transplant Cyclophosphamide-based GVHD prophylaxis with those receiving standard GVHD prophylaxis. Patients over the age of 60, and therefore at greater risk for GVHD, will also be specifically examined in a subset analysis.

We anticipate that an ASH abstract will be submitted by August 2019. Further, the initial draft of the manuscript is expected to be received by August 2019 and circulated to the Writing Committee by September 2019. The final manuscript will be submitted by November 2019. 70 statistical hours have been allocated to accomplish these goals.

c. **GV18-01** Comparison of late effects among alloHCT survivors with and without cGVHD (C Lee/ D Couriel)
This study will test whether the cumulative incidence rate of late effects is greater among alloHCT survivors with cGVHD versus those without cGVHD.
We anticipate circulating the revised protocol to the GVWC by October 2019, and then finalizing the protocol by December 2019. We further anticipate preparing the data file for analysis by March 2020. 200 statistical hours have been allocated to accomplish these goals.

d. **GV18-02** Comparison of antibacterial prophylaxis strategies and outcomes in alloHCT patients with acute GVHD (W Wallis/ A Alousi/ A Gulbis)
This study will evaluate the cumulative incidence of bacterial blood stream infections in patients with aGVHD grade II-IV, and compare patients between centers that give antibiotics for antibacterial prophylaxis versus those centers that do not.
We anticipate having the data file prepared for analysis by July 2019, with the aspirations to submit an abstract to ASH by August 2019. We further anticipate receiving the initial draft of the manuscript by October 2019, and circulating a revised draft to the Writing Committee by December 2019. We finally expect to submit the final manuscript for publication by March 2020. 130 statistical hours have been allocated to accomplish these goals.

e. **GV18-03** Impact of chronic GVHD on non-relapse mortality and disease relapse (V Bhatt/S Lee)
This study will evaluate the cumulative incidence of non-relapse mortality and relapse between patients who have cGVHD versus those without cGVHD, as well as between older versus younger patients.
We anticipate circulating the revised protocol to the GVWC by November 2019, and then finalizing the protocol by January 2020. 100 statistical hours have been allocated to accomplish this goal.

f. **GV19-01** Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients (N Gillis/ E Padron/ A Lazaryan)
This study will investigate the incidence of clonal hematopoiesis among matched sibling and unrelated donors, as well as determine if clonal hematopoiesis is associated with an increased rate of acute and chronic GVHD.
We anticipate receiving the draft protocol by July 2019, and finalizing the protocol by October 2019. 100 statistical hours have been allocated to accomplish this goal.

Study number and title	Current status	Goal with date	Total hours to complete	Total hours to goal	Hours allocated to 6/30/2019	Hours allocated 7/1/2018-6/30/2019	Total Hours allocated
GV17-01 Investigating antibiotic exposure and risk of aGVHD in children undergoing HCT for acute leukemia	Protocol development	Submission – Jan 2020	250	**250**	170	80	**250**
GV17-03 Characteristics and outcomes of acute and chronic GVHD after haploidentical related donor allogeneic HCT	Data file preparation	Submission – Nov 2019	155	**155**	85	70	**155**
GV18-01 Comparison of late effects among alloHCT survivors with and without cGVHD	Protocol pending	Analysis – Mar 2020	310	**200**	0	200	**200**
GV18-02 Comparison of antibacterial prophylaxis strategies and outcomes in alloHCT patients with acute GVHD	Protocol development	Submission – Mar 2020	300	**300**	170	130	**300**
GV18-03 Impact of chronic GVHD on non-relapse mortality and disease relapse	Protocol pending	Data file prep – Jan 2020	310	**100**	0	100	**100**
GV19-01 Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients	Protocol pending	Data file prep – Nov 2019	310	**100**	0	100	**100**

Oversight Assignment for Working Committee Leadership (March 2019)

Joseph Pidala	**GV17-03** Characteristics and outcomes of acute and chronic GVHD after haploidentical related donor allogeneic HCT **GV18-01**: Comparison of late effects among alloHCT survivors with and without cGVHD
Madan Jagasia	**GV18-02**: Comparison of antibacterial prophylaxis strategies and outcomes in alloHCT patients with acute GVHD **GV18-03**: Impact of chronic GVHD on non-relapse mortality and disease relapse
Margy MacMillan	**GV17-01**: Investigating antibiotic exposure and risk of acute GVHD in children undergoing HCT for acute leukemia **GV19-01**: Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients