



MINUTES AND OVERVIEW PLAN

CIBMTR WORKING COMMITTEE FOR GRAFT-VERSUS-HOST DISEASE

Orlando, FL

Saturday, February 22, 2020 2:45 – 4:45 PM

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1. Introduction

Dr. Joseph Pidala called the meeting to order and introduced the current GVWC leadership members and the incoming GVWC Co-Chair, Dr. Carrie Kitko, who will replace Dr. Pidala in the upcoming year. The attendees were reminded to have their badges scanned to be included in the working committee email list. Dr. Pidala discussed the goals, expectations, and limitations of the GVWC and gave an overview of the active study status. Dr. Madan Jagasia explained the voting process, how current and future studies will be prioritized, criteria that must be met in order to be considered for authorship on a manuscript. Additionally, the differences between TED and CRF sources of data were briefly reviewed. Dr. Jagasia thanked Dr. Pidala for his contributions over the last five years as part of the GVWC leadership and presented him with a gift.

2. Accrual Summary

Stephen Spellman gave an overview of the CIBMTR, BMT CTN, and Chronic GVHD Consortium research sample repositories and discussed the sample usage policy.

3. Presentations, published or submitted papers

Details regarding presentations and publications were mentioned and made available to attendees as an attachment. There were 4 manuscripts that were submitted or published, and 2 presentations in national meetings.

4. Studies in progress

Dr. Pidala presented a graphic illustrating the status of current studies. There were 2 studies in the phase of manuscript preparation, one in data file preparation (sample typing) and 3 in protocol development.

5. Future/proposed studies

Drs. Pidala, Jagasia, and Margaret MacMillan led this session. Presenters were reminded to limit their presentations to 5 minutes to ensure time for discussion (5 minutes).

- a. **PROP 1911-80/1911-175** Determining the optimal anti-thymocyte globulin dosing in patients with hematologic malignancies (N Sharma/L Metheny/M Byrne/M de Lima/Y Efebera)
Dr. Nidhi Sharma presented the proposal. The aim of the proposed study is to identify optimal ATG dose for myeloablative (MAC) and reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplant (RIC allo-HCT). Given the increasing use of RIC allo-HCT for treating malignant hematologic conditions, optimized dosing of ATG will have an impact across the centers in improving transplantation outcomes.
Members of the GVWC asked several questions regarding availability of the following data: timing of ATG administration, absolute lymphocyte count (ALC) at time ATG is given, and if G-CSF was given. The GVWC leadership informed them that information on timing is not available for the majority of the patients and that G-CSF information is available, but not collected specifically at the time of ATG administration. A member of the GVWC asked how the MAC and RIC categorizations are defined to which the GVWC leadership responded that the conditioning intensity classifications are based on CIBMTR standards. Two members asked about the primary endpoint of acute GVHD, since the incidence of GVHD correlates with ATG dose, and suggested changing it to disease free survival or GRFS, since ATG may impact other outcomes. Dr. Sharma agreed, but mentioned that previous studies did not show an association between ATG dose and GRFS. Another member brought up the concern about the heterogeneity of the patient population due to the multiple different donor types and graft sources included.
- b. **PROP 1911-52** HLA-DQ2/DQ8 and GVHD risk in pediatric patients undergoing hematopoietic stem cell transplant (A Seif)
Dr. Alix Seif presented the proposal. The hypothesis is that HLA DQ2/8 haplotypes will have a dose-dependent protective effect against GVHD. The proposed study aims to establish the predictive value of HLA DQ2/8 haplotypes for acute and chronic GVHD in pediatric transplants and to evaluate the effect of these haplotypes on transplant outcomes. Clinical impacts of this study include the potential for targeted interventions and personalized GVHD prophylaxis.
A GVWC member asked about the possible biological mechanisms behind the association of DQ2/DQ8 and GVHD that was found in the preliminary data. Dr. Seif speculated that these HLA haplotypes may modify the microbiome and suggested a potential future project to investigate this interaction. Another member asked why the study is limited to pediatric patients; Dr. Seif responded that she would be open to expanding the population to include adult patients. An additional suggestion was to limit the study to gut GVHD.
- c. **PROP 1911-81** Investigate the association of HLA-A*0101 allele expression and risk for acute cutaneous GVHD (A Markova/A Jakubowski/D Ponce)
Dr. Alina Markova presented the proposal. The hypothesis is that HLA-A*0101 expression is associated with increased risk of severe acute cutaneous GVHD. The specific aims are to investigate whether HLA-A*0101 expression is associated with increased risk of grade II-IV and III-IV cutaneous aGVHD after allo-HCT, to assess if HLA-A*0101 expression in patients has an impact on transplant-related mortality (TRM) and overall survival (OS), to determine the effect of T-cell depletion on associations between HLA-A*0101 expression and cutaneous aGVHD, TRM, OS, and to determine association between CMV, HHV6, Adenovirus, and EBV viremia and cutaneous

aGVHD onset in patients with and without HLA-A*0101. These findings would have practical implications for allogeneic transplant recipients, both in the development of prophylactic therapies to reduce their risk for cutaneous aGVHD, and of early therapeutic strategies targeting the skin in this high-risk HLA-A*01:01 population.

A GVWC member asked if the extended HLA-A*0101 haplotypes were examined in their preliminary data analysis. A member of the GVWC leadership asked how the proposed study will address non-skin GVHD and whether that would be a competing risk for their outcome of interest. Dr. Markova responded that the preliminary analysis presented did not include either the extended haplotype or non-skin GVHD and would consider those factors in the proposed study. Another member inquired about the ability to differentiate between late acute and chronic skin GVHD; one of the leadership members clarified which variables related to skin GVHD are collected on the forms.

- d. **PROP 1911-252** Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly-multiplexed proteomics assay: MHC-PepSeq (K Sandhu/J Altin/M Askar/R Nakamura)
- Dr. Karamjeet Sandhu presented the proposal. The hypothesis is that the risk score derived from the MHC-PepSeq assay is associated with the incidence and severity of acute and chronic GVHD. The proposed study aims to evaluate the performance of the MHC-PepSeq model in predicting acute and chronic GVHD in recipients of allo-HCT from a 8/8 matched donor with a mismatch in HLA-DP and from a 7/8 HLA mismatched donor. This risk score could be used to personalize selection of donors and GVHD prophylaxis.
- A member of the GVWC leadership asked for a description of the distribution of the risk scores from the model; Dr. Sandhu responded that preliminary data illustrating the score distribution is available, but not included in the proposal.
- e. **PROP 1911-102** Machine learning models and clinical decision support tool for acute and chronic graft versus host disease (GvHD) in patients with acute myeloid leukemia (AML) undergoing allogeneic hematopoietic cell transplant (HCT) (T Kindwall-Keller/B Lobo)
- Dr. Tamila Kindwall-Keller presented the proposal. The hypothesis is that pre- and post-HCT data collected for AML patients undergoing allogeneic HCT can be used in statistical and machine learning models to develop a clinical decision support tool (DST) providing more precise information regarding the likelihood of developing GvHD along with type and severity of GvHD. The proposed study aims to enhance the understanding of how clinical risks interplay with development of GVHD, improve outcomes, and enhance personalized care.
- Two members of the GVWC pointed out that CIBMTR data has been analyzed extensively by traditional statistical methods and questioned the advantages of using machine learning; Dr. Kindwall-Keller responded that unlike other statistical methods, machine learning does not make any assumptions about the data and will not need to restrict to specific variables. Another member asked about grouping grade II-IV acute GVHD together as the endpoint since clinicians would be unlikely to change the transplant plan if grade II acute GVHD was predicted. Dr. Kindwall-Keller explained that it was chosen as an outcome because it is most commonly reported by current studies but is willing to include grade III-IV as an outcome as well. Another member suggested including pediatric patients and using age as a continuous variable in the machine learning model. Another member asked about type of information that would be outputted by the DST; Dr. Kindwall-Keller clarified that the model will compute a risk score based on patient specific factors that clinicians can take into consideration when comparing treatment options.
- f. **PROP 1911-270** Clinical significance of pediatric late acute GVHD and chronic GVHD: why does it matter to differentiate? (T Takahashi/M MacMillan)

Dr. Takuto Takahashi presented the proposal. The hypothesis is that risk factors and outcomes of pediatric late aGVHD and cGVHD differ from each other. The proposed study aims to identify the incidence, risk factors, and presentation of late aGVHD and cGVHD and to assess non-relapse mortality, overall survival, and presentation of late aGVHD and cGVHD.

A member of the GVWC asked how the proponents will address patients who recover from late aGVHD and then develop cGVHD in the analysis; Dr. Takahashi responded that they will work with the study statisticians on the analysis plan for these patients. A leadership member raised the concern that late aGVHD patients may be misreported as having cGVHD to which another leadership member responded that clinical presentation including organ involvement at diagnosis as reported in the forms, is reviewed in detail for these patients to minimize misclassification, however, its likely that not all misclassifications can be corrected.

- g. **PROP 1911-25** Influence of combination of GVHD prophylaxis and stem cell source on GRFS (S Farhan)

Dr. Shatha Farhan presented the proposal. The hypothesis is that peripheral blood stem cell source with in-vivo T-cell depletion or post-transplant cyclophosphamide (PT-Cy), used as risk adapted GVHD prophylaxis, is non-inferior to bone marrow stem cell source regarding GRFS in transplant for malignant hematological disorders. If the hypothesis is proven, this would expand the source of stem cells from unrelated donors.

A member of the GVWC leadership asked if it was reasonable to group together patients who received ATG/Campath and PT-Cy to which Dr. Farhan responded that they would be open to separating the two populations for homogeneity. Another question asked was if there were differences in any variables, aside from graft source and GVHD prophylaxis, provided in the demographics table; Dr. Farhan indicated that there were no differences.

- h. **PROP 1912-01** Exploring the impact of allogeneic stem cell transplant volume on GRFS: a matched cohort study in contemporary era (R Shallis/L Gowda/A Zeidan/B Betts)

Dr. Rory Shallis presented the proposal. The hypothesis is that the outcomes of patients with AML or MDS proceeding to allo-HSCT in first complete remission at higher-volume centers will have favorable GVHD/relapse-free survival (GRFS) compared to those treated at lower-volume centers. The results of this proposed study can potentially be used to help patients choose their transplant centers, establish volume guidelines for human resource development and creating training programs, increase access to trials at low volume centers, and seek further NIH funding in expanding GVHD/infection mitigation consortium work.

A member of the GVWC asked at which time point post-transplant would GRFS be evaluated; Dr. Shallis responded that they have not yet decided on the time point but indicated that 100 days post-transplant would be one of the possibilities. This member also suggested including presence of a survivorship clinic within the center as a variable if long term outcomes will be evaluated. Several members asked if the study questions are already addressed by the center-specific outcomes report generated by the SCTOD; a leadership member clarified that this report only includes overall survival, while the proposed study will focus on GRFS. Two members raised the concern that focusing on only center volume would be too simplistic and suggested including social risk factors as well. Another member suggested including GVHD prophylaxis in the analysis.

- i. **PROP 1906-03/1911-31/1911-139/1911-169/1911-196** Comparison of outcomes with post-transplant cyclophosphamide in haploidentical donor transplant versus 8/8 HLA-matched related and unrelated, and 7/8 mismatched unrelated donor allogeneic stem cell transplantation for acute leukemia and myelodysplastic syndrome (D Modi/F Socola/K Caldwell)

Dr. Dipenkumar Modi presented the proposal. The hypothesis is that clinical outcomes of patients receiving transplants from HLA-MRD, MUD, and 7/8 MMUD with post-transplant cyclophosphamide (PT-Cy) are similar to those of haploidentical donor transplants. If this

hypothesis is proven, the potential donor pool can be expanded for patients who currently do not have an available matched donor and will reduce the time required for the donor search process. A member of the GVWC questioned whether the small number of MRD, MUD, and 7/8 MMUD transplants with PT-Cy would be adequate to perform the study; Dr. Modi responded that those groups may be combined for comparison with the haploidentical donor group. Another member asked if the study could be expanded to include more diseases so that the results can be more generalizable; Dr. Modi explained that they restricted the proposal to AML, ALL, and MDS for a more homogeneous population, but is willing to include additional diseases. Another member raised the concern about sufficient follow-up for matched donor PT-Cy transplants and that it may be better to do the study at a later point; Dr. Modi disagreed and mentioned an ASH plenary comparing PT-Cy and cyclosporine use in conventional transplants.

Dropped proposed studies

Dr. Mukta Arora briefly discussed the reasons for dropping the proposals that were not accepted for presentation and emphasized that most of them could not proceed due to feasibility issues.

- j. **PROP 1909-07** Matched control dataset from CIBMTR for an FDA requested phase II expansion cohort study on CD24Fc in prophylaxis of acute GVHD in myeloablative matched unrelated donor HCT. *Forwarded to CIBMTR Corporate Program.*
- k. **PROP 1911-21** Use of therapeutic agents for treatment of steroid-refractory GVHD before and after FDA approval of ruxolitinib and ibrutinib. *Data for steroid refractory GVHD is unavailable.*
- l. **PROP 1911-152** Is age an independent risk factor in younger age allogeneic stem cell transplant recipients with hematological malignancies (age 0.1-29.99 years) for grade II-IV acute GVHD and chronic GVHD? *Overlap with CIBMTR study GV14-02.*
- m. **PROP 1911-154** Validating predictive biomarkers of aGVHD from a humanized mouse model of HSCT. *Post-transplant samples not available in CIBMTR sample repository.*
- n. **PROP 1911-183** Graft-versus-host-disease (GVHD) relapse-free survival (GRFS) and chronic GVHD relapse free survival (CRFS) following haploidentical transplant for hematological malignancies: a comparison of T cell replete vs ex vivo T cell depletion approaches in a contemporary cohort of patients. *Sample size issue.*
- o. **PROP 1911-212** Can calcineurin inhibitors be avoided for GVHD prophylaxis for umbilical cord transplant recipients in the era of anti-thymocyte globulin (ATG)? *Sample size issue.*
- p. **PROP 1911-219** Role of post-allogeneic hematopoietic cell transplant hypomethylating agents on the incidence and severity of graft-versus-host disease in patients with myeloid neoplasms. *Sample size issue.*
- q. **PROP 1911-233** Mesenchymal stem cells (MSC) as therapy for steroid refractory acute graft versus host disease (SRaGVHD) in patients undergoing allogeneic stem cell transplant. *Data for steroid refractory GVHD and response to GVHD therapy is unavailable.*
- r. **PROP 1911-240** Impact of cryopreservation versus fresh donor lymphocyte infusions on non-relapse and relapse mortality/morbidity. *Data on cryopreservation status is unavailable.*
- s. **PROP 1911-241** Comparison of graft versus host disease (GVHD) and survival outcomes in alternate mismatched graft sources for allogeneic transplant. *Sample size issue.*

6. Other Business

Dr. Jagasia adjourned the meeting at 4:30 PM and reminded the attendees that the leadership would remain at the table for 10-15 minutes after the meeting to accept questions and comments.

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, scientific merit, available number of

relevant cases, and the impact of the study on the field, the following studies will move forward as a part of the committee's research portfolio for the upcoming year:

- **PROP 1911-102** Machine learning models and clinical decision support tool for acute and chronic graft versus host disease in patients with acute myeloid leukemia undergoing allogeneic hematopoietic cell transplant (T Kindwall-Keller/B Lobo)
- **PROP 1911-252** Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly-multiplexed proteomics assay: MHC-PepSeq (K Sandhu/J Altin/M Askar/R Nakamura)

Working Committee Overview Plan for 2020 – 2021

- 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 protocol to the GVWC in April 2020 and having the data file prepared for analysis by July 2020. The goal is to submit an abstract to ASH by August 2020. We expect to finalize the analysis and have the manuscript written and submitted by July 2021. 240 statistical hours have been allocated to accomplish these goals.
- 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 circulating the protocol to the GVWC in April 2020 and having the data file prepared for analysis by July 2020. We expect to finalize the analysis and have the manuscript written and submitted by July 2021. 200 statistical hours have been allocated to accomplish these goals.
- 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 protocol to the GVWC in April 2020 and having the data file prepared for analysis by July 2020. We expect to finalize the analysis and have the manuscript written and submitted by July 2021. 310 statistical hours have been allocated to accomplish these goals.
- 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 having the analysis completed by July 2020 with the goal of submitting an abstract to ASH by August 2020. We expect to have the manuscript written and submitted by July 2021. 190 statistical hours have been allocated to accomplish these goals.

- e. **GV20-01** Machine learning models and clinical decision support tool for acute and chronic GVHD in patients with AML undergoing allogeneic HCT (T Kindwall-Keller/ B Lobo)
 This study aims to develop machine learning models and evaluate their efficacy in predicting the probability of a patient developing acute or chronic GVHD based on reported characteristics. We anticipate receiving the draft protocol by July 2020 and finalizing the protocol by July 2021. 100 statistical hours have been allocated to accomplish these goals.
- f. **GV20-02** Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly multiplexed proteomics assay: MHC-PepSeq (K Sandhu/ J Altin/ A Medhat/ R Nakamura)
 This study will evaluate the effectiveness of MHC-PepSeq derived risk scores in predicting acute and chronic GVHD in recipients of allo-HCT from 8/8 HLA matched donors with mismatch in HLA-DP and from 7/8 HLA matched donors. We anticipate receiving the draft protocol by July 2020 and finalizing the protocol by July 2021. 100 statistical hours have been allocated to accomplish these goals.

Oversight Assignments for Working Committee Leadership (March 2020)

Carrie Kitko	GV18-01 Comparison of late effects among alloHCT survivors with and without cGVHD GV20-01 Machine learning models and clinical decision support tool for acute and chronic GVHD in patients with AML undergoing allogeneic HCT
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	GV19-01 Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients GV20-02 Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly multiplexed proteomics assay: MHC-PepSeq

Study number and title	Current status	Goal with date	Total hours to complete	Total hours to goal	Hours allocated to 6/30/2020	Hours allocated 7/1/2020-6/30/2021	Total Hours allocated
GV18-01: Comparison of late effects among alloHCT survivors with and without cGVHD	Protocol development	Submitted – July 2021	240	240	110	130	240
GV18-02: Comparison of antibacterial prophylaxis strategies and outcomes in alloHCT patients with acute GVHD	Protocol development	Submitted – July 2021	200	200	70	130	200
GV18-03: Impact of chronic GVHD on non-relapse mortality and disease relapse	Protocol development	Submitted – July 2021	310	310	180	130	310
GV19-01: Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients	Data file preparation	Submitted – July 2021	190	190	60	130	190
GV20-01: Machine learning models and clinical decision support tool for acute and chronic GVHD in patients with AML undergoing allogeneic HCT	Protocol pending	Data file prep – July 2021	330	100	0	100	100
GV20-02: Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly multiplexed proteomics assay: MHC-PepSeq	Protocol pending	Data file prep – July 2021	330	100	0	100	100