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MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR INFECTION AND IMMUNE RECONSTITUTION
San Antonio, TX
Wednesday, February 21, 2024, 1:00 – 3:00 PM CT

Co-Chair:	**Roy Chemaly, MD, MPH; UT MD Anderson Cancer Center, Houston, TX; Telephone: 713-792-0007; E-mail: rfchemaly@mdanderson.org;**
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Co-Chair:	**Joshua Hill, MD; Fred Hutchinson Cancer Center, Seattle, WA; E-mail: jahill3@fredhutch.org**
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Statistician:	**Qiran(Lexie) Ye, MPH; CIBMTR® (Center for International Blood and Marrow Transplant Research), Medical College of Wisconsin, Milwaukee, WI; E-mail: qye@mcw.edu**
WCTL Program Participant	**Zeinab El Boghdadly, MD; Ohio State University, Columbus, OH; Email: Zeinab.ElBoghdadly@osumc.edu**

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1. Introduction

a. Welcome and Introduction
b. Minutes from February 2023 meeting

The meeting was called to order at 1pm by Dr. Marcie Riches. She introduced the current working committee leadership and reviewed the CIBMTR COI policy, described Working Committee Membership, goals, expectations, guidelines for voting, and rules of authorship. The two sources of HCT data (TED vs. CRF level) were introduced as well as cellular therapy data.

2. Accrual summary

3. Presentations, Published or Submitted papers

a. **1801a** Celalettin Ustun, Min Chen, Soyoung Kim, Jeffery J Auletta, Marjorie V Batist, Minoo Battiwalla, Jan Cerny, Lohith Gowda, Joshua A Hill, Hongtao Liu, Pashna N Munshi, Sunita Nathan, Matthew D Seftel, John R Wingard, Roy F Chemaly, Christopher E Dandoy, Miguel-Angel Perales, Marcie Riches, Genovefa A Papanicolaou, Post-transplantation cyclophosphamide is associated with increased bacterial infections. ***Bone Marrow Transplant, 2023, PMID: 37903992, doi.org:10.1038/s41409-023-02131-z.***

b. **1801b** Genovefa A. Papanicolaou, Min Chen, Naya He, Michael J. Martens, Soyoung Kim, Marjorie V. Batista, Neel S. Bhatt, Peiman Hematti, Joshua A. Hill, Hongtao Liu, Sunita Nathan, Matthew D. Seftel, Akshay Sharma, Edmund K. Waller, John R. Wingard, Jo-Anne H. Young, Christopher E. Dandoy, Miguel-Angel Perales, Roy F. Chemaly, Marcie Riches, Celalettin Ustun, Incidence and Impact of Fungal Infections in Post-Transplantation Cyclophosphamide-Based Graft-versus-Host Disease Prophylaxis and Haploidentical Hematopoietic Cell Transplantation: A Center for International Blood and Marrow Transplant Research Analysis, ***Transplantation and Cellular Therapy, 2023, ISSN 2666-6367, doi.org:10.1016/j.jtct.2023.09.017.***

4. Studies in progress

a. **IN19-01** Immune recovery predicts post-transplant outcomes (MA Perales/ P Szabolcs): Tandem 2023 Abstract. **Manuscript preparation**.
b. **IN19-02** Impact of Antibiotic Prophylaxis in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation in the Current Era (Z El Boghdadly/ C Dandoy/ P Badia Alonso). **Protocol development**.
c. **IN20-01** Infectious complications in patients with B-Lymphoid hematologic malignancy treated with CD19 chimeric antigen receptor T cell therapy (K Wudhikarn/ M McGhee/ J Hill/ M Herr). **Analysis**.
d. **CV20-04d** COVID-19 in Hematopoietic Cell Transplant Recipients- Outcomes early v late (R Chemaly/ MS Infante). **Protocol development**.
e. **IN22-01** Viral Hepatitis after allogeneic hematopoietic cell transplant using post-transplant cyclophosphamide for graft versus host disease prophylaxis (K Wudhikarn/ MA Perales). **Protocol development.**
f. **IN23-01** Infectious complications in patients with relapsed/refractory multiple myeloma receiving B-cell maturation antigen targeted chimeric antigen receptor T cells (K Wudhikarn/ MA Perales/ A Mirza/ L Gowda/ MB Abid/ S Devarakonda/ Y Efebera). **Protocol development.**

5. Future/proposed studies

a. **PROP 2310-52** Impact of Donor Stem Cell Graft Composition on Immune Reconstitution in Allogeneic Hematopoietic Cell Transplantation (H Murthy/N Farhadfar)

Dr. Murthy presented the proposal. The scientific aims of this study are: 1. To determine the effect of donor graft subsets of CD4+, CD8+ and CD56+ on incidence of day 100 infection rate (viral, bacterial, fungal) 2. To determine the effect of donor graft subsets of CD4+, CD8+ and CD56+ on Infection free survival: OS, PFS, NRM, GVHD (acute, chronic), relapse/progression. 3. To determine the effect graft composition on day 100 immune recovery of CD4+, CD8+, and CD56+
Discussion:

1. *Recommendations from the committee where include the following:*
    a. *Consider adding GVHD prophylaxis*
    b. *Add ALC at Day 100*
    c. *Adjust for CST/other GVHD Rx*
2. *Question about the definition of infection free survival vs infection related mortality. Recommend that for IFS, do not to combine all infections and focus on important infections only (i.e. CMV, mold, etc).*
3. *Concerns about low number of mismatched unrelated donor which can affect the power of immune recovery. Suggest having day 100 recovery data.*
4. *Concerns about exclusion of pediatric patients.*

5. *Concerns about data:*
    a. *Given small #s of patients with IR data, consider limiting the population to those with both graft composition and IR data. Note: this will be small numbers and likely only descriptive.*
    b. *The CIBMTR does not have data on duration of GVHD treatment except as follows: start date (all agents); end date steroids; end date for 'final IS taken' stating in January 2017*

Potential benefits: This would be the second analysis utilizing the IR data.

b. **PROP 2310-57** Impact Of Mycophenolate Mofetil And Cytomegalovirus Serostatus In Patients Undergoing HLA Matched Donor HCT (R Mehta/R Saliba)

Dr. Saliba presented the proposal. The scientific aim of this study is: the results of this study could call for a change in the GVHD prophylaxis in select patients, i.e., exclusion of MMF in CMV seropositive AML patients.
Discussion:
The WC has several suggestions including:

1. *Mismatched transplants should be added*
2. *Pediatric patients should be added*
3. *Letermovir was added to the forms to capture discretely in Sep 2022. To account for letermovir in the analysis, would need to consider patients pre vs post approval date(s) for letermovir*
4. *Consider adding disease specific lines of therapy*
5. *Look at MDS separately*

Potential concerns about data:

1. *Duration of MMF is not collected*

Potential benefits

1. *There are 168 patients of the selected population who have supplemental form 2150 (CMV/EBV/ADV/BK/HHV6) form to provide additional detailed information for CMV.*

c. **PROP 2310-75** Evaluating Infection Rates in Autologous Hematopoietic Stem Cell Transplants for Primary Solid Tumors and Lymphoma (J Koo/C Dandoy)

Dr. Koo presented this proposal. The specific aims of this study are: 1. Primary Aim: Report the incidence of clinically significant bacterial, viral, and fungal infections during the first 100 days after auto-HSCT for solid tumor, MM and lymphoma recipients. 2. Secondary Aim: Evaluate the overall survival (OS), non-relapse mortality (NRM), transplant-related mortality (TRM) between solid tumor, MM, and lymphoma auto-HSCT recipients who developed clinically significant infections and who did not develop infections.
Discussion:
Suggestions:

1. *Add infection prophylaxis*
2. *Suggested looking at outcomes at D30 instead of D100 to avoid maintenance therapy bias and making this less heterogeneous. Consider adding two timeframes: <30, 30-100 day*

Analyze the disease groups separately
Concerns:

1. *The screening of new viral infection and the first viral infection.*

2. *Prophylaxis data include only the first drug given in ea of antibacterial, antiviral, antifungal, and anti PJP. These data were not collected as discrete data for analysis prior to January 2017.*

Potential Benefits:

1. *There have been no systematic analyses for infections following autologous HCT. This may create another data set that will then be able to also compare to the CAR-T populations (studies IN20-01 and IN23-01).*

d. **PROP 2310-185** PBSC versus BM Grafts in AlloHSCT for Hematological Malignancies with PTCY-Based GVHD Prophylaxis: A Comparative Analysis (A Mina/S Pavletic)

Dr. Mina presented the proposal. The specific aims of this study are: 1. Primary Endpoints: a. Rates of hematopoietic recovery (absolute neutrophil count, absolute lymphocyte count, platelets); b. Incidence of primary engraftment failure and secondary engraftment failure; c. 100-day post-transplant infectious complications; and 2. Secondary Endpoints: a. Overall survival; b. Non-relapse mortality; c. Malignancy progression; d. GVHD rates, severity and GVHD-free survival and GVHD-free, relapse-free survival (GRFS); e. 100-day post-transplant bleeding complications; f. Primary causes of death; g. Duration of initial hospitalization; h. RBC transfusion independence

Discussions:

Suggestions:

1. *The consideration of letermovir's role as a competing risk in the assessment of viral infections may be explored through a sub-analysis extending from 2017 and beyond.*
2. *Consider the cell dose/size of the patient.*
3. *Factor in the year of transplant due to practice changes (from bone marrow to peripheral blood).*
4. *Consider the inclusion of pediatric patients as they undergo more bone marrow transplants.*
5. *Consider incorporating information about immune reconstitution.*

Concerns:

1. *Clearly difficult to convince the adult MDs to use BM so is there utility in performing this.*
2. *The letermovir data are not discrete prior to Sep 2022 so the incorporation of year of HCT allows a surrogate for pre/post letermovir availability*
3. *The BM cohort is fairly small*

e. **PROP 2310-49** Infection and Immune Reconstitution Factors Associated with Poor Outcomes for Acute Invasive Fungal Sinusitis (L Roland/I Pusic)

Dr. Ji presented the proposal. The specific aims of this study are: 1. Primary: a) Define the incidence of AIFS in alloHCT recipients (expect incidence of AIFS to be ~1% in alloHCT recipients). b) Identify risk factors for development of AIFS in patients undergoing AlloHCT (expect patients who have a longer ANC nadir, more comorbidities, GvHD, and PTCy as initial GvHD prophylaxis to be more likely to develop AIFS). c) Identify risk factors for poor outcomes in alloHCT recipients with AIFS (expect patients who have a longer ANC nadir and more comorbidities to have worse outcomes). 2. Secondary: a) Compare efficacy of specific initial antifungal prophylaxis agents on the incidence of AIFS (expect those who received posaconazole as prophylaxis to have lower rates of AIFS) b) Categorize changes in incidence of AIFS and potential geographical distribution (expect incidence of AIFS to go up over time with increased rates of transplantation and to be higher in regions with more warm and humid climates).

Discussions:

1. *Number of patients are limited because patients must have supplemental for 2146.*
2. *Suggested to add aplastic anemia*
3. *Consider adding comorbidity index*
4. *Can we include information of duration of steroids? This is available for steroid use for GVHD but not if given for other reasons.*

Concerns:
Working Committee proposed that given this is a small number of patients (and ~1 pt/center), is this the opportune study in which to try and obtain supplemental data (beyond captured on the 2146) where information about detailed diagnostic criteria, surgical resection, details of all prophylaxis and treatment, including use of granulocyte transfusions, can be obtained. Marcie cautioned that this will add a year to the study, require supplemental funding to pay for the additional information, and require the involvement of the MDs at the sites to work with the DM/complete the form themselves to ensure these data are captured.

Proposed studies; not accepted for consideration at this time

f. **PROP 2310-29** Infection and Immune Reconstitution Respiratory Syncytial Virus (RSV), Severe Acute Respiratory Syndrome Coronavirus 2 (Sars-CoV-2, Also Referred to as Covid-19), and Influenza (Flu) Virus Infections Occurring Among Patients as Eras in Vaccination Practice are Evolving (J Young). *Supplemental data needed.*
g. **PROP 2310-30** Viral Infections After CD19 and BCMA CAR T Cell Therapy (J Sassine/E Siegrist). *Overlap with current study/publication.*
h. **PROP 2310-56** Incidence of Late Cytomegalovirus (CMV) reactivation in the Era of Post-transplant Cyclophosphamide (PtCY) in patients receiving Letermovir Prophylaxis (I Varadarajan/K Ballen). *Small sample size.*
i. **PROP 2310-207** Incidence, Risk factors, and Outcomes of Infections Following Anti-CD19 Directed CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (D Modi). *Overlap with current study/publication.*
j. **PROP 2310-241** A Comprehensive Analysis of Cytomegalovirus (CMV) Reactivation and its Impact on Outcomes After CAR-T Cell Therapy (S Gupta/V Bachanova). *Overlap with current study/publication.*
k. **PROP 2310-248** Potential for Granulocyte-Colony Stimulating Factor in Preventing Infections in CAR-T Recipients without Worsening Immune-Related Toxicities (M Abid). *Supplemental data needed.*
l. **PROP 2310-251** Impact of Corticosteroid Usage on the Risk of Infections in Patients Receiving CAR-T Therapy (M Abid). *Overlap with current study/publication.*
m. **PROP 2310-254** Impact of Antibiotics on the Efficacy and Toxicity of Anti-CD19 CAR T Cell Therapy (M Abid). *Supplemental data needed.*

6. Other business

Marcie Riches is stepping down as the Scientific Director of the INWC after 20 years. She will remain available as an external consultant given her long history with the committee. The next Sci Director has not been determined.

Not for publication or presentation

Working Committee Overview Plan 2024 - 2025		
Study number and title	**Current Status**	**Chairs Priority**
IN18-01b: Comparison of early (by day+100) bacterial infections between post transplantation cyclophosphamide and other graft-vs-host disease prophylaxis.	Published	1
IN19-01: Immune recovery predicts post-transplant outcomes.	Submitted Manuscript	2
IN19-02: Impact of antibacterial prophylaxis on outcomes after allogeneic hematopoietic stem cell transplant.	Submitted Manuscript	6
CV20-04d: Early v late outcomes for COVID-19 in hematopoietic cell transplant recipients.	Submitted Manuscript	3
IN20-01: Infectious complications in patients with B-Lymphoid hematologic malignancy treated with CD19 chimeric antigen receptor T cell therapy.	Submitted Manuscript	4
IN22-01: Viral Hepatitis after allogeneic hematopoietic cell transplant using post-transplant cyclophosphamide for graft versus host disease prophylaxis.	Submitted Manuscript	7
IN23-01: Infectious complications in patients with relapsed/refractory multiple myeloma receiving B-cell maturation antigen targeted chimeric antigen receptor T cells.	Submitted Manuscript	5
IN24-01: Evaluating infection rates in autologous hematopoietic stem cell transplants for primary solid tumors and lymphoma.	Protocol Development	

Work Assignments for Working Committee Leadership (March 2024)	
Miguel-Angel Perales	**IN18-01a:** Comparison of early (by day+100) viral infections between post transplantation cyclophosphamide and other graft-vs-host disease prophylaxis **IN18-01b:** Comparison of early (by day+100) bacterial infections between post transplantation cyclophosphamide and other graft-vs-host disease prophylaxis
Chris Dandoy	**IN18-02:** Study the Incidence, and impact of C diff infection within 100 days on Transplant outcomes after allogeneic stem cell transplant (Muthalagu Ramanathan/ Bipin Savani) **IN20-01:** Infectious complications after CAR.T Cell therapy
Roy Chemaly	**IN19-01:** Immune recovery predicts post-transplant outcomes (Miguel-Angel Perales) **IN19-02:** Impact of antibacterial prophylaxis on outcomes after allogeneic hematopoietic stem cell transplant (C Dandoy/ P Alonso/ Z El Boghdadly)
Joshua Hill	**IN23-01:** Infectious complications in patients with relapsed/refractory multiple myeloma receiving B-cell maturation antigen targeted chimeric antigen receptor T cells