Not for publication or presentation

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR INFECTION AND IMMUNE RECONSTITUTION
Salt Lake City, UT
Monday, April 25, 2022, 6:45 AM – 8:15 AM MDT

Co-Chair:	**Christopher Dandoy, M.D, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Telephone: 513-803-7495; E-mail: christopher.dandoy@cchmc.org;**
Co-Chair:	**Miguel-Angel Perales, MD, Memorial Sloan Kettering Cancer Center, New York, NY; Telephone: 212-639-8682; E-mail: peralesm@mskcc.org;**
Co-Chair:	**Roy Chemaly, MD, UT MD Anderson Cancer Center, Houston, TX; Telephone: 713-792-0007; E-mail: rfchemaly@mdanderson.org;**
Scientific Director:	**Marcie Riches, MD, MS; Telephone: 813-943-2800; E-mail: mlrichesmd@outlook.com**
Statistical Directors:	**Michael Martens, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-955-8371; E-mail: mmartens@mcw.edu;**
Statistician:	**Naya He, MS, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0685; E-mail: nhe@mcw.edu**

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1. Introduction

a. *Welcome and introduction*
b. *Minutes from February 2021 meeting (Attachment 1)*

The meeting was called to order at 6:45am by Dr. Marcie Riches. She introduced the current working committee leadership and reviewed the CIBMTR COI policy and described Working Committees 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 (Attachment 2)

Due to the full agenda, the accrual summary of registration and research cases between 2008 and 2019 were not presented to the committee but were available as part of the Working Committee attachments.

3. Studies published/submitted/Preliminary results

Dr. Marcie Riches gave an update on study presentations, and manuscripts that were published or submitted within the last year.

a. **IN17-01a:** Goldsmith SR, Abid MB, Auletta JJ, Bashey A, Beitinjaneh A, Castillo P, Chemaly RF, Chen M, Ciurea S, Dandoy CE, Díaz MÁ, Fuchs E, Ganguly S, Kanakry CG, Kanakry JA, Kim S, Komanduri KV, Krem MM, Lazarus HM, Liu H, Ljungman P, Masiarz R, Mulroney C, Nathan S, Nishihori T, Page KM, Perales MA, Taplitz R, Romee R, Riches M. Posttransplant cyclophosphamide is associated with increased cytomegalovirus infection: a CIBMTR analysis. ***Blood. 2021 Jun 10;137(23):3291-3305. doi: 10.1182/blood.2020009362. PMID: 33657221; PMCID: PMC8351903. Published.***

b. **IN17-01b:** Singh A, Dandoy CE, Chen M, Kim S, Mulroney CM, Kharfan-Dabaja MA, Ganguly S, Maziarz RT, Kanakry CG, Kanakry JA, Patel SS, Hill JA, De Oliveir S, Taplitz R, Hematti P, Lazarus HM, Abid MB, Goldsmith SR, Romee R, Komanduri KV, Badawy SM, Friend BD, Beitinjaneh A, Politikos I, Perales MA, Riches M. Post-Transplantation Cyclophosphamide Is Associated with an Increase in Non-Cytomegalovirus Herpesvirus Infections in Patients with Acute Leukemia and Myelodysplastic Syndrome. ***Transplant Cell Ther. 2021 Sep 26:S2666-6367(21)01257-4. doi: 10.1016/j.jtct.2021.09.015. Epub ahead of print. PMID: 34587551. Published.***

c. **IN17-01c:** Mulroney CM, Abid MB, Bashey A, Chemaly RF, Ciurea SO, Chen M, Dandoy CE, Diaz Perez MA, Friend BD, Fuchs E, Ganguly S, Goldsmith SR, Kanakry CG, Kim S, Komanduri KV, Krem MM, Lazarus HM, Ljungman P, Maziarz R, Nishihori T, Patel SS, Perales MA, Romee R, Singh AK, Reid Wingard J, Yared J, Riches M, Taplitz R. Incidence and impact of community respiratory viral infections in post-transplant cyclophosphamide-based graft-versus-host disease prophylaxis and haploidentical stem cell transplantation. ***Br J Haematol. 2021 Jul;194(1):145-157. doi: 10.1111/bjh.17563. Epub 2021 Jun 14. PMID: 34124796. Published.***

d. **COV20-04a:** Sharma A, Bhatt NS, St. Martin A, Abid MB, Bloomquist J, Chemaly RF, Dandoy C, Gauthier J, Gowda L, Perales M-A, Seropian S, Shaw BE, Tuschl EE, Zeidan AM, Riches ML, Shah GL. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study. ***The Lancet Haematology. doi:10.1016/S2352-3026(20)30429-4. Epub 2021 Jan 19. PMC7816949. Published.***

e. **COV20-04b:** Bhatt NS, Sharma A, St. Martin A, Martens M, Riches ML, Dandoy CE, Auletta JJ. COVID-19 in Pediatric Hematopoietic Cell Transplant Recipients: A CIBMTR Study, ***Blood 2021; 138 (Supplement 1):2868. doi: https://doi.org/10.1182/blood-2021-147924. Poster presentation, ASH 2021.***

f. **IN18-02:** Muthalagu Ramanathan, Bipin B. Savani, Naya He, Soyoung Kim, Min Chen, Roy Chemaly, Christopher E Dandoy, Miguel-Angel Perales, Marcie L. Riches, Celalettin Ustun; The Incidence and Impact of Clostridioides Difficile Infection (CDI) on Outcomes after Allogeneic Hematopoietic Cell Transplant (alloHCT) – a CIBMTR Study. *Blood* 2021; 138 (Supplement 1): 2894. Doi: https://doi.org/10.1182/blood-2021-145774. ***Poster presentation, TCT 2021.***

4. Studies in progress (Attachment 3)
Dr. Marcie Riches briefly listed all studies in progress.

a. **IN18-01a:** Comparison of early (by day 180) bacterial infections after haploidentical HSCT between patients receiving cyclophosphamide-based or other GVHD prophylaxis (Celalettin

Ustun/Genovefa Papanicolaou): ***Manuscript preparation.***

b. **IN18-01b:** Comparison of early (by day 180) fungal infections after haploidentical HSCT between patients receiving cyclophosphamide-based or other GVHD prophylaxis (Celalettin Ustun/Genovefa Papanicolaou): ***Manuscript preparation.***

c. **IN18-02:** The Incidence, and impact of Clostridium difficile infection within 100 days on Transplant outcomes after allogeneic stem cell transplant (Muthalagu Ramanathan/ Bipin Savani/ Celalettin Ustun): ***Manuscript preparation.***

d. **IN19-01:** Immune recovery predicts post transplant outcomes (Miguel-Angel Perales/ Paul Szabolcs): ***Analysis.***

e. **IN19-02:** Impact of Antibiotic Prophylaxis in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation in the Current Era (Zeinab El Boghdadly/ Christopher Eugene Dandoy/ Priscila Badia Alonso): ***Protocol development.***

f. **IN20-01:** Infectious complications in patients with B-Lymphoid hematologic malignancy treated with CD19 chimeric antigen receptor T cell therapy (Kitsada Wudhikarn/ Miranda McGhee/ Joshua A. Hill/ Megan Herr, etc): ***Datafile preparation.***

g. **COV20-04b:** Clinical Characteristics and Outcomes of COVID-19 in Pediatric Hematopoietic Stem Cell Transplant Recipients: A Cohort Study **(**Bhatt, Sharma, Auletta, Dandoy): ***Manuscript submitted.***

h. **COV20-04c:** COVID-19 in Hematopoietic Cell Transplant Recipients-Race/Ethnicity (Abid, Gowda, Chemaly): ***Protocol Development.***

i. **COV20-04d:** COVID-19 in Hematopoietic Cell Transplant Recipients- Outcomes early v late (Chemaly, Riches): ***Protocol Development.***

j. **COV20-04e:** COVID-19 in CAR-T Recipients (G Shah, Politikos, Murthy, Hamandani, N Shah, Hossain, Stiff): ***Protocol Development.***

5. Future/proposed studies

a. **PROP 2110-84:** Impact of Engraftment Syndrome on Immune Reconstitution and Clinical Outcomes with Predictive Modeling and Clinical Score Generation (S Goldsmith) (Attachment 4)

Dr. Goldsmith presented the proposal. The specific aims of this study are four-fold: 1. Characterize the incidence of reported ES in both Auto-HCT and Allo-HCT and draw comparisons between reported ES and probable ES (patients with a non-infectious fever occurring within the peri-engraftment period possibly associated with other syndromic symptoms). 2. Analyze, independently, the transplant-related outcomes among Auto-HCT and Allo-HCT recipients who do or do not experience ES to compare hospitalization/rehospitalization, non-relapse mortality, incidence of acute and chronic GVHD (in allo-HCT recipients), disease response (myeloma and lymphoma), relapse incidence, progression-free and overall survival. 3. Develop a scoring model to predict the likelihood of ES that could then be prospectively validated and guide management

on de-escalation of anti-infectious therapies or institution of immune suppression. 4. Leverage the immune-reconstitution data available through the CIBMTR to characterize the variances in immune cell reconstitution among patients with or without ES.

Discussion:

- *Is there a way to categorize the severity of engraftment symptoms? Need to limit to population after 2013.*
- *It is challenging to define and toss out engraftment symptoms for allogeneic population.*
- *It was noted that a similar ES study in autologous patients had previously been proposed to the RRT WC.*

b. **PROP 2110-180:** Influence of non-enterobacterales gram-negative bacilli bloodstream infections (BSIs) on hematopoietic cell transplantation (HCT) and cellular therapy outcomes (N Tran/ Z El Boghdadly) (Attachment 5)

Dr. Boghdadly presented the proposal. The specific aims of this study are four-fold: 1. Assess the cumulative incidence non-Enterobacterales gram-negative bacilli BSIs within the first 100 days post HCT and cellular therapy. 2. Identify risk factors for non-Enterobacterales gram-negative bacilli BSIs within the first 100 days post HCT and cellular therapy. 3. Assess influence of non-Enterobacterales gram-negative bacilli BSIs on relapse, GVHD, non-relapse mortality, time to engraftment post HCT. 4. Compare clinical characteristics, risk factors, and post-HCT outcomes between patients with no BSIs vs Enterobacterales BSIs (MBI-LCBI) vs non- Enterobacterales gram-negative bacilli BSIs cohort (if sample size allows).

Discussion:

- *Consider how the data is collected to design the study in order to have enough follow up for the patients.*
- *Will do a sub-analysis for patients after 2017 to compare different antibiotic prophylaxis.*
- *This study could make use of some of the cleaned data from other INWC studies that examined BSI.*

c. **PROP 2110-203:** Epidemiology and risk factors associated with polyoma virus (BKV) viremia/viruria and/or BKV associated hemorrhagic cystitis (HC) in allogeneic Hematopoietic Cell Transplant (HCT) recipients (Z Shahid/R Chemaly) (Attachment 6)

Dr. Shahid presented the proposal. The specific aims of this study are six-fold: 1. To assess the incidence of BKV associated HC, BK viremia and/or BK viuria in allogeneic HCT recipients including CBT. 2. To evaluate the differences in epidemiology of BKV associated disease based on underlying disease, conditioning regimens, graft source, intensity and GvHD prophylaxis and presence of GvHD. 3. To study risk factors associated with the development of BKV associated

HC, BK viremia and BK viuria including gender, laboratory parameters at time of diagnosis, and ethnic differences. 4. To study the impact of BK viremia and BK viruria on kidney function in the absence or presence of BKV associated HC. 5. To study the association of BKV associated HC with other viral reactivations in early and late post-transplant period. 6.To study the impact of BKV associated HC on clinical outcomes including overall survival and non-relapse mortality (adjusted for AKI, CKI).

Discussion:

- *Concerned that what is intended to study is not available in the dataset. Many centers are not routinely checking viremia or viuria and these are often tested in qualitive and not quantitative way.*
- *Questioned that if CIBMTR data could answer all the questions regarding symptoms.*
- *Reviewed that the 2150 form does capture information on symptoms, treatment, and viral loads for BK*

d. **PROP 2110-07**: Viral Hepatitis after allogeneic hematopoietic cell transplant using post-transplant cyclophosphamide for graft versus host disease prophylaxis (K Wudhikarn / M-A Perales) (Attachment 7)

Dr. Perales presented the proposal. The specific aims of this study are four-fold: 1. To assess the rate of viral hepatitis reactivation in patients who underwent allogeneic HCT with GVHD prophylaxis using post-transplant cyclophosphamide. 2. To compare the viral hepatitis reactivation rate in patients who underwent allogeneic HCT with GVHD prophylaxis using post-transplant cyclophosphamide with non-PTCy platform. 3. To assess the factors associated with viral hepatitis reactivation in patients who underwent allogeneic HCT with GVHD prophylaxis using PTCy. 4. To evaluate the impact of chronic viral hepatitis on hepatic complications and survival after alloHCT with PTCy.

Discussion:

- *Clarification that the study period is from 2007 to 2018, since viral forms stated from 2007 and CIBMTR already did Hepatitis B and C study looking at earlier years, prior to the commonality of PTCy use.*
- *CIBMTR viral hepatitis forms collect information on viral loads, prophylaxis, treatment, but these data have not been assessed for completeness.*
- *The committee is concerned about a potential low number of reactivation events.*
- *This study will have a global impact as not all regions have ready access to treatment and prophylaxis.*

e. **PROP 2110-107** Retrospective study of the impact of mammalian target of rapamycin inhibitors (mTORi) in the incidence of virus associated complications after allogeneic hematopoietic cell transplantation (HCT) (K Rechache / J Kanakry)(Attachment 8)

Dr. Kanakry presented the proposal. The specific aims of this study are three-fold: 1. Estimate the cumulative incidences of herpesvirus complications (human cytomegalovirus (CMV) infection, CMV disease, pre-emptive treatment for Epstein-Barr virus (EBV), EBV-post transplant lymphoproliferative disorder (PTLD), and human herpesvirus 6 (HHV6) encephalitis), and BK virus-associated hemorrhagic cystitis through 1-year post-HCT, comparing outcomes between mTORi-containing vs non-mTORi-containing GVHD regimens. 2. Compare NRM, OS, and GVHD rates at 1 year between mTORi-containing approaches and non-mTORi-containing approaches. 3. Evaluate cofactors related to differences in the incidence of viral complications, including conditioning intensity (NMA/RIC vs MAC), donor and recipient serostatus (for CMV and EBV), graft source (PBSC vs BM).

Discussion:

- *Suggested to exclude Letermovir prophylaxis. It was reviewed that the data on Letermovir use are incomplete due to how the question was asked prior to the recent 2100 revision. One option would be to examine by years (pre v post letermovir prophylaxis).*
- *The impact of the study is considered that sites could choose to use and mTORi if seen as beneficial, particularly in the PTCy population.*
- *Will consider comparing PTCY + mTORi to PTCY CNI.*
- *The committee would like to characterize patients who started with mTORi then switch to CNI or vice versa; however, this is not possible with the registry data*
- *It was noted that the EBV population was low and would be unable to be examined by use of pre-emptive therapy.*

f. **PROP 2110-123 & 2110-124** The impact of donor source and graft-vs-host disease prophylaxis on the incidence of late viral infections after allogeneic hematopoietic cell transplantation **(**M B Abid/ E L Baumrin/ A W Loren) (Attachment 9)

Dr. Abid presented the proposal. The specific aims of this study are three-fold: 1. To describe the types and incidence of late (>D+180) CMV and non-CMV viral infections in allogeneic hematopoietic cell transplantation (alloHCT) recipients. 2. To compare the types and incidence of late CMV and non-CMV viral infections in alloHCT recipients receiving matched related / unrelated vs haploidentical donor types, stratified by post-transplant cyclophosphamide (PTCy) vs non-PTCy GVHD prophylaxis. 3. To evaluate the impact of late viral infections on transplant outcomes, stratified by donor type and GVHD prophylaxis: a.Overall survival; b.Disease free survival; c.Relapse; d.Non relapse mortality.

Discussion:

- *This study will look at incidence and impact of late viral infections beyond 6 months. The Letermovir prophylaxis impact on late CMV will not be able to examined in this study as the data for Letermovir use are incomplete due to how the question was asked prior to the recent 2100 revision.*

GVHD is a confounder since a lot of CMV developed after GVHD treatment. CIBMTR using dynamic landmark analysis try to tease out the interaction of GVHD with these late infections.

g. **PROP 2110-176:** Impact of Public and Healthcare Infection Control Measures on Non-COVID-19 Community Respiratory Viral Infections in Transplant and Cellular Therapy Patients (S Patel/H Imlay) (Attachment 10)

Dr. Imlay presented the proposal. The specific aims of this study are two-fold: 1. Identify the impact of public and healthcare infection control measures on the incidence and severity of non-COVID- 19 CRVIs in transplant and cellular therapy patients during the COVID-19 pandemic in the United States. 2. Assess the impact of infection control measures on non-relapse mortality (NRM), treatment-related mortality (TRM), disease-free survival (DFS), and acute and chronic graft-versus-host disease (GVHD) severity and incidence.

Discussion:

- *Not all the centers were impacted by COVID at the same time so impact of COVID prevention measures are different across the country.*
- *CIBMTR cannot look the severity of respiratory virus infection and only can look at present or absent as it's reported.*
- *Recommended to censor patients at a diagnosis of COVID.*
- *Suggested to add pediatric patients to the study.*

h. **PROP 2110-201:** Incidence and Impact of Invasive Fungal Infection in Allogeneic Hematopoietic Stem Cell Transplant Recipients with FLT3-ITD-mutated Acute Myeloid Leukemia (P Vergidis/ S Chesdachai) (Attachment 11)

Dr. Chesdachai presented the proposal. The specific aims of this study are four-fold: 1. To compare the cumulative incidence and infection density of invasive fungal infection (candidiasis, cryptococcosis, aspergillosis, non-Aspergillus mold infection) occurring within 1 year after HSCT between patients with wild-type and mutated FLT3. 2. To determine fungal infection-related mortality in patients with wild-type and mutated FLT3. 3. To compare the impact of invasive fungal infection on 5-year transplant outcomes (relapse, non-relapse mortality, leukemia-free survival, overall survival, chronic GVHD) between patients with wild-type and mutated FLT3. 4. To identify pre-transplant risk factors for development of post-transplant fungal infection in FLT3-mutated AML.

Discussion:

- *From the prophylaxis perspective, based on how the data collected at the CIBMTR, will limit to the 2017 population.*

- *Suggested include acute and chronic GVHD as potential confounders for infection.*

Dropped proposed studies

a. **PROP 2109-03:** COVID-19 outcomes in chimeric antigen receptor T cell therapy (CART) recipients. ***Dropped due to overlap with current study/publication in process (CV20-04).***

b. **PROP 2109-12:** Epidemiology and management of invasive fungal infections after autologous hematopoietic stem cell transplantation for the treatment of lymphoma and solid tumors. ***Dropped due to small sample size.***

c. **PROP 2109-24:** Toxoplasmosis epidemiology in hematopoietic stem cell transplantation recipients across the United States. ***Dropped due to small sample size.***

d. **PROP 2110-04:** The Effect of Antibacterial Prophylaxis on Early Post-transplant Mortality in Patients with Multiple Myeloma and Lymphoma Undergoing High-dose Chemotherapy and Autologous Hematopoietic Cell Transplantation: a Retrospective Study on Behalf of the Infection and Immune Reconstitution Working Committee. ***Dropped due to small sample size.***

e. **PROP 2110-33:** Infectious complications in patient with relapsed relapsed/refractory multiple myeloma receiving BCMA-targeted CAR-T therapy. ***Dropped-small sample size.***

f. **PROP 2110-103:** COVID-19 infection outcomes in patients receiving chimeric antigen receptor T-cell therapy (CAR-T). ***Dropped due to overlap with current study/publication (CV20-04).***

g. **PROP 2110-126:** Evaluating the extended use of letermovir as CMV prophylaxis beyond day 100 in allogeneic stem cell transplant. ***Dropped due to supplemental data needed.***

h. **PROP 2110-189:** CMV reactivation and role of pre-emptive therapy in patients undergoing commercial CAR T cell treatment for non-Hodgkin's lymphoma. ***Dropped due to supplemental data needed as the CAR-T patients do not report infections on the 2150 form.***

i. **PROP 2110-214:** Associations between COVID-19 infection, COVID-19 vaccination, and post-allogeneic hematopoietic cell transplantation (allo-HCT) complications. ***Dropped due to overlap with current study/publication (CV20-04).***

j. **PROP 2110-245:** An observational review of allogeneic hematopoietic cell transplantation in HIV infected patients with hematologic malignancy during the era of effective antiretroviral therapy and expanded unrelated and alternative donor sources. ***Dropped due to small sample size.***

k. **PROP 2110-312:** Impact of Letermovir prophylaxis on GVHD and relapse after allo-HCT. ***Dropped due to supplemental data needed.***

l. **PROP 2110-334:** Impact of Human Herpesvirus 6 infection on short- and long-term outcomes in hematopoietic stem cell transplant recipients. ***Dropped due to significant limitations based upon center practice for screening leading to low scientific impact.***

m. **PROP 2110-335:** Infectious complications post-CAR-T cell therapy for multiple myeloma. ***Dropped due to small sample size.***

6. Other Business

PROP 2110-338: Impact of HLA Genotype on CMV Reactivation Following Allogeneic Hematopoietic Stem Cell Transplant (Camacho-Bydume/Hsu) **P*resentation at Collaborative Study Proposals Session.***

Not for publication or presentation

Working Committee Overview Plan for 2022-2023

Study Number and Title	Current Status	Chairs Priority
IN18-01a: Comparison of early (by day+100) viral infections between post transplantation cyclophosphamide and other graft-vs-host disease prophylaxis	Manuscript Preparation	1
IN18-01b: Comparison of early (by day+100) bacterial infections between post transplantation cyclophosphamide and other graft-vs-host disease prophylaxis	Manuscript Preparation	4
IN18-02: Study the Incidence, and impact of C diff infection within 100 days on Transplant outcomes after allogeneic stem cell transplant	Submitted	7
IN19-01: Immune recovery predicts post-transplant outcomes	Analysis	3
IN19-02: Impact of antibacterial prophylaxis on outcomes after allogeneic hematopoietic stem cell transplant	Protocol development	6
IN20-01: Infectious complications after CAR.T Cell therapy	Data File Preparation	2
IN22-01 Viral Hepatitis after allogeneic hematopoietic cell transplant using post-transplant cyclophosphamide for graft versus host disease prophylaxis.	Protocol pending	5

Working Assignments for Working Committee Leadership (May 2022)

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
	IN20-01: Infectious complications after CAR.T Cell therapy
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)
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)