MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR INFECTION AND IMMUNE RECONSTITUTION
Orlando, FL
Wednesday, February 15, 2023, 1:00 PM – 3:00 PM (EST)

Co-Chair:	**Christopher Dandoy, MD, MS, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; 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, MPH, UT MD Anderson Cancer Center, Houston, TX; Telephone: 713-792-0007; E-mail: rfchemaly@mdanderson.org;**
Scientific Director:	**Marcie Riches, MD, MS; CIBMTR Statistical Center, Milwaukee, WI; 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**

---

1. **Introduction**
   a. **Welcome and introduction**
   b. **Minutes from February 2022 meeting** (Attachment 1)

   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** (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. **Presentations, Published or Submitted Papers**
   Dr. Marcie Riches gave an update on study presentations, and manuscripts that were published or submitted within the last year.

a. **CV20-04b** Bhatt NS, Sharma A, St Martin A, Abid MB, Brown VI, Diaz Perez MA, Frangoul H, Gadalla SM, Herr MM, Krem MM, Lazarus HM, Martens MJ, Mehta PA, Nishihori T, Prestidge T, Pulsipher MA, Rangarajan HG, Williams KM, Winestone LE, Yin DE, Riches ML, Dandoy CE, Auletta JJ. Clinical Characteristics and Outcomes of COVID-19 in Pediatric and Early Adolescent and Young Adult Hematopoietic Stem Cell Transplant Recipients: A Cohort Study. ***Transplant Cell Ther. 2022 Oct; 28(10):696.e1-696.e7. doi: 10.1016/j.jtct.2022.06.026. Epub 2022 Jul 4. PMID: 35798233; PMCID: PMC9251957.***

b. **IN18-02** Muthalagu Ramanathan, Soyoung Kim, Naya He, Min Chen, Peiman Hematti, Muhammad Bilal Abid, Seth J. Rotz, Kirsten M. Williams, Hillard M. Lazarus, Baldeep Wirk, Dwight E. Yin, Christopher G. Kanakry, Miguel-Angel Perales, Roy F. Chemaly, Christopher E. Dandoy, Marcie Riches, Celalettin Ustun; The Incidence and Impact of Clostridioides Difficile Infection on Transplant Outcomes in Acute Leukemia and MDS after Allogeneic Hematopoietic Cell Transplant– A CIBMTR Study. ***Bone Marrow Transplant. 2022 Dec 21. doi: 10.1038/s41409-022-01896-z. Online ahead of print. PMID: 36543999.***

c. **IN19-01** Miguel-Angel Perales, Paul Szabolcs, Michael Martens, Naya He, Christopher Dandoy, Roy Chemaly, Marcie Riches. Delayed immune recovery after allogeneic hematopoietic cell transplantation is associated with decreased overall survival in adult but not pediatric recipients. ***Poster Presentation, 2023 Tandem Meetings.***

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. **IN19-01** Immune recovery predicts post-transplant outcomes (Miguel-Angel Perales/ Paul Szabolcs): **Tandem 2023 Abstract, Manuscript Preparation.**

d. **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.**

e. **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.**

f. **CV20-04c** COVID-19 in Hematopoietic Cell Transplant Recipients-Race/Ethnicity (Abid, Gowda, Chemaly): **Protocol Development.**

h. **CV20-04d** COVID-19 in Hematopoietic Cell Transplant Recipients- Outcomes early v late (Chemaly,Infante): **Protocol Development.**

i. **CV20-04e** COVID-19 in CAR-T Recipients (G Shah, Politikos, Murthy, Hamandani, N Shah, Hossain, Stiff): **Protocol Development.**

5. Future/Proposed Studies

a. **PROP 2210-175** 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 4)

Dr Boghdadly presented the proposal. The specific aims of this study are four-fold: 1) Determine the cumulative incidence and timing of non-Enterobacterales Gram negative bacilli BSIs within the first 100 days post-HCT and cellular therapy. 2) Identify risk factors within the first 100 days post HCT & cellular therapy. 3) Determine impact on transplant related outcomes (time to engraftment, overall survival, GVHD, etc.) 4) Compare clinical characteristics, risk factors, and post-HCT & cellular therapy outcomes between patients with no BSIs vs. Enterobacterales BSIs vs. non-Enterobacterales Gram negative bacilli BSIs cohort (if sample size allows).

Discussion:

1. Recommendations from the committee were to include the following:
    a. CAR-T population.
    b. Time to engraftment as one variable
2. Questioned about the management of patients with a BSI that is neither Enterobacterales BSIs nor non-Enterobacterales Gram negative bacilli. The recommendation was to include this group of patients as "Other BSI" so there will be four groups compared.
3. Concerns about timing of infection and whether the study would limit to only the transplant hospitalization or any infection through 100 days. The study will analyze BSI through day 100, particularly since not all patients are hospitalized for transplant.
4. Concerns about data:
    a. CIBMTR doesn't collect treatment data for bacterial infection.
    b. How much data that CIBMTR has for one year point. Will look at completeness of follow up to make sure have complete data through one year.

b. **PROP 2210-36; 2210-57; 2210-163; 2210-241** Infectious complications in patients with relapsed/refractory multiple myeloma receiving B-cell maturation antigen (BCMA) targeted chimeric antigen receptor (CAR) T cells (M B Abid/ Kitsada Wudhikarn/ M-A Perales/ S Mirza/ L Gowda/ S Devarakonda/ Y Efebera) (Attachment 5)

Dr Perales presented the proposal. The specific aims of this study are three-fold: 1. To describe the incidence, infection density, patterns and outcomes of infections in patients treated with BCMA CAR T-cell therapy. 2. To identify risk factors for infection in patients treated with BCMA CAR T-cell therapy. 3. To explore the impact of infectious complications on both short-term and long-term clinical outcomes following CAR T-cell therapy.

It was also pointed out that this proposal would essentially be an additional population to examine as the INWC is already looking at infectious complications in the lymphoma and ALL population (IN 20-01)

Discussion:

The WC has several suggestions including:

1. Incorporate IVIG use. The data have limitations as we only know if the patient received IVIG without information on IgG levels or the frequency of IVIG infusions.
2. Include number of hospitalizations. These data are not captured.

3. Consider a formal comparison between the lymphoma and the myeloma populations
4. Compare early infection vs later infection if there are sufficient patients.

Potential concerns raised during the disucssion:

1. No prophylaxis data collected on CAR-T forms.
2. Not all the centers reporting the clinical trial patients and only 50% of CAR-T patients being reported to the CIBMTR. Therefore, will need to examine center effect.
3. Will need to account for the effects of proteasome inhibitors and immunomodulatory agents on outcomes.

c. **PROP 2210-64** 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 understand incidence of BKv associated HC, BK viremia and/or BK viuria in allogeneic HCT recipients including cord blood transplants. 2.To study the differences in epidemiology of BKV associated disease based on underlying malignancy, conditioning regimens and intensity, graft source, GvHD prophylaxis including post-transplant cyclophosphamide and presence of GvHD. 3.Identify risk factors associated with the development of BKv associated HC, BK viremia and BK viuria. 4.To study the impact of BK viremia and BK viuria on kidney function in the absence or presence of BKv associated HC. 5. To study the association of BKv disease with other viral reactivations in early and late post-transplant period for 1 year. 6.To study the impact of BKv associated disease on clinical outcomes including overall survival and non-relapse mortality at 1 year.

It was pointed out that there are more than 900 patients reported with BK who have a supplemental 2150 form providing more granular detail on the infection including viral loads and treatment.

Discussion:
Suggested additions to the proposal:

1. Examine TMA association with BK infection and renal dysfunction
2. Incorporate treatment in the analysis

Concerns raised by the committee:

1. IGG level and CD4 are captured on Day 100 and Day 180, but not at the other times of interest proposed in the study.
2. For kidney function, CIBMTR collects renal toxicity but won't have decline in creatinine.
3. Discordant surveillance at centers will limit the ability to detect a true incidence.

d. **PROP 2210-124** Impact of anti-fungal prophylaxis agent on the incidence of invasive fungal infections (IFI) among allogeneic transplant recipients (H Imlay/ S Patel) (Attachment 7)

Dr Imlay presented the proposal. The specific aims of this study are three-fold: 1. Compare the efficacy of specific antifungal prophylaxis agents (fluconazole, posaconazole, isavuconazole, voriconazole, echinocandin) on diagnosis of IFI, invasive Aspergillosis, and invasive non-

Aspergillosis mold infections among allogeneic HCT recipients. 2. Determine other risk factors associated with diagnosis of IFI, invasive mold infection (IMI), and invasive non-Aspergillus mold infection. 3. Determine the impact of IFI diagnosis and use of anti-mold prophylaxis on relapse, non-relapse mortality (NRM), acute and chronic graft-versus-host disease (GVHD), disease-free survival (DFS).

Discussion:
The committee suggested the following:

1. Adjusting for center effect due to the ascertainment bias with differential monitoring and the choice of prophylaxis may be driven by uncaptured data (i.e. marijuana use).
2. Consider excluding patients with pre HCT IFI

There are certain limitations on this analysis including

1. CIBMTR data only capture the first prophylaxis drug used and can't capture the drug switch.
2. Will not be able to include CAR-T patients as prophylaxis is not captured on the Cell Therapy forms.
3. CIBMTR prophylaxis data before 2017 are not analyzable due to how the data were collected.

There were some suggestions on how to improve reporting of prophylaxis.

e. **PROP 2210-188** 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/ Emily Baumrin/ Alison Loren) (Attachment 8)

Dr Loren presented the proposal. The specific aims of this study are three-fold: 1. To describe the types and incidence of late CMV and non-CMV viral infections in alloHCT pts. 2. Compare types and incidence of late CMV and non-CMV infections between donor types (MRD/MUD vs haploHCT) and GVHD prophylaxis (PTCy vs non-PTCy). 3. Compare the impact of late viral infections on transplant outcomes between donor types (MRD/MUD vs haploHCT) and GVHD prophylaxis (PTCy vs non-PTCy).

Discussion:

1. There are concerns with ensuring a comparison of pre-letermovir and post-letermovir by time frames as letermovir prophylaxis was not well captured and the forms have recently been revised to allow for this.
2. Recommendation to examine as a landmark analysis for patients alive at day 180.

f. **PROP 2210-244** Early Infectious Complications Associated with CART Cell Therapy Compared to Autologous Stem Cell Transplant in Lymphoma (F Khwaja/ S Ahmed) (Attachment 9)

Dr Khawaja presented the proposal. The specific aims of this study are four-fold: 1. To compare the rates of infections between non Hodgkin lymphoma (NHL) patients post

CAR T cell or autologous HCT within 100 days after cellular therapy. 2. Rates of specific infectious etiologies (viral, bacterial and fungal) and severity of infection. 3. Identify unique host or therapy related characteristics that increase the risk of viral, bacterial or fungal infections. 4. Comparison of clinical outcomes between patients with infections after CAR T cell therapy and after autologous HCT.

Discussion:
The committee had several recommendations:

1. The study should focus only on infections and not compare outcomes such as relapse.
2. The comparison should be auto no CAR-T vs CAR-T with no prior auto vs CAR-T with prior auto.

Potential limitations identified include:

1. CIBMTR doesn't collect the hospitalization of ICU level of care, only mortality information.
2. There are limited numbers of auto patients as the algorithm for CRF track has these patients at a lower priority.

Dropped Proposed Studies

a. **PROP 2208-01** Outcomes and Management of SARS-CoV2 Omicron Variant in Recipients of Hematopoietic Cell Transplantation (HCT) and CAR-T therapy. *Dropped due to overlap with current study/publication.*
b. **PROP 2209-11** Impact of Gastrointestinal Graft versus Host Disease on Infections occurring among patients with Steroid Sensitive, Steroid Dependent, and Steroid Resistant acute Graft versus Host Disease. *Dropped due to supplemental data needed.*
c. **PROP 2210-34** Impact of corticosteroid usage on the risk of infections in patients receiving CAR-T therapy. *Dropped due to supplemental data needed.*
d. **PROP 2210-37** Incidence of hypogammaglobulinemia following CD19-directed CAR-T therapy and its impact on CAR-T persistence and outcomes. *Dropped due to supplemental data needed.*
e. **PROP 2210-101** Reactivation of Chagas disease (CD) following autologous and allogeneic hematopoietic cell transplantation (HCT). A CIBMTR Analysis. *Dropped-small sample size.*
f. **PROP 2210-118** Characteristics of hypogammaglobulinemia after CAR T-cell therapy and effect of immunoglobulin replacement on infectious complications. *Dropped due to supplemental data needed.*
g. **PROP 2210-125** Incidence of CMV infection and disease in low-risk CMV serostatus (D+R-) allogeneic transplant recipients. *Dropped due to overlap with recent publications [IN1201, IN1701]*
h. **PROP 2210-154** Early platelet count recovery before white cell count recovery after allogeneic hematopoietic cell transplantation and effect on clinical outcome. *Dropped due to lower scientific priority.*
i. **PROP 2210-226** Impact of seasons and climates on outcomes of allogenic hematopoietic cell transplantation (HCT) in North America. *Dropped due to lower scientific priority.*
j. **PROP 2210-249** Incidence and Impact of Invasive Fungal Infection in Allogeneic Hematopoietic Stem Cell Transplant Recipients with FLT3-ITD-mutated Acute Myeloid Leukemia. *Dropped due to lower scientific priority.*

Working Committee Overview Plan for 2023-24		
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	Submitted	1
IN18-01b: Comparison of early (by day+100) bacterial infections between post transplantation cyclophosphamide and other graft-vs-host disease prophylaxis	Manuscript Preparation	1
IN19-01: Immune recovery predicts post-transplant outcomes	Manuscript Preparation	2
IN19-02: Impact of antibacterial prophylaxis on outcomes after allogeneic hematopoietic stem cell transplant	Protocol Development	4
IN20-01: Infectious complications after CAR.T Cell therapy	Data File Preparation	3
IN22-01 Viral Hepatitis after allogeneic hematopoietic cell transplant using post-transplant cyclophosphamide for graft versus host disease prophylaxis	Protocol Development	4
IN23-01 Infectious complications in patients with relapsed/refractory multiple myeloma receiving B-cell maturation antigen targeted chimeric antigen receptor T cells	Protocol Pending	3

Not for publication or presentation

Work Assignments for Working Committee Leadership (April 2023)	
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