*Not for publication or presentation*

**A G E N D A**
**CIBMTR WORKING COMMITTEE FOR INFECTION AND IMMUNE RECONSTITUTION**
**Honolulu, HI**
**Thursday, February 13, 2025, 1:00 – 3:00 PM HST**


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|---|---|
| **Co-Chair:** | **Hemant Murthy, MD; Mayo Clinic, Jacksonville, FL; Telephone: 352-273-7822; E-mail: Murthy.hemant@mayo.edu** |
| **Co-Chair:** | **Christopher Dandoy, MD, MS; Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Telephone: 801-209-3843; E-mail: christopher.dandoy@cchmc.org** |
| **Co-Chair:** | **Joshua Hill, MD; Fred Hutchinson Cancer Center, Seattle, WA; Telephone: 206-667-6504; E-mail: jahill3@fredhutch.org** |
| **Page Scholar:** | **Zeinab El Boghdadly, Ohio State University, Columbus , OH; Email: zeinab.elboghdadly@osumc.edu** |
| **Scientific Director:** | **Jeffery Auletta, MD; CIBMTR® (Center for International Blood and Marrow Transplant Research), Minneapolis, MN; E-mail: jaulett3@nmdp.org** |
| **Scientific Director:** | **Anna Huppler; CIBMTR® (Center for International Blood and Marrow Transplant Research), Milwaukee, WI; E-mail: ahuppler@mcw.edu** |
| **Statistical Director:** | **Michael Martens, PhD; CIBMTR® (Center for International Blood and Marrow Transplant Research), Milwaukee, WI; Telephone: 414-955-8674; E-mail: mmartens@mcw.edu** |
| **Statistician:** | **Qiran (Lexie) Ye, MPH; CIBMTR® (Center for International Blood and Marrow Transplant Research), Milwaukee, WI; E-mail: qye@mcw.edu** |


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1. **Introduction**
   a. Minutes from February 2024 (Attachment 1)

2. **Accrual summary** (Attachment 2)

3. **Presentations, Publications or Submitted papers**
   a. **IN19-01** Delayed T cell recovery after hematopoietic cell transplantation is associated with decreased overall survival in adults (M-A Perales). ***Submitted.***
   b. **IN20-01a** Infectious complications in patients with B-Lymphoid hematologic malignancy (Lymphoma cohort) treated with CD19 chimeric antigen receptor T cell therapy. (K Wudhikarn/ M McGhee/ J Hill/ M Herr/ H Rangarajan/ P Satwani/ J Baird/ E McGehee/ L Gowda/ G Fatobene). ***Submitted***.
   c. **IN20-01b** Infectious complications in patients with B-Lymphoid hematologic malignancy (ALL cohort) treated with CD19 chimeric antigen receptor T cell therapy. (K Wudhikarn/ M McGhee/ J Hill/ M Herr/ H Rangarajan/ P Satwani/ J Baird/ E McGehee/ L Gowda/ G Fatobene). ***Submitted***.

4. **Studies in progress** (Attachment 3)
   a. **IN19-02** Impact of Antibiotic Prophylaxis in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation in the Current Era (C Dandoy/ C Alonso/Z El Boghdadly). **Protocol Development.**

b. **IN22-01** Viral Hepatitis after allogeneic hematopoietic cell transplant using post-transplant cyclophosphamide for graft versus host disease prophylaxis (K Wudhikarn/ M Perales). **Protocol Received.**
c. **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). **Datafile Preparation.**
d. **IN24-01** Evaluating infection rates in autologous hematopoietic stem cell transplants for primary solid tumors and lymphoma (J Koo/ C Dandoy). **Protocol Received.**

**5. Future/proposed studies**

a. **PROP 2410-45; 2410-206** Risk Stratification and Letermovir Prophylaxis Strategies for Cytomegalovirus in Hematopoietic Cell Transplantation: A Focus on Late CMV Infections, All-Cause Mortality, and Mismatched Donor-Recipient Serostatus (R Chemaly/ M Batista/ J Tossey/ J Sen). (Attachment 4)
b. **PROP 2410-55** Peri-transplant Norovirus infection as a risk factor for allogeneic HSCT outcomes (K Lind/ L McLaughlin). (Attachment 5)
c. **PROP 2410-61** The Incidence and Impact of Clostridioides Difficile Infection on CAR-T Cell Therapy Outcomes – A CIBMTR Study (M Bilal Abid/ M Aljurf). (Attachment 6)
d. **PROP 2410-137** Impact of Letermovir Prophylaxis on the Epidemiology of CMV Infection Among Allogenic Hematopoietic Cellular Therapy Recipients Receiving Post-Transplant Cyclophosphamide (Z Shahid/ H Murthy). (Attachment 7)
e. **PROP 2410-141** Epidemiology of Respiratory Virus Infections among Hematopoietic Cellular Therapy and Chimeric Antigen Receptor T-cell Therapy Recipients in the Post COVID-19 and Respiratory Syncytial Virus Vaccine Era (Z Shahid/ H Murthy). (Attachment 8)

***Proposed studies; not accepted for consideration at this time***

f. **PROP 2408-08** Comparing Levofloxacin with Ciprofloxacin in the area of Hematopoietic Stem Cell Transplantation (M Pamukcuoglu). ***Dropped due to overlap with current study/publication.***
g. **PROP 2409-27** Impact of Chimeric Antigen Receptor Therapy (CART) followed by AlloSCT on post-transplant infection risk in Lymphoid Malignancies – A CIBMTR Analysis (N Hossain, P Munshi). ***Dropped due to overlap with current study/publication.***
h. **PROP 2409-29** Impact of Granulocyte Infusions on Outcomes for Allogeneic Stem Cell Transplant patients prior to initial engraftment - A CIBMTR Analysis (N Hossain). ***Dropped due to small sample size.***
i. **PROP 2409-31** Characterization of infectious complications post-CAR T Cell therapy (L Liu/ M Janakiram). ***Dropped due to overlap with current study/publication.***
j. **PROP 2410-01** Impact of post-transplant G-CSF in allogeneic transplant in the post-transplant cyclophosphamide era (N Agarwal/ L Metheny). ***Dropped due to overlap with current study/publication.***
k. **PROP 2410-18** Impact of HLA disparity on infection-related complications in patients undergoing allogeneic HSCT with post-transplant cyclophosphamide GVHD prophylaxis (K Wudhikarn/ M Perales). ***Dropped due to overlap with current study/publication.***
l. **PROP 2410-32** Infections and Immune Reconstitution in Adults with B-Cell Acute Lymphoblastic Leukemia Who Received CAR-T Therapy Prior to Allogeneic Hematopoietic Stem Cell Transplantation (H De Sa/ B Hayes-Lattin). ***Dropped due to overlap with current study/publication.***

m. **PROP 2410-38** Infectious Complications in patients with Hematologic Malignancies Receiving CD19 vs. BCMA-targeted CAR-T Therapy (M Bilal Abid). ***Dropped due to overlap with current study/publication.***
n. **PROP 2410-63** Potential for granulocyte-colony stimulating factor in preventing infections in CAR-T recipients without worsening immune-related toxicities (M Bilal Abid/ M Aljurf). ***Dropped due to overlap with current study/publication.***
o. **PROP 2410-75** Donor Selection in Cytomegalovirus Seronegative Patients Undergoing HCT with Post-Transplant Cyclophosphamide-based Graft-versus-Host Disease Prophylaxis (R Mehta). ***Dropped due to small sample size.***
p. **PROP 2410-128** Outcomes of CD34-selected stem cell boost following allogeneic hematopoietic stem cell transplantation in the contemporary era (X Bi/ U Gergis). ***Dropped due to small sample size.***
q. **PROP 2410-135** Impact of Granulocyte Stimulating Factor on Infectious Complications, Treatment Response and Outcomes after CAR T-cell therapy (S Bowden/ P Bindal). ***Dropped due to small sample size.***
r. **PROP 2410-144** Safety and Efficacy of BCMA-directed CAR T-cell Therapy in the Treatment of Relapsed/Refractory Multiple Myeloma in Patients with HIV Infection (P Bindal/ C Reimonn). ***Dropped due to supplemental data needed.***
s. **PROP 2410-186** Real world analysis of non-respiratory viral diseases in BCMA and CD 19 CART cell therapy recipients (N Vojjala/ N Ahmed). ***Dropped due to overlap with current study/publication.***
t. **PROP 2410-245** Real World Evidence of Infectious Complications, HIV Disease Control, and Outcome among Patients with HIV who Receive Hematopoietic Stem Cell Transplant or Chimeric Antigen Receptor T cell therapy (L Gowda/ B Emu). ***Dropped due to supplemental data needed.***
u. **PROP 2410-253** Incidence of severe infections (BMTCTN grade 3) early after HCT (100 days) and its impact on survival (OS) and non-relapse mortality (NRM) - development of a composite endpoint: GVHD-free, relapse-free, and infection-free survival (GRIFS) (R Nakamura). ***Dropped due to overlap with current study/publication.***

**6. Other business**

**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**


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|---|---|
| **Co-Chair:** | **Roy Chemaly, MD, MPH; UT MD Anderson Cancer Center, Houston, TX; Telephone: 713-792-0007; E-mail: rfchemaly@mdanderson.org;** |
| **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:** | **Joshua Hill, MD; Fred Hutchinson Cancer Center, Seattle, WA; E-mail: jahill3@fredhutch.org** |
| **Scientific Director:** | **Marcie Riches, MD, MS; CIBMTR® (Center for International Blood and Marrow Transplant Research), Medical College of Wisconsin, Milwaukee, WI; Telephone: 813-943-2800; E-mail: mlrichesmd@outlook.com** |
| **Statistical Director:** | **Michael Martens, PhD; CIBMTR® (Center for International Blood and Marrow Transplant Research), Medical College of Wisconsin, Milwaukee, WI; Telephone: 414-955-8371; E-mail: mmartens@mcw.edu** |
| **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.*

| 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<br>**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)<br>**IN20-01:** Infectious complications after CAR.T Cell therapy |
| Roy Chemaly | **IN19-01:** Immune recovery predicts post-transplant outcomes (Miguel-Angel Perales)<br>**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 |

**Accrual Summary for Infection and Immune Reconstitution Working Committee**
**Donor-recipient and Infection information reported to the CIBMTR after 2008**

| Characteristic | ALLO - Allogeneic | AUTO - Autologous |
|---|---|---|
| Number of patients - no. (%) | 52292 | 19846 |
| **Infection** | | |
| Donor/receipient CMV status - no. (%) | | |
| -/- | 10919 (20.9) | 0 (0.0) |
| +/- | 5475 (10.5) | 0 (0.0) |
| -/+ | 12352 (23.6) | 0 (0.0) |
| +/+ | 18837 (36.0) | 2 (0.0) |
| Missing/not tested | 4709 (9.0) | 19844 (100) |
| Donor/recipient hepatitis B status - no. (%) | | |
| -/- | 10857 (20.8) | 15136 (76.3) |
| +/- | 337 (0.6) | 0 (0.0) |
| -/+ | 3184 (6.1) | 0 (0.0) |
| +/+ | 295 (0.6) | 1884 (9.5) |
| -/? | 249 (0.5) | 0 (0.0) |
| +/? | 7 (0.0) | 0 (0.0) |
| ?/- | 20074 (38.4) | 0 (0.0) |
| ?/+ | 6514 (12.5) | 0 (0.0) |
| Missing/not tested | 10775 (20.6) | 2826 (14.2) |
| Donor/recipient hepatitis C status - no. (%) | | |
| -/- | 13738 (26.3) | 16070 (81.0) |
| +/- | 93 (0.2) | 0 (0.0) |
| -/+ | 152 (0.3) | 0 (0.0) |
| +/+ | 9 (0.0) | 267 (1.3) |
| -/? | 108 (0.2) | 0 (0.0) |
| ?/- | 23752 (45.4) | 0 (0.0) |
| ?/+ | 359 (0.7) | 0 (0.0) |
| Missing/not tested | 14081 (26.9) | 3509 (17.7) |
| Fungal infection history - no. (%) | | |
| No | 48546 (92.8) | 19623 (98.9) |
| Yes | 3676 (7.0) | 217 (1.1) |
| Not reported | 70 (0.1) | 6 (0.0) |
| Fungal infection after starting of conditioning - no. (%) | | |
| No | 44132 (84.4) | 18829 (94.9) |
| Yes | 8059 (15.4) | 1007 (5.1) |

| Characteristic | ALLO - Allogeneic | AUTO - Autologous |
|---|---|---|
| Not reported | 101 (0.2) | 10 (0.1) |
| **Immune Reconstitution** | | |
| IgG at 100 day - no. (%) | | |
| Data not available | 18854 (36.1) | 7496 (37.8) |
| Data available | 33438 (63.9) | 12350 (62.2) |
| IgM at 100 day - no. (%) | | |
| Data not available | 35043 (67.0) | 8916 (44.9) |
| Data available | 17249 (33.0) | 10930 (55.1) |
| IgA at 100 day - no. (%) | | |
| Data not available | 35028 (67.0) | 8823 (44.5) |
| Data available | 17264 (33.0) | 11023 (55.5) |
| CD3 at 100 day - no. (%) | | |
| Data not available | 38648 (73.9) | 18723 (94.3) |
| Data available | 13644 (26.1) | 1123 (5.7) |
| CD4 at 100 day - no. (%) | | |
| Data not available | 38517 (73.7) | 18652 (94.0) |
| Data available | 13775 (26.3) | 1194 (6.0) |
| CD8 at 100 day - no. (%) | | |
| Data not available | 38947 (74.5) | 18762 (94.5) |
| Data available | 13345 (25.5) | 1084 (5.5) |
| CD20 at 100 day - no. (%) | | |
| Data not available | 49534 (94.7) | 19671 (99.1) |
| Data available | 2758 (5.3) | 175 (0.9) |
| CD56 at 100 day - no. (%) | | |
| Data not available | 42795 (81.8) | 19360 (97.6) |
| Data available | 9497 (18.2) | 486 (2.4) |
| **Infection Prophylaxis** | | |
| Infection prophylaxis - no. (%) | | |
| No | 169 (0.3) | 54 (0.3) |
| Yes | 50942 (97.4) | 18988 (95.7) |
| Not reported | 1181 (2.3) | 804 (4.1) |
| Antibacterial Prophylaxis - no. (%) | | |
| No | 1820 (3.5) | 350 (1.8) |
| Yes | 18092 (34.6) | 7028 (35.4) |
| Not reported | 32380 (61.9) | 12468 (62.8) |
| Antiviral Prophylaxis - no. (%) | | |
| No | 1063 (2.0) | 311 (1.6) |
| Yes | 49263 (94.2) | 18532 (93.4) |

| Characteristic | ALLO - Allogeneic | AUTO - Autologous |
|---|---|---|
| Not reported | 1966 (3.8) | 1003 (5.1) |
| Antifungal Prophylaxis - no. (%) | | |
| No | 1236 (2.4) | 886 (4.5) |
| Yes | 48146 (92.1) | 16617 (83.7) |
| Not reported | 2910 (5.6) | 2343 (11.8) |
| first antibacterial drug given as prophylaxis - Amoxicillin clavulanate oral - no. (%) | | |
| No | 19564 (37.4) | 7300 (36.8) |
| Yes | 366 (0.7) | 84 (0.4) |
| Not reported | 32362 (61.9) | 12462 (62.8) |
| first antibacterial drug given as prophylaxis - Moxifloxacin IV or oral - no. (%) | | |
| No | 19537 (37.4) | 7307 (36.8) |
| Yes | 392 (0.7) | 78 (0.4) |
| Not reported | 32363 (61.9) | 12461 (62.8) |
| first antibacterial drug given as prophylaxis - Ciprofloxacin IV or oral - no. (%) | | |
| No | 16641 (31.8) | 5976 (30.1) |
| Yes | 3288 (6.3) | 1409 (7.1) |
| Not reported | 32363 (61.9) | 12461 (62.8) |
| first antibacterial drug given as prophylaxis - Levofloxacin IV or oral - no. (%) | | |
| No | 10607 (20.3) | 2696 (13.6) |
| Yes | 9320 (17.8) | 4690 (23.6) |
| Not reported | 32365 (61.9) | 12460 (62.8) |
| first antibacterial drug given as prophylaxis - Other antibacterial drug - no. (%) | | |
| No | 15699 (30.0) | 6304 (31.8) |
| Yes | 4228 (8.1) | 1080 (5.4) |
| Not reported | 32365 (61.9) | 12462 (62.8) |
| first antibacterial drug given as prophylaxis - Cefdinir oral - no. (%) | | |
| No | 19791 (37.8) | 7308 (36.8) |
| Yes | 139 (0.3) | 77 (0.4) |
| Not reported | 32362 (61.9) | 12461 (62.8) |
| first antibacterial drug given as prophylaxis - Penicillin - no. (%) | | |
| No | 8562 (16.4) | 2031 (10.2) |
| Yes | 300 (0.6) | 27 (0.1) |
| Not reported | 43430 (83.1) | 17788 (89.6) |

| Characteristic | ALLO - Allogeneic | AUTO - Autologous |
|---|---|---|
| first antibacterial drug given as prophylaxis - Cefpodoxime oral - no. (%) | | |
| No | 19777 (37.8) | 7350 (37.0) |
| Yes | 153 (0.3) | 35 (0.2) |
| Not reported | 32362 (61.9) | 12461 (62.8) |
| Was vancomycin IV also given as prophylaxis? - no. (%) | | |
| No | 17361 (33.2) | 6893 (34.7) |
| Yes | 1851 (3.5) | 432 (2.2) |
| Not reported | 33080 (63.3) | 12521 (63.1) |
| first antiviral drug given as prophylaxis - Acyclovir - no. (%) | | |
| No | 11836 (22.6) | 3863 (19.5) |
| Yes | 39716 (76.0) | 15477 (78.0) |
| Not reported | 740 (1.4) | 506 (2.5) |
| Was letermovir (Prevymis) given as prophylaxis? - no. (%) | | |
| No | 20923 (40.0) | 8361 (42.1) |
| Yes | 2833 (5.4) | 8 (0.0) |
| Not reported | 28536 (54.6) | 11477 (57.8) |
| first antiviral drug given as prophylaxis - Famciclovir (Famvir) - no. (%) | | |
| No | 23542 (45.0) | 8351 (42.1) |
| Yes | 209 (0.4) | 18 (0.1) |
| Not reported | 28541 (54.6) | 11477 (57.8) |
| first antiviral drug given as prophylaxis - Ganciclovir - no. (%) | | |
| No | 48966 (93.6) | 19282 (97.2) |
| Yes | 2586 (4.9) | 58 (0.3) |
| Not reported | 740 (1.4) | 506 (2.5) |
| first antiviral drug given as prophylaxis - Other antiviral drug - no. (%) | | |
| No | 50126 (95.9) | 19117 (96.3) |
| Yes | 1425 (2.7) | 223 (1.1) |
| Not reported | 741 (1.4) | 506 (2.5) |
| first antiviral drug given as prophylaxis - Valacyclovir (Valtrex) - no. (%) | | |
| No | 40126 (76.7) | 15300 (77.1) |
| Yes | 11426 (21.9) | 4040 (20.4) |
| Not reported | 740 (1.4) | 506 (2.5) |
| first antiviral drug given as prophylaxis - Valganciclovir (Valcyte) - no. (%) | | |

| Characteristic | ALLO - Allogeneic | AUTO - Autologous |
|---|---|---|
| No | 48484 (92.7) | 19175 (96.6) |
| Yes | 3065 (5.9) | 165 (0.8) |
| Not reported | 743 (1.4) | 506 (2.5) |
| first antifungal drug given as prophylaxis - Amphotericin products - no. (%) | | |
| No | 49328 (94.3) | 19236 (96.9) |
| Yes | 2207 (4.2) | 90 (0.5) |
| Not reported | 757 (1.4) | 520 (2.6) |
| first antifungal drug given as prophylaxis - Caspofungin (Cancidas) - no. (%) | | |
| No | 48355 (92.5) | 19148 (96.5) |
| Yes | 3180 (6.1) | 178 (0.9) |
| Not reported | 757 (1.4) | 520 (2.6) |
| first antifungal drug given as prophylaxis - Isavuconazole (Cresemba) - no. (%) | | |
| No | 23324 (44.6) | 8352 (42.1) |
| Yes | 410 (0.8) | 4 (0.0) |
| Not reported | 28558 (54.6) | 11490 (57.9) |
| first antifungal drug given as prophylaxis - Anidulafungin (Eraxis) - no. (%) | | |
| No | 23627 (45.2) | 8353 (42.1) |
| Yes | 107 (0.2) | 3 (0.0) |
| Not reported | 28558 (54.6) | 11490 (57.9) |
| first antifungal drug given as prophylaxis - Fluconazole (Diflucan) - no. (%) | | |
| No | 25814 (49.4) | 3547 (17.9) |
| Yes | 25720 (49.2) | 15779 (79.5) |
| Not reported | 758 (1.4) | 520 (2.6) |
| first antifungal drug given as prophylaxis - Itraconazole - no. (%) | | |
| No | 50481 (96.5) | 19230 (96.9) |
| Yes | 1054 (2.0) | 96 (0.5) |
| Not reported | 757 (1.4) | 520 (2.6) |
| first antifungal drug given as prophylaxis - Micafungin (Mycamine) - no. (%) | | |
| No | 41304 (79.0) | 18786 (94.7) |
| Yes | 10231 (19.6) | 540 (2.7) |
| Not reported | 757 (1.4) | 520 (2.6) |
| first antifungal drug given as prophylaxis - Other antiviral drug - no. (%) | | |

| Characteristic | ALLO - Allogeneic | AUTO - Autologous |
|---|---|---|
| No | 50163 (95.9) | 19075 (96.1) |
| Yes | 1371 (2.6) | 251 (1.3) |
| Not reported | 758 (1.4) | 520 (2.6) |
| first antifungal drug given as prophylaxis - Posaconazole (Noxafil) - no. (%) | | |
| No | 43748 (83.7) | 19212 (96.8) |
| Yes | 7786 (14.9) | 114 (0.6) |
| Not reported | 758 (1.4) | 520 (2.6) |
| first antifungal drug given as prophylaxis - Voriconazole (Vfend) - no. (%) | | |
| No | 38828 (74.3) | 18870 (95.1) |
| Yes | 12706 (24.3) | 456 (2.3) |
| Not reported | 758 (1.4) | 520 (2.6) |
| Disease Grouping - no. (%) | | |
| MM/PCD | 718 (1.4) | 12172 (61.3) |
| AML | 14680 (28.1) | 183 (0.9) |
| ALL | 5880 (11.2) | 15 (0.1) |
| CML | 1182 (2.3) | 0 (0.0) |
| Other Leukemias | 459 (0.9) | 2 (0.0) |
| NHL | 2916 (5.6) | 3956 (19.9) |
| HD | 1263 (2.4) | 1357 (6.8) |
| MDS/MPN | 12400 (23.7) | 2 (0.0) |
| CLL | 1015 (1.9) | 16 (0.1) |
| Acquired Aplastic Anemia | 3934 (7.5) | 2 (0.0) |
| Congenital Bone Marrow Failure Syndrome | 1022 (2.0) | 2 (0.0) |
| Hemoglobinopathies | 3409 (6.5) | 84 (0.4) |
| Primary Immune Deficiency | 1960 (3.7) | 72 (0.4) |
| Histiocytic Disorder | 499 (1.0) | 2 (0.0) |
| Platelet Disorders | 54 (0.1) | 0 (0.0) |
| Inherited Disorders of Metabolism | 737 (1.4) | 16 (0.1) |
| Autoimmune Disease | 31 (0.1) | 62 (0.3) |
| Solid tumors | 34 (0.1) | 1893 (9.5) |
| Other Diseases | 56 (0.1) | 9 (0.0) |
| Not reported | 43 (0.1) | 1 (0.0) |
| Year of current transplant - no. (%) | | |
| 2008 | 4368 (8.4) | 2657 (13.4) |
| 2009 | 3962 (7.6) | 1272 (6.4) |
| 2010 | 2437 (4.7) | 579 (2.9) |

| Characteristic | ALLO - Allogeneic | AUTO - Autologous |
|---|---|---|
| 2011 | 1792 (3.4) | 691 (3.5) |
| 2012 | 1865 (3.6) | 726 (3.7) |
| 2013 | 3317 (6.3) | 1462 (7.4) |
| 2014 | 4176 (8.0) | 1466 (7.4) |
| 2015 | 4180 (8.0) | 1684 (8.5) |
| 2016 | 3977 (7.6) | 1754 (8.8) |
| 2017 | 3812 (7.3) | 1643 (8.3) |
| 2018 | 3791 (7.2) | 2256 (11.4) |
| 2019 | 3569 (6.8) | 1352 (6.8) |
| 2020 | 2301 (4.4) | 373 (1.9) |
| 2021 | 2446 (4.7) | 318 (1.6) |
| 2022 | 2511 (4.8) | 670 (3.4) |
| 2023 | 2769 (5.3) | 671 (3.4) |
| 2024 | 1019 (1.9) | 272 (1.4) |

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A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

**TO:** Infection and Immune Reconstitution Working Committee Members

**FROM:** Jeffery Auletta, MD and Anna Huppler, MD; Scientific Directors for the Infection and Immune Reconstitution Working Committee

**RE:** 2024-2025 Studies in Progress Summary

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**IN19-02 Impact of Antibiotic Prophylaxis in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation in the Current Era** (C Dandoy/ C Alonso/Z El Boghdadly). Antibiotic prophylaxis in patients undergoing allogenic HSCT has been the standard of practice for decades. However, there are some collateral consequences of this practice such as early microbiome disruption, acute GVHD, emergence of resistant bacterial infections and increased risk for Clostridioides difficile infection (CDI). This study will assess the efficacy of antibiotic prophylaxis in the modern era and results will have implications on current clinical practice.

Status: **Protocol Development**

**IN22-01 Viral Hepatitis after allogeneic hematopoietic cell transplant using post-transplant cyclophosphamide for graft versus host disease prophylaxis** (K Wudhikarn/ M Perales). The study hypothesizes that patients undergoing allogeneic HCT with post-transplant cyclophosphamide (PTCy) have a higher incidence of viral hepatitis reactivation compared to those without PTCy. It aims to assess the rate and risk factors of viral hepatitis reactivation, compare reactivation rates between PTCy and non-PTCy platforms, and evaluate the impact of chronic viral hepatitis on hepatic complications and survival. The study will provide critical insights into the incidence, patterns, and predisposing factors of hepatitis B and C reactivation, as well as the proper approach to antimicrobial prophylaxis in these patients.

Status: **Protocol Received**

**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). The study hypothesizes that infectious complications after idecabtagene vicleucel are common and likely higher in real-world settings compared to clinical trials, associated with specific disease, host, and CAR T-cell characteristics, and linked to poorer outcomes. It aims to describe the incidence, patterns, and mortality of infections, identify risk factors, and explore the impact on clinical outcomes. This research will provide critical insights into infection prevention strategies and improve patient care for those treated with BCMA CAR T-cells.

Status: **Datafile Preparation**

**IN24-01 Evaluating infection rates in autologous hematopoietic stem cell transplants for primary solid tumors and lymphoma** (J Koo/ C Dandoy). This observational, cross-sectional study will examine the primary endpoint of the incidence of clinically significant bacterial, viral and fungal infections during the first 100 days following auto-HSCT for patients with solid tumors and lymphomas.

Status: **Protocol Received**

| Field | Response |
|---|---|
| Proposal Number | 2410-45-CHEMALY |
| Proposal Title | Risk factors for late cytomegalovirus infection after letermovir prophylaxis discontinuation in Allogeneic hematopoietic cell transplantation (HCT). |
| Key Words | cytomegalovirus, letermovir, late infection, risk factors, Allo-HCT |
| Principal Investigator #1: - First and last name, degree(s) | Roy Chemaly, MD, MPH, FIDSA, FACP |
| Principal Investigator #1: - Email address | rfchemaly@mdanderson.org |
| Principal Investigator #1: - Institution name | MD Anderson Cancer Center |
| Principal Investigator #1: - Academic rank | Professor of Medicine |
| Junior investigator status (defined as ≤5 years from fellowship) | No |
| Do you identify as an underrepresented/minority? | No |
| Principal Investigator #2 (If applicable): - First and last name, degree(s): | Marjorie Batista, MD, TID, PhD |
| Principal Investigator #2 (If applicable): - Email address:) | marjorie.batista@accamargo.org.br |
| Principal Investigator #2 (If applicable): - Institution name: | AC Camargo Cancer Center |
| Principal Investigator #2 (If applicable): - Academic rank: | Professor at Graduate Program |
| Junior investigator status (defined as ≤5 years from fellowship) | Yes |
| Do you identify as an underrepresented/minority? | No |
| We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below: | Roy Chemaly |
| If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below: | Yes, I am a junior investigator and would like assistance identifying a senior mentor for my project |
| Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role. | Dr. Roy Chemaly was one of the co-chair of the WORKING COMMITTEE FOR INFECTION AND IMMUNE RECONSTITUTION and was involved in many protocols and studies over the past few years. Dr. Marjorie Batista is working as a junior leader of Paramyxovirus Guideline that will be presented at 2025 Tandem Meetings \| Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR Session Title: (ID) TID Guidelines Update Session Date: Thursday, February 13, 2025 Session Time: 10:30 AM HST And was involved in other protocols (VRS GUIDELINE) and studies over the past 2 years. |
| Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months? | Yes |

| Field | Response |
|---|---|
| PROPOSED WORKING COMMITTEE: | Infection and Immune Reconstitution |
| Please indicate if you have already spoken with a scientific director or working committee chair regarding this study. | No |
| If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who: | - |
| RESEARCH QUESTION: | Are there specific risk factors for late cytomegalovirus (CMV) infection following the discontinuation of letermovir prophylaxis that could identify a target subgroup of patients who may benefit from extended prophylaxis? |
| RESEARCH HYPOTHESIS: | Risk factors for Late CMV infection after letermovir discontinuation could help to stratify patients who are at higher risk of clinically significant CMV infection (cs-CMVi) and all-cause of mortality. |
| SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.): | • Define risk factors for late cs-CMVi after letermovir discontinuation •Assess the incidence of late cs-CMVi • Assess transplant outcomes in adult allo-HCT recipients with late cs-CMVi o Overall Survival o Non-relapsed Mortality (NRM) o Co-infections • Descriptive analysis of indirect effect of cs-CMVi after letermovir discontinuation Outcomes: a. Overall Survival (OS): time to death. Death from any cause is an event. Surviving patients are censored at the time of last follow-up. b. Non-relapse mortality (NRM): death without evidence of disease relapse/progression. Relapse is the competing risk c. Relapse: non-relapse mortality is the competing risk. d. Chronic GVHD (cGVHD): Death is the competing risk. e. Cumulative incidence of bacterial infections: death is the competing risk f. Cumulative incidence of viral infections: death is the competing risk g. Cumulative incidence of fungal infections: death is the competing risk h. Cause of death: primary and infections as contributing cause |
| SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care. | Several centers have reported cases of late CMVi following completion of letermovir prophylaxis, which may adversely affect HCT outcomes. Expanding these findings to a larger multicenter population will help validate the results and identify higher-risk populations who may have poorer outcomes. Furthermore, this could facilitate additional studies within the CIBMTR and potentially inform future interventional studies. |

| Field | Response |
|---|---|
| SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary. | CMV infections represent a significant burden in immunocompromised population, particularly in patients undergoing allo-HCT. Despite the administration of letermovir as a prophylactic agent, there are emerging reports of late CMVi occurring after the discontinuation of prophylaxis. Understanding the risk factors associated with these late infections is critical for identifying patient subgroups that are at increased risk for cs-CMVi and related adverse outcomes. Current literature highlights the potential impact of late CMV infection on HCT outcomes, suggesting that patients who experience these infections may have higher rates of morbidity and mortality. Identifying specific risk factors for late CMV infection will enable clinicians to stratify patients according to their risk and make informed decisions about the need for extended letermovir prophylaxis.<br>The proposed research question—"Are there specific risk factors for late CMV infection following the discontinuation of letermovir prophylaxis that could identify a target subgroup of patients who may benefit from extended prophylaxis?"—aims to address this critical gap in knowledge. By investigating the demographics, clinical characteristics, and immunological profiles of patients who develop late CMV infections, we hypothesize that these factors can provide valuable insights for risk stratification. Our research hypothesis posits that risk factors for late CMV infection after the discontinuation of letermovir prophylaxis could effectively stratify patients who are at higher risk of cs-CMVi and all-cause mortality. This stratification is essential for optimizing therapeutic interventions, as it may lead to the identification of patients who would benefit most from prolonged prophylactic measures. In conclusion, this research proposal is not only timely but also essential for improving patient outcomes in the context of HCT. By elucidating the specific risk factors associated with late CMV infections from a very large cohort of patients, we can enhance the understanding of patients' vulnerabilities and inform future clinical guidelines regarding prophylaxis strategies. Additionally, the findings from this study could serve as a foundation for future research initiatives aimed at addressing CMV-related complications in immunocompromised patients. |

| Field | Response |
|---|---|
| PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria. | This study will include patients who are CMV seropositive who received an allo-HCT and letermovir prophylaxis for the first 100 days, between 01/2018 and 12/2023. Inclusion criteria: • Age ≥ 18 to ≤ 75 years • allo-HCT who are CMV seropositive between 01/2018 and 12/2023. • Any donor • Letermovir prophylaxis for the first 100 days after allogeneic HCT Exclusion Criteria • Letermovir prophylaxis duration less than 60 days • Cs-CMVi within the first 28 days after allo-HCT • No consent |
| Does this study include pediatric patients? | No |
| If this study does not include pediatric patients, please provide justification: | Letermovir has not yet been approved in the label for pediatric patients. |
| DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required. | 8. Data Requirements a. Variables to be examined Recipient Related: • Recipient Age at transplant • Recipient Gender • Race/ethnicity • aa HCT-CI •Karnofsky/Lansky Performance Score Donor Related: • Donor CMV Serostatus Disease/Transplant Related: • Disease • Time from diagnosis to transplant • Disease status at transplant • Conditioning intensity: Myeloablative vs Reduced Intensity/Non-myeloablative • Stem Cell Source: Bone Marrow vs Peripheral Blood vs Cord Blood •GVHD Prophylaxis: Calcineurin inhibitor based (CSA/TAC) vs Sirolimus based vs PTCy based vs Other • Ex vivo T-cell depletion: Yes vs No • In vivo T-cell depletion: ATG (ATGAM) vs ATG (Thymoglobulin) vs Alemtuzumab • GVHD yes x No • GVHD grade (higher grade) Immune Recovery labs @ day 100 • Absolute Lymphocyte Count at day 100 • CD4 • CD8 • CD4:CD8 ratio • CD19/20 • CD56 • IgG • IgA • IgM Time Dependent variable • Days to neutrophil engraftment • Days to onset of acute GVHD Infections after letermovir discontinuation to day 365 • Bacterial infections: Median, range • Viral infections: Median, range • Fungal infections: Median, range • Total infections: Median, range |
| Types of cellular therapy data this proposal includes: | Hematopoietic Cell Transplantation (HCT) |

| Field | Response |
|---|---|
| PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis speci | - |
| MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions. | - |
| SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous e | - |
| NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required. | - |

| | |
|---|---|
| REFERENCES: | 1: Sadowska-Klasa A, Özkök S, Xie H, Leisenring W, Zamora D, Seo S, Sheldon J, Lee SJ, Jerome KR, Green ML, Boeckh M. Late cytomegalovirus disease after hematopoietic cell transplantation: significance of novel transplantation techniques. Blood Adv. 2024 Jul 23;8(14):3639-3651. 2: Włodarczyk M, Wieczorkiewicz-Kabut A, Białas K, Koclęga A, Noster I, Zielińska P, Helbig G. Real-Life Data on the Efficacy and Safety of Letermovir for Primary Prophylaxis of Cytomegalovirus in Allogeneic Hematopoietic Stem Cell Recipients: A Single-Center Analysis. Turk J Haematol. 2024 Mar 1;41(1):9-15. 3: Lauruschkat CD, Muchsin I, Rein AF, Erhard F, Grathwohl D, Dölken L, Köchel C, Nehmer A, Falk CS, Grigoleit GU, Einsele H, Wurster S, Kraus S. Impaired T cells and "memory-like" NK-cell reconstitution is linked to late-onset HCMV reactivation after letermovir cessation. Blood Adv. 2024 Jun 11;8(11):2967-2979. 4: Russo D, Schmitt M, Pilorge S, Stelljes M, Kawakita T, Teal VL, Haber B, Bopp C, Dadwal SS, Badshah C. Efficacy and safety of extended duration letermovir prophylaxis in recipients of haematopoietic stem-cell transplantation at risk of cytomegalovirus infection: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol. 2024 Feb;11(2):e127-e135. 5: Takenaka K, Fuji S, Matsukawa T, Uchida N, Kobayashi T, Tanaka M, Ara T, Ikegame K, Ozawa Y, Kanda Y, Sawa M, Maruyama Y, Fukuda T, Nakamae H, Kimura T, Ogata M, Seo S, Atsuta Y, Matsuo K, Nakasone H. Outcomes of allogeneic hematopoietic cell transplantation under letermovir prophylaxis for cytomegalovirus infection. Ann Hematol. 2024 Jan;103(1):285-296. 6: Febres-Aldana A, Khawaja F, Morado-Aramburo O, Shigle TL, Rondon G, Sassine J, Spallone A, Srinivasan K, Ramdial J, Alousi A, Champlin R, Chen G, Daher M, Rezvani K, Ariza-Heredia EJ, Shpall EJ, Chemaly RF. Mortality in recipients of allogeneic haematopoietic cell transplantation in the era of cytomegalovirus primary prophylaxis: a single-centre retrospective experience. Clin Microbiol Infect. 2024 Jun;30(6):803-809. 7: Ariza-Heredia EJ, Winston DJ, Rowley SD, Mullane K, Chandrasekar P, Hari P, Avery RK, Peggs KS, Kumar D, Nath R, Ljungman P, Mossad SB, El Haddad L, Shah DP, Jiang Y, Khawaja F, Dadwal S, Blanchard T, Chemaly RF. Impact of Baseline and Week 2 and Week 4 Posttransplant CMV Cell-Mediated Immunity on Risk of CMV Infections and Mortality in Recipients of Allogeneic Hematopoietic Cell Transplant. Open Forum Infect Dis. 2023 Jul 22;10(8):ofad386. 8: Liu LW, Yn A, Gao F, Olson M, Crain M, Abboud R, Westervelt P, Abboud C, Vij R, Stockerl-Goldstein K, |

| Field | Response |
|---|---|
| | Pusic I, Cashen AF, Schroeder MA. Letermovir Discontinuation at Day 100 After Allogeneic Stem Cell Transplant Is Associated With Increased CMV-Related Mortality. Transplant Cell Ther. 2022 Aug;28(8):510.e1-510.e9. 9: Mori Y, Harada T, Yoshimoto G, Shima T, Numata A, Jinnouchi F, Yamauchi T, Kikushige Y, Kunisaki Y, Kato K, Takenaka K, Akashi K, Miyamoto T. Risk factors for late cytomegalovirus infection after completing letermovir prophylaxis. Int J Hematol. 2022 Aug;116(2):258-265. 10: Vyas A, Raval AD, Kamat S, LaPlante K, Tang Y, Chemaly RF. Real-World Outcomes Associated With Letermovir Use for Cytomegalovirus Primary Prophylaxis in Allogeneic Hematopoietic Cell Transplant Recipients: A Systematic Review and Meta-analysis of Observational Studies. Open Forum Infect Dis. 2022 Dec 22;10(1):ofac687. 11: Liu LW, Yn A, Gao F, Olson M, Crain M, Abboud R, Westervelt P, Abboud C, Vij R, Stockerl-Goldstein K, Pusic I, Cashen AF, Schroeder MA. Letermovir Discontinuation at Day 100 After Allogeneic Stem Cell Transplant Is Associated With Increased CMV-Related Mortality. Transplant Cell Ther. 2022 Aug;28(8):510.e1-510.e9. 12: Gabanti E, Borsani O, Colombo AA, Zavaglio F, Binaschi L, Caldera D, Sciarra R, Cassinelli G, Alessandrino EP, Bernasconi P, Ferretti VV, Lilleri D, Baldanti F. Human Cytomegalovirus-Specific T-Cell Reconstitution and Late-Onset Cytomegalovirus Infection in Hematopoietic Stem Cell Transplantation Recipients following Letermovir Prophylaxis. Transplant Cell Ther. 2022 Apr;28(4):211.e1-211.e9. 13: Zamora D, Duke ER, Xie H, Edmison BC, Akoto B, Kiener R, Stevens-Ayers T, Wagner R, Mielcarek M, Leisenring WM, Jerome KR, Schiffer JT, Finak G, De Rosa SC, Boeckh M. Cytomegalovirus-specific T-cell reconstitution following letermovir prophylaxis after hematopoietic cell transplantation. Blood. 2021 Jul 8;138(1):34-43. 14: Kachur E, Roshdy D, Hamadeh I, Dodd B, Shahid Z. Single-center experience with use of letermovir for treatment of CMV infection in stem cell transplant recipients. Transpl Infect Dis. 2021 Apr;23(2):e13502. 15: Sassine J, Khawaja F, Shigle TL, Handy V, Foolad F, Aitken SL, Jiang Y, Champlin R, Shpall E, Rezvani K, Ariza-Heredia EJ, Chemaly RF. Refractory and Resistant Cytomegalovirus After Hematopoietic Cell Transplant in the Letermovir Primary Prophylaxis Era. Clin Infect Dis. 2021 Oct 20;73(8):1346-1354. |
| CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning? | Yes, I have conflicts of interest pertinent to this proposal |

| Field | Response |
|---|---|
| If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually. | R.F.C.: Consultant/Speaker/Advisor for MSD and Research grants paid to his institution from MSD. The renumeration is >$5000 annually. MVB: Speaker/Advisor for MSD. The renumeration is less than $5000 annually |

| Field | Response |
|---|---|
| Proposal Number | 2410-206-TOSSEY |
| Proposal Title | Letermovir prophylaxis in cytomegalovirus seronegative recipients with seropositive donor allogeneic stem cell transplant |
| Key Words | cytomegalovirus, letermovir prophylaxis, D+/R-, CMV infection |
| Principal Investigator #1: - First and last name, degree(s) | Justin Tossey, PharmD |
| Principal Investigator #1: - Email address | justin.tossey@osumc.edu |
| Principal Investigator #1: - Institution name | The Ohio State University Comprehensive Cancer Center - James Cancer Hospital |
| Principal Investigator #1: - Academic rank | Clinical Specialist Pharmacist |
| Junior investigator status (defined as ≤5 years from fellowship) | Yes |
| Do you identify as an underrepresented/minority? | No |
| Principal Investigator #2 (If applicable): - First and last name, degree(s): | Jeremy Sen, PharmD |
| Principal Investigator #2 (If applicable): - Email address:) | jeremy.sen@osumc.edu |
| Principal Investigator #2 (If applicable): - Institution name: | The Ohio State University Comprehensive Cancer Center - James Cancer Hospital |
| Principal Investigator #2 (If applicable): - Academic rank: | Clinical Specialist Pharmacist |
| Junior investigator status (defined as ≤5 years from fellowship) | Yes |
| Do you identify as an underrepresented/minority? | No |
| We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below: | Corresponding PI: Justin Tossey; also contributing as Co-Investigator: Zeinab El Boghdadly, MD (Ohio State, Associate Professor) |
| If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below: | - |
| Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role. | None |
| Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months? | No |
| PROPOSED WORKING COMMITTEE: | Infection and Immune Reconstitution |
| Please indicate if you have already spoken with a scientific director or working committee chair regarding this study. | No |
| If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who: | - |

| Field | Response |
|---|---|
| RESEARCH QUESTION: | Previous studies have clearly established the role of letermovir (LTV) for primary prophylaxis of cytomegalovirus (CMV) infection in CMV-seropositive recipients (R+) of an allogeneic hematopoietic cell transplant (HCT). CMV-seronegative recipients (R-) with a CMV-seropositive donor (D+) have a 20-30% risk of CMV infection but have been excluded from LTV clinical trials. The effectiveness of LTV prophylaxis in CMV D+/R- HCT remains unknown. Therefore, the purpose of this study is to compare the incidence of CMV infection (CMVi)—defined as CMV DNAemia ± organ involvement—in CMV D+/R- adult HCT patients who did or did not receive LTV prophylaxis. |
| RESEARCH HYPOTHESIS: | We hypothesize that LTV prophylaxis reduces the incidence of CMVi in CMV D+/R- patients within the first 100 days after HCT. We also hypothesize that LTV prophylaxis reduces the incidence of CMVi among D+/R- HCT patients at high risk for CMV reactivation, including those who receive post-transplant cyclophosphamide (PTCy). |
| SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.): | The primary objective of this study is to compare the incidence of CMVi in CMV D+/R- adults within the first 100 days post-HCT among two groups: those who received LTV for CMV primary prophylaxis versus those who did not receive any CMV primary prophylaxis. Secondary objectives of this study include evaluating the incidence of CMVi within 6 months and 1 year post-HCT, incidence of CMVi stratified by graft-versus-host disease (GVHD) prophylaxis (PTCy-based vs calcineurin inhibitor[CNI]-based), time to CMVi, and 1-year non-relapse mortality (NRM) and overall survival (OS) among the above cohorts. |

| Field | Response |
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| SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care. | CMV infection after HCT is associated with significant morbidity and mortality(1). The availability of LTV for primary prophylaxis of CMV has made a substantial impact on the outcome of CMV R+ HCT regardless of donor serostatus by decreasing the risk of CMV infection, leading to an improvement in OS(2,3). CMV D+/R- HCT patients have a comparatively lower risk of CMV infection, but with a 20-30% incidence of CMV infection these patients are still impacted by CMV-related comorbidity(4). CMV D+/R- patients have been excluded from clinical trials of LTV, so the potential benefits of LTV prophylaxis remains unknown. LTV was granted Food and Drug Administration (FDA) approval in the United States in 2017 for the prevention of CMV in R+ patients after HCT. The use of LTV in D+/R- HCT remains off-label without robust data to support its use, thus creating a barrier to access due to high cost and challenges with insurance approval. LTV prophylaxis is generally well-tolerated post-HCT with very little risk of serious adverse events. The potential benefits and limited risks associated with LTV prophylaxis warrant evaluation in a CMV D+/R- HCT population. Completion of this study would impact clinical care by elucidating whether these patients benefit from and should receive LTV prophylaxis, and if so, would support providers, institutions, payors, and industry in pursuit of ensuring medication access. |

| | |
|---|---|
| SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary. | Cytomegalovirus (CMV) is a member of the human herpesvirus family which establishes latency in the granulocyte-monocyte lineage after primary infection(5). After establishing latency, CMV may reactivate, particularly in immunocompromised patient populations. CMV disease may lead to end organ damage manifesting as pneumonia, colitis, retinitis, hepatitis, or encephalitis. Monitoring, prophylaxis, and treatment are important considerations in immunocompromised patients. CMV reactivation remains one of the most common viral infectious complications that can occur after allogeneic hematopoietic stem cell transplant (HCT). The risk of CMV reactivation among recipients of HCT depends on many factors, the most important of which is pre-transplant donor and recipient CMV serostatus. CMV-seropositive recipients (R+) are at highest risk, regardless of donor serostatus, with approximately 60% to 70% of patients having CMV reactivation. Primary infection may occur in 20% to 30% of CMV-seronegative recipients (R-) with a CMV-seropositive donor (D+)(4). The lowest risk for CMV reactivation after allo-HCT is among recipient and donor pairs who are both CMV seronegative (D-/R-). Other risk factors include acute GVHD, high-dose corticosteroids, T-cell depletion, degree of HLA-mismatch, and use of PTCy (6,7) Letermovir (LTV) is an oral antiviral that inhibits the CMV-terminase complex to inhibit viral DNA packaging into capsids. A phase 3 randomized controlled trial that compared LTV to placebo as primary prophylaxis in CMV R+ HCT patients reported a significant decrease in clinically significant CMV infection (37.5% vs 60.6%; p < 0.001)(2). Letermovir additionally reduced all-cause mortality in a post-hoc analysis of this trial (HR 0.58 [95% CI 0.25-0.98; p = 0.04])(3). A meta-analysis of real-world data, which included more than 7,000 patients, reaffirmed this finding with significantly reduced odds of all-cause mortality (pOR 0.73; p < 0.01)(8). Letermovir has since become standard of care in CMV R+ HCT patients. However, it is unknown whether CMV D+/R- patients—who are at risk of CMV infection, albeit less compared to R+ patients—may also benefit from LTV prophylaxis. To date there have been no studies evaluating the impact of LTV prophylaxis in a CMV D+/R- HCT population. However, a few single-center retrospective studies have reported LTV use in subpopulations of CMV D+/R- patients. A study by Mizuno, et al. reported a total of 15 patients with CMVi occurring in 30% of the control group and 0% of the LTV |

| Field | Response |
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| | group(9). No statistical analysis is reported with this outcome, and there are otherwise few details on the patient population. Archambeau and colleagues described a similar population (n = 17) with 30% of the control group versus 0% of the LTV group developing CMVi (p = 0.104)(10). Lastly, Liu, et al. completed a study that included the largest population of CMV D+/R- patients to date (n = 66) that compared patients who received LTV to a historical control group. In the CMV D+/R- subpopulation, there was no difference in the incidence of CMVi between LTV and control groups (p = 0.194)(11). Intriguingly, they found that the patients who received post-transplant cyclophosphamide (PTCy) had significantly less CMVi with LTV prophylaxis (p = 0.03). This study has significant limitations given that the PTCy group is a subpopulation of a subpopulation in this study and patient characteristics are not reported in this comparison. Therefore, there is an unmet need to evaluate the efficacy of LTV prophylaxis in preventing CMVi in CMV D+/R- HCT patients. |
| PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria. | Inclusion Criteria Adult and pediatric allogeneic HCT recipients with pre-transplant serologic testing confirming CMV IgG negative status Donor pre-transplant serologic testing confirming CMV IgG positive status Any stem cell source (peripheral blood, bone marrow, cord blood) Any degree of HLA match and donor type (matched related, matched unrelated, mismatched unrelated, haploidentical) Any transplant indication Any conditioning regimen intensity (myeloablative, reduced intensity, non-myeloablative) GVHD prophylaxis: CNI-based (tacrolimus or cyclosporine, with or without methotrexate [MTX], mycophenolate [MMF], or sirolimus) or PTCy-based (PTCy with or without additional agents, such as tacrolimus, sirolimus, mycophenolate, etc.) Year of transplant: July 2021 to 2024 Exclusion criteria Use of any CMV primary prophylaxis other than LTV No Form 2100 available or Q220 not answered |
| Does this study include pediatric patients? | Yes |
| If this study does not include pediatric patients, please provide justification: | - |

| Field | Response |
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| DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required. | Patient-specific: Age Gender Race/ethnicity Recipient CMV serostatus Transplant-specific: Donor CMV serostatus Transplant indication Conditioning regimen intensity Stem cell source (bone marrow, peripheral blood, cord blood) GVHD prophylaxis (CNI ± other vs PTCy ± other) Donor type (related vs unrelated) HLA match Use of ATG or alemtuzumab Date of transplant Date of acute GVHD diagnosis Date of chronic GVHD diagnosis Use of steroids: yes or no Date of relapse Date of death Infection-related: LTV used as prophylaxis: yes or no Date of LTV start Date of CMV infection (DNAemia ± organ involvement) Site of infection Other post-HCT infections (non-CMV viral infections, fungal, bacteria) No supplementary data required |
| Types of cellular therapy data this proposal includes: | Hematopoietic Cell Transplantation (HCT) |
| PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis speci | N/A |
| MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions. | N/A |
| SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous e | N/A |
| NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required. | N/A |

| Field | Response |
|---|---|
| REFERENCES: | 1. Teira P, Battiwalla M, Ramanathan M, et al. Early cytomegalovirus reactivation remains associated with increased transplant-related mortality in the current era: a CIBMTR analysis. Blood. 2016 May 19;127(20):2427-38. 2. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. N Engl J Med. 2017 Dec 21;377(25):2433-2444. 3. Ljungman P, Schmitt M, Marty FM, et al. A Mortality Analysis of Letermovir Prophylaxis for Cytomegalovirus (CMV) in CMV-seropositive Recipients of Allogeneic Hematopoietic Cell Transplantation. Clin Infect Dis. 2020 Apr 10;70(8):1525-1533. 4. Einsele H, Ljungman P, Boeckh M. How I treat CMV reactivation after allogeneic hematopoietic stem cell transplantation. Blood. 2020 May 7;135(19):1619-1629 5. Ljungman P, Hakki M, Boeckh M. Cytomegalovirus in hematopoietic stem cell transplant recipients. Hematol Oncol Clin North Am. 2011 Feb;25(1):151-69. 6. Hakki M, Aitken SL, Danziger-Isakov L, et al. American Society for Transplantation and Cellular Therapy Series: #3-Prevention of Cytomegalovirus Infection and Disease After Hematopoietic Cell Transplantation. Transplant Cell Ther. 2021 Sep;27(9):707-719. 7. Goldsmith SR, Abid MB, Auletta JJ, et al. Posttransplant cyclophosphamide is associated with increased cytomegalovirus infection: a CIBMTR analysis. Blood. 2021 Jun 10;137(23):3291-3305. 8. Vyas A, Raval AD, Kamat S, et al. Real-World Outcomes Associated With Letermovir Use for Cytomegalovirus Primary Prophylaxis in Allogeneic Hematopoietic Cell Transplant Recipients: A Systematic Review and Meta-analysis of Observational Studies. Open Forum Infect Dis. 2022 Dec 22;10(1):ofac687. 9. Mizuno K, Sakurai M, Kato J, et al. Risk factor analysis for cytomegalovirus reactivation under prophylaxis with letermovir after allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis. 2022 Dec;24(6):e13904. 10. Archambeau B, Leece AM, Patel D, et al. Impact of Letermovir for Cytomegalovirus Prophylaxis in High-Risk Patients Undergoing Allogeneic Hematopoietic Stem-Cell Transplantation. JHOP. 2022;12(2):80-86. 11.Liu LW, Yn A, Gao F, et al. Letermovir Discontinuation at Day 100 After Allogeneic Stem Cell Transplant Is Associated With Increased CMV-Related Mortality. Transplant Cell Ther. 2022 Aug;28(8):510.e1-510.e9. |
| CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning? | No, I do not have any conflicts of interest pertinent to this proposal |

| Field | Response |
|---|---|
| If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually. | - |

**2410-45-Chemaly&2410-206-Tossey**

**Risk Stratification and Letermovir Prophylaxis Strategies for Cytomegalovirus in Hematopoietic Cell Transplantation: A Focus on Late CMV Infections, All-Cause Mortality, and Mismatched Donor-Recipient Serostatus**

**US patient who underwent first allo HCT in 2018-2023, with available CMV information**

| Characteristic | LTM D+/R+ | LTM D+/R- | LTM D-/R+ | LTM D-/R- | No LTM D+/R+ | No LTM D+/R- | No LTM D-/R+ | No LTM D-/R- |
|---|---|---|---|---|---|---|---|---|
| Number of patients | 922 | 145 | 745 | 84 | 595 | 427 | 495 | 1086 |
| No. of centers | 117 | 70 | 110 | 42 | 115 | 111 | 112 | 140 |
| **Patient related** | | | | | | | | |
| Age at HCT - no. (%) | | | | | | | | |
| Median (min-max) | 59.1 (0.4-78.7) | 50.7 (0.5-74.7) | 60.7 (1.1-79.0) | 59.1 (3.1-78.8) | 30.8 (0.1-80.6) | 55.0 (0.3-81.4) | 46.6 (0.2-76.8) | 57.9 (0.1-80.8) |
| 0 to <=10 | 25 (2.7) | 8 (5.5) | 13 (1.7) | 1 (1.2) | 156 (26.2) | 80 (18.7) | 118 (23.8) | 128 (11.8) |
| 10 to <=18 | 30 (3.3) | 14 (9.7) | 24 (3.2) | 2 (2.4) | 76 (12.8) | 29 (6.8) | 42 (8.5) | 66 (6.1) |
| 18 to <=30 | 105 (11.4) | 26 (17.9) | 63 (8.5) | 12 (14.3) | 65 (10.9) | 31 (7.3) | 43 (8.7) | 100 (9.2) |
| 30 to <=40 | 82 (8.9) | 17 (11.7) | 54 (7.2) | 6 (7.1) | 32 (5.4) | 32 (7.5) | 23 (4.6) | 61 (5.6) |
| 40 to <=50 | 92 (10.0) | 5 (3.4) | 80 (10.7) | 9 (10.7) | 24 (4.0) | 26 (6.1) | 33 (6.7) | 63 (5.8) |
| 50 to <=60 | 149 (16.2) | 28 (19.3) | 126 (16.9) | 13 (15.5) | 56 (9.4) | 54 (12.6) | 38 (7.7) | 175 (16.1) |
| 60 to <=75 | 422 (45.8) | 47 (32.4) | 373 (50.1) | 40 (47.6) | 174 (29.2) | 167 (39.1) | 193 (39.0) | 471 (43.4) |
| 75+ | 17 (1.8) | 0 (0.0) | 12 (1.6) | 1 (1.2) | 12 (2.0) | 8 (1.9) | 5 (1.0) | 22 (2.0) |
| Sex - no. (%) | | | | | | | | |
| Male | 492 (53.4) | 88 (60.7) | 400 (53.7) | 53 (63.1) | 342 (57.5) | 291 (68.1) | 301 (60.8) | 694 (63.9) |
| Female | 430 (46.6) | 57 (39.3) | 345 (46.3) | 31 (36.9) | 253 (42.5) | 136 (31.9) | 194 (39.2) | 392 (36.1) |
| Race - no. (%) | | | | | | | | |
| White | 597 (64.8) | 106 (73.1) | 580 (77.9) | 67 (79.8) | 371 (62.4) | 320 (74.9) | 373 (75.4) | 925 (85.2) |
| Black or African American | 142 (15.4) | 24 (16.6) | 77 (10.3) | 8 (9.5) | 104 (17.5) | 57 (13.3) | 60 (12.1) | 96 (8.8) |
| Asian | 96 (10.4) | 2 (1.4) | 35 (4.7) | 2 (2.4) | 54 (9.1) | 15 (3.5) | 24 (4.8) | 15 (1.4) |

| Characteristic | LTM D+/R+ | LTM D+/R- | LTM D-/R+ | LTM D-/R- | No LTM D+/R+ | No LTM D+/R- | No LTM D-/R+ | No LTM D-/R- |
|---|---|---|---|---|---|---|---|---|
| Native Hawaiian or other Pacific Islander | 5 (0.5) | 0 (0.0) | 4 (0.5) | 0 (0.0) | 1 (0.2) | 0 (0.0) | 1 (0.2) | 2 (0.2) |
| American Indian or Alaska Native | 4 (0.4) | 0 (0.0) | 2 (0.3) | 1 (1.2) | 4 (0.7) | 5 (1.2) | 2 (0.4) | 2 (0.2) |
| More than one race | 9 (1.0) | 2 (1.4) | 11 (1.5) | 2 (2.4) | 12 (2.0) | 4 (0.9) | 11 (2.2) | 14 (1.3) |
| Not reported | 69 (7.5) | 11 (7.6) | 36 (4.8) | 4 (4.8) | 49 (8.2) | 26 (6.1) | 24 (4.8) | 32 (2.9) |
| Ethnicity - no. (%) | | | | | | | | |
| Hispanic or Latino | 159 (17.2) | 19 (13.1) | 81 (10.9) | 9 (10.7) | 114 (19.2) | 49 (11.5) | 60 (12.1) | 69 (6.4) |
| Non Hispanic or non-Latino | 731 (79.3) | 118 (81.4) | 643 (86.3) | 74 (88.1) | 440 (73.9) | 361 (84.5) | 420 (84.8) | 986 (90.8) |
| Non-resident of the U.S. | 2 (0.2) | 1 (0.7) | 3 (0.4) | 0 (0.0) | 16 (2.7) | 5 (1.2) | 1 (0.2) | 3 (0.3) |
| Not reported | 30 (3.3) | 7 (4.8) | 18 (2.4) | 1 (1.2) | 25 (4.2) | 12 (2.8) | 14 (2.8) | 28 (2.6) |
| Karnofsky score prior to HCT - no. (%) | | | | | | | | |
| 90-100% | 499 (54.1) | 81 (55.9) | 387 (51.9) | 51 (60.7) | 330 (55.5) | 237 (55.5) | 261 (52.7) | 608 (56.0) |
| < 90% | 416 (45.1) | 62 (42.8) | 355 (47.7) | 30 (35.7) | 225 (37.8) | 165 (38.6) | 203 (41.0) | 447 (41.2) |
| Not reported | 7 (0.8) | 2 (1.4) | 3 (0.4) | 3 (3.6) | 40 (6.7) | 25 (5.9) | 31 (6.3) | 31 (2.9) |
| HCT-CI - no. (%) | | | | | | | | |
| 0 | 198 (21.5) | 38 (26.2) | 140 (18.8) | 23 (27.4) | 202 (33.9) | 117 (27.4) | 156 (31.5) | 267 (24.6) |
| 1 | 152 (16.5) | 25 (17.2) | 122 (16.4) | 16 (19.0) | 100 (16.8) | 82 (19.2) | 88 (17.8) | 200 (18.4) |
| 2 | 163 (17.7) | 27 (18.6) | 129 (17.3) | 13 (15.5) | 66 (11.1) | 52 (12.2) | 56 (11.3) | 157 (14.5) |
| 3+ | 404 (43.8) | 55 (37.9) | 350 (47.0) | 32 (38.1) | 224 (37.6) | 170 (39.8) | 191 (38.6) | 456 (42.0) |
| Not reported | 5 (0.5) | 0 (0.0) | 4 (0.5) | 0 (0.0) | 3 (0.5) | 6 (1.4) | 4 (0.8) | 6 (0.6) |
| **Disease related** | | | | | | | | |
| Primary disease - no. (%) | | | | | | | | |
| Acute myelogenous leukemia or ANLL | 249 (27.0) | 32 (22.1) | 211 (28.3) | 18 (21.4) | 95 (16.0) | 82 (19.2) | 123 (24.8) | 206 (19.0) |
| Acute lymphoblastic leukemia | 73 (7.9) | 11 (7.6) | 64 (8.6) | 12 (14.3) | 62 (10.4) | 20 (4.7) | 37 (7.5) | 72 (6.6) |
| Other leukemia | 4 (0.4) | 0 (0.0) | 2 (0.3) | 1 (1.2) | 3 (0.5) | 3 (0.7) | 3 (0.6) | 6 (0.6) |
| Chronic myelogenous leukemia | 15 (1.6) | 1 (0.7) | 13 (1.7) | 2 (2.4) | 1 (0.2) | 3 (0.7) | 5 (1.0) | 17 (1.6) |
| Myelodysplastic/myeloprolifterative disorders (please classify all preleukemias) | 111 (12.0) | 10 (6.9) | 86 (11.5) | 13 (15.5) | 63 (10.6) | 52 (12.2) | 50 (10.1) | 149 (13.7) |

| Characteristic | LTM D+/R+ | LTM D+/R- | LTM D-/R+ | LTM D-/R- | No LTM D+/R+ | No LTM D+/R- | No LTM D-/R+ | No LTM D-/R- |
|---|---|---|---|---|---|---|---|---|
| Other acute leukemia | 3 (0.3) | 1 (0.7) | 6 (0.8) | 1 (1.2) | 2 (0.3) | 1 (0.2) | 4 (0.8) | 8 (0.7) |
| Non-Hodgkin lymphoma | 34 (3.7) | 5 (3.4) | 33 (4.4) | 4 (4.8) | 24 (4.0) | 15 (3.5) | 14 (2.8) | 41 (3.8) |
| Hodgkin lymphoma | 43 (4.7) | 8 (5.5) | 13 (1.7) | 1 (1.2) | 19 (3.2) | 17 (4.0) | 10 (2.0) | 45 (4.1) |
| Plasma cell disorder/Multiple Myeloma | 3 (0.3) | 0 (0.0) | 2 (0.3) | 0 (0.0) | 2 (0.3) | 1 (0.2) | 2 (0.4) | 3 (0.3) |
| Severe aplastic anemia | 123 (13.3) | 17 (11.7) | 92 (12.3) | 8 (9.5) | 93 (15.6) | 25 (5.9) | 87 (17.6) | 81 (7.5) |
| Inherited bone marrow failure syndromes | 8 (0.9) | 2 (1.4) | 5 (0.7) | 1 (1.2) | 22 (3.7) | 12 (2.8) | 14 (2.8) | 29 (2.7) |
| Hemoglobinopathies | 39 (4.2) | 15 (10.3) | 17 (2.3) | 2 (2.4) | 70 (11.8) | 45 (10.5) | 28 (5.7) | 76 (7.0) |
| Paroxysmal nocturnal hemoglobinuria | 2 (0.2) | 0 (0.0) | 2 (0.3) | 0 (0.0) | 3 (0.5) | 1 (0.2) | 2 (0.4) | 2 (0.2) |
| SCID and other immune system disorders | 7 (0.8) | 5 (3.4) | 4 (0.5) | 0 (0.0) | 51 (8.6) | 26 (6.1) | 34 (6.9) | 39 (3.6) |
| Inherited abnormalities of platelets | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| Inherited disorders of metabolism | 2 (0.2) | 2 (1.4) | 2 (0.3) | 1 (1.2) | 4 (0.7) | 18 (4.2) | 6 (1.2) | 25 (2.3) |
| Autoimmune Diseases | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 7 (1.2) | 3 (0.7) | 1 (0.2) | 0 (0.0) |
| Other, specify | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Tolerance induction associated with solid organ transplant | 0 (0.0) | 1 (0.7) | 0 (0.0) | 0 (0.0) | 1 (0.2) | 1 (0.2) | 1 (0.2) | 0 (0.0) |
| Myeloproliferative Neoplasms | 203 (22.0) | 35 (24.1) | 193 (25.9) | 19 (22.6) | 72 (12.1) | 102 (23.9) | 74 (14.9) | 286 (26.3) |
| Time from diagnosis to transplant, month - median (min-max) | 9.7 (0.2-589.8) | 16.6 (1.2-421.0) | 8.3 (1.2-566.0) | 11.4 (3.2-272.0) | 9.3 (1.0-384.7) | 11.3 (1.3-610.8) | 8.3 (1.2-630.2) | 12.3 (0.5-607.3) |
| **Infection related** | | | | | | | | |
| First antiviral drug given as prophylaxis(yes/no) - no. (%) | | | | | | | | |
| No | 6 (0.7) | 1 (0.7) | 6 (0.8) | 2 (2.4) | 19 (3.2) | 24 (5.6) | 12 (2.4) | 50 (4.6) |
| Yes | 894 (97.0) | 142 (97.9) | 721 (96.8) | 82 (97.6) | 575 (96.6) | 403 (94.4) | 483 (97.6) | 1036 (95.4) |
| first antiviral drug given as prophylaxis - Valacyclovir (Valtrex) | 168 (18.2) | 32 (22.1) | 148 (19.9) | 19 (22.6) | 102 (17.1) | 76 (17.8) | 100 (20.2) | 200 (18.4) |
| first antiviral drug given as prophylaxis - Valganciclovir (Valcyte) | 10 (1.1) | 4 (2.8) | 7 (0.9) | 1 (1.2) | 17 (2.9) | 3 (0.7) | 9 (1.8) | 6 (0.6) |

| Characteristic | LTM D+/R+ | LTM D+/R- | LTM D-/R+ | LTM D-/R- | No LTM D+/R+ | No LTM D+/R- | No LTM D-/R+ | No LTM D-/R- |
|---|---|---|---|---|---|---|---|---|
| first antiviral drug given as prophylaxis - Famciclovir (Famvir) | 14 (1.5) | 1 (0.7) | 10 (1.3) | 0 (0.0) | 2 (0.3) | 3 (0.7) | 0 (0.0) | 10 (0.9) |
| first antiviral drug given as prophylaxis - Ganciclovir | 3 (0.3) | 0 (0.0) | 1 (0.1) | 1 (1.2) | 12 (2.0) | 2 (0.5) | 11 (2.2) | 1 (0.1) |
| first antiviral drug given as prophylaxis - Other antiviral drug | 6 (0.7) | 1 (0.7) | 2 (0.3) | 0 (0.0) | 5 (0.8) | 2 (0.5) | 2 (0.4) | 2 (0.2) |
| first antiviral drug given as prophylaxis - Acyclovir | 710 (77.0) | 106 (73.1) | 558 (74.9) | 65 (77.4) | 456 (76.6) | 322 (75.4) | 374 (75.6) | 829 (76.3) |
| Not reported | 22 (2.4) | 2 (1.4) | 18 (2.4) | 0 (0.0) | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Bacterial - no. (%) | | | | | | | | |
| No | 607 (65.8) | 99 (68.3) | 500 (67.1) | 55 (65.5) | 411 (69.1) | 304 (71.2) | 329 (66.5) | 765 (70.4) |
| Yes | 315 (34.2) | 46 (31.7) | 245 (32.9) | 29 (34.5) | 184 (30.9) | 123 (28.8) | 166 (33.5) | 321 (29.6) |
| Viral - no. (%) | | | | | | | | |
| No | 600 (65.1) | 101 (69.7) | 487 (65.4) | 62 (73.8) | 312 (52.4) | 295 (69.1) | 294 (59.4) | 807 (74.3) |
| Yes | 322 (34.9) | 44 (30.3) | 258 (34.6) | 22 (26.2) | 283 (47.6) | 132 (30.9) | 201 (40.6) | 279 (25.7) |
| Fungal - no. (%) | | | | | | | | |
| No | 880 (95.4) | 137 (94.5) | 710 (95.3) | 82 (97.6) | 573 (96.3) | 417 (97.7) | 474 (95.8) | 1043 (96.0) |
| Yes | 42 (4.6) | 8 (5.5) | 35 (4.7) | 2 (2.4) | 22 (3.7) | 10 (2.3) | 21 (4.2) | 43 (4.0) |
| CMV - no. (%) | | | | | | | | |
| No | 817 (88.6) | 141 (97.2) | 660 (88.6) | 81 (96.4) | 422 (70.9) | 405 (94.8) | 380 (76.8) | 1082 (99.6) |
| Yes | 105 (11.4) | 4 (2.8) | 85 (11.4) | 3 (3.6) | 173 (29.1) | 22 (5.2) | 115 (23.2) | 4 (0.4) |
| **Transplant related** | | | | | | | | |
| Product type - no. (%) | | | | | | | | |
| BM | 178 (19.3) | 33 (22.8) | 113 (15.2) | 12 (14.3) | 213 (35.8) | 99 (23.2) | 157 (31.7) | 238 (21.9) |
| PBSC | 740 (80.3) | 111 (76.6) | 619 (83.1) | 69 (82.1) | 365 (61.3) | 309 (72.4) | 321 (64.8) | 828 (76.2) |
| UCB | 4 (0.4) | 1 (0.7) | 13 (1.7) | 3 (3.6) | 17 (2.9) | 19 (4.4) | 17 (3.4) | 19 (1.7) |
| Other | | | | | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| Donor type - no. (%) | | | | | | | | |

| Characteristic | LTM D+/R+ | LTM D+/R- | LTM D-/R+ | LTM D-/R- | No LTM D+/R+ | No LTM D+/R- | No LTM D-/R+ | No LTM D-/R- |
|---|---|---|---|---|---|---|---|---|
| HLA identical sibling | 145 (15.7) | 13 (9.0) | 94 (12.6) | 8 (9.5) | 145 (24.4) | 67 (15.7) | 99 (20.0) | 197 (18.1) |
| Haploidentical donor | 215 (23.3) | 32 (22.1) | 111 (14.9) | 20 (23.8) | 127 (21.3) | 56 (13.1) | 68 (13.7) | 157 (14.5) |
| Other related | 11 (1.2) | 4 (2.8) | 3 (0.4) | 2 (2.4) | 11 (1.8) | 5 (1.2) | 5 (1.0) | 15 (1.4) |
| Well-matched unrelated(8/8) | 360 (39.0) | 60 (41.4) | 354 (47.5) | 35 (41.7) | 201 (33.8) | 183 (42.9) | 224 (45.3) | 547 (50.4) |
| Partially-matched unrelated(7/8) | 151 (16.4) | 27 (18.6) | 136 (18.3) | 13 (15.5) | 73 (12.3) | 78 (18.3) | 59 (11.9) | 104 (9.6) |
| Mismatched unrelated(<=6/8) | 21 (2.3) | 2 (1.4) | 11 (1.5) | 2 (2.4) | 4 (0.7) | 3 (0.7) | 7 (1.4) | 10 (0.9) |
| Multi-donor | 2 (0.2) | 4 (2.8) | 3 (0.4) | 1 (1.2) | 5 (0.8) | 3 (0.7) | 3 (0.6) | 8 (0.7) |
| Unrelated (matching cannot be determined) | 14 (1.5) | 3 (2.1) | 22 (3.0) | 1 (1.2) | 13 (2.2) | 13 (3.0) | 13 (2.6) | 29 (2.7) |
| Cord blood | 3 (0.3) | 0 (0.0) | 11 (1.5) | 2 (2.4) | 16 (2.7) | 19 (4.4) | 17 (3.4) | 19 (1.7) |
| Classify the recipient's prescribed preparative regimen - no. (%) | | | | | | | | |
| Myeloablative | 281 (30.5) | 51 (35.2) | 234 (31.4) | 29 (34.5) | 219 (36.8) | 149 (34.9) | 174 (35.2) | 375 (34.5) |
| Non-myeloablative (NST) | 154 (16.7) | 18 (12.4) | 109 (14.6) | 14 (16.7) | 112 (18.8) | 66 (15.5) | 73 (14.7) | 183 (16.9) |
| Reduced intensity (RIC) | 487 (52.8) | 75 (51.7) | 399 (53.6) | 41 (48.8) | 253 (42.5) | 210 (49.2) | 243 (49.1) | 523 (48.2) |
| Not reported | 0 (0.0) | 1 (0.7) | 3 (0.4) | 0 (0.0) | 11 (1.8) | 2 (0.5) | 5 (1.0) | 5 (0.5) |
| Was irradiation performed as part of the pre-HCT preparative regimen? - no. (%) | | | | | | | | |
| No | 500 (54.2) | 83 (57.2) | 445 (59.7) | 46 (54.8) | 376 (63.2) | 277 (64.9) | 333 (67.3) | 668 (61.5) |
| Yes | 407 (44.1) | 59 (40.7) | 290 (38.9) | 37 (44.0) | 204 (34.3) | 142 (33.3) | 150 (30.3) | 390 (35.9) |
| Not reported | 15 (1.6) | 3 (2.1) | 10 (1.3) | 1 (1.2) | 15 (2.5) | 8 (1.9) | 12 (2.4) | 28 (2.6) |
| given radiation field (2000) - no. (%) | | | | | | | | |
| TBI | 397 (43.1) | 55 (37.9) | 284 (38.1) | 36 (42.9) | 201 (33.8) | 134 (31.4) | 146 (29.5) | 379 (34.9) |
| TLI | 2 (0.2) | 2 (1.4) | 3 (0.4) | 0 (0.0) | 1 (0.2) | 4 (0.9) | 1 (0.2) | 6 (0.6) |
| TAI | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) | 0 (0.0) |
| IMRT | 8 (0.9) | 1 (0.7) | 3 (0.4) | 1 (1.2) | 1 (0.2) | 4 (0.9) | 2 (0.4) | 4 (0.4) |
| Not reported | 515 (55.9) | 87 (60.0) | 455 (61.1) | 47 (56.0) | 392 (65.9) | 285 (66.7) | 345 (69.7) | 697 (64.2) |
| GVHD prophylaxis - no. (%) | | | | | | | | |

| Characteristic | LTM D+/R+ | LTM D+/R- | LTM D-/R+ | LTM D-/R- | No LTM D+/R+ | No LTM D+/R- | No LTM D-/R+ | No LTM D-/R- |
|---|---|---|---|---|---|---|---|---|
| None | 15 (1.6) | 2 (1.4) | 9 (1.2) | 3 (3.6) | 28 (4.7) | 17 (4.0) | 25 (5.1) | 44 (4.1) |
| Ex-vivo T-cell depletion | 5 (0.5) | 1 (0.7) | 3 (0.4) | 0 (0.0) | 18 (3.0) | 11 (2.6) | 13 (2.6) | 14 (1.3) |
| CD34 selection | 17 (1.8) | 6 (4.1) | 10 (1.3) | 0 (0.0) | 23 (3.9) | 10 (2.3) | 10 (2.0) | 16 (1.5) |
| PtCy | 490 (53.1) | 70 (48.3) | 335 (45.0) | 43 (51.2) | 165 (27.7) | 147 (34.4) | 133 (26.9) | 401 (36.9) |
| TAC based | 346 (37.5) | 62 (42.8) | 350 (47.0) | 36 (42.9) | 273 (45.9) | 195 (45.7) | 248 (50.1) | 523 (48.2) |
| CSA based | 32 (3.5) | 4 (2.8) | 32 (4.3) | 2 (2.4) | 72 (12.1) | 38 (8.9) | 53 (10.7) | 64 (5.9) |
| Other | 16 (1.7) | 0 (0.0) | 6 (0.8) | 0 (0.0) | 15 (2.5) | 9 (2.1) | 13 (2.6) | 23 (2.1) |
| Not reported | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| ATG/Campath - no. (%) | | | | | | | | |
| ATG + CAMPATH | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| ATG alone | 197 (21.4) | 48 (33.1) | 181 (24.3) | 17 (20.2) | 210 (35.3) | 104 (24.4) | 134 (27.1) | 268 (24.7) |
| CAMPATH alone | 49 (5.3) | 12 (8.3) | 26 (3.5) | 4 (4.8) | 71 (11.9) | 41 (9.6) | 54 (10.9) | 80 (7.4) |
| No ATG or CAMPATH | 676 (73.3) | 85 (58.6) | 538 (72.2) | 63 (75.0) | 313 (52.6) | 281 (65.8) | 307 (62.0) | 738 (68.0) |
| CD4 at day100 (yes/no) - no. (%) | | | | | | | | |
| No | 646 (70.1) | 96 (66.2) | 512 (68.7) | 55 (65.5) | 385 (64.7) | 279 (65.3) | 342 (69.1) | 728 (67.0) |
| Yes | 276 (29.9) | 49 (33.8) | 233 (31.3) | 29 (34.5) | 210 (35.3) | 148 (34.7) | 153 (30.9) | 358 (33.0) |
| CD8 at day100 (yes/no) - no. (%) | | | | | | | | |
| No | 661 (71.7) | 98 (67.6) | 548 (73.6) | 58 (69.0) | 385 (64.7) | 286 (67.0) | 350 (70.7) | 752 (69.2) |
| Yes | 261 (28.3) | 47 (32.4) | 197 (26.4) | 26 (31.0) | 210 (35.3) | 141 (33.0) | 145 (29.3) | 334 (30.8) |
| CD56 at day100 (yes/no) - no. (%) | | | | | | | | |
| No | 734 (79.6) | 111 (76.6) | 610 (81.9) | 66 (78.6) | 419 (70.4) | 320 (74.9) | 367 (74.1) | 847 (78.0) |
| Yes | 188 (20.4) | 34 (23.4) | 135 (18.1) | 18 (21.4) | 176 (29.6) | 107 (25.1) | 128 (25.9) | 239 (22.0) |
| Year of current transplant - no. (%) | | | | | | | | |
| 2018 | 20 (2.2) | 1 (0.7) | 9 (1.2) | 2 (2.4) | 15 (2.5) | 1 (0.2) | 6 (1.2) | 11 (1.0) |
| 2019 | 18 (2.0) | 4 (2.8) | 16 (2.1) | 3 (3.6) | 20 (3.4) | 8 (1.9) | 10 (2.0) | 26 (2.4) |
| 2020 | 56 (6.1) | 10 (6.9) | 55 (7.4) | 5 (6.0) | 44 (7.4) | 26 (6.1) | 44 (8.9) | 59 (5.4) |
| 2021 | 255 (27.7) | 39 (26.9) | 220 (29.5) | 26 (31.0) | 209 (35.1) | 111 (26.0) | 176 (35.6) | 351 (32.3) |

| Characteristic | LTM D+/R+ | LTM D+/R- | LTM D-/R+ | LTM D-/R- | No LTM D+/R+ | No LTM D+/R- | No LTM D-/R+ | No LTM D-/R- |
|---|---|---|---|---|---|---|---|---|
| 2022 | 299 (32.4) | 47 (32.4) | 240 (32.2) | 23 (27.4) | 185 (31.1) | 146 (34.2) | 152 (30.7) | 349 (32.1) |
| 2023 | 274 (29.7) | 44 (30.3) | 205 (27.5) | 25 (29.8) | 122 (20.5) | 135 (31.6) | 107 (21.6) | 290 (26.7) |

| Field | Response |
|---|---|
| Proposal Number | 2410-55-LIND |
| Proposal Title | Peri-transplant Norovirus infection as a risk factor for allogeneic HSCT outcomes |
| Key Words | Norovirus, TRM, allogeneic HSCT, immunosuppression |
| Principal Investigator #1: - First and last name, degree(s) | Katherine Lind, MD MSc |
| Principal Investigator #1: - Email address | katherine.lind@cuanschutz.edu |
| Principal Investigator #1: - Institution name | University of Colorado School of Medicine/Children's Hospital Colorado |
| Principal Investigator #1: - Academic rank | Clinical BMT/CT Fellow |
| Junior investigator status (defined as ≤5 years from fellowship) | Yes |
| Do you identify as an underrepresented/minority? | No |
| Principal Investigator #2 (If applicable): - First and last name, degree(s): | Laura McLaughlin, MD |
| Principal Investigator #2 (If applicable): - Email address:) | Laura.McLaughlin@CUAnschutz.edu |
| Principal Investigator #2 (If applicable): - Institution name: | University of Colorado School of Medicine/Children's Hospital Colorado |
| Principal Investigator #2 (If applicable): - Academic rank: | Assistant Professor |
| Junior investigator status (defined as ≤5 years from fellowship) | Yes |
| Do you identify as an underrepresented/minority? | No |
| We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below: | Lind |
| If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below: | - |
| Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role. | None |
| Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months? | No |
| PROPOSED WORKING COMMITTEE: | Infection and Immune Reconstitution |
| Please indicate if you have already spoken with a scientific director or working committee chair regarding this study. | Yes |
| If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who: | Jeffery Auletta |

| Field | Response |
|---|---|
| RESEARCH QUESTION: | Does peri-transplant Norovirus infection confer inferior transplant outcomes i.e. increased transplant-related mortality (TRM)? |
| RESEARCH HYPOTHESIS: | Allogeneic transplant recipients who develop Norovirus infection prior to or within 100 days post-transplant have inferior OS compared to recipients without Norovirus. |
| SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.): | The primary objective is to describe the incidence and impact of norovirus infection on OS amongst allogeneic HSCT patients through a case-control retrospective cohort study. Cases and controls will be matched, and outcomes and sub stratified based on the following factors: age (pediatric vs. adult), transplant indication (malignant vs. non-malignant), preparatory regimen, stem cell source and GVHD prophylaxis regimen. Secondary objectives are to describe the rates of additional transplant-related outcomes in cases vs. matched controls including: relapse, number of inpatient days in first 100 days post-transplant, change in recipient weight from pre-transplant to 100 days post-transplant and occurrence of renal impairment and GVHD (including organs affected, severity and treatments given). |

| Field | Response |
|---|---|
| SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care. | Post-HSCT, diarrhea impacts 20-44% of patients, with approximately 40% of cases attributed to infectious etiologies.(1) This high incidence is primarily due to mucosal injury caused by conditioning regimens, which can be exacerbated by acute GVHD.(2) Norovirus, typically a self-limited infection in immunocompetent individuals, presents a significant risk in immunocompromised recipients, where it can cause a prolonged diarrheal illness. This poses a risk of dehydration, malnutrition, prolonged hospitalization, and mortality.(1,3-5) In one prospective observational study, over 50% of HSCT patients with norovirus experienced diarrhea lasting more than 14 days, and 29% had symptom recurrence after initial resolution.(3) Norovirus infection in HSCT patients was associated with significantly higher rates of ICU admission, serum creatinine elevation, and weight loss compared to those without the infection.(3) Another prospective trial across eight sites evaluated norovirus infection in both solid organ and HSCT recipients, finding that most infected patients had more than three episodes of diarrhea a day with 71% requiring hospitalization and 21% having clinically significant renal dysfunction. In this cohort, 30% of patients suffered from diarrhea for more than 30 days.(5) Despite the known impact of norovirus on prolonged diarrheal illness in HSCT patients, there is a lack of data on how it specifically affects key HSCT outcomes, including TRM and OS. Additional data on the incidence and consequences of norovirus in HSCT recipients will inform the prognosis of recipients who develop norovirus in the peri-transplant period. |

| Field | Response |
|---|---|
| SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary. | Data on the incidence of norovirus infection in patients undergoing HSCT is limited, with reported ranges from 0 to 32% among allogeneic HSCT recipients.(2,6,7) While norovirus is thought to occur more frequently in pediatric patients and in those transplanted for immune deficiencies , this is not been well-characterized in the literature. (2) Infection with norovirus or sapovirus, another calicivirus, has also been associated with increased rates of steroid-refractory and chronic GVHD in a single study, though small numbers of infections did not lend to statistical significance.(1) Although the cited prospective and retrospective studies have shown that norovirus significantly contributes to morbidity and mortality in HSCT patients,(3-5) the majority of these studies involved small patient cohorts primarily conducted at single centers and were subject to several limitations. These limitations include short follow-up periods, limited patient groups, and variability in the treatment protocols used. With limited numbers of infections occurring amongst recipients, larger data sets, such as those from CIBMTR, are needed to fully understand the impact of norovirus across different patient populations and transplant types. |
| PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria. | Inclusion: Recipients undergoing first allogeneic HSCT from 2008 -2019 who had a reported Norovirus infection either pre-transplant and/or in the first 100 days following transplant. Exclusion: Patients who experienced primary graft failure and patients lacking follow-up data at Day 100 (except for patient death occurring prior to Day 100). |
| Does this study include pediatric patients? | Yes |
| If this study does not include pediatric patients, please provide justification: | - |

| Field | Response |
|---|---|
| DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required. | Pre-Transplant variables: • Age, sex, race, ethnicity, donor type, stem cell donor source (UCB, BM, PBSC), degree of donor mismatch, donor and recipient CMV status, preparative regimen intensity, use of serotherapy, transplant indication (disease classification), recipient weight Infusion variables: • HCT type, product type, donor sex, graft manipulation (CD34+ selection, ex-vivo T-cell depletion) Post Transplant Variables: • Clinically significant infection (Norovirus) and time of onset pre-transplant and/or post-transplant • Specific therapies used to prevent acute GVHD • Time of onset, organs involved and maximum grade of acute GVHD • Time of onset, organs involved and maximum grade of chronic GVHD • Renal impairment/disorder, date of onset & resolution, need for dialysis • Recipient weight at 100 days post-transplant • Total number of inpatient days in the first 100 days post-infusion • Relapse • Survival • Time of death, primary and contributing causes of death |
| Types of cellular therapy data this proposal includes: | Hematopoietic Cell Transplantation (HCT) |
| PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis speci | n/a |
| MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions. | no |
| SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous e | n/a |
| NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required. | n/a |

| Field | Response |
|---|---|
| REFERENCES: | 1. Mageau A, Ambert-Balay K, Boutolleau D, et al. Norovirus and sapovirus infections after allogeneic hematopoietic stem cell transplantation: is it worth it to look for them? Leuk Lymphoma 2023;64(7):1295-1303. DOI: 10.1080/10428194.2023.2211186. 2. Castillo Almeida NE, Cichon CJ, Gomez CA. How I approach diarrhea in hematological transplant patients: A practical tool. Transpl Infect Dis 2023;25 Suppl 1:e14184. DOI: 10.1111/tid.14184. 3. Ye X, Van JN, Munoz FM, et al. Noroviruses as a Cause of Diarrhea in Immunocompromised Pediatric Hematopoietic Stem Cell and Solid Organ Transplant Recipients. Am J Transplant 2015;15(7):1874-81. DOI: 10.1111/ajt.13227. 4. Robles JD, Cheuk DK, Ha SY, Chiang AK, Chan GC. Norovirus infection in pediatric hematopoietic stem cell transplantation recipients: incidence, risk factors, and outcome. Biol Blood Marrow Transplant 2012;18(12):1883-9. DOI: 10.1016/j.bbmt.2012.07.005. 5. Callegari M, Danziger-Isakov LA, Rose A, et al. Presentation, management, and outcomes of norovirus in adult and pediatric solid organ and hematopoietic stem cell transplant recipients: A multicenter, retrospective study. Transpl Infect Dis 2024;26(3):e14270. DOI: 10.1111/tid.14270. 6. Schuster JE, Johnston SH, Piya B,
et al. Infectious Causes of Acute Gastroenteritis in US Children Undergoing Allogeneic Hematopoietic Cell Transplant: A Longitudinal, Multicenter Study. J Pediatric Infect Dis Soc 2020;9(4):421-427. DOI: 10.1093/jpids/piz063. 7. Mhaissen MN, Rodriguez A, Gu Z, et al. Epidemiology of Diarrheal Illness in Pediatric Oncology Patients. J Pediatric Infect Dis Soc 2017;6(3):275-280. DOI: 10.1093/jpids/piw050. |
| CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning? | No, I do not have any conflicts of interest pertinent to this proposal |
| If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually. | - |

**2410-55 Peri-transplant Norovirus infection as a risk factor for allogeneic HSCT outcomes**

**First allo patient between 2008 and 2024 who had a reported Norovirus infection by the first 100 days following transplant**

| **Characteristic** | |
|---|---|
| Number of patients | 136 |
| No. of centers | 61 |
| **Patient related** | |
| Age at HCT - no. (%) | |
| 0 to <=10 | 58 (42.6) |
| 10 to <=18 | 10 (7.4) |
| 18 to <=30 | 10 (7.4) |
| 30 to <=40 | 3 (2.2) |
| 40 to <=50 | 10 (7.4) |
| 50 to <=60 | 16 (11.8) |
| 60 to <=70 | 23 (16.9) |
| 70+ | 6 (4.4) |
| Sex - no. (%) | |
| Male | 80 (58.8) |
| Female | 56 (41.2) |
| Race - no. (%) | |
| White | 97 (71.3) |
| Black or African American | 11 (8.1) |
| Asian | 5 (3.7) |
| More than one race | 11 (8.1) |
| Not reported | 12 (8.8) |
| Ethnicity - no. (%) | |
| Hispanic or Latino | 23 (16.9) |
| Not Hispanic or Latino | 96 (70.6) |
| Non-resident of the U.S. | 12 (8.8) |
| Not reported | 5 (3.7) |
| Region of patient - no. (%) | |
| US | 124 (91.2) |
| Canada | 2 (1.5) |
| Europe | 1 (0.7) |
| Australia/New Zealand | 6 (4.4) |
| Mideast/Africa | 2 (1.5) |
| Central/South America | 1 (0.7) |
| Karnofsky score prior to HCT - no. (%) | |
| 90-100 | 78 (57.4) |

| Characteristic | |
|---|---|
| < 90 | 47 (34.6) |
| Not reported | 11 (8.1) |
| HCT-CI - no. (%) | |
| 0 | 43 (31.6) |
| 1 | 32 (23.5) |
| 2 | 14 (10.3) |
| 3+ | 45 (33.1) |
| Not reported | 2 (1.5) |
| **Disease related** | |
| Primary disease - no. (%) | |
| Acute myelogenous leukemia or ANLL | 20 (14.7) |
| Acute lymphoblastic leukemia | 17 (12.5) |
| Other leukemia | 1 (0.7) |
| Chronic myelogenous leukemia | 4 (2.9) |
| Myelodysplastic/myeloprolifterative disorders (please classify all preleukemias) | 16 (11.8) |
| Other acute leukemia | 2 (1.5) |
| Hodgkin lymphoma | 1 (0.7) |
| Severe aplastic anemia | 12 (8.8) |
| Inherited bone marrow failure syndromes | 2 (1.5) |
| Hemoglobinopathies | 10 (7.4) |
| Paroxysmal nocturnal hemoglobinuria | 1 (0.7) |
| SCID and other immune system disorders | 28 (20.6) |
| Inherited disorders of metabolism | 5 (3.7) |
| Histiocytic disorders | 2 (1.5) |
| Myeloproliferative Neoplasms | 15 (11.0) |
| **Transplant related** | |
| Calculated Graft (Product) type or all the products in the transplant - no. (%) | |
| Bone marrow | 51 (37.5) |
| Peripheral blood | 61 (44.9) |
| Umbilical cord blood | 19 (14.0) |
| PB + UCB | 5 (3.7) |
| Donor type - no. (%) | |
| HLA identical sibling | 21 (15.4) |
| Haploidentical donor | 24 (17.6) |
| Other related | 5 (3.7) |
| Well-matched unrelated(8/8) | 43 (31.6) |
| Partially matched unrelated(7/8) | 14 (10.3) |
| Mismatched unrelated(<=6/8) | 1 (0.7) |
| Multi-donor | 1 (0.7) |
| Unrelated (matching cannot be determined) | 6 (4.4) |

| **Characteristic** | |
|---|---|
| Cord blood | 21 (15.4) |
| Donor CMV-antibodies (IgG or Total) - no. (%) | |
| Negative | 58 (42.6) |
| Positive | 66 (48.5) |
| Not reported | 12 (8.8) |
| Recipient CMV-antibodies (IgG or Total) - no. (%) | |
| Negative | 40 (29.4) |
| Positive | 93 (68.4) |
| Not tested or not reported | 3 (2.2) |
| Conditioning intensity reported by center - no. (%) | |
| MAC | 70 (51.5) |
| NMA | 18 (13.2) |
| RIC | 46 (33.8) |
| Not reported | 2 (1.5) |
| GVHD prophylaxis - no. (%) | |
| None | 2 (1.5) |
| Ex-vivo T-cell depletion | 7 (5.2) |
| CD34 selection | 6 (4.4) |
| PtCy | 32 (23.5) |
| TAC based | 58 (42.7) |
| CSA based | 31 (22.8) |
| Ex-vivo T-cell depletion planned for GVHD prophylaxis - no. (%) | |
| Yes | 2 (1.5) |
| Not reported | 134 (98.5) |
| CD34+ selection planned for GVHD prophylaxis - no. (%) | |
| Yes | 1 (0.7) |
| Not reported | 135 (99.3) |

| Field | Response |
|---|---|
| Proposal Number | 2410-61-ABID |
| Proposal Title | The Incidence and Impact of Clostridioides Difficile Infection on CAR-T Cell Therapy Outcomes – A CIBMTR Study |
| Key Words | Clostridioides Difficile Infection: CAR-T; NRM |
| Principal Investigator #1: - First and last name, degree(s) | Muhammad Bilal Abid, MD MS |
| Principal Investigator #1: - Email address | Bilal_abid@hotmail.com |
| Principal Investigator #1: - Institution name | University of Texas Houston |
| Principal Investigator #1: - Academic rank | Fellow |
| Junior investigator status (defined as ≤5 years from fellowship) | Yes |
| Do you identify as an underrepresented/minority? | - |
| Principal Investigator #2 (If applicable): - First and last name, degree(s): | Mahmoud Aljurf, MD MPH |
| Principal Investigator #2 (If applicable): - Email address:) | maljurf@kfshrc.edu.sa |
| Principal Investigator #2 (If applicable): - Institution name: | Oncology Center, King Faisal Specialist Hospital Center & Research, Riyadh, Saudi Arabia |
| Principal Investigator #2 (If applicable): - Academic rank: | Professor, Chair |
| Junior investigator status (defined as ≤5 years from fellowship) | No |
| Do you identify as an underrepresented/minority? | No |
| We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below: | Muhammad Bilal Abid |
| If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below: | Yes, I am a junior investigator and would like assistance identifying a senior mentor for my project |
| Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role. | CAR-T and INWC studies |
| Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months? | No |
| PROPOSED WORKING COMMITTEE: | Infection and Immune Reconstitution |
| Please indicate if you have already spoken with a scientific director or working committee chair regarding this study. | No |
| If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who: | - |

| Field | Response |
|---|---|
| RESEARCH QUESTION: | • What is the incidence of C. Difficile infection (CDI) among CAR T-cell therapy recipients? • What are the differences between infection density and cumulative incidence of CDI in patients receiving CD19+CAR-T vs BCMA-directed CAR T-cell therapy? • What are the risk factors for the development of CDI after CAR T-cell therapy? • How does CDI impact CAR-T outcomes? |
| RESEARCH HYPOTHESIS: | We hypothesize that even though the incidence of CDI in CAR-T patients is low, the infection confers inferior survival. |

| | |
|---|---|
| SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.): | Part A: To compare non-relapse mortality (NRM) between CD19+CAR-T vs BCMA-directed CAR T-cell therapy recipients. Part B: To estimate and compare the infection density and cumulative incidence of overall, bacterial, viral, and fungal infections between CD19+CAR-T vs BCMA-directed CAR T-cell therapy recipients. 1.1 Determine the Incidence of CDI in CAR T-cell therapy recipients. 1.2 Determine the Impact of CDI on CAR-T outcomes 1.2.1 PFS 1.2.2 OS 1.2.3 Non-relapse mortality (NRM) 1.3 Identify pre-CAR-T risk factors for the development of CDI. 1.4 Identify if there are differences in CDI burden by disease type (LBCL vs RRMM) and target antigen (BCMA vs CD19) Primary Outcomes: • Cumulative incidence of CDI infection: This will be evaluated for CDI through day 100 after CAR T-cell infusion. This cumulative incidence will be studied separately for infections occurring during days 0-30 and days 31-100. Relapse/progressive disease and new anti-neoplastic treatment initiation (including hematopoietic cell transplantation) after CAR T-cell therapy are considered to be competing events for infection onset. Median times of all-cause and type-specific infections will be reported among infected patients. Separate estimates for pediatric (2 – 18y) and adult (>18y) patients Secondary Outcomes: • Non-relapse mortality (NRM): Cumulative incidence of NRM. NRM is defined as death without preceding disease relapse/progression. Relapse and progression are competing events. • Infection density: Defined as the number of infections per patient days at risk. The densities of bacterial, viral, fungal, and all-cause infections will be studied separately over the time periods day 0-30, and day 31-100 from the time of CAR T-cell infusion. Infection density will also be evaluated pre- and post- ANC recovery. Infection density is the primary endpoint of the study. • Infection-Related mortality (IRM) by 1 year: Cumulative incidence of death caused by infection. Relapse and death from non-infectious causes are competing events. This will be examined as a Dynamic landmark analysis at day 30, 60 and 100. • Relapse/Progression by 1 year: Cumulative incidence of disease relapse/progression, with TRM as competing event. This will be examined as a dynamic landmark analysis for patients at day 30, 60 and 100. • Progression-free survival by 1 year: will be |

| Field | Response |
|---|---|
| | defined as time to relapse or death from any cause. Patients are censored at last follow-up. This will be examined as a dynamic landmark analysis for patients at day 30, 60 and 100. • Overall survival (OS) by 1 year: time to death. Death from any cause will be considered an event. Surviving patients will be censored at time of last follow-up. This will be examined as a dynamic landmark analysis for patients at day 30, 60 and 100. • Cause of death by 1 year: descriptive only. This will include Primary cause of death and infection as a secondary COD • Frequency of recurrent CDI by 1 year: descriptive only • Frequency of Gram Negative BSI occurring ± 7 days of CDI: descriptive only |
| SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care. | Chimeric antigen receptor (CAR) T-cell therapy has resulted in unprecedented response rates among patients with B-cell hematologic malignancies (HMs). However, the on-target-off-tumor toxicities associated with CAR-T lead to significant morbidity and mortality. Prolonged cytopenia and B-cell aplasia, coupled with prolonged hypogammaglobulinemia, result in a heightened risk for infections for an extended duration. Infections are one of the most common causes of death among CAR-T recipients, second only to disease relapse. CDI remains a common infection among transplant and cellular therapy recipients. However, the incidence, risk factors, and impact of CDI on CAR-T outcomes have never been examined. Such data will aid in the development of risk-adapted and target antigen-specific infection prevention guidelines. |

| | |
|---|---|
| SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary. | Clostridioides difficile infection (CDI) is the most common healthcare-associated infection in the United States. In 2015, the Centers for Disease Control reported the incidence of CDI to be approximately 453,000 cases per year, with an associated annual mortality of 29,300 patients1. In patients undergoing transplantation, the incidence of CDI ranges between 6%-33% with most cases occurring early post-transplantation (within 30 days)2,3. This incidence is considerably higher than in the general patient population (<1%) [7]. The incidence of CDI among allogeneic hematopoietic cell transplant (alloHCT) recipients ranges between 10%-33%1,4,5. Among HCT recipients, risk factors include antibiotic prophylaxis, graft-vs-host disease (GVHD), chemotherapy, mucositis, and increased rates of CD colonization4,6. The incidence of CDI in solid organ transplant (SOT) recipients varies based on the type of organ transplanted, with the lowest incidence in kidney transplant and highest in liver and lung transplant recipients7,8. Chimeric antigen receptor (CAR) T-cell therapy has resulted in unprecedented response rates among patients with B-cell hematologic malignancies (HMs)9. However, the on-target-off-tumor toxicities associated with CAR-T lead to significant morbidity and mortality. Prolonged cytopenia and B-cell aplasia, coupled with prolonged hypogammaglobulinemia, result in a heightened risk for infections for an extended duration10. Infections are one of the most common causes of death among CAR-T recipients, second only to disease relapse11,12. CDI remains a common infection among transplant and cellular therapy recipients5,12. However, the incidence, risk factors, and impact of CDI on CAR-T outcomes have never been examined. We estimated the cumulative incidence of CDI in CAR-T recipients at pre-defined time points, risk factors, and IRM in a disease-specific and tumor-associated antigen (TAA)-specific manner to aid in the development of risk-adapted infection prevention guidelines. While there is no data related to the burden and mortality associated with CDI in CAR-T setting, our prior large CIBMTR analysis in 826 alloHCT recipients with CDI and 6723 controls from 127 centers showed a cumulative incidence of CDI by D+100 of 18.7% (99% CI: 15% – 22.7%) and 10.2% (99% CI: 9.2% – 11.1%) in pediatric and adult patients, respectively. CDI was associated with inferior overall survival (p=0.0018) and a 2.58-fold [99% CI: 1.43 – 4.66; p<0.001] increase in infection-related mortality. There was a significant overlap in the onset of GVHD and CDI. IRM increased to >4 fold when CDI + acute GVHD was |

| Field | Response |
|---|---|
| | considered5. Another prospective study across 4 US transplant centers in 444 recipients [14] demonstrated an incidence of 33% by 30 months4. The incidence of CDI in SOT recipients varies based on the type of organ transplanted, with kidney transplant recipients demonstrating the lowest incidence (1%–11%) and liver and lung transplant recipients experiencing the highest incidence (1%-19% and 2%-23%, respectively)7,8,15,16. Heart transplant recipients have a CDI incidence ranging from 1%-8%17. Regardless of organ transplanted, CDI incidence in SOT is lower than that found in hematology-oncology patients, but still higher than in the general population1. |
| SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Id | F_3Pn05cGwPQc9Zka |
| SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Name | C.diff infection after CAR-T.docx |
| SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Size | 86722 |
| SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Type | application/vnd.openxmlformats-officedocument .wordprocessingml.document |
| PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria. | Inclusion criteria: 1) Adult patients: 18-75 years of age. 2) First CAR T-cell therapy. 3) Patients with relapsed/refractory multiple myeloma who received BCMA-directed CAR-T (Ide-cel or cilta-cel). 4) Patients with Aggressive B cell NHL patients who underwent FDA-approved CD19 CAR T cell therapy. 5) Patients with R/R B-cell ALL (stratified into pediatric [2 – 18y] and adult (>18y)]. 6) At least 2 prior lines of therapy. 7) No prior history of other CAR-T therapy. Exclusion criteria: 1) Patients < 2 years old 2) No consent for research 3) Clinical trial CAR-T, including out-of-specification products 4) Non-CD19 or BCMA-directed CAR-T. |
| Does this study include pediatric patients? | Yes |
| If this study does not include pediatric patients, please provide justification: | - |
| DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required. | This data needed for the study is available on form 4100, Q179-Q182. No supplemental data will be needed. |
| Types of cellular therapy data this proposal includes: | Chimeric Antigen Receptor (CAR) T-Cell Therapy (CAR-T) |

| Field | Response |
|---|---|
| PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis speci | N/A |
| MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions. | N/A |
| SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous e | N/A |
| NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required. | N/A |

| | |
|---|---|
| REFERENCES: | 1. Meir J, Abid MA, Abid MB. State of the CAR-T: Risk of Infections with Chimeric Antigen Receptor T Cell Therapy and Determinants of SARS-CoV-2 Vaccine Responses. Transplant Cell Ther 2021. 2. Infectious Complications in Patients with Hematologic Malignancies Receiving CD19 Vs. BCMA Targeted CAR-T Therapy Abid, Dr. Muhammad Bilal et al. Transplantation and Cellular Therapy, Official Publication of the American Society for Transplantation and Cellular Therapy, Volume 30, Issue 2, S210 - S211 1. Lessa FC, Mu Y, Bamberg WM, et al. Burden of Clostridium difficile infection in the United States. N Engl J Med. 2015;372(9):825-834. 2. Alonso CD, Treadway SB, Hanna DB, et al. Epidemiology and outcomes of Clostridium difficile infections in hematopoietic stem cell transplant recipients. Clin Infect Dis. 2012;54(8):1053-1063. 3. Dubberke ER, Reske KA, Olsen MA, et al. Epidemiology and outcomes of Clostridium difficile infection in allogeneic hematopoietic cell and lung transplant recipients. Transpl Infect Dis. 2018;20(2):e12855. 4. Schuster MG, Cleveland AA, Dubberke ER, et al. Infections in Hematopoietic Cell Transplant Recipients: Results From the Organ Transplant Infection Project, a Multicenter, Prospective, Cohort Study. Open Forum Infect Dis. 2017;4(2):ofx050. 5. Ramanathan M, Kim S, He N, et al. 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. 2023;58(4):360-366. 6. Shah NN, McClellan W, Flowers CR, et al. Evaluating Risk Factors for Clostridium difficile Infection In Stem Cell Transplant Recipients: A National Study. Infect Control Hosp Epidemiol. 2017;38(6):651-657. 7. Boutros M, Al-Shaibi M, Chan G, et al. Clostridium difficile colitis: increasing incidence, risk factors, and outcomes in solid organ transplant recipients. Transplantation. 2012;93(10):1051-1057. 8. Len O, Rodriguez-Pardo D, Gavalda J, et al. Outcome of Clostridium difficile-associated disease in solid organ transplant recipients: a prospective and multicentre cohort study. Transpl Int. 2012;25(12):1275-1281. 9. Locke FL, Siddiqi T, Jacobson CA, et al. Real-World and Clinical Trial Outcomes in Large B-cell Lymphoma with Axicabtagene Ciloleucel Across Race and Ethnicity. Blood. |

| Field | Response |
|---|---|
| | 2024. 10. Doan A, Pulsipher MA. Hypogammaglobulinemia due to CAR T-cell therapy. Pediatr Blood Cancer. 2018;65(4). 11. Haroon A, Muhsen IN, Abid MB, et al. Infectious Complications and Preventative Strategies following Chimeric Antigen Receptor T-cells (CAR-T cells) Therapy for B-Cell Malignancies. Hematol Oncol Stem Cell Ther. 2022;15(3):153-158. 12. Meir J, Abid MA, Abid MB. State of the CAR-T: Risk of Infections with Chimeric Antigen Receptor T-Cell Therapy and Determinants of SARS-CoV-2 Vaccine Responses. Transplant Cell Ther. 2021;27(12):973-987. 13. Abid MB, Hamadani M, Szabo A, et al. Severity of Cytokine Release Syndrome and Its Association with Infections after T Cell-Replete Haploidentical Related Donor Transplantation. Biol Blood Marrow Transplant. 2020;26(9):1670-1678. 14. Abid MB. Early immunomodulators with CAR T-cell immunotherapy in the COVID-19 era. Lancet Oncol. 2022;23(1):16-18. 15. Sullivan T, Weinberg A, Rana M, Patel G, Huprikar S. The Epidemiology and Clinical Features of Clostridium difficile Infection in Liver Transplant Recipients. Transplantation. 2016;100(9):1939-1943. 16. Lee JT, Kelly RF, Hertz MI, Dunitz JM, Shumway SJ. Clostridium difficile infection increases mortality risk in lung transplant recipients. J Heart Lung Transplant. 2013;32(10):1020-1026. 17. Bruminhent J, Cawcutt KA, Thongprayoon C, Petterson TM, Kremers WK, Razonable RR. Epidemiology, risk factors, and outcome of Clostridium difficile infection in heart and heart-lung transplant recipients. Clin Transplant. 2017;31(6). 18. Abid MB, Shah NN, Maatman TC, Hari PN. Gut microbiome and CAR-T therapy. Exp Hematol Oncol. 2019;8:31. |
| CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning? | No, I do not have any conflicts of interest pertinent to this proposal |
| If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually. | - |

# CIBMTR Study Proposal 2024

## Study Title: The Incidence and Impact of Clostridioides Difficile Infection on CAR-T Cell Therapy Outcomes – A CIBMTR Study

**1st PI Information:**
PI Name (First, Middle, Last): Muhammad Bilal Abid
Degree(s): MD, MS
Academic Rank: Fellow, Hematology/Oncology
Junior Investigator (yes/no), *if applicable*: yes
Junior Investigator Status (# years from fellowship), *if applicable*: N/A
Email Address: bilal_abid@hotmail.com
Institution Name: University of Texas Houston / McGovern School of Medicine

**Senior PI Information:**
PI Name (First, Middle, Last): Mahmoud Aljurf
Degree(s): MD MPH
Academic Rank: Professor, Departments of Hematology/Oncology
Junior Investigator (yes/no), *if applicable*: No
Junior Investigator Status (# years from fellowship), *if applicable*: N/A
Email Address: maljurf@kfshrc.edu.sa
Institution Name: Oncology Center, King Faisal Specialist Hospital Center & Research, Riyadh, Saudi Arabia

### 1.0 Research Question:

- What is the incidence of C. Difficile infection (CDI) among CAR T-cell therapy recipients?
- What are the differences between infection density and cumulative incidence of CDI in patients receiving CD19+CAR-T vs BCMA-directed CAR T-cell therapy?
- What are the risk factors for the development of CDI after CAR T-cell therapy?

- How does CDI impact CAR-T outcomes?

## 1.0 Research Hypothesis:

We hypothesize that even though the incidence of CDI in CAR-T patients is low, the infection confers inferior survival.

## 2.0 Specific Aims:

**Part A:** To compare non-relapse mortality (NRM) between CD19+CAR-T vs BCMA-directed CAR T-cell therapy recipients.

**Part B:** To estimate and compare the infection density and cumulative incidence of overall, bacterial, viral, and fungal infections between CD19+CAR-T vs BCMA-directed CAR T-cell therapy recipients.

1.1 Determine the Incidence of CDI in CAR T-cell therapy recipients.
1.2 Determine the Impact of CDI on CAR-T outcomes
  1.2.1 PFS
  1.2.2 OS
  1.2.3 Non-relapse mortality (NRM)
1.3 Identify pre-CAR-T risk factors for the development of CDI.
1.4 Identify if there are differences in CDI burden by disease type (LBCL vs RRMM) and target antigen (BCMA vs CD19)

## 3.0 Scientific Impact:

Chimeric antigen receptor (CAR) T-cell therapy has resulted in unprecedented response rates among patients with B-cell hematologic malignancies (HMs). However, the on-target-off-tumor toxicities associated with CAR-T lead to significant morbidity and mortality. Prolonged cytopenia and B-cell aplasia, coupled with prolonged hypogammaglobulinemia, result in a heightened risk for infections for an extended duration. Infections are one of the most common causes of death among CAR-T recipients, second only to disease relapse. CDI remains a common infection among transplant and cellular therapy recipients. However, the incidence, risk factors, and impact of CDI on CAR-T outcomes have never been

examined. Such data will aid in the development of risk-adapted and target antigen-specific infection prevention guidelines.

**4.0 Scientific Justification:**

*Clostridioides difficile infection* (CDI) is the most common healthcare-associated infection in the United States. In 2015, the Centers for Disease Control reported the incidence of CDI to be approximately 453,000 cases per year, with an associated annual mortality of 29,300 patients[1]. In patients undergoing transplantation, the incidence of CDI ranges between 6%-33% with most cases occurring early post-transplantation (within 30 days)[2,3]. This incidence is considerably higher than in the general patient population (<1%) [7]. The incidence of CDI among allogeneic hematopoietic cell transplant (alloHCT) recipients ranges between 10%-33%[1,4,5]. Among HCT recipients, risk factors include antibiotic prophylaxis, graft-vs-host disease (GVHD), chemotherapy, mucositis, and increased rates of CD colonization[4,6]. The incidence of CDI in solid organ transplant (SOT) recipients varies based on the type of organ transplanted, with the lowest incidence in kidney transplant and highest in liver and lung transplant recipients[7,8].

Chimeric antigen receptor (CAR) T-cell therapy has resulted in unprecedented response rates among patients with B-cell hematologic malignancies (HMs)[9]. However, the on-target-off-tumor toxicities associated with CAR-T lead to significant morbidity and mortality. Prolonged cytopenia and B-cell aplasia, coupled with prolonged hypogammaglobulinemia, result in a heightened risk for infections for an extended duration[10]. Infections are one of the most common causes of death among CAR-T recipients, second only to disease relapse[11,12]. CDI remains a common infection among transplant and cellular therapy recipients[5,12]. However, the incidence, risk factors, and impact of CDI on CAR-T outcomes have never been examined. We estimated the cumulative incidence of CDI in CAR-T recipients at pre-defined time points, risk factors, and IRM in a disease-specific and tumor-associated antigen (TAA)-specific manner to aid in the development of risk-adapted infection prevention guidelines.
While there is no data related to the burden and mortality associated with CDI in CAR-T setting, our prior large CIBMTR analysis in 826 alloHCT recipients with CDI and 6723 controls from 127 centers showed a cumulative incidence of CDI by D+100 of 18.7% (99% CI: 15% – 22.7%) and 10.2% (99% CI: 9.2% – 11.1%) in pediatric and adult patients, respectively. CDI was associated with inferior overall survival (p=0.0018) and a 2.58-fold [99% CI: 1.43 – 4.66; p<0.001] increase in infection-related mortality. There was a significant overlap in the onset of GVHD and CDI. IRM increased to >4 fold when CDI + acute GVHD was considered[5]. Another prospective study across 4 US transplant centers in 444 recipients [14] demonstrated an incidence of 33% by 30 months[4].

The incidence of CDI in SOT recipients varies based on the type of organ transplanted, with kidney transplant recipients demonstrating the lowest incidence (1%–11%) and liver and lung transplant recipients experiencing the highest incidence (1%-19% and 2%-23%, respectively)[7,8,15,16]. Heart transplant recipients have a CDI incidence ranging from 1%-8%[17]. Regardless of organ transplanted, CDI incidence in

SOT is lower than that found in hematology-oncology patients, but still higher than in the general population[1].

## 5.0 Patient Eligibility Population:

Inclusion criteria:

1) Adult patients: 18-75 years of age.
2) First CAR T-cell therapy.
3) Patients with relapsed/refractory multiple myeloma who received BCMA-directed CAR-T (Ide-cel or cilta-cel).
4) Patients with Aggressive B cell NHL patients who underwent FDA-approved CD19 CAR T cell therapy.
5) Patients with R/R B-cell ALL (stratified into pediatric [2 – 18y] and adult (>18y)].
6) At least 2 prior lines of therapy.
7) No prior history of other CAR-T therapy

Exclusion criteria:

1) Patients < 2 years old
2) No consent for research
3) Clinical trial CAR-T, including out-of-specification products
4) Non-CD19 or BCMA-directed CAR-T.

## 6.0 Outcomes (Combined parts A & B):

***Primary Outcomes:***

- Cumulative incidence of CDI infection: This will be evaluated for CDI through day 100 after CAR T-cell infusion. This cumulative incidence will be studied separately for infections occurring during days 0-30 and days 31-100. Relapse/progressive disease and new anti-neoplastic treatment initiation (including hematopoietic cell transplantation) after CAR T-cell therapy are considered to be competing events for infection onset. Median times of all-cause and type-specific infections will be reported among infected patients. Separate estimates for pediatric (2 – 18y) and adult (>18y) patients

***Secondary Outcomes:***

- Non-relapse mortality (NRM): Cumulative incidence of NRM. NRM is defined as death without preceding disease relapse/progression. Relapse and progression are competing events.

- Infection density: Defined as the number of infections per patient days at risk. The densities of bacterial, viral, fungal, and all-cause infections will be studied separately over the time periods day 0-30, and day 31-100 from the time of CAR T-cell infusion. Infection density will also be evaluated pre- and post- ANC recovery. Infection density is the primary endpoint of the study.

- Infection-Related mortality (IRM) by 1 year: Cumulative incidence of death caused by infection. Relapse and death from non-infectious causes are competing events. This will be examined as a Dynamic landmark analysis at day 30, 60 and 100.
- Relapse/Progression by 1 year: Cumulative incidence of disease relapse/progression, with TRM as competing event. This will be examined as a dynamic landmark analysis for patients at day 30, 60 and 100.
- Progression-free survival by 1 year: will be defined as time to relapse or death from any cause. Patients are censored at last follow-up. This will be examined as a dynamic landmark analysis for patients at day 30, 60 and 100.
- Overall survival (OS) by 1 year: time to death. Death from any cause will be considered an event. Surviving patients will be censored at time of last follow-up. This will be examined as a dynamic landmark analysis for patients at day 30, 60 and 100.
- Cause of death by 1 year: descriptive only. This will include Primary cause of death and infection as a secondary COD
- Frequency of recurrent CDI by 1 year: descriptive only
- Frequency of Gram Negative BSI occurring ± 7 days of CDI: descriptive only

## 7.0 Variables to be described:

(**bolded variables** to be considered for multivariate analysis)

7.1 Patient-related:

- **Age at CAR-T:** continuous and categorical by decade
- **Gender: male vs. female**
- Body mass index: <30, 30-35, >35
- Race: White vs. African American vs. Asian vs. others vs missing
- Ethnicity: Hispanic or Latino vs non-Hispanic or non-Latino vs missing

- **Comorbid conditions** prior to CAR T cells according to HCT-CI: 0 vs. 1-2 vs. ≥3 vs. missing
- **Performance score** at CAR T cell infusion (KPS): < 90% vs. ≥90% vs. missing
- **ECOG Performance status**

7.2 CAR-T-related:

- **CAR-T product in 2L setting (BCMA vs CD19)**
- **Time from diagnosis to CAR-T**: 0-6 months vs. 6-12 months vs. 1-2 years vs. 2-3 years
- **Bridging Therapy: Yes vs. No (defined as therapy between leukapheresis and lymphodepletion)**
- Type of CAR-T lymphodepletion: FluCy vs. Bendamustine vs others
- **Lines of therapy: 2 vs ≥3 (details of therapies)**
- **Prior autoHCT**
- **Year of CAR-T: 2017-2023**
- **Year of CAR-T: 2017 vs. 2018 vs. 2019 vs 2020 vs 2021 vs 2022 vs 2023**
- Dose of CAR T-cell (if available)
- Cytokines, Maximum level within the first 100 days and time to maximum level (CRP, Ferritin).
- Exploratory variables:
- Best response to CAR T-cell therapy by IMWG/Lugano criteria:
- CR vs. Non-CR

7.3 Disease Related

**[Evaluate disease burden/status prior to LD. Nearly 20% of patients receive bridging therapy between leukapheresis and CAR-T infusion].**

**NHL:**

- NHL Disease classification (DLBCL, FL, MCL, Others)
- Stage at diagnosis I/II/III/IV
- **LDH prior to infusion: normal or elevated**
- CNS involvement Y/N
- Number of prior lines of therapy: 1, 2, >=3, missing
- **Disease status at CAR T cell infusion: CR, PR, resistant, untreated, unknown, not reported**

**MM:**

- Penta-exposed MM vs not
- Number of prior lines of therapy (continuous)
- Cytogenetics (High-risk vs Standard risk)
- ISS stage: stage I vs stage II vs. stage III vs missing
- Extramedullary disease: Yes vs no

Confidential CIBMTR Proposal: C. diff infection in CAR-T (MBA, MA et al)

- Bone marrow involvement prior to CAR-T (>50% plasma cells yes vs no)
- Presence of cytopenias prior to CAR-T (Yes vs No)
- Bridging therapy (Yes or No)

7.4 Time-dependent

- Neutrophil recovery prior to infection: Yes/No
- Median time to neutrophil recovery
- Neutrophil count at day 100
- Lymphocyte count at day 100
- Grade 4 organ toxicity prior to infection: Yes/No
- Median time to grade 4 toxicity
- Graft Versus Host Disease (for patients with prior alloHCT receiving allo-T-cells) prior to infection (after CAR T infusion): Yes/No
- Median onset of GVHD after CAR T
- CRS prior to infection: Yes/No
- CRS grade: (as a calculated variable)
- Median time to CRS
- ICANS prior to infection: Yes/No
- ICANS grade (as a calculated variable)
- Median time to ICANS
- Received steroids: Yes/No
- Received Tocilizumab: No vs. Yes
- Received Siltuximab: No vs. Yes
- Received Anakinra: No vs. Yes
- Relapse/Progression prior to infection: Yes/No (as a competing event)
- Time from last HCT to CT in months: <6mo, 6-<12mo, <=12mo
- Alive Status: Live vs. Death

## 8.0 Study Design:

This is a retrospective cohort analysis of data from the CIBMTR to estimate the burden of CDI and the NRM and its impact on CAR-T outcomes. Patients will be eligible if they satisfy the criteria detailed in the "Study population" section. The objective of this analysis is to study the impact of CDI on transplant outcomes by 1 year when compared to control cohort from the same center without documented CDI.

By using the dynamic landmark analysis, univariate analysis will be performed using Kaplan-Meier Method for OS and PFS.

Multivariable analyses will be performed using Cox proportional hazard model for OS, PFS, NRM, IRM, and relapse. The main effect of CDI versus No CDI will be kept in all models as time-dependent variable. The proportional hazards (PH) assumption for each factor in the Cox model will be tested. If some covariates violate the PH assumptions, time-dependent covariates will be added. A stepwise model selection procedure will be used to identify all significant risk factors. Potential interactions between main effect and significant covariates will be tested.

**9.0 Data Requirements:**
*If supplemental data is required, please review data collection forms at:*
*http://www.cibmtr.org/DataManagement/DataCollectionForms/Pages/index.aspx*

**This data needed for the study is available on form 4100, Q179-Q182.** *No supplemental data will be needed.*

**10.0 Request for Additional Data:**

- **Requested Data**: N/A

**11.0 Non-CIBMTR Data Source:** N/A

**12.0 Conflicts of Interest:** *No conflicts of interest related to this proposal.*

**13.0 Proposal submission: E-mail your observational study proposal to:**
proposals.cibmtr@mcw.edu

**14.0 References:**

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2. **Infectious Complications in Patients with Hematologic Malignancies Receiving CD19 Vs. BCMA Targeted CAR-T Therapy**

   **Abid, Dr. Muhammad Bilal et al.**

   **Transplantation and Cellular Therapy, Official Publication of the American Society for Transplantation and Cellular Therapy, Volume 30, Issue 2, S210 - S211**

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**2410-61 The Incidence and Impact of Clostridioides Difficile Infection on CAR-T Cell Therapy Outcomes – A CIBMTR Study**

**US adult patients aged 18-75 years with relapsed/refractory multiple myeloma who received first BCMA-directed CAR-T (Ide-cel or cilta-cel). And US patients aged 2-75 years with R/R B-cell ALL who received first CD19 CAR-T. And US adult patients aged 18-75 years with Aggressive B cell NHL patients who underwent FDA-approved CD19 CAR T cell therapy**

| Characteristic | CD19+CAR-T ALL | CD19+CAR-T NHL | BCMA ide-cel MM | BCMA cilta-cel MM |
|---|---|---|---|---|
| Number of patients | 818 | 4296 | 600 | 123 |
| No. of centers | 114 | 130 | 61 | 35 |
| **Patient related** | | | | |
| Level Age at CT Treatment - median (min-max) | 16.2 (2.0-72.3) | 62.2 (18.3-75.0) | 63.7 (29.3-74.9) | 64.9 (37.6-74.9) |
| Age group - no. (%) | | | | |
| <=10 | 215 (26.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 11-18 | 270 (33.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 19-30 | 260 (31.8) | 140 (3.3) | 1 (0.2) | 0 (0.0) |
| 31-40 | 25 (3.1) | 236 (5.5) | 3 (0.5) | 4 (3.3) |
| 41-50 | 13 (1.6) | 440 (10.2) | 38 (6.3) | 12 (9.8) |
| 51-60 | 18 (2.2) | 1021 (23.8) | 160 (26.7) | 35 (28.5) |
| 61-70 | 16 (2.0) | 1738 (40.5) | 282 (47.0) | 45 (36.6) |
| >70 | 1 (0.1) | 721 (16.8) | 116 (19.3) | 27 (22.0) |
| Age group - no. (%) | | | | |
| 2-18 | 485 (59.3) | NA | NA | NA |
| >=18 | 333 (40.7) | NA | NA | NA |
| Recipient Sex - no. (%) | | | | |
| Male | 498 (60.9) | 2706 (63.0) | 351 (58.5) | 65 (52.8) |
| Female | 320 (39.1) | 1590 (37.0) | 249 (41.5) | 58 (47.2) |

| Characteristic | CD19+CAR-T ALL | CD19+CAR-T NHL | BCMA ide-cel MM | BCMA cilta-cel MM |
|---|---|---|---|---|
| Recipient race - no. (%) | | | | |
| White | 582 (71.1) | 3472 (80.8) | 471 (78.5) | 95 (77.2) |
| Black or African American | 52 (6.4) | 260 (6.1) | 93 (15.5) | 17 (13.8) |
| Asian | 33 (4.0) | 231 (5.4) | 12 (2.0) | 1 (0.8) |
| Native Hawaiian or other Pacific Islander | 2 (0.2) | 9 (0.2) | 1 (0.2) | 0 (0.0) |
| American Indian or Alaska Native | 6 (0.7) | 18 (0.4) | 2 (0.3) | 0 (0.0) |
| Other | 22 (2.7) | 25 (0.6) | 3 (0.5) | 1 (0.8) |
| More than one race | 91 (11.1) | 209 (4.9) | 9 (1.5) | 7 (5.7) |
| Missing | 30 (3.7) | 72 (1.7) | 9 (1.5) | 2 (1.6) |
| Ethnicity - no. (%) | | | | |
| Hispanic or Latino | 360 (44.0) | 506 (11.8) | 44 (7.3) | 14 (11.4) |
| Not Hispanic or Latino | 425 (52.0) | 3619 (84.2) | 545 (90.8) | 104 (84.6) |
| Non-resident of the U.S. | 12 (1.5) | 37 (0.9) | 0 (0.0) | 0 (0.0) |
| Not reported | 21 (2.6) | 134 (3.1) | 11 (1.8) | 5 (4.1) |
| Karnofsky performance score prior to CT - no. (%) | | | | |
| 90-100 | 486 (59.4) | 1725 (40.2) | 206 (34.3) | 50 (40.7) |
| 80 | 153 (18.7) | 1274 (29.7) | 236 (39.3) | 45 (36.6) |
| < 80 | 129 (15.8) | 896 (20.9) | 129 (21.5) | 21 (17.1) |
| Not reported | 50 (6.1) | 401 (9.3) | 29 (4.8) | 7 (5.7) |
| ECOG performance status prior to CT - no. (%) | | | | |
| Asymptomatic | 486 (59.4) | 1725 (40.2) | 206 (34.3) | 50 (40.7) |
| Symptomatic but completely ambulatory | 239 (29.2) | 1975 (46.0) | 331 (55.2) | 60 (48.8) |
| Symptomatic,<50% in bed during the day | 39 (4.8) | 180 (4.2) | 31 (5.2) | 6 (4.9) |
| Symptomatic,>50% in bed,but not bedbound | 4 (0.5) | 13 (0.3) | 2 (0.3) | 0 (0.0) |
| Bedbound | 0 (0.0) | 2 (0.0) | 1 (0.2) | 0 (0.0) |
| Not reported | 50 (6.1) | 401 (9.3) | 29 (4.8) | 7 (5.7) |

| Characteristic | CD19+CAR-T ALL | CD19+CAR-T NHL | BCMA ide-cel MM | BCMA cilta-cel MM |
|---|---|---|---|---|
| **Infection** | | | | |
| Fungal - no. (%) | | | | |
| No | 797 (97.4) | 4174 (97.2) | 589 (98.2) | 122 (99.2) |
| Yes | 21 (2.6) | 122 (2.8) | 11 (1.8) | 1 (0.8) |
| Viral - no. (%) | | | | |
| No | 657 (80.3) | 3723 (86.7) | 503 (83.8) | 110 (89.4) |
| Yes | 161 (19.7) | 573 (13.3) | 97 (16.2) | 13 (10.6) |
| Bacterial - no. (%) | | | | |
| No | 676 (82.6) | 3681 (85.7) | 518 (86.3) | 107 (87.0) |
| Yes | 142 (17.4) | 615 (14.3) | 82 (13.7) | 16 (13.0) |
| C. Difficile | 50 | 150 | 26 | 6 |
| **Disease related** | | | | |
| Disease - no. (%) | | | | |
| Acute lymphoblastic leukemia (ALL) | 818 (100) | NA | NA | NA |
| Non-Hodgkin lymphoma (NHL) | NA | 4296 (100) | NA | NA |
| Plasma cell disorder/multiple myeloma (PCD/MM) | NA | NA | 600 (100) | 123 (100) |
| Year of CT - no. (%) | | | | |
| 2017 | 8 (1.0) | 4 (0.1) | 0 (0.0) | 0 (0.0) |
| 2018 | 104 (12.7) | 420 (9.8) | 0 (0.0) | 0 (0.0) |
| 2019 | 141 (17.2) | 788 (18.3) | 0 (0.0) | 0 (0.0) |
| 2020 | 127 (15.5) | 842 (19.6) | 0 (0.0) | 0 (0.0) |
| 2021 | 133 (16.3) | 829 (19.3) | 239 (39.8) | 0 (0.0) |
| 2022 | 187 (22.9) | 989 (23.0) | 317 (52.8) | 95 (77.2) |
| 2023 | 90 (11.0) | 417 (9.7) | 44 (7.3) | 15 (12.2) |
| 2024 | 28 (3.4) | 7 (0.2) | 0 (0.0) | 13 (10.6) |

| Field | Response |
|---|---|
| Proposal Number | 2410-137-SHAHID |
| Proposal Title | Impact of Letermovir Prophylaxis on the Epidemiology of CMV Infection Among Allogenic Hematopoietic Cellular Therapy Recipients Receiving Post-Transplant Cyclophosphamide |
| Key Words | Letermovir, CMV prophylaxis, early CMV infection, late CMV infection, post-transplant cyclophosphamide, hematopoietic cellular therapy recipients |
| Principal Investigator #1: - First and last name, degree(s) | Zainab Shahid |
| Principal Investigator #1: - Email address | shahidz@mskcc.org |
| Principal Investigator #1: - Institution name | Memorial Sloan Kettering Cancer Center |
| Principal Investigator #1: - Academic rank | Associated Attending |
| Junior investigator status (defined as ≤5 years from fellowship) | No |
| Do you identify as an underrepresented/minority? | Yes |
| Principal Investigator #2 (If applicable): - First and last name, degree(s): | Hemant Murthy |
| Principal Investigator #2 (If applicable): - Email address:) | murthy.hemant@mayo.edu |
| Principal Investigator #2 (If applicable): - Institution name: | Mayo Clinic Florida |
| Principal Investigator #2 (If applicable): - Academic rank: | Professor |
| Junior investigator status (defined as ≤5 years from fellowship) | No |
| Do you identify as an underrepresented/minority? | - |
| We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below: | shahidz@mskcc.org |
| If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below: | - |
| Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role. | I do not have any active studies with CIBMTR currently |
| Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months? | No |
| PROPOSED WORKING COMMITTEE: | Infection and Immune Reconstitution |
| Please indicate if you have already spoken with a scientific director or working committee chair regarding this study. | Yes |
| If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who: | Hemant Murthy |

| Field | Response |
|---|---|
| RESEARCH QUESTION: | • What is the impact of letermovir prophylaxis on the epidemiology of Cytomegalovirus (CMV) infection (both in early and late risk periods) among allogeneic hematopoietic cell therapy (HCT) recipients receiving post-transplant cyclophosphamide as graft vs. host disease (GvHD) prophylaxis in the real world? • What is the impact of letermovir prophylaxis on non-CMV-related clinical outcomes in post Tx- Cy settings? |
| RESEARCH HYPOTHESIS: | Post-transplant CMV prophylaxis with Letermovir has changed the epidemiology of CMV disease after HCT. Letermovir prophylaxis is approved for CMV seropositive recipients (R+) with a high risk of CMV reactivation. It has now become standard of care to implement post-transplant CMV prophylaxis with letermovir for the first 100 days to prevent clinically significant CMV disease. However, CMV prophylaxis among CMV (R+) recipients is not universal and many centers report difficulty obtaining insurance clearance for letermovir. Post-transplant Cyclophosphamide (post-Tx Cy) is gradually becoming the standard of care for GvHD prophylaxis, and it is associated with a high risk of CMV infection. Because of the increased CMV risk patients receiving post-Tx Cy are placed on Letermovir for the first 100 days to prevent CMV-associated morbidity. We aim to study differences in the epidemiology of CMV infection among CMV R+ HCT recipients receiving post-transplant cyclophosphamide on letermovir prophylaxis with CMV R+ HCT recipients not receiving CMV prophylaxis in the real-world setting and its impact on clinical outcomes such as non-relapse mortality and overall survival. We hypothesize that CMV prophylaxis will impact short-term and long-term clinical outcomes, affecting not only CMV-related but also CMV-unrelated complications. |

| Field | Response |
|---|---|
| SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.): | Primary Objective - To study the incidence of CMV infection among CMV R+ HCT recipients receiving post-TX Cy as GvHD prophylaxis both in the absence and presence of CMV prophylaxis Secondary Objective - To evaluate differences in the epidemiology of early and late CMV infection in the presence and absence of CMV prophylaxis - To study the risk factors associated with early and late CMV infection (day 100, 180, and 365) with or without CMV prophylaxis in different transplant settings utilizing post-Tx Cy as GvHD prophylaxis. - To study the differences in the epidemiology of other viral reactivation among the two comparator groups - To study the impact of CMV infection on clinical overall survival and non-relapse mortality in the study population |
| SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care. | The results from our proposed study will provide an opportunity to analyze a multicenter large cohort of allogeneic HCT recipients receiving post-Tx Cy to better understand the impact of CMV prophylaxis on the epidemiology of early and late CMV infection. The risk assessment analysis generated with this study will help identify risk factors for CMV infections in the post-Tx cy settings. The results from the study will enhance our understanding of CMV infection with the current transplant modalities and will help establish further guidelines to improve CMV prophylaxis strategies. |

| Field | Response |
|---|---|
| SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary. | Utilization of posttransplant cyclophosphamide is associated with increased risk of CMV infection1,2. Letermovir for CMV prophylaxis showed a significantly reduced risk of clinically significant CMV infection3. CMV prophylaxis has changed the epidemiology of CMV infection. Breakthrough infections are uncommon and post-prophylaxis CMV reactivation is not uncommon4. Letermovir prophylaxis practices across different institutions can be variable. Single-center studies have reported CMV-related morbidity and overall mortality benefits; however, this has not been validated in large multicenter studies and the results are conflicting5-8. Importantly, early Letermovir studies did not include patients receiving post-transplant cyclophosphamide, and later studies are limited9,10. This highlights the critical need to address this gap in current research. Results from our study will allow us to understand the role of CMV prophylaxis and help guide future prophylaxis strategies for patients receiving post-transplant cyclophosphamide for GvHD prophylaxis. |
| PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria. | Inclusion criteria: All patients who have received allogeneic hematopoietic cell transplantation who received post-transplant cyclophosphamide as GvHD prophylaxis and are CMV seropositive (R+) between 2022 and 2024. Exclusion criteria: Relapse or death in the first 6 months post HCT. |
| Does this study include pediatric patients? | No |
| If this study does not include pediatric patients, please provide justification: | Letermovir was just approved for the pediatric population. The number might be too low. |

| Field | Response |
|---|---|
| DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required. | The following variables will need to be collected. Patient-related: • Age at transplant • Gender: male vs. female • Karnofsky performance status at transplant: ≥ 90 vs. < 90 vs. missing • Race: Caucasian vs. others vs. missing • Ethnicity • Recipient CMV serostatus Transplant Course: • Letermovir prophylaxis yes vs no • CMV reactivation yes vs no • CMV end-organ disease yes vs no • CMV treatment detail if available • HHV-6 reactivation: yes vs. no • AKI yes vs no • CD4 count at day 100, 180, 365 • ALC at 100, 180 and 365 • IgG at 100, 180 and 365 Disease-related: • Underlying malignancy • Time from diagnosis to transplantation • Disease state at the time of transplant: CR vs Cri vs PR vs SD Transplant-related: • Graft source: peripheral blood vs bone marrow vs cord blood • Transplant donor type: Match related donor vs. match unrelated donor vs. mismatch unrelated donor vs. haploidentical • Conditioning intensity: myeloablative vs. reduced intensity conditioning/ non-myeloablative • Total Body Irradiation: TBI vs non-TBI based conditioning regimen. • Graft manipulation (ex-vivo TCD, CD34 selection)- yes vs no • GVHD prophylaxis • ATG/alemtuzumab use in conditioning: no vs. yes • Donor-recipient sex match: male-male vs. male-female vs. female-male vs. female-female vs. missing • CMV serostatus of the donor • Year of transplant: Continuous • GvHD grade II-IV yes vs no |
| Types of cellular therapy data this proposal includes: | Hematopoietic Cell Transplantation (HCT) |
| PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis speci | NA |
| MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions. | NA |

| Field | Response |
|---|---|
| SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous e | NA |
| NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required. | NA |

| | |
|---|---|
| REFERENCES: | 1. Sadowska-Klasa A, Özkök S, Xie H, et al. Late cytomegalovirus disease after hematopoietic cell transplantation: significance of novel transplantation techniques. Blood Adv. Jul 23 2024;8(14):3639-3651. doi:10.1182/bloodadvances.2023012175 2. Goldsmith SR, Abid MB, Auletta JJ, et al. Posttransplant cyclophosphamide is associated with increased cytomegalovirus infection: a CIBMTR analysis. Blood. Jun 10 2021;137(23):3291-3305. doi:10.1182/blood.2020009362 3. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. N Engl J Med. Dec 21 2017;377(25):2433-2444. doi:10.1056/NEJMoa1706640 4. Chen K, Arbona-Haddad E, Cheng MP, et al. Cytomegalovirus events in high-risk allogeneic hematopoietic-cell transplantation patients who received letermovir prophylaxis. Transpl Infect Dis. Aug 2021;23(4):e13619. doi:10.1111/tid.13619 5. Ljungman P, Schmitt M, Marty FM, et al. A Mortality Analysis of Letermovir Prophylaxis for Cytomegalovirus (CMV) in CMV-seropositive Recipients of Allogeneic Hematopoietic Cell Transplantation. Clin Infect Dis. Apr 10 2020;70(8):1525-1533. doi:10.1093/cid/ciz490 6. Febres-Aldana A, Khawaja F, Morado-Aramburo O, et al. Mortality in recipients of allogeneic haematopoietic cell transplantation in the era of cytomegalovirus primary prophylaxis: a single-centre retrospective experience. Clin Microbiol Infect. Jun 2024;30(6):803-809. doi:10.1016/j.cmi.2024.03.001 7. Pang I, Chen P, Trinh GV, et al. Letermovir prophylaxis for cytomegalovirus reactivation in allogeneic hematopoietic cell transplant recipients: Single center Canadian data. Eur J Haematol. Feb 2024;112(2):301-309. doi:10.1111/ejh.14117 8. Toya T, Mizuno K, Sakurai M, et al. Differential clinical impact of letermovir prophylaxis according to graft sources: a KSGCT multicenter retrospective analysis. Blood Adv. Mar 12 2024;8(5):1084-1093. doi:10.1182/bloodadvances.2023010735 9. Nguyen A, Bubalo JS, Saultz JN, et al. Breakthrough CMV Viremia Outcomes of Letermovir Prophylaxis in Haploidentical Stem Cell Transplant with Post-Transplant Cyclophosphamide. Blood. 2022;140(Supplement 1):12856-12858. doi:10.1182/blood-2022-156011 10. Jamy O, Hebert C, Dunn-Valadez S, Magnusson T, Watts N, McGwin G, |

| Field | Response |
|---|---|
| | Saad A. Risk of Cytomegalovirus Infection with Post-Transplantation Cyclophosphamide in Haploidentical and HLA-Matched Unrelated Donor Transplantation. Transplantation and Cellular Therapy. 2022/04/01/ 2022;28(4):213.e1-213.e6. doi:https://doi.org/10.1016/j.jtct.2022.01.011 |
| CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning? | No, I do not have any conflicts of interest pertinent to this proposal |
| If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually. | - |

**2410-137 Impact of Letermovir Prophylaxis on the Epidemiology of CMV Infection Among Allogenic Hematopoietic Cellular Therapy Recipients Receiving Post-Transplant Cyclophosphamide**

**US patients who underwent their first allogeneic transplant between 2022 and 2024, received post-transplant cyclophosphamide for GvHD prophylaxis, were CMV R+, and did not relapse or die within six months post-transplant**

| Characteristic | Not received letermovir | Received letermovir |
|---|---|---|
| Number of patients | 160 | 458 |
| No. of centers | 69 | 99 |
| **Patient related** | | |
| Age at HCT - no. (%) | | |
| Median (min-max) | 43.2 (0.3-77.9) | 58.0 (3.2-79.0) |
| <18 | 43 (26.9) | 19 (4.1) |
| 18 to 49 | 48 (30.0) | 144 (31.4) |
| 50 to 65 | 34 (21.3) | 164 (35.8) |
| >=65 | 35 (21.9) | 131 (28.6) |
| Sex - no. (%) | | |
| Male | 90 (56.3) | 235 (51.3) |
| Female | 70 (43.8) | 223 (48.7) |
| Race - no. (%) | | |
| White | 86 (53.8) | 296 (64.6) |
| Black or African American | 37 (23.1) | 85 (18.6) |
| Asian | 14 (8.8) | 41 (9.0) |
| Native Hawaiian or other Pacific Islander | 1 (0.6) | 2 (0.4) |
| American Indian or Alaska Native | 2 (1.3) | 1 (0.2) |
| More than one race | 4 (2.5) | 6 (1.3) |
| Not reported | 16 (10.0) | 27 (5.9) |
| Ethnicity - no. (%) | | |
| Hispanic or Latino | 32 (20.0) | 79 (17.2) |
| Non Hispanic or non-Latino | 117 (73.1) | 365 (79.7) |
| Non-resident of the U.S. | 1 (0.6) | 2 (0.4) |
| Not reported | 10 (6.3) | 12 (2.6) |
| Karnofsky score prior to HCT - no. (%) | | |
| 90-100% | 79 (49.4) | 234 (51.1) |
| < 90% | 68 (42.5) | 223 (48.7) |
| Not reported | 13 (8.1) | 1 (0.2) |
| HCT-CI - no. (%) | | |
| 0 | 52 (32.5) | 96 (21.0) |
| 1 | 25 (15.6) | 79 (17.2) |

| Characteristic | Not received letermovir | Received letermovir |
|---|---|---|
| 2 | 18 (11.3) | 85 (18.6) |
| 3+ | 63 (39.4) | 195 (42.6) |
| Not reported | 2 (1.3) | 3 (0.6) |
| **Disease related** | | |
| Primary disease - no. (%) | | |
| Leukemia | 77 (48.1) | 245 (53.5) |
| Lymphoma | 11 (6.9) | 29 (6.3) |
| MDS/MNP | 20 (12.5) | 102 (22.3) |
| Non-malignant disorders | 52 (32.5) | 82 (17.9) |
| Leukemia | 77 (48.1) | 245 (53.5) |
| Time from diagnosis to transplant, month - median (min-max) | 8.5 (1.5-459.5) | 9.7 (0.2-571.0) |
| **Infection related** | | |
| Was letermovir (Prevymis) given as prophylaxis? - no. (%) | | |
| No | 146 (91.3) | 0 (0.0) |
| Yes | 0 (0.0) | 458 (100) |
| Not reported/Other prophylaxis given | 14 (8.8) | 0 (0.0) |
| CMV reactivation - no. (%) | | |
| No | 124 (77.5) | 394 (86.0) |
| Yes | 36 (22.5) | 64 (14.0) |
| HHV-6 - no. (%) | | |
| Yes | 10 (6.3) | 31 (6.8) |
| No | 150 (93.8) | 427 (93.2) |
| **Transplant related** | | |
| Product type - no. (%) | | |
| BM | 51 (31.9) | 66 (14.4) |
| PBSC | 109 (68.1) | 391 (85.4) |
| UCB | 0 (0.0) | 1 (0.2) |
| Donor CMV-antibodies (IgG or Total) - no. (%) | | |
| Negative | 76 (47.5) | 193 (42.1) |
| Positive | 83 (51.9) | 262 (57.2) |
| Not reported | 1 (0.6) | 3 (0.7) |
| Donor type - no. (%) | | |
| HLA identical sibling | 15 (9.4) | 43 (9.4) |
| Haploidentical donor | 60 (37.5) | 115 (25.1) |
| Other related | 1 (0.6) | 4 (0.9) |
| Well-matched unrelated(8/8) | 37 (23.1) | 121 (26.4) |
| Partially matched unrelated(7/8) | 38 (23.8) | 149 (32.5) |
| Mismatched unrelated(<=6/8) | 5 (3.1) | 20 (4.4) |

| Characteristic | Not received letermovir | Received letermovir |
|---|---|---|
| Multi-donor | 1 (0.6) | 2 (0.4) |
| Unrelated (matching cannot be determined) | 3 (1.9) | 3 (0.7) |
| Cord blood | 0 (0.0) | 1 (0.2) |
| Classify the recipient's prescribed preparative regimen - no. (%) | | |
| Myeloablative | 56 (35.0) | 141 (30.8) |
| Non-myeloablative (NST) | 33 (20.6) | 77 (16.8) |
| Reduced intensity (RIC) | 70 (43.8) | 238 (52.0) |
| Not reported | 1 (0.6) | 2 (0.4) |
| Was irradiation performed as part of the pre-HCT preparative regimen? - no. (%) | | |
| No | 82 (51.3) | 213 (46.5) |
| Yes | 77 (48.1) | 238 (52.0) |
| Not reported | 1 (0.6) | 7 (1.5) |
| Given radiation field (2000) - no. (%) | | |
| TBI | 77 (48.1) | 235 (51.3) |
| IMRT | 0 (0.0) | 3 (0.7) |
| Not reported | 83 (51.9) | 220 (48.0) |
| GVHD prophylaxis - no. (%) | | |
| CD34 selection | 1 (0.6) | 2 (0.4) |
| PtCy | 159 (99.4) | 456 (99.6) |
| ATG/Campath - no. (%) | | |
| ATG alone | 44 (27.5) | 69 (15.1) |
| CAMPATH alone | 8 (5.0) | 2 (0.4) |
| No ATG or CAMPATH | 108 (67.5) | 387 (84.5) |
| Recipient CMV-antibodies (IgG or Total) - no. (%) | | |
| Positive | 160 (100) | 458 (100) |
| Donor CMV-antibodies (IgG or Total) - no. (%) | | |
| Negative | 76 (47.5) | 192 (41.9) |
| Positive | 83 (51.9) | 262 (57.2) |
| Not reported | 1 (0.6) | 4 (0.8) |
| Year of current transplant - no. (%) | | |
| 2022 | 85 (53.1) | 215 (46.9) |
| 2023 | 75 (46.9) | 243 (53.1) |

| Field | Response |
|---|---|
| Proposal Number | 2410-141-SHAHID |
| Proposal Title | Epidemiology of Respiratory Virus Infections among Hematopoietic Cellular Therapy and Chimeric Antigen Receptor T-cell Therapy Recipients in the Post COVID-19 and Respiratory Syncytial Virus Vaccine Era |
| Key Words | Respiratory Virus Infections, Hematopoietic Cellular Therapy, CAR T-cell therapy |
| Principal Investigator #1: - First and last name, degree(s) | Zainab Shahid |
| Principal Investigator #1: - Email address | shahidz@mskcc.org |
| Principal Investigator #1: - Institution name | Memorial Sloan Kettering Cancer Center |
| Principal Investigator #1: - Academic rank | Associated Attending |
| Junior investigator status (defined as ≤5 years from fellowship) | No |
| Do you identify as an underrepresented/minority? | Yes |
| Principal Investigator #2 (If applicable): - First and last name, degree(s): | Hemant Murthy |
| Principal Investigator #2 (If applicable): - Email address:) | murthy.hemant@mayo.edu |
| Principal Investigator #2 (If applicable): - Institution name: | Mayo Clinic Florida |
| Principal Investigator #2 (If applicable): - Academic rank: | Professor of Medicine |
| Junior investigator status (defined as ≤5 years from fellowship) | No |
| Do you identify as an underrepresented/minority? | - |
| We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below: | shahidzQmskcc.org |
| If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below: | - |
| Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role. | NA |
| Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months? | No |
| PROPOSED WORKING COMMITTEE: | Infection and Immune Reconstitution |
| Please indicate if you have already spoken with a scientific director or working committee chair regarding this study. | Yes |
| If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who: | Hemant Murthy |

| Field | Response |
|---|---|
| RESEARCH QUESTION: | - What is the epidemiology of respiratory virus infections (RVIs) among hematopoietic cellular therapy (HCT) and chimeric antigen receptor (CAR) T-cell therapy patients in the post-COVID-19 pandemic and respiratory syncytial virus (RSV) vaccine era? - What is the impact of RVI on clinical outcomes among HCT and CAR-T cell therapy recipients? |
| RESEARCH HYPOTHESIS: | The impact of SARS-CoV-2's emergence as a community virus, along with the availability of vaccines against SARS-CoV-2 and RSV, on the epidemiology of respiratory virus infections (RVIs) among hematopoietic cell transplant (HCT) and CAR T-cell therapy recipients remains largely unknown. We hypothesize that the epidemiology of RVIs in these patient populations has evolved over the past 4 years. This study aims to investigate the shifting landscape of RVI epidemiology during the first-year post-transplant, examining how these changes may influence infection patterns and outcomes. |
| SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.): | Primary Objective: To study the epidemiology of different respiratory viruses post-HCT and CAR T-cell Secondary Objectives To study the severity of different RVIs post HCT and CAR T. To Identify risk factors associated with severe RVIs among HCT and CAR T recipients To study overall survival and non-relapse mortality among patients with RVIs To assess the mortality associated with RVIs To study to correlate the severity of infection with time from transplantation or infusion. To study immune correlates of RVI post-HCT and CAR T cell therapy |
| SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care. | . This study aims to bridge the current knowledge gap, shedding light on the distribution and clinical impact of RVIs in this high-risk population during the post-pandemic era. We aim to inform clinical decision-making and infection prevention strategies. The findings of this study will improve clinical outcomes among HCT and CAR T-cell therapy recipients. |

| Field | Response |
|---|---|
| SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary. | Respiratory viral infections (RVIs) represent a substantial risk to patients with hematologic malignancies (HM), particularly those who have undergone hematopoietic stem cell transplants (HCT) or received chimeric antigen receptor (CAR) T-cell therapy. The COVID-19 pandemic has intensified the burden of RVIs within these vulnerable populations. However, the post-pandemic landscape of RVIs remains poorly understood. Factors such as altered masking behaviors, expanded availability of molecular testing for RVIs, and diverse preventative practices across communities, combined with rising vaccine hesitancy, contribute to an evolving epidemiology of these infections. The impact of these shifts on the epidemiology of RVIs and the relative contribution of each virus in this highly susceptible patient group remains unclear. Historically, respiratory syncytial virus has been the predominant RVI in these populations. The recent approval of an RSV vaccine in 2023 highlights the need to assess its impact on RVI epidemiology. At present, FDA-approved vaccines are available for three key respiratory viruses: Influenza, SARS-CoV-2, and RSV. Thoroughly understanding the infection patterns and disease burden among HM patients is essential for developing targeted mitigation strategies and enhancing vaccine advocacy |
| PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria. | Inclusions Criteria: Patients diagnosed with RVIs receiving CAR-T cell therapy and HCT starting Jan 2022 –Dec 2024 that are alive at one-year post infusion. |
| Does this study include pediatric patients? | No |
| If this study does not include pediatric patients, please provide justification: | NA |

| | |
|---|---|
| DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required. | We hope to capture two respiratory viral seasons for this study: 2022-2023, and 2023-24. Dataline variables: Patient-related: • Age at transplant • Gender • Race • Ethnicity • HCT comorbidity index • Gender: male vs. female • Karnofsky performance status at transplant: ≥ 90 vs. < 90 vs. missing • Race: Caucasian vs. others vs. missing • Ethnicity Transplant Course: • RVI yes, no • CMV reactivation: yes vs. no • HHV-6 reactivation: yes vs. no • AKI yes vs no • CD4 at day 100, 180, 365 • ALC at day 100, 180, 365 • WBC at day 100,180,365 • IgG at day 100, 180,365 Disease-related: • Underlying malignancy • Time from diagnosis to transplantation • Disease state at the time of transplant: CR vs Cri vs PR vs SD Transplant-related: • Transplant type: Auto vs. Allo • Graft source: peripheral blood vs bone marrow vs cord blood • Transplant donor type: Match related donor vs. match unrelated donor vs. mismatch unrelated donor vs. haploidentical • Conditioning intensity: myeloablative vs. reduced intensity conditioning/ non-myeloablative • Total Body Irradiation: TBI vs non-TBI based conditioning regimen. • Graft manipulation (ex-vivo TCD, CD34 selection)- yes vs no • GVHD prophylaxis: CNI + MTX ± others except MMF, post Cy vs. CNI + MMF ±others except post Cy vs. CNI + others except MMF, MTX vs. missing vs. other • ATG/alemtuzumab use in conditioning: no vs. yes • Donor-recipient sex match: male-male vs. male-female vs. female-male vs. female-female vs. missing • CMV serostatus matching (+/-, +/+, -/-, -/+) between donor and recipient. • Year of transplant: Continuous • GvHD grade II-IV yes vs no CAR T related: • CRS Yes vs no • ICANS yes vs no • Steroids given yes vs no • In remission at 1 year yes vs no Respiratory Viral Infections: • RVI date • Name of the Respiratory virus • Upper vs Lower: CXR vs CT chest findings • Systemic steroids use in the past 30 days: yes/no • Hospitalization: yes/no • Supplemental oxygen: yes/no • Intubation yes/no • Death: yes/no • Date of death Lab data at the time of RVI diagnosis +/- 7 days: |

| Field | Response |
|---|---|
| | • ANC • ALC • IgG • CD4 • Creatinine • GFR |
| Types of cellular therapy data this proposal includes: | Chimeric Antigen Receptor (CAR) T-Cell Therapy (CAR-T) |
| PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis speci | NA |
| MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions. | NA |
| SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous e | NA |
| NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required. | NA- Please note that this study includes both HCT and CAR-T patients. I was unable to pick both choices. |

| | |
|---|---|
| REFERENCES: | 1. Pochon C, Voigt S. Respiratory Virus Infections in Hematopoietic Cell Transplant Recipients. Front Microbiol. 2019 Jan 9;9:3294. doi: 10.3389/fmicb.2018.03294. PMID: 30687278; PMCID: PMC6333648. 2. Infante MS, Nemirovsky D, Devlin S, DeWolf S, Tamari R, Dahi PB, Lee YJ, Chung DJ, Politikos I, Barker J, Giralt SA, Babady NE, Ramanathan L, Papanicolaou GA, Seo S, Kamboj M, Perales MA, Shah GL. Outcomes and Management of the SARS-CoV2 Omicron Variant in Recipients of Hematopoietic Cell Transplantation and Chimeric Antigen Receptor T Cell Therapy. Transplant Cell Ther. 2024 Jan;30(1):116.e1-116.e12. doi: 10.1016/j.jtct.2023.09.027. Epub 2023 Oct 6. PMID: 37806446; PMCID: PMC11220618. 3. Waghmare A, Campbell AP, Xie H, Seo S, Kuypers J, Leisenring W, Jerome KR, Englund JA, Boeckh M. Respiratory syncytial virus lower respiratory disease in hematopoietic cell transplant recipients: viral RNA detection in blood, antiviral treatment, and clinical outcomes. Clin Infect Dis. 2013 Dec;57(12):1731-41. doi: 10.1093/cid/cit639. Epub 2013 Sep 24. PMID: 24065324; PMCID: PMC3840404. 4. Kim YJ, Guthrie KA, Waghmare A, Walsh EE, Falsey AR, Kuypers J, Cent A, Englund JA, Boeckh M. Respiratory syncytial virus in hematopoietic cell transplant recipients: factors determining progression to lower respiratory tract disease. J Infect Dis. 2014 Apr 15;209(8):1195-204. doi: 10.1093/infdis/jit832. Epub 2013 Dec 23. PMID: 24368837; PMCID: PMC3969549. 5. Ison MG, Marty FM, Chao N, Moon SH, Zhang Z, Chandak A. Economic and clinical burden associated with respiratory viral infections after allogeneic hematopoietic cell transplant in the United States. Transpl Infect Dis. 2022 Aug;24(4):e13866. doi: 10.1111/tid.13866. Epub 2022 Jun 1. PMID: 35598293; PMCID: PMC9542538. 6. Sheshadri A, Chemaly RF, Alousi AM, Shah PK, Rondon G, Bashoura L, Kmeid J, Azzi J, Blanco DW, Kaous M, Dickey BF, Champlin RE, Shah DP. Pulmonary Impairment after Respiratory Viral Infections Is Associated with High Mortality in Allogeneic Hematopoietic Cell Transplant Recipients. Biol Blood Marrow Transplant. 2019 Apr;25(4):800-809. doi: 10.1016/j.bbmt.2018.11.022. Epub 2018 Dec 3. PMID: 30521974; PMCID: PMC6453743. 7. Wilson Dib R, Ariza-Heredia E, Spallone A, Chemaly RF. Respiratory Viral Infections in Recipients of Cellular Therapies: A Review of Incidence, Outcomes, Treatment, and Prevention. Open Forum Infect Dis. 2023 Mar |

| Field | Response |
|---|---|
| | 25;10(4):ofad166. doi: 10.1093/ofid/ofad166. PMID: 37065990; PMCID: PMC10096899. 8. Little JS, Tandon M, Hong JS, Nadeem O, Sperling AS, Raje N, Munshi N, Frigault M, Barmettler S, Hammond SP. Respiratory infections predominate after day 100 following B-cell maturation antigen-directed CAR T-cell therapy. Blood Adv. 2023 Sep 26;7(18):5485-5495. doi: 10.1182/bloodadvances.2023010524. PMID: 37486599; PMCID: PMC10514400. 9. Versluys AB, Boelens JJ. Morbidity and Mortality Associated With Respiratory Virus Infections in Allogeneic Hematopoietic Cell Transplant: Too Little Defense or Harmful Immunity? Front Microbiol. 2018 Nov 21;9:2795. doi: 10.3389/fmicb.2018.02795. PMID: 30519222; PMCID: PMC6258814. 10. Hutspardol S, Essa M, Richardson S, Schechter T, Ali M, Krueger J, Fujii H, Egeler RM, Gassas A. Significant Transplantation-Related Mortality from Respiratory Virus Infections within the First One Hundred Days in Children after Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2015 Oct;21(10):1802-7. doi: 10.1016/j.bbmt.2015.06.015. Epub 2015 Jun 25. PMID: 26117558; PMCID: PMC7110880. 11. Campbell AP, Guthrie KA, Englund JA, Farney RM, Minerich EL, Kuypers J, Corey L, Boeckh M. Clinical outcomes associated with respiratory virus detection before allogeneic hematopoietic stem cell transplant. Clin Infect Dis. 2015 Jul 15;61(2):192-202. doi: 10.1093/cid/civ272. Epub 2015 Apr 5. Erratum in: Clin Infect Dis. 2015 Nov 15;61(10):1635. doi: 10.1093/cid/civ800. PMID: 25847977; PMCID: PMC4565994. |
| CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning? | No, I do not have any conflicts of interest pertinent to this proposal |
| If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually. | - |

**2410-141 Epidemiology of Respiratory Virus Infections among Hematopoietic Cellular Therapy and Chimeric Antigen Receptor T-cell Therapy Recipients in the Post COVID-19 and Respiratory Syncytial Virus Vaccine Era**

**US adult patients underwent first HCT/CAR-T in 2022-2024 diagnosed with RVIs* with any disease and at least 1-year follow up**

| Characteristic | HCT | CAR-T |
|---|---|---|
| Number of patients | 109 | 106 |
| No. of centers | 48 | 53 |
| **Patient related** | | |
| Age at HCT - no. (%) | | |
| Median (min-max) | 52.5 (18.1-76.0) | 64.4 (20.6-91.2) |
| 18 to 49 | 52 (47.7) | 20 (18.9) |
| 50 to 65 | 32 (29.4) | 35 (33.0) |
| >=65 | 25 (22.9) | 51 (48.1) |
| Sex - no. (%) | | |
| Male | 61 (56.0) | 66 (62.3) |
| Female | 48 (44.0) | 40 (37.7) |
| Race - no. (%) | | |
| White | 69 (63.3) | 78 (73.6) |
| Black or African American | 17 (15.6) | 14 (13.2) |
| Asian | 4 (3.7) | 5 (4.7) |
| Native Hawaiian or other Pacific Islander | 3 (2.8) | 0 (0.0) |
| Other | 0 (0.0) | 3 (2.8) |
| More than one race | 4 (3.7) | 3 (2.8) |
| Not reported | 12 (11.0) | 3 (2.8) |
| Ethnicity - no. (%) | | |
| Hispanic or Latino | 25 (22.9) | 20 (18.9) |
| Non-Hispanic or non-Latino | 80 (73.4) | 86 (81.1) |
| Non-resident of the U.S. | 3 (2.8) | 0 (0.0) |
| Not reported | 1 (0.9) | 0 (0.0) |
| Current CCN region of patient - no. (%) | | |
| US | 109 (100) | 106 (100) |
| Karnofsky score prior to HCT - no. (%) | | |
| 90-100% | 51 (46.8) | 37 (34.9) |
| < 90% | 54 (49.5) | 60 (56.6) |
| Not reported | 4 (3.7) | 9 (8.5) |
| HCT/CT-CI - no. (%) | | |
| 0 | 17 (15.6) | 28 (26.4) |
| 1 | 21 (19.3) | 24 (22.6) |

| Characteristic | HCT | CAR-T |
|---|---|---|
| 2 | 22 (20.2) | 12 (11.3) |
| 3+ | 49 (45.0) | 42 (39.6) |
| **Disease related** | | |
| Primary disease - no. (%) | | |
| Leukemia | 54 (49.5) | 8 (7.5) |
| Lymphoma | 13 (11.9) | 62 (58.5) |
| Myeloma/Plasma Cell Disorder | 10 (9.2) | 36 (34.0) |
| MDS/MNP | 13 (11.9) | 0 (0.0) |
| Non-malignant disorders | 19 (17.4) | 0 (0.0) |
| Time from diagnosis to transplant/CAR-T, month - median (min-max) | 8.7 (3.0-400.5) | 42.1 (1.5-240.5) |
| **Infection related** | | |
| CMV reactivation - no. (%) | | |
| No | 90 (82.6) | 95 (89.6) |
| Yes | 19 (17.4) | 11 (10.4) |
| HHV-6 - no. (%) | | |
| No | 96 (88.1) | 106 (100) |
| Yes | 13 (11.9) | 0 (0.0) |
| **Transplant related** | | |
| Auto/Allo/CAR-T - no. (%) | | |
| Allogeneic | 94 (86.2) | NA |
| Autologous | 15 (13.8) | NA |
| CAR-T | NA | 106 (100) |
| Product type - no. (%) | | |
| BM | 15 (13.8) | NA |
| PBSC | 93 (85.3) | NA |
| UCB | 1 (0.9) | NA |
| Donor type - no. (%) | | |
| Cord blood | 15 (13.8) | NA |
| HLA identical sibling | 11 (10.1) | NA |
| Haploidentical donor | 12 (11.0) | NA |
| Other related | 1 (0.9) | NA |
| Well-matched unrelated(8/8) | 25 (22.9) | NA |
| Partially matched unrelated(7/8) | 14 (12.8) | NA |
| Multi-donor | 30 (27.5) | NA |
| Cord blood | 1 (0.9) | NA |
| Classify the recipient’s prescribed preparative regimen - no. (%) | | |
| Myeloablative | 26 (23.9) | NA |
| Non-myeloablative (NST) | 18 (16.5) | NA |
| Reduced intensity (RIC) | 50 (45.9) | NA |

| Characteristic | HCT | CAR-T |
|---|---|---|
| Was irradiation performed as part of the pre-HCT preparative regimen? - no. (%) | | |
| No | 67 (61.5) | NA |
| Yes | 42 (38.5) | NA |
| Given radiation field (2000) - no. (%) | | |
| TBI | 42 (38.5) | NA |
| Not reported | 67 (61.5) | NA |
| GVHD prophylaxis - no. (%) | | |
| None | 16 (14.7) | NA |
| CD34 selection | 1 (0.9) | NA |
| PtCy | 54 (49.5) | NA |
| TAC based | 33 (30.3) | NA |
| CSA based | 4 (3.7) | NA |
| Other | 1 (0.9) | NA |
| ATG/Campath - no. (%) | | |
| ATG alone | 18 (16.5) | NA |
| CAMPATH alone | 5 (4.6) | NA |
| No ATG or CAMPATH | 86 (78.9) | NA |
| Recipient CMV-antibodies (IgG or Total) - no. (%) | | |
| Negative | 23 (21.1) | NA |
| Positive | 84 (77.1) | NA |
| Not reported | 2 (1.8) | NA |
| Donor CMV-antibodies (IgG or Total) - no. (%) | | |
| Negative | 47 (43.1) | NA |
| Positive | 47 (43.1) | NA |
| Year of current transplant - no. (%) | | |
| 2022 | 86 (78.9) | NA |
| 2023 | 23 (21.1) | NA |
| **CAR-T related** | | |
| CRS (during follow-up for this CT) - no. (%) | | |
| No | NA | 14 (13.2) |
| Yes | NA | 92 (86.8) |
| Neurotoxicity (during follow-up for this CT) - no. (%) | | |
| No | NA | 60 (56.6) |
| Yes | NA | 46 (43.4) |
| Corticosteroid use - no. (%) | | |
| No | NA | 46 (43.4) |
| Yes | NA | 43 (40.6) |
| Not reported | NA | 17 (16.0) |
| Year of CT - no. (%) | NA | |

| Characteristic | HCT | CAR-T |
|---|---|---|
| 2022 | NA | 73 (68.9) |
| 2023 | NA | 33 (31.1) |

**RVIs: Adenovirus, Coronavirus, Enterovirus (coxsackie, echo, polio), Enterovirus (ECHO, Coxsackie), Enterovirus (polio), Enterovirus D68 (EV-D68), Enterovirus NOS, Human metapneumovirus, Human Parainfluenza Virus (all species), Influenza A Virus, Influenza B Virus, Influenza, NOS, Respiratory Syncytial Virus (RSV), Rhinovirus (all species), SARs-CoV-2, Rhino/Entero*