Not for publication or presentation

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR CELLULAR IMMUNOTHERAPY FOR CANCER
Orlando, FL
Friday, February 17, 2023, 12:00 PM – 2:00 PM

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1. **INTRODUCTION**
    a. Dr. Moskop opened the meeting by introducing Dr. Hematti as the outgoing chair. Dr. Hematti then spoke about the expectations of being a part of the CICWC and to the junior faculty to take advantage of the CICWC.
    b. Dr. Moskop then went back to the podium and introduced the new incoming chair, Dr. Christine Phillips, from Cincinnati Children's Hospital Medical Center. She then spoke about the committee members' conflicts of interest, available datasets for secondary analyses, patient reported outcomes datasets and the Early Career Investigator opportunity.
2. **ACCRUAL SUMMARY**
    a. Dr. Moskop explained that all the data for cellular therapy studies is from CRF track data. Dr. Moskop spoke about the current numbers for CAR-T infusions - There are now over 9900 cellular therapy infusions with new and increasing numbers of indications.
3. **PRESENTATION, PUBLISHED OR SUBMITTED PAPERS**
    a. Details regarding presentations and publications were not presented due to time constraints but were made available to attendees as an attachment
4. **STUDIES IN PROGRESS**
    a. Dr. Moskop reviewed the current studies in the WC:
        i. **AC16-01** Pattern of use and outcomes with donor lymphocyte infusion after HLA-haploidentical allogeneic hematopoietic stem cell transplant **Manuscript prep**
        ii. **AC17-01** CAR-T with or without subsequent HCT for ALL **Manuscript submitted**

iii. **AC18-01** Effect of stem cell boost and donor lymphocyte infusion on the incidence of GVHD **Data file prep**
iv. **CT19-02** Prolonged cytopenia following CAR-T for DLBCL **Manuscript Prep**
v. **CT20-01** Comparison of commercial CAR T cells for DLBCL **Manuscript Prep/submitted**
vi. **CT20-02** Health Resource utilization in CAR T cells **Data file prep**
vii. **CT20-03** Determinants of outcomes after CAR T cells for Lymphoma **Manuscript Prep**
viii. **CT20-04** Determinants of outcomes after CAR T cells for ALL **Data file prep**
ix. **CT21-01** Outcomes of elderly patients receiving CAR-T for DLBCL Manuscript Prep CT22-01 CD19-CAR-T therapy failure: Impact of subsequent therapy in patients with B-cell malignancies **Protocol Development**
x. **CT22-02** Machine learning for predicting toxicity and early clinical outcomes in DLBCL and B-ALL patients treated with commercial CAR T products in the real-world setting: an analysis of the CIBMTR registry **Protocol Development**

5. **FUTURE / PROPOSED STUDIES**
    a. Dr. Moskop closed the welcome slides by saying the CICWC is open to any individual willing to be active in study development and completion; explaining the app, voting, scoring; and how the WC makes their decision regarding the presentations; and rules of authorship. She also introduced the collaborative session and said that the CICWC has two presentations that will be given at the Collaborative session.

1. **Presentation #1**: Dr. Nausheen Ahmed presented, "Outcomes of CD19 CAR-T in patients who received lymphodepleting chemotherapy using fludarabine-containing versus other regimens" which was combined from the following proposals:
    a. i. PROP 2207-02 Fludarabine alternatives in CAR-T therapy (R Kamble) (Attachment 4a) ii. PROP 2209-05 Outcomes of CD19 CAR-T in patients with r/r B cell lymphoma who received lymphodepleting chemotherapy using fludarabine-containing versus other regimens (N Ahmed, S Ganguly) (Attachment 4b) iii. PROP 2210-89 What is the influence of conditioning regimen on the efficacy of CAR T cell therapy (A Sieg, C Strouse) (Attachment 4c) iv. PROP 2210-114 Patterns of conditioning before CAR T-cell therapy for large B cell lymphoma and the effect on clinical outcomes (A Ali, C Rodriguez-Bonilla) (Attachment 4d) v. PROP 2210-252 Impact of lymphodepleting agents on the outcomes of Chimeric Antigen Receptor T-cell therapies (K Nadiminti, P Pophali) (Attachment 4e) vi. PROP 2210-264 Alternative lymphodepletion before CAR-T cell therapy (S Mirza, L Gowda) (Attachment 4f)
    b. **Background**: Fludarabine is more efficacious than non-Fludarabine containing treatments, but there are toxicity concerns. Bendamustine is an alternative treatment believed to have reduced toxicity. There was also a shortage of Fludarabine in 2022, so this left clinicians with having to use alternate treatments.
    c. **Hypothesis**:

i. Flu/Cy lymphodepletion with CD19 and BCMA CAR-T cell therapy has superior efficacy outcomes compared to Bendamustine.

d. End points:

i. Primary:

I. To compare PFS of Flu/Cy vs Bendamustine, based on disease.

ii. Secondary:

I. Day 100- and 1-year relapse free survival (RFS)

II. ORR

III. CRS, ICANS, infection: incidence and severity

IV. Cytopenia: Prolonged (>90 day) any grade/high grade neutropenia, thrombocytopenia

V. Days of admission, ICU admission

VI. Identify characteristics associated with choice of Bendamustine or other (baseline cytopenia, ECOG, disease burden, comorbidities)

e. **Impacts**:

i. Critical unmet need for evidence-based alternative regimens given fludarabine-toxicity profile and shortage.

f. **Questions / Comments from Audience**:

i. For non-fludarabine arm, just do bendamustine instead of all the other combos?

I. Dr. Nausheen Ahmed: We can do flu/cy vs bendamustine if that is a better design.

ii. I would be concerned about comparing lymphoma and myeloma for PFS and the MMWC has ongoing studies reviewing CAR T and myeloma. How would you address these concerns?

I. Dr. Nausheen Ahmed: Would keep analysis disease specific. We are also a part of the myeloma proposals so we would be able to collaborate if needed. Those studies don't look at lymphodepleting chemo which makes this study different.

II. We might be clear from fludarabine shortage, but it may happen again. May have short follow up so can SPMs be included? Discussed that SPMs are included in another WC study

iii. From the audience: Concern about primary endpoints for comparing flu/cy and bendamustine and CAR-T LD persistence

a. Will review endpoints based on final indication inclusion

2. **Presentation #2** – Dr. Wang presented "Impact of prophylactic steroids and tocilizumab on incidence of CRS and ICANS in patients undergoing treatment with CAR T-cell therapy" (Attachment 5) (combined from the following proposals):

a. i. PROP 2207-01 Impact of prophylactic steroids and tocilizumab on incidence of CRS and ICANS in patients undergoing treatment with axicabtagene ciloleucel for lymphoma (O Oluwole, S Bhaskar) Not for publication or presentation ii. PROP 2210-01 Explore the Efficacy and Safety of Three Prophylactic Measures to Mitigate the Toxicities in Chimeric Antigen Receptor (CAR) T-cell Therapy (J

Wang, L Metheny) iii. PROP 2210-77 Impact of prophylactic steroids and tocilizumab on incidence of CRS and ICANS in patients undergoing treatment with axicabtagene ciloleucel for lymphoma (O Oluwole, S Bhaskar)

- **b. Background:**
  - i. CRS and ICANS, particularly grade 3 or higher, remains a challenge in CAR T-cell therapy. Prophylactic measures are needed.
  - ii. The use of prophylactic steroids has been demonstrated in cohort 6 of the ZUMA-1 and showed good efficacy and safety profile. Although it has been included in the label update for Axi-cel, this measure has not been widely adopted.
  - iii. The use of prophylactic tocilizumab has been reported in small case studies and showed encouraging preliminary results.
  - iv. The use of anti-epileptic medications (AEDs), specifically levetiracetam, have been widely used for the prevention of seizures and ICANS, despite little evidence.
- **c. Hypothesis:**
  - i. In adult patients with large B-cell lymphoma receiving first-time commercial CAR T-cell products, prophylactic administration or tocilizumab and steroids are associated with fewer and less severe CRS and/or ICANS without impacting response rate or overall survival.
  - ii. Prophylactic use of anti-epileptic medications (AEDs) is associated with fewer and less sever ICANS.
- **d. End Points:**
  - i. Primary
    - I. Incidence of all-grade CRS/ICANS
    - II. Incidence of grade 3 or higher CRS/ICANS
  - ii. Secondary
    - I. Duration of CRS/ICANS
    - II. Subsequent treatment for CRS/ICANS
    - III. ORR, CR rate
    - IV. Infection rate
    - V. PFS, OS
- **e. Impact:**
  - i. Prophylactic tocilizumab and steroids, as well as anti-epileptics have been adopted in some centers to mitigate these toxicities despite weak evidence. This proposed study would provide further evidence regarding the efficacy of these three prophylactic methods and pave the way for potential randomized trials.

3. **Presentation #3:** Dr. Mian presented PROP 2209-13, " Comparative Outcomes Analysis of Patients with Aggressive B-Cell Lymphoma Treated With Axicabtagene CiloleucelI vs. LisocabtageneI Maraleucel" (Mian, Hill)

- **a. Research Question:**
  - i. In patients with relapse or refractory aggressive B-cell lymphoma, is there a significant difference in the survival outcomes and toxicities

between those treated with axicabtagene ciloleucel (Axi-cel) versus lisocabtagene maraleucel (Liso-cel)?

b. Background

i. Axi-cel and Liso-cel share the same indications for large B-cell lymphoma.
i. No head-to-head RCT comparing the two treatments.
ii. It is usually the institutional preference, manufacturing availability, and/or received efficacy and tolerability.
iii. Efficacy outcomes have been conflicting.
iv. This study will inform practice immediately.

b. End Points:

i. Primary
    1. Progression Free Survival
ii. Secondary
    1. Overall Survival (OS), Best objective response rate (ORR), complete remission (CR), partial remission (PR), rates and incidence of relapse/progression
    2. Incidence and severity of CRS and ICANS
    3. Treatment-related mortality (TRM) and primary causes of death

c. Questions / Comments from Audience:

i. What is the rationale for excluding FL 3b?
    1. Dr. Mian: One treatment is not approved for FL 3b.
        a. Dr. Moskop: We do have data on FL 3b for Axi-cel.
        b. Dr. Mian: We wanted to focus on DLBCL but can include those FL 3b cases if needed.
ii. Why not do a three-way comparison?
    1. Dr. Mian: An existing proposal already looks at Tisa-cel vs Axi-cel.
        a. From the audience: So why not wait until later and do a three-way comparison? I also agree that the years should be restricted to 2021 and after.
iii. What parameter with be used for tumor burden in matched propensity scoring.
    1. Dr. Moskop: We have data on LDH and bulky disease, but some tumor size data is missing.
iv. Another study in progress (referring to Tisa-cel and Axi-cel study?) and 6 month follow up for Liso-cel is a concern. You should also restrict years to 2021 and after
    1. Dr. Mian: We can restrict by year. For the follow up, the data has cutoff in December 2022 so will have about 9 or more months of follow up by the time the study is ready.
v. What will you do about the high percent of Liso-cel cases that are out of spec?
    1. If those are reported, we do collect some of those.

4. **Presentation 4:** Dr. Patel presented PROP 2210-28, "Comparative Outcomes Analysis of Outpatient and Inpatient Administration of Chimeric Antigen Receptor (CAR) T-cell Therapy for Aggressive B Cell Lymphomas" (V Patel, O Oluwole)
    a. **Background:**
        i. CAR-T therapies have changed the treatment landscape for aggressive non-Hodgkin B-cell lymphomas.
        ii. Given the risk of CRS and ICANS, early registrational trials required hospitalization for close monitoring.
            I. In the TRANSCEND trial for Liso-cel, only 9% received treatment as an outpatient and 72% of those patients required hospitalization.
        iii. CAR-T toxicity management process has improved with corticosteroids and tocilizumab with lower rates of acute high-grade toxicities allowing for outpatient CAR-T administration.
        iv. There are only limited single center reports on safety and efficacy of outpatient CAR-T without comparison to inpatient controls.
    b. **Hypothesis**:
        i. Adult patients with R/r B-cell lymphomas will have no significant differences in survival outcomes between those who received outpatient vs inpatient CAR-T therapy.
        ii. There will be similar rates, durations, and severity of CRS and ICANS
        iii. Inpatient resource utilization will be lower in the outpatient cohort compared to the inpatient cohort.
    c. End Points:
        i. Primary:
            I. Overall Survival (OS)
        ii. Secondary:
            I. PFS, ORR, CR.
            II. Incidence, maximum severity, and duration of CRS and ICANS.
            III. Use of steroids and anti IL-6 therapy.
            IV. Need for pressors and/or positive pressure ventilation for CRS.
            V. Inpatient hospital length of stay.
            VI. Infection rate.
    d. Impacts:
        i. Unknown whether outpatient CAR-T yields similar safety and efficacy outcomes as inpatient administration.
        ii. Understanding differences in safety, efficacy, and resource utilization could enhance patient quality of life and cost savings.
        iii. Provide insight into potential optimal selection criteria for outpatient vs inpatient CAR-T administration.
    e. **Questions / Comments from Audience**:
        i. Dr. Sairah Ahmed: Even within the same product, there will be bias by age, kps, tumor burden. How will you deal with this?

I. Dr. Patel: We can look at effect modification for intra-product bias, but it will be difficult with data available and biases.

ii. Dr. Moskop: We collect limited resource utilization data. It is mostly administered inpatient vs outpatient and length of stay.

I. Dr. Patel: We can reframe as length of stay vs actual resource utilization.

iii. This question is disease agnostic, why choose just NHL?

I. Dr. Patel: Protoplasms will be different between lymphoma and myeloma, for example. We decided on lymphomas due to the higher sample size.

iv. Is the CIBMTR database the best database to use? The cell therapy consortium has more granular data? Does CIBMTR have LDH?

I. Dr. Patel: This is the biggest dataset available and other datasets have more missing data despite the granularity of the data.

II. Dr. Moskop: We have added LDH in the last few years.

5. **Presentation 5:** Dr. Jallouk presented PROP 2210-15, "Effect of Delayed Cell Infusion on Outcomes in Patients with Large B-cell Lymphoma Receiving Chimeric Antigen Receptor (CAR) T-cell Therapy" (A Jallouk, P Strati)

a. **Background:**

i. Lymphodepleting chemotherapy (LDC) is critical for optimal efficacy of CAR T-cell therapy.

ii. The recommended dose and time of LDC varies by CAR T-cell product indication.

b. **Rationale:**

i. Longer vein-to-vein times have been associated with worse outcomes following Axi-cel treatment.

ii. Even after LDC is started, cell infusion may be delayed for multiple reasons, including clinical and logistical complications.

iii. A single-center retrospective analysis at our institution found significantly worse PFS and os when cell infusion was delayed after the start of LDC

I. Longer delays were associated with worse survival.

II. Worse outcomes persisted even after propensity score matching on baseline characteristics.

c. **Hypothesis:** Patients with large B-cell lymphoma receiving CAR T-cell therapy, regardless of product, who have delayed cell infusion (> 5 days after initiation of LDC) will have inferior outcomes compared to patients with on-time infusion (=< 5 days after initiation of LDC).

d. **End Points:**

i. Primary outcomes

I. CR rates at day 30 and day 100

II. PFS and OS

ii. Secondary outcomes

I. CRS and ICANS onset, maximum grade, and duration

II. Grade 3-4 cytopenia rates at day 30

e. **Questions:**

i. From the audience: Some delays are caused by infection so they are necessary, how will we know this information?

1. Dr. Jallouk: This is a good point. It will be helpful to know if there is a difference caused by delays either way. If there is no difference, then we know it is okay to wait out a fever, but if there is a worse outcome with delays, we should readminister LDC to produce the best environment for the CAR-T.

ii. Dr. Sairah Ahmed: Will you be looking at the differences in the type of LDC in these patients?

1. Dr. Jallouk: The numbers would probably be small to analyze that, but it would be interesting to see if the different LDC's behave differently.

6. **Presentation 6**: Dr. Elgarten presented PROP 2210-194, "Antibiotics exposure correlates of response and toxicity following anti-CD19 CAR T cell therapy" (C Elgarten, R Myers)

a. **Background:**

i. The gut microbiota is increasingly implicated in playing a role in anti-cancer immunity, including adoptive cellular therapies.

ii. As drivers of microbiota change, antibiotics have been associated with worse. outcomes after immune-based therapies.

iii. Early data suggests that antibiotics may modify response to CAR.

b. **Research Objective:**

i. To determine the independent association of antibiotics commonly administered for neutropenic fever with toxicities and outcomes after CD19-directed CAR T-cell therapy in children, adolescents, and young adults with ALL.

c. **Hypothesis:**

i. The efficacy and toxicity of CD19 CAR will be differential based on exposure to antibiotics immediately pre- and post- CAR infusion.

d. **Impact:**

i. First pediatric study to assess differential impact of antibiotics on outcomes of CD19 CAR.

ii. Inform supportive care guidelines for patients receiving CD19 CARs.

I. Immediate impact on antibiotic selection.

iii. Leverages a merged dataset to assess daily resource utilization on post-CAR outcomes.

I. Can be applied to other research questions.

II. Platform for investigating patient-level or center-level variation in supportive care measures.

iv. Potential to inform translational studies assessing gut microbiota during CD19 CAR.

e. **Questions:**

i. Dr. Sairah Ahmed: There will be a bias of sicker patients receiving antibiotics. How will this be addressed?
    I. Dr. Elgarten: This is why we need disease burden info prior to CAR T, ALL should have the pre-CAR disease burden.
ii. From the audience: Broad spectrum are for sicker patients, and this will introduce some bias. What will you do about this?
    I. There is some variability between centers so this center variation can be analyzed.
iii. Dr. Hematti: Will you look at cultures?
    I. No, just the exposure. It will be agnostic to the reason that the antibiotics were used.

6. **Future/proposed studies to be presented at the CIBMTR Collaborative Working Committee Study Proposals Session**
    a. Dr. Moskop closed with statements about voting and collaborative session, including announcing the CICWC presentations that will be presented at the collaborative session:
        i. Prolonged Cytopenia Following anti-B Cell Maturation Antigen (BCMA) CAR T-cell Therapy for Relapsed/Refractory Multiple Myeloma (RRMM) (combined from the following proposals:)
            a. **PROP 2210-69** Prolonged Cytopenia Following anti-B Cell Maturation Antigen (BCMA) Chimeric Antigen Receptor (CAR) T-cell Therapy for Relapsed/Refractory Multiple Myeloma (RRMM)
            b. **PROP 2210-79** Prolonged Cytopenia Following Car-t Therapy For Multiple Myeloma
        ii. **PROP 2210-293** Temporal Trends in Outcomes after CAR T-Cell Therapy for relapsed or refractory B-cell Lymphoma

7. **Proposed studies; not accepted for consideration at this time**
    a. **PROP 2210-02** Explore the Efficacy of CAR T-cell Therapy in Uncommon Types of Large B-cell Lymphomas
    b. **PROP 2210-29** Toxicity and Outcomes of patients with B-cell acute lymphoblastic leukemia with negative measurable residual disease at the time of CD19 CAR T-cells therapy
    c. **PROP 2210-33** Characterizing differences in clinical outcomes of CAR T-cell therapy for relapsed/refractory ALL and LBCL based on gender
    d. **PROP 2210-35** Pre-emptive and early tocilizumab usage and risk of infections in patients receiving CAR-T therapy
    e. **PROP 2210-38** Potential for granulocyte-colony stimulating factor in preventing infections in CAR-T recipients without worsening immune-related toxicities
    f. **PROP 2210-45** Outcomes of CAR T-cell-associated HLH Toxicities in B-ALL, NHL, and Multiple Myeloma
    g. **PROP 2210-83** Assessing safety and efficacy of allogeneic stem cell transplant after CD19-targeted chimeric antigen receptor T-cell therapy
    h. **PROP 2210-138** Outcomes of CD19 chimeric antigen receptor (CAR) T cell therapy post targeted immunotherapy in relapsed/refractory (R/R) diffuse large B cell lymphoma (DLBCL), B-cell acute lymphoblastic leukemia (B-ALL) and Multiple Myeloma (MM)
    i. **PROP 2210-178,** Fludarabine Lymphodepletion Exposure As A Driver Of Clinical Outcomes After Car-t

j. **PROP 2210-184** The impact of pre-therapy vitamin D status on outcomes of patients with large B-cell lymphoma treated with CD19-directed chimeric antigen receptor T-cell therapy

k. **PROP 2210-220** Outcomes of CAR-T therapy in adult patients with relapsed or refractory (R/R) B-ALL

l. **PROP 2210-267** Outcomes of chimeric antigen receptor T-cell treatment for B-cell malignancies relapsing after allogeneic hematopoietic cell transplantation.

m. **PROP 2210-268** Impact of HLA-B leader peptide dimorphism on outcomes of patients treated with CAR T therapy for lymphoid malignancies

n. **PROP 2210-274** CAR T cell therapy in Adults with B-cell Acute lymphoblastic leukemia (B-ALL): Clinical Predictors of Toxicity and Efficacy.

o. **PROP 2210-275** Outcomes of Anti-CD19 CAR T-cell therapy for Relapsed Refractory Mantle cell lymphoma

p. **PROP 2210-292** Outcomes of CAR T Therapy Among Patients with Hematologic Malignancies who Relapse After Allogeneic Hematopoietic Cell Transplantation

q. **PROP 2210-295** Outcomes of patients with B-cell lymphomas relapsing following CD19 directed Chimeric Antigen Receptor (CAR) T-cell therapy: Real-World Data from the Center for International Blood and Marrow Transplant Research (CIBMTR)

r. **PROP 2210-300** Impact of obesity on outcomes in CD19-directed CAR-T patients

The meeting was then adjourned at 2 pm.

Not for publication or presentation

Working Committee Overview Plan For 2023-2024		
Study #	**Study Status**	**Chairs Priority**
AC16-01: Pattern of use and outcomes with donor lymphocyte infusion after HLA-haploidentical allogeneic hematopoietic stem cell transplant	Manuscript Preparation	2
AC17-01: CAR-T with or without subsequent HCT for ALL	Submitted	1
AC18-01: Effect of stem cell boost and donor lymphocyte infusion on the incidence of GVHD	Protocol Development	3
CT19-02: Prolonged cytopenia following CAR-T for DLBCL	Manuscript Preparation	1
CT20-01: Comparison of commercial CAR T cells for DLBCL	Manuscript Preparation	1
CT20-02: Health Resource utilization in CAR T cells	Protocol Development	2
CT20-03: Determinants of outcomes after CAR T cells for Lymphoma	Manuscript Preparation	2
CT20-04: Determinants of outcomes after CAR T cells for ALL	Data File Preparation	2
CT21-01: Outcomes of elderly patients receiving CAR-T for DLBCL	Manuscript Preparation	3
CT22-01: CD19-CAR-T therapy failure: Impact of subsequent therapy in patients with B-cell malignancies	Protocol Development	3
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