COMPREHENSIVE IMMUNE RECONSTITUTION AND FUNCTIONAL PROFILING IN HEMATOLOGIC MALIGNANCY PATIENTS POST-CAR-T THERAPY: CORRELATION WITH CLINICAL OUTCOMES

S. KUNGWANKIATTICHAI [1,2]; A. CHEN[1]; A. DESAI[1]; W. OWATTANAPANICH[2]; W. XIE[3]; Y. SAWYER[3]; I. JOHNSON[1]; R. T. MAZIARZ[1]

1. BMT & Cell Therapy Program, Knight Cancer Institute; Oregon Health & Science University; Portland, Oregon, USA.
2. Division of Hematology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
3. Department of Pathology and Laboratory Medicine, Oregon Health & Science University, Portland, Oregon, USA.

Introduction

Chimeric Antigen Receptor T (CAR-T) cell therapy has revolutionized the treatment of hematologic malignancies. Significant challenges persist regarding disease relapse and infection-related morbidity, impacted by delayed immune reconstitution (IR). Although immune recovery patterns following hematopoietic cell transplantation is well understood, detailed characterization of CAR-T therapy IR remains limited. Understanding IR and relationship to clinical outcomes is crucial for limiting complications, improving survival rates, and optimizing post-CAR-T patient care.

Objectives

To characterize IR patterns following CAR-T cell therapy and evaluate their association with survival outcomes

Methods

We conducted a single-centered, retrospective cohort study analyzing IR patterns in consecutive patients treated with a commercial CAR-T product between January 2016 and September 2024. The primary outcome was IR patterns. The secondary outcomes were survival analysis outcomes associated with IR.

Flow cytometric analysis measured immune cell subsets, including myeloid cells, monocytes, dendritic cells, T cells (CD4+, CD8+, T regulatory (Treg), αβ, γδ, naïve, memory, activated, and exhausted), B cells, NK cells and NK-T cells. Planned measurements were prior to lymphodepletion, at CAR-T infusion, at defined intervals of +/- 7 days at 30, 90, 180, and 365 post-infusion. Clinical data were collected to analyze IR pattern and IR-related survival analysis differences including patient demographics and clinical characteristics, complete blood count, and CAR-T-related immune side effects.

Results

A total of 319 patients were analyzed, including 221 B-cell lymphoma (BCL) and 38 acute B lymphoblastic leukemia (B-ALL) patients who received CD19-CAR-T cells, and 60 multiple myeloma (MM) patients receiving BCMA CAR-T cells.

Bendamustine lymphodepletion was associated with less immune suppression at CAR-T infusion than fludarabine/cyclophosphamide, particularly for dendritic cell subsets.

Early IR defined at around D30 post-CAR-T infusion occurred in monocytes, dendritic cells, CD8 T, NK-T, and Treg cells while CD4 T and B cells showed delayed IR.(figures 1 and 2) B cell recovery was disease-specific, occurring first in MM, followed by BCL and B-ALL.(figure 2)

CD4 T cell recovery was disease-specific, occurring first in BCL, followed by MM, and B-ALL. Day-30 T cell expansion patterns varied from significant expansion, especially γδ T cells, to absence of recovery. Pairwise comparisons at time points of immune subsets by ICANS grades 0-2 and 3-4 resolved around D30 showed almost all had significantly lower log absolute values around D30 except for NK, NK-T, PD1 T, and B cell, significantly for some T cell subsets lower around D180, and for B cell around D365.

MM patients with unsuppressed myeloid dendritic cells ≥ 3 cell/μL at infusion had inferior progression-free survival [adjusted HR 2.53 (95%CI 1.07, 5.98); p = 0.034]. Across all disease cohorts, patients with T cell < 300 or CD4 T cell < 100 cells/μL around D30 had significantly inferior overall survival (OS). Patients with Treg < 10 cells/μL around D30 had significantly higher cumulative incidence of non-relapse mortality (NRM) (Gray's test p = 0.006). Patients with ICANS grade ≥ 3 had a significantly greater proportions below the cutoffs.(figure 3) B cell reconstitution was not associated with survival.

Summary

IR patterns post-CAR-T infusion varied by immune subset, disease, and ICANS grade. Lack of early IR in specific T cell immune subsets may prognosticate OS and NRM at 1-month post-CAR-T infusion.

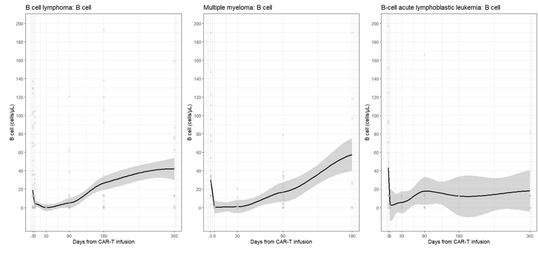


Figure 2: B cell recovery patterns by disease type post-CAR-T therapy

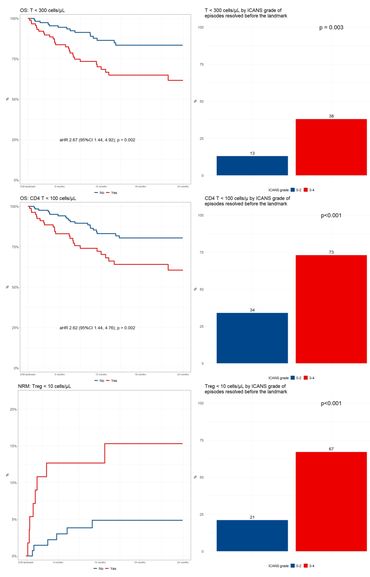


Figure 3: Day 38 landmark analysis of clinical outcomes by early IR

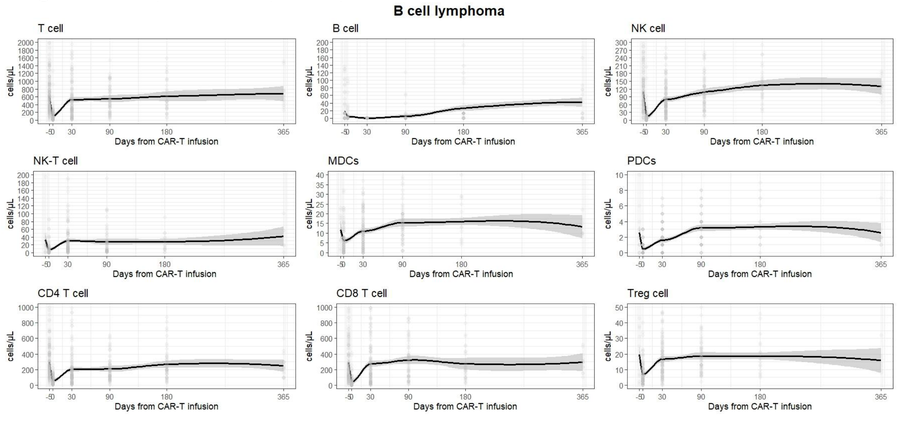


Figure 1: Temporal dynamics of immune cell subset recovery in B-cell lymphoma patients during the first year post-CAR-T cell therapy