Immune reconstitution after CD19 CAR-T cell therapy in patients with relapsed/refractory B cell Acute lymphoblastic leukemia/lymphoma (r/r B-ALL/L)

Mohammed Yasar, Hamenth Kumar Palani, Arun Kumar Arunachalam, Phaneendra Datari, Sushil Selvarajan, Uday Kulkarni, Anu Korula, Biju George, Aby Abraham, Vikram Mathews

Department of Haematology, Christian Medical College, Ranipet Campus, Vellore, India

Abstract

Background

Immune reconstitution following Chimeric Antigen Receptor (CAR) T cell therapy in r/r B-ALL/L is crucial in shaping the overall immune response and long-term efficacy.

Methods

Ten patients (n=6 r/r B-ALL; n=4 DLBCL) with a median age of 45 (range 6-59) were enrolled. Autologous CAR T cells targeting CD19 (LTG1563; Miltenyi Biotec) were infused under a dose escalation strategy (0.5-2x10^6 cells/kg; 3+3+4). Circulating lymphocytes, T cell subsets - CAR^+, CAR^- T cells and memory subsets were evaluated in peripheral blood samples using flow cytometry with a standardized antibody panel at specified time points. Data analysis was done using Kaluza 2.1 (Beckman), and GraphPad Prism (v8.0.1).

Results

Median T cell transduction efficiency (CAR positivity) was 38% (range 16-55). Total T cell normalized by day 14 (range 14-28; Fig 1a). Median CAR^+ T cell expansion was observed on Day 14 (range 14-28; Fig 1b). Among CAR^+ T cells, rapid recovery was seen in $CD8^+$ T cells compared to $CD4^+$ T cells, resulting in a CD4/CD8 ratio <1.0 (Fig 1c). Subset analysis revealed a rapid expansion of central memory T cells initially followed by a robust expansion of effector memory T cells (Fig 1d). CAR^-T cell subset followed the same recovery and memory subsets pattern. In the innate compartment, NK cells were first to recover, returning to normal levels within 30 days (range, 14-28 (Fig 1e). B cell aplasia persisted in all patients on early assessment (day 7), B cells were detected in 1/10 (10%) on day 14 but remained below the normal level until last follow up in all remaining patients (Fig 1f).

Conclusion

This study shows that immune reconstitution after CAR T cell therapy follows a distinct recovery pattern among different cell types. While overall normalization of various cell types occurred earlier in r/r B-ALL patients compared to DLBCL, earlier NK cell recovery was observed in all patients. Prolonged B cell aplasia in most patients indicates the ongoing CAR T cell function.

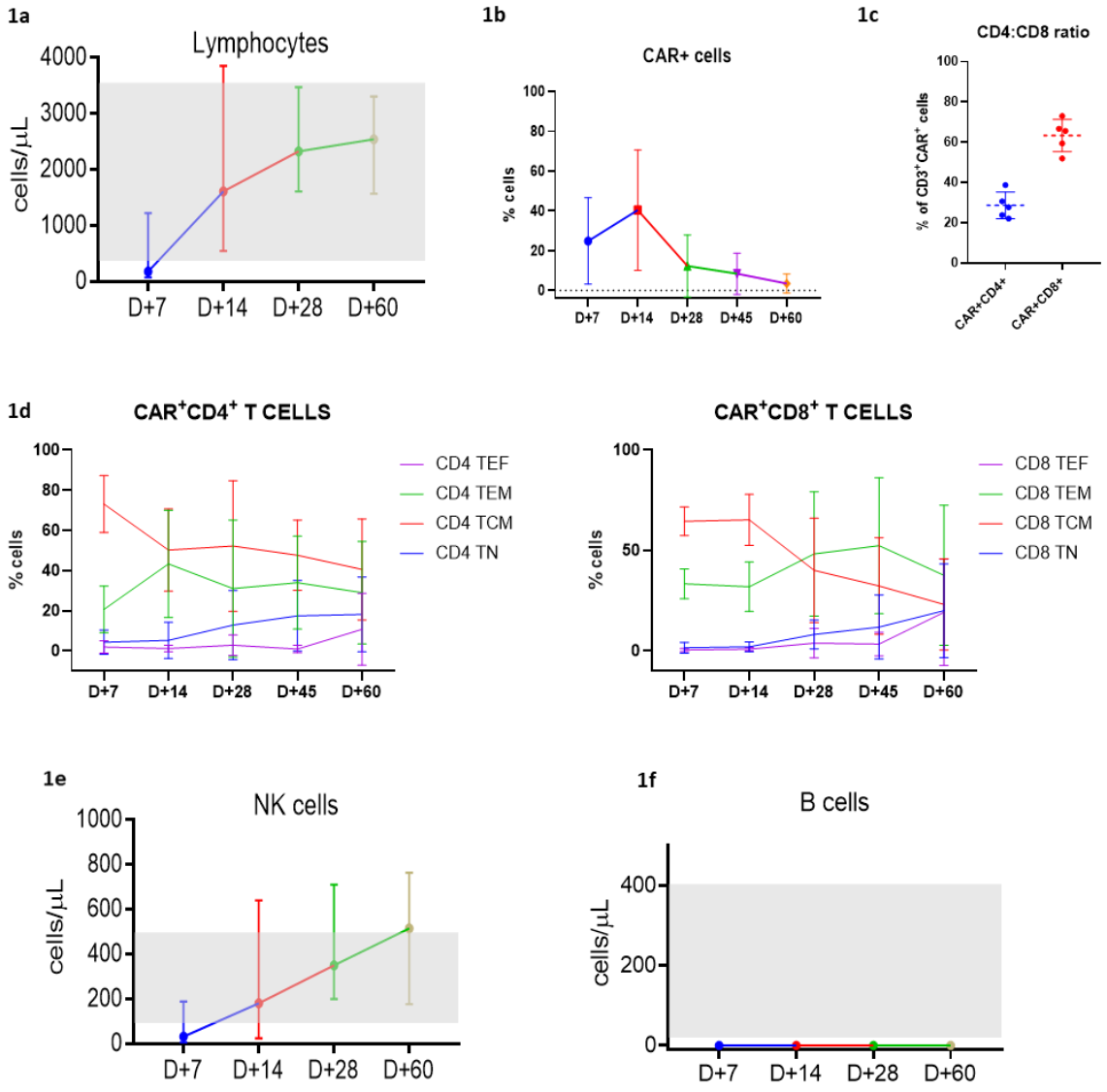

Figure 1. Profile of immune reconstitution after anti-CD19 CAR-T cell therapy. A) Recovery of Total lymphocyte counts post CAR T cell infusion. B) Distribution, expansion, contraction and persistence of CAR T cells. C) Inverted CD4/CD8 ratio among CAR^+ T cells indicating sustained immune response. D) Subset analysis via multi-parameter flow cytometry using CD45RO and CD62L. $CD8^+$ T cells showing an inverse relationship in expansion between central and effector memory phenotype. E) Rapid NK cell recovery and transient increase in cell numbers thereafter. F) B cell kinetics, indicated by $CD19^+$ cell numbers using FCM, demonstrating prolonged aplasia until the last follow-up.