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LONG-TERM FOLLOW-UP OF SEQUENTIAL CD19-22 CAR T-CELL THERAY IN 20 CHILDREN WITH REFRACTORY OR RELAPSED B-ALL

Topic: 02. Acute lymphoblastic leukemia - Clinical

Keywords: B cell acute lymphoblastic leukemia, CAR-T, Immune therapy

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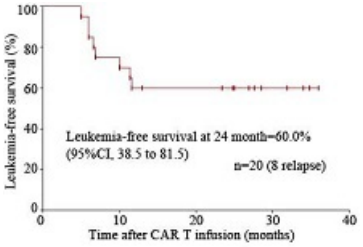
Background: Despite high response rates induced by CD19 chimeric antigen receptor (CAR) T-cell therapy in refractory or relapsed B-cell acute lymphoblastic leukemia (r/r B-ALL), a majority of patients relapsed due to either target antigen loss or insufficient CAR T-cell persistence in long-term follow up. Here, we report updated results from a phase 1 trial, demonstrating long-term outcome of pediatric patients with r/r B-ALL after sequential CD19-22 CAR T-cell therapy.

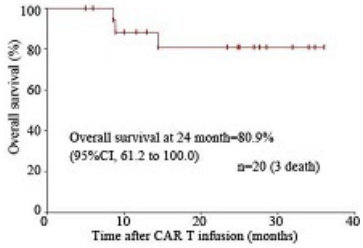
Aims: To evaluate long-term outcome of sequential CD19-22 CAR T-cell therapy in 20 r/r B-ALL children without post-CAR stem cell transplantation.

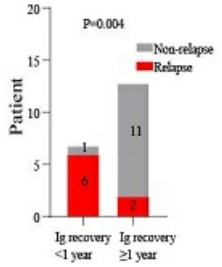
Methods: Between August, 2017 and February, 2021, consecutive 20 pediatric patients (pts) with r/r B-ALL received sequential CD19-22 CAR T-cell therapy in Beijing Boren Hospital. There were 13 males and 7 females, with a median age of 6 (range, 1 to 15) years. Fourteen pts relapsed and 6 pts had refractory minimal residual disease by flow cytometry (FCM-MRD$^+$) after previous chemotherapies. The previous median treatment time were 19 (range, 3 to 95) months in relapsed pts and 19.5 (range, 4 to 47) in FCM-MRD$^+$ pts. Severn pts had extramedullary diseases (EMDs), including 4 with exclusive EMDs. The median marrow blasts were 19.94% (range, 0.16%>93.18%) by FCM. Chromosome aberration and gene mutations were commonly observed including *TP53* mutation. All pts expressed CD19 and CD22 on blasts. CD19 or CD22 CAR lentiviral vector comprised ScFvs fragments derived from a murine anti-CD19 antibody or a humanized anti-CD22 antibody, and 4-1BB co-stimulatory and CD3z signaling domains. CAR T cells manufacture from PBMCs commenced since leukapheresis and was completed within 7-8 days, and protocols of 19 and 22 CAR T cell manufacturing were the same. CD19 and CD22 CAR T cells were infused with a median interval of 1.7 (range, 1.1 to 5.2) months. The median dose of infused 19 CAR T cells (cycle 1) was 10 (range, 3.3 to 42.8) × 10^5/kg and CD22 CAR T cells (cycle 2) was 10 (range, 0.25 to 47.4) × 10^5/kg (P=0.813). The 19 and 22 CAR T cell expansion and cytokine release syndrome (CRS) were monitored after infusion. The BM status and EMDs firstly evaluated on day 30 after CD19 CAR T cell infusion (cycle 1). Long term follow-up was carried out since infusion of 22-CART cells (cycle 2), at a median follow up time of 27.3 (range, 9.8 to 36) months.

Results: Median peak expansion of CD19 and CD22 CART cells were 9.84% (range, 0.19% to 68.7%) and 23.9% (range, 0.30 to 85.20%) among CD3$^+$ T cells respectively. All 20 pts achieved CR/CRi, FCM-MRD$^-$ and resolution of EMDs after cycle 1. CRS occurred in 18/20 (90.0%) pts in cycle 1 and 16/20 (80.0%) in cycle 2. Grade 1 neurotoxicity occurred in 3/20 (15%) pts in cycle 1 and 3/20 (15%) in cycle 2. Only 1 pt had grade 3 neurotoxicity in cycle 1 but he fully recovered after interventions. At a median follow-up time of 27.3 (range, 9.8 to 36) months, 8 pts relapsed and 3 of them died. Two (25%) of the 8 relapsed pts had CD19 antigen loss. The 8 relapsed patients included 6 out of 7 patients (85.7%) who had early Ig recovery (within 1 year), and 2 out of the 13 (15.3%) pts who had late Ig recovery (beyond 1 year) (P=0.004), suggesting that long-term disease free survival were associated with longer duration of CAR T cell persistence. 2-year LFS and OS was 60% (95%CI, 38.5-81.5%) and 80.9% (95%CI, 61.2-100.0%) respectively.

Image:







Summary/Conclusion: Sequential CD19-22 CAR T cell therapy can achieve promising long-term outcome with a 2-year LFS of 60% in pediatric patient with r/r B-ALL without post-CAR transplantation. Early Ig recovery has high risk of relapse.

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