(S286) CD19/CD22 BISPECIFIC CAR-T CELL THERAPY FOR RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA AND MECHANISTIC INVESTIGATION: A PROSPECTIVE, SINGLE-ARM, SINGLE-CENTER, PHASE 2 CLINICAL TRIAL

Topic: 26. Gene therapy, cellular immunotherapy and vaccination - Clinical

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Background

Chimeric antigen receptor T-cells (CAR-T) targeting CD19 have shown promising benefits to patients of relapsed or refractory large B-cell lymphoma (R/R LBCL), but only one-third patients got durable remission and the resistance mechanisms were complicated. CAR-T cells targeting CD22 were found to be effective in patients who failed previous anti-CD19 CAR-T cell therapy.

Aims

In this prospective study, we aimed to evaluate the efficacy and safety of CD19/CD22 bispecific CAR-T cell therapy (CAR2219) in patients with R/R LBCL, and to explore the underlying mechanisms associated with therapeutic response using single-cell sequencing and in vitro experiments.

Methods

Till February 10, 2026, this ongoing phase 2 clinical trial have enrolled 73 patients with R/R LBCL, and all were evaluable for efficacy and safety profiles. Bridging therapy was allowed. A 3-day lymphodepletion (cyclophosphamide: 250 mg/m2/d; fludarabine: 25 mg/m2/d) was followed by an intravenous dose of CAR2219 (2×10e6/kg). For patients who responded to CAR2219 therapy, maintenance therapy using PD-1 inhibitors, XPO1 inhibitors, BTK inhibitors, or HDAC inhibitors were also allowed. The primary endpoint was best overall response rate (ORR) as of 3 months post-CAR-T cells infusion. The secondary endpoints included best complete response rate (CRR), progression-free survival (PFS), overall survival (OS), and adverse events (AE). Meanwhile, single-cell RNA sequencing was performed on CAR-T cell products collected from 14 patients; clustering and functional analyses were conducted after stratification by PFS with a cutoff of 6 months, and double-stranded RNA (dsRNA) levels in CAR-T cell products were detected by immunofluorescence.

Results

All enrolled patients had undergone a median of three (range 3-8) prior lines of therapy. The median IPI score was 4 (range 1-5) at the time of CAR-T cell therapy. *TP53* mutation was positive in 22 of 24 patients. CAR2219 was successfully manufactured and infused to all 73 patients. With a median follow-up of 10.43 months after CAR-T cells infusion, the best ORR was 95.9%, including a CRR of 56.2%. The median PFS and OS were not reached. Estimated 24-month PFS and OS rates were 68.5% [95%CI: 57.2-79.8%] and 82.3% [73.5-91.1%], respectively. The most common AEs included neutropenia (93.2%), thrombocytopenia (76.7%), and anemia (76.7%). Cytokine release syndrome (CRS) occurred in 83.6% of patients, with 2 cases of grade 3. Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 5.5% of patients, including 2 cases of grade 3 and 1 case of grade 4. Tocilizumab and corticosteroids were effective in managing CRS and ICANS, and no treatment-related deaths were reported. Single-cell RNA sequencing analysis revealed that the proportions of $CD4^+$ T cell subsets associated with memory and cytotoxicity were significantly higher in patients with longer PFS. Pathway scoring of these two subsets demonstrated marked activation of the DDX58 pathway and interferon pathways. In parallel, in vitro immunofluorescence assays showed significantly higher dsRNA expression in CAR-T cell products from patients with longer PFS.

Summary/Conclusion

CD19/CD22 bispecific CAR-T cell therapy demonstrated encouraging efficacy and a favorable safety profile in patients with R/R LBCL. Enrichment of specific $CD4^+$ T cell subsets, activation of the interferon pathway, and activation of viral mimicry may be closely associated with the efficacy of this therapy. (ClinicalTrials.gov Identifier: NCT06081478)