(PS2342) MAINTENANCE THERAPY WITH PD-1 INHIBITOR AND SELINEXOR FOLLOWING CD19/CD22 BISPECIFIC CAR-T CELL THERAPY IN RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA: A RETROSPECTIVE ANALYSIS

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

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Background

Chimeric antigen receptor T-cell (CAR-T) therapy targeting CD19 has revolutionized the treatment landscape for relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL). Despite impressive initial response rates, disease relapse remains a significant challenge, often attributed to CAR-T cell exhaustion and immune evasion mechanisms. In our prospective phase 2 trial, CD19/CD22 bispecific CAR-T (CAR2219) demonstrated a remarkable 100% best overall response rate; however, strategies to prolong remission duration and prevent relapse are urgently needed. Maintenance therapy represents a promising approach to enhance response persistence by targeting underlying mechanisms of treatment failure. Programmed cell death protein 1 (PD-1) inhibitors have shown potential to reverse CAR-T cell exhaustion and restore anti-tumor immunity, while the exportin 1 (XPO1) inhibitor selinexor exhibits direct anti-lymphoma activity and synergistic effects when combined with immunomodulatory agents.

Aims

To evaluate the efficacy, safety, and immunomodulatory effects of maintenance therapy combining PD-1 inhibitor with selinexor following CAR2219 therapy in patients with R/R DLBCL.

Methods

This retrospective analysis included 32 patients enrolled in our prospective phase 2 clinical trial (NCT06081478) who achieved disease control following CAR2219 infusion and subsequently received planned maintenance therapy. The maintenance regimen consisted of PD-1 inhibitor (tislelizumab 200 mg or serplulimab 240 mg intravenously every 3 weeks) plus selinexor (40-60 mg orally once weekly) for 1-2 years duration. The primary endpoint was progression-free survival (PFS). Secondary endpoints included duration of response (DOR), overall survival (OS), safety profiles, and correlative biomarker analyses. Treatment responses were assessed according to Lugano 2014 criteria, and adverse events were graded per CTCAE version 5.0. Longitudinal monitoring of circulating T-cell subsets, including CD3+PD-1+ T-cells, was performed by flow cytometry in a subset of patients.

Results

A total of 32 patients were included, with a median follow-up of 260 days (range 59-529). Baseline characteristics revealed high-risk disease features. Notably, only 12 patients (38%) had achieved complete response (CR) prior to maintenance initiation. Response rates improved progressively over time during maintenance therapy: overall response rate (ORR) increased from 56% (CR rate 38%) at month 1 to 83% (CR rate 57%) at month 3, and further to 81% (CR rate 71%) at month 6, indicating deepening of responses with continued treatment. With a median PFS of 407 days, the estimated 1-year PFS and OS rates were 56.8% (95%CI: 0.40-0.80) and 71.2% (95%CI: 0.53-0.95), respectively. Median OS was not reached at the time of analysis. Immunophenotypic analysis demonstrated a substantial reduction in circulating CD3+PD-1+ T-cells in all 15 evaluated patients, suggesting effective reversal of T-cell exhaustion. The combination regimen demonstrated manageable toxicity overall.

Summary/Conclusion

Maintenance therapy combining PD-1 inhibitor and selinexor following CD19/CD22 bispecific CAR-T cell therapy demonstrates promising clinical activity in R/R DLBCL, characterized by deepening responses over time and durable disease control. The observed reduction in PD-1+ T-cells supports an immunomodulatory mechanism of action. These findings warrant further investigation in prospective randomized trials to establish the optimal maintenance strategy post-CAR-T therapy.