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shRNA-mediated PD1 gene knock-down anti-CD19 CAR-T cell therapy for relapsed/refractory b cell malignancies

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Background

PD-1 is expressed on CD4+ and CD8+ T lymphocytes,PD-L1 is mainly expressed on tumor cells. The PD-1/PD-L1 binding can inhibit T cell activation. Many studies have proved that blockade of PD-1/ PD-L1 axis is effective to enhance the function of CAR-T cells. However, this strategy has mainly been studied in vitro and the antitumor properties of CAR-T cells that continuously knock down PD-1 in vivo have not been thoroughly investigated.

Methods

Patients with relapsed or refractory CD19+ B-cell malignancies were included in this trial. Patients underwent leukapheresis , followed by FC conditioning chemotherapy and a single infusion of shRNA-mediated PD1 Gene knock-down anti-CD19 CAR-T Cells at a dose of 1–2×10^6/kg. The objective was to assess the safety and efficacy.

Results

16 patients with relapsed or refractory B-cell malignancies were enrolled, including 8 with DLBCL, 4 with B-ALL, 2 with FL, one with CLL and one with HGBL. 6 patients achieved complete response(CR) (3 cases of B-ALL, 2 cases of DLBCL and one case of FL), and 4 patients achieved partial response (PR) (3 cases of DLBCL and one case of FL). 2 patients with DLBCL and one patient with FL who achieved CR have not relapsed so far, the duration of CR is 36, 34 and 29 months, respectively. Three patients with B-ALL who obtained CR relapsed on day 59–78 and 110 after CAR-T infusion, respectively. CRS occurred in 11 patients (68.8%), 7 were grade 1 and 4 were grade 2. None had neurotoxicity. There was no death from CAR-T treatment-related toxicity. After infusion of CAR-T cells, most patients had an increase in IL6 level, but the degree of increase is significantly individualized, which seems to have no inevitable relationship with the severity of CRS. Two patients without CRS have an IL6 higher than 1000 pg/ml. The change of CRP and Ferritin was not as significant as that of IL6 after CAR-T infusion. It is suggested that cytokines are difficult to predict the occurrence and severity of CRS.

Conclusions

PD1 Gene knock-down anti-CD19 CAR-T therapy showed acceptable safety and anti-tumor activity in patients with relapsed or refractory CD19+ B cell malignancies.

Clinical trial identification

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Legal entity responsible for the study

Department of Oncology, Guangxi Medical University Affiliated Tumor Hospital.

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Disclosure

All authors have declared no conflicts of interest.