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704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Efficacy and Safety of Chimeric Antigen Receptor T Cells Therapy Strategy That Dual Targeting CD19 and CD22 to Treat Relapsed/Refractory Acute Lymphoblastic Leukemia in Adults

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Background: Chimeric antigen receptor T-cells (CAR-T) targeting CD19 therapy is reported to induce 83-93% response in relapsed/refractory acute lymphoblastic leukemia (r/r-ALL) in adults. However, 30-60% of patients relapse after CAR-T treatment, of which 14-25% CD19-negative relapse. In spite of CAR-T cells persistence, CD19 absent causing tumors that evade CAR-T cells mediated recognition and clearance. For CD19-negative relapse, it is necessary to explore more effective targets. There are some research proved that compared with single-targeted CARs, CD19/CD22 dual-targeted CARs induce more IFN-γ and IL-2 in vitro and eradicate patient-derived xenografts (PDX) produced with CD19-negative relapse of CD19-directing CAR-T treatment. Therefore, our study explored the efficacy and safety of clinical studies on mixture of CD19 CAR-T and CD22 CAR-T cells in the treatment of r/r ALL in adults.

Patients and Methods: CD3 $^{+}$ cells were selected from the apheresis PBMC and activated before lentiviral CAR T cells infection. The cells were transduced with a caspase9-inducible, safety-engineered lentivector CAR containing anti-CD19 or -CD22 scFv fused with multiple intracellular signaling domains: CD28/CD27/CD3z-iCasp9. The quality of apheresis cells, gene transfer and T cell proliferation efficiencies, and effective CAR-T infusion dose were quantitatively scored and documented. All enrolled patients expressed CD19 and CD22 positively. All patients received fludarabine (FLU) and cyclophosphamide (CTX) conditioning chemotherapy (FLU 30mg/m ^{2}, d1-3; CTX 500mg/m ^{2}, d1-3) before CAR-T infusions.

Results: The study included 16 r/r ALL patients, median age is 26 years, and median of previous theraples is 6, all of patient details can be found in the table (Fig.1). In the first month after CD19/CD22 CAR-T cells infusion, total of 93.8% (15/16) of patients achieved complete response (CR), 1 case (6.25%) was evaluated as non-remission (NR). In the evaluation of safety, 68.75% (11/16) of patients did not experience cytokine release syndrome (CRS), 25% of patients (4/16) occurred grade 1 CRS and 6.25% (1/16) of patients occurred grade 2 CRS, no case of severe CRS defined as≥grade 3 and no any immune effector cell-associated neurotoxicity syndrome (ICANS) occurred. After a median follow-up of 9.9 months, 4 patients maintained CR, while other 11 patients were relapsed, with a duration of response (DOR) of 25% (4/16), median LFS was 6.1 months and median OS were not reached (Fig.2).

Conclusions: In summary, CD19/CD22 exhibited a manageable safety but limited antileukemia activity. Our study showed that mixture of CD19 CAR-T and CD22 CAR-T cells infusion is fail to expected to compensate for the treatment of relapsed in r/r ALL and prolonging the leukemia-free survival of patients. The low-efficacy of dual-targeted CAR-T cells may be caused by the CAR19 and CAR22 cells interfere with each other and weaken the CAR-T amplification in vivo. From our data, it seems that the timing of treatment and tumor burden status may play a more important role rather than new targets CAR-T cells infusion for r/r ALL in adults.

Disclosures No relevant conflicts of interest to declare.

Group		No.of patients
Overall		16
Gender		
	Female	10(62.5%)
	Male	6(37.5%)
Age group(year old)		
	≤40	10(62.5%)
	>40	6(37.5%)
Disease status		
	Relapse	0
	Refractory	2(12.5%)
	Relapse and refractory	14(87.5%)
Ph status		
	Ph+	5(31.2%)
	Ph-	11(68.8%)
Disease burden		
	Low(blasts≤50%)	7(43.7%)
	High(blasts>50%)	9(56.3%)
Pre-CART HSCT		
	Yes	7(43.7%)
	No	9(56.3%)

Fig.1 Patient details list

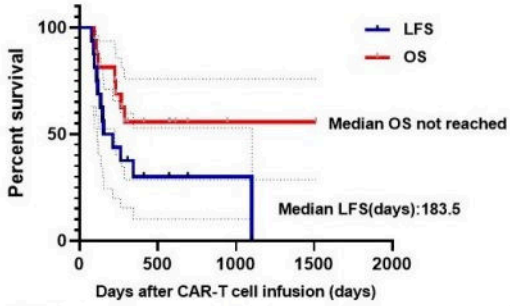

Fig.2 Survival of CAR-T treated patients leukemia-free survival period and overall survival of all the enrolled patients were shown. The dashed lines indicate the 95% confidential interval.

Figure 1

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