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Title: NATURALLY SELECTED CD7-TARGETED CAR-T CELL THERAPY FOR RELAPSED OR REFRACTORY CENTRAL NERVOUS SYSTEM T-CELL LYMPHOBLASTIC LEUKEMIA/LYMPHOMA

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Session Title: Acute lymphoblastic leukemia - Clinical

Background:

Limited studies have demonstrated that CD7-targeted chimeric antigen receptor (CAR) T-cell therapy is effective and safe for T-cell acute lymphoblastic leukemia(T-ALL) and T-cell lymphoblastic lymphoma (T-LBL). However, it remains unclear whether CD7 CAR-T cells can penetrate the blood-brain barrier and be effective in treating central nervous system (CNS) T-ALL/LBL without increasing neurotoxicity.

Aims:

Here we explored the efficacy and safety of NS7CAR T-cells for relapsed or refractory (R/R) T-ALL/LBL with CNS involvement in phase I/II clinical trial (NCT04572308 &NCT04916860).

Methods:

Peripheral blood mononuclear cells were collected from patients by leukapheresis. A novel fratricide-resistant approach to derive naturally selected anti-CD7 CAR (NS7CAR) T cells was developed using lentiviral transduction of peripheral T cells that could overcome CD7-directed fratricide without additional genetic modifications. NS7CAR is a 2^{nd} generation murine-based CAR-T containing 4-1BB and CD3ζ co-stimulatory domains. Intravenous fludarabine (30mg/m^2/d) and cyclophosphamide (300mg/m^2/d) were given to all patients on day -5 to day -3 prior to NS7 CAR T cells infusion. The proliferation of CAR-T cells in cerebrospinal fluid (CSF) was detected by flow cytometry (FCM).

Results:

From Dec. 2020 to Jun. 2022, 10 patients with CNS T-ALL (n=8) and T-LBL (n=2) were enrolled and received NS7CAR T cells. The median age was 14.5 (2-37) years old. Patient characteristics and clinical results were shown in Table 1. Three patients who relapsed from prior allogeneic hematopoietic stem cell transplantation (allo-HSCT) were also enrolled. At enrollment, 6 patients were CNS-3 status (blasts≥5/μL in CSF), and 4 were CNS-2 status (blasts<5/μL in CSF). Eight patients had leukemic cells both in bone marrow (BM) and CNS. Combined extramedullary disease (EMD) except for CNS involvements was found in 5 patients.

The transduction efficiency was 91.2% (64.4%-97.4%). A single dose of NSCAR T cells was infused to patients at a low dose (5×10^5cells/kg, n=2), and a medium dose ($1\text{-}1.5\times10^6$cells/kg, n=8).

At a median of day 17 (day 14-day 51) post infusion, 10/10 (100%) achieved complete remission (CR) in CSF. The median follow-up time was 220 days (61-621 days). Two patients had early CNS relapse on day 56 (then received salvage transplant and were still alive at the last follow-up of day 412), and day 72, respectively. For the other 8 patients without CNS relapsed regardless of EMD/BM relapse, 5 who received consolidation/salvage allo-HSCT were still progression-free at a median follow-up of 286 days(188-621days), 1 lost follow-up on day 180, 1 relapsed in BM on day116 and withdrew for other clinical trials, and the other 1 remained CR on day 61.

Mild cytokine release syndrome (CRS, ≤grade II) occurred in 8/10 (80%) patients, and 2/10(20%) patients had grade III CRS. One patient had grade IV neurotoxicity, and others did not develop neurotoxicity. All were controlled after the administration of corticosteroids and/or tocilizumab.

Following infusion, the median maximum proliferation of NS7CAR T-cells in CSF was 22.56% (0-65.35%), which

occurred on day 17(13-33) as detected by FCM.

Summary/Conclusion:

This study demonstrated that NS7 CAR-T is a promising method in treating patients who had R/R CNS T-ALL/LBL without increasing the risk of severe neurotoxicity. Safety was manageable. However, more data on additional patients and longer observation time are needed to fully evaluate the efficacy of NS7 CAR-T products in patients with CNS involvement.

Table 1. Patient characteristics and clinical outcomes

Patient #	Age	Diagnosis at enrollment	Relapsed post allo-HSCT prior to CAR-T	CNS status	Combined EMD	BM blasts	CAR-T cell dose(cells/kg)	BM Response in 2 weeks	BM Response in 4 weeks	CNS response	EMD response	CRS	ICANS	CNS relapse	Disease status at last evaluation
1	14	T-ALL	No	CNS-3	No	0.18%	1*10^6	MRD-CRi	MRD-CR	CR	CR	1	0		Consolidation HSCT, day 621, PFS
2	19	T-ALL	No	CNS-3	Yes	60.23%	1*10^6	MRD-CRi	MRD-CR	CR	CR	1	0		day180, lost follow-up
3	11	T-ALL	No	CNS-2	Yes	14.50%	1.5*10^6	MRD-CRi	NR	CR	NR	2	0		Salvalge transplant, survived at last follow-up (day 448)
4	15	T-ALL	No	CNS-3	No	4.42%	1*10^6	MRD-CRi	MRD-CRi	CR	CR	1	0	CNS/BM relaplse on day56, CD7-positive	Salvalge transplant, survived at last follow-up (day 412)
5	8	T-ALL	No	CNS-2	No	2.25%	1*10^6	MRD-CRi	MRD-CRi	CR	CR	3	0		Relapsed on d54, CD7-negative. Survived at last follow-up (day286)
6	37	T-LBL	Yes	CNS-2	Yes	7.87%	5*10^5	MRD-CRi	MRD-CRi	CR	PR	1	0		salvage 2nd transplant, survived at last follow-up (day251)
7	19	T-LBL	No	CNS-3	Yes	0.00%	1*10^6	MRD-CRi	MRD-CRi	CR	PR	1	0		salvage transplant, survived at last follow-up (day188)
8	15	T-ALL	Yes	CNS-2	Yes	0.07%	5*10^5	MRD-CRi	MRD-CRi	CR	PR	1	0		Relapsed on d116, CD7-positive, then withdrew
9	2	T-ALL	No	CNS-3	No	3.81%	1*10^6	MRD-CRi	MRD-CRi	CR	CR	3	4	d72 CNS relapse, CD7-positive	Died from progression disease on day 79
10	6	T-ALL	Yes	CNS-3	No	0.11%	1*10^6	MRD-CRi	MRD-CRi	CR	CR	1	0		PFS, day61

Abbreviations: T-ALL, T-cell acute lymphoblastic leukemia; T-LBL, T-cell lymphoblastic lymphoma; CNS, central nervous system; CR, complete remission; PR, partial response; NR, no response; MRD, minimal residual disease; BM, bone marrow; EMD, extramedullary disease; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; HSCT, hematopoietic stem cell transplantation; PFS, progression-free survival

Keywords: CNS, CAR-T, T cell acute lymphoblastic leukemia, relapsed/refractory