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POSTER ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

CAR T-Cell Therapy in Relapsed or Refractory T-Cell Acute Lymphoblastic Leukemia/Lymphoma: A Retrospective Study

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Background
Patients with relapsed or refractory T cell acute lymphoblastic leukemia/lymphoma (r/r T-ALL/LBL) often have limited treatment options available and poor prognoses. Clinical trials of autologous CD7, donor-derived CD7 and donor-derived CD5 CAR T-cell therapy in r/r T-ALL/LBL conducted in our center have showed encouraging efficacy and a shaky safety. To evaluate the safety and efficacy of the three therapies, we conducted a retrospective study and analyzed the results of the clinical trials across three different CAR T-cell therapies.

Methods
This is a retrospective comparative analysis of CAR T-cell therapies with different targets and sources in r/r T-ALL/LBL, including a phase I trial of autologous CD7 CAR T-cell therapy (NCT04840875), a phase I trial (ChiCTR2000034762) and a phase II trial (NCT04689659) of donor-derived CD7 CAR T-cell therapy, and a phase I trial of donor-derived CD5 CAR T-cell therapy (NCT05032599). Adverse events and pharmacokinetics were not collected after patients received stem-cell transplantation. In univariate analysis, Chi-square test and Fisher's exact test were used to compare categorical outcome; in multivariate analysis, linear regression was used for the continuous outcome and Logistic regression was used for the categorical outcome.

Results
A total of 102 patients were included in this analysis, consisting three cohorts: 20 patients receiving autologous CD7 CAR T cells, 66 with donor-derived CD7 CAR T-cell therapy, and 16 receiving donor-derived CD5 CAR T cells.
Although with comparable complete remission rates, patients in the three cohorts had different adverse events. Especially, patients who received autologous CD7 CAR T-cell therapy had a significant lower severe infection rate than those with donor-derived CD7 CAR T cells (odds ratio [OR], 0.06; 95% confidence interval [95%CI], 0.01 to 1.03; P=0.019 by exact method) and donor-derived CD5 CAR T cells (OR, 0.03; 95%CI, 0.01 to 0.60; P=0.006) (Table 1). Despite that all patients developed grade 3-4 cytopenias, more patients who received autologous CD7 CAR T-cell therapy reverted grade 3-4 cytopenias to grade 2 or lower within one month compared with donor-derived CD7 CAR T cells (OR, 13.00; 95%CI, 3.99 to 42.32; P<0.001) and donor-derived CD5 CAR T cells (OR, 27.86; 95%CI, 3.02 to 257.28; P<0.001).
Based on the multivariate analyses, CD7 CAR T-cell therapy led to lower severe infection rate compared with CD5 CAR T-cell therapy (OR, 0.08; 95%CI, 0 to 0.56; P=0.015) (Table 2), and it should be noted that in this study, the vector uesd in autologous and donor-derived CD7 CAR T-cell therapy was different from that in CD5 CAR T-cell therapy; larger proportion of patients treated with CAR T cells manufactured from their own T cells retured all grade 3-4 cytopenias to grade 0-2 within one month (OR, 68.08; 95%CI, 3.21 to 1446.20; P=0.005), versus patients receiving donor-derived therapy. No factors were identified as independently influencing CRS, ICANS and CR/CRi rate at one month, including central nervous system leukemia not associated with ICANS. Although the source of CAR T cells has not been shown to be a factor in CRS and ICANS, patients with autologous CAR T-cell therapy had lower peak levels of cytokines than donor-derived, including IL-6, sCD25 and TNF-α with the maximal P value of 0.02 in multivariate analysis.

Conclusion
Despite the risk of tumor contamination and CAR T-cell manufacture failure in autologous CD7 CAR T-cell therapy, some clinical experience have emerged against for them recently. In addition to the fact that autologous therapy cause no GVHD

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and the faster recovery from hematologic toxicity, being beneficial for long-term defense against infection, it produces lower levels of several cytokines in vivo compared to donor-derived therapy, providing a guarantee for lower incidence of CRS and ICANS. Hence, given the comparable remission rate and remarkable safety, autologous CD7 CAR T-cell therapy would be prioritized for recommendation for r/r T-ALL/LBL patients with low tumor load and access to collect enough normal T cells from their own body for CAR T-cell manufacture. CD5 CAR T-cell therapy is regarded as an option for patients with CD5 positive encountering treatment failure or relapse after CD7 CAR T-cell therapy.

Disclosures No relevant conflicts of interest to declare.

Table 1. Safety* and efficacy according to different CAR T-cell therapies

	Auto CD7 (n=20)	Donor CD7 (n=66)	Donor CD5 (n=16)	*P* value
CR/CRi at one month, No.(%)	17 (85)	53 (80)	16 (100)	0.148
Severe infection[a], No.(%)	0 (0)	19 (29)	7 (44)	0.002
CRS, No.(%)				
0-2	18 (90)	59 (89)	16 (100)	0.515
3-4	2 (10)	7 (11)	0 (0)	
ICANS, No.(%)	1 (5)	6 (9)	2 (13)	0.485
Grade 3-4 cytopenia within 30 days, No.(%)	20 (100)	66 (100)	16 (100)	
Cytopenia recovery[b], No.(%)	13 (65)	8 (12)	1 (6)	0.001

* CRS and ICANS were graded according to the 2019 ASTCT consensus. Other AEs were graded according to CTCAE, Version 5.0.

[a] refers to grade 3 to 5 infection.

[b] indicates that all grade 3-4 cytopenias recover to grade 2 or lower within 30 days post CAR T-cell infusion.

Auto, autologous; CR, complete remission, CRi, complete remission with with incomplete hematologic recovery, CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; donor, donor-derived.

Table 2. Logistics regression examining factors associated with safety and efficacy

	CR/CRi at one month		Severe infection		CRS		ICANS		Cytopenia recovery [d]	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
T-cell source [a]	1.47	0.12-26.17	0.08*	0-0.56	0.80	0.02-22.17	0.89	0.02-46.73	68.08*	3.21-1446.20
CAR	0.09	0.77-infinity	1.27	0.27-5.52	0.39	0-2.44	2.01	0.29-13.77	0.44	0.04-4.92
Tumor load in BM										
<5	ref		ref		ref		ref		ref	
≥5, <25	2.10	0.23-105.19	0.72	0.15-3.03	4.78	0.66-44.24	6.28	0.74-53.63	1.95	0.40-9.56
≥25	0.43	0.09-2.07	0.24	0.04-1.08	0.70	0.01-12.17	3.29	0.55-19.60	0.07	0.01-1.14
Prior SCT	2.01	0.28-13.48	1.66	0.36-9.82	0.11	0.01-1.55	0.69	0.08-5.81	5.46	0.40-74.26
Previous lines of therapy										
1-2	ref		ref		ref		ref		ref	
3-4	0.52	0.07-3.88	0.78	0.11-5.03	4.11	0.23-82.79	8.92	0.38-208.84	0.59	0.07-5.13
5-10	0.47	0.03-9.28	1.08	0.12-9.03	7.87	0.07-433.70	26.84	0.70-1026.58	0.51	0.04-7.32
Infusion dose [b]										
Underdose	ref		ref		ref		ref		ref	
Dose 1	0.72	0.01-19.55	1.53	0.01-166.59	2.59	0.27-infinity	5.62	0.13-246.56	0.46	0.05-4.65
Dose 2	0.99	0.01-32.20	0.52	0.01-49.01	0.43	0.04-infinity	1.27	0.03-50.27	3.26	0.20-52.97
EMDs	0.25	0.04-1.15	1.65	0.49-6.04	1.03	0.17-7.02	6.15	0.78-48.53	0.85	0.20-3.52
Grade ≥3 cytopenias[c]			0.92	0.25-3.92	2.25	0.21-36.46	0.39	0.06-2.61	0.46	0.11-1.88
CNSL							5.74	0.78-42.01		

* indicates the corresponding P value less than 0.05.

a indicates whether the T cells used for CAR T-cell manufacture were collected from the patients themselves or healthy donors.

b in this analysis, patients were divided into three groups according to infusion dose, including Dose 1: 5×10^5 (±30%)/kg, Dose 2: 1×10^6 (±30%)/kg, Underdose: $<3.5\times10^5$/kg.

c cytopenia status was measured before lymphodepletion.

d indicate that all grade 3-4 cytopenias recover to grade 2 or lower within 30 days post CAR T-cell infusion.

BM, bone marrow; CR, complete remission, CRi, complete remission with with incomplete hematologic recovery, CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; OR, odds ratio; CI, confidence interval; EMDs, extramedullary diseases; CNSL, central nervous system leukemia.

Figure 1

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