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ORAL ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Naturally Selected CD7-Targeted Chimeric Antigen Receptor (CAR)-T Cell Therapy for Refractory/Relapsed Acute Myeloid Leukemia: Phase I Clinical Trial

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Introduction

Refractory or relapsed (r/r) acute myeloid leukemia (AML) is associated with a relatively poor prognosis, even in patients who undergo allogeneic hematopoietic stem cell transplantation (allo-HSCT), emphasizing the critical need for novel therapies. Approximately 30% of AML patients express CD7 on their leukemic blasts and malignant progenitor cells. Naturally selected CD7 CAR-T (NS7CAR-T) therapy has shown significant efficacy with a favorable safety profile in T-cell lymphoid malignancies. In a phase I clinical study (https://clinicaltrials.gov NCT04938115), we investigated the safety and efficacy of CAR-T therapy for treating r/r AML patients with CD7-positive disease.

Methods

Peripheral blood mononuclear cells were obtained from either the patients themselves (n=9) or the transplant donor (n=1) in cases of relapse post-transplant. T-cells were then purified using CD3+ magnetic beads. The second-generation CD7CAR with a 4-1BB costimulatory domain was manufactured following the manufacturer's protocol. Before the CAR-T cell infusion, bridging therapies were permitted for patients with rapid disease progression. All patients received intravenous fludarabine (30mg/m ^{2}/d) and cyclophosphamide (300mg/m ^{2}/d) lymphodepletion chemotherapy for three consecutive days (Day -5 to Day -3). The median time from leukapheresis to CAR-T cell infusion was 15 days.

Results

Between June 2021 and January 2023, we enrolled 10 patients with CD7-positive r/r AML (CD7 expression >50% with good intensity) and administered NS7CAR-T cell infusions, with 4 receiving a low dose (5×10^5/kg) and 6 receiving a medium dose (1×10^6/kg). **Table 1** displays the characteristics of the enrolled patients, revealing a median age of 34 years (7-63 years) and median bone marrow (BM) blasts percentage by flow cytometry (FCM) of 17.0% (2.0-72.7%) at enrollment. One patient presented with diffuse extramedullary disease (EMD). Before enrollment, patients had undergone a median of 9 (range: 3-17) prior lines of therapy. Seven patients had a history of allo-HSCT and the median interval period from the prior transplant to relapse was 12.5 months (3.5-19.5 months). Following infusion, the median peak of circulating NS7CAR-T cells was 2.72×10^5 copies/μg (0.671~5.41×10^5 copies/μg) genomic DNA, which occurred around Day 21 (Day 14 - Day 21) based on q-PCR, with 64.68% (40.08%~92.02%) occurring on Day 17 (Day 11 - Day 21) according to FCM. The median transduction efficiency of the products was 95.6% (70.4%-98.5%).

At four weeks post NS7CAR-T cell infusion, 7/10 (70%) patients achieved complete remission (CR) in BM, and 6 of them attained minimal residual disease (MRD)-negative CR. Three patients showed no remission (NR), including 1 with EMD who had partial remission (PR) based on PET-CT evaluation on Day 35. All NR patients were found lost CD7. The median observation time was 178 days (28-752 days). Among the 7 patients who achieved CR, 3 who relapsed from prior transplants underwent consolidative 2 nd allo-HSCT about 2 months after CD7 CAR T-cell infusion. Two patients remained in leukemia-free survival on day 752 and day 315, respectively, while 1 patient died on day 241 due to transplant-related mortality. Among the other 4 patients without consolidative allo-HSCT, 3 relapsed on day 47, day 83, and day 115, respectively (all 3 patients were found to have CD7 loss), and 1 patient died from lung infection.

Post-infusion, the majority of patients (80%) experienced mild cytokine release syndrome (CRS), with 7 displaying grade I and 1 having grade II CRS, while 2 patients (20%) experienced grade III CRS. None of the patients had neurotoxicity. Among

the 7 patients with prior allo-HSCT, 1 who had a relapse approximately 100 days after prior allo-HSCT developed mild skin graft-versus-host disease following CAR-T therapy.

Conclusion

Our study highlights the NS7CAR-T therapy as a promising approach for achieving a favorable initial CR in CD7-positive AML patients, even in those who have undergone extensive prior treatments and experienced relapse post allo-HSCT. It potentially could serve as a bridging therapy before transplant. CD7 loss is a major issue either in NR patients or relapsed patients. The safety profile of NS7CAR-T therapy was manageable. However, to comprehensively assess the efficacy of NS7CAR-T in treating CD7-positive AML, further data from a larger cohort of patients and longer follow-up time are essential.

Disclosures No relevant conflicts of interest to declare.

Table 1. Characteristics of the 10 acute myeloid leukemia (AML) patients

Patient #	Age	Relapsed post allo-HSCT prior to CAR-T	Interval time from prior HSCT to relapse (days)	CAR-T cell dose(cells /kg)	Response in 4 weeks	CRS	ICANS	Brigde into allo-HSCT	Relapse post CAR-T	Disease status at last evaluation
1	21	Yes	551	1*10^6	MRD-negative CR	1	0	Yes	No	Died from TRM on d241
2	37	Yes	373	1*10^6	MRD-negative CR	1	0	Yes	No	Remained in LFS till d752
3	35	No		5*10^5	MRD-positive CR	3	0	No	d47 relapse, CD7 lost	d68 received salvage transplant, d318 died from TRM
4	63	No		5*10^5	NR, CD7 lost	1	0	No	No	NR, withdrew
5	21	Yes	256	5*10^5	MRD-negative CR	3	0	No	No	Died from TRM on d48
6	40	Yes	130	1*10^6	MRD-negative CR	1	0	No	d83 relapse, CD7 lost	d115 received salvage transplant, d326 survived
7	7	Yes	436	1*10^6	MRD-negative CR	1	0	Yes	No	Remained in LFS till d315
8	31	Yes	101	1*10^6	MRD-negative CR	1	0	No	d98 relapse, CD7 lost	d115 lost follow-up
9	33	No		1*10^6	NR, CD7 lost	2	0	No	No	NR, withdrew
10	39	Yes	587	5*10^5	BM NR CD7 lost, EMD PR	1	0	Yes	NA	NR, withdrew

AML: acute myeloid leukemia, **BM:** bone marrow, **allo-HSCT:** allogenic hematopoietic stem cell transplantation, **CRS:** cytokine release syndrome, **ICANS:** immune effector cell-associated neurotoxicity syndrome, **NR:** no remission, **MRD:** minimal residual disease, **CR:** complete remission, **d**: day, **EMD:** extramedullary disease, **TRM:** transplant-related mortality

Figure 1

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