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LETTER

CAR T-cell therapy for relapsed/refractory CD5-positive diffuse large B-cell lymphoma yields more favorable outcomes than standard therapy

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CD5-positive (CD5+) diffuse large B-cell lymphoma (DLBCL) represents a special subgroup of DLBCL with a more aggressive disease course and is more likely to develop into relapsed/refractory (r/r) DLBCL in response to immunochemotherapy. The incidence of CD5+ DLBCL is 5%–10% among DLBCL patients[1]. Current therapies, such as high-dose chemotherapy, radiation, and some targeted medicines, have a nominal impact on patient outcomes[2]. The largest series conducted in Western countries involving 102 CD5+ DLBCL patients reported that 68% of the patients relapsed after first-line treatment and 48% received second-line therapy, among whom 83.7% relapsed. The median time to the second treatment failure was < 3 months and intensive chemotherapy followed by hematopoietic stem-cell transplantation (HSCT) failed to improve prognosis[3]. Previous studies have generally supported the independent prognostic value of CD5 in patients with DLBCL[4] but no effective molecular-targeted drugs have been identified to date. Indeed, the poor prognosis associated with traditional drug therapies highlight the urgent need to explore novel therapeutic options.

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In recent years a variety of studies have shown that chimeric antigen receptor (CAR) T-cell therapy is a promising immunotherapy for r/r B-cell lymphoma. Anti-CD19 CAR T-cell therapy in second-line DLBCL treatment has shown encouraging results with an estimated 4-year overall survival (OS) of 54.6% and a median progression-free survival (PFS) of 14.7 months[5]. Furthermore, the first-line administration of anti-CD19 CAR T-cells in high-risk large B-cell lymphoma demonstrated an 86% complete response rate and a 3-year PFS of 75%[6]. CAR T-cell therapy is effective in first-line refractory or early relapsed DLBCL compared to conventional therapy and has been approved for second-line treatment. However, the response and long-term efficacy of CAR T-cell therapy in r/r CD5+ DLBCL remain unknown. Therefore, the safety and efficacy of CAR T-cell therapy for treating r/r CD5+ DLBCL was determined.

Forty patients with CD5+ DLBCL were diagnosed in our center between May 2020 and February 2024, of whom 15 were excluded, as illustrated in **Figure 1A**. The remaining 25 patients were consecutively recruited into this retrospective observational cohort study, including 13 who received CAR T-therapy in a clinical trial (Registration no. NCT05388695), 1 who received CAR T-therapy from ChiCTR-OPN-16008526 (**Table S2**), and 11 who received salvage immunochemotherapy as controls. The characteristics of the patients were as follows: median age in the CAR-T group, 45.5 years (range, 24–60 years); 64.3% were male; 57.1% were non-GCB subtype; 78.6% were stage III–IV; 57.1% had an IPI score > 2; 42.9% had extranodal involvement; 21.4% had bulky disease > 5 cm; and 71.4% were primary refractory. No significant differences existed in these parameters between the CAR-T and control groups. Approximately one-half of the subjects in both groups

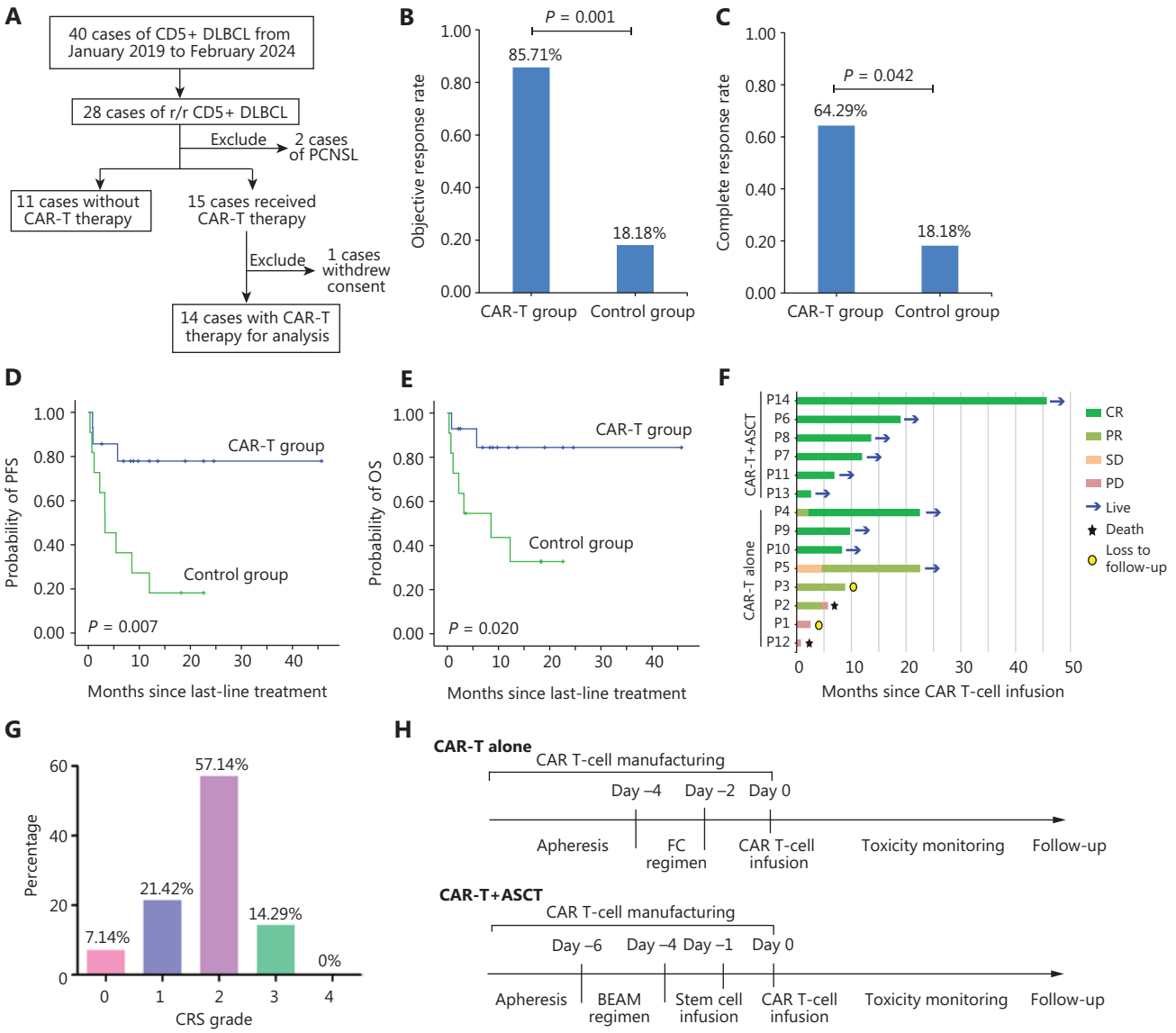


Figure 1 (A) Flow chart of patient screening. Forty patients with CD5+ DLBCL were diagnosed in our center between May 2020 and February 2024, among whom 28 were refractory or relapsed. Two patients with primary lymphoma of the central nervous system (PCNSL) and one that withdrew consent were excluded from the study. Therefore, 25 patients were consecutively recruited into this retrospective observational cohort study. Comparison of objective response (B), complete response (C), PFS (D), and OS (E) between CAR-T and control therapy for r/r CD5+ DLBCL. Chi-square and Fisher's tests were applied for comparison of the response rates. The PFS and OS were analyzed using the Kaplan-Meier method and the log-rank test was used for comparison of survival. (F) Duration of response and outcomes of r/r CD5+ DLBCL with CAR T-cell therapy alone or in combination with ASCT. (G) Proportion of CRS grades from 0–4 in all CAR-T patients (n = 14). (H) The CAR T-cell therapy procedure. Patients received the FC regimen for 3 days before CAR T-cell infusion, followed by infusion of CAR-T cells on day 0 for CAR T-cell therapy alone. CAR-T patients were administered a standard dose of BEAM regimen with or without fludarabine as preconditioning in tandem with ASCT, which was determined/decided at the discretion of the investigators based on the clinical conditions of patients. HSCs were infused on day 0, followed by infusion of CAR-T cells on days 3–4. PCNSL, primary lymphoma of the central nervous system; PFS, progression-free survival; OS, overall survival; ASCT, autologous hematopoietic stem-cell transplantation; CR, complete response; PR, partial response; SD, stable disease, PD, progressive disease; CRS, cytokine release syndrome; FC, fludarabine and cyclophosphamide; BEAM, bis-carmusitine, etoposide, cytarabine and melphalan

harbored high-risk genetic abnormalities, including double-hit rearrangements, *TP53* mutations, *NOTCH1* mutations, and MCD subtypes (*MYD88* L265P and *CD79B* mutations; **Table 1**).

Prior to CAR T-cell therapy 78.6% received treatment lines > 2 (**Table S1**), including immunochemotherapy and/or molecular targeted therapy and all patients had progressive disease (PD) or stable disease (SD). Nearly one-half of the patients also received treatment lines > 2 in the control group (**Table S1**). Only one patient in the control group underwent ASCT consolidation due to a to low objective response rate (ORR) after late-line salvage therapy. CAR-T group had a significantly higher ORR (18.18% *vs.* 85.71%, $P = 0.001$; **Figure 1B**) and complete response rate [CRR] (18.18% *vs.* 65.29%, $P = 0.042$; **Figure 1C**) compared to the control group. All patients ($n = 6$) receiving CAR T-cell therapy plus ASCT achieved a CR 3 months after CAR T-cell infusion and no patients had PD or died (**Figure 1F**). Among the 8 patients on CAR T-cell therapy only, 3 attained a CR and 3 had a partial response (PR). Patients responses and the CAR T-cell therapy procedure are presented in **Figure 1F and 1H**.

The median follow-up time for the CAR-T group after CAR T-cell infusion and the control group after last-line treatment was 9.3 months (range, 0.8–45.7 months) and 3.6 months (range, 0.3–22.6 months), respectively. The CAR-T group had a significantly favorable 1-year PFS (77.9% *vs.* 18.2%, $P = 0.007$) and 1-year OS (84.4% *vs.* 43.6%, $P = 0.020$) compared to the controls (**Figure 1D and 1E**). Neither the median PFS nor the OS were reached in the CAR-T group. The median PFS and OS in the control group were 3.3 months (95% CI: 0–6.7 months) and 8.5 months (95% CI: 0–18.1 months), respectively. In the current study r/r CD5+ DLBCL was commonly superimposed by other high-risk factors. Patients on CAR T-cell therapy had a significantly better PFS and/or OS than controls in the subgroups with other high-risk factors, including non-GCB subtype, stage III-IV, IPI score > 2, treatment line failure > 2, extranodal involvement, and high-risk genetic abnormalities (**Table 1**). Thus, r/r CD5+ DLBCL patients achieved better long-term benefits than immunochemotherapy, especially patients with other high-risk factors.

In the CAR-T group 78.6% patients (11/14) had grade 1–2 cytokine release syndrome (CRS) and 2 had grade 3 CRS (**Figure 1G**). Most patients had an obvious increase in lentivirus copies of CAR-T cells, serum IL-6, and ferritin (**Figure S1A-F**). Immune effector cell-associated neurotoxicity syndrome (ICANS) is rare; one patient had grade 4 ICANS. The patients who experienced severe CRS and ICANS were managed well and had no signs of a short-term recurrence. Severe hematologic toxicities, such as grade 3–4 neutropenia [14/14 (100%)], anemia [9/14 (64.3%)], and thrombocytopenia [9/14 (64.3%)], were common and other non-hematologic toxicities, such as secondary infections, occurred occasionally (**Table S3**). No significant differences in toxicity profiles were observed between the CAR T-cell therapy alone and CAR T-cell combined with ASCT groups (**Table S4**).

This is the first study to examine the therapeutic effect and safety of CAR T-cell therapy for r/r CD5+ DLBCL. CAR T-cell therapy alone or in combination with ASCT substantially improved the ORR and CRR of r/r CD5+ DLBCL patients, while salvage therapy, including immunochemotherapy and/or molecular targeted therapy, was ineffective for most of the patients. Of the 8 patients who received CAR T-cell therapy alone, 62.5% achieved a PR or CR in the following 3 months, which was a similar finding to a previously report involving CAR T-cell therapy in r/r DLBCL patients (ORR, 50%–81%)[7] and superior to immunochemotherapy in r/r CD5+ DLBCL. Prior studies have shown that 83.7% of CD5+ DLBCL patients relapse after second-line immunochemotherapy and the median time to second treatment failure is < 3 months[3]. Even though all patients developed SD/PD before ASCT, all patients ($n = 6$) who received CAR T-cell therapy plus ASCT in the current study achieved a CR and no patients relapsed during the follow-up period. In contrast, a previous study reported that 71.4% of CD5+ DLBCL patients, of whom 92.9% achieved a CR or PR prior to HSCT, relapsed after autologous or/and allogeneic stem cell transplantation alone[3]. The data herein verified the feasibility and advantage of CAR T-cell therapy in r/r CD5+ DLBCL.

Most r/r CD5+ DLBCL patients had one or more one high-risk factors and nearly one-half of the patients had high-risk genetic abnormalities, which is in agreement with the findings of previous reports[4,8]. Prior studies reported that CD5+ DLBCL patients with other high-risk factors, such as extranodal involvement, had a worse prognosis than patients without high-risk factors[8]. The findings herein indicated that the efficacy of CAR-T therapy in r/r CD5+ DLBCL is unaffected by other high-risk factors and is even better when combined with such factors. For example, the non-GCB subtype in the CAR-T group exhibited a significantly longer PFS and OS compared to the control group, whereas no significant difference was detected in the GCB subtype. Although CD19-negative relapse was noted in cases of single-target CD19 therapy in *TP53*-disrupted B-cell lymphoma, the use of dual targets or

Table 1 Comparison of clinical characteristics and prognosis between CAR-T and control groups in relapsed/refractory CD5-positive diffuse large B-cell lymphoma

Characteristics	Values		*P*-value[a]	Comparison of prognosis[b]	
	CAR-T group	Control group		PFS (*P*-value)	OS (*P*-value)
Patients, *n*	14	11			
Age, median (range), years	45.5 (24–60)	55 (23–67)	0.395		
Gender (female/male)	5/9	5/6	0.697		
Cell of origin, *n* (%)			0.234		
Non-GCB	8 (57.1%)	9 (81.8%)		0.039	0.058
GCB	6 (42.9%)	2 (18.2%)		0.592	0.592
Ann Arbor staging, *n* (%)			0.656		
I or II	3 (21.4%)	4 (36.5%)		0.121	0.386
III or IV	11 (78.6%)	7 (63.6%)		0.026	0.009
IPI score, *n* (%)			1.000		
0–2	6 (42.9%)	4 (36.5%)		0.120	0.221
3–4	8 (57.1%)	7 (63.6%)		0.048	0.061
Disease status, *n* (%)			0.434		
Primary refractory	10 (71.4%)	5 (45.5%)		0.016	0.038
Relapsed	4 (28.6%)	6 (54.5%)		0.078	0.180
No. of treatment lines, *n* (%)			0.389		
1–2	3 (21.4%)	5 (45.5%)		0.124	0.271
≥ 3	11 (78.6%)	6 (54.5%)		0.104	0.073
Extranodal involvement, *n* (%)			0.695		
Yes	6 (42.9%)	6 (54.5%)		0.043	0.018
Tumor mass, *n* (%)			0.604		
≥ 5 cm	3 (21.4%)	1 (10.0%)		0.515	0.157
Genetic abnormalities[c], *n* (%)					
Double-hit rearrangement	1 (9.1%)	0 (0.0%)	1.000		
TP53 mutation	4 (30.8%)	3 (37.5%)	1.000	0.171	0.029
N1 subtype	1 (7.7%)	0 (0.0%)	1.000		
MCD subtype	2 (15.4%)	1 (33.3%)	0.489		
Any of the above four genetic abnormalities	6 (42.9%)	4 (44.4%)	1.000	0.136	0.023

[a]Comparison of clinical characteristics between CAR-T and control groups by Chi-square or Fisher's test. Non-parametric test was applied for comparison of age. [b]Comparison of PFS and OS between subgroups with CAR T-cell therapy and corresponding subgroups in control by log-rank test. [c]The percentage of genetic abnormalities was calculated by the number of genetic abnormalities/total patients tested. GCB, germinal center B-cell like; N1 subtype, *NOTCH1* mutation; MCD subtype, *MYD88* L265P and *CD79B* mutation; PFS, progress-free survival; OS, overall survival

combined ASCT, as used in the current study, effectively overcame the adverse effects of TP53 mutations in CD5+ DLBCL patients[9,10]. The variation in CAR-T targets in the current study did not affect the conclusions and even suggested that the flexible selection of CAR T-cell targets or different CAR-T products could improve prognosis.

Additionally, most patients in the CAR T-cell therapy group had few severe adverse events and no treatment-related deaths occurred during the therapeutic period. Moreover, no factors, such as genetic abnormalities and treatment lines before CAR T-cell therapy, increased the occurrence of severe adverse events (**Figure S2A-D**).

The current study had several limitations. Although the findings herein demonstrated promising efficacy in r/r CD5+ DLBCL patients, the small sample size and retrospective design constrained the generalizability of the results. Therefore, a prospective study with a larger cohort is warranted to validate these findings.

In conclusion, the current study showed that CAR T-cell therapy has an obvious advantage over immunochemotherapy in terms of response and long-term outcomes in r/r CD5+ DLBCL patients. CAR T-cell therapy alone or combined with ASCT is a very promising alternative for management of r/r CD5+ DLBCL patients.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Xiaoxi Zhou.
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Contributed data: Fankai Meng, Zhenya Hong, Yang Cao, Gaoxiang Wang, Liang Huang.
Performed the analysis: Hui Luo, Tongjuan Li.
Wrote the paper: Xiaoxi Zhou, Hui Luo, Tongjuan Li.

Data availability statement

The data generated in this study are available upon request from the corresponding author.

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