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LETTER

Patients with CML in the lymphoid blastic phase have inferior response to anti-CD19 CAR T-cell therapy compared to de novo Ph-positive B cell acute lymphoblastic leukemia

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Philadelphia-positive acute B cell lymphoblastic leukemia (Ph-positive B-ALL) is the most common type of adult B-ALL. Although the advent of tyrosine kinase inhibitors (TKIs) with conventional treatment strategies has improved the prognosis, the relapse/refractory (R/R) status is observed in certain patients with Ph-positive B-ALL. Chronic myeloid leukemia in the lymphoid blast phase (CML-LBP) has similar immunophenotype and cytogenetic characteristics with Ph-positive ALL.[1,2] Anti-CD19 chimeric antigen receptor (CAR) T-cell therapy has achieved great success in treating R/R B-ALL.[3–6] Currently, there is a lack of data comparing the efficacy of anti-CD19 CAR T-cell therapy between de novo Ph-positive B-ALL and CML-LBP.[7,8]

Here, we performed a post hoc analysis of study NCT03919240, in which all patients received anti-CD19 CAR T-cell therapy between January 2017 and May 2022 at the First Affiliated Hospital of Soochow University. Adult patients with relapsed or measurable residual disease (MRD) positive Ph-positive B-ALL or CML were included. MRD was detected by multiparameter flow cytometry. An MRD level higher than 0.01% was considered MRD positivity.

A total of 34R/R Ph-positive B-ALL patients were included, comprising 9 CML-LBP patients and 25 de novo Ph-positive B-ALL patients. Autologous CD19 CAR T-cells were manufactured by the Unicar-Therapy Bio Medicine Technology Co. All patients received lymphodepletion chemotherapy and dose-escalating infusions of CAR T-cells as previously described.[9] TKIs were continued in all patients after at least 12 weeks of CAR T-cell infusion. Bone marrow (BM) evaluations were performed on Day 28 after CAR T-cell infusion. Simultaneously, flow cytometry and quantitative polymerase chain reaction (PCR) of *BCR::ABL1* transcript were detected to evaluate the MRD level. The quantitative PCR of *BCR::ABL1* was performed on the International Scale. Major molecular remission (MMR) was defined *BCR::ABL1* transcript lower than 0.1% as detected by quantitative PCR. All statistical analyses were performed using GraphPad Prism 9.0.0 (GraphPad Software Inc.) and R software, version 4.2.2. Intergroup comparisons were performed using the χ^2 (and Fisher's exact) test. The probabilities of duration of response (DOR), cumulative incident rate (CIR), event-free survival (EFS), and overall survival (OS) were estimated by means of the Kaplan–Meier method and were compared with the use of the log-rank test. It was considered significant at $p < 0.05$ for all tests.

The baseline characteristics, disease status, disease burden before CAR T-cell therapy, and the grades of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome of patients are shown in Table 1, there was no significance between the two cohorts ($p > 0.05$). 5/9 (56%) of patients with CML-LBP and 11/25 (44%) of patients with de novo Ph-positive B-ALL had BM blasts higher than 5% prior to CAR T-cell infusion. Moreover, 2/9 (22%) of CML-LBP patients had a history of isolated central nervous system leukemia (CNSL). No patients had received other anti-CD19 immunotherapy prior to CAR T-cell treatment. Of the 9 patients with CML-LBP, 7/9 (78%) had *ABL1* kinase domain mutations, and 8/9 (89%) were treated with second- or third-generation TKIs. The clinical characteristics of the nine patients with CML-LBP are shown in Table S1.

At the Day 28 evaluation post-CAR T-cell therapy, the complete hematologic remission (CHR) was significantly lower in patients with CML-LBP than those with de novo Ph-positive B-ALL (44% vs. 84%, $p = 0.034$) (Figure 1A). Two CML-LBP patients with isolated central nervous system involvement showed no response to CAR-T therapy and succumbed to CNSL. Although there was no statistical significance, MRD negative complete remission (CR) (MRD-CR) in patients with CML-LBP was also lower than that in patients with de novo Ph-positive B-ALL (25% vs. 43%, $p = 0.627$) (Figure 1B). Similarly, MMR in patients with CML-LBP was lower than that in patients with de novo Ph-positive B-ALL (50% vs. 86%, $p = 0.166$), although

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TABLE 1 The baseline characteristics, disease status, disease burden before CAR T-cell therapy, and the grades of CRS and ICANS of the two cohorts.

Item	CML-LBP	De novo Ph+ B-ALL	*p* Value
No. of patients	9	25	
Age, years, median (range)	37 (19–57)	45 (18–66)	>0.05
Sex, No. (%)			
Female/male	5 (56%)/4 (44%)	9 (36%)/16 (64%)	>0.05
Initial WBC, No. (%)			
≥30/<30 (10^9/L)	7 (78%)/2 (22%)	21 (84%)/4(16%)	>0.05
Bone marrow blasts, No. (%)			
≥5%/<5%	5 (56%)/4 (44%)	11 (44%)/14 (56%)	>0.05
Extramedullary disease, No. (%)			
Yes/no	2 (22%)/7 (78%)	0 (0%)/25 (100%)	>0.05
T315I mutation, No. (%)			
Yes/no	7 (78%)/2 (22%)	11 (44%)/14 (56%)	>0.05
Number of previous therapies, No. (%)			
<4/>3	6 (67%)/3 (33%)	18 (72%)/7 (28%)	>0.05
TKI, No. (%)			
1–2 generation/>2 generation	7 (78%)/2 (22%)	20 (80%)/5 (20%)	>0.05
Previous allo-HSCT, No. (%)			
Yes/no	1 (11%)/8 (89%)	3 (12%)/22 (88%)	>0.05
allo-HSCT after CAR-T, No. (%)			
Yes/no	4 (44%)/5 (56%)	12 (48%)/13 (52%)	>0.05
CRS, No. (%)			
0–2/>2	8 (89%)/1 (11%)	18 (72%)/7 (28%)	>0.05
ICANS, No. (%)			
0–2/>2	9 (100%)/0 (0%)	25 (100%)/0 (0%)	>0.05

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; TKI, tyrosine kinase inhibitors; WBC, white blood cells.

with no statistical significance (Figure 1C). Relapse after CAR T-cell therapy has become a key challenging issue to address in patients with B-ALL.[10] Of the responding patients, 3/4 (75%) of CML-LBP patients relapsed at 2.7, 3.3, and 11.6 months, and 8/21 (38%) of patients with de novo Ph-positive B-ALL relapsed in a median time of 6.6 months (range, 1.3–8.9 months) after CAR T-cell therapy. The 2-year DOR of the two cohorts was 25% (1/4) and 43% (9/21), respectively ($p = 0.240$) (Figure 1D). The 2-year CIR of the two cohorts was 75% (3/4) and 52% (11/21), respectively ($p = 0.110$) (Figure 1E). The median EFS was 2.3 months (range, 0.6–27.2 months) in patients with CML-LBP and 9.8 months (range, 0.3–9.2 months) in de novo Ph-positive B-ALL, and patients with CML-LBP had a significantly lower 4-year EFS than those with de novo Ph-positive ALL ($p = 0.017$) (Figure 1F). The median OS was 14 months (range, 0.6–63.8 months) in patients with CML-LBP and 30 months (range, 0.5–79.2 months) in de novo Ph-positive B-ALL, respectively. The 5-year OS was comparable between the two cohorts ($p = 0.170$) (Figure 1G).

A worse response to anti-CD19 CAR T-cell therapy is independently associated with worse survival in B-ALL patients.[11] In accordance with this report, our data showed that patients with CML-LBP had poorer CHR and worse EFS after anti-CD19 CAR T-cell therapy as compared with de novo Ph-positive B-ALL patients, especially in those with BM blasts higher than 5% or extramedullary involvement. In an ongoing phase 2 study, 5/6 (83%) of CML-LBP patients achieved response with ponatinib in combination with blinatumomab, but only 2/6 (33%) patients showed patients showed molecularly undetectable leukemia.[12] Therefore, the efficacy of CAR T-cell versus ponatinib plus blinatumomab in CML-LBP patients needed to be explored in more patients. Some reports have demonstrated that TKIs and anti-CD19 CAR T-cells could not eliminate the CML stem cell population.[13,14] Therefore, an allogeneic hematopoietic stem cell transplant is necessary for patients with CML-LBP who achieve MMR with anti-CD19 CAR T-cell treatment.

In summary, our data suggest that patients with CML-LBP had inferior response and EFS to anti-CD19 CAR T-cell therapy compared to those with de novo Ph-positive B-ALL, implying that other immunotherapies are needed for CML-LBP patients. Due to the limited number of CML-LBP patients in this study, our findings need to be validated in multicenter, prospective studies. In addition, the mechanisms underlying the poor response of CML-LBP to anti-CD19 CAR T-cell therapy deserve further investigation.

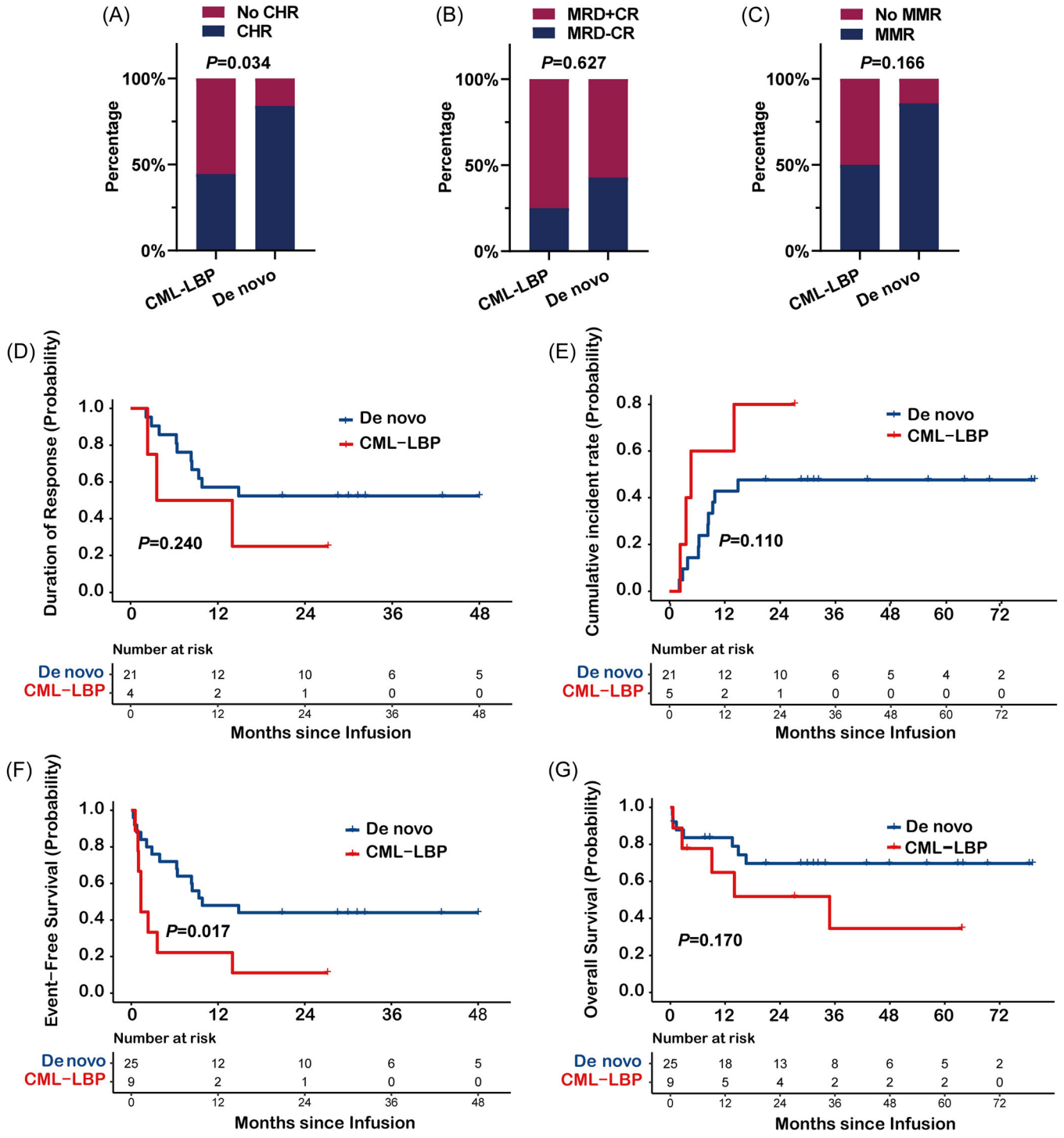

FIGURE 1 The treatment response and survival of patients with CML-LBP and de novo Ph-positive B-ALL to anti-CD19 CAR T-cell therapy. (A–C) Percentage of patients of the two cohorts according to the CHR status (A), MRD status (B), and MMR status (C). (D, E) DOR (D) and CIR (E) of the two cohorts. (F, G) EFS (F) and OS (G) of the two cohorts. CHR, complete hematologic remission; CIR, cumulative incident rate; CML-LBP, chronic myeloid leukemia in the lymphoid blast phase; DOR, duration of response; EFS, event-free survival; MMR, major molecular remission; MRD, measurable residual disease; OS, overall survival; Ph-positive B-ALL, Philadelphia-positive acute B-cell lymphoblastic leukemia.

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AUTHOR CONTRIBUTIONS

Wen-Jie Gong, Hai-Ping Dai, and Sheng-Li Xue conceived, designed the clinical trial, and edited the manuscript. Mei-Jing Liu, Kai-Wen Tan, Han-Yu Cao, and Si-Man Huang collected, analyzed the data and

wrote the manuscript. Mei-Jing Liu and Kai-Wen Tan collected the data. Han-Yu Cao and Si-Man Huang discussed the clinical trial. Wen-Jie Gong and Hai-Ping Dai read the manuscript and gave comments. All authors reviewed the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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