Research article

CD19 chimeric antigen receptor-T cells as bridging therapy to allogeneic hematopoietic cell transplantation improves outcome in patients with refractory/relapsed B-cell acute lymphoblastic leukemia

Jie Liu [b,1], Mengyuan Xu [a,1], Xiaoqian Zhang [a], Zhuo Zhang [a], Tao Zhong [a],
Hongjuan Yu [b], Yueyue Fu [b], Hongbin Meng [b], Jiawei Feng [a], Xindi Zou [a],
Xueying Han [a], Liqing Kang [c], Lei Yu [c], Limin Li [a,b,*]

[a] *Department of Hematology, South University of Science and Technology Hospital, Shenzhen, Guangdong, PR China*
[b] *Department of Hematology, The First Affiliated Hospital, Harbin Medical University, The Institute of the Hematology and Oncology of Heilongjiang Province, Harbin, Heilongjiang, PR China*
[c] *Shanghai Unicar-Therapy Bio-medicine Technology Co., Ltd, Shanghai, PR China*

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ABSTRACT

Chimeric antigen receptor (CAR)-T cell therapy has been confirmed improving remission rates in refractory patients or relapsed B-cell acute lymphoblastic leukemia (R/R B-ALL). However, the added benefits of undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) following CAR-T therapy remain a subject of debate. In this research we investigated the efficiency and long-term outcomes of CD19 CAR-T bridging with allo-HSCT in R/R B-ALL patients. A total of 42 patients were brought into the cohort studies. Our findings revealed that patients who appected CAR-T followed by HSCT had a 1-year overall survival (OS) rate of 70 % and a 1-year leukemia-free survival (LFS) rate of 95 %. Moreover, patients who underwent this combined treatment had higher OS and LFS rates compared to those who received CAR-T therapy alone. In conclusion, the results of this clinical trial provide compelling evidence for the safety and efficacy of using CAR-T therapy as a bridging strategy to allo-HSCT in patients with R/R B-ALL.

1. Introduction

Refractory/relapsed B-cell acute lymphoblastic leukemia (R/R B-ALL) presents a grave prognosis in patients of different ages, with a median survival expectation of less than 6 months and a reported 3-year overall survival (OS) rate of just 14–16 % [1]. Despite efforts with intensive chemotherapy, targeted drugs, and allogeneic hematopoietic stem cell transplantation (allo-HSCT), satisfactory remission rates have remained elusive [2–4]. There is an urgent need for new treatments.

Chimeric antigen receptor (CAR)-T cell therapy has become a promising new option, instilling hope in R/R B-ALL patients. Clinical findings from multiple institutions have demonstrated impressive complete remission (CR) rates ranging from 68 % to 94 % following CAR-T therapy [5–7]. However, studies have also indicated a notable relapse rate of 21–45 % after CAR-T treatment [8,9], highlighting the crucial nature of maintaining remission post-CAR-T treatment.

Historically, hematopoietic stem cell transplantation (HSCT) has been a cornerstone therapy for R/R B-ALL with the potential for cure [10,11]. Research suggests that utilizing CAR-T therapy in conjunction with allo-HSCT may reduce relapse rates, improve event-free survival (EFS), and enhance OS in R/R B-ALL patients [12,13], with some studies demonstrating an extended median follow-up period of 49 months. Our team has previously reported promising treatment responses, survival outcomes, and safety appraisal associated with CAR-T therapy in the management of R/R B-ALL [17]. In our current study, we perormed a retrospective
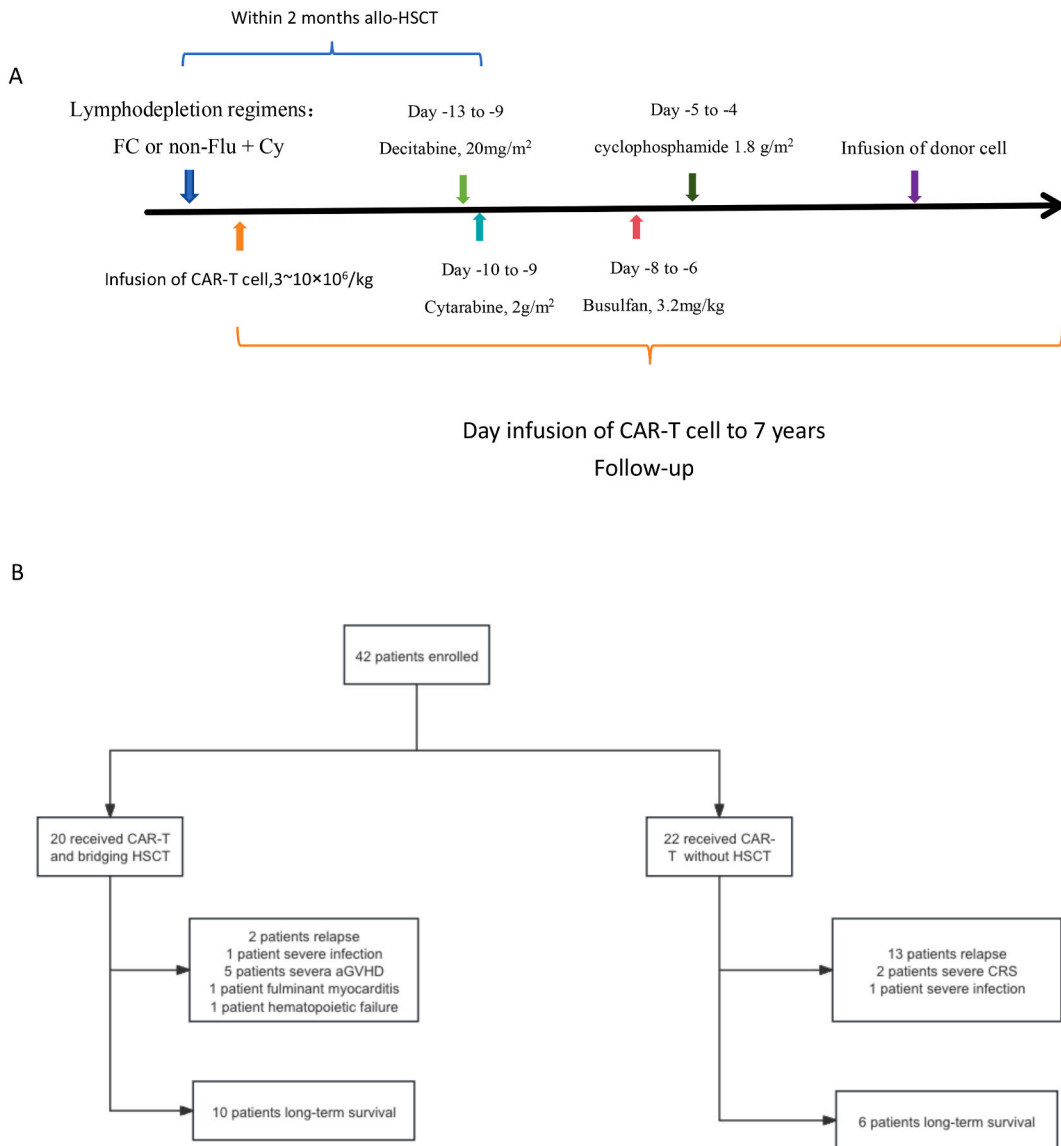

Fig. 1. Study design and trial profile. A, Patients underwent leukapheresis, lymphodepleting chemotherapy, and infusion of CAR-T cells. Suitable patients received allo-HSCT within 2 months after CAR-T therapy. The follow-up was scheduled to last 7 years. B, the treatment flow of 42 patients, including 20 CAR-T bridging HSCT patients and 22 CAR-T alone patients.

evaluation to evaluate the effectiveness and long-term survival outcomes of CAR-T therapy bridged to allo-HSCT compared to CAR-T therapy alone for patients with R/R B-ALL.

2. Methods

2.1. Patients and study design

A retrospective analysis was performed in 42 R/R B-ALL patients who received CAR-T therapy bridged to HSCT(n = 20) or un-bridged (n = 22) in The First Affiliated Hospital of Harbin Medical University from August 2015 to May 2023. The inclusion criteria were: (a) the CD19$^+$ B-ALL patients based on MICM (morphology、immunology、cytogenetics、molecular biology) ; (b) presented with refractory or relapsed disease; (c) underwent CAR-T cell therapy; (d) patients with complete and accessible medical and regular review records, those with lymphoma or complicated with other malignancies were excluded.

2.2. Baseline data collection

The collection of baseline data, which included gender, age, previous chemotherapies, status of disease (refractory or/and relapsed), disease burden (BM blasts, extramedullary disease) and lymphodepletion regimens before CAR-T cells infusion, fusion gene, gene mutation, characteristics of CAR-T cells and the data involved with HSCT, were from patients' electronic medical records, .The data collection got consent from all enrolling participants.

2.3. CAR-T cell production

The overall study design was described in Fig. 1A, and the treatment flow was shown in Fig. 1B. After confirming CAR-T therapy qualification and CAR-T manufacturing feasibility, we used lymphocyte separation medium to separate the patients' peripheral blood mononuclear cells (PBMCs) from patients' leukocytes. Then, used CD3 MicroBeads (MiltenyiBiotec GmbH, Shanghai, China) to isolate CD3$^+$ T cells from PBMCs, activated T cells by stimulating with antiCD3/CD28 monoclonal antibodies (mAbs) 24 h, and amplified with recombinant human interleukin-2 (IL-2100 IU/mL) for 48 h. Then we transduced excitation T cells with supernatants of lentiviral vector. The vector encodes a antigen receptor for chimeric T cell, which was composed of a single-chain fragment variable (scFv) for specific CD19/CD22, the transmembrane domains from CD8α and intracellular domain from 4-1BB).The details were shown in our previous article [17].

2.4. Toxicity assessment with CAR T-cell treated

Under the guidance of the American Society for Transplantation and Cellular Therapy (ASTCT) consensus, Cytokine release syndrome (CRS) and neurotoxicity were graded [15,16,18–20]. Severe CRS is defined as CRS of grade 3 or higher, and severe neurotoxicity is identified when seizure or toxicity is grade 3 or higher.

2.5. Clinical transplant protocol

Cyclophosphamide (Cy) (300 mg/m^2) plus fludarabine (Flu) (30 mg/m^2) for 5 days were as lymphodepletion regimen for some enrolling patients and other Cy-based(300 mg/m^2) lymphodepletion regimens for the other patients before CAR-T cell infusion. After the lymphatic clearance chemotherapy, CAR-T cell with doses ranging from 3×10^6/kg to 10×10^6/kg was infused on day 2 or day 3, which was 10 %, 30 %, and 60 % of the expected total dose depended on reaction to infusion. Patients were shifted into intensive care unit (ICU) when appearing severe CRS, and received anti-IL-6 treatment along with tocilizumab and corticosteroids in accordance with the clinical symptoms. The details were shown in our previous article [17].

After CAR-T treatment, patients who meet all the following conditions received HSCT: (a) MRD negative; (b) The level of inflammatory factors in the patient decreased to less than twice the normal value, and there was no CRS manifestation; (c) Normal organ function; (d) Donors with HLA matching; (e) Economic conditions can support. All recipients received haploidentical allo-HSCT. Patients received intensive myeloablative conditioning regimens, which based on busulfan (Bu) plus cyclophosphamide according to each patient's status before transplantation. Decitabine was given daily at 20 mg/m^2 from day −13 to day −9,Cytarabine was used daily at 2 g/m^2 from day −10 to day −9, Bu was administered daily at 3.2 mg/kg from day −8 to day −6, Cyclophosphamide 1.8 g/m^2/day was then applied from day −5 to day −4. The recipients received mononuclear cells at 10 to 25×10^8/kg and CD34$^+$ cells at 4 to 6 $\times 10^6$/kg. Thymoglobuline (ATG, Sanofifi-Aventis, dose of 2.5 mg/kg daily for 4 days) was employed on days −5 to −2 in haploidentical transplantation. Cyclosporine, short-term methotrexate (15 mg/m^2 on day +1, then 10 mg/m^2 on days +3, +6, and +11 intravenous injection after migration), and mycophenolate mofetil was used for graft-versus-host disease (GVHD) prophylaxis and the duration of immunosuppression ranged from 3 to 12 months according to patient GVHD status. The donor recieved granulocyte colony-stimulating factor (G-CSF) to mobilize grafts from BM and peripheral blood (PB) cells as what mentioned before [21]. The modified Glucksberg criteria defined and graded the acute GVHD (aGVHD) [22–25]. Chronic GVHD (cGVHD) was diagnosed and graded under the guidance of the 2014 National Institutes of Health consensus [26].

Table 1
Baseline characteristics of the patients.

Characteristics	CAR-T bridgingallo-HSCT (n = 20)	CAR-T alone (n = 22)	z/χ2	P
Age (years)–no. (%)	16 (11.5–35.75)	11.5 (5.5–17)	2.22	0.0265
Age ≥13			6.31	0.012
No	5 (25)	14 (63.64)		
Yes	15 (75)	8 (36.36)		
Age ≥18			2.34	0.1262
No	11 (55)	17 (77.27)		
Yes	9 (45)	5 (22.73)		
Gender			0.06	0.8085
Male	12 (60)	14 (63.64)		
Female	8 (40)	8 (36.36)		
Number of previous chemotherapies			7.64	0.0057
< 4	13 (65)	5 (22.73)		
≥ 4	7 (35)	17 (77.27)		
Refractory disease			3.58	0.0585
No	14 (70)	9 (40.91)		
Yes	6 (30)	13 (59.09)		
Relapsed disease			<0.01	>0.9999
No	2 (10)	2 (9.09)		
Yes	18 (90)	20 (90.91)		
Extramedullary disease			0.89	0.3459
No	8 (40)	12 (54.55)		
Yes	12 (60)	10 (45.45)		
CNSL			1.46	0.2265
No	12 (60)	17 (77.27)		
Yes	8 (40)	5 (22.73)		
BAR/ABL1 (P190)			6.48	0.0109
Negative	10 (50)	19 (86.36)		
Positive	10 (50)	3 (13.64)		
SH2B3 mutation			0	0.9522
Negative	12 (60)	13 (59.09)		
Positive	8 (40)	9 (40.91)		
PAX5 mutation			0.31	0.5805
Negative	12 (60)	15 (68.18)		
Positive	8 (40)	7 (31.82)		
WBC ≥30 (× 109/L)			1.62	0.2037
No	13 (65)	10 (45.45)		
Yes	7 (35)	12 (54.55)		
Lymphodepletion regimens			5.6	0.018
FC	1 (5)	9 (40.91)		
Non-Flu + Cy	19 (95)	13 (59.09)		
CR after CAR-T				
Yes	20 (100)	22 (100)		
CR before CAR-T			4.55	0.033
No	3 (15)	10 (45.45)		
Yes	17 (85)	12 (54.55)		
MRD before CAR-T			0.01	0.9317
Positive	18 (90)	21 (95.45)		
Negative	2 (10)	1 (4.55)		
Days of MRD after CAR-T	12.5 (8,14.25)	14.5 (10,17.75)	−1.53	0.1272
MRD after CAR-T			–	>0.9999
Positive	0 (0)	1 (4.55)		
Negative	20 (100)	21 (95.45)		
Severe CRS ≥3 grade			1.19	0.2747
No	15 (75)	13 (59.09)		
Yes	5 (25)	9 (40.91)		
Neurotoxicity			0.03	0.8671
No	15 (75)	16 (72.73)		
Yes	5 (25)	6 (27.27)		
Capillary leak syndrome			0.63	0.4263
No	15 (75)	14 (63.64)		
Yes	5 (25)	8 (36.36)		
Hepatic injury ≥2 grade			0.03	0.8718
No	15 (75)	18 (81.82)		
Yes	5 (25)	4 (18.18)		
Heart injury			0.18	0.6701
No	19 (95)	19 (86.36)		
Yes	1 (5)	3 (13.64)		
Hematologic toxicities ≥4 grade			6.19	0.0129

Table 1 (*continued*)

Characteristics	CAR-T bridgingallo-HSCT (n = 20)	CAR-T alone (n = 22)	z/χ2	P
No	11 (55)	4 (18.18)		
Yes	9 (45)	18 (81.82)		
Infection			2.14	0.1432
No	16 (80)	13 (59.09)		
Yes	4 (20)	9 (40.91)		
Treatments for CRS			0.96	0.3266
No	13(65)	11 (50)		
Yes	7 (35)	11 (50)		
Glucocorticoids			0.24	0.6252
No	15 (75)	15 (68.18)		
Yes	5 (25)	7 (31.82)		
Tocilizumab injection			2.78	0.0957
No	15 (75)	11 (50)		
Yes	5(25)	11(50)		

2.6. Definitions

The definition of CR and CR with incomplete count recovery (CRi) was in accordance with the National Cancer Comprehensive Network (NCCN) Guideline 1.2018 [27]. MRD-negative is defined when Multiparameter flow cytometry can not detect leukemic cells at a sensitivity threshold of $10-4$ (<0.01 %) bone marrow mononuclear cells and RT-PCR method can not detect leukemia-related fusion gene. Refractory disease was defined as failure at the end of induction treatment to CR or involved with extramedullary disease or continuing MRD-positive for 3–6 months. According to the NCCN Guidelines of Acute Lymphoblastic Leukemia (Version 1.2018),relapsed disease was defined as reappearance of blasts in the blood or BM (>5 %) or in any extramedullary site after a CR. The calculation of LFS and OS were from the day of CAR-T therapy to the day of positive-MRD or positive fusion gene or the last follow-up time or death.

2.7. Statistical analysis

R 4.1.0 wad used for statistical analysis. If the numerical variables obeyed normal distribution, the mean ± standard deviation was used to represent, and the difference between the two groups was compared by *t*-test. When the numerical variables were not normally distributed, the median (upper quartile, lower quartile) was used, and the differences between the two groups was compared by the Wilcoxon signed-ranktest. Categorical variables were represented by the number of cases (%), and differences between the two groups were compared by χ^2 test, calculating the deviation between the actual observed value and the theoretical inferred value of the sample
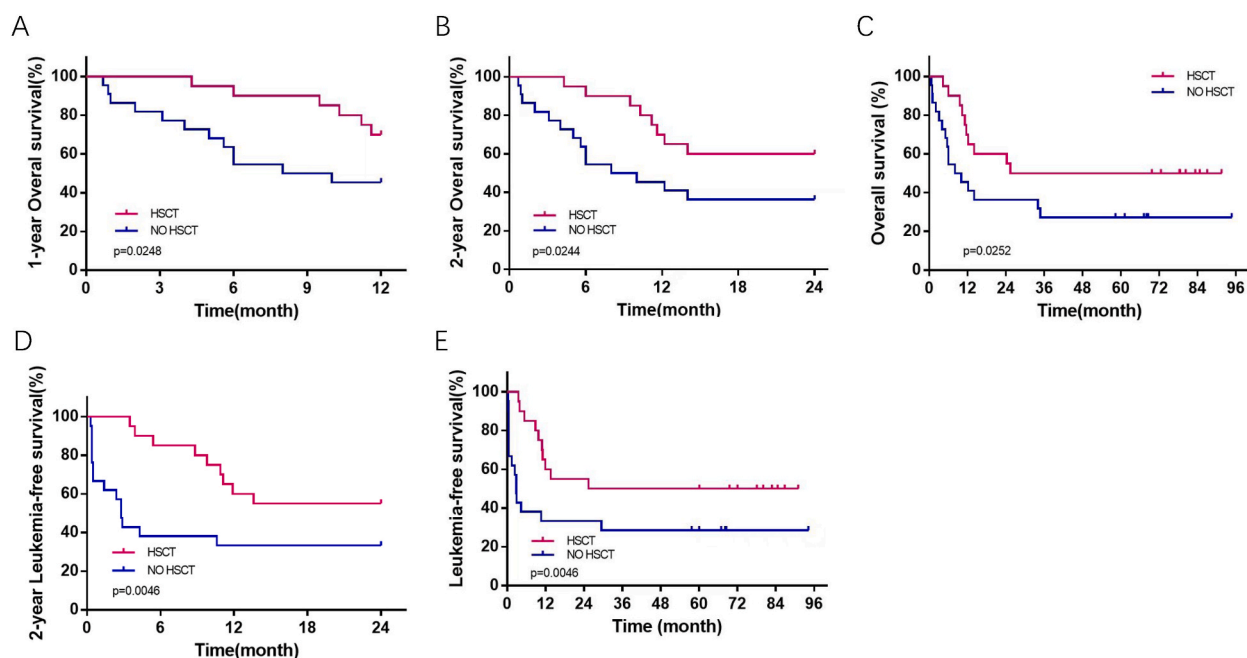

Fig. 2. 1-year OS (A), 2-year OS (B) and OS (C); 2-year LFS (D), LFS (E) of the CAR-T bridging HSCT and CAR-T alone group.

[28]. If the χ^2 test conditions were disobeyed, the Fisher's exact test probability method was used to compare the differences between the two groups. The log-rank test was used to compare the OS and leukemia-free survival (LFS) of the two groups, and survival curves were drawn to visualize the survival of the two groups and compare the differences between groups. COX proportional risk model is an important model in survival analysis, analyzing the influence of many factors on survival time [29], and it was used to explore the impact of these factors on OS and LFS. To compare the survival of patients in two groups, Kaplan-Meier curves were plotted, which mainly analyze the impact of a single factor on survival [30]. $P < 0.05$ was statistically significant.

3. Results

3.1. Patient characteristics

Table 1 summarizes the detailed characteristics of the two groups. The median age of patients in the CAR-T bridging allo-HSCT group was 16 years (interquartile range: 11.5–35.75), whereas in the CAR-T alone group, it was 11.5 years (interquartile range: 5.5–17). The CAR-T bridging allo-HSCT group consisted of 30 % patients with refractory disease and 90 % patients with relapsed disease, while the 59.09 % of CAR-T alone group patients was refractory and 90.91 % was relapsed. Additionally, in the CAR-T bridging allo-HSCT group, 60 % of patients had extramedullary disease, and 50 % of patients had the BCR-ABL1 fusion gene. A statistically significant difference was observed in complete remission (CR) status before CAR-T cell therapy (P = 0.033), whereas no difference was noted in minimal residual disease (MRD) status before CAR-T between the two groups (P = 0.9317).

3.2. Allogeneic hematopoietic cell transplantation after CAR-T therapy improve R/R B-ALL outcome

To evaluate the safety and efficacy of HSCT as a consolidation therapy after CAR-T treatment, we conducted Kaplan-Meier analysis correlating patients' long-term survival outcomes with HSCT status. With a median follow-up of 13.5 months (range: 0.9–90.7 months) for surviving patients, 10 patients in the HSCT group achieved long-term survival compared to only 6 patients in the CAR-T alone group, as illustrated in Fig. 1B. The 1-year overall survival (OS) rate was 70 % in the HSCT group, significantly higher than the 45.45 % rate in the CAR-T alone group (P = 0.0248) (Fig. 2A). Similarly, the 2-year OS rate was 60 % in the HSCT group versus 36.36 % in the CAR-T alone group (P = 0.0244) (Fig. 2B). The OS rates remained around 50 % up to the latest follow-up beyond 24 months post-transplantation (Table S1), with the HSCT group showing superior OS compared to the CAR-T alone group (P = 0.0252) (Fig. 2C). The 1-year and 2-year leukemia-free survival (LFS) rates were 60 % and 55 %, respectively, in the HSCT group, higher than the 31.82 % LFS rate in the CAR-T alone group (P < 0.05) (Fig. 2D and E), with the LFS rate maintaining at approximately 50 % in the HSCT group versus declining to 27.27 % in the CAR-T alone group beyond 24 months post-treatment (Table 2). These results indicated that combining CAR-T therapy with bridging to allo-HSCT improves outcomes in refractory/relapsed patients with acute B-cell lymphoblastic leukemia.

3.3. Cox regression analysis of OS in CAR-T and bridging HSCT therapy

Exploring potential factors influencing long-term remission after CAR-T bridging HSCT, we conducted Cox proportional hazards regression analysis to assess the relationship between patients' baseline characteristics and prognostic outcomes. Univariate analysis highlighted that refractory disease (≥5 % vs. <5 %) (Hazard ratio (HR) = 2.78, P = 0.0461), relapse post-CAR-T (HR = 4.78, P = 0.0206), and adverse reactions of CAR-T were associated with poor OS, including severe CRS grade (≥3 vs.<3) (HR = 3.3, P = 0.0212), capillary leak syndrome (HR = 3.29, P = 0.0204) and infection (HR = 3.43, P = 0.0194), while CR before CAR-T (HR = 0.36, P = 0.0461) was involved with better OS (Table S4) in CART alone group. Multi-analysis did not identify any remarkable factors involved with OS in the CAR-T alone group. However, in the combined analysis of all patients, factors like undergoing HSCT (HR = 0.44, P = 0.0446), a non-Flu + Cy lymphodepletion regimen (HR = 0.32, P = 0.0078), and accepting CR pre-CAR-T cell treatment (HR = 0.32, P = 0.0045) were associated with improved OS, whereas bone marrow blast ≥5 % pre-CAR-T therapy (HR = 3.15, P = 0.0045), post-CAR-T relapse (HR = 4.83, P = 0.0002), severe CRS grade ≥3 (HR = 2.27, P = 0.0405), capillary leak syndrome (HR = 2.77, P = 0.0111), heart injury (HR = 3.91, P = 0.0128), and infections (HR = 2.77, P = 0.0113) were linked to poorer OS (Table S6). Unfortunately, the multivariate analysis did not reveal any factors remarkable involved with OS (Table 2).

Table 2
Multivariate analysis of risk factors for OS in two groups.

Factor	*β*	*Se*	*z*	*P*	HR (95%CI)
HSCT vs. No HSCT	0.22	0.76	0.29	0.7752	1.24 (0.28, 5.5)
Bone marrow blast before CAR-T (≥5 % vs. < 5 %)	1.07	0.57	1.88	0.0602	2.92 (0.96, 8.95)
Lymphodepletion regimens (non-Flu + Cy vs. Flu + Cy)	−0.62	0.64	−0.97	0.3332	0.54 (0.15, 1.89)
Relapse after CAR-T (yes vs. no)	1.03	0.8	1.29	0.1978	2.79 (0.58, 13.36)
Severe CRS grade (≥3 vs. < 3)	0.51	0.72	0.71	0.4779	1.66 (0.41, 6.76)
Capillary leak syndrome (yes vs. no)	0.54	1.02	0.53	0.5942	1.72 (0.23, 12.78)
Heart injury (yes vs. no)	0.93	0.87	1.07	0.285	2.54 (0.46, 14.06)
Infection (yes vs. no)	−0.71	0.75	−0.95	0.3437	0.49 (0.11, 2.13)

3.4. Cox regression analysis of LFS in CAR-T and bridging HSCT therapy

Examining the subgroup analysis related to leukemia-free survival (LFS), no factors were found to be involved with LFS in the HSCT group. Univariate Cox analysis indicated that post-CAR-T infection (HR = 3.44, P = 0.0364) was linked to poorer LFS, while the multivariate analysis did not identify any factors affecting LFS in the CAR-T alone group. In addition, univariate analysis for all patients displayed that undergoing HSCT (HR = 0.1, P = 0.003), achieving CR pre-CAR-T (HR = 0.28, P = 0.0165), and a non-Flu + Cy lymphodepletion regimen (HR = 0.29, P = 0.0222) were involved with better LFS, whereas refractory disease status (HR = 3.38, P = 0.0272), bone marrow blast ≥5 % pre-CAR-T therapy (HR = 3.57, P = 0.0165), post-CAR-T relapse (HR = 37.28, P < 0.0001), severe hematologic toxicities ≥4 grade (HR = 5.34, P = 0.0278), and infections (HR = 3.05, P = 0.0338) were linked to poorer LFS (Table S9). The multivariate analysis did not identify any factors significantly associated with LFS (Table 3).

3.5. Effects of CRS classification, CRES and cytokines on the OS of CAR-T bridged to HSCT patients

Further insights into patients bridged to HSCT following CAR-T therapy revealed cytokine levels post-CAR-T treatment, including IL-6, IL-10, and IFN-γ (excluding TNF), as correlated with worse overall survival (OS) in the CAR-T bridged to HSCT cohort (Fig. 3C–F), whereas CRS classification and CRES did not significantly impact OS (Fig. 3A–B).

3.6. aGVHD and cGVHD for patients caused by CAR-T bridging to haplo-HSCT

In our research, the CAR-T bridged to HSCT group exhibited a 70 % incidence of acute GVHD (aGVHD), with 5 patients diagnosed with Grade IV aGVHD, including 4 cases of hepatic aGVHD and 1 case of skin aGVHD. Additionally, chronic GVHD occurred in 6 patients, with 1 case of severe cGVHD recorded (Table 4).

4. Discussion

Relapsed/refractory (R/R) B-ALL is involved with a particularly bleak prognosis. While CAR-T cell treatment offers a beacon of hope for R/R B-ALL patients, a subset may still experience relapse during this treatment [31]. Patients with MRD-positive before undergoing allo-HSCT show poorer prognoses compared to MRD-negative individuals [32].Therefore, we carefully included appropriate patients who received allo-HSCT as a consistent treatment post-CAR-T cell therapy to sustain long-term remission. Encouragingly, we observed extended survival in certain R/R B-ALL patients who accepted allo-HSCT following CAR-T cell therapy. In our study, the 1-year overall survival (OS) was 70 %, the 2-year OS was 60 %, the 1-year leukemia-free survival (LFS) was 60 %, and the 2-year LFS was 55 %. Notably, the OS and LFS rates remained at 50 % after 3 years up to the latest follow-up post-transplantation. Our 1-year OS after HSCT was slightly lower than reported in the literature, potentially due to the side effects of CAR-T cell therapy and increased early non-relapse mortality [8]. However, the relapse rate was significantly decreased in the bridging transplantation group compared to the non-bridge group. Furthermore, our data indicates that both OS and LFS of patients, with or without bridging HSCT, declined after 2 years, suggesting ongoing relapse risk, though the bridge group exhibited significantly lower relapse rates. Moreover, we observed no decrease in OS and LFS even after 3 years post bridging HSCT with long-term follow-up, indicating a relapse risk window of within 3 years. Impressively, the longest survival recorded in the bridging HSCT group at our institution was 91.5 months at the time of analysis.

Some studies have analyzed influencing factors on long-term remission after CAR-T bridging haplo-HSCT [33]. Multivariate analysis showed that MRD-positive at transplantation is an independent factor involved with lower LFS (P = 0.005), OS (P = 0.035), and a higher cumulative relapse incidence rate (P = 0.045) [12]. In our investigation, the univariate analysis did not identify statistically significant factors in the bridging HSCT group, so multivariate analysis was not performed. Considering all patients were MRD-negative before bridge HSCT, the effect of negative MRD on OS and LFS was not observed. The findings emphasized the significance of CR status before CAR-T cell treatment, relapse occurrence, and severe CRS post CAR-T treatment on OS, not only in the non-transplantation group but also in all-enrolled patients. However, no factors affecting OS and LFS were identified in the multivariate analysis of the two groups, likely due to the limited sample size. Additionally, the non-Flu + Cy lymphodepletion regimens demonstrated improved OS in the univariate analysis of risk factors across all patients, possibly influenced by statistical bias, as most of the regimen was in the transplant group, predominantly featuring decitabine + cyclophosphamide, known for both its immunomodulatory and antitumor effects.

Table 3

Multivariate analysis of risk factors for LFS in two groups.

| Factor	β	Se	z	P	HR (95%CI)
HSCT vs. No HSCT	18.73	11672.02	<0.01	0.9987	–
Refractory disease (yes vs. no)	−0.22	1.04	−0.21	0.8337	0.8 (0.1, 6.17)
Bone marrow blast before CAR-T (≥5 % vs. < 5 %)	1.38	0.97	1.42	0.1544	3.96 (0.6, 26.38)
Lymphodepletion regimens (non-Flu + Cy vs. Flu + Cy)	0.6	0.8	0.74	0.4571	1.82 (0.38, 8.74)
Relapse after CAR-T (yes vs. no)	22.34	11672.02	<0.01	0.9985	–
Hematologic toxicities grade (≥4 vs. < 4)	0.03	1.01	0.03	0.9748	1.03 (0.14, 7.53)
Infection (yes vs. no)	−0.46	0.76	−0.6	0.5452	0.63 (0.14, 2.81)
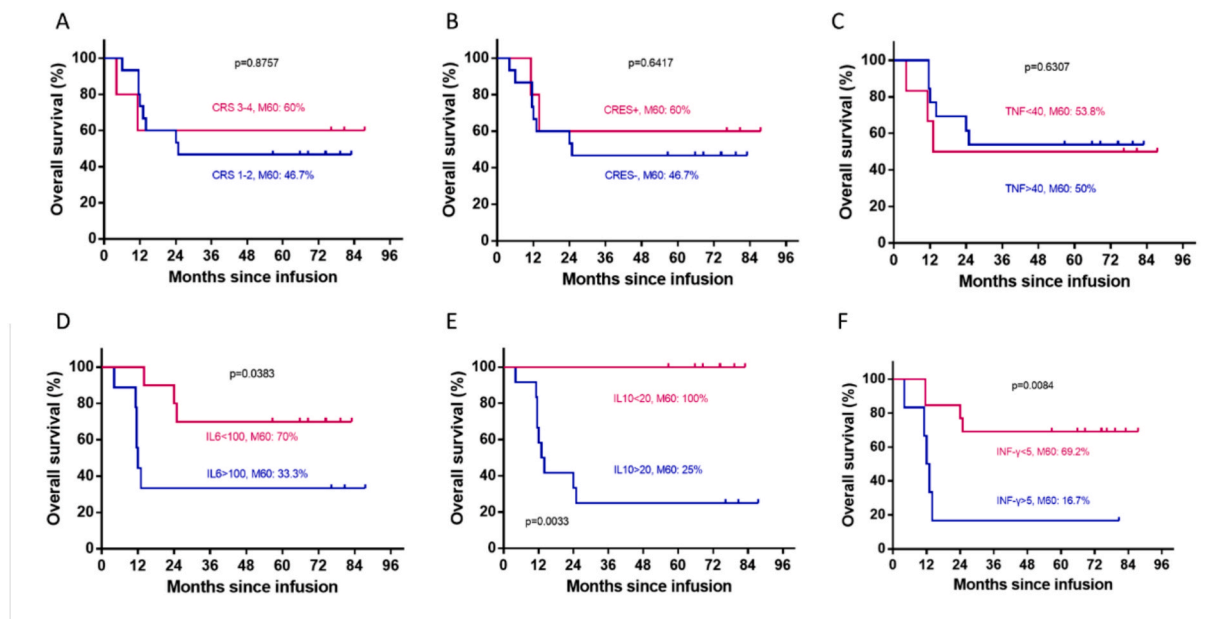
Fig. 3. Effects of CRS classification, CRES and cytokines on the OS of CAR-T bridged to HSCT patients. A, B, C: CRS classification, CRES and TNF have no significant effect on the OS of CAR-T bridged to HSCT patients, and there is no statistical difference between the two groups. D, E, F: The OS of patients with increased levels of IL-6, IL10, and IFN-γ shown in the figure was significantly lower after transplantation, with statistical differences.

Table 4
GVHD of CAR-T bridging to hematopoietic stem cell transplantation.

Characteristics	n(%)
aGVHD(n/%)	
No	6(30)
Yes	14(70)
Degreeof aGVHD(n/%)	
0	6(30)
1	3(15)
2	6(30)
4	5(25)
aGVHD_≥3 grade(n/%)	
No	15(75)
Yes	5(25)
cGVHD(n/%)	
No	14(70)
Yes	6(30)
Mild cGVHD(n/%)	4(20)
Moderate cGVHD(n/%)	1(5)
Severe cGVHD(n/%)	1(5)

Our study, encompassing univariate and multivariate analyses, showed that central nervous system leukemia (CNSL) did not impact the overall survival (OS) and leukemia-free survival (LFS) of patients, regardless of bridge transplantation. Intriguingly, our results unveiled the persistent presence of CAR-T cells in the cerebrospinal fluid of select patients, suggesting potential sustained benefits for patients with CNSL undergoing CAR-T bridging therapy followed by HSCT. We also noted a high complete remission (CR) rate of 92.3 % in CAR-T cell therapy for BCR-ABL + ALL, with a CR rate of MRD-negative cases at 76.9 %. Notably, some BCR-ABL + ALL patients who underwent CAR-T bridged to haplo-HSCT maintained continuous remission without TKI maintenance therapy post-transplantation, indicating the potential to overcome high-risk genetic factors and play a role as an alternative therapy for these patients.

The incidence of Grade IV acute graft-versus-host disease (aGVHD) in our study was 25 %, surpassing reported rates in the literature [14], possibly influenced by small sample size statistical bias. Furthermore, we observed that peak levels of IL-6, IL-10, and IFN-γ during CAR-T cell therapy substantially impacted OS post haplo-HSCT, while CRS grade and CRES had no significant effects on OS in patients who underwent HSCT. This suggests that cytokine release serves as the initial step of CRS during CAR-T cell therapy, necessitating comprehensive organ-based impact analysis, with CRS-related damage potentially repaired before bridge HSCT.

Unfortunately, relevant studies on this aspect are lacking. However, our retrospective single-center analysis warrants validation through a larger, multi-center prospective study.

In conclusion, CAR-T cell therapy bridging allo-HSCT has demonstrated efficacy in lowering relapse rates and improving long-term survival among R/R B-ALL patients. Our findings suggest this combined approach is safe and effective for managing R/R B-ALL.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Boards of the First Affiliated Hospital of Harbin Medical University, and obtained written informed consents of all patients or their guardians. This study was retrospectively registered on ClinicalTrials. gov (https://clinicaltrials.gov/, no: NCT03423706).

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CRediT authorship contribution statement

Jie Liu: Conceptualization. **Mengyuan Xu:** Data curation. **Xiaoqian Zhang:** Formal analysis. **Zhuo Zhang:** Funding acquisition. **Tao Zhong:** Investigation. **Hongjuan Yu:** Methodology, Investigation. **Yueyue Fu:** Methodology. **Hongbin Meng:** Project administration. **Jiawei Feng:** Project administration. **Xindi Zou:** Project administration. **Xueying Han:** Resources. **Liqing Kang:** Software. **Lei Yu:** Supervision. **Limin Li:** Writing – review & editing, Writing – original draft, Visualization, Validation, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33937.

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