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Efficacy and safety comparison of CAR-T and blinatumomab immunotherapy as bridge-to-transplant strategies in relapsed/refractory B cell acute lymphoblastic leukemia

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Abstract

Background Despite recent advances, B cell acute lymphoblastic leukemia (B-ALL) remains a therapeutic challenge. Hematopoietic stem cell transplantation (HSCT) provides a potential cure but is hindered by various limitations. Emerging immunotherapies, including chimeric antigen receptor T cell (CAR-T) therapy and blinatumomab, have shown potential as bridging strategies to HSCT in relapsed/refractory (R/R) patients.

Methods This retrospective study was conducted at Tongji Hospital from March 2017 to March 2023 and involved 36 R/R B-ALL patients who underwent HSCT. Prior to transplantation, 27 patients received CD19/CD22 CAR-T therapy, while 9 received blinatumomab. The outcomes assessed included overall survival (OS), progression-free survival (PFS), graft-versus-host disease-free and relapse-free survival (GRFS), and non-relapse mortality (NRM), with comparisons between treatment groups. Hematopoietic reconstitution and transplant-related complications were also evaluated.

Results The median follow-up time was 28.07 months (range: 2.29–92.21 months). The 2-year OS, PFS, GRFS, and NRM rates of the entire cohort were 76.54%, 54.97%, 40.12%, and 9.93%, respectively. In the CAR-T and blinatumomab treatment groups before transplantation, the 2-year OS rates were 73.89% and 88.89% ($P=0.862$), the PFS rates were 59.03% and 44.44% ($P=0.501$), the GRFS rates were 47.86% and 13.89% ($P=0.083$), and the NRM rates were 8.52% and 11.11% ($P=0.713$), respectively. The safety profiles were similar, with no significant differences observed in hematopoietic reconstitution, infection, incidence of grade II-IV acute graft-versus-host disease (GVHD), or chronic GVHD incidence between the CAR-T and blinatumomab groups.

Conclusion CAR-T and blinatumomab therapies demonstrate comparable safety and efficacy as bridging treatments to HSCT in patients with R/R B-ALL. Further studies are needed to optimize these treatment strategies.

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Keywords Chimeric antigen receptor T cell, Blinatumomab, Hematopoietic stem cell transplantation, B-cell acute lymphoblastic leukemia

Introduction

B cell acute lymphoblastic leukemia (B-ALL) is a highly aggressive hematological malignancy with a poor prognosis, particularly in relapsed or refractory (R/R) patients [1, 2]; for these patients, the 3-year survival rate ranges from 25–40% [3]. Allogeneic hematopoietic stem cell transplantation (HSCT) has emerged as a potentially curative approach for B-ALL. However, for many patients with R/R disease, HSCT remains an unsuitable option due to their inability to achieve complete remission (CR) prior to transplantation. Pretransplant CR status is a critical prognostic factor that is strongly associated with successful engraftment, reduced morbidity, and improved survival outcomes [4]. In recent years, immunotherapy has emerged as a promising therapeutic option, demonstrating significant clinical advantages for R/R B-ALL patients. Two innovative immunotherapy approaches have demonstrated remarkable efficacy: chimeric antigen receptor T cell (CAR-T) therapy and bispecific antibody engagers.

CAR-T therapy involves engineering T cells to express chimeric antigen receptors that specifically target tumor-associated antigens, thereby mediating potent and precise antitumor activity. In patients with R/R B-ALL, CAR-T cell therapy has achieved CR rates of 63–93% at one month post-infusion [5, 6]. Furthermore, the progression-free survival (PFS) rate was 45%, and the overall survival (OS) rate was 60% at three years [7, 8]. Blinatumomab, a bispecific T-cell engager, enables CD3-positive T cells to recognize and eliminate CD19-positive blasts [9, 10]. Notably, blinatumomab has achieved a CR rate as high as 69% in patients with R/R B-ALL [11], leading to its approval for this formidable condition. Studies indicate that for heavily pretreated patients with R/R B-ALL, HSCT performed after achieving CR with blinatumomab resulted in impressive 2-year PFS and OS rates of 48% and 58%, respectively [12].

Bridging therapy prior to HSCT is intended to control disease, potentially increase response rates, and improve outcomes by providing a therapeutic "bridge" to definitive treatment [13–15]. However, for patients with R/R B-ALL, the understanding of the immune system alterations associated with CAR-T therapy and blinatumomab that could influence engraftment, increase the risk of graft-versus-host disease (GVHD), or affect long-term outcomes is limited. Moreover, the comparative effectiveness and safety of these two therapies in the pretransplant setting have yet to be thoroughly investigated.

This study aimed to conduct a comprehensive evaluation and comparison of the efficacy and safety profiles of CAR-T therapy and blinatumomab as bridging therapies for patients with R/R B-ALL at our center. By analyzing the relative strengths and potential limitations of each therapeutic approach, we seek to provide valuable insights for clinical decision-making and optimize management strategies for high-risk patients.

Methods

Patients and study design

This retrospective study included 36 patients with R/R B-ALL who received allogeneic HSCT subsequent to CAR-T or blinatumomab immunotherapy between March 2017 and March 2023 at our institution. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Tongji Hospital. Long-term follow-up was conducted, with a statistical cutoff date of March 31, 2024. The primary objectives of the study included posttransplant overall survival (OS), progression-free survival (PFS), non-relapse mortality (NRM), and incidence of acute and chronic GVHD, as well as graft-versus-host disease-free and relapse-free survival (GRFS), defined by relapse, death, Grade III–IV acute GVHD, or severe chronic GVHD.

Patients in the blinatumomab cohort received continuous intravenous infusions of blinatumomab (9 μg/day for the first 7 days and 28 μg/day thereafter) every 6 weeks for 4 weeks (up to 5 cycles). The CAR-T cohort underwent a single treatment with CD19/CD22 CAR-T cells (ChiCTR-OPN-16008526), which were generated following established protocols [16] (Supplementary Fig. 1).

Conditioning regimen and GVHD prophylaxis

All patients received a pretreatment regimen based on total body irradiation/cyclophosphamide (TBI/Cy), busulfan/cyclophosphamide (Bu/Cy), or fludarabine/busulfan (Flu/Bu) [17]. Specifically, the TBI/Cy regimen consisted of TBI (8–12 Gy) and cyclophosphamide (1.8 g/m^2/day, 2 days). The Bu/Cy regimen consisted of busulfan (3.2 mg/kg/day, 4 days) and cyclophosphamide (1.8 g/m^2/day, 2 days). The Flu/Bu regimen included fludarabine (30 mg/m^2/day, 5 days) and busulfan (3.2 mg/kg/day, 4 days).

Thirty-four patients with conditioning regimens of Bu/Cy or TBI/Cy received GVHD prophylaxis based on methotrexate (MTX, 15 mg/m2, day + 1, 10 mg/m2 day + 3 and day + 6), cyclosporine A (CsA, 2.5 mg/kg from day-7 and adjusted between 200 and 250 ng/mL for the first month, tapering according to patient condition) and mycophenolate mofetil (MMF, 15 mg/kg from day − 1 to day + 40). Two patients with conditioning regimen of Flu/

Bu received GVHD prophylaxis based on CsA (2.5 mg/kg from day + 1 and adjusted between 200 and 250 ng/mL for the first month, tapering according to patient condition), cyclophosphamide (PT-CY, 50 mg/kg day + 3 and day + 4), and MMF (15 mg/kg from day + 1 to day + 40). Anti-human thymocyte globulin (ATG: total dose 10 mg/kg) was used in patients who underwent haploidentical donor (HID) or matched unrelated donor (MUD) transplantation. ATG (total dose of 4–4.5 mg/kg) was used in patients with matched sibling donor (MSD) transplantation, donors and patients aged > 40 years.

Laboratory tests

Minimal residual disease (MRD) negativity was defined as bone marrow (BM) cells < 0.01% by flow cytometry or a real-time quantitative PCR copy ratio < 0.01% for patients with fusion mutations. Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) replication were monitored via real-time quantitative PCR [18, 19].

Definition and assessment

CR was defined as <5% naive and primitive lymphocytes in bone marrow blasts, >1 × 10^9/L neutrophil count, and >100 × 10^9/L platelet count, with no extramedullary disease. OS was defined as the time from transplantation until the time of death or follow-up cutoff. PFS was defined as the time from transplantation until the time of relapse, death, or follow-up cutoff. NRM was defined as death from any cause other than relapse occurring post-transplantation.

Neutrophil engraftment was defined as a neutrophil count of ≥ 0.5 × 10^9/L for the first 3 consecutive days without the use of stimulating factors. Platelet engraftment was defined as a platelet count of ≥ 20 × 10^9/L for 7 consecutive days without transfusion dependence. Acute GVHD (aGVHD) and chronic GVHD (cGVHD) were diagnosed and graded according to the modified Glucksberg grading scale [20] and the modified Seattle Classification Criteria [21]. GRFS was evaluated from the time of transplantation until the occurrence of relapse, Grade III-IV acute GVHD, severe chronic GVHD, death, or the follow-up cutoff. CMV reactivation was defined as CMV DNA level of ≥ 400 copies/mL in blood. EBV reactivation was defined as EBV DNA level of ≥ 500 copies/mL in plasma or peripheral blood mononuclear cells.

Statistical analysis

Statistical analyses were performed using SPSS (version 22.0), GraphPad Prism (version 8.0) and R (version 4.2.3). Independent samples t-tests and chi-square tests were used to determine differences in demographic and clinical variables between groups of patients. Survival and cumulative incidence were analyzed via Kaplan-Meier survival analysis, with comparisons by log-rank test. Sensitivity analyses were conducted using the inverse probability of treatment weighting (IPTW) adjustment. Adjustment for all covariates was performed through the IPTW methodology using the Cox regression analysis and the unadjusted and adjusted Kaplan–Meier curves were plotted. Multivariate Cox analysis was performed to evaluate the risk factors for prognosis. Multivariate analysis was performed via stepwise selection on the basis of the P value of variables with a P value < 0.10 in the univariate analysis. A P value < 0.05 was considered to indicate statistical significance.

Results

Patient baseline characteristics

This study included 36 patients, all of whom were diagnosed with R/R B-ALL. The baseline characteristics of the entire cohort are shown in Table 1. The median follow-up time was 28.07 months (range: 2.29–92.21 months). The median age of the patients was 27.5 years old (range: 6–58 years old). Among the participants, 10 exhibited primary refractory disease. Eighteen patients had one relapse, five had two relapses, and three had three or more relapses. Among the patients harboring Philadelphia chromosome (Ph)-positive genes, five had the T315I mutation. Six patients demonstrated extramedullary invasion prior to immunotherapy, and 4 patients had undergone HSCT before receiving immunotherapy.

Among the patients, 27 received CAR-T, while 9 patients were treated with blinatumomab prior to HSCT. No statistically significant differences were observed in the baseline characteristics between these two treatment groups. All patients achieved CR; however, 4 patients remained MRD positive after immunotherapy: 1 in the blinatumomab group and 3 in the CAR-T-cell group. Cytokine release syndrome (CRS) was observed in 29 patients, with no significant differences noted in the proportions of CRS grades 1–2 ($P = 0.686$) and CRS grade 3 ($P = 0.558$) between the groups. Additionally, 4 patients experienced immune effector cell-associated neurotoxicity syndrome (ICANS) following immunotherapy (Supplementary Table 1).

Post-immunotherapy, a total of 26 patients (72.22%) underwent haploidentical donor (HID) transplantation, 8 patients (22.22%) received matched sibling donor (MSD) transplantation, and 2 patients (5.56%) underwent matched unrelated donor (MUD) transplantation. No significant differences were observed in the distribution of graft types between the two groups ($P = 0.722$). The two groups were well matched in terms of donor age ($P = 0.111$), HCT-CI score ($P = 0.281$), conditioning regimen ($P = 1.000$), median CD34 cell count ($P = 0.820$), median nucleated cell count ($P = 0.621$), and GVHD prophylaxis ($P = 1.000$). Notably, the combination of peripheral blood (PB) and bone marrow (BM) as graft sources

Table 1 Patient and treatment characteristics

Characteristics	Whole Cohort (*n* = 36)	Blinatumomab (*n* = 9)	CAR-T (*n* = 27)	*P* Value
Age groups, years, n, (%)				0.409
>40	11(30.6%)	4(44.4%)	7(25.9%)	
≤ 40	25(69.4%)	5(55.6%)	20(74.1%)	
Gender (M/F)	20/16	6/3	14/13	0.700
Disease status, n, (%)				0.324
Primary refractory	10(27.8%)	4(44.4%)	6(22.2%)	
First relapse	18(50.0%)	4(44.4%)	14(51.9%)	
Second relapse	5(13.9%)	0(0.0%)	5(18.5%)	
≥Third relapse	3(8.3%)	1(11.2%)	2(7.4%)	
Genetics, n, (%)				
Ph-positive	13(36.1%)	4(44.4%)	9(33.3%)	0.693
TP53 mutation	2(5.6%)	0(0.0%)	2(7.4%)	-
MLL rearrangement	2(5.6%)	1(11.1%)	1(2.7%)	0.443
Ikaros isoform 6	5(13.9%)	1(11.1%)	4(14.8%)	1.000
E2A/PBX1 rearrangement	1(2.8%)	0(0.0%)	1(2.7%)	-
NOTCH1 mutation	1(2.8%)	0(0.0%)	1(2.7%)	-
Ph-like	4(11.1%)	1(11.1%)	3(11.1%)	1.000
Complex karyotype	9(25.0%)	2(22.2%)	7(25.9%)	1.000
Extramedullary disease before immunotherapy, n, (%)	3(8.3%)	0(0.0%)	3(11.1%)	-
MRD status pretransplant, n, (%)				0.587
CR, MRD+	5(13.9%)	2(22.2%)	3(11.1%)	
CR, MRD-	31(86.1%)	7(77.8%)	24(88.9%)	
HCT-CI, n, (%)				0.285
0	24(66.7%)	8(88.9%)	16(59.3%)	
1	9(25.0%)	0(0.0%)	9(33.3%)	
2	1(2.8%)	1(11.1%)	0(0.0%)	
≥ 3	2(5.6%)	0(0.0%)	2(7.4%)	
Donor age groups, years, n, (%)	35.5(12–58)	46(22–58)	31(12–54)	0.111
>40	14(38.9%)	6(66.7%)	8(29.6%)	
≤ 40	22(61.1%)	3(33.3%)	19(70.4%)	
Donor gender (M/F)	26/10	6/3	20/7	0.686
Donor type, n, (%)				0.722
HID	26(72.2%)	6(66.7%)	20(74.1%)	
MSD	8(22.2%)	3(33.3%)	5(18.5%)	
MUD	2(5.6%)	0(0.0%)	2(7.4%)	
ABO compatibility, n, (%)				
Matched	18(50.0%)	2(22.2%)	16(59.3%)	0.121
Minor mismatched	9(25.0%)	5(55.6%)	4(14.8%)	0.026
Major mismatched	9(25.0%)	2(22.2%)	7(25.9%)	1.000
Conditioning regimen, n, (%)				1.000
TBI-based therapy	16(44.4%)	4(44.4%)	12(44.4%)	
chemotherapy-based therapy	20(55.6%)	5(55.6%)	15(55.6%)	
Graft source, n, (%)				0.005
PB	16(44.4%)	8(88.9%)	8(29.6%)	
PB and BM	20(55.6%)	1(11.1%)	19(70.4%)	
CD34 + cells count, $\times 10^6$/kg, median(range)	5.335(2.5–14.2)	5.56(2.5-10.25)	5.33(3.33–14.2)	0.82
Nucleated cells count, $\times 10^8$/kg, median (range)	17.52(7.67–37.17)	17.49(7.87–30.45)	17.60(7.67–37.17)	0.621
Follow-up, median months (range)	28.07(2.29–92.21)	16.82(7.29–62.21)	32.71(2.29–92.21)	0.027

Abbreviations: CAR-T, chimeric antigen receptor T cell; HSCT, hematopoietic stem cell transplant; MRD, minimal residual disease; CR, complete remission; HCT-CI, hematopoietic cell transplant comorbidity index; HID, haploidentical donor; MSD, matched sibling donor; MUD, matched unrelated donor; TBI, total body irradiation; PB, peripheral blood; BM, bone marrow; MTX, methotrexate; CsA, cyclosporin A; MMF, mycophenolate mofetil; PT-Cy, post-transplant cyclophosphamide

was significantly greater in the CAR-T group than in the blinatumomab group (70.4% vs. 11.1%, $P=0.005$). Additionally, the proportion of patients with minor ABO blood group incompatibility was higher in the blinatumomab group than in the CAR-T-cell group (55.6% vs. 14.8%, $P=0.026$).

OS and PFS

The 2-year OS rate for the entire cohort was 76.54% (95% confidence interval [CI]: 58.29-87.5%), and the 2-year PFS rate was 54.97% (95% CI: 32.28-69.57%). The median OS time was not reached, and the median PFS time was 31.96 months. There were no significant differences in the 2-year OS rate (77.78% [57.09-89.36%] vs. 88.89% [43.30-98.36%], $P=0.862$) or 2-year PFS rate (59.03% [38.31-74.86%] vs. 44.44% [13.59-71.93%], $P=0.501$) between the CAR-T and blinatumomab groups, *respectively* (Fig. 1). Univariate analysis revealed that patients with IKZF1 mutations had a significantly lower 2-year OS rate *than* those without IKZF1 mutations (40.00% vs. 86.85%, $P=0.037$) (Supplementary Fig. 2). Additionally, patients who exhibited detectable pretransplant MRD had poorer 2-year PFS rates than those with undetectable MRD (20.00% vs. 60.57%, $P=0.086$) (Supplementary Fig. 3).

GRFS

The 2-year GRFS rate for the entire cohort was 41.11% (95% CI: 24.65-56.36%), with a median GRFS duration of 13.64 months. No significant difference in the 2-year GRFS rate between the CAR-T and blinatumomab groups was observed (47.86% [28.34-65.02%] vs. 22.22% [3.37-51.31%], $P=0.134$). Univariate analysis revealed a trend toward higher 2-year GRFS rates in the PB and BM groups than in the PB group (55.00% vs. 25.00%, $P=0.060$) (Fig. 2) (Supplementary Fig. 4).

NRM

The 2-year NRM rate for the entire cohort was 9.93% (95% CI: 0.06-48.56%). There was no statistically significant difference between the CAR-T and blinatumomab groups, with rates of 8.52% and 11.11%, respectively ($P=0.714$). Univariate analysis of NRM did not reveal any independent risk factors (Fig. 3).

GVHD

The 100-day *Grade* II-IV aGVHD incidence for the entire cohort was 25% (95% CI: 6.92-48.70%), with a 100-day *Grade* III-IV aGVHD incidence of 13.89% (95% CI: 0.87-44%) and a 2-year extensive cGVHD incidence of 15.22% (95% CI: 1.07-45.79%). The incidences of 100-day *Grade* II-IV aGVHD (22.22% vs. 33.33%, $P=0.556$), 100-day *Grade* III-IV aGVHD (11.11% vs. 22.22%, $P=0.383$), and 2-year cGVHD (12.35% vs. 23.81%, $P=0.536$) in the CAR-T and blinatumomab groups did not show significant differences (Fig. 4).

According to the univariate analysis, patients older than 40 years had a significantly greater incidence of grade II-IV acute GVHD than younger patients did (45.46% vs. 16.00%, $P=0.041$). Subgroup analysis by donor sex revealed that female donors were associated with a significantly greater two-year incidence of chronic GVHD than male donors were (42.86% vs. 4.35%, $P=0.013$). Additionally, although the 100-day incidence of grade III-IV acute GVHD was lower in patients receiving peripheral blood or bone marrow grafts than in those receiving other types of grafts (5.00% vs. 25.00%), this difference was not statistically significant ($P=0.082$). Multivariate Cox regression analysis identified age>40 years in the patient age subgroup as an independent risk factor for grade III-IV aGVHD (hazard ratio [HR] 32.51 [95% CI: 3.68–287.20]) (Table 2).

Engraftment and infection

The median neutrophil engraftment time for the entire cohort was 13 days (*range*: 10–24 days), and the median platelet engraftment time was 15 days (*range*: 10–35 days), with no instances of graft failure (GF) (Supplementary Fig. 5). There were no significant differences in the median neutrophil implantation time (13 days vs. 13 days, $P=0.753$) or median platelet implantation time (17 days vs. 14 days, $P=0.143$) between the CAR-T and blinatumomab groups (Table 2).

The CMV reactivation rate for the entire cohort was 61.1%, with 3 patients developing CMV disease. There was no significant difference in the CMV reactivation rates between the CAR-T and blinatumomab groups ($P=0.267$). The EBV reactivation rate for the entire cohort was 80.6% and was comparable between the two treatment groups ($P=0.652$). Three patients developed posttransplant lymphoproliferative disorders (PTLD), with no significant difference observed between the CAR-T and blinatumomab groups ($P=1.000$). Additionally, 5 patients developed herpes zoster virus activation, while 1 patient exhibited human herpesvirus 6 (HHV-6) activation following transplantation. The most prevalent infectious complication was pulmonary infection, which occurred in 61.1% of patients, followed by upper respiratory infection (47.2%) and soft tissue infection (38.9%). The incidence rates of urinary tract infection, gastrointestinal infection and bloodstream infection were 5.6%, 25% and 22.2%, respectively (Table 3). The incidence rates for these infections were similar across both the CAR-T and blinatumomab *groups* ($P>0.05$). Thrombotic microangiopathy (TMA) occurred in 4 of the patients; however, there was no significant difference in incidence between those receiving CAR-T therapy and those treated with blinatumomab ($P=1.000$).

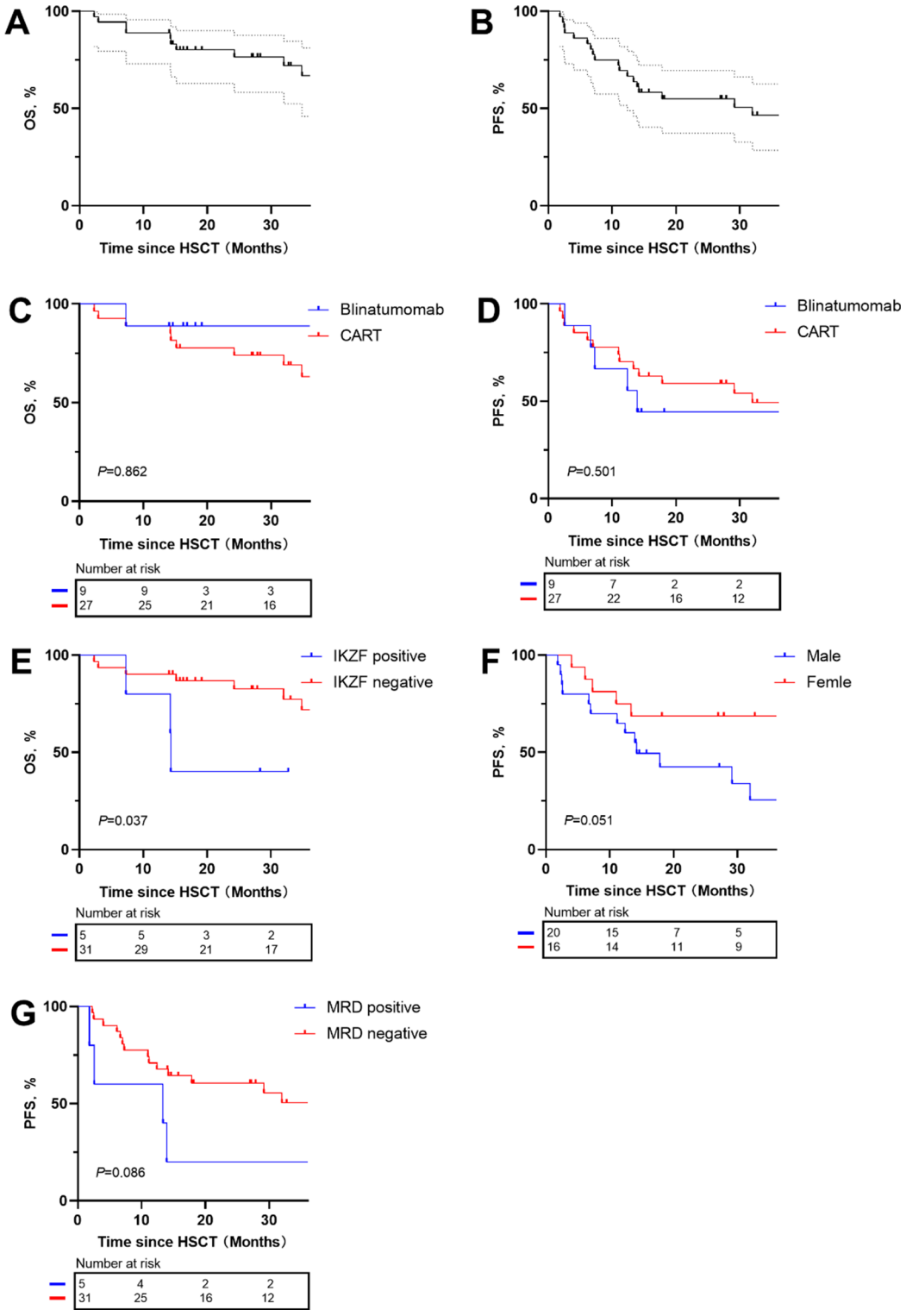

Fig. 1 The Kaplan–Meier curves for the survival of R/R B-ALL patients receiving immunotherapy as pretransplant treatment. (**A-B**) OS and PFS in the entire cohort, with 2-year OS and PFS rates of 76.54% and 54.97%, respectively. (**C-D**) Comparison of OS and PFS between the CAR-T and blinatumomab groups. The CAR-T group had a 2-year OS of 73.89% and PFS of 59.03%, while the blinatumomab group showed 88.89% OS and 44.44% PFS ($P=0.862$ for OS, $P=0.501$ for PFS). (**E**) OS stratified by IKZF1 mutation status, showing significantly lower OS in IKZF1-positive vs. IKZF1-negative patients (40.00% vs. 86.85%, $P=0.037$). (**F**) PFS by patient gender in the whole cohort. (**G**) OS of pretransplant MRD-positive vs. MRD-negative patients in the whole cohort. R/R B-ALL, relapsed/refractory B-cell acute lymphoblastic leukemia; OS, overall survival; PFS, progression-free survival; CAR-T, chimeric antigen receptor T cell; MRD, minimal residual disease

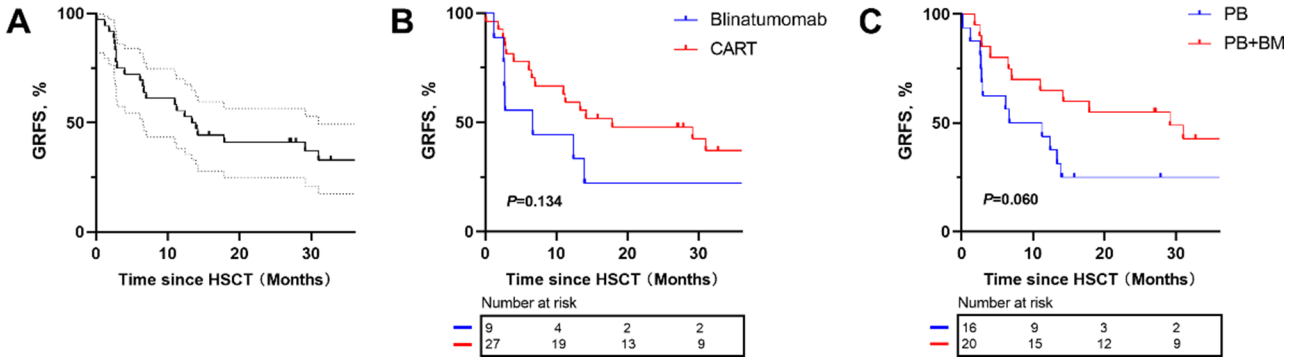

Fig. 2 The Kaplan–Meier curves for GRFS of R/R B-ALL patients receiving immunotherapy as pretransplant treatments. (**A**) The GRFS in the entire cohort. (**B**) The GRFS in CAR-T group and Blinatumomab group. (**C**) The GRFS of PB and PB + BM subgroups in the whole cohort. (**D**) The GRFS of patient gender subgroups in the whole group. GRFS, graft-versus-host disease-free and relapse-free survival; R/R B-ALL, relapsed/refractory B-cell acute lymphoblastic leukemia; CAR-T, chimeric antigen receptor T-cell; PB, peripheral blood; BM, bone marrow

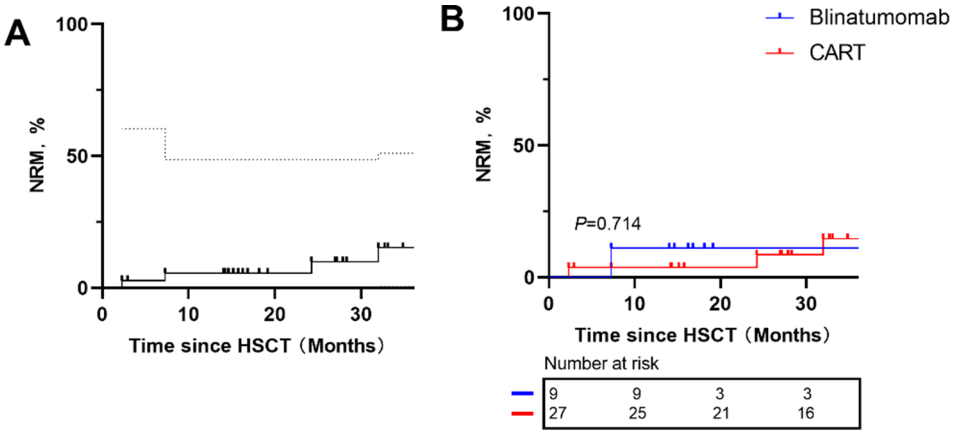

Fig. 3 The Kaplan–Meier curves for the NRM of R/R B-ALL patients receiving immunotherapy as pretransplant treatment. (**A**) NRM in the entire cohort. (**B**) NRM in the CAR-T and blinatumomab groups. NRM, non-relapse mortality; R/R B-ALL, relapsed/refractory B-cell acute lymphoblastic leukemia; CAR-T, chimeric antigen receptor T cell

Discussion

Recent advancements in immunotherapy, particularly CAR-T therapy and blinatumomab, have profoundly influenced treatment strategies for R/R B-ALL. Nevertheless, the optimal integration of these therapies with allogeneic HSCT remains an area of active investigation. While numerous studies have evaluated the efficacy of CAR-T and blinatumomab individually [22–24], limited data exist comparing their outcomes when followed by HSCT. Our study aimed to address this gap by systematically evaluating survival outcomes, GVHD incidence, and infection risks in patients treated with either immunotherapy prior to allogeneic HSCT.

Our results demonstrate promising outcomes, with a 2-year OS of 76.54% and PFS of 54.97%, despite the aggressive nature of the diseases treated. A notable proportion (28%) of patients had primary refractory disease, and 38% of Ph-positive patients carried the T315I mutation, contributing to the cohort's genetic complexity. Additionally, 25% of patients exhibited a complex karyotype [25], further highlighting the intricate and challenging nature of this patient cohort. The OS and PFS rates align with outcomes from larger trials evaluating CAR-T and blinatumomab therapies [26–28], suggesting that advanced immunotherapies followed by HSCT can achieve favorable outcomes even in challenging cases.

Notably, the 2-year OS, PFS, and GRFS rates were comparable between patients treated with CAR-T and blinatumomab prior to HSCT. To ensure robustness, we applied the IPTW statistical method for sensitivity analysis of OS, PFS, GRFS, and grade III-IV aGVHD. The adjusted Kaplan-Meier curves showed no statistically significant differences between the two immunotherapy groups ($P > 0.05$) [29] (Supplementary Fig. 6). These findings indicate that, after adjusting for confounding factors, the safety and efficacy of CAR-T and blinatumomab were similar. The consistent achievement of CR in both groups underscores their effectiveness in preparing patients for HSCT and supports flexible, personalized treatment choices based on individual patient characteristics.

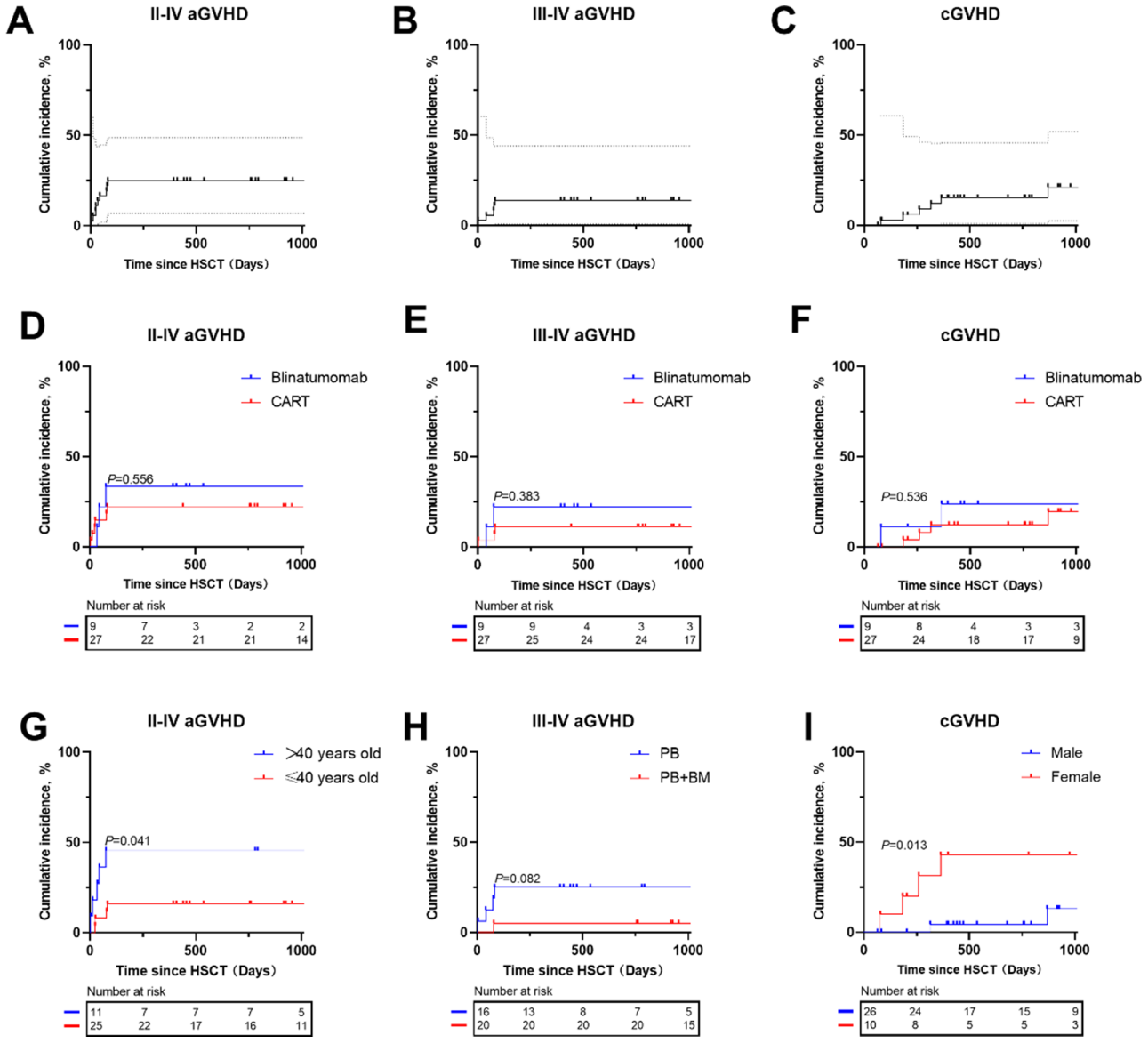

Fig. 4 Cumulative incidence (CI) of GVHD in R/R B-ALL patients receiving immunotherapy as pretransplant treatment. CI of (**A**) Grade II–IV acute GVHD, (**B**) Grade III–IV acute GVHD and (**C**) intensive chronic GVHD in the entire cohort. CI of (**D**) Grade II–IV acute GVHD, (**E**) Grade III–IV acute GVHD and (**F**) extensive chronic GVHD in the CAR-T and blinatumomab groups. (**G**) CI of Grade II–IV acute GVHD *by patient age group* in the entire cohort. (**H**) CI of Grade III–IV acute GVHD by graft source in the *entire* cohort. (**I**) CI of Grade III–IV acute GVHD *by* donor gender in the *entire* cohort. GVHD, graft-versus-host disease; R/R B-ALL, relapsed/refractory B-cell acute lymphoblastic leukemia; CAR-T, chimeric antigen receptor T cell

In our study, there was a nonsignificant trend toward lower 2-year PFS rates in MRD-positive patients compared to MRD-negative patients ($P = 0.086$), reinforcing the role of MRD status as a key prognostic factor [30, 31]. Additionally, patients with IKZF1 mutations had a significantly reduced 2-year OS rate compared to those without the mutation ($P = 0.037$). Recently, an independent research group reported that these findings are highly consistent with our results [32]. Given that Ikaros isoform 6, the primary form of IKZF1 deficiency, contributes significantly to B-ALL pathogenesis, current treatments may not fully address its adverse effects. These results highlight that while both CAR-T and blinatumomab are effective as bridge-to-transplant therapies, tailored strategies might be necessary to improve outcomes in high-risk subgroups, particularly in patients with persistent MRD or IKZF1 mutations.

Delayed hematopoietic recovery has been associated with increased rates of infections, relapse, and mortality in HSCT patients [33]. Our study demonstrated successful neutrophil and platelet engraftment in all patients. Furthermore, the absence of significant differences in engraftment kinetics between the CAR-T and

Table 2 Multivariate analysis of III-IV aGVHD and cGVHD

Outcome	Variate	HR(95%CI)	*P* Value
III-IV aGVHD			
	Patient age groups	32.51(3.68–287.20)	0.002
	Conditioning regimen	4.06(0.68–24.05)	0.123
	Graft source	0.25(0.03–2.13)	0.207
	Donor types	1.26(0.20–7.94)	0.805
cGVHD			
	Donor gender	4.52(0.74–27.65)	0.102
	Graft source	0.27(0.04–1.80)	0.177
	Second HSCT	4.42(0.32–60.31)	0.265

Abbreviations: aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; HR, hazard ratio

Table 3 Transplant outcomes

Outcomes	Whole Cohort (*n* = 36)	Blinatumomab (*n* = 9)	CAR-T (*n* = 27)	*P*-Value
Time to neutrophil engraftment, d, median (range)	13(10–24)	13(10–24)	13(10–20)	0.753
Time to platelet engraftment, d, median (range)	15(10–35)	14(10–24)	17(10–35)	0.143
aGVHD grade, n, (%)				
II-IV	9(25.0%)	3(33.3%)	6(22.2%)	0.660
III-IV	5(13.9%)	2(22.2%)	3(11.1%)	0.581
cGVHD, n, (%)	6(16.7%)	2(22.2%)	4(14.8%)	0.627
TMA, n, (%)	4(11.1%)	1(11.1%)	3(11.1%)	1.000
Hemorrhagic cystitis, n, (%)	10(27.8%)	1(11.1%)	9(33.3%)	0.392
PTLD, n, (%)	3(8.3%)	1(11.1%)	2(7.4%)	1.000
Virus reaction, n, (%)				
CMV	22(61.1%)	4(44.4%)	18(66.6%)	0.267
EBV	29(80.6%)	8(88.9%)	21(77.8%)	0.652
Herpes zoster virus and HHV-6	5(13.9%)	2(22.2%)	3(12.5%)	0.581
Infection, n, (%)				
Pulmonary infection	22(61.1%)	8(88.9%)	14(51.9%)	0.062
Upper respiratory infection	17(47.2%)	4(44.4%)	13(48.1%)	1.000
Soft tissue infection	14(38.9%)	4(44.4%)	10(37.0%)	0.712
Gastrointestinal infection	9(25.0%)	2(22.2%)	7(25.9%)	1.000
Bloodstream infection	8(22.2%)	2(22.2%)	6(22.2%)	1.000
Urinary tract infection	2(5.6%)	0(0.0%)	2(7.4%)	-

Abbreviations: CAR-T, chimeric antigen receptor T-cell; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; TA-TMA, transplant-associated thrombotic microangiopathy; PTLD, posttransplant lymphoproliferative disorders; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6

blinatumomab groups highlights the practicality and safety of both treatment approaches.

GVHD represents a critical complication in transplantation procedures and is closely associated with NRM. From a safety standpoint, the overall incidence of grade III-IV aGVHD (13.89%) and cGVHD (21.42%) was consistent with that reported in previous studies [34, 35]. The rates of grade III-IV aGVHD and cGVHD were similar between the CAR-T and blinatumomab groups, indicating that the type of immunotherapy did not significantly affect GVHD risk. The implementation of standardized GVHD prophylaxis protocols effectively mitigated the occurrence of severe GVHD. Univariate analysis revealed that older recipients presented significantly higher rates of grade II-IV aGVHD, whereas female donors were associated with an increased incidence of cGVHD at 2 years post-transplantation. These findings highlight the importance of optimizing both patient and donor selection to manage GVHD risk more effectively [36].

Infections continue to pose a prevalent complication not only in immunotherapy but also in HSCT. Our study revealed no significant differences in EBV or CMV reactivation between the two groups at different stages of transplantation. EBV reactivation and PTLD development rates were similar to those seen in the general population [19]. However, a noteworthy incidence of CMV reactivation was observed in 44.4% of patients within the blinatumomab group, and an even higher rate of 66.6% was noted in the CAR-T group, exceeding the frequency typically encountered in conventional transplant recipients [37]. This elevated reactivation rate is postulated to be associated with the immunomodulatory effects of these therapeutic modalities on cellular functions [38, 39]. Regular monitoring and the use of prophylactic and preemptive CMV management strategies are critical to reducing this risk and enhancing patient outcomes.

Several limitations should be considered when interpreting our findings. The retrospective design of this study introduces potential selection and information biases, as patient management and treatment protocols were not standardized prospectively. Additionally, the relatively small sample size limits the statistical power to detect significant differences between subgroups, particularly for rare outcomes such as specific GVHD subtypes and NRM. To address these limitations, future studies should adopt prospective designs with larger, multicenter cohorts and standardized treatment protocols. Extended follow-up periods are also necessary to evaluate long-term survival outcomes and late-onset complications. These measures would provide more robust evidence to inform optimal bridge-to-transplant strategies for patients with R/R B-ALL.

Conclusions

In conclusion, our study demonstrated that both CAR-T and blinatumomab immunotherapies are effective and safe bridge-to-transplant strategies for patients with R/R B-ALL, with comparable survival, GVHD, and infection outcomes. Proactive monitoring and prompt

management of posttransplant infectious complications remain essential to enhancing outcomes in this high-risk patient population.

Abbreviations

aGVHD	Acute graft-versus-host disease
ALL	Acute lymphoblastic leukemia
ATG	Anti-human thymocyte globulin
B-ALL	B-cell acute lymphoblastic leukemia
BM	Bone marrow
Bu/Cy	Busulfan/cyclophosphamide
CAR-T	Chimeric antigen receptor T cell
CI	Confidence interval
CMV	Cytomegalovirus
CR	Complete remission
CRS	Cytokine release syndrome
cGVHD	Chronic graft-versus-host disease
EBV	Epstein-Barr virus
Flu/Bu	Fludarabine/busulfan
GRFS	Graft-versus-host disease-free and relapse-free survival
GVHD	Graft-versus-host disease
HID	Haploidentical donor
HHV-6	Human herpesvirus 6
HSCT	Hematopoietic stem cell transplantation
ICANS	Immune effector cell-associated neurotoxicity syndrome
MLL	Mixed-lineage leukemia
MRD	Minimal residual disease
MSD	Matched sibling donor
MUD	Matched unrelated donor
NRM	Non-relapse mortality
OS	Overall survival
PB	Peripheral blood
PB + BM	Peripheral blood and bone marrow
PFS	Progression-free survival
PTLD	Posttransplant lymphoproliferative disorder
PT-CY	Post-transplant cyclophosphamide
R/R	Relapsed/refractory
TBI/Cy	Total body irradiation/cyclophosphamide
TMA	Thrombotic microangiopathy
TRM	Transplant-related mortality

Supplementary Information

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Supplementary Material 1

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Author contributions

WC and NL collected and analyzed the data, and drafted the initial manuscript. YC and NW conceptualized the study, verified the data, and critically revised the manuscript. GW, HX, YY, JW, JX, YL, and YZ participated in project management and provided additional support during the study. All authors read and approved the final manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (Approval Number: TJ-IRB202412159).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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