Posttransplant maintenance with blinatumomab for children, adolescents, and young adults with relapsed and refractory B-cell acute lymphoblastic leukemia: results of phase I in SCT-ALL-BLIN21

Relapsed and refractory B-cell acute lymphoblastic leukemia (R/R-B-ALL) is a significant risk factor for relapse following allogeneic hematopoietic cell transplantation (allo-HCT) in children, adolescents, and young adults (CAYA). Posttransplant blinatumomab may improve the graft-*versus*-leukemic effect for CD19-positive minimum residual disease. We conducted a multi-center, uncontrolled, phase I-II trial (SCT-ALL-BLIN21) to evaluate the safety and efficacy of posttransplant maintenance therapy with blinatumomab (2 courses of 4 weeks each) in CAYA with CD19-positive R/R-B-ALL who underwent allo-HCT beyond the first complete remission (CR). Phase I involved nine patients (median age, 10 years; range, 4-20), six (67%) of whom completed the planned treatment. All grade 4 adverse events (AE) were hematological toxicities, primarily lymphocytopenia and neutropenia. Increased transaminase (grade 3, N=1), acute graft-*versus*-host disease (GVHD; grade 3, N=1), and neutropenia (grade 4, N=1) caused treatment discontinuation. The observed safety profile of phase I was acceptable, enabling the study to proceed to phase II, where the efficacy of blinatumomab will be evaluated.

Despite a long-term survival rate of 80-90% for B-ALL in CAYA,[1,2] the R/R-B-ALL relapse rate remains high after allo-HCT and is associated with poor patient outcomes.[3-5] Developing new strategies is crucial to reduce the posttransplant relapse rate and improve patient prognosis, such as by posttransplant maintenance therapy. CD19 is a surface antigen expressed on most B-ALL with limited expression in normal tissues and is an ideal target for immunotherapy. Blinatumomab exhibits its antileukemic effect by mediating the engagement of CD3-positive T cells with CD19-positive cells.[6] Posttransplant blinatumomab administration potentially improves the antileukemic effect of donor-derived CD3-positive T cells on residual CD19-positive leukemia cells, causing lower relapse and improved survival rates. However, concerns remain regarding its potential AE, including the development or exacerbation of GVHD, cytopenia, and cytokine release syndrome (CRS).[7-10] Gaballa *et al*. conducted a prospective, single-center study and revealed the safety and efficacy of blinatumomab in adult patients with B-ALL at a high risk of relapse.[11] Our multi-center, uncontrolled, phase I-II trial (SCT-ALL-BLIN21), sponsored by the Japanese Childhood Cancer Group, aimed to evaluate the safety and efficacy of posttransplant maintenance therapy with blinatumomab (2 courses of 4 weeks each) in CAYA with CD19-positive R/R-B-ALL who underwent allo-HCT beyond first CR. This report presents the results of the phase I trial, focusing on blinatumomab safety evaluation. The National Hospital Organization Review Board for Clinical Trials (Nagoya, Japan) approved this study protocol (receipt number, C2021-004), which was previously published as a protocol paper.[12] This study adhered to the Declaration of Helsinki and the Clinical Trial Act, and was registered at the Japan Registry of Clinical Trials (jRCTs041210154; https://jrct.niph.go.jp/en-latest-detail/jRCTs041210154). All patients and/or guardians signed written informed consent. Eighty-five pediatric oncology centers across Japan participated in patient recruitment, treatment administration, follow-up, and data reporting. Our protocol paper[12] elaborated on the trial protocol details. Eligibility criteria were patients (i) aged ≤25 years, (ii) receiving allo-HCT for CD19-positive B-ALL beyond the first CR (patients in the second CR were included starting March 2023 after the central review board approval), (iii) Eastern Cooperative Oncology Group performance status of ≤2, (iv) with hematological recovery (a neutrophil count of 0.5×10^9/L or higher for at least 48 hours [h] without granulocyte colony-stimulating factor administration and a platelet count of 20×10^9/L or higher for at least 72 h without platelet transfusion), and (v) confirmed hematological remission upon enrollment. Exclusion criteria were patients (i) receiving antileukemic agents after allo-HCT to treat the primary disease, (ii) with active grade 2–4 acute GVHD or were receiving immunosuppressive agents for GVHD treatment (excluding prophylaxis), (iii) with active central nervous system (CNS) lesions, (iv) with CD19 expression of <20% of diagnostic or relapsed blasts, (v) with active infection, or (vi) with any organ failures: hepatic impairment, renal impairment, respiratory impairment requiring oxygenation, heart failure, or neurological disease.

Enrollment occurred within 30 to 100 days after allo-HCT, as previously reported.[11,12] Two blinatumomab courses were administered within 1 week after enrolment as a continuous intravenous infusion over 4 weeks at 2-week interval. Dosing and administration followed standard guidelines for patients with R/R-B-ALL in children and adults. Although the $CD19^+$ tumor burden is expected to be low post-HSCT, the step-up dosing schedule in course 1 was adopted based on established pediatric protocols to minimize the risk of cytokine release syndrome, which can theoretically occur

Table 1. Patient characteristics.

UPN	Age, years/ sex	LPS or KPS	Immuno-therapy before allo-HCT	Stage	N of allo-HCT	Conditioning regimen	GVHD prophylaxis	Donor source	Days of neutrophil engraftment/ enrollment	T-cell/B-cell count in PB at enrollment, x10^9/L	MRD at enrollment	Immunesuppressive agents at enrolment	aGvHD grade at enrollment/ worst aGVHD grade before enrollment
1	5/M	100	BLIN, INO, Tisa-cel	Third CR	2	BU 23.3 mg/kg ETP 1,800 mg/m^2	PT-CY, Tacrolimus, MMF	Haplo-BMT	15/90	0.39/0.03	Negative	Tacrolimus PSL MMF	0/2
2	20/M	100	BLIN, INO, Tisa-cel	Third CR	1	CY 120 mg/kg ETP 1,800 mg/m^2 TBI 12 Gy	Tacrolimus, sMTX	HLA 7/8, UR-BMT	22/97	0.13/0.01	Negative	Tacrolimus PSL	1/1
3	11/F	100	BLIN	Second CR	1	CY 120 mg/kg ETP 1,800 mg/m^2 TBI 12 Gy	Tacrolimus, sMTX	HLA 7/8, UR-CBT	16/97	0.22 / 0.01	Negative	Tacrolimus PSL	0/2
4	12/F	100	BLIN	Second CR	1	ETP 1800 mg/m^2 TBI 12 Gy	PT-CY	HLA 7/8, UR-BMT	17/62	0.18/0.05	Negative	PSL	0/1
5	10/M	80	BLIN	Second CR	1	MEL 180 mg/m^2 TBI 12 Gy	Cyclosporin A, sMTX	HLA 8/8, R-BMT	17/68	0.09/0.09	Negative	Cyclosporin A	0/0
6	16/M	70	INO	Second CR	1	ETP 30 mg/kg TBI 12 Gy	PT-CY, Tacrolimus, MMF	Haplo-BMT	38/75	0.06/0.02	Negative	Tacrolimus	0/0
7	4/M	80	BLIN	Second CR	1	ETP 1,800 mg/m^2 TBI 12 Gy	PT-CY	HLA 8/8, R-BMT	15/64	1.23/0.01	Negative	-	0/0
8	9/F	80	BLIN, INO, Tisa-cel	Third CR	2	FLU 120 mg/ kgMEL 180 mg/m^2 TBI 3 Gy	Tacrolimuss MTX	HLA 6/8, UR-CBT	19/56	0.08/1.54	Negative	Tacrolimus	0/0
9	8/F	100	BLIN	Second CR	1	ETP 30 mg/kg TBI 12 Gy	PT-CY	HLA 8/8, R-PBSCT	12/30	0.38/0.01	Negative	-	0/0

aGVHD: acute graft-*versus*-host disease; allo-HCT: allogeneic hematopoietic cell transplantation; BLIN: blinatumomab; BMT: bone marrow transplantation; BU: busulfan; CBT: cord blood transplantation; CR: complete remission; CY: cyclophosphamide; ETP: etoposide; F: female; FLU: fludarabine; Haplo: haploidentical; HLA: human leukocyte antigen; INO: inotuzumab ozogamicin; KPS: Karnofsky performance status; LPS: Lansky performance status; M: male; MEL: melphalan; MMF: mycophenolate mofetil; MRD, minimal residual disease; PB: peripheral blood; PBSCT: peripheral blood stem cell transplantation; PSL: prednisolone; PT: posttransplant; R: related; sMTX: short-term methotrexate; TBI: total body irradiation; Tisa-cel: tisagenlecleucel; UPN: unique patient number; UR: unrelated.

even in patients with low CD19$^+$ burden. Course 1 involves administering 9 μg (patients weighing <45 kg received 5 μg/m^2/day [maximum: 9 μg/day]) of blinatumomab daily on days 1-7, then 28 μg/day (patients weighing <45 kg received 15 μg/m^2/day [maximum: 28 μg/day]) on days 8-28 both as continuous infusions for patients weighing ≥45 kg. Course 2 involves administering 28 μg (patients weighing <45 kg received 15 μg/m^2/day [maximum: 28 μg/day]) of blinatumomab daily on days 1-28 as a continuous infusion in patients weighing ≥45 kg. Blinatumomab administration was interrupted or discontinued based on AE according to the drug information. Blinatumomab was not provided by the manufacturer; its cost was covered by the Japanese national health insurance, as it is approved in Japan for the treatment of relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia.

The primary endpoint in the phase I trial included treatment completion rate, whereas the secondary endpoint involved treatment-related AE (National Cancer Institute-Common Terminology Criteria version 5.0 grade ≥3) within each course. Phase I trial enrollment was temporarily suspended after the first six enrollments, with a completion rate of ≥66% considered acceptable. Three additional participants were enrolled if the completion rate was 50% to reevaluate a total of nine completion rates. Finally, the phase I trial was considered successful and proceeded to phase II if the completion rate was ≥66%. Minimal residual disease (MRD) measurements by central laboratory were certified by EuroMRD and conducted in the laboratory in accordance with the EuroMRD guidelines.[13] The results of polymerase chain reaction-based MRD are considered valid if both the sensitivity and the quantitative range are ≤10^{-4}. Based on these criteria, a measurement value of 10^{-3} or higher is determined to be positive. For flow cytometry-based MRD, if a cluster exhibiting blast-like characteristics is observed and its proportion is 0.1% or higher, it is determined to be positive. Peripheral blood lymphocyte subset was serially analyzed on days 0, 15, and 29. Flow cytometry was used to quantify the proportions of CD19$^+$, CD56$^+$, CD3$^+$, CD4$^+$, and CD8$^+$ cells.

The phase I study enrolled a total of nine patients (4 females and 5 males; median age: 10 years [range, 4-20 years]). The median days from allo-HCT to enrollment was 68 days (range, 10-97 days). Table 1 shows detailed patient characteristics. Prior to enrollment, three patients experienced CD19-positive relapse after CD19 chimeric antigen receptor T-cell therapy (tisagenlecleucel) treatment. Additionally, eight patients previously received blinatumomab, and four reported receiving inotuzumab ozogamicin. Seven patients underwent a first allo-HCT using high-dose total body irradiation-based myeloablative conditioning (MAC). One of the two subsequent transplant recipients received busulfan-based MAC, whereas the other received fludarabine-melphalan-based conditioning. Two patients who underwent haploidentical bone marrow transplantation received posttransplant cyclophosphamide (PT-CY), tac-

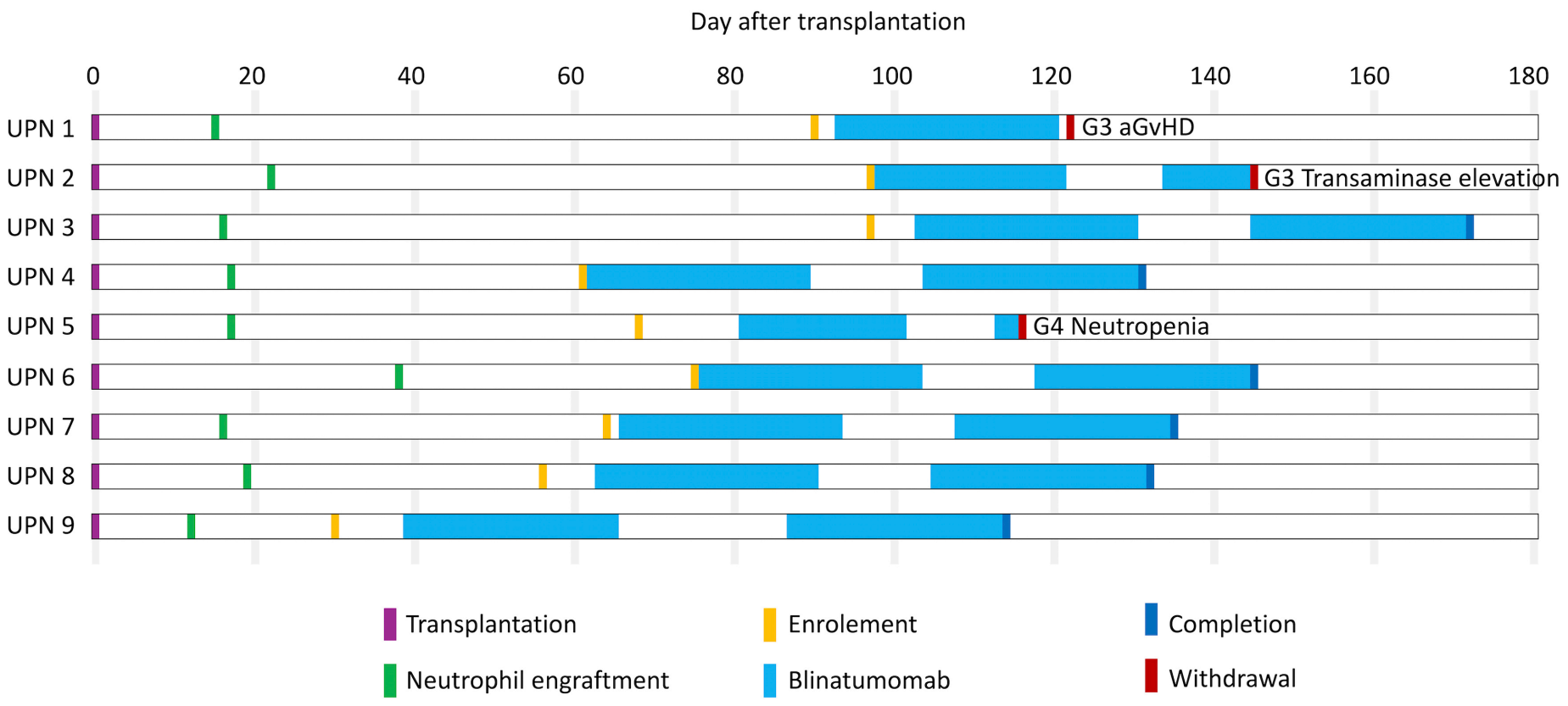

Figure 1. Swimmer plots for clinical courses. Swimmer plots illustrating the clinical courses of enrolled patients who received maintenance therapy with blinatumomab following allogeneic hematopoietic cell transplant for relapsed/refractory B-cell acute lymphoblastic leukemia. The horizontal axis represents days after transplantation, with the purple mark on the starting line indicating the transplantation date and the green mark denoting the neutrophil engraftment date. Blue indicates study enrollment, light blue denotes blinatumomab treatment duration, navy represents study treatment completion, and red demonstrates withdrawal. G3: grade 3; G4: grade 4; UPN: unique patient number. aGVHD: acute graft-*versus*-host disease.

A

Adverse events	First course									Second course								
	UPN 1	UPN 2	UPN 3	UPN 4	UPN 5	UPN 6	UPN 7	UPN 8	UPN 9	UPN 1	UPN 2	UPN 3	UPN 4	UPN 5	UPN 6	UPN 7	UPN 8	UPN 9
Lymphocytopenia										-								
Thrombocytopenia										-								
Neutropenia										-				★				
Leukocytopenia										-								
Anemia										-								
ALT increased										-	★							
Fever										-								
AST increased										-								
CRS										-								
aGVHD	★																	
Febrile neutropenia										-								
Catheter related infection										-								
Creatinine increased										-								
Diarrhea										-								
Lung infection										-								
Urinary tract infection										-								
Fibrinogen decreased										-								
Vomit										-								
Headache										-								
Tremor										-								
Hypertriglyceridemia										-								
Rash maculopapular										-								
Cholesterol high										-								

Grade 4
Grade 3
Grade 2
Grade 1
★ Cause of Discontinuation

B

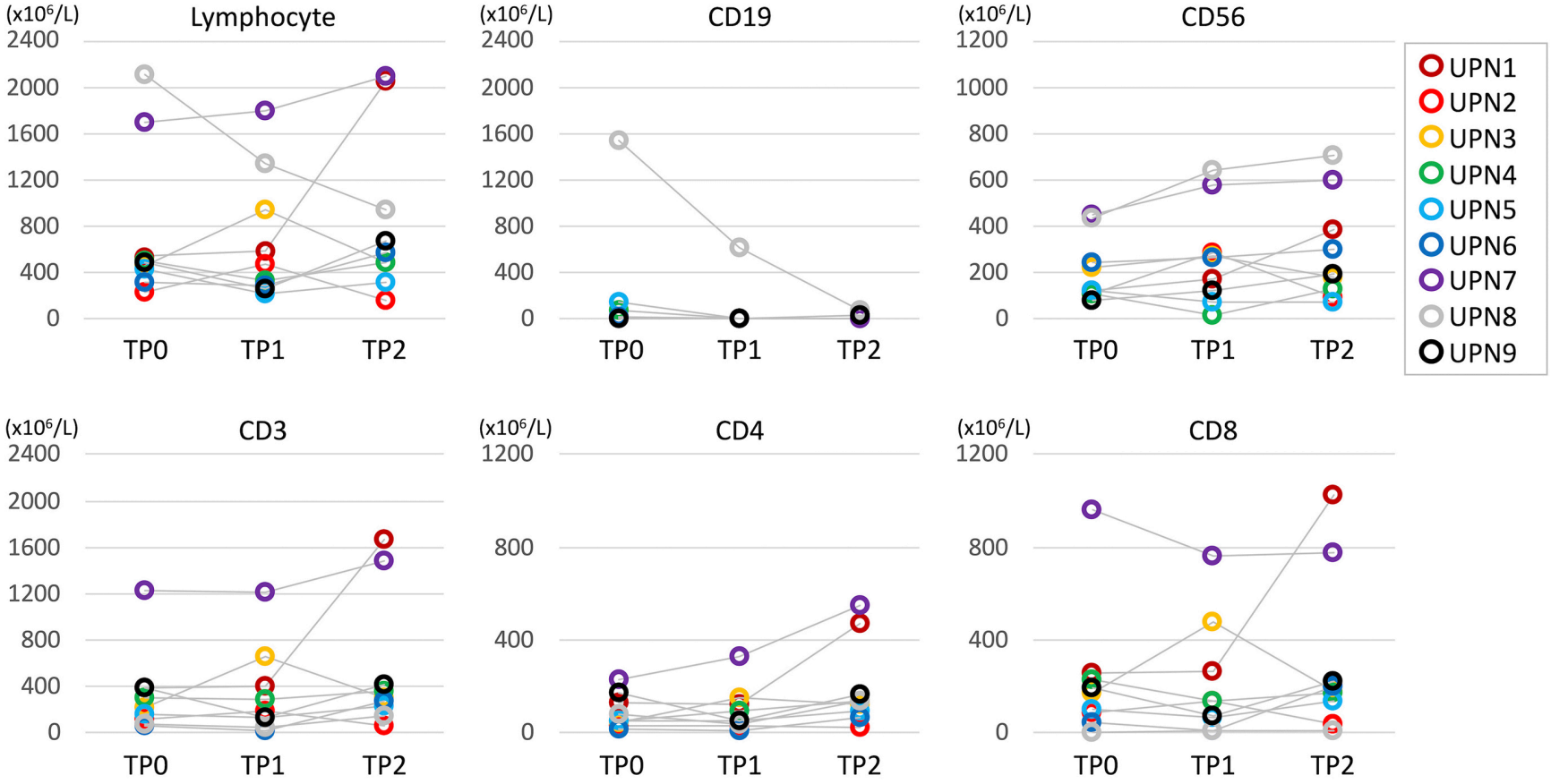

Figure 2. Adverse events and immune monitoring. (A) The panels illustrate any grade of adverse events (AE) occurring during each course for each patient. Purple, red, orange, and yellow panels indicate grades 4, 3, 2, and 1, respectively. AE marked with an asterisk (*) are those that caused medication discontinuation. aGVHD: acute graft-*versus*-host disease; ALT: alanine transaminase; AST: aspartate transaminase; CRS: cytokine releasing syndrome; UPN: unique patient number. (B) Each panel shows the changes in peripheral blood counts of total lymphocytes, CD19⁺ B cells, CD56⁺ NK cells, CD3⁺ T cells, CD4⁺ helper T cells, and CD8⁺ cytotoxic T cells at 3 time points: prior to blinatumomab initiation (day 0), on day 15, and at the end of course 1 (day 29). Data are presented for all 9 patients (N=9) enrolled in the study. Each colored circle represents an individual patient, with consistent colors used across panels to indicate the same patient.

rolimus, and mycophenolate mofetil as GVHD prophylaxis. Four of the remaining seven patients received conventional GVHD prophylaxis, consisting of calcineurin inhibitors + methotrexate, whereas the remaining three received PT-CY alone. Two patients received the study treatment without immunosuppressive agents. Four patients developed acute GVHD after allo-HCT, but only one demonstrated residual grade 1 symptoms upon enrollment. All others were GVHD-free upon enrollment. Figure 1 shows that all nine enrolled patients received at least one blinatumomab cycle, with six completing the planned two courses (completion rate, 67%). Figure 2A illustrates any AE grades that occurred during each course for each patient. All grade 4 AE were hematological toxicities, primarily lymphocytopenia ($<0.2\times10^9$/L), and neutropenia ($<0.5\times10^9$/L). These hematological toxicities did not interfere with study treatment continuation in all patients, except for unique patient number (UPN)-5, as they were present before blinatumomab initiation or were transient. Only three patients experienced grade 3 non-hematological toxicities; patient UPN-1 experienced grade 3 acute GVHD; patient UPN-2 had both febrile neutropenia and transaminase elevation; and patient UPN-6 developed a catheter-related infection. Three patients experienced grade 1 CRS, but none developed grade ≥2 CRS, further supporting the manageable safety profile of blinatumomab. The observed AE profile was comparable to that reported in adult patients,[11] suggesting that the safety profile is similar across age groups. Three patients withdrew from the trial due to severe AE, including grade 3 acute GVHD (UPN-1), grade 4 elevated transaminase (UPN-2), and grade 4 neutropenia (UPN-5). Patient UPN-1 who developed grade 3 acute GVHD (skin 1, gut 2, liver 0) after completing the first course of blinatumomab and withdrew from the study, received systemic corticosteroids and remained alive in complete remission as of 1 year after enrollment. No other patients experienced acute GVHD development or exacerbation. Efficacy was not assessed in phase I, but no patient relapsed or died within 1 year of enrollment, with a median observation period of 341 days (range, 140-383 days). Of the eight patients with evaluable bone marrow samples for MRD assessment following the second blinatumomab course, all were confirmed to be MRD-negative. None of the enrolled patients had CNS involvement at enrollment or experienced CNS relapse during the observation period. Dynamic changes in peripheral blood $CD19^+$, $CD56^+$, $CD3^+$, $CD4^+$, and $CD8^+$ cell counts across treatment courses are summarized in Figure 2B. Notably, even in patients with detectable $CD19^+$ cells at day 0, these cells disappeared by day 29, suggesting effective depletion of residual B cells during blinatumomab therapy. The observed safety profile for the posttransplant maintenance therapy with blinatumomab for CAYA patients was acceptable. Based on these results, the "SCT-ALL-BLIN21" study will proceed to phase II to assess the efficacy of posttransplant maintenance therapy with blinatumomab using the 1-year GVHD-free/relapse-free survival[14] rate as the primary endpoint. Moreover, the phase II trial will include the central laboratory assessments of MRD monitoring, immune profiling, and microbiome analysis. We plan to analyze the correlation between these central laboratory examinations with relapse, GVHD, and CRS development as an exploratory endpoint.

In this trial, the number of patients was small and their characteristics were heterogenous. Nonetheless, these results offer a promising step toward improving outcomes for CAYA patients with R/R-B-ALL following allo-HCT.

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Disclosures

No conflicts of interest to disclose.

Contributions

HS, KS, IK, NH, HH, HI, HY, HG, YT, AMS, and KU conceived and designed the study. HS and KU wrote the manuscript. HN served as the statistician. AMS was responsible for the data management. IK, YK, YIY, MS, TD, and YT performed central laboratory tests. HS, KK, MT, KO, and TT contributed to patient care and data registration. KH, YO, KK, and AM contributed to administrative support. All authors contributed to the study and provided final manuscript approval.

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Data-sharing statement

The original data may be available from the corresponding author upon reasonable request and with permission of the Transplantation and Cellular Therapy Committee of the Japanese Children's Cancer Group.

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