International Journal of Hematology (2024) 119:450–458
https://doi.org/10.1007/s12185-024-03710-6

ORIGINAL ARTICLE

TBI, etoposide, and cyclophosphamide conditioning for intermediate-risk relapsed childhood acute lymphoblastic leukemia

Hideaki Ueki[1] · Chitose Ogawa[2] · Hiroaki Goto[3] · Masanori Nishi[4] · Junko Yamanaka[5] · Shinji Mochizuki[5] · Takuro Nishikawa[6] · Tadashi Kumamoto[2] · Ritsuo Nishiuchi[7] · Atsushi Kikuta[8] · Shohei Yamamoto[9] · Shunji Igarashi[1] · Atsushi Sato[10] · Toshinori Hori[11] · Akiko M. Saito[12] · Tomoyuki Watanabe[13] · Takao Deguchi[14] · Atsushi Manabe[15] · Keizo Horibe[12] · Hidemi Toyoda[16]

Received: 26 April 2023 / Revised: 27 December 2023 / Accepted: 8 January 2024 / Published online: 25 January 2024

Abstract

Background In children with intermediate-risk relapsed acute lymphoblastic leukemia (ALL), allogeneic hematopoietic stem cell transplantation (allo-HSCT) has markedly improved the outcome of patients with an unsatisfactory minimal residual disease (MRD) response. Total body irradiation (TBI), etoposide (ETP), and cyclophosphamide (CY) have been shown to be equivalent to or better than TBI + ETP for conditioning, so we hypothesized that even greater survival could be achieved due to recent advances in HSCT and supportive care.

Procedure We prospectively analyzed the efficacy and safety of allo-HSCT with a unified conditioning regimen of TBI + ETP + CY in children with intermediate-risk relapsed ALL, based on MRD in the bone marrow after induction, from the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) ALL-R08-II nationwide cohort (UMIN000002025).

Results Twenty patients with post-induction MRD $\geq 10^{-3}$ and two not evaluated for MRD underwent allo-HSCT. Engraftment was confirmed in all patients, and no transplantation-related mortality was observed. The 3-year event-free survival and overall survival rates after transplantation were 86.4% ± 7.3% and 95.5% ± 4.4%, respectively.

Conclusion Allo-HSCT based on post-induction MRD with TBI + ETP + CY conditioning was feasible in Japanese children with intermediate-risk relapsed ALL.

Keywords Acute lymphoblastic leukemia · Childhood · Transplantation · Etoposide · Cyclophosphamide

Introduction

Although treatment outcomes of children with relapsed acute lymphoblastic leukemia (ALL) have improved in recent years, they are still unsatisfactory. Time to relapse, immunophenotype, and relapse site are the well-established prognostic factors and are used in most protocols for risk stratification at the time of relapse [1, 2]. Children with late relapses of B-cell precursor ALL and bone marrow involvement have intermediate risk. Children with early combined or isolated extramedullary B-cell precursor ALL relapse are also classified as intermediate risk because they achieve better event-free survival (EFS) than children with very early or early isolated bone marrow relapse.

In children with intermediate-risk relapsed ALL, the efficacy of allogeneic hematopoietic stem cell transplantation (allo-HSCT), assessed as minimal residual disease (MRD), has been investigated in recent years. The probability of EFS in patients with post-induction MRD $\geq 10^{-3}$ who were allocated to allo-HSCT as reported by the Berlin–Frankfurt–Münster group was 64% ± 5% in the ALL-REZ BFM 2002 study and 18% ± 7% in the predecessor ALL-REZ BFM P95/96 trial ($P = 0.001$) [3]. However, no unified allo-HSCT conditioning regimens were used in these studies.

Historically, the outcome of allo-HSCT with total body irradiation (TBI) + cyclophosphamide (CY) has not been satisfactory, with an EFS of 35% to 55% in children with late relapse of ALL [4–8]. For allo-HSCT in children with ALL in general, HSCT conditioned with TBI + etoposide (ETP) resulted in good 2y-EFS and 2y-overall survival (OS) rates of 86% and 91%, respectively [9].

Extended author information available on the last page of the article

Allo-HSCT with TBI + ETP conditioning for children with ALL in second remission reportedly showed an EFS of 60–86% [5, 9–12].

The mechanisms of anti-leukemia activity of ETP and CY are different. ETP exert cytotoxic effects by interfering with the repair of double-stranded DNA breaks by topoisomerase II [13]. CY is an alkylating agent, damages leukemic cells through DNA crosslinking [14]. In addition, ETP reportedly has synergistic activity with CY in vitro [15–17]. Conditioning regimens comprising TBI + ETP + CY were found to be equivalent to or better than the TBI + ETP conditioning in previous reports [5, 10–12, 18–20]. However, since TBI + ETP + CY conditioning regimens were studied in the 1990s, we hypothesized that with the recent advancements in HSCT and supportive care, even better survival could be achieved.

The aim of this study was to investigate the efficacy and incidence of adverse events with HSCT using the unified conditioning regimen of TBI + ETP + CY in this era of advanced supportive care and transplant medicine. For this purpose, we conducted a prospective, non-randomized nationwide multicenter trial of allo-HSCT conditioned with the TBI + ETP + CY regimen in children with intermediate-risk first-relapsed ALL who had an unsatisfactory MRD response despite achieving second remission.

Materials and methods

Study design

The Japanese Pediatric Leukemia/Lymphoma Study Group's (JPLSG) ALL-R08 study was the first nationwide prospective multicenter trial in the children with first relapse of ALL in Japan. The ALL-R08 study contained two parts: ALL-R08-I observational study and ALL-R08-II clinical trial. The ALL-R08-II trial was for children with intermediate-risk (S2) group of the multicenter ALL-REZ BFM trial stratification of relapsed ALL [21] and was registered in the University Hospital Medical Information Network Clinical Trials Registry in Japan as UMIN000002025. The intermediate-risk (S2) relapsed ALL group included children with an early (≥ 18 months after the primary diagnosis and < 6 months after completion of primary therapy) or late (≥ 6 months after completion of primary therapy) combined bone marrow relapse, late isolated bone marrow relapse, and very early (< 18 months after the primary diagnosis and < 6 months after completion of primary therapy) and early isolated extramedullary relapse. Patients with MRD < 10^{-3} in the bone marrow after induction therapy were treated without allo-HSCT, whereas patients with MRD ≥ 10^{-3} were transplanted at the end of the therapy. The study design was approved by the relevant local ethics committees. One of the endpoints of the ALL-R08-II trial is the rate of adverse event. Since the adverse event profile of HSCT is different from that of chemotherapy as defined by the study protocol, this study focused on the adverse events of HSCT with TBI + CY + ETP conditioning.

Patients

Children with intermediate-risk first-relapsed ALL were enrolled in the ALL-R08-II trial between June 1, 2009 and October 31, 2013. The inclusion criteria for this trial were as follows: intermediate-risk (S2) first relapse of non-T-cell ALL; age < 18 years at onset of ALL; age < 20 years at diagnosis of relapse; no evident abnormality of the liver, kidney, and heart; Eastern Cooperative Oncology Group performance status score of 0–2 or a score of 3 caused by ALL (baseline performance status was scored 0–2, but if the exacerbation of performance status was attributed to leukemia, a score of 3 was allowed).

The exclusion criteria were as follows: mature B-cell ALL; Ph + ALL; infant leukemia with rearrangement of the mixed lineage leukemia gene; Down syndrome; bleeding ≥ CTCAE v3.0 grade 3 in the central nervous system; uncontrollable infections; pregnancy or possibility of pregnancy; past history of congenital or acquired immunodeficiency; contraindication to any agent planned to be used in the trial; any other condition that physicians consider inadequate and relapses after HSCT. Written informed consent was obtained from patients aged ≥ 16 years and/or from the legal guardians according to the Helsinki Declaration and ethical guidelines for clinical research in Japan.

Treatment protocol

The treatment protocol was based on the ALL-REZ BFM P95/96 trial. An outline of the therapeutic protocol is shown in Fig. 1. Following a cytoreductive pre-phase with dexamethasone, remission induction therapy was administered. The induction therapy consisted of two blocks (F1 and F2, Table S1). MRD in the bone marrow was evaluated after block F2, and patients with positive MRD (≥ 10^{-3}) were assigned to the allo-HSCT arm. Patients with unevaluable MRD were assigned to either the chemotherapy arm or allo-HSCT arm at the physicians' discretion. Patients assigned to the allo-HSCT arm underwent five courses of block chemotherapy (R2/R1/R2/R1/R2, Table S1) followed by allo-HSCT. Patients who were not in hematological remission (≥ 5% leukemic cells in the bone marrow) after the first R1

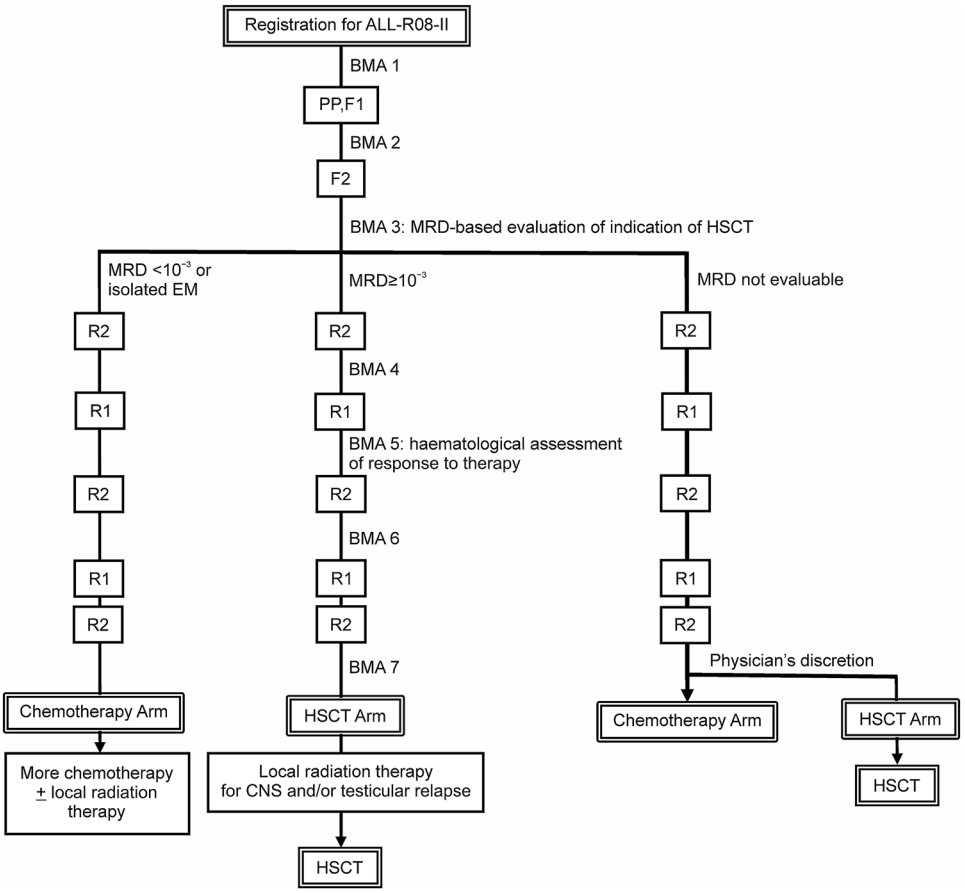

Fig. 1 Outline of the JPLSG ALL-R08-II clinical trial. Following the cytoreductive pre-phase, remission induction therapy (F1 and F2) was administered. MRD was evaluated in BMA 3, and patients with MRD $\geq 10^{-}3$ were assigned to the allo-HSCT arm. Patients with non-evaluable MRD were assigned to either the chemotherapy arm or the allo-HSCT arm at the physicians' discretion. Patients assigned to the allo-HSCT arm underwent five courses of block chemotherapy (R2/R1/R2/R1/R2), followed by allo-HSCT. Each block of chemotherapy is shown in Table S1 in detail. ALL, acute lymphoblastic leukemia; BMA, bone marrow aspiration; CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; PP, pre-phase

course were excluded from the study. All patients underwent HSCT in second remission.

Hematopoietic stem cell transplantation

A standard donor for allo-HSCT in the trial was defined as follows: related donor (bone marrow or peripheral blood stem cell) who was at least five out of six human leukocyte antigen (HLA) serologically identical with typing of HLA A, B, and DR; non-related donor obtained from the Japan Marrow Donor Program who was six out of six HLA serologically identical; non-related cord blood donor who was at least four out of six HLA serologically identical with typing of HLA A, B, and DR, and with a nuclear cell count $\geq 2.5 \times 10^7$/kg.

The conditioning regimen for allo-HSCT was as follows: TBI 12 Gy + ETP 60 mg/kg × 1 day + CY 60 mg/kg × 2 days for patients with < 30 kg body weight; TBI 12 Gy + ETP 1800 mg/m^2 × 1 day + CY 60 mg/kg × 2 days for patients weighing ≥ 30 kg. In patients with no standard donor, the donor selection and conditioning regimen were at the discretion of the institution where the patient was hospitalized.

Graft-versus-host disease prophylaxis

Graft-versus-host disease (GVHD) prophylaxis was performed as follows. For patients aged < 10 years who received transplantation from HLA identical siblings, either methotrexate (MTX) only or cyclosporine (CsA) only were administered. MTX was administered at a dose of 15 mg /m^2 intravenously on day + 1 and 10 mg/m^2 on days + 3, 6, 11, 18, 25 and once a week subsequently until day + 60. CsA was started at 3 mg/kg/day delivered in two intravenous infusions over 2 h with a target trough level of 150–250 ng/mL or as a continuous infusion with a target trough level of 200–300 ng/mL. For patients aged ≥ 10 years who received transplantation from HLA identical siblings, both MTX and CsA were administered (MTX was administered intravenously at 15 mg/m^2 on day + 1 and at 10 mg/m^2 on days + 3, 6, and 11. The protocol for CsA administration was the same as above). For patients with transplant received from other types of standard donors, MTX (15 mg/m^2 on day + 1 and 10 mg/m^2 on days + 3, 6 and 11) and tacrolimus (started at 0.02 mg/kg/day as a continuous intravenous infusion, adjusted for

a target trough level of 5–15 ng/mL) were administered. GVHD prophylaxis for patients who received transplantation from a non-standard donor was not regulated.

Local therapy for extramedullary lesion

In patients with unilateral testicular involvement on physical examination, orchiectomy of the involved side was performed. If the biopsy result of the contralateral testis was negative, the testis was irradiated with 3 Gy prior to TBI. If the biopsy result of the contralateral testis was positive, the testis was irradiated with 6 Gy prior to TBI. In patients with bilateral testicular involvement on physical examination, the bilateral testes were removed or irradiated with 12 Gy prior to TBI.

Patients with central nervous system involvement at diagnosis of relapse were boosted with 6 Gy of cranial irradiation prior to TBI.

MRD assessment

MRD in bone marrow samples was quantified using real-time quantitative polymerase chain reaction (RQ-PCR) at the end of induction (after F2). The data of RQ-PCR were analyzed on the basis of the EuroMRD Consortium guidelines [22]. An MRD level $\geq 10^{-3}$ was considered positive in this study.

Statistical methods

EFS and OS were estimated using the Kaplan–Meier method and calculated from the date of allo-HSCT until the event date. Data were censored on October 31, 2016. Patients who were lost to follow-up were censored at the last-contact date. The 95% confidence interval was calculated using Greenwood's formula. Second relapse, death from any cause and secondary malignancies were considered as events for EFS calculation. OS was calculated from the date of allo-HSCT to death from any cause. The calculations were performed in StataCorp 2015 software (Stata Statistical Software: Release 14. College Station, TX, USA: StataCorp LP).

Results

Patient characteristics

From June 2009 to October 2013, 81 patients from 34 centers in Japan were enrolled in the ALL-R08-II trial. The trial profile is shown in Fig. 2. Four patients who did not meet the inclusion criteria after enrollment were excluded. Of the 73 patients who underwent bone marrow aspiration 3 at the end of induction, MRD was positive in 31 patients and not evaluable in eight patients. Finally, 20 of 31 patients with positive MRD and two of eight patients

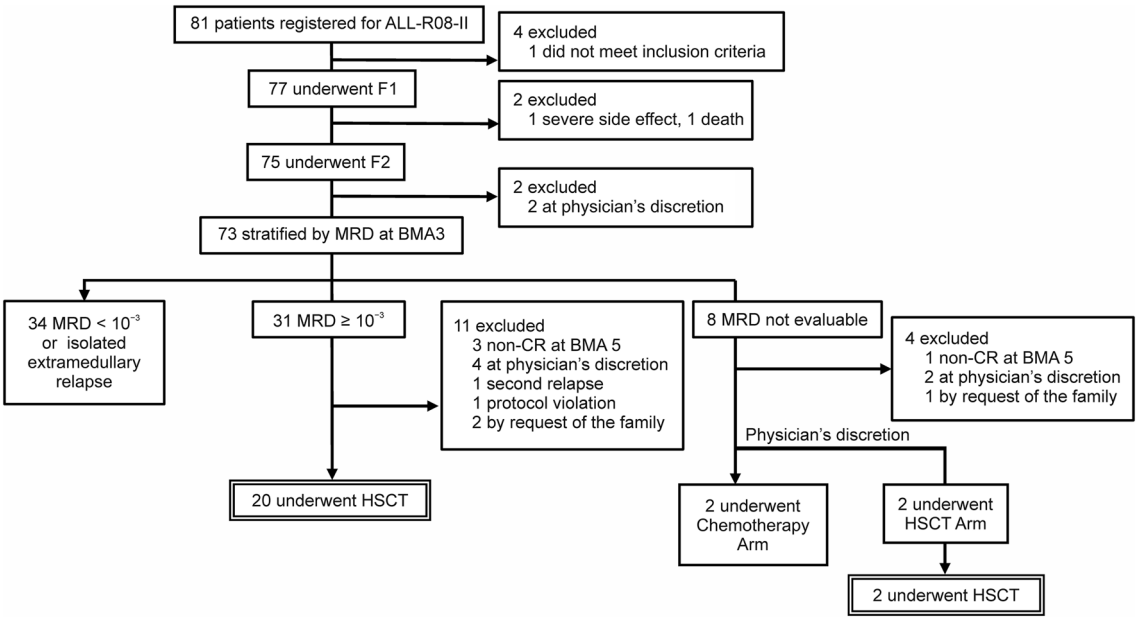

Fig. 2 Trial profile. Of the 81 patients registered for the JPLSG ALL-R08-II trial, 22 underwent HSCT in total, including 20 patients with MRD $\geq 10^{-3}$ and two patients with not evaluable MRD at the physician's discretion. ALL, acute lymphoblastic leukemia; BMA, bone marrow aspiration; CR, complete remission; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease

Table 1 Characteristics of patients who underwent transplantation in the Japanese Pediatric Leukemia/Lymphoma Study Group R08-II trial

	Total $N=22$	UBMT $N=14$	UCBT $N=8$
Age at HSCT (years)			
Median (range)	9 (2–20)	10.5 (5–18)	7.5 (2–20)
Sex			
Female	10	6	4
Male	12	8	4
Time point of relapse			
Very early	0	0	0
Early	1	0	1
Late	21	14	7
Site of relapse			
EM isolated	0	0	0
BM/EM combined	2	0	2
BM isolated	20	14	6
HLA serological disparity			
6/6 identical		10	2
5/6 identical		4	4
4/6 identical		0	2
Cell dose ($\times 10^7$ cells/kg)		29.4	4.3
Median (range)		(5–51.3)	(2.2–5.8)

UBMT bone marrow transplantation from unrelated donor, *UCBT* cord blood transplantation from unrelated donor, *HSCT* hematopoietic stem cell transplantation, *EM* extramedullary, *BM* bone marrow, *HLA* human leukocyte antigen

with non-evaluable MRD (assigned to the allo-HSCT arm at the physicians' discretion) underwent allo-HSCT in the second remission. The characteristics of the patients who underwent transplantation are shown in Table 1.

Engraftment

Table 2 shows the engraftment profile. Engraftment (absolute neutrophil counts $\geq 5.0\times10^8$/L) was confirmed in all patients who underwent transplantation. For patients who underwent unrelated bone marrow transplantation (BMT, $n=14$) and unrelated cord blood transplantation (CBT, $n=8$), the median time to reach an absolute neutrophil count of 5.0×10^8/L was 18 (range 12–28) days and 19 (range 13–65) days, respectively. The median time to achieve platelets $\geq 2.0\times10^{10}$/L was 27 (range 12–43) days for patients who underwent BMT, and 39.5 (range 26–109) days for patients who underwent CBT. The median time to reticulocytes $\geq 1\%$ was 20.5 (range 15–84) days and 24.5 (range, 16–77) days for patients who underwent BMT and CBT, respectively.

Safety outcomes

Table 3 shows the incidence of GVHD. Acute GVHD was observed in 11 (79%) of 14 patients who underwent BMT and six (75%) of eight patients who underwent CBT. Grade III–IV acute GVHD was observed in three (21%) of 14 patients who underwent BMT and one (13%) of eight patients who underwent CBT. The number of patients with chronic GVHD in the BMT and CBT groups were five (36%) and two (25%), respectively.

Table 4 shows the incidence of adverse effects (grade 3–4, CTCAE version 3.0) from the start of conditioning until day 28. Grade 4 allergy and grade 3 mucositis were observed in one patient each. No other grade 4 non-hematological toxicity was observed in this period. During the later follow-up, thrombotic microangiopathy was observed in one patient on day 67. Neither sinusoidal obstruction syndrome nor

Table 2 Engraftment

Factor	Donor source		
	All patients $N=22$	UBM $N=14$	UCB $N=8$
Engraftment (patients, %)			
Neutrophils $\geq 5.0\times10^8$/L	22 (100%)	14 (100%)	8 (100%)
Platelets $\geq 2.0\times10^{10}$/L	22 (100%)	14 (100%)	8 (100%)
Reticulocytes $\geq 1.0\%$	22 (100%)	14 (100%)	8 (100%)
Rejection (patients, %)	0 (0%)	0 (0%)	0 (0%)
Days from HSCT to engraftment (median, range)			
Neutrophils $\geq 5.0\times10^8$/L		18 (12–28)	19 (13–65)
Platelets $\geq 2.0\times10^{10}$/L		27 (12–43)	39.5 (26–109)
Reticulocytes $\geq 1.0\%$		20.5 (15–84)	24.5 (16–77)

UBM bone marrow from unrelated donor, *UCB* cord blood from unrelated donor, *HSCT* hematopoietic stem cell transplantation

Table 3 Graft-versus-host disease

Factor	Donor source		
	All patients $N=22$	UBM $N=14$	UCB $N=8$
Acute GVHD			
Total	17 (77%)	11 (79%)	6 (75%)
Grade II–IV	14 (64%)	8 (57%)	6 (75%)
Grade III–IV	4 (18%)	3 (21%)	1 (13%)
Chronic GVHD			
Total	7 (32%)	5 (36%)	2 (25%)
Limited	4 (18%)	2 (14%)	2 (25%)
Extensive	3 (14%)	3 (21%)	0 (0%)

UBM bone marrow from unrelated donor, *UCB* cord blood from unrelated donor, *GVHD* graft-versus-host disease

post-HSCT lung disease was reported in any patient. No transplantation-related mortality was observed.

Survival

Three of the 22 patients who underwent allo-HSCT relapsed and died eventually. The cause of death was relapse of ALL in all three patients. With a median follow-up of 4.0 years (range 1.6–6.5 years), the 3y-EFS and 3y-OS after transplantation were 86.4% ± 7.3% and 95.5% ± 4.4%, respectively (Fig. 3).

Four patients were excluded from the study and did not undergo HSCT at the physicians' discretion (Fig. 2). Of these four patients, two had a second relapse later, while the other two are currently alive without a second relapse. Two

Table 4 Adverse effect (CTCAE v3.0) from start of conditioning until day 28

Symptoms	*N*	Grade 3	Grade 4	Grade 5
Hemoglobin	22	15 (68%)	4 (18%)	0 (0%)
Leukocytes	22	0 (0%)	22 (100%)	0 (0%)
Neutrophils	22	0 (0%)	22 (100%)	0 (0%)
Platelets	22	0 (0%)	22 (100%)	0 (0%)
Left-ventricular systolic dysfunction	21	0 (0%)	0 (0%)	0 (0%)
DIC	22	0 (0%)	0 (0%)	0 (0%)
Fibrinogen	22	1 (5%)	0 (0%)	0 (0%)
Fever	22	7 (32%)	0 (0%)	0 (0%)
SIADH	22	1 (5%)	0 (0%)	0 (0%)
Mucositis/stomatitis	22	1 (5%)	0 (0%)	0 (0%)
Nausea	22	19 (86%)	0 (0%)	0 (0%)
Vomiting	22	8 (36%)	0 (0%)	0 (0%)
Ileus	22	3 (14%)	0 (0%)	0 (0%)
Diarrhea	22	7 (32%)	0 (0%)	0 (0%)
Genitourinary bleeding	22	0 (0%)	0 (0%)	0 (0%)
Pancreatitis	22	0 (0%)	0 (0%)	0 (0%)
Creatinine	22	1 (5%)	0 (0%)	0 (0%)
Hyperglycemia	22	3 (14%)	0 (0%)	0 (0%)
Proteinuria	22	0 (0%)	0 (0%)	0 (0%)
AST	22	0 (0%)	0 (0%)	0 (0%)
ALT	22	5 (23%)	0 (0%)	0 (0%)
Bilirubin	22	0 (0%)	0 (0%)	0 (0%)
Osteonecrosis	22	1 (5%)	0 (0%)	0 (0%)
Allergic reaction/hypersensitivity	22	0 (0%)	1 (5%)	0 (0%)
Tumor lysis syndrome	22	0 (0%)	0 (0%)	0 (0%)
Thrombosis/embolism	22	0 (0%)	0 (0%)	0 (0%)
Febrile neutropenia	22	16 (73%)	0 (0%)	0 (0%)
Infection with Gr. 3 or 4 neutrophils	22	7 (32%)	0 (0%)	0 (0%)
Infection with normal ANC or Gr. 1 or 2 neutrophils	22	3 (14%)	0 (0%)	0 (0%)
Hypernatremia	22	1 (5%)	0 (0%)	0 (0%)

CTCAE v3.0 common terminology criteria for adverse events version 3.0, *DIC* disseminated intravascular coagulation, *SIADH* syndrome of inappropriate antidiuretic hormone, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ANC* absolute neutrophil count

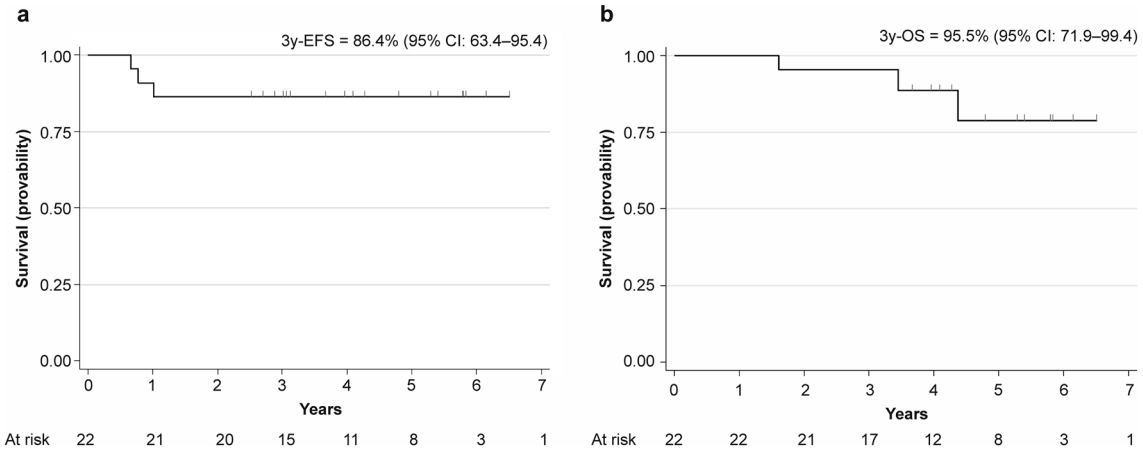

Fig. 3 Kaplan–Meier curves of EFS (**A**) and OS (**B**) in patients who underwent transplantation in JPLSG ALL-R08-II. EFS and OS were calculated from date of HSCT. The 3y-EFS and 3y-OS were 86.4% (95% CI 63.4–95.4) and 95.5% (95% CI 71.9–99.4), respectively. The median follow-up was 49 (range 20–80) months. *CI* confidence interval, *EFS* event-free survival, *OS* overall survival

patients with non-evaluable MRD did not undergo HSCT at the physicians' discretion, according to the protocol. Of these two patients, one had a second relapse and the other patient is alive without a relapse.

Discussion

This study showed that allo-HSCT with conditioning regimen consisting of TBI + ETP + CY was feasible in children with intermediate-risk first-relapsed ALL who had a poor MRD response despite achieving second remission, and the 3y-EFS and 3y-OS rates of the transplanted children were 86.4% and 95.5%, respectively.

Regarding the adverse effects, no transplantation-related mortality was observed in this study and no grade 4 adverse effects were observed except in one patient with grade 4 allergy. Grade III–IV acute GVHD was observed in three (21%) of 14 patients who underwent BMT and one (13%) of eight patients who underwent CBT. The incidences of chronic GVHD observed in the BMT and CBT groups were five (36%) and two (25%), respectively. A study conducted in the 2010s showed that the frequency rates of grade III–IV acute GVHD and chronic GVHD were 12% and 15%, respectively, in children with ALL who underwent HSCT with TBI + ETP conditioning regimen [9]. One of the reasons for the high incidence of acute and chronic GVHD in our study could be the use of anti-thymocyte globulin (ATG). In a study by Peters et al. [9], ATG was used as GVHD prophylaxis in the setting of HSCT from an alternative donor using TBI + ETP conditioning, but not in the ALL-R08-II study. Although CY is a potent immunosuppressive agent as well as a widely utilized antineoplastic drugs, the administration of 120 mg/kg of CY in addition to 12 Gy of TBI and 60 mg/kg of ETP may have caused tissue damage leading to GVHD. In addition, differences in supportive care between different clinical studies may also have influenced the development of GVHD.

This study showed that the 3 y-EFS was 86.4% and 3 y-OS was 95.5% in children with intermediate-risk first-relapsed ALL who underwent HSCT with unified TBI + ETP + CY conditioning regimen owing to a poor MRD response despite second remission post-induction chemotherapy. It has been reported that allo-HSCT markedly improved the prognosis of patients with intermediate risk of relapse of childhood ALL and unsatisfactory MRD response [3, 23]. In the ALL-REZ BFM 2002 study, the 8y-EFS and 8y-OS were 64% and 68%, respectively, in patients with post-induction MRD $\geq 10^{-3}$ who were allocated to allo-HSCT with non-unified conditioning [3]. In the ALL-R3 study, for patients with high MRD at the end of induction chemotherapy, receiving allo-HSCT with non-unified conditioning reduced their relapse risk (hazard ratio 0·36) compared to chemotherapy alone [23].

Regarding the conditioning regimen of allo-HSCT, Peters et al. compared TBI + ETP conditioning versus chemotherapy-based conditioning in children with ALL [9]. Among 87 patients transplanted in the second remission who relapsed > 30 months after the diagnosis, the 2y-EFS and 2y-OS were 69% and 89%, respectively [9]. The MRD status did not significantly influence the OS or EFS [9]. In analyses limited to patients who actually received transplants, our results seem to be favorable compared to previous reports. However, only patients in the second remission were included in our study, whereas the other studies included patients in the first and third remission as well as the second remission; therefore, results should be compared with caution.

This study has several limitations. First, this was not a randomized controlled trial because of the small size of cohort. Second, there may be selection bias as four patients were excluded at the physician's discretion out of 31 patients with positive MRD after induction therapy (Fig. 2). Finally, because of the different backgrounds, such as supportive therapy for infections, it is difficult to simply compare the outcomes of this study to those of previous studies.

In conclusion, allo-HSCT based on post-induction MRD with a unified conditioning regimen of TBI + ETP + CY was feasible in children with intermediate-risk relapsed ALL in the JPLSG ALL-R08-II cohort. Because of the small number of children with relapsed ALL in each country, an international study using the allo-HSCT regimen is needed to optimize the regimen for children with intermediate-risk relapsed ALL.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12185-024-03710-6.

Acknowledgements We thank all of the patients, their families, physicians, and staff in the Japanese Pediatric Leukemia/Lymphoma Study Group and Japan Children's Cancer Group who contributed to this study, especially Kimiyoshi Sakaguchi, Shogo Kobayashi, Ayumu Arakawa, Sakiko Yoshida, Kazuhiro Nakamura, Akihiro Iguchi, Yoshihisa Nagatoshi, Katsuyoshi Koh, Takeji Matsushita, Setsuo Ota, Toshiyuki Kito, Keiko Okada, Takeshi Asano, Itaru Kato, Yoshiyuki Takahashi, Yuichi Mitani, Reita Tanoshima, Yoshihiro Gocho, Yuta Kawahara, and Takeo Sarashina who are or were members of the JPLSG relapsed ALL committee. We thank Enago (www.enago.jp) for the English language review. This work was supported by Grants for Clinical Cancer Research from the Ministry of Health, Labor and Welfare of Japan (H20-GanRinsho-Ippan-017 and H23-GanRinsho-Ippan-014 to KH) and by the Japan Agency for Medical Research and Development (15ck0106071h0002) to AM.

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

Declarations

Conflict of interest The authors have no conflict of interest.

References

1. Eckert C, Groeneveld-Krentz S, Kirschner-Schwabe R, Hagedorn N, Chen-Santel C, Bader P, et al. Improving stratification for children with late bone marrow B-cell acute lymphoblastic leukemia relapses with refined response classification and integration of genetics. J Clin Oncol. 2019;37(36):3493–506.
2. Lew G, Chen Y, Lu X, Rheingold SR, Whitlock JA, Devidas M, et al. Outcomes after late bone marrow and very early central nervous system relapse of childhood B-acute lymphoblastic leukemia: a report from the Children's Oncology Group phase III study AALL0433. Haematologica. 2021;106(1):46–55.
3. Eckert C, Henze G, Seeger K, Hagedorn N, Mann G, Panzer-Grümayer R, et al. Use of allogeneic hematopoietic stem-cell transplantation based on minimal residual disease response improves outcomes for children with relapsed acute lymphoblastic leukemia in the intermediate-risk group. J Clin Oncol. 2013;31(21):2736–42.
4. Badell I, Muñoz A, Ortega JJ, Martínez A, Madero L, Bureo E, et al. Long-term outcome of allogeneic or autologous haemopoietic cell transplantation for acute lymphoblastic leukaemia in second remission in children. GETMON experience 1983–1998. Bone Marrow Transplant. 2005;35(9):895–901.
5. Dopfer R, Henze G, Bender-Götze C, Ebell W, Ehninger G, Friedrich W, et al. Allogeneic bone marrow transplantation for childhood acute lymphoblastic leukemia in second remission after intensive primary and relapse therapy according to the BFM- and CoALL-protocols: results of the German Cooperative Study. Blood. 1991;78(10):2780–4.
6. Oakhill A, Pamphilon DH, Potter MN, Steward CG, Goodman S, Green A, et al. Unrelated donor bone marrow transplantation for children with relapsed acute lymphoblastic leukaemia in second complete remission. Br J Haematol. 1996;94(3):574–8.
7. Uderzo C, Valsecchi MG, Bacigalupo A, Meloni G, Messina C, Polchi P, et al. Treatment of childhood acute lymphoblastic leukemia in second remission with allogeneic bone marrow transplantation and chemotherapy: ten-year experience of the Italian Bone Marrow Transplantation Group and the Italian Pediatric Hematology Oncology Association. J Clin Oncol. 1995;13(2):352–8.
8. Wheeler K, Richards S, Bailey C, Chessells J. Comparison of bone marrow transplant and chemotherapy for relapsed childhood acute lymphoblastic leukaemia: the MRC UKALL X experience. Medical Research Council Working Party on Childhood Leukaemia. Br J Haematol. 1998;101(1):94–103.
9. Peters C, Dalle JH, Locatelli F, Poetschger U, Sedlacek P, Buechner J, et al. Total body irradiation or chemotherapy conditioning in childhood ALL: a multinational, randomized, noninferiority phase III study. J Clin Oncol. 2021;39(4):295–307.
10. Al-Kasim FA, Thornley I, Rolland M, Lau W, Tsang R, Freedman MH, et al. Single-centre experience with allogeneic bone marrow transplantation for acute lymphoblastic leukaemia in childhood: similar survival after matched-related and matched-unrelated donor transplants. Br J Haematol. 2002;116(2):483–90.
11. Jamieson CH, Amylon MD, Wong RM, Blume KG. Allogeneic hematopoietic cell transplantation for patients with high-risk acute lymphoblastic leukemia in first or second complete remission using fractionated total-body irradiation and high-dose etoposide: a 15-year experience. Exp Hematol. 2003;31(10):981–6.
12. Marks DI, Forman SJ, Blume KG, Pérez WS, Weisdorf DJ, Keating A, et al. A comparison of cyclophosphamide and total body irradiation with etoposide and total body irradiation as conditioning regimens for patients undergoing sibling allografting for acute lymphoblastic leukemia in first or second complete remission. Biol Blood Marrow Transplant. 2006;12(4):438–53.
13. den Boer ML, Pieters R. Genetics and cellular drug resistance in acute leukemia. In: Pui C-H, editor. Childhood leukemias. 3rd ed. Cambridge: Cambridge University Press; 2012. p. 257–75.
14. Hall AG, Tilby MJ. Mechanisms of action of, and modes of resistance to, alkylating agents used in the treatment of haematological malignancies. Blood Rev. 1992;6(3):163–73.
15. Chang TT, Gulati S, Chou TC, Colvin M, Clarkson B. Comparative cytotoxicity of various drug combinations for human leukemic cells and normal hematopoietic precursors. Cancer Res. 1987;47(1):119–22.
16. Chang TT, Gulati SC, Chou TC, Vega R, Gandola L, Ibrahim SM, et al. Synergistic effect of 4-hydroperoxycyclophosphamide and etoposide on a human promyelocytic leukemia cell line (HL-60) demonstrated by computer analysis. Cancer Res. 1985;45(6):2434–9.

17. O'Dwyer PJ, Leyland-Jones B, Alonso MT, Marsoni S, Wittes RE. Etoposide (VP-16-213). Current status of an active anticancer drug. N Engl J Med. 1985;312(11):692–700.
18. Biagi E, Rovelli A, Balduzzi A, De Lorenzo P, Tagliabue A, Uderzo C. TBI, etoposide and cyclophosphamide as a promising conditioning regimen for BMT in childhood ALL in second remission. Bone Marrow Transplant. 2000;26(11):1260–2.
19. Jacobsohn DA, Hewlett B, Ranalli M, Seshadri R, Duerst R, Kletzel M. Outcomes of unrelated cord blood transplants and allogeneic-related hematopoietic stem cell transplants in children with high-risk acute lymphocytic leukemia. Bone Marrow Transplant. 2004;34(10):901–7.
20. Pirich L, Haut P, Morgan E, Marymount M, Kletzel M. Total body irradiation, cyclophosphamide, and etoposide with stem cell transplant as treatment for infants with acute lymphocytic leukemia. Med Pediatr Oncol. 1999;32(1):1–6.
21. Bader P, Kreyenberg H, Henze GH, Eckert C, Reising M, Willasch A, et al. Prognostic value of minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the ALL-REZ BFM Study Group. J Clin Oncol. 2009;27(3):377–84.
22. van der Velden VH, Cazzaniga G, Schrauder A, Hancock J, Bader P, Panzer-Grumayer ER, et al. Analysis of minimal residual disease by Ig/TCR gene rearrangements: guidelines for interpretation of real-time quantitative PCR data. Leukemia. 2007;21(4):604–11.
23. Parker C, Krishnan S, Hamadeh L, Irving JAE, Kuiper RP, Révész T, et al. Outcomes of patients with childhood B-cell precursor acute lymphoblastic leukaemia with late bone marrow relapses: long-term follow-up of the ALLR3 open-label randomised trial. Lancet Haematol. 2019;6(4):e204–16.

Authors and Affiliations

Hideaki Ueki[1] · Chitose Ogawa[2] · Hiroaki Goto[3] · Masanori Nishi[4] · Junko Yamanaka[5] · Shinji Mochizuki[5] · Takuro Nishikawa[6] · Tadashi Kumamoto[2] · Ritsuo Nishiuchi[7] · Atsushi Kikuta[8] · Shohei Yamamoto[9] · Shunji Igarashi[1] · Atsushi Sato[10] · Toshinori Hori[11] · Akiko M. Saito[12] · Tomoyuki Watanabe[13] · Takao Deguchi[14] · Atsushi Manabe[15] · Keizo Horibe[12] · Hidemi Toyoda[16]

✉ Hidemi Toyoda
htoyoda@med.mie-u.ac.jp

1 Department of Pediatric Hematology/Oncology, Japanese Red Cross Narita Hospital, Narita, Japan

2 Department of Pediatric Oncology, National Cancer Center Hospital, Tokyo, Japan

3 Division of Hematology/Oncology, Kanagawa Children's Medical Center, Yokohama, Japan

4 Department of Pediatrics, Faculty of Medicine, Saga University, Saga, Japan

5 Department of Pediatrics, National Center for Global Health and Medicine, Tokyo, Japan

6 Department of Pediatrics, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan

7 Department of Pediatrics, Kochi Health Sciences Center, Kochi, Japan

8 Department of Pediatric Oncology, Fukushima Medical University Hospital, Fukushima, Japan

9 Department of Pediatrics, Tokai University School of Medicine, Isehara, Japan

10 Department of Hematology/Oncology, Miyagi Children's Hospital, Sendai, Japan

11 Department of Pediatrics, Aichi Medical University School of Medicine, Nagakute, Japan

12 Clinical Research Center, NHO Nagoya Medical Center, Nagoya, Japan

13 Department of Nutritional Science, Faculty of Psychological and Physical Science, Aichi Gakuin University, Nisshin, Japan

14 Division of Cancer Immunodiagnostics, Children's Cancer Center, National Center for Child Health and Development, Tokyo, Japan

15 Department of Pediatrics, Hokkaido University, Sapporo, Japan

16 Department of Pediatrics, Graduate School of Medicine, Mie University, 2-174 Edobashi, Tsu, Mie 514-8507, Japan