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Q1 Favorable Outcome of Post-Transplantation Cyclophosphamide Haploidentical Peripheral Blood Stem Cell Transplantation with Targeted Busulfan-Based Myeloablative Conditioning Using Intensive Pharmacokinetic Monitoring in Pediatric Patients

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A B S T R A C T

Haploidentical hematopoietic stem cell transplantation (haplo-HSCT) with post-transplantation cyclophosphamide (PTCy) was performed previously in adults using a nonmyeloablative conditioning regimen and bone marrow as a graft source. In an effort to reduce relapse rates, myeloablative conditioning regimens with higher intensities are now used. We used an intensive daily pharmacokinetic monitoring method for busulfan dosing in children for effective myeloablation and to reduce toxicity. Here, we report the retrospective results of 34 patients (median age 11.1 years) who underwent haplo-HSCT with PTCy using a targeted busulfan-based myeloablative conditioning regimen and peripheral blood as a stem cell source. The donor-type neutrophil engraftment rate was 97.1%, and the cumulative incidence rates of grade II to IV and grade III to IV acute and extensive chronic graft-versus-host disease were 38.2%, 5.9%, and 9.1%, respectively. The overall survival and event-free survival rates, and treatment-related mortality were 85.0%, 79.4%, and 2.9%, respectively. Based on the subgroup analysis of patients with malignancies (n = 23), the relapse incidence rate was 21.7%. Haplo-HSCT using PTCy with targeted busulfan-based myeloablative conditioning and peripheral blood as a stem cell source was a safe and promising therapeutic option for children.

INTRODUCTION

Over the past decade, the use of a haploidentical donor in hematopoietic stem cell transplantation (HSCT) has shown promise as a therapeutic option for individuals with hematological malignancies and nonmalignant diseases, particularly in cases in which an HLA-matched donor is not available [1]. Haploidentical donors are available for nearly all patients. Thus, delays in conducting the procedure due to an unrelated donor search can be avoided [2]. The outcomes associated with the procedure when haploidentical donors and alternative donor sources, such as umbilical cord blood or HLA-mismatched unrelated donors, are used are comparable [3].

To address the high incidence rate of treatment-related toxicity caused by the HLA mismatches associated with haploidentical HSCT (haplo-HSCT) [4,5], 3 different approaches have generally been used worldwide over the past 2 decades [6,7]. T cell depletion (TCD) was initially used to prevent lethal graft-versus-host disease (GVHD) in cases of haplo-HSCT [8]. Previously, its use was limited because of the associated slow immune reconstitution, severe infection, and graft failure [9]. However, with recent technological advancements, ex vivo techniques that remove cells, such as $\alpha\beta^+$ T cells and B cells, have been developed and showed excellent outcomes [10-12]. Moreover, the use of T cell–adoptive immunotherapy with TCD haplo-HSCT has shown promising results in more recent times [13,14]. However, the procedure is expensive and the complex equipment required makes the performance of the procedure difficult.

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Tcell–replete haploidentical grafts along with various GVHD prevention methods are preferred currently [6,7]. Of these methods, post-transplantation cyclophosphamide (PTCy) as a GVHD prophylaxis is frequently used these days, particularly because it leads to decreased incidences of GVHD, and is associated with promising outcomes [15-17]. Above all, PTCy could be a simpler method of performing haplo-HSCT than TCD, without the need for equipment and supplies for cell depletion.

Previously, haplo-HSCT with PTCy was performed in adults using a nonmyeloablative conditioning regimen and bone marrow as a graft source [18]. Acceptable GVHD and treatment-related mortality (TRM) were encouraging; however, the relatively higher rates of relapse were a cause of concern [19]. In an effort to reduce relapse rates, the use of myeloablative conditioning regimens with higher intensities using busulfan [20] or total body irradiation (TBI) [21,22] was investigated in adults, and showed promising results. Given that pediatric patients have higher bone marrow cellularity [23-25], and are more vulnerable to irradiation-associated late adverse effects, an effective myeloablative conditioning regimen without TBI may be preferred in children.

Unfortunately, there are insufficient data on haplo-HSCT with PTCy in children, and the efficiency and safety of the procedure, as estimated by previously conducted studies, are difficult to compare due to the small number of patients and various conditioning regimens [26-32].

In the present study, we used an intensive daily pharmacokinetic (PK) monitoring method for busulfan dosing and optimized the intensity of the conditioning regimen by calculating the total exposure of busulfan [33-36]. Here, we applied this targeted-busulfan method using the daily PK monitoring of haplo-HSCT using PTCy in pediatric patients, and the safety and outcomes were evaluated.

PATIENTS AND METHODS

Study Population and Study Design

We retrospectively studied 34 patients who underwent HSCT using a uniform targeted busulfan-based myeloablative conditioning regimen at the Seoul National University Children's Hospital from February 2014 to April 2017. Patients who were below 21 years of age when they underwent stem cell transplantation were included. This study was approved by the Institutional Review Board of the Seoul National University Hospital (H-1107-024-368).

Donor Selection

For the donor selection, HLA-A, HLA-B, HLA-C, and HLA-DRB1 matching was confirmed through a high-resolution molecular method in all patients and donors, and DNA samples from the donors and patients were tested for the presence or absence of 16 killer cell immunoglobulin-like receptor (KIR) genes using KIR gene-specific primer extension and bead array hybridization [37]. Donors with the KIR B haplotype were given preference [38].

Transplantation Protocol

The haplo-HSCT conditioning regimen comprised busulfan, fludarabine (40 mg/m^2 i.v. once daily from days −8 to −4), and cyclophosphamide (14.5 mg/kg i.v. once daily from days −3 to −2). Busulfan (120 mg/m^2 for patients ≥1 year of age and 80 mg/m^2 for patients <1 year of age) was administered as a starter dose on day −8 and administered once daily thereafter. A subsequent targeted dose of busulfan was analyzed according to the therapeutic drug monitoring (TDM) results from days −7 to −5 [33,35].

The total target area under the curve (AUC) of busulfan was set at 74,000 to 76,000 μg × h/L according to our previous data. The daily target AUC was 18,500 to 19,000 μg × h/L, and the target AUC on the fourth day was calculated as: (median value of the total target AUC − cumulative AUC during 3 days) μg × h/L/day [35,36].

We proceeded to HSCT if the result of a pre-HSCT bone marrow examination pointed to morphologically complete remission (CR), regardless of the minimal residual disease status. All patients received an infusion of granulocyte colony-stimulating factor (10 μg/kg s.c. once daily, from days −3 to day 0) mobilized peripheral blood stem cells from the haploidentical donors.

GVHD Prophylaxis and Supportive Care

Patients were also treated with GVHD prophylaxis for haplo-HSCT with PTCy (50 mg/kg i.v. once daily via IV on days 3 and 4), tacrolimus (from day 5), and mycophenolate mofetil (from days 5 to 35). Tacrolimus was generally administered until 8 months after HSCT for malignant diseases and until 1 year after for nonmalignant diseases. Prophylactic treatments for veno-occlusive disease (VOD) and infections were administered according to our institutional guidelines for HSCT [35].

Engraftment, Toxicities, and Minimal Residual Disease

Neutrophil engraftment was defined as the first of 3 consecutive days on which the absolute neutrophil count was >.5 × 10^9/L, and platelet recovery was defined as the day on which the platelet count was >20 × 10^9/L, without platelet transfusions in the prior 7 days. Bone marrow examination was performed at 1, 3, 6, and 12 months after HSCT, and hematopoietic chimerism was evaluated through the molecular analysis of short tandem repeat regions. Regimen-related toxicity except GVHD, up to 42 days after transplantation, was graded according to the National Cancer Institute Common Toxicity Criteria (v4.0). Minimal residual disease (MRD) detection before transplantation was performed using 4-color flow cytometry, and the cutoff used was .01%.

Statistical Analyses

The cumulative incidences (CIs) of neutrophil and platelet engraftment were evaluated with death before engraftment as the competing risk, and the CIs of acute and chronic GVHD were evaluated with graft failure, relapse, and TRM as the competing risks. The relapse incidence and TRM were also evaluated using a CI curve, with all deaths without relapse and relapse as the competing risks, respectively. Events were defined as relapse, TRM, or graft failure. The overall survival (OS) and event-free survival (EFS) were analyzed using the Kaplan-Meier method. The difference in the survival rates was investigated through a log-rank test. A P value <.05 was considered statistically significant. Statistical analyses were conducted using R version 3.2.2 (R Project for Statistical Computing, Vienna, Austria) and SPSS 23.0 (IBM Corp, Armonk, NY).

RESULTS

Characteristics of the Patients

The clinical characteristics of the patients are summarized in Table 1. The median age at the time of HSCT was 11.1 years. Of the 34 patients, 23 patients had malignancies and 11 patients had nonmalignant disease. All patients received peripheral blood as the stem cell source. A majority of the donors were parents of the patients, and 61.8% of donors had the KIR B haplotype. Of the 23 patients with malignancies, 16 had a CR1 status and 7 had a status above CR2 before HSCT. There was no refractory case. Of the 21 patients with acute leukemia, only 2 were MRD negative. Of the 19 MRD-positive patients, the flow cytometry results of 6 patients suggested the presence of leukemia cells or regenerating lymphoid or myeloid cells.

The median follow-up period was 26 (range, 1 to 50) months, and the corresponding values for those with malignant diseases and nonmalignant diseases were 24 (range, 4 to 47) months and 28 (range, 1 to 50) months, respectively.

Targeted Busulfan

The AUC of the first day of busulfan was 21,884 (range, 19,929 to 40,619) μg × h/L, and the coefficient of variance was 26.4%. Consequently, the median AUC value of the total infused busulfan was 74,078 (range, 67,302 to 78,478) μg × h/L, of which the coefficient of variance was 2.7%. Using TDM and daily dose adjustment, an acceptable total busulfan exposure range could be achieved, although the AUC for busulfan on the first day varied widely.

Engraftment

The median number of neutrophil and platelet engraftment days were 15 (range, 13 to 22) and 29 (range, 13 to 87), respectively. The CI rates of neutrophil and platelet engraftment were 97.1% and 96.6%, respectively. Primary engraftment failure occurred in 1 patient with severe congenital neutropenia who

Table 1
Patient Characteristics (N = 34).

Age, yr	11.1 (.9-20.3)
Sex	
Male	21 (61.8)
Female	13 (38.2)
BSA, m^2	1.19 (.45-2.13)
Body weight	32.2 (9.7-91.3)
Diagnosis	
Acute lymphoblastic leukemia	11 (32.4)
Acute myeloid leukemia	7 (20.6)
Mixed phenotype acute leukemia	3 (8.8)
Other malignancies*	2 (5.9)
Other nonmalignant diseases†	11 (32.4)
Donor	
Parents	30 (88.2)
Siblings	4 (11.8)
Donor-to-recipient sex direction	
Male → Male	14 (41.2)
Female → Male	7 (20.6)
Female → Female	9 (26.5)
Male → Female	4 (11.8)
Donor KIR haplotype	
A	11 (32.4)
B	21 (61.8)
N/D	2 (5.9)
CMV serology (donor/recipient)	
Positive/Positive	32 (94.1)
Positive/Negative	2 (5.9)
Disease status	
CR1	16 (47.1)
≥CR2	7 (20.6)
N/A	11 (32.4)
Previous transplantation	
No	30 (88.2)
Yes (≥1)	4 (11.8)
Infused busulfan AUC, μg x h/L	74,078 (67,302-78,478)
Infused TNC, $x10^8$/kg	14.1 (9.2-20.8)
Infused CD34+ cells, $x10^6$/kg	7.3 (4.5-23.6)

Data are presented as median (range) or n (%).
BSA indicates body surface area; N/D, not done; N/A, not applicable; TNC, total nuclear cells.
* One case of Ewing sarcoma and 1 case of Hodgkin disease were included.
† Four cases of adrenoleukodystrophy, 2 of Krabbe disease, 1 of congenital neutropenia, 1 of Wiskott-Aldrich syndrome, 1 of autoimmune lymphoproliferative syndrome, 1 of beta-thalassemia, and 1 of familial hemophagocytic lymphohistiocytosis were included.

received a second haplo-HSCT from the same donor (father) 134 days after the first haplo-HSCT. Neutrophil and platelet engraftment were achieved on days 13 and 24, respectively, and the patient was still disease-free at the last follow-up, 9 months from the second haplo-HSCT.

Complications and Neurological Status

The presence of VOD was observed in 7 (20.6%) cases, and this was resolved successfully using antithrombin III and/or tissue plasminogen activator. There was no statistically significant difference in the first-day busulfan AUC (VOD group: median 22,629 [range, 12,929 to 40,619] μg × h/L; non-VOD group: median 21,383 μg × h/L [range, 15,728 to 38,921]; $P = .306$) or the total busulfan AUC (VOD group: median 73,407 μg × h/L [range, 72,400 to 76,816]; non-VOD group: median 74,086 [range, 67,302 to 78,478] μg × h/L; $P = .800$) between both groups. Furthermore, the pretransplant ferritin levels were not different between the groups (VOD group: median 481 [range, 8 to 2052] ng/mL; non-VOD group: median 1157 [range, 12 to 14,391] ng/mL; $P = .356$). The elevation of aspartate or alanine aminotransferase levels and total bilirubin levels of at least grade 3 severity were shown in 23.5% and 5.9% of the patients, respectively. The incidence of hemorrhagic cystitis with severity higher than grade 3 was 35.3% (12 patients), and the median onset time from transplantation and the duration were 32 (range, 5 to 40) days and 12 (range 3 to 50) days, respectively; this was successfully managed with massive intravenous hydration.

Cytomegalovirus (CMV) antigenemia occurred in 76.5% of the patients, and according to our institutional guideline for CMV management, half-dose ganciclovir preemptive therapy (5 mg/kg once daily, 6 days/week) was administered to patients with CMV antigenemia levels <10/200,000 cells [39]. The requirement of ganciclovir induction therapy was observed in 8 (23.5%) patients with CMV antigenemia levels ≥10/200,000 cells. None of the patients had CMV disease.

With respect to the neurological status of 6 patients with adrenoleukodystrophy (n = 4, with pre-HSCT Loes scores of 0, 3.5, 8 and 12, respectively) [40] or Krabbe disease (n = 2), 5 presented with no significant changes in the brain magnetic resonance imaging (MRI) scans taken 1 year after HSCT. The neurological examinations at the last follow-up were comparable to those before haplo-HSCT. Unfortunately, the patient with advanced adrenoleukodystrophy who previously had progressive visual and hearing impairment experienced a rapid deterioration of visual and hearing function during the conditioning period. Afterward, no further neurological deterioration occurred after HSCT.

Graft-Versus-Host Disease

The CI rates of grade II to IV and grade III to IV acute GVHD were 38.2% and 5.9%, respectively (Figure 1A). Two patients had grade III GVHD, 1 with stage 3 skin involvement and stage 2 lower gastrointestinal involvement and the other with stage 3 lower gastrointestinal tract involvement; none of the patients had grade IV GVHD. The signs and symptoms of acute GVHD in all patients were resolved by the use of systemic corticosteroids. The CI of extensive chronic GVHD was 9.1% (Figure 1B). The organs involved were the skin in 1 patient; skin and liver in 1 patient; and skin, mouth and lung in a 1 patient. Cyclosporine and prednisolone [41] were used in 2 patients for 7 and 12 months, respectively, and for the remaining patient who had post-transplant thrombotic microangiopathy and could not be treated with cyclosporine, mycophenolate mofetil plus prednisolone was used for 8 months. The resolution of chronic GVHD was achieved in all patients.

When the patients were categorized by age at diagnosis (<10 years of age or ≥10 years of age), there was no statistically significant difference in the CI rates of grade II to IV (37.5% versus 25.0%; $P = .308$) and grade III to IV acute GVHD (6.3% versus 5.0%; $P = .857$), and extensive chronic GVHD (12.0% versus 5.0%; $P = .316$) between the younger (n = 16) and older groups.

Relapse

To compare the relapse incidence rates, we performed a subgroup analysis of patients with malignant diseases (n = 23). The relapse incidence rate at 2 years was 21.7% (Figure 1D). The diagnoses and disease status before haplo-HSCT of the relapse patients were relapsed acute myelogenous leukemia (CR2, MRD positive), therapy-related acute myelogenous leukemia (CR1, MRD-negative), B cell acute lymphoblastic leukemia with *MLL* rearrangement (CR1, MRD positive), T cell acute lymphoblastic leukemia with central nervous system involvement (CR1, MRD positive), and relapsed mixed-phenotype acute leukemia after unrelated HSCT (CR2, MRD positive). The

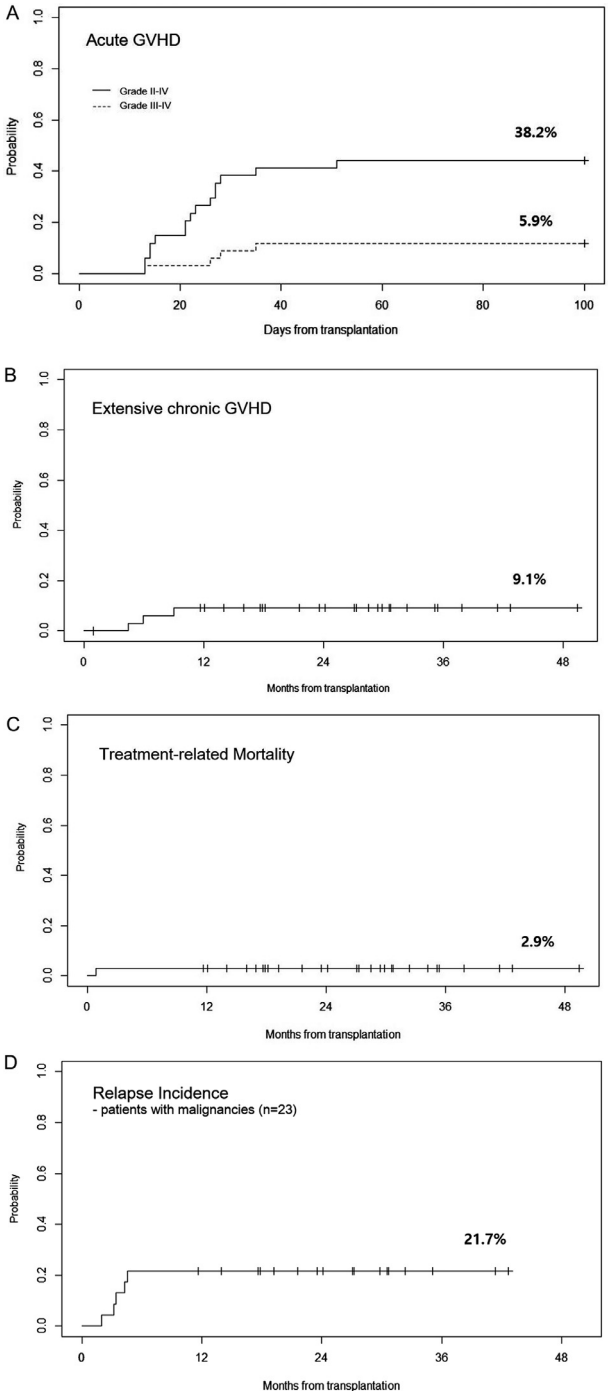

Figure 1. The CIs of (A) grade II to IV and grade III to IV acute GVHD and (B) extensive chronic GVHD were 38.2%, 5.9%, and 9.1%, respectively. (C) The CI rate of TRM was 2.9%. (D) The relapse incidence rate of the patients with malignancy (n = 23) was 21.7%.

median number of days to relapse from HSCT was 103 (range, 60 to 138) days.

In 2 of the relapse patients, CR was achieved by the administration of donor lymphocyte infusion (DLI), which was combined with chemotherapy at first and was subsequently conducted alone due to poor bone marrow recovery. In the first course of DLI, a target dose of $.5 \times 10^6$/kg of $CD3^+$ cells was infused. If there was no evidence of GVHD development, the subsequent dose of DLI was increased to 1.0×10^6/kg of $CD3^+$ cells and was finally increased up to 5.0×10^6/kg of $CD3^+$ cells, every 3 or 4 weeks. A patient who received DLI 15 times developed chronic GVHD and was still alive without disease at 34 months from relapse, while the other patient experienced relapse after receiving DLI 5 times.

Survival and Treatment-Related Mortality

The EFS rate and OS rate at 2 years were 79.4 ± 6.9% and 85.0 ± 6.2%, respectively (Figure 2A). In the subgroup analysis of the patients with malignant diseases (n = 23), the EFS and OS rates at 2 years were 78.3 ± 8.6% and 82.1 ± 8.1%, respectively (Figure 2B), and the corresponding values for patients with nonmalignant diseases (n = 11) were 81.8 ± 11.6% and 90.9 ± 8.7%, respectively (Figure 2C).

In the subgroup analysis of patients with malignant diseases (n = 23), survival outcomes were not affected by KIR haplotype B donors (n = 16) compared with cases with haplotype A donors (EFS rate: 75.0 ± 10.8% versus 85.7 ± 13.2%, $P = .582$; OS rate: 73.1 ± 11.3% versus 100%, $P = .148$, respectively).

Of 4 patients who received previous HSCT (2 allogeneic and 2 autologous), 3 patients were alive without disease at the last follow-up, whereas 1 patient experienced relapse after 136 days from haplo-HSCT and died.

The CI of TRM at 2 years was 2.9% (1 of 34 patients) (Figure 1C). One patient with recurrent Epstein-Barr virus–associated hemophagocytic lymphohistiocytosis who underwent haplo-HSCT died of hepatic failure. Initially, this patient had VOD, which was improving; however, the patient subsequently died of Epstein-Barr virus–induced fulminant hepatitis.

DISCUSSION

This retrospective study aimed to assess the efficacy and safety of haplo-HSCT in children using PTCy, along with a targeted busulfan-based myeloablative conditioning regimen. Based on our analysis, the EFS and OS rates associated with haplo-HSCT with PTCy were favorable, indicating promising survival rates among children who received haplo-HSCT compared with the results reported in previous studies [27,29-32]. Furthermore, incidences of GVHD, TRM, and other transplantation-related toxicities were acceptable, although all our patients received a busulfan-based myeloablative conditioning regimen and peripheral blood as a graft source.

One reason for the favorable outcome could be the use of targeted busulfan, which is a drug well-known for its inter- and intravariable pharmacokinetics; therefore, adequate dosing is important [36]. Given that children have a higher number of stem cells than adults (children have a higher proportion of red than yellow bone marrow while adults have a higher proportion of yellow bone marrow) [42], a higher concentration of busulfan may need to be used as a myeloablative regimen to obtain effective niches for an increased hematopoietic competition between donor and residual recipient stem cells [25]. Recently, similar nonrelapse mortality was observed in adult patients who underwent myeloablative haplo-HSCT with a busulfan-based regimen, when compared with those who received a nonmyeloablative conditioning regimen [20]. To improve the outcomes in pediatric patients using a busulfan-based myeloablative conditioning regimen, we optimized the busulfan exposure of each patient using daily TDM, which already showed a favorable clinical outcome [35], and acceptable busulfan pharmacokinetic results [34]. To the best of our knowledge, the present study includes the largest number of pediatric patients who underwent haplo-HSCT using PTCy along with a targeted busulfan-based myeloablative conditioning regimen.

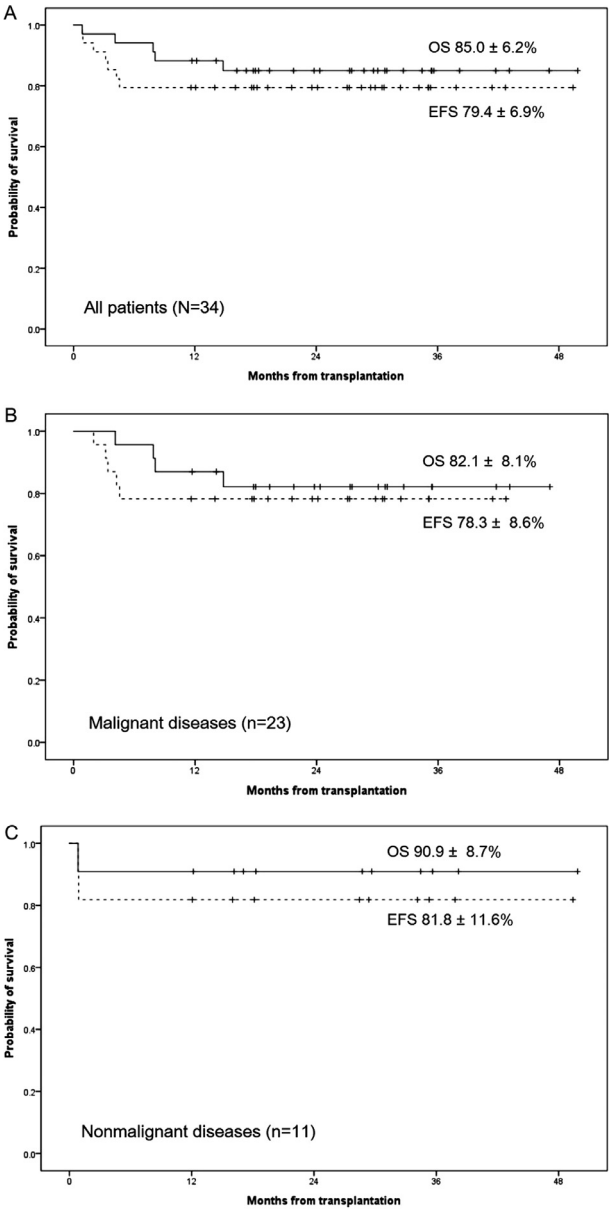

Figure 2. (A) The EFS rates and OS rates at the time of the median follow-up of all cases were 79.4 ± 6.9% and 85.0 ± 6.2%, respectively. (B) In the subgroup analysis of cases with malignant disease (n = 23), the EFS rate and OS rate were 78.3 ± 8.6% and 82.1 ± 8.1%, respectively, and (C) the corresponding values in cases with nonmalignant diseases (n = 11) were 81.8 ± 11.6% and 90.9 ± 8.7%, respectively.

All patients, except 1, underwent neutrophil and platelet engraftment. Although the timing of the engraftment of the haplo-HSCT using PTCy was relatively delayed compared with that of related or unrelated HLA-matched HSCT [43], the range of the engraftment time was predictable without any episode of prolonged unexpected neutropenia; thus, patients could be safely protected against opportunistic infections.

Higher GVHD occurrence rates and TRM were reported in younger children who underwent haplo-HSCT with PTCy [27]; however, our results showed acceptable rates of GVHD and TRM, and a majority of the patients with events experienced disease progression rather than TRM or GVHD-related problems. Furthermore, the use of peripheral blood as a stem cell source did not increase the risk of chronic GVHD development in our study compared with recent adult data [44]. Nevertheless, a relatively higher incidence of VOD was observed. Therefore, haplo-HSCT with PTCy with a myeloablative conditioning regimen should be performed cautiously in patients with high-risk factors for VOD.

The use of DLI with haplo-HSCT may be helpful in children with advanced leukemia [45]. Although we observed only 2 cases of DLI after relapse, 1 patient achieved a long-term CR status. This could be a useful tool after haplo-HSCT to prevent relapse in high-risk patients as well as to treat relapse in patients who have difficulties in receiving additional cytotoxic chemotherapy. Moreover, relapse occurred relatively earlier, as observed in this study, at a median of 103 days from transplantation (range, 60 to 138 days). This could be attributed to the high-risk disease characteristics of relapse patients, as well as the fact that the MRD status may have been underestimated by 4-color flow cytometry. Further efforts, such as planned DLI [26] or intensified chemotherapy in pre-HSCT MRD-positive patients before HSCT [46], may be needed in the future.

In addition, 6 patients with inborn errors of metabolism, such as adrenoleukodystrophy or Krabbe disease, received haplo-HSCT. Generally, the search for a compatible stem cell donor may not prove productive because of the rapid disease progression in the central nervous system after diagnosis. Pierpont et al. [47] demonstrated that higher baseline MRI severity scores among cerebral adrenoleukodystrophy patients were associated with greater neurocognitive decline after HSCT, indicating that performing HSCT earlier, even before disease evidence is observed on MRI scans or before the occurrence of neurological problems, could be recommended. Thus, haplo-HSCT may be a beneficial therapeutic option under these circumstances. As of the end date of the study, all the patients with inborn errors of metabolism were alive without severe transplantation-related complications.

However, our study has several limitations associated with its retrospective design, relatively small sample size nature, and insufficient follow-up time to evaluate long-term outcomes.

In conclusion, haplo-HSCT using PTCy, along with a targeted busulfan-based myeloablative conditioning regimen and peripheral blood as a stem cell source, may be a safe and promising therapeutic option for children with hematological malignancies and nonmalignant diseases.

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SUPPLEMENTARY DATA

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