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Post-Transplantation Cyclophosphamide-Based Haploidentical versus Matched Unrelated Donor Peripheral Blood Hematopoietic Stem Cell Transplantation Using Myeloablative Targeted Busulfan-Based Conditioning for Pediatric Acute Leukemia

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The use of haploidentical related donors (HRDs) is a common alternative donor strategy used when matched sibling or unrelated donors are not available for hematopoietic stem cell transplantation (HSCT). However, there have been no studies comparing HRD HSCT with post-transplantation cyclophosphamide (PTCy) and matched unrelated donor (MUD) HSCT with antithymocyte globulin using similar busulfan-based myeloablative conditioning regimens in pediatric acute leukemia. Here we compared the outcomes in children and adolescents with high-risk acute leukemia who underwent HRD HSCT with PTCy (n = 35) or MUD HSCT (n = 45) after targeted busulfan-based myeloablative conditioning using intensive pharmacokinetic monitoring. The median duration of follow-up was 3.7 years in the HRD group and 4.6 years in the MUD group. No engraftment failure was observed in either group. There were no significant between-group differences in the cumulative incidence of grade II-IV acute graft-versus-host disease (GVHD) (34.3% versus 48.9%; $P = .142$), grade III-IV acute GVHD (2.9% versus 8.9%; $P = .272$), moderate to severe chronic GVHD (11.4% versus 18.3%; $P = .417$), relapse (25.6% versus 28.0%; $P = .832$), and nonrelapse mortality (0% versus 2.2%; $P = .420$). The 3-year severe chronic GVHD-free/relapse-free survival (GRFS), leukemia-free survival (LFS), and overall survival (OS) rates in the HRD and MUD groups were 62.9% (95% confidence interval [CI], 45.8% to 80.0%) versus 49.8% (95% CI, 34.9% to 64.7%; $P = .318$), 74.4% (95% CI, 58.7% to 90.1%) versus 67.5% (95% CI, 53.4% to 81.6%; $P = .585$), and 88.6% (95% CI, 78.0% to 99.2%) versus 83.7% (95% CI, 72.5% to 94.9%; $P = .968$), respectively. In a subgroup analysis of patients with acute lymphoblastic leukemia (HRD, n = 17; MUD, n = 26), the 3-year GRFS, LFS, and OS rates in the HRD and MUD groups were 49.4% (95% CI, 24.3% to 74.5%) versus 39.5% (95% CI, 19.7% to 59.3%; $P = .601$), 61.8% (95% CI, 37.5% to 86.1%) versus 63.6% (95% CI, 44.4% to 82.8%; $P = .872$), and 82.4% (95% CI, 64.4%, 100%) versus 84.2% (95% CI, 70.1% to 98.3%; $P = .445$), respectively. In patients with acute myelogenous leukemia (AML) (HRD, n = 16; MUD, n = 16), the 3-year GRFS, LFS, and OS rates in the HRD and MUD groups were 80.8% (95% CI, 61.2% to 100%) versus 61.9% (95% CI, 37.8% to 86.0%; $P = .326$), 87.1% (95% CI, 70.2% to 100%) versus 73.9% (95% CI, 51.8% to 96.0%; $P = .478$), and 93.8% (95% CI, 81.8% to 100%) versus 85.6% (95% CI, 67.0% to 100%; $P = .628$), respectively. Although the difference was not statistically significant and the number of patients was small, the promising outcomes of HRD HSCT in AML patients were encouraging. Our results demonstrate that HRD HSCT with PTCy using a targeted busulfan-based myeloablative conditioning regimen has outcomes similar to those of MUD HSCT with antithymocyte globulin. HRD HSCT with PTCy could be a feasible option for pediatric high-risk acute leukemia patients who lack an HLA-matched related or unrelated donor.

INTRODUCTION

The use of a haploidentical related donor (HRD) is a common alternative donor strategy used when a matched sibling or unrelated donor is not available for hematopoietic stem cell transplantation (HSCT) [1]. AN HSCT candidate has a 25% to 80% chance of not having a matched unrelated donor (MUD), depending on ethnicity [2]. Moreover, the use of umbilical

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cord blood grafts has been steadily declining in the absence of matched donors; consequently, the use of HRDs has been increasing in recent decades [1]. HRD HSCTs using T cell-depleted or T cell-replete approaches have been developed and show promising results, including high engraftment and low rates of graft-versus-host disease (GVHD) and nonrelapse mortality (NRM) [3–5]. Among the various available HRD HSCT approaches, a recent study reported better leukemia-free survival (LFS) and GVHD-free survival after GVHD prophylaxis with post-transplantation cyclophosphamide (PTCy) compared with antithymocyte globulin (ATG) [6]. PTCy-based GVHD prophylaxis is an attractive option in HRD HSCT because of its promising outcomes and easy application [7].

Several studies related to adult acute leukemia have shown promising results of HRD HSCT compared with MUD HSCT [8–10]. In addition, some studies have shown favorable results of HRD HSCT in the pediatric population; among these, an Italian multicenter study found similar survival outcomes with α/β T cell- and B cell-depleted HRD HSCT as in MUD HSCT [11]. Furthermore, a recent study reported that PTCy-based HRD HSCT using a nonmyeloablative conditioning regimen in pediatric patients showed similar overall survival (OS) rates but lower event-free survival rates due to graft rejection compared with MUD HSCT [12].

HRD HSCT with PTCy was initially designed for use with nonmyeloablative conditioning regimens and bone marrow (BM) as the stem cell source [13]. However, the use of myeloablative conditioning in PTCy-based HRD HSCT has been increasing and has shown comparable toxicity to nonmyeloablative conditioning [14]. Since 2009, our institution has used a targeted busulfan-based myeloablative conditioning regimen using intensive pharmacokinetic (PK) monitoring and ATG-based GVHD prophylaxis in matched donor and umbilical cord HSCT, which have shown promising outcomes [15]. Moreover, we also reported favorable outcomes of PTCy-based HRD HSCT with a targeted busulfan-based myeloablative conditioning regimen [5]. However, to our knowledge, there have been no studies comparing HRD HSCT with PTCy and MUD HSCT with ATG using a similar busulfan-based myeloablative conditioning regimen in pediatric acute leukemia. In the present study, we compared outcomes in children and adolescents with high-risk acute leukemia after a busulfan-based myeloablative conditioning regimen along with HRD HSCT with PTCy or MUD HSCT.

METHODS

Patients

We retrospectively analyzed the outcomes of 80 pediatric patients with high-risk acute leukemia, such as relapse, induction failure, and other high-risk cytogenetics. The patients underwent a first allogeneic HSCT from an HRD (n = 35) or an MUD (n = 45) at Seoul National University Children's Hospital between January 2013 and April 2020, using intensive PK monitoring of the targeted busulfan-based myeloablative conditioning regimen. All consecutive patients were analyzed. The Institutional Review Board of the Seoul National University Hospital approved the procedure for reviewing medical records and waived the need for consent (H-1107-024-368).

Donor Selection and Stem Cell Source

For the selection of HRDs and MUDs, HLA-A, -B, -C, and -DRB1 matching in all patients and donors was confirmed through a high-resolution molecular method; HRDs with the killer cell immunoglobulin-like receptor B haplotype were given preference in the absence of anti-HLA antibodies. If the patient did not have a donor with 9 or 10 out of 10 matching antigens (HLA-matched MUD), an HRD was considered as an alternative donor. All patients received granulocyte colony-stimulating factor-mobilized (10 mg/kg s.c. once daily, from day -3 to day 0) peripheral blood stem cells (PBSCs) from an HRD or MUD.

Transplantation Protocol

All patients received a busulfan-based myeloablative conditioning regimen. Busulfan (120 mg/m^2 for patients age ≥1 year and 80 mg/m^2 for those age <1 year) was administered i.v. once daily as a starter dose on day -9. Subsequently, the targeted busulfan dose was analyzed according to the therapeutic drug monitoring results of the previous day and administered once daily on days -8 to -6. The total target range of the busulfan area under the curve was 74 to 76 mg·h/L [15].

The HRD group received targeted 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) as a conditioning regimen. The majority of patients in the MUD group received targeted busulfan and fludarabine (40 mg/m^2 i.v. once daily from days -8 to -4) with or without etoposide (20 mg/kg i.v. once daily from days -4 to -2), with ATG (2.5 mg/kg i.v. once daily from days -4 to -2; Thymoglobulin; Genzyme Transplant, Cambridge, MA). Etoposide was administered to patients with acute lymphoblastic leukemia (ALL) or high-risk acute myelogenous leukemia (AML).

For GVHD prophylaxis, PTCy (50 mg/kg i.v. once daily on days +3 and +4) and tacrolimus (from days +5 to +240) and mycophenolate mofetil (from days +5 to +35) were used in the HRD group, and tacrolimus (from days -1 to +240) and methotrexate (days +1, +3, +6, and +11) in the MUD group. Three AML patients in the HRD group who received donor lymphocyte infusion after HSCT received tacrolimus up to day +60 and mycophenolate mofetil up to day +21. Prophylactic treatments for veno-occlusive disease and infections were administered according to our institutional guidelines for HSCT [15]. All patients received ciprofloxacin as prophylaxis against BK virus. Periodic screening for cytomegalovirus (CMV), Epstein-Barr virus, and BK virus was performed, and treatment for reactivation was provided as described previously [16,17].

Definitions

Neutrophil engraftment was defined as the first 3 days with a neutrophil count $>0.5 \times 10^9$/L, and platelet engraftment was defined as the first 3 days with a platelet count $>20 \times 10^9$/L, without transfusion for at least 7 days. Acute and chronic GVHD were diagnosed and graded according to standard criteria [18,19]. Regimen-related toxicity (except for GVHD) up to 42 days after transplantation was graded according to the National Cancer Institute's Common Toxicity Criteria (version 4.03).

Statistical Analyses

Categorical variables were compared using the chi-square test, and continuous variables were compared using the Student *t* test or one-way analysis of variance. Relapse incidence, NRM, and GVHD were calculated using the cumulative incidence function. The competing risk for relapse was NRM, the competing risk for NRM was relapse, and the competing risks for GVHD were graft failure and NRM. Events were defined as death, relapse, or graft failure. Survival was analyzed using the Kaplan-Meier method. The difference in cumulative incidence curves was examined using Gray's test, and the difference in survival rates was determined using the log-rank test. A Cox proportional hazard regression model was used for the multivariate analysis of prognostic factors affecting survival; independent variables ($P < .2$) were included in this model. Statistical significance was set at $P < .05$. Statistical analyses were conducted using R version 3.2.2 (www.r-project.org) and SPSS 23.0 (IBM, Armonk, NY).

RESULTS

Patient Characteristics

The clinical characteristics of the patients are summarized in Table 1. A total of 80 patients were classified into the HRD group (n = 35) and the MUD group (n = 45). The median age at HSCT, sex, body surface area, distribution of diagnosis, and remission status at HSCT were not different between the groups. The pediatric Disease Risk Index (DRI) [20] also was similar in the 2 groups; however, the 3 patients with a vary high DRI were included in the HRD group. The median duration of follow-up was 3.7 years in the HRD group and 4.6 years in the MRD group. The HRD group tended to have longer hospital stays, although the between-group difference was not statistically significant.

Engraftment, Complications, and GVHD

The median infused total nucleated and CD34$^+$ cell counts were 15.1×10^8/kg and 7.5×10^6/kg, respectively, in the HRD group and 13.0×10^8/kg and 6.5×10^6/kg, respectively, in the MUD group. All patients achieved engraftment. However, the

Table 1
Patient Characteristics

Characteristic	HRD (N = 35)	MUD (N = 45)	*P* Value
Age, yr, median (range)	7.0 (1.0-16.4)	8.9 (0.8-18.2)	.789
Sex, n (%)			.884
Male	22 (62.9)	29 (64.4)	
Female	13 (37.1)	16 (35.6)	
BSA, m^2, median (range)	0.92 (0.45-2.13)	1.02 (0.39-1.68)	.460
Body weight, kg, median (range)	25.9 (9.8-91.3)	28.1 (7.7-64.6)	.344
Height, m, median (range)	127.6 (73.8-179.0)	131.6 (71.9-176.1)	.733
Diagnosis, n (%)			.655
ALL	17 (48.6)	26 (57.8)	
AML	16 (45.7)	16 (35.6)	
MPAL and others	2 (5.7)	3 (6.7)*	
Disease status, n (%)			.101
CR1	24 (68.6)	37 (82.2)	
CR2	8 (22.9)	8 (17.8)	
Not in remission	3 (8.6)	0 (0.0)	
Pediatric DRI, n (%)			.072
Low	11 (31.4)	21 (46.7)	
Intermediate	19 (54.3)	18 (40.0)	
High	2 (5.7)	6 (13.3)	
Very high	3 (8.6)	0 (0.0)	
CMV serostatus, n, (%)			.189
Donor + /recipient +	31 (88.6)	37 (82.2)	
Donor - /recipient +	4 (11.4)	4 (8.9)	
Donor +/recipient -	0 (0.0)	4 (8.9)	
HLA matching, n (%)			<.001
10/10	0 (0.0)	35 (77.8)	
9/10	0 (0.0)	10 (22.2)	
Haploidentical	35 (100.0)	0 (0.0)	
Killer cell immunoglobulin-like receptor, n (%)			
Ligand mismatch (GVH)	8 (22.9)		
B haplotype	23 (65.7)		
Infused TNCs, $\times 10^8$/kg (range)	15.1 (7.0-36.8)	13.0 (6.0-39.0)	.274
Infused $CD34^+$ cells, $\times 10^6$/kg, median (range)	7.5 (4.5-19.7)	6.5 (0.9-23.9)	.197
Infused busulfan AUC, mg·h/L (range)	74.3 (70.6-81.4)	74.5 (70.5-78.3)	.258
Duration of follow-up, yr, median (range)†	3.7 (0.8-6.5)	4.6 (1.1-8.1)	.086
Duration of hospitalization, d, median (range)	52 (32-96)	40 (29-214)	.388

BSA indicates body surface area; CR, complete remission; MPAL, mixed phenotype acute leukemia; GVH, graft versus host; TNCs, total nucleated cells; AUC, area under the curve.

* One MPAL and 1 natural killer cell leukemia.

† Patients who died were excluded.

time to neutrophil engraftment was significantly longer in the HRD group compared with the MUD group (median, 15 [range, 13 to 18] days versus 10 [range, 9 to 13] days; $P < .001$). The time to platelet engraftment also was significantly longer in the HRD group (median, 26 [range, 13 to 84] days versus 14 [range, 9 to 42] days; $P < .001$).

There were no statistically significant differences between the HRD and MUD groups in the incidence of severe hepatic veno-occlusive disease (14.3% versus 6.7%; $P = .260$), CMV antigenemia positivity (74.3% versus 62.2%; $P = .253$), and antigenemia level ≥10/200,000 cells (34.3% versus 17.8%; $P = .091$), although the HRD group showed relatively higher tendencies. However, CMV disease occurred in 5 patients (11%) in the MUD group and was treated successfully, compared with no patients in the HRD group. All patients with severe hepatic veno-occlusive disease were treated with supportive care, including defibrotide. There were no significant between-group differences in the incidence of hepatic toxicity, such as liver enzyme elevation grade ≥3 (HRD, 14.3% versus MUD, 22.2%; $P = .367$) or hyperbilirubinemia grade ≥3 (5.7% versus 6.7%; $P = .861$), or in the incidence of BK viruria (54.3% versus 40.0%; $P = .204$); however, hemorrhagic cystitis grade ≥3 occurred more frequently in the HRD group (34.3% versus 4.4%; $P < .001$). All patients with hemorrhagic cystitis received sufficient i.v. hydration and symptomatic treatment using an α1 blocker or an anticholinergic agent, depending on the patient's symptoms. Two of these patients received cidofovir, and all patients were treated successfully (Supplementary Table S1)

The cumulative incidence rates (CIRs) of grade II-IV and grade III-IV acute GVHD in the HRD and MUD groups were 34.3% versus 48.9% ($P = .142$) and 2.9% versus 8.9% ($P = .272$), respectively (Figure 1A). The CIR of overall chronic GVHD was 40.0% in the HRD group versus 41.3% in the MUD group ($P = .723$), and that of moderate to severe chronic GVHD also was similar in the 2 groups (11.4% versus 18.3%; $P = .417$) (Figure 1B). There were no deaths associated with GVHD in either group.

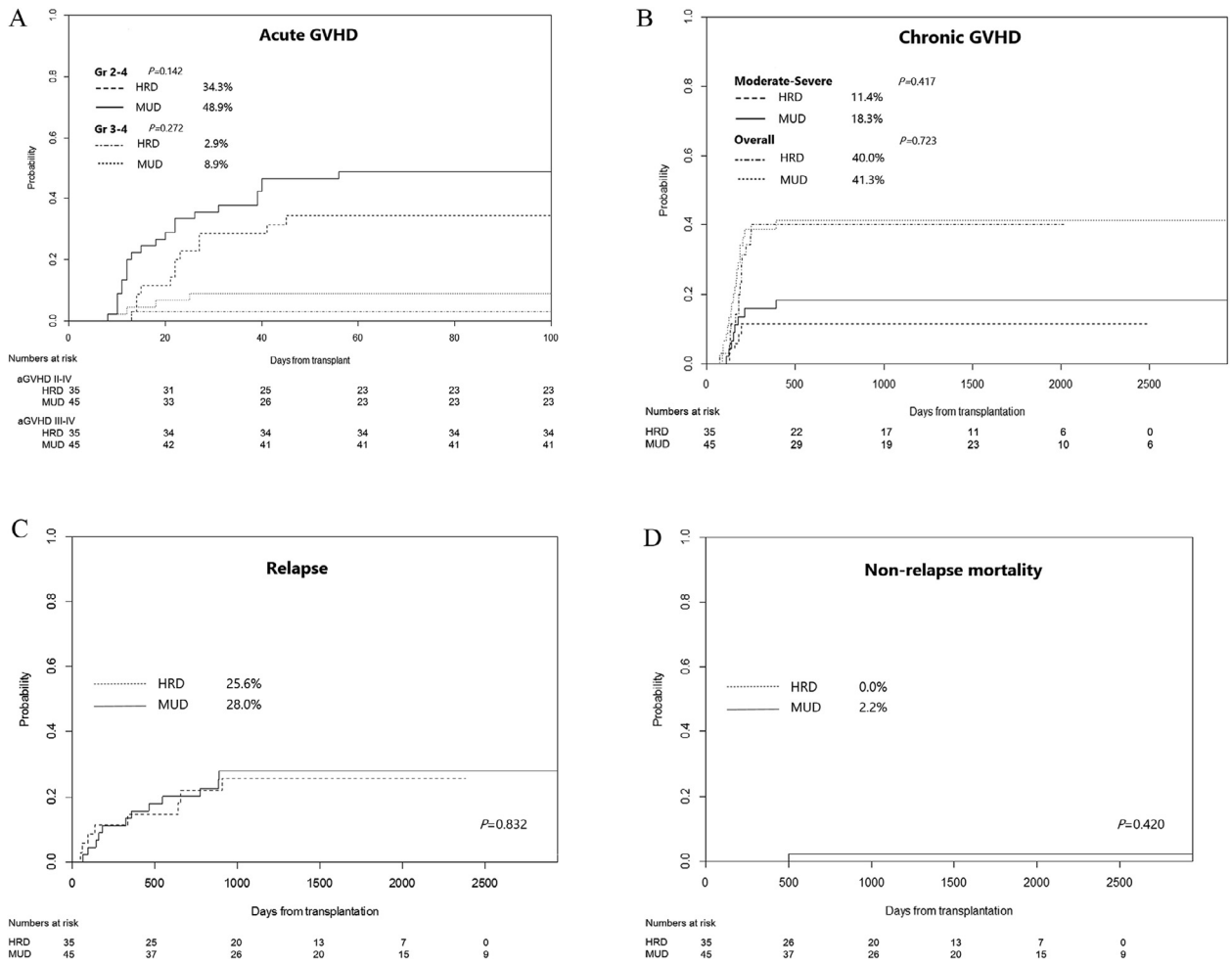

Figure 1. The cumulative incidences of grade II-IV and grade III-IV acute GVHD (A) and moderate to severe chronic GVHD (B) for the HRD and MUD groups were 34.3% versus 48.9% (P = .142), 2.9% versus 8.9% (*P* = .272), and 11.4% versus 18.3% (*P* = .417), respectively. The cumulative incidences of relapse (C) and NRM (D) for the HRD and MUD groups were 25.6% versus 28.0% (*P* = .832) and 0.0% versus 2.2% (*P* = .420), respectively.

Relapse, NRM, and Survival

The relapse incidence in the HRD group was not significantly different from that in the MUD group (25.6% versus 28.0%; *P* = .832) (Figure 1C). Moreover, none of the patients in the HRD group died of NRM, whereas the CIR of NRM in the MUD group was 2.2% (n = 1) (*P* = .420). The cause of NRM in the MUD group was pneumonia (Figure 1D). This patient was diagnosed with infant leukemia, positive for *MLL-AFF1* translocation, and received a long course of prednisolone owing to Evans syndrome after HSCT. At 14 months after transplantation, he died from rapid deterioration of pulmonary function after hospitalization due to pneumonia caused by infection with parainfluenza virus 3 and respiratory syncytial virus A.

The 3-year severe chronic GVHD-free/relapse-free survival (GRFS) rates in the HRD and MUD groups were 62.9% (95% confidence interval [CI], 45.8% to 80.0%) versus 49.8% (95% CI, 34.9% to 64.7%; *P* = .318) (Supplementary Figure S1). The 3-year LFS and OS rates of the 2 groups were 74.4% (95% CI, 58.7% to 90.1%) versus 67.5% (95% CI, 53.4% to 81.6%; *P* = .585) and 88.6% (95% CI, 78.0% to 99.2%) versus 83.7% (95% CI, 72.5% to 94.9%; *P* = .968), respectively (Figure 2). Among the variables, including disease, age, pediatric DRI, infused CD34$^+$ cell counts, infused busulfan area under the curve, and CMV serostatus, there was no statistically significant difference in univariate analyses of GRFS, LFS, and OS. When the MUD group was divided into MUD 10/10 (n = 35) and MUD 9/10 (n = 10), the 3-year GRFS, LFS, and OS rates of the HRD, MUD 10/10, and MUD 9/10 groups were not significantly different (Supplementary Figure S2). In the multivariate analysis including donor group, diagnosis, and infused cell counts, there were no significant prognostic factors for GRFS, LFS, or OS (Supplementary Table S2).

Subgroup Analysis of ALL and AML

In a subgroup analysis of ALL patients (HRD, n = 17; MUD, n = 26), the 3-year GRFS, LFS, and OS rates of the HRD and MUD groups were 49.4% (95% CI, 24.3% to 74.5%) versus 39.5% (95% CI, 19.7% to 59.3%; *P* = .601), 61.8% (95% CI, 37.5% to 86.1%) versus 63.6% (95% CI, 44.4% to 82.8%; *P* = .872), and 82.4% (95% CI, 64.4% to 100%) versus 84.2% (95% CI, 70.1% to 98.3%; *P* = .445), respectively (Figure 3A and B). In the MUD group, 5 of the 8 relapsed patients survived. Two of these patients were Philadelphia chromosome-positive and survived without additional HSCT by salvage chemotherapy using another tyrosine kinase inhibitor. One patient survived after undergoing a second HSCT using total body irradiation (TBI) after blinatumomab, and 1 patient with central nervous system relapse survived after craniospinal irradiation and then a second HSCT using busulfan and cyclophosphamide. The remaining patient underwent a second HSCT using TBI but

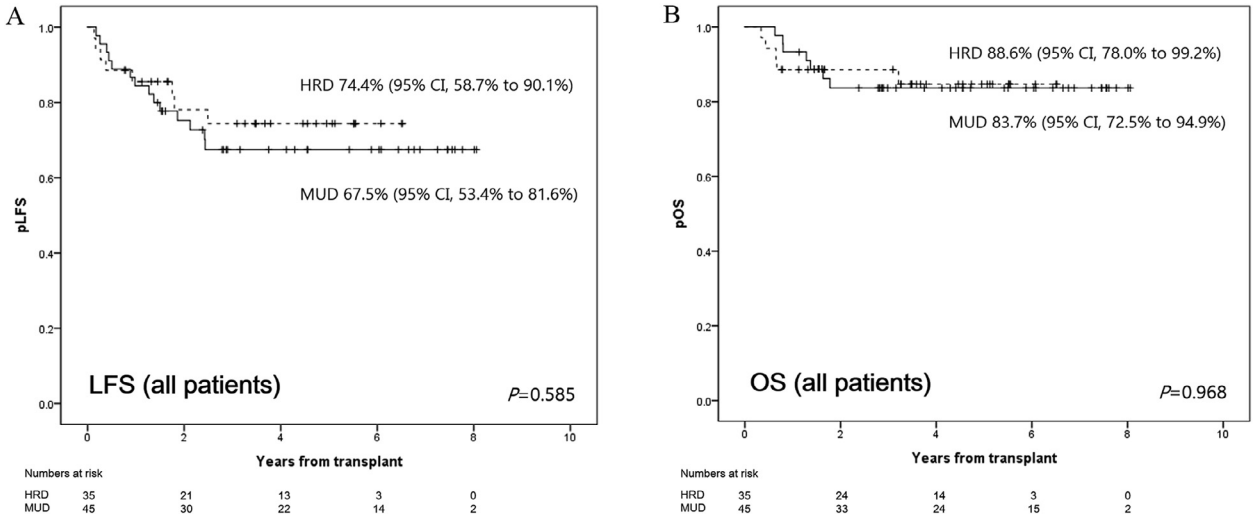

Figure 2. The LFS rates (A) and OS rates (B) at 3 years for the HRD and MUD groups were 74.4% versus 67.5% ($P = .585$) and 88.6% versus 83.7% ($P = .968$), respectively.

then recurred again, and at the time of this report had survived for 4 years without recurrence after a third HSCT using busulfan and cyclophosphamide after obtaining remission using blinatumomab. In the HRD group, 2 out of 6 relapsed patients survived. Among them, 1 patient was Philadelphia chromosome-positive and survived without additional HSCT by salvage chemotherapy in combination with another tyrosine kinase inhibitor, and the other patient survived after a second HSCT using TBI after blinatumomab.

In AML patients (HRD, n = 16; MUD, n = 16), the 3-year GRFS, LFS, and OS rates in the HRD and MUD groups were 80.8% (95% CI, 61.2% to 100%) versus 61.9% (95% CI, 37.8% to 86.0%; $P = .326$), 87.1% (95% CI, 70.2% to 100%) versus 73.9% (95% CI, 51.8% to 96.0%; $P = .478$), and 93.8% (95% CI, 81.8% to 100%) versus 85.6% (95% CI, 67.0% to 100%; $P = .628$), respectively (Figure 3C and D). Remarkably, 3 patients who were not in remission at transplantation and had a very high pediatric DRI were successfully treated by HRD HSCT and donor lymphocyte infusion of 1×10^6/kg of $CD3^+$ cells on day +21 and 5×10^6/kg of $CD3^+$ cells on days +35 and +60. All 3 patients had primary refractory AML and did not achieve complete remission despite third-line or higher chemotherapy; 2 patients had received PBSC grafts from their mothers, and 1 patient received a PBSC graft from his brother. All 3 donor lymphocyte infusions were completed, and no patients experienced acute GVHD. One of the patients was diagnosed with severe chronic GVHD involving the lungs and skin on day +194 post-HSCT and was treated with ruxolitinib and prednisolone. At the time of this report, all 3 patients were alive without recurrence at 4.3, 2.2, and 2.0 years post-HSCT, respectively.

DISCUSSION

Our study shows that unmanipulated HRD HSCT using PTCy provides comparable outcomes to MUD HSCT for pediatric high-risk leukemia in terms of GVHD, relapse incidence, NRM, GRFS, LFS, and OS, using a targeted busulfan-based myeloablative conditioning regimen with intensive PK monitoring. It is noteworthy that the NRM rate was low despite the use of a myeloablative busulfan-based conditioning regimen and PBSC grafts; in particular, there were no NRM cases in the HRD group.

HRD HSCT has been proven safe and effective in several recent studies. In a recent randomized trial, HRD HSCT showed better OS when comparing HRD HSCT using BM with double-unit cord blood transplantation in adults [21]. Furthermore, similar treatment outcomes of HRD HSCT have been reported in various studies comparing HRDs with matched sibling donors as well as MUDs [8-10,22-27]. In many cases, a nonmyeloablative conditioning regimen was used in HRD HSCT with PTCy, whereas reports of myeloablative conditioning with PTCy in pediatric patients are rare [22,28]. In a recently published study comparing HRD HSCT using PTCy and MUD HSCT in children, nonmyeloablative conditioning was used for HRD HSCT, and the 26% graft rejection rate resulted in lower event-free survival in the HRD group [12]. Although the time to engraftment was slower in the HRD group compared with the MUD group, our cohort had a 100% engraftment rate, superior to the rate in other studies using BM as the stem cell source [28]. HRD HSCT using PTCy was initially started using BM [13]; however, promising outcomes also have been reported using myeloablative conditioning and PBSC grafts in adults [14]. Our institution has performed HRD HSCT similarly using PBSCs and reported favorable outcomes in terms of good engraftment rate and low NRM rate [5]. Reducing toxicity by avoiding irradiation and using busulfan at an optimal dose by careful PK monitoring may be one reason for the good treatment outcomes. Our study demonstrates that the use of busulfan-based myeloablative conditioning is relatively safe with PTCy and results in treatment outcomes similar to those with MUD HSCT using ATG.

In particular, the treatment outcomes of HRD HSCT in patients with AML are encouraging. Although not statistically significant owing to the small number of patients, the HRD group showed tendencies toward better GRFS, LFS, and OS compared with the MUD group. All 3 patients who were not in remission survived without recurrence for 4.3, 2.2, and 2.0 years after HRD HSCT including donor lymphocyte infusion [29], and 1 of them was being treated for severe chronic GVHD. This is in line with a previous study that reported better treatment results of HRD HSCT compared with matched sibling donor HSCT in patients with refractory/relapsed AML not in remission [27]. Their results showed that the graft-versus-leukemia effect through HRD HSCT is more effective in AML patients, which is thought to lead to better outcomes with a myeloablative conditioning regimen.

The 3-year OS rate in the ALL patients exceeded 80% in both groups. Although the 3-year LFS rates were around 60%, many

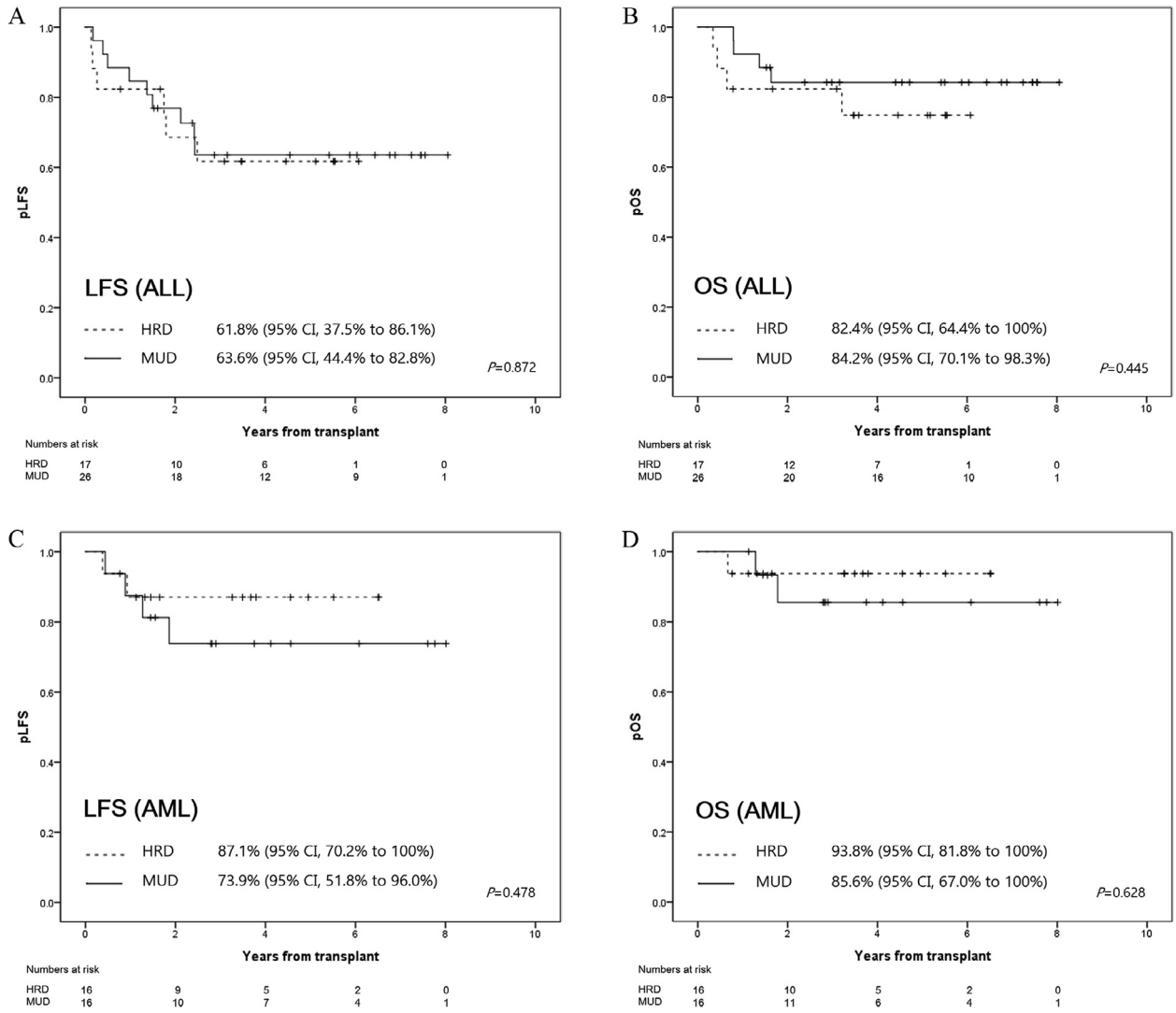

Figure 3. Among patients with ALL, the LFS rates (A) and OS rates (B) at 3 years for the HRD and MUD groups were 61.8% versus 63.6% ($P = .872$) and 82.4% versus 84.2% ($P = .445$), respectively. Among patients with AML, the LFS and OS rates at 3 years for the 2 groups were 87.1% versus 73.9% ($P = .478$) (C) and 93.8% versus 85.6% ($P = .628$), respectively (D).

patients could be rescued with additional chemotherapy and/or a second HSCT. A recent randomized trial confirmed that conditioning using TBI showed a higher survival rate than chemoconditioning in high-risk ALL patients aged ≥4 years [30]. However, considering the life-long adverse effects of TBI, the use of the optimal dose of busulfan using intensive PK as in this study also could minimize the treatment-related mortality rate and enable rescue treatment in case of recurrence, which could translate to a similar OS rate.

In our present cohort, the 0% NRM rate in the HRD group is encouraging; however, the combination of myeloablative conditioning and PTCy showed a higher tendency toward severe veno-occlusive disease and hemorrhagic cystitis compared with the MUD group. Although not statistically significant, the hospital length of stay tended to be longer in the HRD group, possibly related to the long-term treatment for these complications. Most patients recovered from severe veno-occlusive disease and hemorrhagic cystitis through conservative treatment; however, further efforts are needed to reduce these complications in the future. The PK of PTCy may be different in children compared with adults [31]. In addition, recent studies have shown promising engraftment and GVHD rates with lower doses of PTCy [32]. Thus, it should be possible to reduce transplantation-related toxicity through PK monitoring and dose adjustment of cyclophosphamide in children.

Taken together, our findings in this study suggest that HRD HSCT with PTCy using an intensive PK-monitored targeted busulfan-based myeloablative conditioning regimen is a promising alternative option for pediatric patients with hematologic disease who lack an HLA-matched donor. Furthermore, our data show comparable treatment results to those of MUD HSCT using ATG. Although our results are promising, especially in patients with AML, further long-term follow-up in more patients is needed.

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DECLARATION OF COMPETING INTEREST

There are no conflicts of interest to report.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2022.01.002.

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