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Unrelated donor hematopoietic stem cell transplantation for pediatric de novo acute myeloid leukemia with intermediate- or high-risk cytogenetics

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Abstract

The role of unrelated donor HSCT for children with de novo AML in CR1 is controversial. We performed this study to investigate the feasibility of unrelated donor HSCT who initially had intermediate- or high-risk cytogenetics. We retrospectively reviewed medical records of patients with AML who received unrelated HSCT in CR1 at Samsung Medical Center between November 2001 and January 2012. Patients were allocated based on karyotype at diagnosis as follows: (a) low-risk: inv(16), t(16;16), t(8;21), and t(15;17); (b) high-risk: -5, 5q-, -7, 3q abnormalities, t(8;16), t(6;9), t(6;11), t(6;21), t(10;11), complex karyotype (≥3 abnormalities), and acute megakaryocytic leukemia without t(1;22); and (c) IR: all the other karyotypes including normal. Patients in intermediate- or high-risk group who were transplanted with either unrelated CB or matched unrelated BM/mobilized PB in their CR1 were included in this study. The projected OS and EFS rates were 74.9% and 71.1%, respectively, with a median follow-up of 87.3 months after transplantation. The EFS was 70.1%, 80.7%, and 73.9% for CB, BM, and mobilized PB groups, respectively ($P = 0.89$), and 73.9% and 70.6% for IR and high-risk groups ($P = 0.76$). The leading cause of death was relapse (n = 8), and only one patient died from non-relapse cause. Unrelated donor HSCT seems a feasible approach for children with intermediate- or high-risk AML in CR1. Relapse remains the leading cause of treatment failure among these patients.

KEYWORDS
acute myeloid leukemia, children, complete remission, cytogenetics, unrelated donor hematopoietic stem cell transplantation

Abbreviations: AML, acute myeloid leukemia; ATG, antithymocyte globulin; BH-AC, N4-behenoyl-1-beta-D-arabinosylcytosine; BM, bone marrow; CB, cord blood; CMV, cytomegalovirus; CNS, central nervous system; CR, complete remission; CR1, first complete remission; CRx, chemotherapy; CSA, cyclosporine; EFS, event-free survival; GVHD, graft-vs-host disease; GVL, graft-vs-leukemia; HR, high-risk; HSCT, Hematopoietic stem cell transplantation; IDA, idarubicin; IR, intermediate-risk; methylPD, methyl-prednisolone; MMF, mycophenolate mofetil; MRD, minimal residual disease; MTX, methotrexate; OS, overall survival; PB, peripheral blood; TBI, total body irradiation; TRM, transplant-related mortality; UBMT, unrelated bone marrow transplantation; UCBT, unrelated cord blood transplantation; UPBSCT, unrelated peripheral blood stem cell transplantation; WBC, white blood cell.

1 | INTRODUCTION

Achievement of CR is the first step in improving clinical outcomes of children with AML.[1] While approximately 85% of pediatric AML patients enter a CR1 after induction CRx, a substantial number experience disease recurrence.[2] According to Gassas et al,[3] despite significant progress in the treatment of pediatric AML, 40%-50% of patients relapse after attaining CR1 with CRx alone, and EFS rates remain at approximately 50% in most large studies.[4-6]

For the prevention of disease recurrence, allogeneic HSCT has been demonstrated to be more effective than standard CRx or autologous HSCT.[7-11] The therapeutic effect of allogeneic HSCT comes from cytoreduction induced by the pretransplantation conditioning regimen and the post-transplantation GVL effect exerted by the donor immune system.[12-14] However, the efficacy of allogeneic HSCT is counterbalanced by a higher risk of transplant-related morbidity and mortality. In addition to this, long-term issues such as GVHD, endocrine dysfunction, impaired growth and fertility, severe bone disorders, and secondary malignancies which can lead to a diminished quality of life have contributed to the continuing debate whether allogeneic HSCT in CR1 is beneficial for patients with AML.[1,15]

The current consensus, reflected in the treatment guidelines of the National Comprehensive Cancer Network (V2.2014: available at http://www.nccn.org), is based on cytogenetic stratification into low-, intermediate-, and high-risk AML.[2] Pediatric AML patients in CR1 who initially had low-risk cytogenetics are recommended to undergo CRx-only as consolidation therapy.[16] On the other hand, the role of allogeneic HSCT in post-remission management of pediatric AML with intermediate- or high-risk cytogenetics in CR1, even in matched related donor HSCT, remains controversial.[16]

In this study, we aimed to investigate the feasibility of unrelated donor HSCT for pediatric AML patients in CR1 who initially had intermediate- or high-risk cytogenetics by assessing and comparing the outcomes between these two cytogenetic risk groups. To verify the feasibility of unrelated donor HSCT, we also compared the outcomes between recipients of unrelated and matched related donors. In addition, we evaluated the survival outcomes between different unrelated donor source groups.

2 | MATERIAL AND METHODS

We retrospectively reviewed the medical records of pediatric patients with AML who received unrelated donor HSCT at Samsung Medical Center between November 2001 and January 2012. Children with therapy-related AML, secondary AML following myelodysplastic syndrome, and AML developed in patients with genetic disorders such as Fanconi anemia and Down syndrome were excluded from this study as they need treatment according to dedicated protocols.

Patients who met the following all three criteria were included in the study: (a) intermediate- or high-risk cytogenetics identified at diagnosis; (b) CR1 at the time of transplantation; and (c) CB, BM, or mobilized PB stem cell transplantation from unrelated donor.

Demographic, clinical, and laboratory data—including age at diagnosis, sex, initial WBC count, presence of CNS leukemia at diagnosis, karyotypes identified at diagnosis, achievement of CR1, stem cell source, conditioning regimens, and GVHD prophylaxis regimens, events of death or relapse—were collected.

Based on results of conventional chromosome studies of BM or blood at diagnosis, we allocated patients into the three cytogenetic risk groups (low-, high-, and intermediate-risk). Low-risk was defined as follows: inv(16), t(16;16), t(8;21), and t(15;17). HR was defined as follows: -5, 5q-, -7, 3q abnormalities, t(8;16), t(6;9), t(6;11), t(6;21), t(10;11), complex karyotype (≥3 abnormalities), and acute megakaryocytic leukemia without t(1;22). IR was defined as all the other karyotypes including normal.

CR was defined by fewer than 5% blast cells in the BM aspirate, with normal cellularity and trilineage haemopoiesis and without any evidence of gross extramedullary disease.

Primary endpoints were EFS and OS. EFS was measured as the time from transplantation to relapse or death from any cause and censored on the date of last follow-up if alive and in remission. OS was defined as the time from transplantation to death from any causes and censored on the date of last follow-up if alive or lost to follow-up. TRM referred to death during continuous CR.

All statistical analyses were performed using SPSS 21.0 for Windows. The Pearson's chi-square test, Student's *t* test, and Kruskal-Wallis test were used to compare the clinical outcomes by donor source and number of post-remission CRx courses. Univariate probabilities of EFS and OS were calculated using the Kaplan-Meier method. A two-tailed *P* value <0.05 was considered to be statistically significant.

Ethical approval for this retrospective study was provided by the Institutional Review Board of Samsung Medical Center (IRB 2015-07-039).

3 | RESULTS

3.1 | Patient and transplant characteristics

Baseline patient-, disease-, and transplant-related characteristics and their distribution for patients with AML are listed in Table 1. Among 69 patients with de novo AML who received unrelated donor HSCT, a total of 36 patients met the inclusion criteria. Patients with AML in CR1 were transplanted at a median age of 3.3 years (range, 0.5-16.4) and showed the male to female ratio of 1.4:1. Median time from diagnosis to transplantation was 5 months (range, 3.3-12.3) and median time from CR1 to transplantation was 3.5 months (range, 0.4-10.7). Median follow-up period of survivors was 87.3 months (range, 9-195.8). Cytogenetic data at diagnosis were available for all 36 patients. Intermediate- and high-risk cytogenetic diseases were presented in 19 patients (52.8%) and 17 patients (47.2%), respectively. CR1 was achieved after 1 to 2 courses of induction therapy including 30 patients (83.3%) after one course and six patients (16.7%) after two courses of induction therapy.

While busulfan-based conditioning regimens were applied in most of the patients (30/36 patients, 83.3%), TBI was used as a part of conditioning regimens in the rest of patients (6/36 patients, 16.7%). ATG was administered prior to transplantation in 11 out of 36 patients (30.5%). While two patients who were transplanted before 2004 received horse ATG (30 mg/kg/d from day 3 to day 1 before transplant), nine patients who were transplanted after 2004 received rabbit ATG (2.5 mg/kg/d from day 3 to day 1 before transplant). As for stem cell sources, CB was used in 15 patients (41.7%), BM in 10 patients (27.8%), and mobilized PB stem cells in 11 patients (30.5%). Conditioning regimens are demonstrated in Table S1.

3.2 | Engraftment

Neutrophil engraftment (absolute neutrophil count >0.5 × 10^9/L) occurred in 34 patients (94.4%) with a median time of 14 days (range, 10-23) after transplantation. As shown in Figure 1, the probability of neutrophil engraftment by day 30 was 94.4%. The median time for neutrophil engraftment was 19, 12.5, and 12 days in CB, BM, and mobilized PB stem cell transplants, respectively (P = 0.025). Therefore, the median days to neutrophil engraftment was longer in CB group when compared to BM and mobilized PB stem cell groups; however, there was no difference between BM and mobilized PB stem cell groups.

Thirty-three of 36 patients (91.7%) achieved platelet engraftment (platelet count >20 × 10^9/L) at a median of 30 days (range, 16-87). The probability of platelet engraftment was 93.5% by day 90 (Figure 1). Time to platelet engraftment was longer in CB group when compared to BM and PB stem cell groups, with a median of 54.5, 25.5, and 20 days, respectively (P = 0.013).

TABLE 1 Patient characteristics

	Number of patients (n = 36)
Age (y) at diagnosis, median (range)	2.9 (0.1-16.1)
Age (y) at transplantation, median (range)	3.3 (0.5-16.4)
Sex ratio (male:female)	1.4:1
Initial WBC/μL, median (range)	13 235 (440-269 630)
CNS leukemia	4 (11.1%)
Induction CRx	
BH–AC + IDA	36 (100%)
Other	0
CR1 achievement	
After 1 induction	30 (83.3%)
After 2 induction	6 (16.7%)
Number of post-induction CRx, median (range)	3 (0-8)
Donor source	
CB	15 (41.7%)
BM	10 (27.8%)
Mobilized PBSC	11 (30.5%)
Conditioning regimen	
Busulfan-based	30 (83.3%)
TBI-based	6 (16.7%)
ATG in conditioning	
Yes	11 (30.5%)
No	25 (69.5%)
GVHD prophylaxis	
CSA + MTX	21 (58.3%)
CSA + MMF	12 (33.3%)
CSA + methylPD	3 (8.3%)

3.3 | Acute and chronic GVHD

The combination of CSA and MTX was the most frequently used form of GVHD prophylaxis (21/36 patients, 58.3%). CSA with MMF (12/36 patients, 33.3%) comprised of the second most common prophylactic medication for GVHD. The diagnosis of acute and chronic GVHD was made according to standard clinical criteria.[17,18] The incidence of grades 2 to 4 acute GVHD within the first 100 days of transplantation was 58.4% (21/36 patients, Table 2). As shown in Table 3, the rates of grades 2 to 4 acute GVHD were 46.7%, 60%, and 72.7% among CB, BM, and mobilized PB stem cell transplants, respectively (P = 0.409). When we compared the rates of grades 2 to 4 acute GVHD according to number of post-remission courses of CRx, no statistically significant difference was observed (Table 4).

All of 36 patients survived beyond 100 days after transplantation, and the incidence of chronic GVHD was 63.9% (23/36 patients) including 14 patients with limited and nine patients with extensive chronic GVHD. As shown in Table 3, there was no significant difference in the rates of limited or extensive chronic GVHD within the groups by donor source. The rate of limited chronic GVHD was significantly higher in patients with less than three courses of post-remission CRx than those with three or more courses of therapy (Table 4). On the other hand, no statistically significant difference

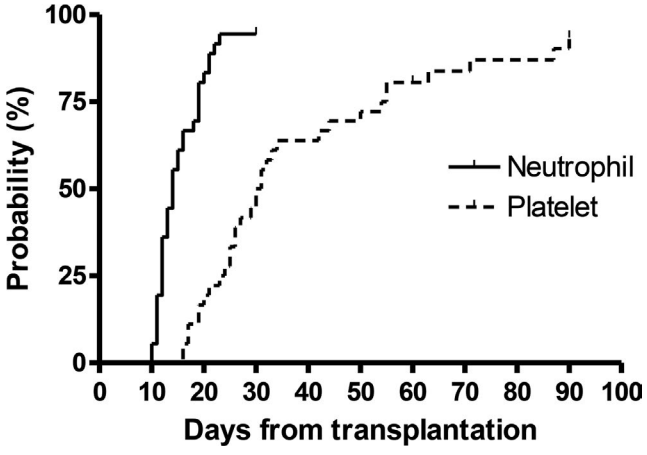

FIGURE 1 Probability of neutrophil and platelet engraftment. The probability of neutrophil engraftment (solid line) by day 30 was 94.4%, while that of platelet engraftment (dashed line) was 93.5% by day 90

was observed in the rates of extensive chronic GVHD within the groups by number of post-remission CRx. No significant difference was observed in the rates of acute and chronic GVHD within the cytogenetic risk groups (Table 5).

3.4 | Toxicity

The distribution of toxicity after CB, BM, and mobilized PB stem cell transplantation is shown in Table 3. The rates of infection including bloodstream infection, CMV antigenemia, and fungal infection after transplantation were similar among CB and BM/mobilized PB stem cell transplants. Patients who developed CMV antigenemia received intravenous ganciclovir as preemptive therapy and CMV disease did not occur. Hormonal deficiency was defined as biochemical and clinical evidence for thyroid dysfunction, growth hormone deficiency, gonadal deficiency, or adrenal insufficiency. There was no significant difference in the incidence of hormonal deficiency, growth disturbance, and cataract within different donor groups and cytogenetic risk groups.

As shown in Table 4, the rates of fungal infection and bloodstream infection were similar between patients with less than three courses of post-remission CRx and those with three or more courses of therapy. CMV antigenemia occurred in all patients who received post-remission CRx less than three courses, whereas 16 patients (59.3%) developed CMV antigenemia after receiving post-remission CRx more than three courses ($P < 0.05$).

TABLE 2 Distribution of acute GVHD

Grade of acute GVHD	Number of patients
Grade 0-1	15 (41.7%)
Grade 2	14 (38.9%)
Grade 3	5 (13.9%)
Grade 4	2 (5.6%)

3.5 | EFS, OS, and causes of death

With a median follow-up of 87.3 months after unrelated donor HSCT, the projected OS and EFS rates of all 36 patients with AML were 74.9% and 71.1%, respectively (Figure 2). The EFS rate of IR group compared to that of HR group is shown in Figure 3. The EFS

TABLE 3 Comparison of clinical characteristics and outcomes according to donor source

Outcomes	UCBT (n = 15)	UBMT (n = 10)	UPBSCT (n = 11)	*P* value
Time from diagnosis to transplantation (months), median (range)	4.8 (3.8-12.3)	5.3 (4.5-5.6)	4.8 (3.3-5.5)	0.192
Time from CR1 to transplantation (months), median (range)	3.7 (0.4-10.7)	3.9 (3.3-4.5)	2.9 (1.9-4)	0.018*
Neutrophil engraftment (days), median (range)	19 (12-23)	12.5 (10-19)	12 (11-18)	0.025
Platelet engraftment (days), median (range)	54.5 (30-87)	25.5 (19-33)	20 (16-50)	0.013
TRM	0	0	1 (9.1%)	0.311
Bloodstream infection	3 (20%)	0	3 (27.3%)	0.222
CMV antigenemia	11 (73.3%)	7 (70%)	4 (36.4%)	0.128
CMV disease	0	0	0	
Fungal infection	4 (26.7%)	1 (10%)	1 (9.1%)	0.396
CNS toxicity	3 (20%)	0	0	0.101
Grade 2-4 acute GVHD	7 (46.7%)	6 (60%)	8 (72.7%)	0.409
Grade 3-4 acute GVHD	3 (20%)	0	4 (36.4%)	0.109
Limited chronic GVHD	5 (33.3%)	4 (40%)	5 (45.5%)	0.819
Extensive chronic GVHD	2 (13.3%)	3 (30%)	4 (36.4%)	0.372
Thyroid hormone replacement	1 (6.7%)	0	0	0.487
Growth hormone replacement	0	0	0	
Hydrocortisone replacement	0	0	1 (9.1%)	0.311
Sex hormone replacement	1 (6.7%)	2 (20%)	1 (9.1%)	0.564
Height <3rd percentile	1 (6.7%)	0	3 (27.3%)	0.108
Weight <3rd percentile	5 (33.3%)	2 (20%)	2 (18.2%)	0.618
Cataract	2 (13.3%)	0	0	0.227
OS rate	73.1%	69.6%	80.9%	0.817
EFS rate	70.1%	80.7%	73.9%	0.890

*Time from CR1 to transplantation was significantly longer in UBMT group when compared to UPBSCT group.

TABLE 4 Comparison of clinical outcomes according to number of post-remission CRx courses

Outcomes	Total number of patients (n = 36)	Number of post-remission CRx		*P* value*
		<3 (n = 9)	≥3 (n = 27)	
TRM	1 (2.8%)	0	1 (3.7%)	1.00
Bloodstream infection	12 (33.3%)	3 (33.3%)	9 (33.3%)	1.00
CMV antigenemia	25 (69.4%)	9 (100%)	16 (59.3%)	0.022
CMV disease	0	0	0	1.00
Fungal infection	4 (11.1%)	0	4 (14.8%)	0.553
Grade 2-4 acute GVHD	21 (58.3%)	7 (77.8%)	14 (51.9%)	0.172
Grade 3-4 acute GVHD	7 (19.4%)	3 (33.3%)	4 (14.8%)	0.333
Limited chronic GVHD	14 (38.9%)	6 (66.7%)	8 (29.6%)	0.048
Extensive chronic GVHD	9 (25%)	2 (22.2%)	7 (25.9%)	0.824

*Comparison between patients with less than three courses of post-remission CRx and those with three or more courses of therapy.

TABLE 5 Comparison of clinical characteristics and outcomes between cytogenetic risk groups

	IR (n = 19)	HR (n = 17)	*P* value
Age (y) at diagnosis, median (range)	3.9 (0.1-16.1)	1.9 (0.5-13.7)	0.399
Age (y) at transplantation, median (range)	4.6 (0.6-16.5)	2.2 (0.8-14.1)	0.397
Gender (female)	7 (36.8%)	8 (47.1%)	0.487
Time from diagnosis to transplantation (mo), median (range)	5.1 (3.6-9.4)	4.8 (3.3-12.3)	0.921
Time from CR1 to transplantation (mo), median (range)	3.7 (0.4-8.2)	3.4 (1.5-10.7)	0.948
Neutrophil engraftment (d), median (range)	14 (10-22)	13 (10-23)	0.620
Platelet engraftment (d), median (range)	30 (17-71)	28 (16-87)	0.662
TRM	1 (5.3%)	0	1.00
Bloodstream infection	4 (21.1%)	2 (11.8%)	0.662
CMV antigenemia	13 (68.4%)	9 (52.9%)	0.495
CMV disease	0	0	
Fungal infection	5 (26.3%)	1 (5.9%)	0.182
CNS toxicity	2 (10.5%)	1 (5.9%)	1.00
Grade 2-4 acute GVHD	10 (52.6%)	11 (64.7%)	0.516
Grade 3-4 acute GVHD	4 (21.1%)	3 (17.6%)	1.00
Limited chronic GVHD	6 (31.6%)	8 (47.1%)	0.495
Extensive chronic GVHD	6 (31.6%)	3 (17.6%)	0.451
Thyroid hormone replacement	0	1 (5.9%)	0.472
Growth hormone replacement	0	0	
Hydrocortisone replacement	1 (5.3%)	0	1.00
Sex hormone replacement	2 (10.5%)	2 (11.8%)	1.00
Cataract	2 (10.5%)	0	0.487

rates showed no statistically significant difference between intermediate- and high-risk cytogenetic groups, with 73.9% and 70.6%, respectively ($P = 0.76$). The OS rates of intermediate- and high-risk cytogenetic groups were 73.7% and 76.1%, respectively ($P = 0.87$).

As shown in Figure 4, the EFS rate of patients categorized by stem cell sources demonstrated 70.1%, 80.7%, and 73.9% for CB, BM, and mobilized PB stem cell transplants, respectively ($P = 0.89$). The OS rates showed no significant difference within the groups by donor source ($P = 0.817$).

The EFS rates were 77.8% and 72.9% among patients who received less than three courses of post-remission CRx and those receiving three or more courses of post-remission CRx, respectively, which showed no statistically significant difference ($P = 0.92$) (Figure 5).

During the period of follow-up, nine out of 36 patients (25%) died. Relapse after transplantation was the predominant cause of death (8/9 patients, 88.9%), and the remaining one patient died of chronic GVHD and infection. No significant difference was observed in the rates of TRM within the groups by donor source (Table 3) and the number of post-remission CRx (Table 4).

3.6 | Comparison between groups with unrelated and matched related donor transplants

The demographic and clinical characteristics of unrelated and matched related donor transplants are shown in Table 6. All patients received intensively timed induction CRx and were in CR1 at the time of transplantation. They received unrelated CB (n = 15), unrelated BM (n = 10), unrelated mobilized PB stem cell (n = 11), matched related BM (n = 2), and matched related PB stem cell (n = 7) transplantation, respectively. Median age at diagnosis was 2.9 years (range, 0.1-16.1) and 11.2 years (range, 2-15.1) for patients with unrelated and matched related donor transplantation, respectively ($P = 0.008$). Median age at HSCT was 3.3 years (range, 0.5-16.4) and 11.6 years (range, 2.2-15.4) for patients with unrelated and matched related donor transplantation, respectively ($P = 0.009$). There was a higher proportion of patients with HR cytogenetics in unrelated donor transplants compared to matched related donor transplants ($P = 0.048$). Time to neutrophil engraftment was similar between the two groups ($P = 0.174$), whereas the median days to platelet engraftment was longer in unrelated donor group ($P = 0.022$).

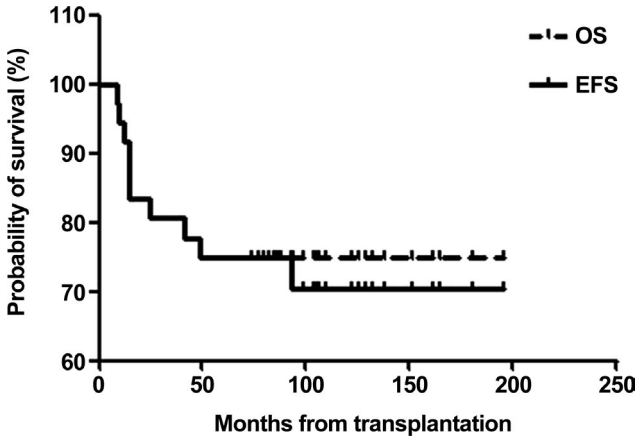

FIGURE 2 Projected OS and EFS rates. The OS (dashed line) and EFS (solid line) rates of all patients were 74.9% and 71.1%, respectively

There was no significant difference between the two groups for the incidence of infection including bloodstream infection, CMV antigenemia, and fungal infection, acute or chronic GVHD, hormonal deficiency, and cataract. Three of nine patients (33.3%) with matched related donor group developed CNS toxicity after receiving HSCT, which was significantly higher than unrelated group ($P = 0.048$). The EFS rates of unrelated and matched related donor recipients were 71.6% and 77.4%, respectively ($P = 0.767$). The OS rates of unrelated and matched related donor recipients were 74.7% and 77.3%, respectively ($P = 0.935$). No significant difference was observed in the rates of TRM between the two groups ($P = 0.613$).

4 | DISCUSSION

Although allogeneic HSCT has been regarded as a curative and effective treatment option for patients with AML, it is associated with higher rates of TRM, morbidity, and long-term sequelae such as GVHD than CRx alone.[16,19] Numerous trials led by the pediatric cooperative groups worldwide have utilized matched sibling donor transplantation for children with intermediate- or high-risk cytogenetics.[16,20,21] On the other hand, the role of HLA-matched unrelated HSCT for pediatric AML patients during the CR1 has been under investigational settings because the reported survival rates of unrelated donor transplantation were not superior to those of intensive CRx or autologous transplantation.[22,23] Therefore, in this study we tried to delineate the feasibility of unrelated donor HSCT for children with AML in CR1 who initially had intermediate- or high-risk cytogenetics. The finding that the EFS rates were similar between IR and HR cytogenetic groups following unrelated donor transplantation in CR1 provided further information on this aspect.

As demonstrated by previous studies, the role of allogeneic HSCT in CR1 for pediatric AML patients with intermediate- or high-risk cytogenetics, even in matched related donor HSCT, is a subject that is under debate. The AML-BFM 98 study, which allocated HR children with an available matched sibling donor to allogeneic HSCT in CR1 and those without a matched sibling donor to receive CRx, showed that the outcomes of HR subgroups other than those with MLL rearrangements were not significantly different between matched sibling donor allogeneic HSCT and CRx alone.[16] According to Burke et al,[24] no significant difference was observed in OS between HR and IR patients undergoing allogeneic transplantation in CR1. In the Children's Oncology Group study, transplantation from matched related donor greatly improved survival outcomes in patients with IR AML.[20] Horan et al[20] also noted that even with transplantation, survival outcomes were unfavorable in HR AML patients.

In our analysis, after transplantation from an unrelated donor in CR1, EFS of 73.9% was achieved in patients with IR cytogenetics,

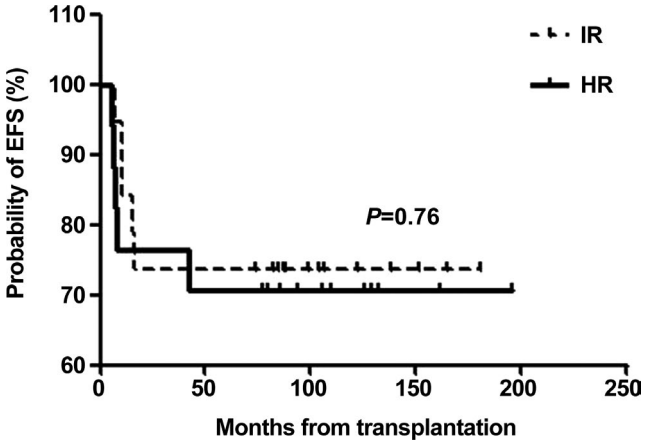

FIGURE 3 Comparison of EFS rates between IR (dashed line) and HR (solid line) groups. The projected EFS rates were similar between two groups (73.9% vs 70.6%, *P* = 0.76)

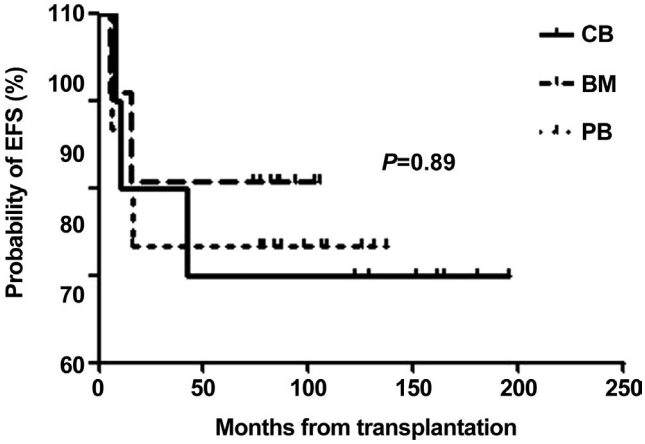

FIGURE 4 Comparison of EFS rates between CB (solid line), BM (dashed line), and mobilized PB stem cell (dotted line) grafts. The projected EFS rates were similar between three groups (70.1%, 80.7%, and 73.9%, respectively, *P* = 0.89)

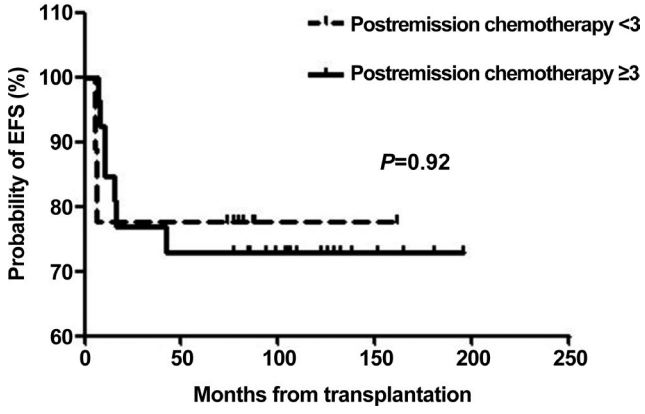

FIGURE 5 Comparison of EFS rates between patients receiving less than three courses of post-remission CRx (dashed line) and those receiving three or more courses of post-remission CRx (solid line). The projected EFS rates were similar between two groups (77.4% vs 72.9%, *P* = 0.92)

which was comparable to EFS of 70.6% observed in patients with HR cytogenetics. There were no significant differences in the development of grades 2 to 4 and 3 to 4 acute GVHD, chronic GVHD, growth impairment, thyroid dysfunction, and cataracts between intermediate- and high-risk cytogenetic groups. In accordance with our findings, a previous study has reported that AML risk status was not a significant factor for grades 2 to 4 and 3 to 4 acute GVHD, or chronic GVHD.[24] Although there was a higher proportion of patients with HR cytogenetics in unrelated donor transplants compared to matched related donor transplants, clinical outcomes after transplantation were remarkably similar in recipients of unrelated and matched related donors in this study. These findings were consistent with previous studies that had addressed the comparable outcomes of unrelated and matched related BM transplants.[25] Our data demonstrated that unrelated donor HSCT is a feasible approach for pediatric AML patients with intermediate- or high-risk cytogenetics during CR1 in that it is associated with clear survival benefit especially in HR patients. Considering that there is not enough convincing evidence about the role of unrelated donor HSCT in children with AML during CR1, our findings may provide a useful platform for further prospective studies regarding this issue.

Several studies have shown that detection of MRD in AML is an independent prognostic factor.[26-28] Since MRD monitoring was not available in our clinical setting, we could not investigate the relationship between MRD and treatment outcome. However, considering that 30 of 36 patients (83.3%) achieved CR after a single cycle of induction, there is a possibility that the patients in our study showed favorable MRD responses to CRx. Further prospective clinical studies with MRD data will have to be performed to verify the prognostic value of MRD.

Among 6 patients who achieved CR after two cycles of induction, three patients (50%) were in IR cytogenetic group and the other three patients (50%) were in HR cytogenetic group. Two of the three patients with HR cytogenetics developed relapse of AML after transplantation. Our data indicated that treatment response, as well as cytogenetic risk stratification, is significant prognostic factors in pediatric patients with AML.

We found that CB transplants had similar rates of grades 2 to 4 and 3 to 4 acute GVHD, limited and extensive chronic GVHD, and EFS compared with BM or mobilized PB stem cell transplants. These findings were consistent with previous studies by Eapen et al[29] that had shown similar rates of acute or chronic GVHD and leukemia-free survival after transplantation of BM and unrelated donor CB. While CB requires less stringent HLA matching and mismatched CB transplants cause less GVHD,[12] a principal obstacle with CB transplantation is the availability of sufficient numbers of hematopoietic precursor cells.[29] Considering that CB cell dose is a key determinant of hematopoietic recovery and TRM, studies in progress including the use of multi-unit transplants, co-infusion of mesenchymal stem cells, injection of CB into the BM, expansion culture of CB hematopoietic stem and progenitor cells ex vivo, and use of growth factors for in vivo hematopoietic stem cell expansion and improved homing could enhance the effectiveness of CB as a source of hematopoietic stem cells.[29]

TABLE 6 Comparison of demographics, clinical characteristics, and outcomes between matched unrelated and matched related donor transplants

	Unrelated HSCT (n = 36)	Matched related HSCT (n = 9)	*P* value
Age (y) at diagnosis, median (range)	2.9 (0.1-16.1)	11.2 (2-15.1)	0.008
Age (y) at transplantation, median (range)	3.3 (0.5-16.4)	11.6 (2.2-15.4)	0.009
Gender (female)	15 (41.7%)	3 (33.3%)	0.648
Risk cytogenetics			
IR	19 (52.8%)	8 (88.9%)	0.048
HR	17 (47.2%)	1 (11.1%)	0.048
Initial WBC/μL, median	13 235 (440-269 630)	11 110 (800-178 900)	0.875
Time from diagnosis to transplantation (mo), median (range)	5 (3.3-12.3)	5.1 (3.6-5.5)	0.606
Time from CR1 to transplantation (mo), median (range)	3.5 (0.4-10.7)	3.5 (1.9-4.5)	0.687
Neutrophil engraftment (d), median (range)	14 (10-23)	13 (11-57)	0.174
Platelet engraftment (d), median (range)	30 (16-87)	16 (10-48)	0.022
CR1 achievement			
After 1 induction	30 (83.3%)	8 (88.9%)	0.681
After 2 induction	6 (16.7%)	1 (11.1%)	0.681
Number of post-induction CRx, median (range)	3 (0-8)	2 (0-3)	0.041
Conditioning regimen			
Busulfan-based	30 (83.3%)	9 (100%)	0.188
TBI-based	6 (16.7%)	0	0.188
TRM	1 (2.8%)	0	0.613
Bloodstream infection	6 (16.7%)	1 (11.1%)	0.681
CMV antigenemia	22 (61.1%)	4 (44.5%)	0.365
CMV disease	0	0	
Fungal infection	6 (16.7%)	1 (11.1%)	0.681
CNS toxicity	3 (8.3%)	3 (33.3%)	0.048
Grade 2-4 acute GVHD	21 (58.3%)	4 (44.5%)	0.453
Grade 3-4 acute GVHD	7 (19.4%)	2 (22.2%)	0.852
Limited chronic GVHD	14 (38.9%)	1 (11.1%)	0.114
Extensive chronic GVHD	9 (25%)	4 (44.5%)	0.250
Thyroid hormone replacement	1 (2.8%)	1 (11.1%)	0.278
Growth hormone replacement	0	0	
Hydrocortisone replacement	1 (2.8%)	0	0.613
Sex hormone replacement	4 (11.2%)	1 (11.1%)	1.00
Cataract	2 (5.6%)	1 (11.1%)	0.550
OS rate	74.7%	77.3%	0.935
EFS rate	71.6%	77.4%	0.767

The impact of post-remission CRx administered before allogeneic HSCT in CR1 has not been adequately addressed. This issue is imperative in that toxicity resulting from consolidation may preclude subsequent allogeneic HSCT or increase the risks of TRM. According to Tallman et al,[30] there is no benefit to adding any post-remission therapy prior to embarking on allogeneic HSCT. In our study, bloodstream or fungal infection, grades 2 to 4 or 3 to 4 acute GVHD, extensive chronic GVHD, and TRM rates were not higher

among patients receiving post-remission therapy three or more courses than they are in patients receiving less than three courses before unrelated donor transplant. These data suggest that patients preparing to undergo unrelated donor transplantation in CR1 do not benefit from consolidation therapy with respect to infection, GVHD, or TRM. On the other hand, there was statistically significant difference of rates of CMV antigenemia and limited chronic GVHD between patients receiving less than three courses of post-remission therapy and those receiving three or more courses of therapy. Considering that the sample size of this study is small for drawing definite associations between number of post-remission therapy and outcomes including CMV antigenemia or limited chronic GVHD, we should be careful not to misinterpret or misrepresent these results of our study.

Even though allogeneic HSCT decreases relapse in AML considerably, the high rate of TRM (15%–50%) remains the most important limiting factor to survival benefit in recipients of unrelated donor transplantation.[31,32] The TRM of our study was lower than that of other reports, although there is insufficiency in comparability between different transplantation centers. Optimization of conditioning regimens, better immunosuppressive therapy, and supportive care measures play critical roles in reducing the incidence of TRM rate.[1] On this aspect, further strategic studies to diminish TRM are required to improve clinical outcomes of unrelated donor transplantation in AML patients.

Our study has several limitations. First, the number of patients sampled meeting our inclusion criteria was not enough to draw a complete conclusion. However, this study may provide preliminary data on the efficacy of unrelated donor HSCT in pediatric AML patients for a large-scale prospective multicenter study in the future. Second, we cannot rule out the possibility that factors not evaluated in our analysis might be sources of heterogeneity in that we could not assess the outcomes for clinically relevant subgroups including somatic mutations (*FLT3*, *NPM1*, and *CEBPA*) other than cytogenetic risks. Finally, due to the retrospective nature of this study, we were constrained by the information from the medical records and recall of individuals.

In conclusion, the results of the present study demonstrated that unrelated donor HSCT in CR1 provides significant EFS benefits for intermediate- and high-risk AML patients. Remarkable advances in allogeneic HSCT for AML in CR1 have achieved through more opportunities to find a donor by expanding donor sources beyond matched related donors and augmentation of transplantation eligibility following the introduction of less intensive conditioning regimens. Despite such improvements, however, relapse after transplantation remains the leading cause of treatment failure, which leads to significant problem, so that further improvements in transplantation outcome need to be pursued. In addition to this, establishment of further individualization of allogeneic HSCT based on factors like patient age, comorbidity, and the presence of additional molecular lesions constitutes another future challenge. Such undertakings provide more accurate risk assessment, which may ultimately provide a more refined treatment approach.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHORS' CONTRIBUTIONS

Eu Gene Park and Keon Hee Yoo: Wrote the manuscript; Eu Gene Park, Eun Sang Yi, Young Bae Choi, Ki Woong Sung, and Hong Hoe Koo: Collected and analyzed the data; Keon Hee Yoo: Supervised all aspects of the analysis and manuscript preparation. All authors have read and approved the final manuscript.

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SUPPORTING INFORMATION

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