Comparison between Matched Related and Alternative Donors of Allogeneic Hematopoietic Stem Cells Transplanted into Adult Patients with Acquired Aplastic Anemia: Multivariate and Propensity Score-Matched Analysis

Hawk Kim,[1] Byung Soo Kim,[2] Dong Hwan Kim,[3] Myung Soo Hyun,[4]
Sung Hyun Kim,[5] Sung Hwa Bae,[6] Jung Hye Choi,[7] Sang Kyun Sohn,[8]
Ho Jin Shin,[9] Jong Ho Won,[10] Sung-Soo Yoon,[11] Deog-Yoen Jo,[12]
Young Don Joo,[13] Jae-Hoo Park,[1] Kyoo-Hyung Lee,[14] on behalf of The Korean
Society of Blood and Marrow Transplantation

We retrospectively compared the outcomes of 225 patients with adult acquired aplastic anemia (AA) who underwent allogeneic hematopoietic stem cell transplantation (alloHSCT) from matched related donors (MRDs), and those treated by alloHSCT from alternative donors (ADs). Univariate and multivariate analyses of factors associated with survival were performed. Multivariate analysis showed that age at alloHSCT of ≤31 years, MRD, successful engraftment, absence of acute graft-versus-host disease (aGVHD), and platelet engraftment at ≤21 days, were independent predictors of longer survival. In addition, time to aGVHD and cumulative nonrelapse mortality (NRM) were better in MRD than in AD recipients. Using propensity score matching (PSM), we performed a case-control study comparing 25 patients in each group who underwent alloHSCT from MRDs and ADs. Pretransplantation clinical factors were well balanced in either group. Median survival time was similar, and no statistically significant difference in transplantation outcomes was apparent when MRD and AD recipients were compared. In conclusion, our results suggest that alloHSCT from an AD should be considered earlier in adult patients with AA who do not have an MRD.

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INTRODUCTION

The standard and definitive treatment of adults with severe aplastic anemia (AA) consists of immune suppression therapy (IST) followed by allogeneic hematopoietic stem cell transplantation (alloHSCT) from a suitable matched related donor (MRD) (if available) [1]. Large-scale studies have shown that the 5-year survival rates of such patients are over 80% [2-5]. Survival rates are higher in younger and minimally transfused patients than in those who are older, or in patients receiving more extensive transfusion. Patients without an MRD are given IST as a substitute for alloHSCT from MRD. Although the response rates to IST are relatively high, ranging from 61% to 77%, the relapse rates are also significant, and range from 12% to 37% [6-9].

An MRD is available for only 20% to 30% of adults with AA. The current therapeutic algorithm recommends that, in patients without an MRD, alloHSCT

from an alternative donor (AD) should be delayed until IST fails, because of the lower survival rate noted following alloHSCT from an AD. The 5-year survival rates range from 39% to 61% in such patients [10-12]. However, in recent decades, the outcomes of alloHSCT-treated patients have improved, suggesting that alloHSCT from ADs may be rendered more viable by controlling the complications of alloHSCT and by adopting high-resolution HLA typing [2,13]. The numbers of alloHSCT treatments from ADs for AA patients have increased in recent years, and the 2- to 4-year survival rates currently range from 73% to 89% [14-19], indicating that alloHSCT from ADs is safe in patients with AA, although the procedure currently serves as an alternative to alloHSCT from MRDs.

Although the results of alloHSCT from MRDs in Korea are similar to those of other countries [3], the outcomes of IST are poorer in Korea than elsewhere. In Korea, the response rate to IST was found to be only 47%, with a 6-year survival rate of 69% [20]. Many transplantation centers hesitate to perform alloHSCT from ADs because of early and high failure rates, and because most guidelines do not recommend alloHSCT from ADs before IST is tried. The recent success of alloHSCT from ADs suggests that this procedure may be considered as a first-line therapy, thus even prior to IST, in Korean patients lacking a suitable MRD. To determine whether the procedure is safe and effective, it is necessary to compare the results of alloHSCT from MRDs and ADs.

Many factors may be prognostic of success in patients undergoing alloHSCT for severe AA; these include age, donor/recipient gender matching, numbers of cells transfused, use of irradiated blood products, time from diagnosis to alloHSCT, stem cell source, dose of irradiation, HLA matching, method of immune suppression to prevent graft-versus-host disease (GVHD), prior IST history, and use of antithymocyte antigen (ATG). However, patients who receive alloHSCT from ADs usually have an unfavorable prognostic factor(s) than do those who are recipients of alloHSCT from MRDs.

Propensity score matching (PSM) is a statistical method adjusting prognostic factors that can affect the choice of 1 among many treatment options, characterized by uneven and differing clinical factors. Thus, PSM analysis of pretransplantation prognostic factors may allow selection of an appropriate alternative treatment method.

In Korea, the frequency of alloHSCT for AA has increased, and more than 60 patients are treated in this manner annually [21]. Although several studies have assessed the features associated with successful alloHSCT for AA, most studies have been conducted in Western countries. Because of differences in ethnicity, outcomes may vary in Korean patients, suggesting

a need for nationwide analysis to assess the outcomes of alloHSCT for AA. We therefore compared the outcomes of AA patients receiving alloHSCT from MRDs and ADs in Korea, and assessed the prognostic significance of donor type with respect to successful alloHSCT, by comparing the results of multivariate and PSM analyses.

PATIENTS AND METHODS

Patient Eligibility

Patients were included if severe acquired aplastic anemia (SAA) was diagnosed, if patients were >15 years of age at the time of alloHSCT treatment; and if patients had undergone alloHSCT from an MRD or AD, regardless of prior IST history. All eligible patients were fully informed on the nature and purpose of the present study, and all provided written informed consent before enrollment. All patients fully understood that they were entitled to exit the study without any negative consequences. Exclusion criteria were the presence of congenital aplasia, including Fanconi anemia, Diamond-Blackfan syndrome, or congenital dyskeratosis; or hypoplastic myelodysplastic syndrome. Data were collected from patients with pure red cell aplasia (PRCA) and paroxysmal nocturnal hemoglobinuria (PNH) during the protocol design phase, but such patients were not included in final analyses. An MRD was defined as an HLA fully matched related donor, and an AD included all other donor types, including both mismatched related and unrelated donors.

Data Collection

The present study was a retrospective multicenter work. This protocol was submitted to and approved by the Korean Society of Blood and Marrow Transplantation (KSBMT) Clinical Study Committee (approval no. KSBMT07-02), and the institutional review board (IRB) of each participating institution also cleared the work. Case report form (CRF) questionnaires defining items to be evaluated were provided to institutional investigators. If CRFs were insufficient or incomplete, principal investigators queried institutional collaborators to obtain missing information. Data collection started in 2007 for 6 months, and 1 institution added data on 2009.

Evaluation Criteria

The purpose of the study was to evaluate significant risk factors predicting survival in patients with AA following alloHSCT. The principal concern of the study, however, was to define whether alloHSCT from ADs was comparable in effect to alloHSCT from MRDs. The hematologic response to IST was assessed during the first 6 months after treatment. Responses to IST were required to be sustained upon transfusion, or by

administration of growth factors, and were confirmed using a minimum of 2 observations at least 4 weeks apart. A complete response (CR) was defined as transfusion independence, combined with test data showing that all cell lines tested were normal with respect to age and gender (the SAA evaluation). A partial response (PR) was defined as transfusion independence but the SAA criteria had not been met. A nonresponse was defined as transfusion dependence or when the peripheral blood count criteria for PR had not been attained. Relapse after IST was defined as a decrease in any peripheral blood cell count to <50% of the median sustained count observed during the response phase, or as dependence on transfusion.

ABO incompatibility between donors and recipients was classified as major (ie, the recipient had anti-A and/or anti-B antibodies capable of reacting with antigens on donor red cells), minor (ie, the donor had anti-A and/or anti-B antibodies capable of reacting with antigens on recipient red cells and tissues), mixed (ie, a transplant involving a group B donor and a group A recipient, or vice versa), and compatible. Neutrophil engraftment was noted on the first of 3 consecutive days on which the absolute neutrophil count (ANC) of a patient was $>0.5 \times 10^9$/L after a nadir, and platelet engraftment was defined as the first of 7 consecutive days on which the unsupported platelet count was $>20 \times 10^9$/L. Primary graft failure (or early rejection) was defined as a peripheral ANC $<0.5 \times 10^9$/L, persisting for more than 21 days after alloHSCT. Secondary graft failure was defined as marrow hypoplasia after engraftment, with a requirement for frequent (more than once weekly) platelet transfusion, or an ANC $<0.5 \times 10^9$/L, but without growth factor requirements extending beyond day 60.

Acute and chronic GVHD (aGVHD, cGVHD) were diagnosed and graded according to the Seattle criteria [22,23], and sinusoidal obstruction syndrome (SOS) was diagnosed using McDonald's guidelines [24]. Performance status was graded by Eastern Cooperative Oncology Group (ECOG) performance scoring. Relapse was defined as reacquisition of transfusion dependence or fulfillment of severe/very severe criteria after full engraftment.

Definitions of Survival Times

The startpoint for determination of survival parameters was the first day of stem cell infusion. Relapse-free survival (RFS), measured only in patients showing successful engraftment and who did not require regular transfusions, was defined as the time from commencement of a conditioning regimen to the date on which the patient was first recorded with disease relapse, or the date of death. Patients without relapse or death were censored at the date of last follow-up. Time to relapse was measured from the day of stem cell infusion to the date on which a patient withdrew from the study

because of adverse events, progressive disease, insufficient therapeutic response, death, failure to return for follow-up, refusal of treatment, refusal to cooperate, or withdrawal of consent. If none of these events occurred, patients were censored on the date of last follow-up. Overall survival (OS) was measured from the time of commencement of a conditioning regimen to the date of death, or the last date on which the patient was known to be alive (this constituted censoring).

Statistical Analysis

All analyses were performed on an intention-to-treat basis. The chi-square test was used to compare categoric variables and Student's *t*-test was employed to compare continuous variables between any 2 groups. Analysis of variance (ANOVA) was used to compare variables among 3 or more groups. Time to engraftment, time to aGVHD and cGVHD, nonrelapse mortality (NRM), and relapse, were estimated using the cumulative incidence function, and differences were compared employing Gray's test [25]. Survival curves were computed according to the Kaplan-Meier method, and differences in survival were compared by the log-rank test. A Cox's proportional hazard model was used to determine the effects on survival of various prognostic factors, including age, donor/recipient gender matching, number of cells transfused, use of irradiated blood products, time from diagnosis to alloHSCT, stem cell source, dose of irradiation, HLA matching, method of immune suppression employed to prevent GVHD, prior IST history, and use of ATG. All variables were dichotomized and converted into categoric classes. The principal objective of the present study was to compare differences in OS between recipients of MRD and AR alloHSCT. To adjust for variations in clinical characteristics among recipients of the 2 types of donor cells, we calculated a propensity score for each recipient, using a linear regression model that considered pretransplantation clinical factors. Employing PSM, we performed a case-control study comparing outcomes of MRD and AD alloHSCT patients. Variables considered in multivariate analysis included MRD versus AD, and all prognostic factors with *P* values <.1 in univariate analysis. Differences were assessed using a 2-sided test at the $P = .05$ level of significance. We used the R package (cmprsk) to analyze cumulative incidence, and SPSS version 17 for all other statistical analyses.

RESULTS

Patients

Our initial patient population included 234 patients with AA who underwent alloHSCT consecutively between 1995 and 2008 at 15 of the 40 transplantation centers in Korea, including most major centers. After excluding 1 patient with PRCA and 8 with PNH,

our patient population consisted of 225 adults with AA who underwent alloHSCT (Table 1). Of these patients, 117 (52.0%) were male; and median age at the time of alloHSCT was 31.2 years (range: 15-63 years). We determined that 103 (45.8%) patients had received prior IST, including 66 (29.3%) who were treated with ATG or ALG; of the latter, only 17 (16.5%) responded, with CR evident in 2 and PR in 15. ABO blood-type matching was compatible in 110 (53.7%) donor-recipient pairs. Stem cell sources included BM only in 172 (76.4%) patients, PB only in 46 (20.4%), and both BM and PB in 7 (3.1%); 185 (82.2%) pairs were fully HLA-matched. Of the 225 donors, 162 (72.0%) were related and 63 (28.0%) unrelated; 152 (67.6%) donors were MRDs and 73 (32.4%) ADs. Cyclophosphamide-ATG/ALG (Cy-ATG/ALG) was the most common conditioning regimen, used in 170 (75.6%) patients.

Clinical Factors Predicting Survival

The ability of various clinical factors to predict survival was evaluated (Table 2). We found that none of patient gender ($P = .640$), female donor-to-male recipient matching ($P = .499$), ECOG performance status at alloHSCT ($P = .948$), prior PRC transfusion ($P = .396$), conditioning regimen, BM as a stem cell source ($P = .224$), development of cGVHD, infused stem cell dose, or days to neutrophil engraftment ($P = .668$), significantly predict survival on univariate analysis, whereas younger age at diagnosis ($P = .055$), compatible ABO typing ($P = .055$), and lower PC transfusion level prior to alloHSCT ($P = .063$) were all marginally significant. However, lack of prior IST ($P = .005$), age at alloHSCT ≤ 31 years ($P = .001$), time from diagnosis to alloHSCT ≤ 6 months ($P = .008$), MRD ($P < .001$), HLA full matching ($P = .019$), successful engraftment ($P < .001$), absence of sinusoidal obstruction syndrome (SOS) ($P = .035$), absence of GVHD ($P = .005$), and platelet engraftment at ≤ 21 days ($P = .025$) were all significantly prognostic of longer survival.

Multivariate analysis showed that age at alloHSCT ≤ 31 years ($P < .001$), MRD ($P = .003$), successful engraftment ($P < .001$), absence of aGVHD ($P < .001$), and platelet engraftment at ≤ 21 days ($P = .026$), were significant independent factors predictive of longer survival (Table 3). Multivariate analysis also indicated

Table 1. Patient Characteristics

Characteristic	n (%)/Median (Range)	Characteristic	n (%)/Median (Range)
Gender		ABO incompatibility (n = 205)	
Male	117 (52.0)	Major	43 (21.0)
Female	108 (48.0)	Minor	38 (17.6)
Median age (years)		Mixed	16 (7.8)
At diagnosis	28 (2-62)	Compatible	110 (53.7)
At alloHSCT	30.9 (15-63)	Stem cell infusion	
Severity of AA		BM only	172 (76.4)
Transfusion-dependent	17 (7.6)	PB only	46 (20.4)
Severe	193 (85.8)	BM and PB	7 (3.1)
Very severe	15 (6.7)	Median TNC ($\times 10^7$/kg)	33.2 (1.8-217)
Prior IST	103 (45.8)	Median MNC ($\times 10^7$/kg)	9.5 (0.2-414.7)
Drug used to treat prior IST		Median CD34 ($\times 10^6$/kg)	3.8 (0.2-30.2)
ATG/ALG	66 (29.3)	Median months from Dx to alloHSCT	6.7 (0.2-251.1)
CsA	69 (30.7)	Conditioning regimen	
Oxymetholone	28 (12.4)	Cy-ATG/ALG	170 (75.6)
Response to prior IST		TBI-containing	24 (10.7)
CR	2 (1.9)	Engraftment	
PR	15 (14.6)	Neutrophil	205 (91.1)
No response	86 (83.5)	PLT	191 (84.9)
2nd IST	16 (7.1)	Primary graft failure	21 (9.3)
Transfusion prior to alloHSCT		Secondary graft failure	27 (12.0)
Median PRC units	12 (0-114)	Median days to ANC $\geq 500/\mu L$	17 (8-32)
Median PC units	86 (0-812)	Median days to PLT $\geq 20,000/\mu L$	21 (5-423)
Donor		SOS	19 (8.4)
Related	162 (72.0)	Mild	10 (4.4)
Unrelated	63 (28.0)	Moderate	6 (2.7)
Matched related	152 (67.6)	Severe	3 (1.3)
Alternative	73 (32.4)	GVHD	
Female-to-male	39 (17.3)	Acute	51 (22.7)
HLA matching		Grade III/IV	15 (6.6)
High-resolution typing		Chronic	49 (21.8)
Full matching	185 (82.2)	Extensive	19 (8.4)
Median no. of mismatches	0 (0-4)	Relapse	14 (6.2)

alloHSCT indicates allogeneic hematopoietic stem cell transplantation; AA, aplastic anemia; IST, immune suppression therapy; CR, complete remission; PR, partial remission; PRC, packed red cells; PC, platelet concentrate; BM, bone marrow; PB, peripheral blood; TNC, total nuclear cells; MNC, mononuclear cells; Dx, diagnosis; Cy-ATG/ALG, cyclophosphamide-antithymocyte globulin/antilymphocyte globulin; TBI, total-body irradiation; PLT, platelets; ANC, absolute neutrophil count; SOS, sinusoidal obstruction syndrome; GVHD, graft-versus-host disease.

Table 2. Factors Predicting Overall Survival

Factor	n	5-Year Survival Rate (%)	P Value
Female versus male	117 versus 108	74.0 versus 67.7	.640
No prior IST versus prior IST	122 versus 103	77.4 versus 61.9	.005
None versus ATG/ALG for prior IST	160 versus 65	74.7 versus 59.5	.012
None versus CsA for prior IST	156 versus 69	74.9 versus 60.6	.006
Age at alloHSCT ≤31 years versus >31 years	113 versus 112	81.3 versus 58.1	.001
Time from Dx to alloHSCT ≤6 months versus >6 months	107 versus 118	78.7 versus 62.8	.008
RD versus URD	162 versus 63	75.6 versus 56.2	.002
MRD versus AD	152 versus 73	76.6 versus 56.8	<.001
ABO compatible versus incompatible	95 versus 110	75.9 versus 59.3	.055
HLA full match versus mismatch	185 versus 40	73.1 versus 55.9	.019
Others versus female donor-to-male recipient	186 versus 39	71.8 versus 63.1	.499
ECOG performance status at alloHSCT; >1 versus ≤1	33 versus 192	71.8 versus 70.0	.948
Prior PRC transfusion ≤12 U versus >12 U	160 versus 65	71.9 versus 65.9	.396
Prior PC transfusion ≤86 U versus >86 U	149 versus 76	75.3 versus 58.7	.063
Conditioning without versus with TBI	24 versus 201	70.9 versus 65.0	.525
Conditioning with versus without ATG/ALG	173 versus 52	71.6 versus 65.5	.628
Cy-ATG/ALG conditioning versus other	170 versus 55	71.6 versus 65.6	.585
BM as a stem cell source versus Others	179 versus 46	72.9 versus 51.6	.224
Successful engraftment versus graft failure	178 versus 47	81.0 versus 32.3	<.001
No SOS versus SOS	206 versus 19	72.0 versus 50.7	.035
No aGVHD versus aGVHD	174 versus 51	75.1 versus 54.4	.005
cGVHD versus No cGVHD	49 versus 176	72.8 versus 70.4	.168
Infused TNC >33 versus ≤33 ($\times 10^7$/kg)	117 versus 108	70.8 versus 69.3	.911
Infused MNC infusion ≤9.5 versus >9.5 ($\times 10^7$/kg)	104 versus 121	72.9 versus 67.7	.647
Infused CD34 infusion >3 versus ≤3 ($\times 10^6$/kg)	144 versus 81	73.3 versus 65.6	.305
Neutrophil engraftment days ≤17 versus >17	135 versus 90	73.0 versus 66.6	.668
Platelet engraftment days ≤21 versus >21	88 versus 137	77.4 versus 65.7	.025

5YSR indicates 5-year survival rate; IST, immune suppression therapy; ATG/ALG, antithymocyte globulin/antilymphocyte globulin; CyA, cyclosporine A; alloHSCT, allogeneic hematopoietic stem cell transplantation; Dx, diagnosis; RD, related donor; URD, unrelated donor; MRD, matched related donor; AD, alternative donor; PRC, packed red cells; PC, platelet concentrate; TBI, total-body irradiation; Cy, cyclophosphamide; BM, bone marrow; SOS, sinusoidal obstruction syndrome; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; TNC, total nuclear cells; MNC, mononuclear cells

that age at diagnosis ≤28 years (P = .090), complete ABO compatibility (P = .070), and absence of SOS (P = .069), were marginally significant.

Calculation of Propensity Scores and PSM

Among the pre-alloHSCT variables used to calculate propensity scores were recipient gender; age at alloHSCT; history of prior IST; ATG/ALG for prior IST; time from diagnosis to alloHSCT; ABO compatibility; HLA matching; female donor-to-male recipient status; ECOG performance status at alloHSCT; PRC transfusion; PC transfusion; total-body irridiation (TBI) conditioning; ATG/ALG conditioning; bone marrow (BM) as a stem cell source; and numbers of total nucleated cells (TNC), mononuclear cell (MNC), and CD34$^+$ cells infused. From our 225 patients, we selected 25 propensity score-matched MRD and AD recipients.

Comparison of Pretransplantation Characteristics in MRD and AD Recipients, with or without PSM

The basic characteristics of MRD and AD recipients differed greatly prior to selection. For example, the percentages of patients who did not undergo prior IST (109/152 [71.7%] versus 13/73 [17.8%]; P < .001), without HLA full matching (152/152 [100%] versus 33/73 [45.2%]; P < .001), with a time from diagnosis to alloHSCT of ≤6 months (87/152 [57.2%] versus 20/73 [27.4%]; P < .001), of an age at alloHSCT ≤31years (69/152 [45.4%] versus 44/73 [60.3%]; P = .046), and with a history of PRC transfusion of ≤12 units prior to alloHSCT (118/152 [77.6%] versus 42/73 [57.5%]; P = .003), differed significantly in MRD and AD recipients; whereas the percentages of patients who received TBI conditioning were marginally different (12/152 [7.9%] versus 12/73 [16.4%]; P = .065). Patient characteristics are shown in Table 4. After PSM, however, all of these pre-alloHSCT characteristics were well matched.

Transplantation Outcomes of MRD and AD Patients Either Unmatched or Matched

In unmatched patients, MRD yielded superior transplantation outcomes as shown in Table 5. The incidences of granulocyte (5.9% versus 15.1%; P = .024), platelet (11.2% versus 23.3%; P = .018), and all (16.4 versus 30.1%; P = .018) graft failures were significantly lower, and the median times to neutrophil (17 versus 20 days; P = .006) and platelet (21 versus 26 days; P = .003) engraftment were significantly shorter in MRD than in AD recipients. In addition, MRD recipients showed significantly lower incidences of aGVHD (17.8% versus 32.9%; P = .011) and treatment-related mortality (TRM) (19.1% versus 39.7%; P = .001), and a significantly longer OS (P < .001), than did AD

Table 3. **Multivariate Analysis of Survival**

Factor	HR	95% CI	P Value
No prior IST versus prior IST	0.827	0.255-2.685	.752
None versus ATG/ALG for prior IST	0.729	0.334-1.593	.428
None versus CsA for prior IST	0.966	0.420-2.224	.936
Age at alloHSCT ≤31 years versus >31 years	0.281	0.126-0.423	<.001
Time from Dx to alloHSCT ≤6 months versus >6 months	0.938	0.482-1.824	.850
MRD versus AD	0.448	0.264-0.759	.003
ABO compatible versus incompatible	0.607	0.354-1.042	.070
HLA full-match versus mismatch	0.261	0.051-1.323	.105
Prior PC transfusion ≤86 U versus >86 U	0.666	0.365-1.213	.184
Successful engraftment versus graft failure	0.136	0.077-0.238	<.001
No SOS versus SOS	0.494	0.232-1.055	.069
No aGVHD versus aGVHD	0.231	0.126-0.423	<.001
Platelet engraftment days ≤21 days versus >21 days	0.473	0.245-0.912	.026

CI indicates confidence interval; IST, immune suppression therapy; ATG/ALG, antithymocyte globulin/antilymphocyte globulin; CyA, cyclosporine A; alloHSCT, allogeneic hematopoietic stem cell transplantation; Dx, diagnosis; MRD, matched related donor; AD, alternative donor; PC, platelet concentrate; TBI, total-body irradiation; Cy, cyclophosphamide; BM, bone marrow; SOS, sinusoidal obstruction syndrome; aGVHD, acute graft-versus-host disease.

recipients (Figures 1 and 2). In addition, times to aGVHD ($P = .01263$) and NRM ($P = .0001583$) were significantly better in the MRD group. In contrast, MRD patients did not differ in incidence of grade 3/4 aGVHD (5.9% versus 8.2%; $P = .572$); presence of any cGVHD (21.7% versus 21.9%; $P = .972$); or development of extensive cGVHD (7.9% versus 9.6%; $P = .669$), SOS (8.6% versus 8.2%; $P = .933$), or relapse (7.9% versus 2.7%; $P = .236$); or in times to relapse ($P = .2308703$) (G3/4 aGVHD [$P = .516318$], cGVHD [$P = .814118$], and extensive cGVHD [$P = .581048$]), compared to AD patients.

Of our propensity score-matched patients, 8 of 25 MRD and 9 of 25 AD recipients died. The median survival times of PSM-matched MRD and AD recipients were 175.4 months and not attained, respectively ($P = .514$). No relapse was evident in either group (Figure 1). Times to ANC ($P = .336$) and platelet ($P = .705$) engraftment, and the incidence of SOS

($P = .235$), did not differ in PSM-matched MRD and AD recipients (Figure 2), nor were statistically significant differences in cumulative incidences of aGVHD ($P = .1550$), grade 3/4 aGVHD ($P = .3275$), cGVHD ($P = .8002$), extensive cGVHD ($P = .5647$), or NRM ($P = .3655$), apparent.

DISCUSSION

AlloHSCT is a curative treatment for patients with severe AA. Many studies have shown that survival is superior in recipients of MRD than in AD recipients [2,10]. General guidelines recommend that alloHSCT be postponed after IST if no suitable MRD is available. However, it is important to consider the clinical settings in which alloHSCT is performed. We found that AD was associated with a greater delay in alloHSCT after diagnosis, older age at alloHSCT, and

Table 4. **Characteristics of Patients with Matched Related and Alternative Donors**

Character	All Patients, n (%)			Patients Matched by Propensity Score, n (%)		
	MRD (n = 152)	AD (n = 73)	P Value	MRD (n = 25)	AD (n = 25)	P Value
Male	79 (52.0)	38 (52.1)	1.000	11 (44.0)	11 (44.0)	1.000
No prior IST	109 (71.7)	13 (17.8)	<.001	4 (16)	5 (20)	.500
HLA full match	152 (100)	33 (45.2)	<.001	25 (100)	25 (100)	—
Female to male	30 (19.7)	9 (12.3)	.192	5 (20.0)	3 (12.0)	.351
ABO-compatible	83 (57.2)	27 (45.0)	.125	9 (36.0)	12 (48.0)	.284
ATG/ALG conditioning	115 (75.7)	58 (79.5)	.614	20 (80.0)	19 (76.0)	1.000
TBI conditioning	12 (7.9)	12 (16.4)	.065	5 (20.0)	3 (12.0)	.351
Time from Dx to alloHSCT ≤6 months	87 (57.2)	20 (27.4)	<.001	4 (16.0)	6 (24.0)	.725
Age at alloHSCT ≤31 years	69 (45.4)	44 (60.3)	.046	12 (48.0)	13 (52.0)	1.000
PB used as stem cells	31 (20.4)	22 (30.1)	.131	5 (20.0)	6 (24.0)	1.000
Prior PRC transfusion ≤12 U	118 (77.6)	42 (57.5)	.003	18 (72.0)	15 (60.0)	.551
Prior PC transfusion ≤86 U	106 (69.7)	43 (58.9)	.132	18 (72.0)	15 (60.0)	.551
Infused TNC ≤33 (×10⁷/kg)	75 (49.3)	33 (45.2)	.572	10 (40.0)	13 (52.0)	.571
Infused MNC ≤9.5 (×10⁷/kg)	70 (46.1)	34 (46.6)	1.000	12 (48.0)	12 (48.0)	1.000
Infused CD34 ≤3 (×10⁶/kg)	54 (35.5)	27 (37.0)	.882	12 (48.0)	10 (40.0)	.776
Performance (ECOG) ≤1	128 (84.2)	64 (87.7)	.551	22 (88.0)	23 (92.0)	.5000

IST indicates immune suppression therapy; ATG/ALG, antithymocyte globulin/antilymphocyte globulin; TBI, total-body irradiation; Dx, diagnosis; alloHSCT, allogeneic hematopoietic stem cell transplantation; PB, peripheral blood; PRC, packed red cells; PC, platelet concentrate; TNC, total nuclear cells; MNC, mononuclear cells.

Table 5. Transplantation Outcomes in Patients with Matched Related and Alternative Donors

Character	All Patients, n (%)			Patients Matched by Propensity Score, n (%)		
	MRD (n = 152)	AD (n = 73)	P Value	MRD (n = 25)	AD (n = 25)	P Value
Graft failure						
Granulocytes	9 (5.9)	11 (15.1)	.024	3 (12)	2 (8)	1.000
Time to ANC500, days	17	20	.006	19	17	.369
Platelets	17 (11.2)	33 (23.3)	.018	5 (20)	4 (16)	1.000
Time to PLT20K, days	21	26	.003	26	24	.914
Any	25 (16.4)	22 (30.1)	.018	4 (16)	4 (16)	1.000
Acute GVHD						
Any	27 (17.8)	24 (32.9)	.011	3 (12)	7 (28)	.157
Grade 3/4	9 (5.9)	6 (8.2)	.572	0 (0.0)	1 (4.0)	1.000
Chronic GVHD						
Any	33 (21.7)	16 (21.9)	.972	6 (24.0)	5 (20.0)	.733
Extensive	12 (7.9)	7 (9.6)	.669	2 (8.0)	1 (4.0)	1.000
SOS	13 (8.6)	6 (8.2)	.933	3 (12.0)	0 (0.0)	.235
TRM	29 (19.1)	29 (39.7)	.001	7 (28.0)	9 (36.0)	.544
Relapse	12 (7.9)	2 (2.7)	.236	0 (0.0)	0 (0.0)	—
OS, median, months	NR	NR	<.001	175.4	NR	.514

ANC500 indicates absolute neutrophil count >500/μL; PLT20K, platelet count >20,000/μL; GVHD, graft-versus-host disease; SOS, sinusoidal obstruction syndrome; TRM, treatment-related mortality; OS, overall survival; NR, not reached.

a requirement for more transfusions; these are unfavorable risk factors for alloHSCT in patients with AA. Although we utilized multivariate analysis to adjust for such imbalances, it remain unclear whether such analysis can completely account for differences in pretransplantation clinical factors, because selection bias may have been in play when risk factors for analysis were chosen. Moreover, our multivariate analysis included posttransplantation risk factors, some of which can interact with pretransplantation factors. In addition, we could not randomize patients to MRD or AD.

PSM is a statistical method used to compare different treatment modalities in clinical settings. PSM can be employed to eliminate causal inference and simple selection bias in nonexperimental settings. The use of PSM allowed us to focus on donor selection itself.

Among the factors that differed significantly in univariate analysis between unmatched recipients of MRD and AD were the absence of prior IST (P = .005), age at alloHSCT ≤31 years (P = .001), time

from diagnosis to alloHSCT ≤6 months (P = .008), MRD (P < .001), full matching of HLA (P = .019), successful engraftment (P < .001), no SOS (P = .035), no aGVHD (P = .005), and platelet engraftment >21 days (P = .025), all of which significantly favored MRD. Several of these factors also featured in pretransplantation risk analysis, including no prior IST, age at alloHSCT ≤31 years, time from diagnosis to alloHSCT ≤6 months, MRD, and full matching of HLA.

Multivariate analysis showed that age at alloHSCT ≤31 years (P < .001), MRD (P = .003), successful engraftment (P < .001), and no aGVHD (P < .001), were independent factors associated with longer patient survival, whereas age at diagnosis ≤28 years (P = .090), ABO compatibility (P = .070), and no SOS (P = .069), were marginally significant. These findings indicate that alloHSCT at a younger age from an MRD, successful engraftment, and the absence of aGVHD, were predictive of optimal results in patients with AA. As we could not control donor choice, we are
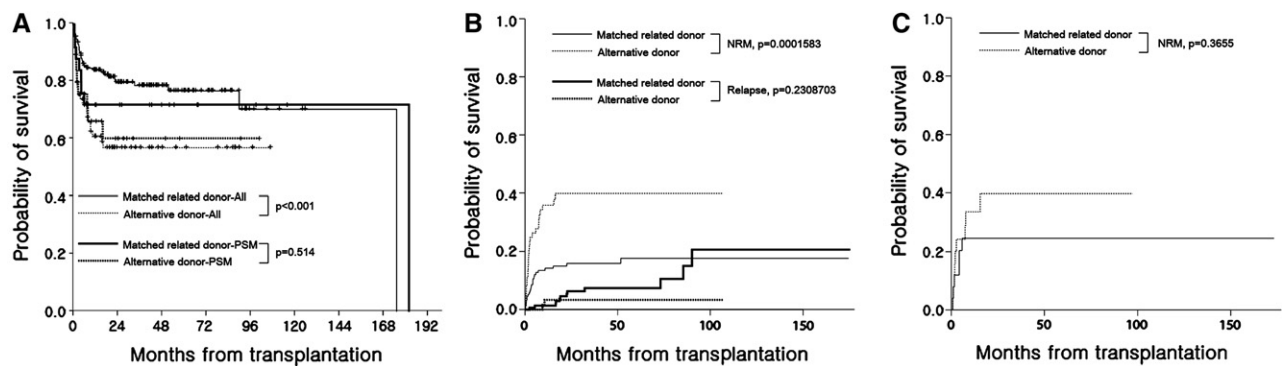

Figure 1. Outcomes of patients undergoing hematopoietic stem cell transplantation. (A) OS, and cumulative incidence of nonrelapse mortality (NRM) and relapse in patients with matched related donors (MRDs); in (B) all patients with unmatched donors, and (C) in patients with PSM-matched ADs. OS was superior in patients with MRDs than in patients with unmatched donors, but did not differ significantly between patients with MRDs and those with propensity-score-matched (PSM) ADs. Only NRM in unmatched patients differed significantly between patients with MRDs and ADs.
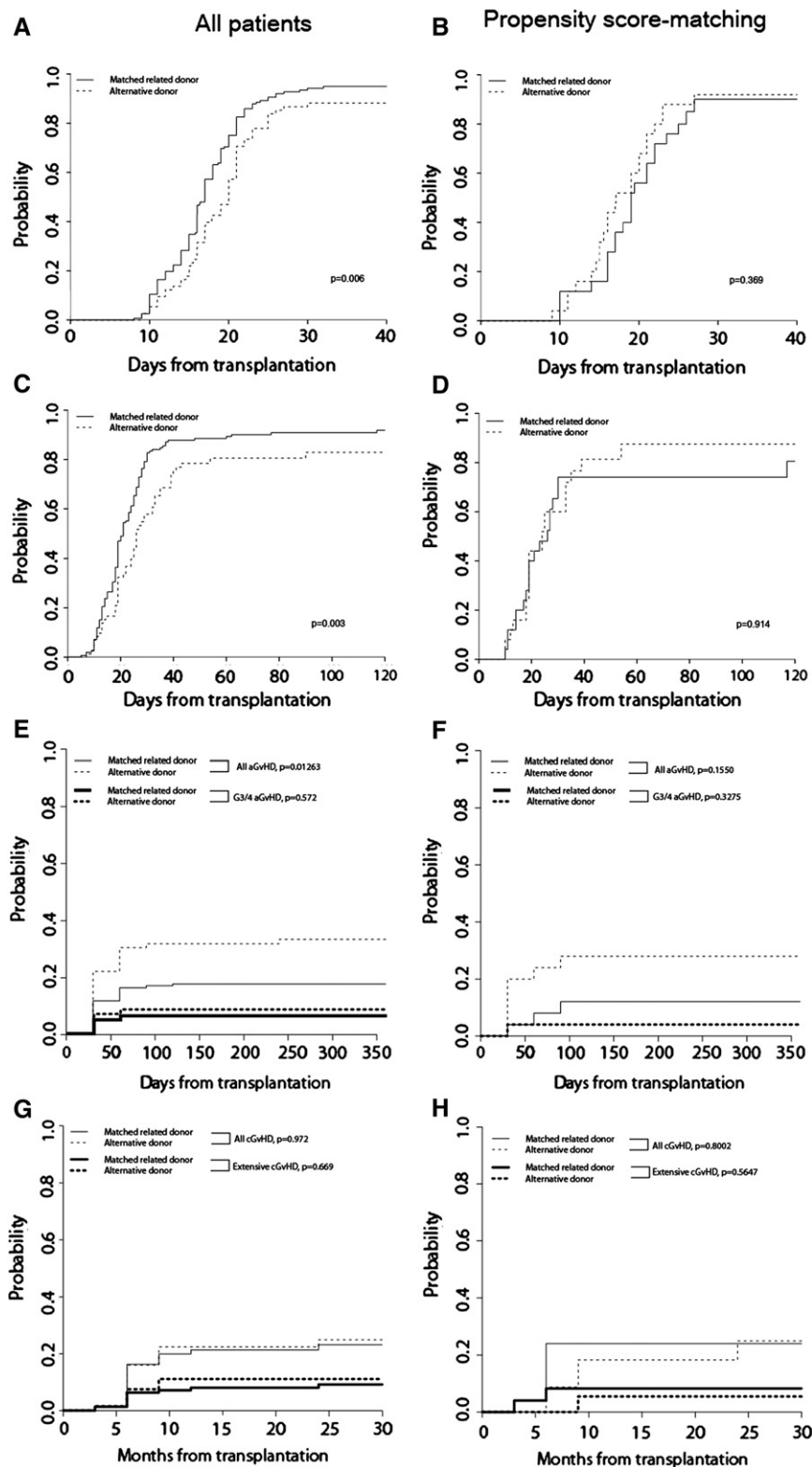
Figure 2. Cumulative incidence of transplantation outcomes. Times to granulocyte engraftment (A, B); times to platelet engraftment (C, D); extent of acute graft-versus-host disease (aGVHD; E, F); and the levels of chronic graft-versus-host disease (cGVHD; G, H), in recipients of all unmatched donors (A, C, E, G), and propensity score-matched donors (B, D, F, H); are shown.

unable to accurately predict successful engraftment or occurrence of aGVHD; it follows that case-control matching balancing pretransplantation clinical factors may provide practical insights into donor selection.

Although cyclophosphamide-ATG is considered to be the standard conditioning regimen, the role of ATG remains questionable when alloHSCT from an MRD is considered [26]. Irradiation as conditioning is not

routinely performed in patients receiving alloHSCT from an MRD. In contrast, irradiation has been regarded as essential for alloHSCT from an AD; many recognized conditioning regimens incorporate such irradiation [11,27-29]. However, minimal irradiation may result in survival outcomes comparable with those of patients receiving alloHSCT from MRDs [12,19,30]. In addition, impressive results have been observed using conditioning regimens lacking irradiation in AD patients receiving alloHSCT [16,31]; Korean data support this proposition [14,18]. These findings indicate that non-TBI conditioning regimens may be successful when alloHSCT from ADs is considered.

Following PSM, pretransplantation clinical factors were well balanced in our 25 MDR and 25 AD patients. Transplantation outcomes were almost identical in these 2 groups; 8 and 9 patients, respectively, died, and similar median survival times ($P = .514$), times to ANC ($P = .336$) and platelet ($P = .705$) engraftment, and incidences of sinusoidal obstruction syndrome ($P = .235$) were observed. Moreover, no differences in the cumulative incidence of aGVHD ($P = .1550$), grade 3/4 aGVHD ($P = .3275$), cGVHD ($P = .8002$), extensive cGVHD ($P = .5647$), or NRM ($P = .3655$), were apparent. Thus, in patients with similar pretransplantation clinical conditions, the outcomes of alloHSCT were also similar, regardless of donor type.

Hidden bias may be significant when PSM is employed because matching of observed variables may result in bias attributable to dormant unobserved confounders [32]. The use of PSM tends to select AD patients with favorable characteristics because all MRD recipients were HLA fully matched. In addition, only half of our PSM AD patients were treated with pretransplantation immunosuppression, another indicator of the relatively favorable characteristics of this group. In addition, the lack of any difference between MRD and AD recipients may be attributable to the small numbers of patients in either group. Although the incidences of aGVHD (28% versus 12%) and TRM (36% versus 28%) were greater in the AD group, the between-group differences were statistically nonsignificant and may be attributable to small sample size. In contrast, the times to neutrophil (19 versus 17 days) and platelet (26 versus 24 days) engraftment were somewhat greater in the AD group, as was the incidence of SOS (12% versus 0%), although none of these differences was statistically significant. Our findings may also have been influenced by ethnic homogeneity. Thus, all patients and donors were Korean, and the use of ethnically homogeneous unrelated donors may have affected our results.

Despite the many limitations of a PSM study, our results differ from those of previous reports in that transplantation outcomes were very similar when MRD and AD groups were compared. AD may be as successful as MRD if alloHSCT is performed soon after diagnosis, in younger patients, and using ABO-compatible and HLA fully matched donors.

AUTHOR CONTRIBUTIONS

H.K., J.H.P., and K.-H.L. designed the project; H.K., B.S.K., D.H.K., M.S.H., S.H.K., S.H.B., J.H.C., S.K.S., H.J.S., J.H.W., S.S.Y., D.Y.J., Y.D.J., and K.-H.L. performed the research; H.K. and K.-H.L. analyzed the data; and H.K. wrote the paper.

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