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ORIGINAL ARTICLE

Utility of allogeneic hematopoietic stem cell transplantation using international donors in a homogenous ethnic population: question in the era of various alternative donors

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Abstract

The advent of various alternative donors in allogeneic hematopoietic stem cell transplantation (HSCT) raises the question of using international donors, especially in ethnically homogenous populations. We analyzed the clinical outcome and medical expense of human leukocyte antigen (HLA)-matched HSCT using domestic and international donors. We analyzed the patients who received allogeneic HSCT at five medical centers in Korea in the last 10 years. Using propensity-score matching, we compared overall survival (OS), relapse-free survival (RFS), and transplantation-related complications. Medical expense was analyzed based on National Health Insurance Service (NHIS) data. A total of 269 patients were analyzed after 3:1 (domestic/international) matching. There was no difference in OS ($p = 0.395$) and RFS ($p = 0.604$) between the domestic and international donor groups (5-year OS rate 42.9 and 37.8%, 5-year RFS rate 37.6 and 33.5% for domestic and international groups, respectively). No difference in chronic graft-versus-host disease (GVHD) incidence was observed (34.2% in domestic and 35.9% in international group, $p = 0.804$). Early infection was more frequent in the domestic group (55.0 vs. 35.8%, $p = 0.007$), whereas infection after 30 days was more frequent in the international group (28.7 vs. 49.3%, $p = 0.001$). Mean medical expense was far higher in the international group, by US $51,944 in the entire follow-up period ($p < 0.001$). We would expect similar outcomes for international and domestic donors in terms of survival and treatment-related complications with HLA-matched HSCT in other ethnically homogenous populations. These findings should be considered together with the high cost of using international donors in the era of various alternative donors.

Keywords Allogeneic stem cell transplantation · HLA · International donor · Alternative donor

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) has been in continuous development over the past 50 years and is now widely performed for various hematologic diseases [1, 2]. Since the concept of human leukocyte antigen (HLA) was introduced, the importance of HLA matching for the outcome of allogeneic HSCT has been emphasized, leading to the

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notion that the selection of HLA-matched donors is the principal factor in determining the success of allogeneic HSCT [3]. Although an HLA-matched sibling is the best candidate for allogeneic HSCT, the majority of patients do not have a matched sibling donor, and HSCT using a national donor registry has been used to circumvent this limitation. In Korea, it is estimated that about 20,000 people are newly registered in the Korea Marrow Donor Program (KMDP) every year, and approximately 300,000 people were registered by 2015. However, even with the national marrow donor registry, a proportion of patients lack an appropriate domestic donor both in Korea and around the globe [4]. It is reported that from 16% of South or Central American descent to 75% of European descent in the USA can be matched with an appropriate domestic stem cell donor [5].

For patients who cannot find an appropriate HLA-matched domestic donor, alternative donors, such as haploidentical donors or cord blood, can be considered. Historically, the primary option in unmatched cases was to seek a matched donor outside the country, and this option is still actively used [6]. It has been reported that about 30% of Korean patients without matched domestic donors found donors in the Japan Marrow Donor program (JMDP) registry [4]. However, use of international donors presents challenges compared to use of haploidentical or cord blood donors. First, foreign national donor programs require additional cost and time for shipping, brokerage, and inspection. In fact, donor search costs represent a large component of total transplantation expense, up to one third of the total cost [7–9]. In addition, time from initiation of coordination to stem cell donation varies and sometimes takes longer with international donors than with domestic donors.

Considering these facts, there is a need to reevaluate the clinical benefit of allogeneic HSCT from an international donor, and this need has become more important with the advances in HSCT techniques using haploidentical family donors or cord blood. In fact, more than 30,000 cord blood transplantations were performed over the past 25 years, with a high percentage of these transplantations serving as the alternative choice in racial minority populations [10]. Haploidentical stem cell transplantation is even more feasible in adults as a result of the technical developments in overcoming allo-responsiveness, which is the major pitfall of such transplantations [11–13].

We doubt whether the same clinical benefit would be observed in cases with international donors even if HLAs were matched, especially in countries with relatively ethnically homogenous populations. This uncertainty is mainly due to ethnic disparity between international donors and recipients. Current data on the clinical outcomes of allogeneic HSCT with foreign vs. domestic HLA-matched donors in Asian countries where ethnicity is relatively homogenous are largely insufficient.

Therefore, we analyzed the outcome of allogeneic HSCT using international donors compared to domestic donors in Korea. We analyzed clinical efficacy and medical costs in an ethnically homogenous population.

Patients and methods

Patients

The list of all patients who received allogeneic HSCT at five medical centers (Seoul National University Hospital, Kyungpook National University Hospital, National Cancer Center, Shinchon Severance Hospital, and Samsung Medical Center) from January 2005 to April 2015 using a KMDP donor or an international donor was obtained. Medical-record review of 661 patients was performed. The primary outcome was overall survival (OS), and the secondary outcome variables included complete remission (CR), relapse-free survival (RFS), and graft-versus-host disease (GVHD). The first clinical-record form (CRF) was developed to collect data objectively from the clinical centers, primarily for propensity-score matching. The second CRF was designed to compare treatment outcomes for propensity score-matched patients. We obtained permission of the Institutional Review Board (IRB) of the National Evidence-based Healthcare Collaborating Agency (NECA) and each medical center (IRB No. NECA IRB15-014).

Comparison of clinical outcome using propensity-score matching

For comparison of the clinical outcomes of allogeneic HSCT between domestic and international donors, we conducted propensity-score matching. The diagnosis was set as the stratification variable, and the propensity score was calculated by logistic regression analysis based on sex, age, stem cell donor, HLA match, and infused $CD34^+$ cell count. Patients were matched by propensity score using the nearest-neighbor method, and the matching ratio was 1:3. The caliper width was equal to 0.2 times the standard deviation of the logit of the propensity score. After matching, the covariate balance was reviewed with statistical significance and standardized difference.

Comparison of medical expense using health insurance claim data

To compare the medical expense of domestic and international allogeneic HSCT, we obtained health insurance claim data from the National Health Insurance Service (NHIS) for 159 patients who received allogeneic HSCT at national public centers (Seoul National University Hospital, Kyungpook National University

Hospital, and National Cancer Center) and analyzed the data for clinical outcomes. When the hematologist decided to pursue allogeneic stem cell transplantation from a foreign donor, an additional cost is incurred in the process of searching, laboratory examination, and transportation, and these costs are primarily covered by the national insurance. We calculated the expense based on the data from the marrow donor program in each country. All costs were estimated and expressed in 2017 US dollars (USDs).

Statistical analysis

We compared the baseline characteristics of patients after propensity-score matching. The covariate balance was confirmed by standardized differences and statistical significance as determined by Student's *t* test for continuous variables and chi-square test for categorical variables.

We used the Cox proportional hazard model and Kaplan-Meier survival curve to compare OS and RFS of allogeneic HSCT with domestic and international donors. As mortality is higher early in the clinical course after transplantation, the Wilcoxon test was used to examine the differences in survival curves when the proportional hazard assumption was satisfied, and the Gehan method of the Renyi type test was used when the proportional hazard assumption was not satisfied. Log-transformed *t* tests were used to determine the statistical significance of the costs. SAS ver. 9.4 and R 3.1.1 were used for analyses, and $p < 0.05$ was considered to be statistically significant.

Results

Patient characteristics

From January 2005 to April 2015, a total of 661 patients were recruited from five institutions. Of these patients, 588 received HSCT from domestic donors, and 73 received HSCT from international donors. Acute leukemia was the leading indication, accounting for about 60% of total allogeneic HSCT. There were 269 propensity score-matched patients, of which 202 received HSCT from domestic donors and 67 from international donors. After propensity-score matching, the national and international donor groups showed an even distribution with respect to stem cell source, hematologic disease, and infused $CD34^+$ cell count. Patient characteristics are summarized in Table 1.

Survival analysis of hematopoietic stem cell transplantation from international donors

The median duration of follow-up of the patients who received HSCT from international donors was 87.4 months (range, 5.4–164.6). The 5-year OS rate was 37.8% (95% confidence interval (CI), 25.4–50.0), and the 5-year RFS rate was 33.5% (95% CI, 21.7–45.6) in the international donor group. Of patients with acute leukemia, the 5-year OS rate was 34.9% (95% CI, 20.3–50.0), and the 5-year RFS was 28.9% (95% CI, 15.8–43.5), which is similar to the survival of the entire international donor population. Lymphoma patients showed inferior survival outcomes compared with the total population, whereas no transplanted aplastic anemia patients died during the entire follow-up period (Fig. 1).

Comparison of clinical outcome by donor nationality

Five-year OS and RFS rates were 42.9% (95% CI, 35.5–50.1) and 37.6% (95% CI, 30.7–44.5), respectively, in the domestic donor group. The survival outcome was not different between the domestic donor group and the international donor group ($p = 0.395$ for OS and 0.604 for RFS; Fig. 2). The multivariate analysis did not reveal any significant differences between two groups (hazard ratio (HR), 1.135; 95% CI, 0.787–1.637; $p = 0.5$).

Further analysis considering factors other than stratification variables was performed. We categorized the patients by disease-risk index (DRI), and the very high-risk group showed significantly poorer survival outcome. Conditioning intensity did not affect survival outcome (HR, 1.32 in the non-myeloablative group compared to the myeloablative group; 95% CI, 0.951–1.831, $p = 0.097$; Table 2).

Additionally, we compared survival outcomes among the patients with acute leukemia, the most common indication for allogeneic HSCT. The 5-year OS was 41.1% (95% CI, 31.8–50.0), and the RFS was 34.9% (95% CI, 26.4–43.5) in the domestic donor group (Fig. 3). In this population, there was no significant difference between the domestic and international donor groups (HR, 1.11; 95% CI, 0.711–1.747; $p = 0.637$).

Complications

To compare complications between the groups, we investigated mortality, GVHD, and infection. Death occurred in 15 of 202 patients (7.43%) within 30 days and 29 of 202 patients (14.36%) within 60 days in the domestic donor group, whereas 2 of 67 patients (2.99%) died within 30 days and 9 of 67 patients (13.43%) died within 60 days in the international donor group. Deaths were mainly among patients with acute leukemia and lymphoma, and there were no deaths in the aplastic anemia group. Early mortality was higher in the domestic donor group, but the difference was not statistically significant ($p = 0.225$ for death within 30 days, $p = 0.851$ for death within 60 days). Disease-specific incidence of mortality for each group is shown in Table 3.

Infection was investigated within and after 30 days from transplantation. Within 30 days, 54.95% of the patients ($N = 111$) in the domestic donor group experienced infection, whereas 35.82% of the patients ($N = 24$) in the international donor group did, and this difference was statistically significant ($p = 0.007$). By contrast, at 60 days after transplantation,

Table 1 Patient characteristics after propensity-score matching

	Total ($N = 269$)	Domestic ($N = 202$)	International ($N = 67$)	p value
Sex: N (%)				0.521
Male	176 (65.43)	130 (64.36)	46 (68.66)	
Female	93 (34.57)	72 (35.64)	21 (31.34)	
Age: years, mean ± SD	37.29 ± 13.25	37.24 ± 13.37	37.45 ± 12.98	0.913
Source: N (%)				0.641
Bone marrow	51 (18.96)	37 (18.32)	14 (20.90)	
Peripheral blood	218 (81.04)	165 (81.68)	53 (79.10)	
HLA: N (%)				0.982
Full-matched (10/10)	189 (70.26)	142 (70.30)	47 (70.15)	
Mismatched	80 (29.74)	60 (29.70)	20 (29.85)	
Disease: N (%)				0.998
Aplastic anemia	20 (7.43)	15 (7.43)	5 (7.46)	
Acute leukemia	171 (63.57)	129 (63.86)	42 (62.69)	
Lymphoma	28 (10.41)	21 (10.40)	7 (10.45)	
Other	50 (18.59)	37 (18.32)	13 (19.40)	
Disease status: N (%)				
Aplastic anemia	20 (7.43)	15 (7.43)	5 (7.46)	
Acute leukemia				
CR	142 (52.79)	109 (53.96)	33 (49.25)	0.374
Non-CR	29 (10.78)	20 (9.90)	9 (13.43)	
Lymphoma				
CR	11 (4.09)	8 (3.96)	3 (4.48)	0.744
NR	10 (3.72)	7 (3.47)	3 (4.48)	
PR	7 (2.60)	6 (2.97)	1 (1.49)	
Other				
CR	9 (3.35)	8 (3.96)	1 (1.49)	0.261
Non-CR	41 (15.24)	29 (14.36)	12 (17.91)	
Infused $CD34^+$: N (%)				
$< 4.0 \times 10^6$/kg	93 (34.57)	65 (32.18)	28 (41.79)	0.339
$\geq 4.0 \times 10^6$/kg	160 (59.48)	124 (61.39)	36 (53.73)	
Unknown	16 (5.95)	13 (6.44)	3 (4.48)	
Conditioning: N (%)				
MAC	106 (39.41)	79 (39.11)	27 (40.30)	0.886
RIC/NMAC	160 (59.48)	121 (59.90)	39 (58.21)	
Unknown	3 (1.11)	2 (0.99)	1 (1.49)	
GVHD prophylaxis: N (%)				
ATG				
Yes	136 (50.56)	103 (50.99)	33 (49.25)	0.888
No	133 (49.44)	99 (49.01)	34 (50.75)	
CNI				
Cyclosporin	117 (43.49)	93 (46.04)	24 (35.82)	0.157
Tacrolimus	145 (53.90)	105 (51.98)	40 (59.70)	0.323
N/A	7 (2.61)	4 (1.98)	3 (4.48)	

HLA human leukocyte antigen, *CR* complete remission, *NR* no response, *PR* partial response, *SD* standard deviation, *kg* kilogram, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *NMAC* non-myeloablative conditioning, *GVHD* graft-versus-host disease, *ATG* anti-thymocyte globulin, *CNI* calcineurin inhibitor, *N/A* not assessed

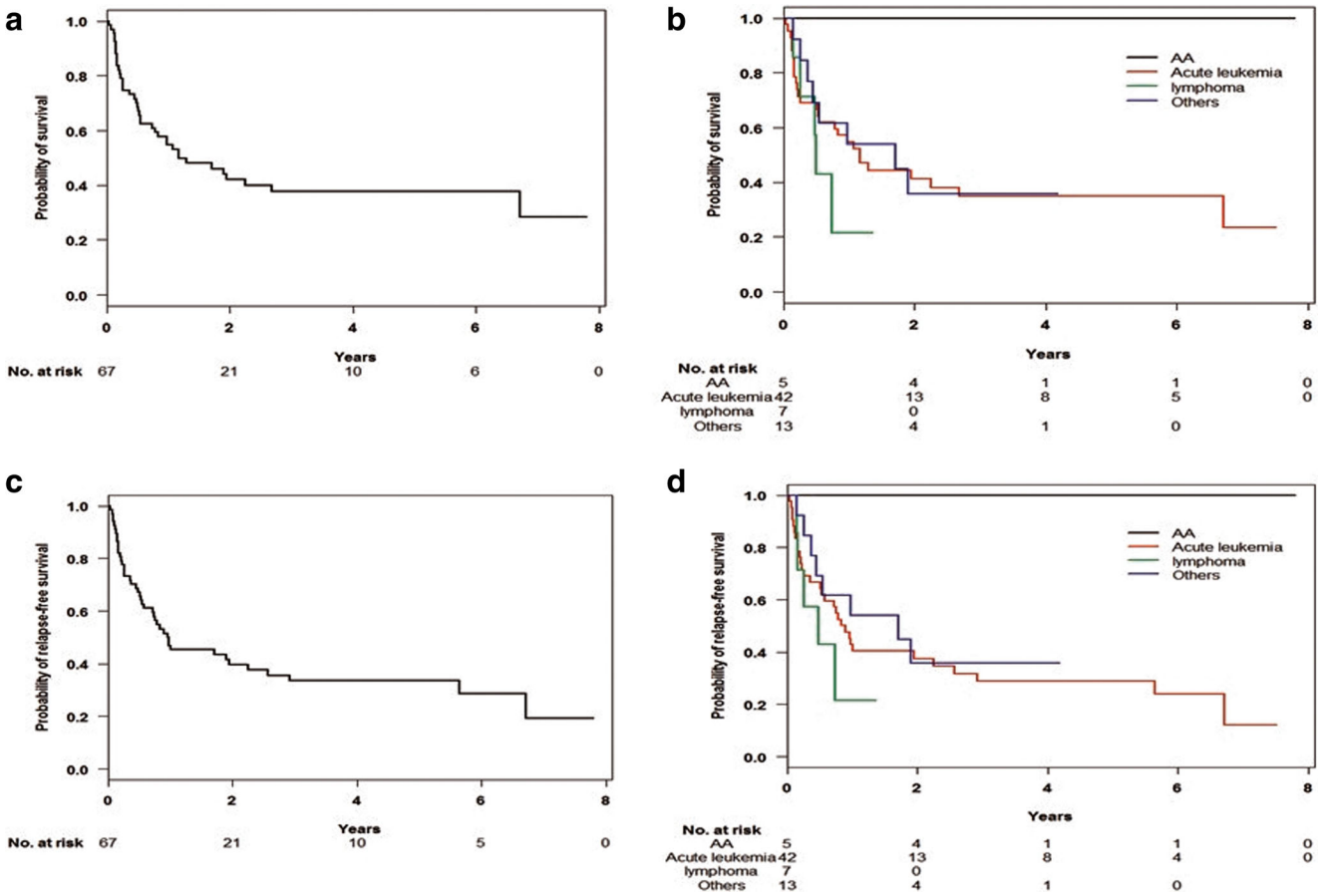

Fig. 1 Survival outcomes following HSCT from international donors. **a** Kaplan-Meier curve of OS of all patients. **b** Kaplan-Meier curves of OS according to the underlying disease. **c** Kaplan-Meier curve of RFS of all patients. **d** Kaplan-Meier curves of RFS according to the underlying disease. *AA* aplastic anemia

28.71% of the patients ($N = 58$) in the domestic donor group experienced an infection whereas 49.25% of the patients ($N = 33$) in the international donor group did ($p < 0.001$).

In terms of GVHD, the outcome was similar in the two groups. Acute GVHD developed in 42.1% of patients ($N = 85$) in the domestic donor group and 41.8% of patients ($N = 28$) in the international group ($p = 0.967$). Similarly, chronic GVHD developed in 34.2% of patients ($N = 69$) in the domestic donor group and 35.8% of patients ($N = 24$) in the international group ($p = 0.804$). In contrast to our conjecture that GVHD would be increased in the international group due to the differences in minor immunologic characteristics arising from differences in ethnicity, incidence of GVHD was not different between the groups (Fig. 4).

Comparison of expense by donor nationality

The average cost of searching for a donor using KMDP is $7884. In contrast, this average cost was $43,802 to find a donor from the USA and $32,413 to find one from Australia. These international searches are four- to fivefold more expensive than finding a domestic donor. The total expense over 1 year for a patient who received allogeneic HSCT was $33,359 in the domestic donor group and $78,554 in the international donor group. The cost gap between these two groups was larger when considering the entire follow-up period (Table 4). The detailed analysis of expenses revealed that the surcharge was mainly associated with the fees for admission, nursing, operation, and examination. This finding reflects more frequent medical examinations by a physician in the international donor group compared to the domestic donor group.

Discussion

This study is intended to analyze the clinical outcomes and medical costs of allogeneic HSCT from domestic and international donors. International donors have been traditionally considered the next option when there is no appropriate matched domestic donor, reflecting the clinician's preference for full-matched donors [14]. However, the ethnic composition of Korea, which shows notable homogeneity, raises doubt regarding the outcome of international donor HSCT. Theoretically, this doubt originates from the assumption that,

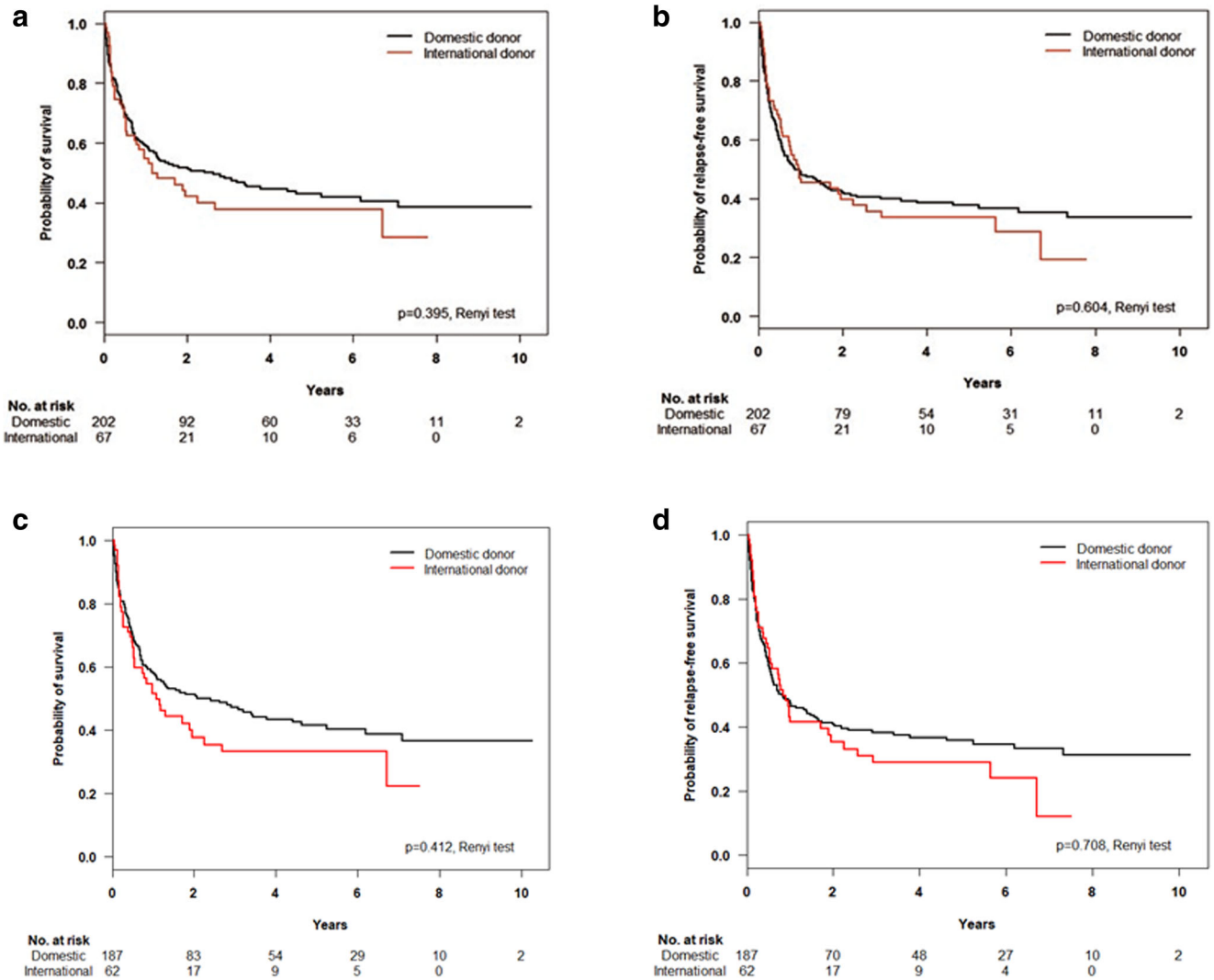

Fig. 2 Comparison of OS and RFS of allogeneic stem cell transplantation from domestic and international donors. **a** OS and **b** RFS of entire study population. **c** OS and **b** RFS of the patients after excluding the nonmalignant disease

in HSCT using international donors, mismatch in genes, including minor histocompatibility complex antigens, would negatively influence the result of HSCT [15–17]. Hence, the comparison between domestic and international donor HSCT is particularly critical in ethnically homogenous countries such as Korea to provide scientific basis for rational clinical judgment in donor selection for allogeneic HSCT. Here, we used propensity-score matching analysis to decrease bias and evaluated the effects of domestic versus international donors on clinical outcomes and cost of HSCT.

Table 2 Comparison of survival outcome by disease-risk index and conditioning regimen

	HR	Confidence internal	*p* value
Disease-risk index			
Low	1		
Intermediate	1.068	0.528–2.16	0.8549
High	1.955	0.912–4.19	0.0849
Very high	4.422	1.954–10.008	0.0004
Unknown	1.412	0.681–2.925	0.3535
Conditioning regimen			
Myeloablative	1		
Non-myeloablative	1.32	0.951–1.831	0.097

HR hazard ratio

First, the 5-year OS was greater than 35% in both groups, and there was no significant difference in OS or RFS between the international and domestic donor groups. These findings, which indicate that we can expect comparable outcomes with international donor transplantation events in the Korean homogeneous population, are the most important from this study. Recently, we conducted further study to compare haploidentical domestic donors with international donors and found that haploidentical donors are indeed a feasible alternative source in Korea [18]. We believe that our study

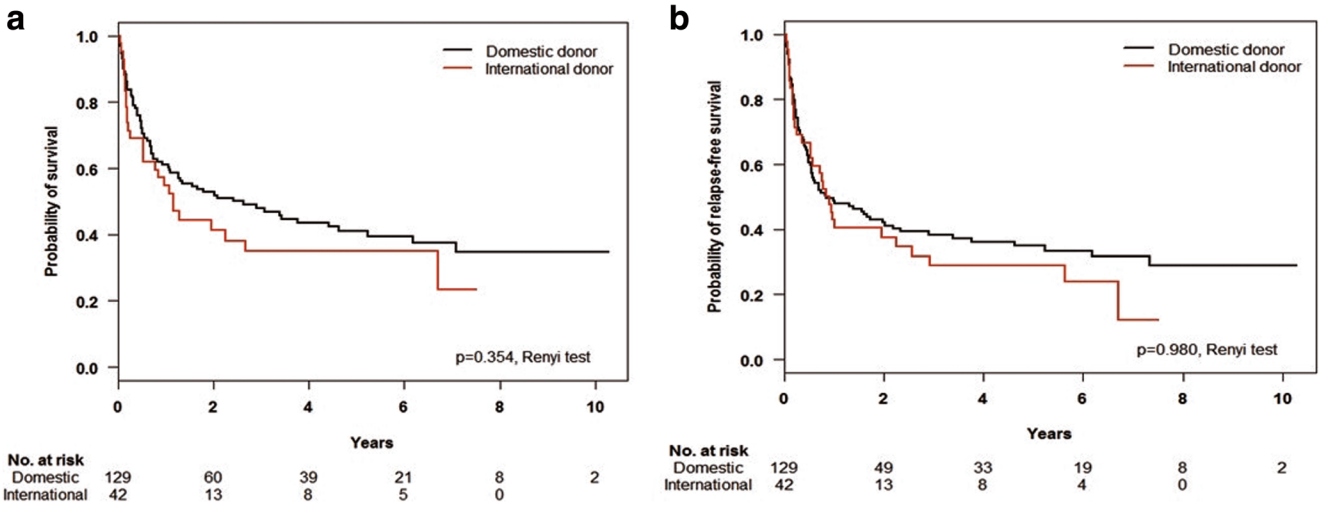

Fig. 3 Comparison of **a** OS and **b** RFS of allogeneic stem cell transplantation from domestic and international donors in leukemia patients

results support the clinical rationale for donor selection in homogeneous populations.

Second, with regard to transplant-related complications, we found no statistically significant differences in development of acute and chronic GVHD between patients who received HSCT from domestic donors and those who received HSCT from international donors. Although we observed a tendency for increased incidence of GVHD in the international donor group, these differences were not statistically significant. Thus, we concluded that minor immunologic differences originating from ethnic differences did not play a critical role in GVHD development in the Korean population. We also found that the severity and extent of GVHD did not differ between the two groups; but unfortunately, we cannot analyze the degree and extent of GVHD at the time of analysis.

Third, one of the most interesting findings was that infection within 30 days of transplantation was more prominent in the domestic transplantation group. This observation may be a reflection of patient status at the time of transplantation. Despite the propensity-score matching, it is possible that patients who underwent international allogeneic HSCT were in a more stable medical condition that enabled them to wait for the delayed donor search. Additionally, clinicians tend to provide hypervigilant medical services to patients who receive international donor HSCT due to fears of high rates of complications. In fact, detailed analysis of medical expenses showed a prominent gap in treatment and examination fees between the two groups, perhaps reflecting more aggressive laboratory testing and antibiotic use in the international group. In contrast, infection after 60 days of transplantation was more common in the international transplantation group, and this difference may originate from an underlying immunologic difference that renders patients more vulnerable to the delayed infection. Looking closely, we found that a substantial proportion of the infections during the early days following transplantation were caused by microbiologically proven bacterial infection or were classified as fever without any demonstrated organism, while fungal and viral infection markedly increased in the late-onset infections. Cytomegalovirus (CMV) was the most common viral pathogen among these later-developing cases. It has been reported that the seropositivity rate of CMV is relatively high in Korea [19], and 89% of the recipients of our study were seropositive to CMV in this study. Although donor CMV serostatus was not investigated in this study, donor CMV status may at least partially explain the difference in late infection between the groups. Another possible explanation is the disparity of the intensity and duration of immunosuppressive therapy. With clinician bias and overzealous GVHD prophylaxis among the patients who received the HSCT from international donors, these patients may have received prolonged immunosuppression, increasing their susceptibility to infection beyond the initial posttransplantation period. Hopefully, improved anti-infection prophylactic

Table 3 Comparison of death within 30 and 60 days from hematopoietic stem cell transplantation

	Domestic *N* (%)	International *N* (%)	*p* value
Within 30 days	15 (7.43)	2 (2.99)	0.255
Aplastic anemia	0 (0.00)	0 (0.00)	
Acute leukemia	7 (3.47)	2 (2.99)	
Lymphoma	6 (2.97)	0 (0.00)	
Other	2 (0.99)	0 (0.00)	
Within 60 days	29 (14.36)	9 (13.43)	0.851
Aplastic anemia	1 (0.50)	0 (0.00)	
Acute leukemia	15 (7.43)	7 (10.45)	
Lymphoma	8 (3.96)	1 (1.49)	
Other	5 (2.48)	1 (1.49)	

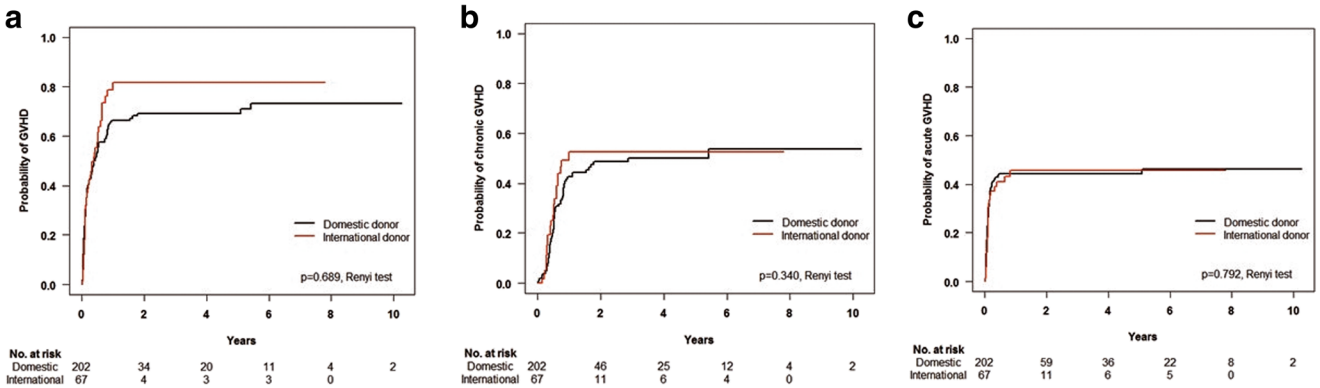

Fig. 4 Comparison of the cumulative incidence of **a** total, **b** chronic, and **c** acute GVHD with domestic and international donors

methods [20] during GVHD treatment will lower the infection rate during later periods post-allogeneic HSCT in this patient population in the future.

Lastly, there was a significant difference in medical expenses between domestic and international donor HSCT. The total gap in treatment cost for 1 year was approximately $50,000. This cost difference stems mainly from examination, admission, and treatment fees. So, it can be presumed that the patients in the international donor group underwent more tests and longer hospital stays. The high medical costs associated with international donors during the follow-up period may, at least in part, reflect more intense follow-up and medical engagement for this group of patients. Most importantly, more reasonable and streamlined follow-up based on objective medical needs rather than physician bias or anxiety is needed to establish follow-up care for these patients.

The cost difference, even though an increase is inevitable due to the international donor aspect, may burden the nationwide medical costs if HSCT from international donor increases. While making clinical decisions only in terms of cost effectiveness is not appropriate, the high cost of international donors should be considered now that there are cost-effective alternative sources, such as haploidentical and cord blood donors [21]. Furthermore, it should be noted that Korea is one of the countries where medical expenditure is low among Organization for Economic Co-operation and Development (OECD) countries, accounting for 7.7% of the gross domestic product (GDP) [22]. Considering the fact that the average medical expenditures of OECD countries account for 9.1% of their GDPs, we can easily presume that the cost difference between domestic and international HSCT would be even higher in other OECD countries, supporting further examination of these issues.

One limitation of this study is that we were not able to analyze the outcomes according to donor nationality. Subgroup analysis was not conducted to determine whether the outcome of HSCT from Asian donors is more favorable than other racial groups due to the limited number of patients for such analysis. There is a chance that a more favorable outcome would be observed with Asian donors than with European or American donors. We expect further detailed data analysis will be possible, enabling us to study subgroups of donor nationalities as the cases of international transplantation accumulate. In addition, we also need further analysis comparing the outcome of international donors with alternative donors to assist the physician's choice of donors in the absence of matched domestic donors.

In conclusion, we observed similar outcomes with international and domestic donors in terms of survival and treatment-related complication in HLA-matched HSCT in the Korean population and thus expect similar results for other ethnically homogenous populations. These findings should be considered carefully together with the high cost of using international donors in the era of various alternative donors.

Table 4 Comparison of medical expense of domestic and international donor stem cell transplantation

Period	Group	Number	Mean (USD)	Range (USD)	Median (USD)	*p* value*
Within 1 year	Domestic	98	33,362	3973–149,577	21,784	< 0.0001
	International	22	78,557	23,904–147,834	65,268	
	Difference		45,194	–	43,484	
Total follow-up	Domestic	98	52,870	3973–328,355	40,102	< 0.0001
	International	22	104,814	33,173–189,524	94,340	
	Difference		51,943	–	54,237	

SD standard deviation, *USD* US dollars

**p* value: *t* test for log-transformed cost

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Compliance with ethical standards

Conflict of interest Sang-A Kim declares that there is *no conflict of interest* regarding the work described in this article.

Jayoun Lee declares that there is *no conflict of interest* regarding the work described in this article.

Junho Moon declares that there is *no conflict of interest* regarding the work described in this article.

Hyewon Lee declares that there is *no conflict of interest* regarding the work described in this article.

Junho Jang declares that there is *no conflict of interest* regarding the work described in this article.

June-Won Cheong declares that there is *no conflict of interest* regarding the work described in this article.

Jeonghwan Youk declares that there is *no conflict of interest* regarding the work described in this article.

Yeonjoo Choi declares that there is *no conflict of interest* regarding the work described in this article.

Minkyung shin declares that there is *no conflict of interest* regarding the work described in this article.

Youngil Koh declares that there is *no conflict of interest* regarding the work described in this article.

Sangjin Shin declares that there is *no conflict of interest* regarding the work described in this article.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was waived due to the retrospective nature of this study.

References

1. Copelan EA (2006) Hematopoietic stem-cell transplantation. N Engl J Med 354(17):1813–1826. https://doi.org/10.1056/NEJMra052638
2. Norkin M, Wingard JR (2017) Recent advances in hematopoietic stem cell transplantation. F1000Res 6:870. https://doi.org/10.12688/f1000research.11233.1
3. Furst D, Muller C, Vucinic V, Bunjes D, Herr W, Gramatzki M, Schwerdtfeger R, Arnold R, Einsele H, Wulf G, Pfreundschuh M, Glass B, Schrezenmeier H, Schwarz K, Mytilineos J (2013) High-resolution HLA matching in hematopoietic stem cell transplantation: a retrospective collaborative analysis. Blood 122(18):3220–3229. https://doi.org/10.1182/blood-2013-02-482547
4. Oh HB, Kim SI, Park MH, Akaza T, Juji T (1999) Probability of finding HLA-matched unrelated marrow donors for Koreans and Japanese from the Korean and Japan Marrow Donor Programs. Tissue Antigens 53(4 Pt 1):347–349
5. Gragert L, Eapen M, Williams E, Freeman J, Spellman S, Baitty R, Hartzman R, Rizzo JD, Horowitz M, Confer D, Maiers M (2014) HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. N Engl J Med 371(4):339–348. https://doi.org/10.1056/NEJMsa1311707
6. Pappas DJ, Tomich A, Garnier F, Marry E, Gourraud PA (2015) Comparison of high-resolution human leukocyte antigen haplotype frequencies in different ethnic groups: consequences of sampling fluctuation and haplotype frequency distribution tail truncation. Hum Immunol 76(5):374–380. https://doi.org/10.1016/j.humimm.2015.01.029
7. Rivera-Franco MM, Leon-Rodriguez E, Castro-Saldana HL (2017) Costs of hematopoietic stem cell transplantation in a developing country. Int J Hematol 106:573–580. https://doi.org/10.1007/s12185-017-2278-1
8. van Agthoven M, Groot MT, Verdonck LF, Lowenberg B, Schattenberg AV, Oudshoorn M, Hagenbeek A, Cornelissen JJ, Uyl-de Groot CA, Willemze R (2002) Cost analysis of HLA-identical sibling and voluntary unrelated allogeneic bone marrow and peripheral blood stem cell transplantation in adults with acute myelocytic leukaemia or acute lymphoblastic leukaemia. Bone Marrow Transplant 30(4):243–251. https://doi.org/10.1038/sj.bmt.1703641
9. Blommestein HM, Verelst SG, Huijgens PC, Blijlevens NM, Cornelissen JJ, Uyl-de Groot CA (2012) Real-world costs of autologous and allogeneic stem cell transplantations for haematological diseases: a multicentre study. Ann Hematol 91(12):1945–1952. https://doi.org/10.1007/s00277-012-1530-2
10. Ballen KK, Gluckman E, Broxmeyer HE (2013) Umbilical cord blood transplantation: the first 25 years and beyond. Blood 122(4):491–498. https://doi.org/10.1182/blood-2013-02-453175
11. Luznik L, O'Donnell PV, Symons HJ, Chen AR, Leffell MS, Zahurak M, Gooley TA, Piantadosi S, Kaup M, Ambinder RF, Huff CA, Matsui W, Bolanos-Meade J, Borrello I, Powell JD, Harrington E, Warnock S, Flowers M, Brodsky RA, Sandmaier BM, Storb RF, Jones RJ, Fuchs EJ (2008) HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transplant 14(6):641–650. https://doi.org/10.1016/j.bbmt.2008.03.005
12. Passweg JR, Baldomero H, Bader P, Bonini C, Duarte RF, Dufour C, Gennery A, Kroger N, Kuball J, Lanza F, Montoto S, Nagler A, Snowden JA, Styczynski J, Mohty M (2017) Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. Bone Marrow Transplant 52:811–817. https://doi.org/10.1038/bmt.2017.34
13. Reisner Y, Hagin D, Martelli MF (2011) Haploidentical hematopoietic transplantation: current status and future perspectives. Blood 118(23):6006–6017. https://doi.org/10.1182/blood-2011-07-338822
14. Shin MK, Shin S, Lee JY, Koh Y (2017) Physicians' preferences and perceptions regarding donor selection in allogeneic stem cell transplantation in Korea when a matched domestic donor is not available. Blood research 52(1):31–36. https://doi.org/10.5045/br.2017.52.1.31
15. Goulmy E, Gratama JW, Blokland E, Zwaan FE, van Rood JJ (1983) A minor transplantation antigen detected by MHC-restricted cytotoxic T lymphocytes during graft-versus-host disease. Nature 302(5904):159–161
16. Khera N, Chang YH, Slack J, Fauble V, Leis JF, Noel P, Sproat L, Palmer J, Adams R, Fitch T, Northfelt D, Guy M, Tilburt J, Mikhael J (2015) Impact of race and ethnicity on outcomes and health care utilization after allogeneic hematopoietic cell transplantation. Leuk Lymphoma 56(4):987–992. https://doi.org/10.3109/10428194.2014.941834
17. Madbouly A, Wang T, Haagenson M, Paunic V, Vierra-Green C, Fleischhauer K, Hsu KC, Verneris MR, Majhail NS, Lee SJ, Spellman SR, Maiers M (2017) Investigating the association of genetic admixture and donor/recipient genetic disparity with transplant outcomes. Biol Blood Marrow Transplant 23(6):1029–1037. https://doi.org/10.1016/j.bbmt.2017.02.019
18. Park H, Lee YJ, Shin SJ, Lee J, Park S, Kim I, Moon JH, Lee H, Jang JH, Yoon SS, Koh Y (2018) Which donor is better when a matched donor is not available domestically? Comparison of

outcomes of allogeneic stem cell transplantation with haploidentical and international donors in a homogenous ethnic population. Leuk Res 69:31–38. https://doi.org/10.1016/j.leukres.2018.04.002

19. Jee Sook H, Sun Ju L, Wang Kyun P, Yun Woong K, Hyun OKK, Samuel YL (1990) A survey on the cytomegalovirus antibodies in blood donors and the diseased. Korean J Blood Transfus 1(1):21–33
20. Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, Greinix H, Morais de Azevedo W, Reddy V, Boparai N, Pedicone L, Patino H, Durrant S (2007) Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 356(4):335–347. https://doi.org/10.1056/NEJMoa061098
21. Apperley J, Niederwieser D, Huang XJ, Nagler A, Fuchs E, Szer J, Kodera Y (2016) Haploidentical hematopoietic stem cell transplantation: a global overview comparing Asia, the European Union, and the United States. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 22(1):23–26. https://doi.org/10.1016/j.bbmt.2015.11.001
22. OECD Health expenditure indicators