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The Impact of HLA and KIR Ligand Mismatching on Unrelated Allogeneic Hematopoietic Stem Cell Transplantation in Korean Adult Patients

Hyewon Park, M.D.[1,3,*], Eun Youn Rho, M.D.[1,*], Ji Won In, M.D.[1], Inho Kim, M.D.[2], Sung-Soo Yoon, M.D.[2], Seonyang Park, M.D.[2], Sue Shin, M.D.[1], Kyoung Un Park, M.D.[1], and Eun Young Song, M.D.[1]

Departments of Laboratory Medicine[1] and Internal Medicine[2], Seoul National University College of Medicine, Seoul; Laboratory Medicine[3], Seegene Medical Foundation, Seoul, Korea

Background: The impact of HLA and KIR ligand mismatching on the outcome of hematopoietic stem cell transplantation (HSCT) remains unclear. Previous reports have identified considerable ethnic differences in the impact of HLA and KIR ligand mismatches, as well as KIR ligand status, on HSCT; however, to date, no data has been acquired in Korean adult patients.

Methods: We investigated the association of high-resolution HLA matching on five loci (HLA-A, -B, -C, -DRB1, and -DQB1), KIR ligand mismatching, and KIR ligand status on the outcome of allogeneic HSCT from unrelated donors in 154 Korean adult patients treated at Seoul National University Hospital.

Results: In a multivariate analysis, less than 9/10 allelic matches in five HLA loci was an independent risk factor for acute graft-versus-host disease (GVHD) (grade II to IV) (P=0.019, odds ratio [OR]=2.7). In addition, HLA-A allele mismatching was increasingly prevalent in patients with acute GVHD compared to patients without (61.9% vs. 34.5%, P=0.06). For KIR ligand status, the patient and donor combination of both C1/C1 ligands showed better event-free and overall survival than combinations with C2 ligand patients or donors (P=0.048, P=0.034, respectively) by log-rank test.

Conclusions: Korean adult transplant patients with less than 9 of 10 HLA allele matches in the HLA-A, -B, -C, -DRB1, and DQB1 loci have a higher likelihood of developing acute GVHD (grade II to IV). Impact of KIR ligand status on clinical outcome should be further studied in a larger patient population.

Key Words: HLA, KIR ligand, Mismatch, Hematopoietic stem cell transplantation

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Corresponding author: Eun Young Song
Department of Laboratory Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea
Tel: +82-2-2072-0197
Fax: +82-2-3672-3337
E-mail: eysong1@snu.ac.kr

*These two authors contributed equally to this work.

INTRODUCTION

HLA-identical related donors are only available for approximately 25% of patients that require allogeneic hematopoietic stem-cell transplantation (HSCT). As such, HLA-matched unrelated donors are widely used [1]. The precise impact of HLA mismatching on unrelated HSCT remains unclear, particularly with regards to the relative importance of different HLA loci, as well as the significance of antigenic versus allelic mismatches [2]. Killer cell immunoglobulin-like receptor (KIR) ligand mismatches have been associated with a significant increase in overall survival, as well as better engraftment and a reduced incidence of graft-versus-host disease (GVHD) in patients with AML [3]; however, debates still exist on the impact of KIR ligand mismatch status in the outcome of unrelated HSCT [4, 5]. In addition, these effects vary greatly among different ethnic groups, especially in Japa-

nese patients [6, 7].

The HLA frequency distribution found in Koreans is most similar to that of the Japanese population [8, 9]. However, to the best of our knowledge, the effect of HLA or KIR ligand mismatching and KIR ligand status on the outcome of HSCT from unrelated donors in Korean adult patients has not yet been examined. In this study, we retrospectively assessed the impact of high-resolution donor-recipient mismatching at the HLA-A, -B, -C, -DRB1, and -DQB1 loci, as well as KIR ligand mismatching and KIR ligand status, on the clinical outcome of 154 Korean adult patients treated with unrelated HSCT.

METHODS

Patients receiving unrelated HSCT between April 2006 and December 2012 in Seoul National University Hospital were included in this study (n=154). Allele SEQR PCR/Sequencing kits for the HLA-A, -B, -C, -DRB1, and -DQB1 alleles were used for sequence-based typing (SBT) at the time of transplantation (all from Atria Genetics, South San Francisco, CA, USA). This study was approved by the institutional review board of Seoul National University Hospital (1309-068-521). Patients were categorized according to their HLA-inhibitory KIR ligand on the basis of their expression of (1) HLA-Bw4 or (2) HLA-Cw groups (C1 or C2) (Table 1) [10]. C1 alleles express Asn80 (such as -Cw1, -Cw3, -Cw7, -Cw8, -Cw12, -Cw12, -Cw14, -Cw16, etc.), whereas C2 alleles express Lys80 (such as -Cw2, -Cw4, -Cw5, -Cw6, -Cw15, -Cw17, -Cw18, etc.) [5]. KIR ligand mismatches were defined by the absence of one donor KIR ligand class I allele in the recipient [11]. For HLA-Cw groups, C1/C1 patients with C1/C2 donors, and C2/C2 patients with C1/C2 donors, were considered KIR ligand mismatches.

High-resolution HLA matching on the HLA-A, -B, -C, -DRB1, and -DQB1 loci, KIR ligand mismatch, and KIR ligand status were analyzed for their associations with the following clinical outcomes: patients' overall survival, event-free survival, relapse of underlying disease, and the occurrence and severity of acute or chronic GVHD [12]. Overall survival was defined as the time from graft infusion to death from any cause at time of analysis (Jun 1, 2014). For event-free survival, death or relapse was considered as events. Clinical characteristics of patients are shown in Table 1. Pre-HSCT patient risk status was classified by the European Group for Blood and Marrow Transplantation (EBMT) scoring system [13]. Antigen-level HLA mismatches were observed only at the HLA-C and -DQB1 loci in our study (Table 1).

Regression analysis was performed to assess the effect of different risk factors on clinical outcome. Categorical variables were analyzed by Chi-square and Fisher's exact tests. The Cox proportional hazard model was applied for multivariate analyses. Survival was analyzed by Kaplan-Meier with log-rank testing. All reported P values are 2-sided, and P value <0.05 was considered statistically significant. All analyses were performed by using SPSS Statistics 21.0 (IBM, Armonk, NY, USA).

RESULTS

Of the five HLA loci, allelic mismatches of >9/10 alleles was considered a risk factor for severe acute GVHD (Grade II-IV) by univariate analysis ($P=0.012$, hazard ratio [HR]=2.6), and was also an independent risk factor for severe acute GVHD (Grade II-IV) by multivariate analysis ($P=0.019$, HR=2.7) (Table 2). The frequency of mismatch at the HLA-A allele was increased in patients with acute GVHD compared to those without (61.9% vs. 34.5%, $P=0.06$), among one mismatched allele in unrelated HSCT (n=50) (Table 3). In contrast, the frequency of mismatch at other HLA loci (HLA-B, -C, -DRB1, and DQB1) failed to show any significant difference between the two groups.

In Cox proportional hazard model, acute GVHD (grade II-IV) was an independent risk factor for event-free survival ($P=0.008$, HR=2.0) and overall survival ($P=0.011$, HR=1.9) (Table 4). In our patient population, KIR ligand mismatch occurred in only five HLA-Cw group recipient-donor combinations (all of which were recipient C1/C1 and donor C1/C2; 5/154, 3.2%) (Table 1) and had no effect on clinical outcome (Table 4). For the analysis of KIR ligand status, recipient-donor combinations of both C1/C1 ligands showed an increased tendency for event-free and overall survival than recipient-donor combinations with C2 ligand (recipient C1/C2 or C2/C2 and donor C1/C2 or C2/C2) ($P=0.078$, $P=0.094$, respectively) but did not reach statistical significance (Table 4). In Kaplan-Meier survival analysis, C1/C1 recipient-donor combinations showed a significant increase in event-free and overall survival compared to C2 recipient-donor combinations (recipient C1/C2 or C2/C2 and donor C1/C2 or C2/C2) ($P=0.048$, $P=0.034$, respectively) (Fig. 1).

DISCUSSION

Previous studies have reported some ethnic variance in the relationship between HLA mismatching and HSCT patient outcome, especially in the Japanese population. Notably, a single HLA-A mismatch was considered to be a significant risk factor for survival (HR=2.27) in the Japanese Marrow Donor Program

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Table 1. Patient Characteristics

Characteristics	N (%)	
Gender (Male/Female)	94/60	
Age (mean; range)	37.1 (16-64)	
Disease		
ALL	32	20.8
AML	57	37.0
ABL	6	3.9
CML	3	1.9
MPD	8	5.2
SAA	17	11.0
MDS	18	11.7
Lymphoma	9	5.8
Others*	4	2.6
Source of stem cells		
Bone marrow	14	9.1
Peripheral blood	140	90.9
CMV IgG		
Positive	153	99.4
Negative	1	0.6
Conditioning regimen		
TBI	4	2.6
Non-TBI	150	97.4
EBMT risk score		
1	5	3.2
2	33	21.4
3	43	27.9
4	39	25.3
5	26	16.9
6	8	5.2
Allele-level HLA matches		
10/10	56	36.4
9/10	50	32.5
8/10	46	29.9
7/10	1	0.6
5/10	1	0.6
Ag-level HLA matches		
10/10	92	59.7
9/10	59	38.3
C Ag mismatch	36	23.4
DQ Ag mismatch	23	14.9
8/10†	3	1.9
KIR ligand status, patient‡		
C1/C1	108	70.1
C1/C2	44	28.6
C2/C2	2	1.3
Bw4/Bw4	28	18.2
Bw4/Bw6	73	47.4
Bw6/Bw6	53	34.4
KIR ligand status, donor‡		
C1/C1	114	74.0
C1/C2	37	24.0
C2/C2	3	1.9
Bw4/Bw4	28	18.2
Bw4/Bw6	73	47.4
Bw6/Bw6	53	34.4
KIR ligand combination (patient-donor)		
C1/C1-C1/C1	103	66.9
C1/C1-C1/C2§	5	3.2
C1/C2-C1/C1	11	7.1
C1/C2-C1/C2	32	20.8
C1/C2-C2/C2	1	0.6
C2/C2-C2/C2	2	1.3
Acute GVHD (grade II-IV)	75	48.7
Relapse	33	21.4
Overall Survival	91	59.1

*Others include NK cell lymphoma (n=2), hemophagocytic lymphohistiocytosis (n=1), and adult T cell leukemia lymphoma (n=1); †All three patients had one HLA-C antigen mismatch and one HLA-DQ antigen mismatch; ‡C1 alleles expressing Asn80 (such as -Cw1, -Cw3, -Cw7, -Cw8, -Cw12, -Cw12, -Cw14, -Cw16, etc.); C2 alleles expressing Lys80 (such as -Cw2, -Cw4, -Cw5, -Cw6, -Cw15, -Cw17, -Cw18,etc.); §KIR ligand mismatch was defined by the absence of one donor KIR ligand in the recipient. Patient C1/C1 and donor C1/C2 combination was the only KIR ligand mismatch in our study. The patient C2/C2 and donor C1/C2 combination was not observed in our study.
Abbreviations: ABL, acute biphenotypic leukemia; MPD, myeloproliferative disorder; SAA, severe aplastic anemia; EBMT, European Group for Blood and Marrow Transplantation; TBI, total body irradiation; CMV, cytomegalovirus; Ag, antigen; KIR, killer cell immunoglobulin-like receptor; GVHD, graft versus host disease.

(JMDP); however, single HLA-C mismatch was a risk factor in non-JMDP transplants (HR=1.68) [6]. In Japanese patients, HLA-A or -B mismatches significantly reduced survival, whereas mismatches at HLA-C or -DRB1/DQB1 did not [14]. In our study, less than nine allelic matches among five HLA loci were significantly associated with acute GVHD (grade II-IV). In addition, the

Table 2. Univariate and multivariate analysis of risk factors for acute GVHD (grade II-IV)

	Univariate		Multivariate	
	P	OR (95% CI)	*P*	OR (95% CI)
Recipient sex, female	0.352		0.548	
Recipient age	0.103		0.163	
Donor sex, female	0.982		0.838	
Donor age	0.684		0.885	
Disease at transplantation*	0.694		0.893	
Graft type, peripheral blood	0.754		0.957	
CMV IgG	0.280		0.199	
Conditioning, TBI-based	0.872		0.363	
EBMT risk score, ≥4	0.173		0.211	
HLA allelic matches, <9/10	0.012	2.6 (1.2-5.4)	0.019	2.7 (1.2-6.2)
Recipient and donor C1/C1	0.670		0.888	
Recipient Bw6 (+)	0.083		0.265	
KIR ligand mismatch	0.263		0.305	

*Disease at transplantation was grouped and described in Table 1.
Abbreviations: GVHD, graft versus host disease; OR, odds ratio; CI, confidence interval; EBMT, European Group for Blood and Marrow Transplantation; CMV, cytomegalovirus; KIR, killer cells immunoglobulin-like receptor.

Table 3. Associations of different HLA loci to acute GVHD (grade II -IV) among one-allele mismatched unrelated HSCT in Koreans (n=50)

	aGVHD (-) (n=29)	aGVHD (+) (n=21)	*P*	OR (95% CI)
	n (%)	n (%)		
HLA-A	10 (34.5)	13 (61.9)	0.06	3.1 (1.0-9.9)
B	1 (3.4)	1 (4.8)	1.00	
C	10 (34.5)	6 (28.6)	0.89	
DRB1	4 (13.8)	1 (4.8)	0.38	
DQB1	4 (13.8)	0 (0.0)	0.13	

Abbreviations: aGVHD, acute graft versus host disease; OR, odds ratio; CI, confidence interval.

Table 4. Multivariate analysis of risk factors for event-free and overall survival using Cox regression

	Event-free survival		Overall survival	
	P	HR (95% CI)	*P*	HR (95% CI)
Recipient sex, female	0.732		0.514	
Recipient age	0.002	1.0 (1.0-1.1)	<0.001	1.0 (1.0-1.1)
Donor sex, female	0.768		0.616	
Donor age	0.482		0.811	
Disease at transplantation*	0.873		0.588	
Graft type, peripheral blood	0.797		0.292	
CMV IgG	0.093		0.084	
Conditioning, TBI-based	0.836		0.674	
EBMT risk score, ≥ 4	0.612		0.594	
Acute GVHD (grade II-IV)	0.008	2.0 (1.2-3.4)	0.011	1.9 (1.2-3.3)
HLA allelic matches, <9/10	0.480		0.714	
Recipient and donor C1/C1	0.078		0.094	
Recipient Bw6 (+)	0.225		0.085	
KIR ligand mismatch	0.432		0.376	

*Disease at transplantation was grouped and described in Table 1.
Abbreviations: CMV, cytomegalovirus; TBI, total body irradiation; EBMT, European Group for Blood and Marrow Transplantation; GVHD, graft versus host disease; KIR, killer cells immunoglobulin-like receptor; HR, hazard ratio; CI, confidence interval.

association between HLA-A mismatching with acute GVHD (grade II-IV) is suspicious, since the other loci failed to show any association, somewhat similar to the previous Japanese reports [6, 14]. In a previous study of 1,047 Japanese patients with HLA-A2, a mismatch combination of HLA-A*02:01-*02:06, revealed inferior survival (HR=1.58) [7]. Non-permissive allelic mismatch combinations of A*02:06-A*02:01, A*02:06-A*02:07, A*26:02-A*26:01, and A*26:03-A*26:01 have been reported in Japanese patients [15]. Koreans are genetically most similar to Japanese [8, 9] and show more allelic diversity, particularly in HLA-A*02 and A*26 than Caucasians [8]. This causes higher allele-level mismatch frequencies of A*02 and A*26. In our study, 22 out of 23 HLA-A allelic mismatches were the result of mismatching at HLA-A*02 (n=16) or A*26 (n=6). In Koreans, those mismatches could be associated with acute GVHD and poor clinical outcome in unrelated HSCT and should be confirmed in a larger patient population.

Furthermore, KIR ligand mismatching was not associated with clinical outcome following unrelated HSCT in this study. Results from previous studies on the impact of KIR ligand mismatching in unrelated HSCT were highly variable, and ranged from highly beneficial to detrimental [17-24]. This was partly due to the differences in the methods used to analyze donor-versus-recipient NK-cell alloreactivity [25]. Differences in patient populations, underlying disease states, conditioning regimens, HLA match status, T-cell depletion, and post-transplant immunosuppressive regimens could also account for these discrepancies [5, 25]. In addition, there were also considerable ethnic differences in KIR gene and ligand frequencies [26]. In Koreans, the frequency of HLA-C2 ligand is much lower than that of Caucasians [8]. In our study, the portion of recipient-donor pairs with KIR ligand mismatch was very small (3.2%, 5/154), which may weaken the statistical power.

For the analysis of KIR ligand status, C1/C1 ligand patient-do-

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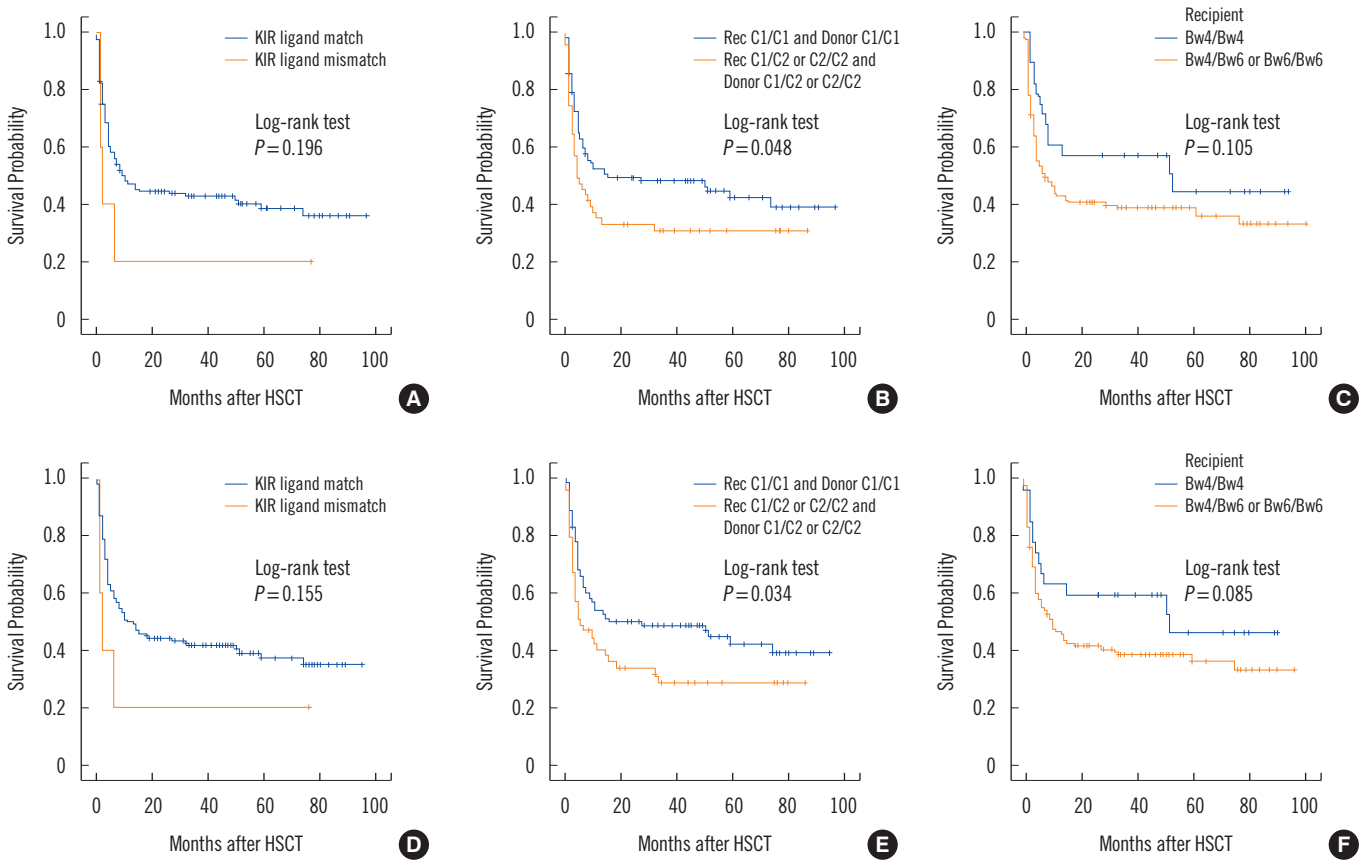

Fig. 1. Kaplan-Meier analysis of event-free and overall survival according to KIR ligand mismatch and ligand status following unrelated hematopoietic stem cell transplantation (HSCT) in Koreans. (A) Event-free survival in recipients with KIR ligand match (n=149) vs. KIR ligand mismatch (n=5), (B) Event-free survival in recipient-donor combination of both with C1/C1 (n=103) vs. recipients with C1/C2 or C2/C2 and donors with C1/C2 or C2/C2 (n=51), (C) Event-free survival in recipient with Bw4/Bw4 (n=28) vs. Bw4/Bw6 or Bw6/Bw6 (n=126), (D) overall survival in recipients with KIR ligand match (n=149) vs. KIR ligand mismatch (n=5), (E) overall survival in recipient-donor combination of both with C1/C1 (n=103) vs. recipients with C1/C2 or C2/C2 and donors with C1/C2 or C2/C2 (n=51), and (F) overall survival in recipient with Bw4/Bw4 (n=28) vs. Bw4/Bw6 or Bw6/Bw6 (n=126).
Abbreviation: Rec, recipient.

nor combinations showed an increase in event-free survival when compared to patient-donor combinations with C2 ligand (recipient C1/C2 or C2/C2 and donor C1/C2 or C2/C2). Further studies are needed with a larger patient population to confirm the impact of KIR ligand status on clinical outcome. In Germany, the increase in overall survival for patients with C1/C1 ligand was reported for those with AML/CML, but did not extend to those with ALL/NHL [20]. On the contrary, a study from the International Histocompatibility Working Group (IHWG) identified a lower rate of relapse in C1/C1 patients and to a similar extent in the AML, CML, and ALL subgroups [17]. In our study, the subgroup analyses failed to reach statistical significance (data not shown). The inconsistent results in ALL patients should be further clarified in future.

HLA-Bw4 ligand was not associated with clinical outcome in our study. A study on 264 cases of unrelated HSCT identified increased relapse rate and decreased overall survival in patients with Bw6/Bw6 ligand with donors with *KIR3DL1/3DS1*[22]. The basis for the association between C1/C1 or Bw4/Bw4 ligand and better overall survival is unclear. Early reconstitution of KIR repertoires has been reported following HSCT in NK cells with C1-specific *KIR2DL2/3* or Bw4-specific *KIR3DL1*, as compared to NK cells with C2-specific *KIR2DL1* [27-29], and may contribute to the better overall survival by facilitating the surveillance of HLA-C expression on leukemic or virus-infected cells. In addition, the affinities of inhibitory KIRs for their respective HLA-C ligands vary, with *KIR2DL1* exhibiting the strongest affinity and inhibitory signals [30]. As NK cell activation depends on a balance between inhibitory and activating signals, another explanation might be that donors with C2 ligand are less effective in activat-

ing leukemia-targeting NK cells than C1 ligand donors.

Despite the small number of cases in our study, all patients were treated at one center under uniform HSCT protocols. In conclusion, matches with less than 9 of 10 alleles from HLA-A, -B, -C, -DRB1, and DQB1 loci were associated with acute GVHD (grade II-IV) in Korean adult patients that received unrelated HSCT. The impact of KIR ligand status on clinical outcome was inconclusive and should be studied in a larger patient population.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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