Donor KIR genotype with KIR2DS3 and/or KIR3DS1 increases survival after non-T-cell depleted HLA-identical sibling hematopoietic stem cell transplantation for acute myeloid leukemia

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Abstract

Background: Natural killer (NK) cell allogeneic reaction, defined as lack of interaction between donor inhibitory killer cells immunoglobulin-like receptors (KIRs) and recipient human leukocyte antigen (HLA) class I molecules, missing KIR ligand, has been shown to affect T-cell depleted hematopoietic stem cell transplantation (HSCT) outcome. However, its influence on non-T-cell depleted setting is still unclear. In addition, the role of donor and recipient activating KIRs in transplant results needs to be more investigated. **Materials and Methods:** In this study, the impact of recipient and donor KIR and KIR ligand genotypes on HSCT outcome was evaluated in 40 transplants for acute myeloid leukemia (AML) and 38 transplants for acute lymphoblastic leukemia (ALL) in a non-T-cell depleted setting from HLA-identical sibling donor. As transplant endpoints, overall survival (OS), disease-free survival (DFS) and relapse were assessed in recipients in a five-year period. **Results:** Regarding 'missing KIR ligand' no impact was found on OS, DFS and relapse for AML and ALL recipients. In AML patients, however, presence of KIR2DS3 and/or KIR3DS1 in donor genotype was associated with a higher five-year OS (P=0.006) and DFS (P=0.021) in a univariate analysis. In these patients, multivariate analysis showed that transplantation using either KIR Bx genotype with KIR2DS3 and/or KIR3DS1 present in donor was related to a trend toward occurrence of cGVHD; although it did not reach to a significant level (P=0.092). **Discussion:** These findings may imply that 'missing KIR ligand' in recipient is of little importance in our matched non-T-cell depleted HSCT outcome. Whereas, presence of KIR2DS3 and/or KIR3DS1 in donor KIR genotype increases survival in AML patients.

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1. Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is an effective therapy for an increasing number of life-threatening hematological, oncological, hereditary and immunological diseases. HSCT outcome is dependent on several factors, including the type and stage of disease, conditioning regimen, degree of human leukocyte antigens (HLA) identity between donor and recipient, and development of graft versus host disease (GVHD). Recent studies with HLA-haploidentical transplantation revealed a potential role of NK cells in mediating enhanced anti-leukemic effect, decreased GVHD, and survival advantage of allogeneic HSCT (1-4).

Invoking donor-recipient killer immunoglobulin-like receptors (KIRs) ligand incompatibility as the basis for NK alloreactivity in HLA haploidentical transplants, several studies have supported the clinical concept of selecting donors for certain myeloid malignancies based on KIR ligand incompatibility in a graft-versus-host direction (1, 2, 5). Other studies examining the KIR ligand incompatibility concept in transplantation, however, have provided conflicting results (6-9). In addition, the impact of KIR ligand mismatching in unrelated HSCT has been associated with controversy (10, 11). Besides the confounding effect of heterogeneity in the transplantation protocols at different treatment centers (including disease type and status, graft sources, use of anti-thymocyte globulin (ATG) before transplantation and the degree of T-cell depletion), another reason for the conflicting results might be the differences in the definition of NK alloreactivity (12). NK alloreactivity was defined as a mismatch between the donor and recipient KIR ligands (mismatch KIR ligand) (1). Because KIR and HLA genes segregate independently, it is possible that

HLA-identical siblings may inherit different KIR genes. A logical extension of these findings is that the prediction of NK alloreactivity need not rely on HLA nonidentity between donor and recipient, but instead on the missing ligand in the recipient, a scenario that can be readily found even in HLA-identical allotransplantations (missing KIR ligand) (13).

Accordingly, Hsu et al investigated the impact of the missing KIR ligand condition in T cell-depleted HLA identical sibling HSCT and demonstrated it to be protective against relapse in cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) (14). Moreover, Cook et al reported a poorer survival for HLA-C2 homozygous patients with AML who received a transplant from a KIR2DS2-positive, HLA-identical sibling donor (15) and more recently, they reported an impact of donor activating KIRs on CMV reactivation (16).

The goal of our study was to test the hypothesis that HLA identical sibling transplant recipients who lack HLA ligands for their donor-inhibitory KIRs have differences in transplantation outcome. In this study, we analyzed the outcomes of patients with AML/ALL who received non-T-cell-depleted transplants from HLA-identical sibling donors, grouped according to lack or presence of recipient HLA ligand for donor-inhibitory KIR. Additionally, as the potential clinical significance of activating KIRs is receiving greater attention (17-21), we further examined whether the presence or absence of any individual activating KIR gene of the donor influenced the clinical outcome. Also, we analyzed the effects of donor and recipient KIR genotypes, number of activating KIR genes in donor compared to recipient's genotype, and KIR/HLA combinations on the clinical outcome.

2. Materials and Methods

2.1. Study subjects and samples

The institutional review board of the Bone Marrow Transplantation center of Shariati Hospital (Tehran, Iran) approved the use of patient samples for this study. All samples were collected with the written consent of the patients or of their legal guardians. Forty patients with AML and 38 patients with ALL receiving non-T-cell-depleted HSCT from HLA-identical siblings were included in this study. Sibling donors were selected prospectively based on matching genomic typing for HLA class I and II loci. Patient and donor DNA was prepared from peripheral blood leukocytes using the standard salting out method and used for HLA typing prior to transplantation and stored at -20°C. The quality and quantity of DNA was determined by ultraviolet spectrophotometry. Clinical information was obtained by reviewing medical records at transplant center.

2.2. Combined KIR-KIR ligand genotyping

All donor and recipient DNA samples were tested for the presence or absence of 17 KIR genes (2DL1, 2DL2, 2DL3, 2DL4, 2DL5A, 2DL5B, 2DS1, 2DS2, 2DS3, 2DS4, 2DS5, 3DL1, 3DL2, 3DL3, 3DS1, 2DP1 and 3DP1) and three major HLA class I KIR ligand groups: HLA-C1 (HLA-C with Asn80), HLA-C2 (HLA-C with Lys80) and HLA-Bw4 (i.e. HLA-B Bw4Ile80, HLA-B Bw4Thr80 and HLA-A Bw4). Genotyping was performed using PCR amplification with primers specific for each locus (PCR-SSP) as previously described (22, 23). KIR ligand genotype of donor and recipient pairs was reconfirmed by their HLA class I typing data.

2.3. Missing KIR ligand algorithm

Donor-recipient pairs were divided into two categories depending on the presence or absence of recipient KIR ligand for donor-inhibitory KIR. Combined KIR-KIR ligand genotyping for donors and recipients identified the presence or absence of KIR2DL1, KIR2DL2, KIR2DL3, and KIR3DL1 in the donors and HLA-C1 (HLA-C with Asn80), HLA-C2 (HLA-C with Lys80) and HLA-Bw4 (HLA-B Bw4Ile80, HLA-B Bw4Thr80 and HLA-A Bw4) in the recipients. KIR ligand presence was defined as the presence of recipient HLA epitopes for the identified donor-inhibitory KIR, and KIR ligand absence (missing KIR ligand) was defined as the absence of one or more recipient HLA epitopes for the identified donor-inhibitory KIR (14).

2.4. Donors and recipients genotype assignment

Samples with detection of at least 1 of the KIR B loci (KIR2DL5, 2DS1, 2DS2, 2DS3, 2DS5, or 3DS1) were assigned the genotype Bx. Samples lacking all KIR B loci were assigned the genotype AA (24).

2.5. Non-T-cell-depleted transplantation

Patient and donor characteristics are listed in Table 1. Patients did not receive ATG and total body irradiation (TBI) during the conditioning. All patients in this study underwent myeloablative therapy. Patients received standard conditioning regimen of Busulfan/cyclophosphamide. Peripheral blood stem cells (PBSC) served as the source of hematopoietic stem cells in all patients. All patients received GVHD prophylaxis with cyclosporine A and methotrexate after transplantation.

2.6. Clinical definitions

Overall survival (OS) was calculated from the time between transplantation and death as a result of any cause, whereas disease-free survival (DFS) was calculated from the time interval from HSCT to either relapse or death in remission, whichever

occurred first. Acute GVHD (aGVHD) and chronic GVHD (cGVHD) were diagnosed and graded according to previously reported criteria (25, 26).

Table 1. Patient and donor characteristics.

	Patients with AML No.(%)	Patients with ALL No.(%)
Age		
<18	13 (32.5)	14 (36.8)
≥18	27 (67.5)	24 (63.2)
Recipient/donor sex		
M/M	17 (42.5)	18 (47.4)
M/F	8 (20)	10 (26.3)
F/M	9 (22.5)	4 (10.5)
F/F	6 (15)	6 (15.8)
Recipient/donor CMV status		
Positive/Positive	24 (60)	21 (55.3)
Positive/Negative	6 (15)	7 (18.4)
Negative/Positive	4 (10)	4 (10.5)
Negative/Negative	6 (15)	6 (15.8)
Disease status		
CR1	29 (72.5)	25 (65.8)
CR2	6 (15)	12 (31.6)
CR3+	3 (7.5)	1 (2.6)
Refractory	1 (2.5)	0 (0.0)
Relaps	1 (2.5)	0 (0.0)
aGVHD		
Yes	33 (82.5)	32 (84.2)
No	7 (17.5)	6 (15.8)
aGVHD grade		
I	11 (33.3)	8 (25)
II	14 (42.4)	13 (40.6)
III	6 (18.2)	8 (25)
IV	2 (6.1)	3 (9.4)
cGVHD		
Yes	17 (42.5)	10 (26.3)
No	23 (57.5)	28 (73.7)
cGVHD grade		
Limited	15 (88.2)	6 (60)
Extensive	2 (11.8)	4 (40)

CMV: Cytomegalovirus; CR: Complete Remission.

2.7. Statistical analysis

The following endpoints were evaluated: OS, DFS, and relapse. The following clinical factors were evaluated for their effects on study endpoints: donor and recipient gender, age, CMV serological status, stage of disease at HSCT, aGvHD and cGVHD. Factors associated with KIR-KIR ligand genotype were as follows: missing KIR ligand, presence or absence of any individual activating KIR gene of the donor and KIR genotypes in donor and recipient, combination of donor activating KIRs and KIR ligands in the recipient, and number of activating KIR genes in the donor compared to the recipient's genotype. The probabilities of OS and DFS were estimated using the Kaplan-Meier method, whereas the rates of relapse were calculated as cumulative incidence, taking into account competing risks. The log-rank test was used to evaluate the univariate effects of KIR and KIR ligand genotype and clinical factors on OS and DFS. Relapse was compared between groups using Gray test. Finally, significant factors in univariate analysis ($P \leq 0.05$) were studied in multivariate analysis to examine reciprocal effects on each other.

3. Results

3.1. Univariate analysis of risk factors for survival

3.1.1. Influence of 'missing KIR ligand'

The distribution of KIR ligands missing for donor KIR is detailed in Table 2. 'Missing KIR ligand', in this cohort of patients, was not associated with any deleterious or beneficial effect on study endpoints (data not shown).

3.1.2. Influence of donor-activating KIR

When donor-recipient pairs were segregated based on the presence or absence of donor activating KIRs, there were differences in DFS for AML patients. Analysis of AML patients revealed a relative beneficial effect on DFS within the pairs with at least one activating KIR in the donor compared with pairs lack all activating KIRs in the donor ($P=0.1$, Table 3). To identify whether a specific donor activating KIR might have contributed to the increased survival seen in the AML patients, donor-recipient pairs was segregated according to the presence or absence of each donor-activating KIR genes (KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5 and KIR3DS1). Univariate analysis of AML patients revealed only a beneficial effects on OS within the pairs characterized by presence of KIR2DS3 ($P=0.05$, Table 3) and KIR3DS1 ($P=0.014$, Table 3) in the donor. The impact of an activating KIR gene presence in the donor in combination with existence of its HLA ligand in the recipient was also tested. That is, donor 2DS1 in presence of C2 ligand, donor 2DS2 in presence of C1 ligand, and donor 3DS1 in presence of HLA-Bw4 in the recipient. Indeed, one combination, donor KIR3DS1 and Bw4 in the recipient resulted in a higher OS in AML patients (Table 3).

3.1.3. Influence of donor and recipient KIR genotype

In this cohort, 28.2% of donors and 33.3% of recipients had the AA KIR genotype; the remainder had the Bx genotype. We analyzed the effect of donor and recipient KIR genotype on outcomes after HLA-identical sibling HSCT for AML and ALL. The donor and recipient KIR genotype had no effect on study end points (data not shown).

Table 2. Characteristics of KIR ligand absence in transplant patients.

	AML recipients with ligand absent no. (%)*	ALL recipients with ligand absent no. (%)**
HLA-C1 (HLA-C with Asn80) absent for donor KIR2DL2/3	7 (30.4)	7 (41.2)
HLA-C2 (HLA-C with Lys80) absent for donor KIR2DL1	9 (39.1)	4 (23.5)
HLA-Bw4 absent for donor KIR3DL1	3 (13)	2 (11.8)
HLA-Bw4 and HLA-C absent for donor KIR	4 (17.5)	4 (23.5)

*n = 23; 57.5% of the 40 AML patients in the study
**n = 17; 44.7% of the 38 ALL patients in the study

Table 3. Factors from univariate analysis found to affect OS and/or DFS for the AML patients.

	OS	DFS
	P value	P value
Donor activating KIRs	0.286	0.1
-At least one present		
-All absent		
Donor KIR2DS3	**0.05***	0.155
-Present		
-Absent		
Donor KIR3DS1	**0.014***	0.064
-Present		
-Absent		
Combination of donor KIR3DS1 and HLA-Bw4 in the recipient	0.061	0.197
-Present		
-Absent		
Donor genotype	**0.006***	**0.021***
-Bx genotype with KIR2DS3 and/or KIR3DS1 present		
-AA or Bx genotype with KIR2DS3 and KIR3DS1 absent		
Number of activating KIRs in the donor genotype	0.177	0.052
-More		
-Less or equal		
cGVHD	**0.024***	**0.033***
Yes		
No		

* $P \leq 0.05$; AML: Acute Myeloid Leukemia; OS: Overall Survival, DFS: Disease-free Survival.

After establishing that Bx genotype donors did not confer a survival advantage over AA donors, we performed further analyses. Indeed, the influence of individual donor KIR genes on survival outcomes was examined. Two activating KIRs showing independent effects on survival were KIR2DS3 and KIR3DS1. To assess the quantitative contribution of KIR2DS3 and/or KIR3DS1 to the favorable survival benefit using Bx donors, we compared donor AA or Bx genotype with KIR2DS3 and KIR3DS1 absent to

donor Bx genotype with KIR2DS3 and/or KIR3DS1 present. Transplantation using either KIR Bx genotype group with KIR2DS3 and/or KIR3DS1 present in donor was associated with significant improvements in OS (P=0.006, Table 3, Figure 1) and DFS (P=0.021, Table 3, Figure 2). Thus presence of KIR2DS3 and/or KIR3DS1 was uniquely responsible for the survival benefit (but not donor Bx genotype).

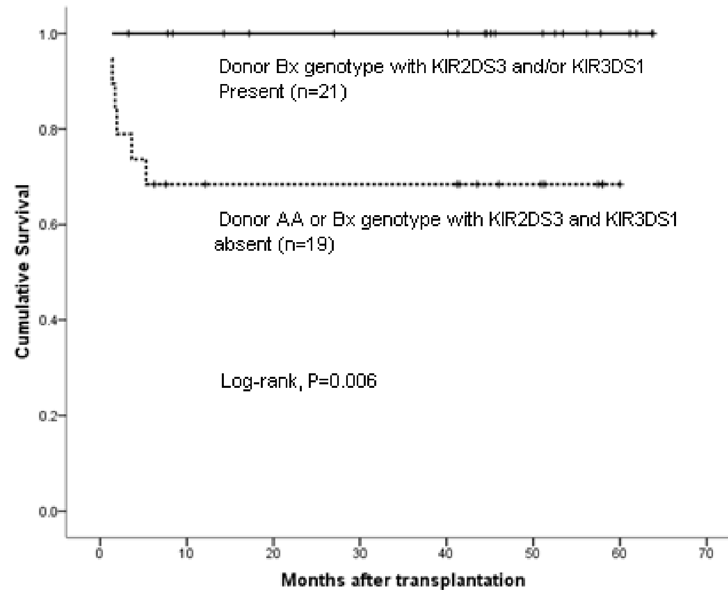

Figure 1. Overall survival of AML patients with donor Bx genotype having KIR2DS3 and/or KIR3DS1 compared to donor AA or Bx genotype without KIR2DS3 and KIR3DS1.

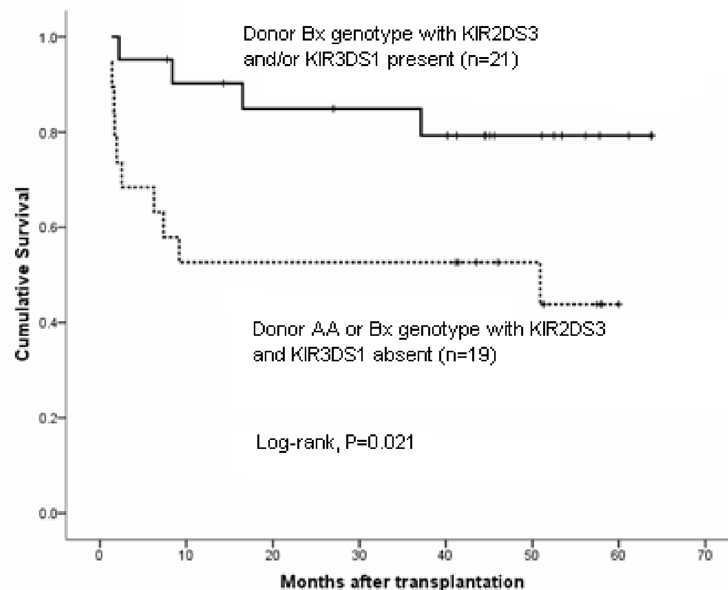

Figure 2. Disease-free survival of AML patients with donor Bx genotype having KIR2DS3 and/or KIR3DS1 compared to donor AA or Bx genotype without KIR2DS3 and KIR3DS.

In addition, the number of activating KIR genes present in the donor genotype without considering recipient genotype was not associated with any endpoints of the study. However, we performed an extensive evaluation for impact of disparity in all activating KIRs between donors and recipients on survival. We classified transplant pairs according to activating KIR genes of donors and recipients into two groups: greater number of activating KIR genes in the donor compared to the recipient and lesser or equal number of activating KIR genes in the donor compared to the recipient. DFS was higher in the cases with greater number of activating KIR genes in the donor (Table 3).

3.1.4. Influence of clinical factors

In this study, clinical factors had no effect on the transplantation outcomes. However, univariate analysis showed that only the occurrence or non-occurrence of cGVHD was effective on the five-year OS (P=0.024, Table 3) and DFS (P=0.033, Table 3) in AML patients.

3.2. Multivariate analysis of risk factors for survival

In AML patients, univariate analysis of KIR factors by the Kaplan-Meier method and Log-rank test showed that the presence or absence of KIR2DS3 or KIR3DS1 and genotype Bx with KIR2DS3 and/or KIR3DS1 in donor had an impact on OS and/or DFS. In these patients, of clinical factors, only the occurrence or non-occurrence of cGVHD was effective on OS and DFS. Also, univariate analysis by cumulative incidence method and Gray test showed that none of these factors had effect on relapse in AML patients. Then, above KIR factors were evaluated for cGVHD occurrence by multivariate analysis. This analysis showed that transplantation using either KIR Bx genotype group with KIR2DS3 and/or KIR3DS1 present in donor was related with a trend toward occurrence of cGVHD; although it did not reach to a significant level (P=0.092). Other multivariate comparisons revealed no association with survival in AML patients.

4. Discussion

The ‘‘missing self hypothesis’’, to explain the regulation of NK cell activation through its inhibitory receptors, has been examined with mixed results in patients who have undergone allogeneic HSCT (5, 8). The KIR ligand incompatibility model predicts inhibitory KIR-driven donor NK alloreactivity in the clinical situation, where HLA disparity between donors and recipients fulfills the criterion of ‘‘missing self’’ (1). Because KIR and HLA genotypes segregate independently of each other, the possibility exists for NK cells to exhibit KIR for which they have no HLA ligand, and conversely for persons to exhibit HLA ligands for which they have no KIR.

First, our study was designed to test the influence of ‘missing KIR ligand’ on OS and DFS following a non-T-depleted HLA-identical sibling HSCT. In contrast to previous studies (1-5, 14, 27), ‘missing KIR ligand’ was not found to be associated with any deleterious or beneficial effect on survival. A key issue in explaining differences between the KIR ligand incompatibility studies in HSCT could be donor T-cell depletion of the graft or the use of ATG during conditioning, or GVHD prophylaxis. All these treatments lead to in vivo depletion of donor T-cells during the early post-transplantation period, thus making apparent NK-cell alloreactivity. In fact, all reported studies showing a beneficial impact of KIR-ligand incompatibilities on relapse and survival are those studying transplants with donor T-cell depletion by $CD34^{+}$ selection, $CD3^{+}$ T-cell depletion (1, 5, 14) or to the use of ATG (27). It is established that the presence of T cells (28, 29) and immunosuppressants (30) both affect NK reconstitution post-HSCT and this may then negate the beneficial effect of NK alloreactivity. Here, we observed no benefit associated with missing KIR ligand, consistent with the previous studies of T cell-replete HSCT (31, 32).

The role of activating KIRs in a setting of both unrelated donor and HLA-identical sibling donor-HSCT has been a subject of numerous retrospective analyses (33, 34). Although in most cases activating KIRs were demonstrated to influence outcome, results were conflicting. The presence of particular receptors in donors was found to either increase (35, 36) or decrease (18, 37) the incidence of relapse as well as increase (19, 38) or decrease (39-41) the risk of GVHD. As a consequence, the presence of activating KIRs as well as donor/recipient incompatibilities resulted in either improved (39, 42) or deteriorated (19, 36, 41, 43) survival. Recent studies reported that survival was significantly higher after transplantation from a KIR Bx donor (24, 44) and Bx donors were associated with a higher incidence of cGVHD (24). Also, Cooly et al showed more recently that the B haplotype genes of the centromeric region had a stronger effect in improve survival of transplanted AML patients than those of the telomeric region (45). In contrast, in this study, increased survival in AML patients was associated with presence of KIR2DS3 and/or KIR3DS1 in the donor but not donor Bx genotype. We have previously showed decreased frequencies of KIR2DS3 and KIR3DS1 in AML patients compared to healthy individuals (21); thus it could propose that replacement of these genes in recipient by donor enhances NK cell recognition of certain ligands on

malignant myeloid cells. As in our AML patients we had only one case of relapse, this indicates that the increased survival in the presence of donor KIR2DS3 and/or KIR3DS1 has not been the result of decreased relapse. On the other hand, our univariate analysis results showed that occurrence of limited form of cGVHD has a beneficial effect on survival. Although, because of small sample size, we failed to show a significant association between the presence of donor KIR2DS3 and/or KIR3DS1 and the occurrence of cGVHD in a multivariate analysis (P=0.092), probably activating KIRs are similarly associated with the chronic inflammation that characterizes autoimmune diseases (46-48). Many observations (38-39) are consistent with the data presented here, which, in addition, emphasize the role of activating KIRs in survival. In fact, in this study we revealed that the impact of donor/recipient KIR genotypes was restricted to activating genes and not to inhibitory ones in donor or recipient.

In summary, we found that the presence of KIR2DS3 and/or KIR3DS1 in donors is the most important issue for better survival in our non-T-cell-depleted HLA-identical sibling HSCT. Therefore, selected donors with KIR genotypes containing KIR2DS3 and/or KIR3DS1 may provide an improved survival in non-T-cell-depleted HLA-identical sibling HSCT for AML patients.

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3/3/2013