REGULAR ARTICLE

blood advances

KIR B donors improve the outcome for AML patients given reduced intensity conditioning and unrelated donor transplantation

Daniel Weisdorf,[1] Sarah Cooley,[1,2] Tao Wang,[3,4] Elizabeth Trachtenberg,[5] Cynthia Vierra-Green,[4] Stephen Spellman,[4] Jennifer A. Sees,[4] Ashley Spahn,[4] Jenny Vogel,[4] Todd A. Fehniger,[6] Ann E. Woolfrey,[7] Steven M. Devine,[4,8] Maureen Ross,[9] Edmund K. Waller,[10] Ronald M. Sobecks,[11] Joseph McGuirk,[12] Betul Oran,[13] Sherif S. Farag,[14] Tsiporah Shore,[15] Koen Van Besien,[15] Steven G. E. Marsh,[16] Lisbeth A. Guethlein,[5] Peter Parham,[5] and Jeffrey S. Miller[1]

[1]Blood and Marrow Transplant Program, University of Minnesota, Minneapolis, MN; [2]Fate Therapeutics, San Diego, CA; [3]Division of Biostatistics, Medical College of Wisconsin, Milwaukee, WI; [4]Center for International Blood and Marrow Transplant Research, Minneapolis, MN; [5]Department of Structural Biology, Stanford University, Stanford, CA; [6]Division of Oncology, Department of Medicine, Washington University, St. Louis, MO; [7]Fred Hutchinson Cancer Research Center, Seattle, WA; [8]National Marrow Donor Program, Minneapolis, MN; [9]Roswell Park Cancer Center, Buffalo, NY; [10]Winship Cancer Institute, Emory University, Atlanta, GA; [11]Cleveland Clinic, Cleveland OH; [12]Kansas University Cancer Center, Kansas City, KS; [13]MD Anderson Cancer Center, Houston, TX; [14]Division of Hematology and Oncology, Indiana University, Bloomington, IN; [15]Cornell Weill Medical Center, New York, NY; and [16]Anthony Nolan Research Institute & UCL Cancer Institute, Royal Free Campus, London, United Kingdom

Key Points

- *KIR B* haplotype donors limit relapse after reduced intensity conditioning URD allotransplantation.
- All donor *KIR B* genes contribute to relapse protection in recipients having C1$^+$ HLA-C.

Natural killer (NK) cell recognition and killing of target cells are enhanced when inhibitory killer immunoglobulin-like receptors (KIR) are unable to engage their cognate HLA class I ligands. The genes of the *KIR* locus are organized into either *KIR B* haplotypes, containing 1 or more activating KIR genes or *KIR A* haplotypes, which lack those genes. Analysis of unrelated donor (URD) hematopoietic cell transplants (HCT), given to acute myeloid leukemia (AML) patients between 1988 and 2009, showed that *KIR B* haplotype donors were associated with better outcomes, primarily from relapse protection. Most of these transplants involved marrow grafts, fully myeloablative (MAC) preparative regimens, and significant HLA mismatch. Because the practice of HCT continues to evolve, with increasing use of reduced intensity conditioning (RIC), peripheral blood stem cell grafts, and better HLA match, we evaluated the impact of URD *KIR* genotype on HCT outcome for AML in the modern era (2010-2016). This analysis combined data from a prospective trial testing URD selection based on *KIR* genotypes (n = 243) with that from a larger contemporaneous cohort of transplants (n = 2419). We found that *KIR B* haplotype donors conferred a significantly reduced risk of leukemia relapse and improved disease-free survival after RIC, but not MAC HCT. All genes defining *KIR B* haplotypes were associated with relapse protection, which was significant only in transplant recipients expressing the C1 epitope of HLA-C. In the context of current HCT practice using RIC, selection of *KIR B* donors could reduce relapse and improve overall outcome for AML patients receiving an allogeneic HCT.

Introduction

After allogeneic hematopoietic cell transplant (HCT), natural killer (NK) cells are the first population of lymphocytes to reconstitute. Consequently, they can affect the outcome by promoting engraftment, preventing acute graft-versus-host disease (GVHD), contributing to a robust immune reconstitution, as well as limiting the risk of leukemic relapse.[1,2] NK cells secrete cytokines and mediate cell killing by direct

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natural cytotoxicity and through antibody-directed cellular cytotoxicity. Several families of activating and inhibitory NK cell receptors contribute to immunosurveillance by these innate immune system components, and the net signaling balance determines the NK cell response to damaged, virally infected, or malignant target cells. The highly polymorphic family of killer-cell immunoglobulin-like receptors (KIR), encoded on chromosome 19, has coevolved with the MHC class I family and has been well studied in the context of HCT.[3,4] In humans, inhibitory KIR (3DL1, 2DL2/3, and 2DL1) recognize the Bw4, C1, or C2 epitopes of HLA class I, respectively. These inhibitory ligand-receptor interactions govern the education and functional maturation of NK cells through the mechanism of missing self-recognition.[5,6] Mature NK cells mediate stronger effector functions when they encounter cells that have downregulated self HLA class I. This phenomenon is common to tumor cells and virally infected cells and is a mechanism that allows them to escape from T-cell recognition. Allogeneic HCT donors can have inhibitory KIR, for which the patient lacks the cognate ligand; during the patient's reconstitution, these alloreactive NK cells can provide a strong antileukemia response. This effect was first demonstrated by Velardi and coworkers in Perugia, who showed that patients receiving haploidentical HCT for leukemia were protected from relapse when the donor:recipient pair were KIR ligand mismatched.[7]

Subsequently, the importance of donor *KIR* gene haplotypes for the outcome of allogeneic transplants for acute myeloid leukemia (AML) was reported.[8,9] The *KIR A* haplotype is defined by a fixed content of genes, encoding 6 inhibitory KIR (KIR3DL3, 2DL3, 2DL1, 2DL4, 3DL1, 3DL2) and 1 activating KIR (KIR2DS4). The *KIR B* haplotypes are characterized by the presence of 1 or more of the genes encoding 5 activating KIR (*KIR2DS1*, *2DS2*, *2DS3*, *2DS5*, *3DS1*) and 2 inhibitory KIR (*2DL2*, *2DL5*). Previously, we showed that donors having *KIR B* haplotypes protect against relapse after myeloablative unrelated donor (URD) HCT for AML, but not for acute lymphocytic leukemia.[8,9] This protection was seen in both HLA-matched and HLA-mismatched transplants, with the strongest relapse protection occurring when the donor is homozygous for centromeric (*Cen*) *KIR B* haplotypes. We also reported that patients homozygous for HLA-C2 epitopes have the worst outcome, whereas the benefit of a *KIR B* donor was most pronounced when patients carried HLA-C1.[10] Other investigators[11,12] have reported a particular benefit associated with KIR2DS1$^+$ donors, especially in patients with HLA-C1. Here we analyze URD HCTs for AML that were all performed after 2010. This study included a cohort collected for a prospective trial of KIR donor selection (KIR DS)[13] and a larger contemporaneous group.

Methods

For the prospective KIR DS trial (2012-2016)[13] and the larger contemporaneous cohort (2012-2016), patient and donor demographics, transplant approach, and outcome data were collected through the Center for International Blood and Marrow Transplant Research (CIBMTR), using standard data collection processes and forms. Data were curated and error checked using CIBMTR procedures supplemented with the *KIR* genotyping data collected for the KIR DS prospective trial. *KIR* genotypes for the contemporaneous cohort of patients and donors (those patients and donors not in the prospective *KIR* DS trial) were collected retrospectively through the retrospective typing project of the National Marrow Donor Program (NMDP).[14] Donor *KIR* genotypes were used to assign *KIR AA* vs *B/x* haplotypes as previously reported.[8,9] Patients and donors provided consent for the data collection and subsequent analyses, with approval by participating institutions and the CIBMTR/NMDP institutional review board.

Using clinical and genotyping data from both our prospective KIR DS trial[13] and the contemporaneous cohort from the NMDP and CIBMTR, we evaluated the demographic and donor *KIR* genotype influences on outcomes, including relapse incidence, nonrelapse mortality (NRM), disease-free survival (DFS), and overall survival (OS). Unadjusted outcomes between groups with differing donor *KIR* genotypes were analyzed with an indicator variable for transplants in the prospective KIR DS trial vs the larger, contemporaneous cohort. Median follow-up of survivors was 36 months in the prospective trial and 44 months for the large contemporaneous cohort.

Clinical and demographic variables were evaluated for their impact on outcome analyses tested in univariate and multivariate analyses. Cox proportional hazards models were used to adjust for significant clinical factors. The proportional hazards assumption was evaluated using a time-dependent covariate method, and factors with nonproportional hazards were adjusted through stratification. Forward stepwise regression modeling was performed to identify clinical and patient factors that influenced transplant outcome: considering patient age, disease status, donor-recipient gender, gender match of donor and recipient, HLA match of donor and recipient, status for the C1 and C2 epitopes of HLA-C for donor and recipient, graft source (either bone marrow or filgrastim-stimulated peripheral blood stem cells [PBSC]), conditioning of the patient (either myeloablative [MAC] or reduced intensity conditioning [RIC]), with the latter including nonmyeloablative (NMA); cytomegalovirus (CMV) serostatus of donor and recipient; pretransplant Karnofsky performance score; antithymocyte globulin (ATG)/alemtuzumab use; GVHD prophylaxis; the use, or not, of total body radiation; the time from diagnosis to HCT; HLA-DP permissive mismatch; and year of HCT. Donor KIR genotype variables were tested separately by forcing each into the multivariate models. Interactions between KIR genotype variables and the adjusted clinical factors were tested, and no significant interactions were detected. Cases (or factors) were excluded from some models if outcome data or significant covariates were missing. To adjust for the multiple testing, the significance threshold of 0.05 was used for the donor KIR haplotypes, 0.025 for donor centromeric regions, and 0.007 (0.05 divided by 7) for the donor KIR genes. All analyses were done using SAS, version 9.4.

Results

Comparison of URD transplants performed in 1988-2009 to those performed in 2010-2016

In previous retrospective analyses, we showed that donors having 1 or 2 *KIR B* haplotypes protect against relapse of AML after URD HCT.[8,9] That study analyzed transplants performed before 2010 using myeloablative conditioning, predominantly marrow graft sources, and HLA- matching characteristics that were less stringent than currently used. Based on the observed advantage conferred by donors with *KIR B* haplotypes, we performed a multicenter prospective KIR DS trial between 2012 and 2016 to enrich for donors with favorable *KIR* haplotypes. In 535 searches, 2080 prospective donors were typed; 243 of these led to transplantation. The process

Table 1. Demographics: contemporaneous and prospective KIR DS trial cohorts

	Contemporaneous cohort		Prospective KIR DS trial	
	RIC/NMA	MAC	RIC/NMA	MAC
N	987	1432	96	147
No. of centers	98	109	10	15
Recipient age, y				
Median (range)	64 (20-84)	49 (20-76)	65 (28-78)	51 (20-75)
Recipient race/ethnicity				
White, non-Hispanic	897 (93)	1250 (89)	93 (97)	139 (95)
Recipient sex				
Male	544 (55)	707 (49)	54 (56)	73 (50)
Female	443 (45)	725 (51)	42 (44)	74 (50)
Karnofsky performance score				
90-100	525 (53)	987 (69)	55 (57)	98 (67)
10-80	450 (46)	425 (30)	41 (43)	49 (33)
HCT–comorbidity index scores				
0	210 (21)	401 (28)	13 (14)	26 (18)
1-3	502 (51)	756 (53)	51 (59)	67 (46)
4+	272 (28)	274 (19)	26 (27)	54 (37)
Recipient CMV serostatus				
Negative	335 (34)	460 (32)	39 (42)	61 (43)
Positive	645 (66)	962 (68)	53 (58)	81 (57)
Donor:recipient HLA allele match				
8/8	849 (86)	1196 (84)	88 (92)	135 (92)
7/8	138 (14)	236 (16)	8 (8)	11 (7)
HLA DP matching				
Fully matched	164 (17)	240 (17)	14 (18)	29 (23)
Permissive mismatch	481 (49)	687 (48)	43 (54)	55 (44)
Nonpermissive mismatch	340 (36)	501 (35)	23 (29)	40 (32)
Recipient C1 allele present				
Yes	866 (88)	1213 (85)	84 (88)	122 (83)
Graft type				
Marrow	79 (8)	274 (19)	11 (11)	33 (22)
PBSC	908 (92)	1158 (81)	85 (89)	114 (78)
Donor age				
Median (range), y	28 (18-61)	29 (18-61)	23 (23-23)	39 (27-50)
Conditioning regimen groups				
RIC/NMA: TBI ± other	177 (18)		29 (30)	
RIC/NMA: Flu/Clof ± other	399 (40)		5 (5)	
RIC/NMA: alkylator based	411 (42)		62 (65)	
MAC: TBI ± Bu or Cy or other		269 (19)		20 (14)
MAC: non-TBI		1164 (81)		127 (86)
ATG/alemtuzumab use				
ATG + alemtuzumab	0 (0)	1 (< 1)	0 (0)	0 (0)
ATG alone	385 (39)	569 (40)	27 (28)	24 (16)
Alemtuzumab alone	39 (4)	25 (2)	4 (4)	7 (5)
No ATG or alemtuzumab	562 (57)	836 (58)	65 (68)	116 (79)
Disease status at transplant				
Early	777 (79)	1084 (76)	69 (72)	79 (54)

Values are n (%) unless otherwise noted.
Bu, busulfan; Clof, clofarabine; Cy, cyclophosphamide; Flu, fludarabine.

Table 1. (continued)

	Contemporaneous cohort		Prospective KIR DS trial	
	RIC/NMA	MAC	RIC/NMA	MAC
Intermediate	210 (21)	348 (24)	13 (14)	28 (19)
Advanced	0 (0)	0 (0)	14 (15)	40 (27)
Cytogenetics				
Good	35 (10)	108 (20)	6 (7)	10 (8)
Intermediate	255 (72)	331 (62)	63 (69)	92 (70)
Poor	64 (18)	97 (18)	22 (24)	29 (22)
Unknown, n	633	896	5	16
Follow-up among survivors, mo				
No. evaluated	440	759	48	74
Median (range)	38 (6-99)	46 (2-98)	36 (12-73)	36 (12-72)
Donor KIR haplotype				
AA	319 (32)	454 (32)	18 (22)	39 (29)
B/x	668 (68)	978 (68)	65 (78)	96 (71)
Donor centromeric region score				
AA	455 (46)	689 (48)	32 (39)	61 (45)
AB	442 (45)	594 (41)	43 (52)	58 (43)
BB	90 (9)	149 (10)	8 (10)	16 (12)

Values are n (%) unless otherwise noted.
Bu, busulfan; Clof, clofarabine; Cy, cyclophosphamide; Flu, fludarabine.

for KIR donor selection and its capacity to enrich for favorable *KIR* haplotype donors has been published.[13] However, there has been no recent analysis to assess the effect of donor *KIR* haplotypes in the modern transplant era. Acknowledging that the modest size of our prospective KIR DS trial prohibited adequately powered evaluation, we addressed this important question with an analysis that included a contemporaneous (2010-2016) CIBMTR retrospective cohort. The supplemental cohort included 2419 transplanted AML patients with available *KIR* genotyping of the donors, none of whom were included in the prospective trial.

The patients enrolled in the prospective KIR DS trial group have similar characteristics to those in the larger contemporaneous cohort. Both cohorts included subgroups receiving MAC and RIC/nonmyeloablative conditioning and within each cohort those 2 groups had comparable race, gender, gender match, donor/recipient CMV serostatus, and HLA matching (Table 1). Nearly 60% of all HCTs did not include either ATG or alemtuzumab, which are known to bind and deplete, at least partially, reconstituting NK cells.[15] When comparing between conditioning regimens irrespective of cohort, a greater proportion of patients undergoing RIC received mobilized PBSC grafts, fewer had Karnofsky performance scores of 90% to 100% vs 10% to 80%, or comorbidity index scores of 0 to 3 vs 4+, and the median age was higher. Compared with the contemporaneous group, a smaller proportion of the KIR DS trial cohort were CMV seropositive, fewer had HLA $<$ 8/8 allele-matched donors, and nearly one-half had HLA-DP permissive mismatches in both cohorts. The frequency of donor *KIR* genotypes (*AA* vs *Bx*), including the centromeric regions was similar in the 2 cohorts.

We previously reported that MAC vs RIC intensity could differentially affect NK cell reconstitution,[10,13] which in turn correlated with clinical outcomes. After combining the contemporaneous and KIR DS trial cohorts, we then analyzed the MAC and RIC groups separately. We also considered interactions between donor KIR and recipient C1 and C2 epitopes, which influence the education and function of donor NK cells and could therefore affect clinical outcomes.[10,11] Recipient HLA-C types were similar in the 2 groups based on higher or lower intensity of conditioning, with homozygous expression of HLA-C2 group ligands (C2/C2) being observed in 15% of MAC patients vs 13% of the RIC patients (Table 2), similar to that observed in the general population. There were minor differences in the MAC recipients' HLA matching across the C1 or C2 subsets, but no differences in any other clinical characteristics, such as graft type, disease status, or cytogenetic risk within either MAC or RIC recipients C1 or C2 subsets.

Clinical outcomes

The overall unadjusted univariate outcomes for RIC vs MAC patients were similar, suggesting there were no underlying differences in selection between the contemporaneous and KIR DS trial cohorts (Table 3). Nearly all (98% to 99%) patients engrafted (data not shown) and only 11% to 13% died of nonrelapse, transplant-related mortality (NRM) by 6 months. The incidences of relapse based on conditioning (RIC vs MAC) were not significantly different in the 2 cohorts, leading to estimated 5-year survival rates of 39% and 44% in the RIC recipients and 49% and 45% in the MAC recipients for the contemporaneous and KIR DS trial cohorts, respectively. Similar 5-year DFS rates were observed (35% and 40% after RIC and 46% and 38% after MAC). None of these minor outcome differences between the prospective and retrospective cohorts were significant in either conditioning intensity subset. Because the demographic profiles and key clinical outcomes were consistent for

Table 2. Recipient HLA C1 group phenotyping

Variable	MAC recipients				RIC recipients			
	C1/C1, n (%)	C1/C2, n (%)	C2/C2, n (%)	*P**	C1/C1, n (%)	C1/C2, n (%)	C2/C2, n (%)	*P**
No. of patients	638 (40)	696 (44)	244 (15)		435 (40)	515 (48)	131 (13)	
No. centers	98	97	80		86	86	61	
Age, median (range), y	49 (20-76)	49 (20-75)	48 (20-73)	.84	64 (24-84)	64 (21-78)	64 (20-76)	.73
Donor recipient HLA allele matches				.01				.28
8/8	562 (88)	571 (82)	197 (81)		385 (89)	441 (86)	110 (84)	
7/8	76 (12)	124 (18)	47 (19)		50 (11)	74 (14)	21 (16)	
HLA DP				.387				.606
Fully matched	112 (18)	116 (17)	40 (17)		72 (17)	81 (16)	25 (19)	
Permissive mismatch	296 (47)	342 (50)	104 (43)		209 (49)	246 (49)	68 (53)	
Nonpermissive mismatch	216 (35)	229 (33)	96 (40)		148 (34)	178 (35)	36 (28)	
Graft type								.72
Marrow	122 (19)	138 (20)	47 (19)		37 (9)	40 (8)	13 (10)	
PBSC	516 (81)	558 (80)	197 (81)		398 (91)	475 (92)	118 (90)	
GVHD prophylaxis								
Tac ± others	595 (93)	643 (92)	215 (88)		363 (83)	423 (82)	109 (83)	.86
CSA ± others	42 (7)	53 (8)	29 (12)		72 (17)	91 (18)	22 (17)	
Conditioning regimen groups				.082				.887
RIC/NMA: TBI ± other					81 (19)	100 (19)	24 (18)	
RIC/NMA: Flu/Clof ± other					156 (36)	197 (38)	51 (39)	
RIC/NMA: alkylators					198 (46)	218 (42)	56 (43)	
MAC: TBI ± Bu or Cy or other	129 (20)	110 (16)	49 (20)					
MAC: non-TBI	509 (80)	586 (84)	195 (80)					
ATG/alemtuzumab use				.743				.292
ATG + alemtuzumab	1 (< 1)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
ATG alone	234 (37)	261 (38)	97 (40)		158 (36)	201 (39)	52 (40)	
Alemtuzumab alone	13 (2)	12 (2)	7 (3)		24 (6)	15 (3)	4 (3)	
No ATG or alemtuzumab	389 (61)	423 (61)	140 (57)		253 (58)	299 (58)	74 (57)	
Disease status at transplant				.44				.53
Early	467 (73)	512 (74)	183 (75)		341 (78)	409 (79)	95 (73)	
Intermediate	156 (24)	168 (24)	52 (21)		90 (21)	99 (19)	33 (25)	
Advanced	13 (2)	16 (2)	9 (4)		4 (1)	6 (1)	3 (2)	
Recipient cytogenetics				.73				.81
Good	51 (19)	45 (16)	22 (19)		15 (9)	21 (9)	5 (11)	
Intermediate	170 (62)	178 (64)	75 (66)		124 (71)	158 (71)	36 (77)	
Poor	52 (19)	56 (20)	17 (15)		36 (21)	43 (19)	6 (13)	
Donor KIR haplotype								.17
AA	183 (29)	225 (32)	85 (35)	.19	136 (32)	169 (33)	32 (25)	
Bx	446 (71)	469 (68)	158 (65)		292 (68)	341 (67)	98 (75)	
Donor centromeric regions score				.11				.37
AA	281 (45)	349 (50)	120 (49)		189 (44)	243 (48)	54 (42)	
AB	281 (45)	280 (40)	91 (37)		194 (45)	223 (44)	67 (52)	
BB	67 (11)	65 (9)	32 (13)		45 (11)	44 (9)	9 (7)	
Year of transplant								
2010	81 (13)	82 (12)	45 (18)	.10	52 (12)	52 (10)	11 (8)	.61
2011	90 (14)	93 (13)	28 (11)		43 (10)	63 (12)	23 (18)	

*The Pearson chi-square test was used for comparing discrete variables and Kruskal-Wallis for continuous variables.

Table 2. (continued)

Variable	MAC recipients				RIC recipients			
	C1/C1, n (%)	C1/C2, n (%)	C2/C2, n (%)	P*	C1/C1, n (%)	C1/C2, n (%)	C2/C2, n (%)	P*
2012	88 (14)	124 (18)	30 (12)		64 (15)	64 (12)	16 (12)	
2013	114 (18)	102 (15)	40 (16)		67 (15)	89 (17)	17 (13)	
2014	136 (21)	151 (22)	43 (18)		101 (23)	112 (22)	29 (22)	
2015	119 (19)	128 (18)	54 (22)		95 (22)	117 (23)	29 (22)	
2016	10 (2)	16 (2)	4 (2)		13 (3)	18 (3)	6 (5)	
Follow-up among survivors, mo								
No. evaluated	337	375	120		201	233	53	
Median (range)	42 (3-98)	46 (5-97)	45 (2-98)	.61	39 (6-99)	38 (10-97)	36 (12-96)	.48

*The Pearson chi-square test was used for comparing discrete variables and Kruskal-Wallis for continuous variables.

the contemporaneous and KIR DS trial cohorts, we combined them to test the effect of donor *KIR* haplotypes on clinical outcome, without significant bias. Statistical interactions between the prospective group and the contemporaneous, nonoverlapping larger retrospective cohort were tested for all reported outcomes.

Donor *KIR B* haplotypes provide relapse protection after RIC HCT

We previously reported that enhanced relapse protection and superior DFS are associated with donor *KIR B* haplotype in recipients of MAC URD HCT,[8-10] but we had not examined this question in the RIC setting. In addition, HCT procedures (and outcomes) have changed over time, reflecting progress in the field and highlighting the importance for analysis of considering the era in which the transplants were performed.[16] Notably, the previously studied cohorts[8-10] had markedly different demographics than the 2010 to 2016 cohort reported here. In our prior analyses, there were 1532 younger patients (median age, 38) with AML, all receiving MAC URD HCT between 1988 and 2009. Only 57% were HLA 8/8 allele matched; 53% received marrow grafts and a larger fraction (32% vs 2%) had advanced-stage AML (supplemental Table 1). The use of RIC, fully matched donors, and PBSC grafts were all substantially more frequent in the 2010 to 2016 cohort of HCTs. Consistent with improvements in the procedures of HCT and HLA matching, the overall outcomes were also improved in the more recently transplanted groups of patients.

In the combined 2010 to 2016 cohort, all multivariate analyses were adjusted for relevant covariates and for *KIR* genotyping variables. For the 1087 patients receiving RIC, use of a *KIR B* haplotype donor (*Bx* vs *AA*) significantly reduced the risk for relapse (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.62-0.97;$P = .026$; Table 4) and was nearly identical (HR, 0.78; 95% CI, 0.63-0.97, $P = .027$) if we excluded the prospective cohort. The favorable effect of the KIR B haplotype on relapse was significant in the fully HLA 8/8 matched group even after excluding the prospective smaller cohort (HR, 0.79; 95% CI, 0.63-0.98; $P = .033$ for Bx vs AA). Bx donors yielded improved DFS (HR, 0.84; 95% CI, 0.72-0.99; $P = .038$; Table 4) and led to small effects in improving OS (HR, 0.85; 95% CI, 0.71-1.01; $P = .069$; supplemental Table 2A), whereas having no significant influence on NRM or GVHD in the combined or only the retrospective cohort (data not shown). For the retrospective MAC cohort, we found that donors homozygous for centromeric *KIR B* haplotype groups were particularly effective in preventing relapse.[9] Among the RIC group, the protection afforded by donors with centromeric *KIR B* genes was similar for *Cen AB* and Cen *BB* and stronger than that observed with Cen AA donors. The combined *Cen AB* and *Cen BB*

Table 3. Post-HCT outcomes

	Contemporaneous cohort				Prospective KIR DS trial			
	RIC		MAC		RIC		MAC	
	n	Probability (95% CI)	n	Probability (95% CI)	n	Probability (95% CI)	n	Probability (95% CI)
Relapse	986		1431		96		147	
At 5 y		37 (33-40)		31 (28-33)		37 (27-47)		40 (31-49)
NRM	986		1427		96		146	
At 6 mo		11 (9-13)		11 (9-12)		13 (7-20)		11 (6-16)
DFS	986		1427		96		144	
At 5 y		35 (31-38)		46 (43-49)		40 (30-51)		38 (28-48)
Overall survival	987		1431		96		147	
At 5 y		39 (35-43)		49 (46-52)		44 (33-55)		45 (36-54)

Kaplan-Meier or competing hazards (relapse, NRM) estimates of outcomes with 95% CIs.

Table 4. Reduced intensity conditioning

Factor	n	Event	HR	HR low	HR upper	*P*
Relapse						
Donor KIR haplotype						**.026***
AA	334	130	1			
BX	730	240	0.77	0.62	0.97	**.026**
Cytogenetics						**.0025***
Disease status						**.0001***
Early	837	277	1			
Intermediate	218	87	1.34	1.05	1.72	**.019**
Advanced	9	6	3.97	1.88	8.36	**.0003**
ATG/alemtuzumab						**.021**
No ATG/alemtuzumab	617	207	1.00			
ATG alone	404	155	1.18	0.88	1.56	.28
Alemtuzumab alone	43	8	0.59	0.36	0.96	**.035**
HLA-DP mismatch						**.54**
Fully matched	178	66	1.00			
Mismatch	872	299	0.99	0.73	1.24	.94
Missing	14	5	1.29	0.77	2.15	.33
Donor KIR centromeric regions						**.051***
AA	483	183	1.00			
AB	483	155	0.77	0.61	0.98	.035
BB	98	32	0.77	0.54	1.09	.14
Cytogenetics						**.0024***
Disease status						**<.0001***
Early	837	277	1.00			
Intermediate	218	87	1.37	1.06	1.75	.014
Advanced	9	6	4.08	1.95	8.51	.0002
ATG/alemtuzumab						**.029**
No ATG/alemtuzumab	617	207	1.00			
ATG alone	404	155	1.16	0.87	1.54	.32
Alemtuzumab alone	43	8	0.59	0.36	0.98	.043
HLA-DP mismatch						.49
Fully matched	178	66	1.00			
Mismatch	872	299	0.98	0.72	1.33	.89
Missing	14	5	1.30	0.78	2.15	.31
DFS						
KIR B haplotype						.038
AA	334	214	1.00			
BX	728	423	0.84	0.72	0.99	.038
HLA matched alleles						**.042**
7/8	145	106	1.00			
8/8	917	531	0.78	0.61	0.99	.042
Cytogenetics						**.0012**
Donor age						.053

Stratified variables: Karnofsky performance score. Poor risk cytogenetics significantly associated with risks of relapse in RIC and MAC adjusted for other covariates. Bolded *P* values are independently significant $P < .05$.

*Adjusted multivariate analysis for the end points shown stratified as indicated.

Table 4. (continued)

Factor	n	Event	HR	HR low	HR upper	*P*
Disease status						**.022**
Early	836	487	1.00			
Intermediate	218	142	1.18	0.98	1.43	.085
Advanced	8	8	3.01	1.22	7.40	.017
Recipient age, y						.20
20-29	23	13	1.00			
30-39	29	15	0.69	0.33	1.44	.32
40-49	57	33	0.98	0.52	1.83	.95
50-59	198	116	0.97	0.58	1.64	.92
≥60	755	460	1.07	0.64	1.80	.80
Recipient CMV status						**.035**
ATG/alemtuzumab						.31
No ATG/alemtuzumab	615	363	1.00			
ATG alone	404	245	1.04	0.85	1.27	.71
Alemtuzumab alone	43	29	1.22	0.95	1.58	.12
HLA-DP mismatch						.10
Fully matched	178	109	1.00			
Mismatch	871	519	1.06	0.84	1.34	.64
Missing	13	9	1.69	1.10	2.60	.017
Donor KIR centromeric regions						**.034**
AA	482	308	1.00			
AB	483	278	0.82	0.70	0.96	.016
BB	97	51	0.76	0.56	1.02	.069
HLA matched alleles						.057
7/8	145	106	1.00			
8/8	917	531	0.79	0.61	1.01	.057
Cytogenetics						**.0009**
Donor age						.054
Disease status						**.013**
Early	836	487	1.00			
Intermediate	218	142	1.20	0.99	1.45	.064
Advanced	8	8	3.06	1.28	7.31	.012
Recipient age, y						
20-29	23	13	1.00			
30-39	29	15	0.68	0.32	1.44	.31
40-49	57	33	0.96	0.52	1.80	.91
50-59	198	116	0.96	0.57	1.62	.88
≥60	755	460	1.05	0.62	1.77	.85
Recipient CMV status						.052
ATG/alemtuzumab						.25
No ATG/alemtuzumab	615	363	1.00			
ATG alone	404	245	1.03	0.84	1.26	.79
Alemtuzumab alone	43	29	1.24	0.96	1.60	.10

Stratified variables: Karnofsky performance score. Poor risk cytogenetics significantly associated with risks of relapse in RIC and MAC adjusted for other covariates. Bolded *P* values are independently significant $P < .05$.

*Adjusted multivariate analysis for the end points shown stratified as indicated.

Table 4. (continued)

Factor	n	Event	HR	HR low	HR upper	P
HLA-DP mismatch						.036
Fully matched	178	109	1.00			
Mismatch	871	519	1.05	0.83	1.33	.66
Missing	13	9	1.71	1.13	2.58	.011

Stratified variables: Karnofsky performance score. Poor risk cytogenetics significantly associated with risks of relapse in RIC and MAC adjusted for other covariates. Bolded *P* values are independently significant $P < .05$.

*Adjusted multivariate analysis for the end points shown stratified as indicated.

donors vs *Cen AA* donors has a HR of 0.77 (95% CI, 0.62-0.96; $P = .018$) for relapse and HR of 0.81 (95% CI, 0.69-0.95; $P = .010$) for DFS. There were no significant interactions between these RIC donor effects prospective KIR DS cohort and the larger group for all end points studied.

No significant associations between donor telomeric *KIR* haplotypes and NRM or GVHD outcomes were observed (data not shown). Additionally, neither ATG/alemtuzumab use nor permissive (or non-permissive) mismatching for HLA-DP (clinical elements previously reported to influence HCT outcomes) had significant influence on relapse in RIC recipients (Table 4).

In marked contrast to our earlier analyses,[8-10] this evaluation of 1552 MAC transplants found no significant influence of donor *KIR B* haplotypes on any of the clinical end points, including OS, DFS, relapse, NRM, acute or chronic GVHD, and engraftment (Table 5 [DFS, relapse]; supplemental Table 2B [OS]), and data not shown (NRM, GVHD). Additionally, there were no significant interactions between the prospective KIR DS cohort and the larger group. As expected, cytogenetics and disease status significantly influenced the risk of relapse for patients in both the RIC and MAC cohorts, confirming the dominance of underlying disease characteristics to predict disease control with URD HCT in the current era.

DFS was significantly improved in patients with HLA-matched donors and in patients with early or intermediate AML disease status. Age and the recipients' CMV serostatus were not independently associated with DFS, although younger age favored better OS after MAC HCT (Table 5; supplemental Table 3B). None of the other donor *KIR* parameters influenced the risks of NRM, acute or chronic GVHD or the time to neutrophil engraftment (data not shown) and there were no significant interactions between the KIR B haplotype and HLA 8/8 matching for any of the end points studied.

Recipients with C1 epitopes of HLA-C benefit most from donor *KIR B* haplotype HCTs

In this analysis, we observed that donor *KIR B* haplotypes were favorable for RIC HCTs, but not for MAC HCTs. Therefore, we explored the RIC group further. The education and long-term functional response of NK cells is strongly influenced by interactions between inhibitory KIR receptors and self-HLA class I. KIR2DL1/S1 recognizes HLA-C2, whereas KIR2DL2/L3 recognizes HLA-C1 and KIR3DL1 recognizes Bw4. We evaluated the 935 RIC recipients (Table 6; Figure 1) having at least 1 C1 epitope of HLA-C (C1/x) compared with those homozygous for HLA-C2 (C2/C2). The strong relapse protection with donor *KIR Bx* haplotypes is maintained in HLA-C1/x recipients (HR, 0.76; 95% CI, 0.61-0.97; $P = .024$, Table 6). In marked contrast, no protective effect of *KIR Bx* haplotypes for C2/C2 recipients was observed (Table 6). No effects of recipient C1/x and/or donor *B* haplotype on outcomes were observed for the MAC HCT recipients (data not shown).

Other researchers have reported improved survival for HCT patients having at least 1 HLA C1 epitope compared with C2/C2 homozygous patients,[11,17-19] particularly if the donor also has KIR2DS1.[12,20] In adjusted multivariate analysis, we observed that donor *KIR2DS3* and *2DL5* genes defining *B* haplotypes provide significant protection against relapse in RIC HCT (supplemental Table 3A). The other *KIR B*-defining genes had similar effects on relapse that did not reach statistical significance. These effects were not apparent in the absence of the C1 epitope of HLA-C (supplemental Table 3B). No relapse protection was observed in recipients homozygous for C2 epitopes (all $P > .48$; data not shown), although the small size of the C2 homozygous cohort precludes definitive analysis. In RIC HCTs, similarly favorable relative risks (RR) for improved DFS were observed with *KIR2DS3* (supplemental Table 3A). Donor *KIR2DS3* conferred the strongest association with protection against relapse (RR, 0.61; 95% CI, 0.47-0.79; $P = .0001$) and DFS (RR, 0.76; 95% CI, 0.62-0.92; $P = .0054$). Like the other *KIR B* genes, donor *KIR2DS1* and other *KIR B* defining genes were associated with relapse protection, yet these effects were not significant after adjustment for multiple testing. Donor *KIR2DS1* was not associated with significant effects on DFS or OS. In MAC HCT, none of the individual genes that define *KIR B* showed any effect on relapse, DFS, or OS (supplemental Table 3A) either in the whole cohort or in those with C1/x recipients (supplemental Table 3B).

Discussion

The interaction of donor *KIR* and recipient class I HLA in URD transplantation for AML is complex. As we previously reported, the donor *KIR B* haplotype and particularly the *Cen B* region reduce the risk of relapse and improve DFS.[8-10,13] In the analysis reported here, the beneficial effect of donor *KIR B* haplotypes was observed only for the transplant patients given RIC, whereas no significant *KIR* gene associations with outcome were observed for MAC transplants. The different results obtained in this study (2010-2016) compared with the earlier cohort (1988-2009), which comprised only MAC HCTs,[8-10] prompted us to examine the demographic features that distinguish the 2 transplant cohorts (supplemental Table 1).

Consistent with current practice standards for HCT, 40% of the later cohort received RIC. The recipients were all older, but they

Table 5. Myeloablative conditioning

Factor	n	Event	HR	HR low	HR upper	*P*
Relapse						
Donor KIR haplotype						.77*
AA	490	153	1.00			
BX	1060	306	0.97	0.82	1.16	.77
Cytogenetics						**.0035***
Disease status						**<.0001***
Early	1148	337	1.00			
Intermediate	370	104	1.09	0.86	1.38	.4822
Advanced	32	18	3.93	1.90	8.14	.0002
ATG/alemtuzumab						.019
No ATG/alemtuzumab	930	258	1.00			
ATG alone	589	190	1.25	1.05	1.49	**.012**
Alemtuzumab alone	31	11	1.43	0.85	2.40	.18
HLA-DP mismatch						.55
Fully matched	267	84	1.00			
Mismatch	1264	370	0.92	0.76	1.12	.42
Missing	19	5	0.74	0.39	1.40	.35
Donor KIR centromeric regions						.23*
AA	744	237	1.00			
AB	644	173	0.86	0.73	1.02	.093
BB	162	49	1.03	0.77	1.37	.86
Cytogenetics						**.0045***
Disease status						**.0003**
Early	1148	337	1.00			
Intermediate	370	104	1.09	0.86	1.38	.50
Advanced	32	18	4.02	1.94	8.33	.0002
ATG/alemtuzumab						**.016**
No ATG/alemtuzumab	930	258	1.00			
ATG alone	589	190	1.26	1.06	1.50	.010
Alemtuzumab alone	31	11	1.42	0.86	2.33	.17
HLA-DP mismatch						.57
Fully matched	267	84	1.00			
Mismatch	1264	370	0.93	0.77	1.12	.44
Missing	19	5	0.74	0.39	1.41	.36
DFS						
KIR B haplotype						.40
AA	489	245	1.00			
BX	1057	541	1.07	0.91	1.25	.40
HLA matched alleles						**.0078**
7/8	245	141	1.00			
8/8	1301	645	0.77	0.63	0.93	.0078
Cytogenetics						**.0041**
Donor age						.40

Stratified variables: Karnofsky performance score. Poor risk cytogenetics significantly associated with risks of Relapse in RIC and MAC adjusted for other covariates. Bolded *P* values are independently significant $P < .05$.

*Adjusted multivariate analysis for the end points shown stratified as indicated.

Table 5. (continued)

Factor	n	Event	HR	HR low	HR upper	*P*
Disease status						**<.0001**
Early	1147	566	1.00			
Intermediate	369	196	1.20	1.03	1.40	.019
Advanced	30	24	2.76	1.60	4.77	.0003
Recipient age, y						**.0058**
20-29	194	78	1.00			
30-39	251	119	1.23	0.97	1.55	.084
40-49	367	175	1.26	0.95	1.65	.10
50-59	467	247	1.41	1.11	1.77	.0040
≥60	267	167	1.72	1.27	2.32	.0005
Recipient CMV status						.23
ATG/alemtuzumab						.81
No ATG/alemtuzumab	929	474	1.00			
ATG alone	586	295	1.02	0.89	1.17	.79
Alemtuzumab alone	31	17	1.16	0.72	1.87	.53
HLA-DP mismatch						.78
Fully matched	265	141	1.00			
Mismatch	1262	635	0.95	0.81	1.11	.49
Missing	19	10	0.93	0.59	1.46	.74
Donor KIR centromeric regions						.72
AA	742	382	1.00			
AB	643	321	0.99	0.84	1.17	.93
BB	161	83	1.09	0.88	1.36	.44
HLA matched alleles						**.0066**
7/8	245	141	1.00			
8/8	1301	645	0.76	0.63	0.93	.0066
Cytogenetics						**.0043**
Donor age						.39
Disease status						**<.0001**
Early	1147	566	1.00			
Intermediate	369	196	1.20	1.03	1.40	.021
Advanced	30	24	2.79	1.61	4.81	.0002
Recipient age, y						.0053
20-29	194	78	1.00			
30-39	251	119	1.23	0.97	1.55	.082
40-49	367	175	1.26	0.96	1.65	.098
50-59	467	247	1.41	1.12	1.77	.0036
≥60	267	167	1.73	1.27	2.34	.0004
Recipient CMV status						.24
ATG/alemtuzumab						.83
No ATG/alemtuzumab	929	474	1.00			
ATG alone	586	295	1.03	0.89	1.18	.73
Alemtuzumab alone	31	17	1.16	0.72	1.87	.55

Stratified variables: Karnofsky performance score. Poor risk cytogenetics significantly associated with risks of Relapse in RIC and MAC adjusted for other covariates. Bolded *P* values are independently significant $P < .05$.

*Adjusted multivariate analysis for the end points shown stratified as indicated.

Table 5. (continued)

Factor	n	Event	HR	HR low	HR upper	P
HLA-DP mismatch						.80
Fully matched	265	141	1.00			
Mismatch	1262	635	0.95	0.81	1.11	.51
Missing	19	10	0.94	0.60	1.47	.77

Stratified variables: Karnofsky performance score. Poor risk cytogenetics significantly associated with risks of Relapse in RIC and MAC adjusted for other covariates. Bolded *P* values are independently significant $P < .05$.

*Adjusted multivariate analysis for the end points shown stratified as indicated.

rarely had advanced disease status or poor risk cytogenetics. In addition, almost all HCTs in the later cohort were performed using filgrastim-mobilized PBSC rather than bone marrow stem cells. Compared with the earlier cohort,[8-10] the MAC recipients in the later cohort were older and almost all of them received PBSC grafts. These recipients rarely had advanced disease, which intrinsically reduced their risk of relapse.

In comparing the 2 eras of transplantation, the overall relapse rate for MAC HCTs improved from 34% at 3 years in the earlier cohort to a 29% 3-year relapse incidence in the current cohort. Similar improvement was not observed for the RIC transplants, for which the 3-year relapse incidence RIC recipients was 34%. Improvements in transplant platforms and more favorable risk patients being transplanted explains in part, whereas *KIR B* haplotype donors did not reduce risks in MAC transplants. Additionally, NRM in the earlier cohort (27% at 1 year) vs the current cohort (15% to 16% at 1 year) has improved, limiting the competing hazard for relapse. Other studies evaluating the role of donor *KIR* in HCT have reported protection from relapse of AML and other hematologic malignancies,[17,19,21,22] as well as associations with increased risk of GVHD, a correlation we did not see in the large cohort studied here.[19,21,23,24]

Our earlier analyses demonstrated a stronger protection from relapse for *KIR B* haplotype donors, for recipients having the C1 epitope, and for patients receiving an HLA-C-mismatched transplant including

Table 6. Recipient C1/x and donor KIR B haplotype in reduced intensity conditioning HCT

	Recipient C1/x				Recipient C2/C2			
Factor	n	HR	95% CI	P	n	HR	95% CI	P
Relapse								
Donor KIR haplotype				**.037***				.57*
AA	302	1			32	1		
BX	631	0.78	0.62-0.98	**.037**	97	0.82	0.40-1.65	.57
Donor KIR B centromeric regions				**.042***				.21*
AA	428	1			54	1		
AB	416	0.80	0.62-1.02	.071	66	0.80	0.40-1.62	.54
BB	89	0.70	0.49-1.01	.055	9	1.74	0.67-4.52	.25
DFS								
Donor KIR B haplotype				**.040***				.36*
AA	302	1			32	1		
BX	629	0.85	0.72-0.99	**.040**	97	0.80	0.50-1.29	.36
Donor KIR B centromeric regions								.66*
AA	427	1			54	1		
AB	416	0.82	0.69-0.98	**.030**	66	0.82	0.49-1.37	.45
BB	88	0.74	0.54-1.01	.060	9	1.17	0.54-2.56	.68
Overall survival								
Donor KIR haplotype								.87*
AA	304	1			32	1		
BX	631	0.82	0.68-0.98	**.029**	97	0.96	0.58-1.57	.87
Donor KIR B centromeric regions				.13*				.77*
AA	430	1			54	1		
AB	416	0.85	0.71-1.01	.067	66	0.84	0.49-1.43	.52
BB	89	0.75	0.52-1.08	.12	9	1.18	0.49-2.83	.71

*Overall *P* value.

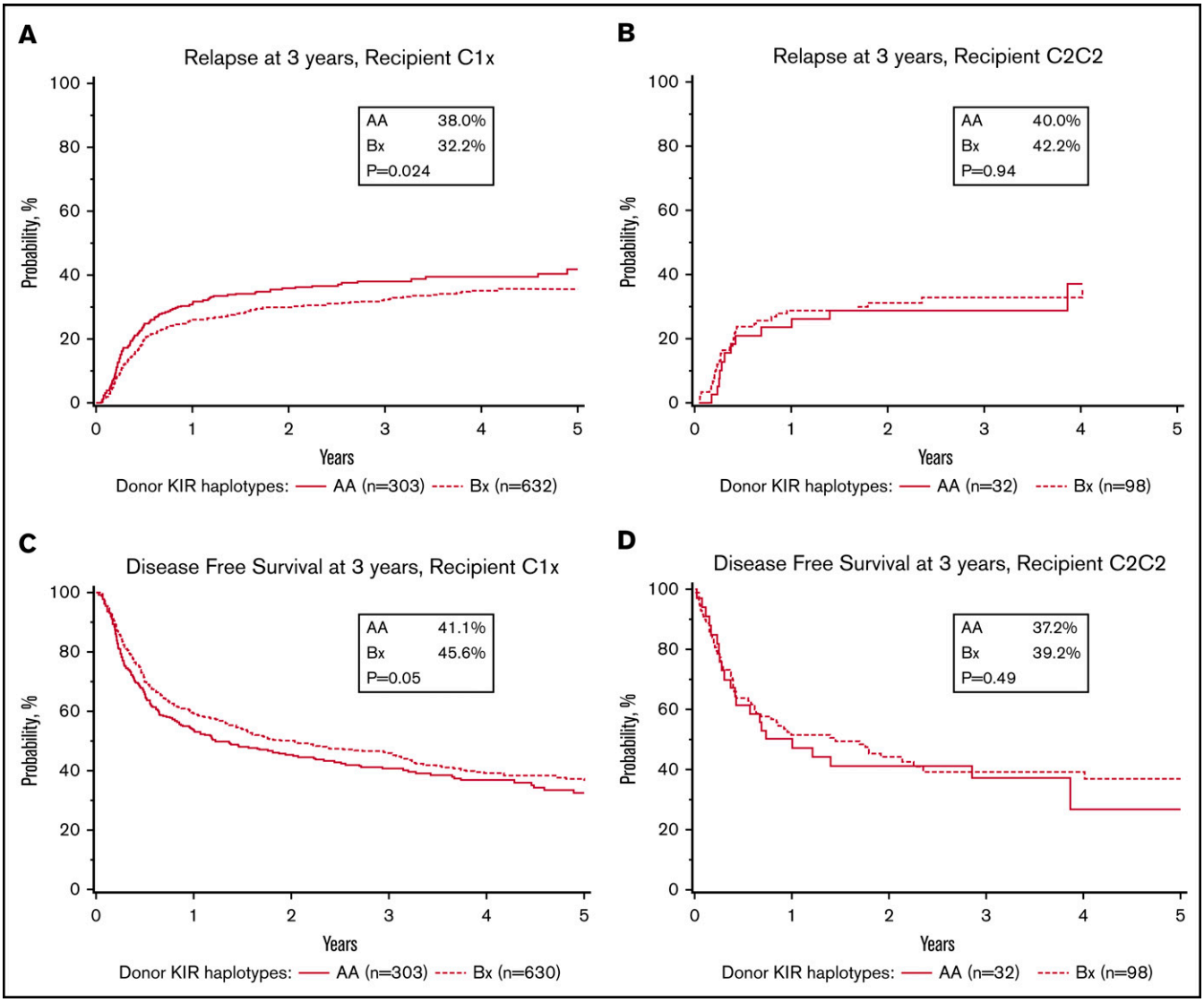

Figure 1. Recipient C1x and donor KIR Bx improves relapse and DFS after RIC HCT. Recipient C1x (A) and C2C2 (B) relapse at 3 years. Recipient C1x (C) and C2C2 (D) DFS at 3 years.

a mismatch for HLA-C1/C2.[10] In the current cohort, HLA mismatching was relatively rare (~15%) and HLA-C mismatch was uncommon, precluding a meaningful examination of HLA-C mismatch. However, RIC recipients having C1 and a *KIR B* donor exhibited a strong relapse protection in comparison with HLA-C2 homozygous recipients. Each of the donor *KIR B* genes was correlated with C1 epitope-mediated protection from relapse. No comparable effect was detected in the MAC HCTs in which the relapse rate was already reduced compared with earlier cohorts.

This analysis of a large cohort of modern URD transplants for AML confirms that strong relapse protection is associated with RIC, donor *KIR B* haplotype, and donor *KIR Cen B*, but not *KIR Tel B*. Donors with these strikingly favorable *KIR* profiles were associated with a 24% reduction in relapse and 23% improvement in DFS. Such protection was not observed in C2/C2 homozygous RIC patients and was not observed in MAC transplants.

In the prospective KIR DS trial,[13] only 40% of the 243 enrolled patients received RIC HCT based on clinical choices made by the participating transplant centers, thus limiting statistical power to determine whether donor *KIR B* haplotypes influence relapse protection. However, analysis of the 992 RIC recipients gave definitive results demonstrating that *KIR B* donors protect against AML relapse. We also hypothesize that NK cell reconstitution could influence current vs early analyses. We have recently shown that graft source (marrow vs granulocyte colony-stimulating factor mobilized peripheral blood) can modify the adaptive NK cell response to CMV.[25] Differences in HLA matching strategies and KIR choice considerations have also been reported to modify relapse risk.[21,26,27] Last, other peritransplant variables and supportive care protocol improvements could also be immunologically important.

In the current era of transplantation, the benefit of donor *KIR B* haplotypes involves all the *KIR B* defining genes and is most

important for HCT using RIC, where relapse rates are higher. The relapse protection is particularly strong in the large population (~85%) of recipients carrying at least 1 copy of the HLA-C1 epitope. We propose that this knowledge is directly applicable to donor selection today. Independent replication of this observation plus further genetic and translational studies should advance patient care and improve clinical outcomes. Methods for high-throughput KIR genotyping are now widely available and can increase the pool of fully characterized donors. When given the choice between otherwise comparable URD, we conclude that there is no disadvantage, and significant potential advantage, in choosing a *KIR B* haplotype donor to decrease post-HCT relapse of AML.

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Authorship

Contribution: D.W., S.C., S.S., S.G.E.M., P.P., L.A.G., and J.S.M. designed this study, analyzed data, and wrote the manuscript; C.V.-G., J.A.S., A.S., J.V., and T.W. collected data and performed the biostatistical analysis for this study and wrote the manuscript; and E.T., T.A.F., A.E.W., S.M.D., M.R., E.K.W., R.M.S., J.M., B.O., S.S.F., T.S., and K.V.B. assisted with data interpretation and assisted in writing the manuscript.

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ORCID profiles: D.W., 0000-0001-8078-8579; A.E.W., 0000-0001-7222-3607; E.K.W., 0000-0003-0816-6729; J.M., 0000-0002-0539-4796; T.S., 0000-0001-6033-0747; K.V.B., 0000-0002-8164-6211; S.G.E.M., 0000-0003-2855-4120; L.A.G., 0000-0002-1301-8301; J.S.M., 0000-0002-0339-4944.

Correspondence: Jeffrey S. Miller, University of Minnesota, 420 Delaware St SE, Minneapolis, MN 55455; e-mail: mille011@umn.edu.

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