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

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**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 B** 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 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{7}

Subsequently, the importance of donor KIR gene haplotypes for the outcome of allogeneic transplants for acute myeloid leukemia (AML) was reported.\textsuperscript{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.\textsuperscript{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.\textsuperscript{10} Other investigators\textsuperscript{11,12} have reported a particular benefit associated with KIR2DS1\textsuperscript{11} 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)\textsuperscript{13} and a larger contemporaneous group.

**Methods**

For the prospective KIR DS trial (2012-2016)\textsuperscript{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).\textsuperscript{14} Donor KIR genotypes were used to assign KIR AA vs Bl\textsuperscript{x} haplotypes as previously reported.\textsuperscript{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\textsuperscript{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.\textsuperscript{8,9} That study analyzed transplants performed before 2010 using myeloablative conditioning, predominantly narrow 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 for KIR donor selection and its capacity to enrich for favorable KIR haplotype donors has been published.\textsuperscript{13} However,
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.
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. 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-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 the contemporaneous

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**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 (6-96)              | 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.
Table 2. Recipient HLA C1 group phenotyping

| Variable                               | MAC recipients | RIC recipients | P*  |
|----------------------------------------|----------------|---------------|-----|
|                                        | C1/C1, n (%)   | C1/C2, n (%)  | C2/C2, n (%)  | 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)    | .73 |
| Donor recipient HLA allele matches     |                |               |              |                |               |               |     |
| 8/8                                    | .01            | .28           |              |                |               |               |     |
| 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)       |     |
| PBSBC                                  | 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 (8)         | 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 |
| 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 |
| 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.
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, 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. Notably, the previously studied cohorts 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; \( P = 0.026 \); Table 4) and was nearly identical (HR, 0.78; 95% CI, 0.63-0.97, \( P = 0.027 \)) 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, 0.63-0.97; \( P = 0.033 \) for Bx vs AA). Bx donors yielded improved DFS (HR, 0.84; 95% CI, 0.72-0.99; \( P = 0.038 \); Table 4) and led to small effects in improving OS (HR, 0.85; 95% CI, 0.71-1.01; \( P = 0.069 \); 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. 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 donors vs Cen AA donors has a HR of 0.77 (95% CI, 0.62-0.96; 0.25).
Table 4. Reduced intensity conditioning

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

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.
| Factor                              | n     | Event | HR    | HR low | HR upper | P    |
|------------------------------------|-------|-------|-------|--------|----------|------|
| Disease status                     |       |       |       |        |          |      |
| Early                              | 836   | 487   | 1.00  |        |          | .022 |
| Intermediate                       | 218   | 142   | 1.18  | 0.98   | 1.43     | .085 |
| Advanced                           | 8     | 8     | 3.01  | 1.22   | 7.40     | .017 |
| Recipient age, y                   |       |       |       |        |          |      |
| 20-29                              | 23    | 13    | 1.00  |        |          | .20  |
| 30-39                              | 29    | 15    | 0.69  | 0.33   | 1.44     | .32  |
| 40-49                              | 57    | 33    | 0.98  | 0.52   | 1.83     | .96  |
| 50-59                              | 198   | 116   | 0.97  | 0.58   | 1.64     | .92  |
| ≥60                                | 755   | 460   | 1.07  | 0.64   | 1.80     | .80  |
| Recipient CMV status               |       |       |       |        |          |      |
| ATG/alemtuzumab                    |       |       |       |        |          | .035 |
| 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                    |       |       |       |        |          |      |
| Fully matched                      | 178   | 109   | 1.00  |        |          | .10  |
| Mismatch                           | 871   | 519   | 1.06  | 0.84   | 1.34     | .64  |
| Missing                            | 13    | 9     | 1.69  | 1.10   | 2.60     | .017 |
| Donor KIR centromeric regions      |       |       |       |        |          |      |
| AA                                 | 482   | 308   | 1.00  |        |          | .034 |
| AB                                 | 483   | 278   | 0.82  | 0.70   | 0.96     | .016 |
| BB                                 | 97    | 51    | 0.76  | 0.56   | 1.02     | .069 |
| HLA matched alleles                |       |       |       |        |          |      |
| 7/8                                | 145   | 106   | 1.00  |        |          | .057 |
| 8/8                                | 917   | 531   | 0.79  | 0.61   | 1.01     | .057 |
| Cytogenetics                       |       |       |       |        |          |      |
| Donor age                          |       |       |       |        |          | .054 |
| Disease status                     |       |       |       |        |          |      |
| Early                              | 836   | 487   | 1.00  |        |          | .013 |
| 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  |        |          | .31  |
| 30-39                              | 29    | 15    | 0.68  | 0.32   | 1.44     | .91  |
| 40-49                              | 57    | 33    | 0.96  | 0.52   | 1.80     | .88  |
| 50-59                              | 198   | 116   | 0.96  | 0.57   | 1.62     | .85  |
| ≥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.
In marked contrast to our earlier analyses, 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). Donor haplotypes 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). Additionally, neither ATG/alemtuzumab use nor permissive (or nonpermissive) mismatching for HLA-DP (clinical elements previously reported to influence HCT outcomes) had significant influence on relapse in RIC recipients (Table 4).

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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 nonpermissive) mismatching for HLA-DP (clinical elements previously reported to influence HCT outcomes) had significant influence on relapse in RIC recipients (Table 4).

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 B/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, particularly if the donor also has KIR2DS1. 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. 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, 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                 | 287 | 84    | 1.00 |        |          |       |
| Mismatch                      | 1284| 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                            | 182 | 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                 | 287 | 84    | 1.00 |        |          |       |
| Mismatch                      | 1284| 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   | 1.66     | .10   |
| 50-59                           | 467  | 247  | 1.41 | 1.11   | 1.77     | .0040 |
| ≥60                             | 287  | 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                        | 1282 | 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                             | 287  | 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.
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

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| Table 5. (continued) |
|----------------------|

| Factor                | n   | Event | HR   | HR low | HR upper | P     |
|-----------------------|-----|-------|------|--------|----------|-------|
| HLA-DP mismatch       |     |       |      |        |          |       |
| Fully matched         | 265 | 141   | 1.00 |        |          | .80   |
| 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.

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

| Relapse                           | Recipient C1/x | Recipient C2/C2 |
|------------------------------------|----------------|-----------------|
| Factor                             | n   | HR   | 95% CI   | P    | n   | HR   | 95% CI   | P    |
| Donor KIR haplotype                |     |      |          |      |     |      |          |      |
| AA                                 | 302 | 1    |          | .037*| 32  | 1    |          | .57* |
| 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                                |     |      |          | .040*|      |      |          | .36  |
| Donor KIR B haplotype              |     |      |          |      |     |      |          |      |
| AA                                 | 302 | 1    |          | .040 | 32  | 1    |          | .36  |
| 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    |     |      |          | .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.
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, 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. Differences in HLA matching strategies and KIR choice considerations have also been reported to modify relapse risk. 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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