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HLA-C–Dependent Prevention of Leukemia Relapse by Donor Activating *KIR2DS1*

Jeffrey M. Venstrom, M.D., **Gianfranco Pittari, M.D.**, **Ted A. Gooley, Ph.D.**, **Joseph H. Chewning, M.D.**, **Stephen Spellman, M.S.**, **Michael Haagenson, M.S.**, **Meighan M. Gallagher, B.A.**, **Mari Malkki, Ph.D.**, **Effie Petersdorf, M.D.**, **Bo Dupont, M.D., D.Sc.**, and **Katharine C. Hsu, M.D., Ph.D.**
Department of Medicine, Memorial, Sloan-Kettering Cancer Center, (J.M.V., K.C.H.), the Immunology Program, Sloan-Kettering Institute for Cancer Research, (G.P., J.H.C., M.M.G., B.D.), and Weill Cornell Medical College (K.C.H.) — all in New York; Fred Hutchinson Cancer, Research Center, Seattle (T.A.G., M.M., E.P.); and the Center for International, Blood and Marrow Transplant Research, Minneapolis (S.S., M.H.)

Abstract

Background—Of the cancers treated with allogeneic hematopoietic stem-cell transplantation (HSCT), acute myeloid leukemia (AML) is most sensitive to natural killer (NK)–cell reactivity. The activating killer-cell immunoglobulin-like receptor (KIR) 2DS1 has ligand specificity for HLA-C2 antigens and activates NK cells in an HLA-dependent manner. Donor-derived NK reactivity controlled by KIR2DS1 and HLA could have beneficial effects in patients with AML who undergo allogeneic HSCT.

Methods—We assessed clinical data, *HLA* genotyping results, and donor cell lines or genomic DNA for 1277 patients with AML who had received hematopoietic stem-cell transplants from unrelated donors matched for *HLA-A, B, C, DR*, and *DQ* or with a single mismatch. We performed donor *KIR* genotyping and evaluated the clinical effect of donor *KIR* genotype and donor and recipient *HLA* genotypes.

Results—Patients with AML who received allografts from donors who were positive for *KIR2DS1* had a lower rate of relapse than those with allografts from donors who were negative for *KIR2DS1* (26.5% vs. 32.5%; hazard ratio, 0.76; 95% confidence interval [CI], 0.61 to 0.96; P = 0.02). Of allografts from donors with *KIR2DS1*, those from donors who were homozygous or heterozygous for HLA-C1 antigens could mediate this antileukemic effect, whereas those from donors who were homozygous for HLA-C2 did not provide any advantage (24.9% with homozygosity or heterozygosity for HLA-C1 vs. 37.3% with homozygosity for HLA-C2; hazard ratio, 0.46; 95% CI, 0.28 to 0.75; P = 0.002). Recipients of *KIR2DS1*-positive allografts mismatched for a single *HLA-C* locus had a lower relapse rate than recipients of *KIR2DS1*-negative allografts with a mismatch at the same locus (17.1% vs. 35.6%; hazard ratio, 0.40; 95% CI, 0.20 to 0.78; P = 0.007). *KIR3DS1*, in positive genetic linkage disequilibrium with *KIR2DS1*, had no effect on leukemia relapse but was associated with decreased mortality (60.1%, vs. 66.9% without *KIR3DS1*; hazard ratio, 0.83; 95% CI, 0.71 to 0.96; P = 0.01).

Conclusions—Activating *KIR* genes from donors were associated with distinct outcomes of allogeneic HSCT for AML. Donor *KIR2DS1* appeared to provide protection against relapse in an

Address reprint requests to Dr. Hsu or Dr. Dupont at the Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10065, or at hsuk@mskcc.org or dupontb@mskcc.org.

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HLA-C–dependent manner, and donor *KIR3DS1* was associated with reduced mortality. (Funded by the National Institutes of Health and others.)

Natural killer (NK) cells are lymphocytes that are critical for innate immunity against malignant or virally infected cells. Acute myeloid leukemia (AML) is the most common indication for hematopoietic stem-cell transplantation (HSCT) from unrelated donors, and the alloreactivity of donor NK cells can exert a potent antileukemic effect in this context.[1,2] NK-cell function is controlled by an array of inhibitory and activating signals that are processed by cell-surface receptors, including the inhibitory and activating killer-cell immunoglobulin-like receptors (KIRs), whose genes vary in number and content from person to person. Inhibitory KIRs recognize the HLA class I ligand groups HLA-C1, C2, and Bw4 and mediate tolerance to self when they encounter self-HLA molecules on putative target cells.[3]

Earlier models of NK alloreactivity in HSCT focused on the interactions between inhibitory KIRs and HLA class I ligands, in which the alloreactivity of donor NK cells is triggered by a lack of self-HLA class I engagement of inhibitory KIRs.[1,2,4,5] This relationship is most evident in *HLA*-haplotype–disparate HSCT, in which recipients who lack the HLA ligand present in the stem-cell donor have a decreased rate of relapse.[1,2,5,6] An *HLA*-haplotype–disparate donor, however, is typically not preferred, because the high degree of *HLA* mismatching is associated with an increased risk of graft-versus-host disease (GVHD) and increased mortality.[7] Therefore, better selection of donors to capture NK alloreactivity and prevent relapse without a high degree of *HLA* mismatching will probably improve the success of allogeneic HSCT.

Most persons have multiple activating KIRs, of which KIR2DS1 is the only one known to play a role in both NK-cell activation and tolerance, through its recognition of *HLA-C2* (Asn 77 and Lys 80) molecules.[8-10] KIR2DS1-positive NK cells isolated from *HLA-C1*–positive persons (with *HLA-C1/C1* or *C1/C2*) secrete interferon-γ and are cytotoxic to target cells, in particular those that express HLA-C2. In *HLA-C2* homozygous persons (with *HLA-C2/C2*), in whom high levels of the ligand are expressed as a self-molecule, NK cells that exclusively express KIR2DS1 are hyporesponsive.[11-13] These findings are consistent with those of studies in transgenic mice, which have shown that the function of NK cells expressing activating receptors specific for self-ligands is diminished.[14-16] These studies suggest that in allogeneic HSCT in humans, the functionally competent KIR2DS1-expressing NK cells from *HLA-C1*–positive donors could mediate leukemic cytotoxicity in the recipient, whereas the KIR2DS1-expressing NK cells from donors with *HLA-C2/C2* would be poorly responsive in the setting of self HLA-C2 and would not mediate leukemic cytotoxicity. However, this hypothesis has not been directly tested either in vitro with the use of leukemia cells obtained from patients or in outcome studies of patients who undergo HSCT from unrelated donors.

We evaluated the effect of activating *KIR2DS1* from donors on the outcome of HSCT. To minimize the contribution of the inhibitory *KIR* to NK alloreactivity,[2,4,17-19] we evaluated HSCT pairs in which donors and recipients were matched for 9 or 10 of the possible 10 alleles at the *HLA-A, B, C, DR*, and *DQ* loci. We also sought to confirm our previous observation that activating *KIR3DS1* is associated with increased survival.[20]

Methods

Study Design

This retrospective study was designed to test the hypothesis that allografts from donors with *KIR2DS1* and favorable *HLA-C* genotypes would improve the outcomes of HSCT from

unrelated donors for patients with AML. Clinical data, *HLA* genotyping, and donor cell lines or genomic DNA for *KIR* genotyping were provided by the Center for International Blood and Marrow Transplant Research (CIBMTR). The CIBMTR is a research affiliate of the International Bone Marrow Transplant Registry, the Autologous Blood and Marrow Transplant Registry, and the National Marrow Donor Program (NMDP), which together account for more than 450 centers worldwide that contribute data on HSCT to a statistical center at the Medical College of Wisconsin in Milwaukee and the NMDP coordinating center in Minneapolis. Patients are followed longitudinally, with yearly follow-up. Studies conducted by the CIBMTR are performed in compliance with the Privacy Rule of the Health Insurance Portability and Accountability Act and with federal regulations pertaining to the protection of human research participants, as determined by the institutional review boards of the NMDP and the Medical College of Wisconsin. The principal investigators made the decision to submit the manuscript for publication. All authors vouch for the accuracy and completeness of the data and analyses; there was no writing assistance from anyone who is not listed as an author. There were no confidentiality agreements between funding agencies and the authors. No commercial support was involved in the study.

Patients and Donors

We evaluated 1277 patients with AML and 427 patients with acute lymphoblastic leukemia (ALL) who received stem-cell transplants between 1989 and 2008 from unrelated donors matched for 9 or 10 of the possible 10 alleles at *HLA-A, B, C, DR*, and *DQ* loci. All transplantations were facilitated by the NMDP, and the CIBMTR provided clinical data, *HLA* genotyping, and cell lines or genomic DNA from donors. *HLA* genotyping with allele-level resolution was verified through the NMDP. Consent from patients and donors was obtained through the CIBMTR. Both surviving and deceased patients were included in the analysis. The inclusion of deceased patients did not require consent, and approximately 4% of surviving patients did not provide consent. A random subset of surviving patients was excluded from the analysis to adjust for potential bias due to the failure to obtain consent from all surviving patients, as previously described.[21]

KIR Genotyping

KIR genotyping was performed on genomic DNA from unrelated donors of hematopoietic stem cells with the use of polymerase-chain-reaction amplification with sequence-specific primers, as described previously,[22] or with the use of a *KIR* genotyping kit (Invitrogen), according to the manufacturer's instructions.

Statistical Analysis

Cox regression was used to examine the association of the hazard of failure for various time-to-event outcomes of HSCT (death from any cause, relapse, disease-free survival, and death without relapse) with donor *KIR* genotype. Failure for disease-free survival was defined as relapse or death, whichever occurred first. Logistic regression was used to assess the association of donor *KIR* genotype with the probability of acute GVHD. Two-sided P values were derived from adjusted regression models and were estimated by means of the Wald test. All models were adjusted for the patient's age, level of risk (low, intermediate, or high), cytomegalovirus (CMV) serostatus (positive or negative), and cytogenetic profile (no abnormalities, good risk, intermediate risk, or poor risk); use of T-cell depletion (yes or no); conditioning regimen (ablative with total-body irradiation, ablative without total-body irradiation, or nonablative); and *HLA* match (10 of 10 alleles vs. 9 of 10 alleles). No adjustments were made for multiple comparisons. Estimates of overall survival were obtained with the use of the Kaplan–Meier method, and cumulative incidence estimates were used to summarize the probability of relapse. Death without relapse was regarded as a competing risk for purposes of estimating the probability of relapse.

Results

Patient and Donor Characteristics

Characteristics of the 1277 patients with AML and their donors are listed in Table 1. The frequencies of activating *KIR* genes in the predominantly white population were consistent with gene frequencies in previously published studies.[22,23] Specifically, the frequency of *KIR2DS1* was 33%, of *KIR3DS1* was 34%, and of *KIR2DS2* was 49%. The *KIR2DS1*-positive and *KIR2DS1*-negative groups were similar with respect to risk level, age, GVHD prophylaxis, degree of *HLA* matching, sex of patient–donor pairs, and patient's race or ethnic group, graft type, and CMV serostatus (Table 1) and with respect to cytogenetic profile. A total of 427 patients with ALL were evaluated in parallel; the characteristics of these and their donors are detailed in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Donor *KIR2DS1* and AML Relapse

We found a significantly reduced risk of relapse among patients with AML whose donors were positive for *KIR2DS1*, as compared with patients whose donors were negative for *KIR2DS1* (26.5% vs. 32.5%; adjusted hazard ratio, 0.76; 95% confidence interval [CI], 0.61 to 0.96; P = 0.02) (Fig. 1A). We hypothesized that this association would be observed only for donors with HLA-C1, not for donors with HLA-C2/C2, because the presence of high levels of the HLA-C2 self-ligand in the latter donors would tolerize KIR2DS1-bearing NK cells and diminish their activity. Allografts from *KIR2DS1*-positive donors with *HLA-C2/C2* were associated with an increased rate of AML relapse, as compared with all allografts from *KIR2DS1*-negative donors (37.3% vs. 32.5%; hazard ratio, 1.51; 95% CI, 0.94 to 2.41; P = 0.09) (Table 2). In contrast, allografts from *KIR2DS1*-positive donors with *HLA-C1/C1* were associated with a decreased rate of relapse, as compared with all allografts from *KIR2DS1*-negative donors (24.7% vs. 32.5%; hazard ratio, 0.71; 95% CI, 0.51 to 0.99; P = 0.05). Patients with AML who received allografts from donors who were heterozygous for *HLA-C1* (i.e., with *HLA-C1/C2*) also had a decreased rate of relapse, as compared with all allografts from *KIR2DS1*-negative donors (25.1% vs. 32.5%; hazard ratio, 0.67; 95% CI, 0.49 to 0.92; P = 0.01). Allografts from *KIR2DS1*-positive donors with *HLA-C1/C1* or *C1/C2* were associated with a reduced relapse rate, as compared with allografts from *KIR2DS1*-negative donors (24.9% vs. 32.5%; hazard ratio, 0.69; 95% CI, 0.54 to 0.88; P = 0.003) (Table 2) and especially as compared with allografts from *KIR2DS1*-positive donors with *HLA-C2/C2* (24.9% vs. 37.3%; hazard ratio, 0.46; 95% CI, 0.28 to 0.75; P = 0.002) (Fig. 1B). Decreased rates of relapse with allografts from *KIR2DS1*-positive donors were seen in low-, intermediate-, and high-risk AML groups; a formal test of interaction did not provide definitive evidence that the KIR2DS1 effect differed across the three groups.

The reduced rate of AML relapse is consistent with the observation in vitro that KIR2DS1-mediated NK function is dependent on *HLA-C* background.[11-13] We therefore examined the effect of donor *KIR2DS1* across the donor HLA-C ligand groups. In contrast to the protective effect of *KIR2DS1* against relapse in patients who received allografts from donors with *HLA-C1/C1* or *C1/C2* (relapse rate, 24.9%, vs. 31.2% among patients who received allografts from *KIR2DS1*-negative donors with *HLA-C1/C1* or *C1/C2*; hazard ratio, 0.71; 95% CI, 0.55 to 0.92; P = 0.009), no protective benefit of *KIR2DS1* against relapse was seen for patients who received allografts from donors with *HLA-C2/C2*. The high levels of activating HLA-C2 ligands for KIR2DS1 in donors with *HLA-C2/C2* tolerize an otherwise potent antileukemic NK population, leading to similarly high relapse rates among recipients of allografts from *KIR2DS1*-positive and *KIR2DS1*-negative donors with *HLA-C2/C2* (37.3% and 41.1%; hazard ratio, 1.17; 95% CI, 0.66 to 2.08; P = 0.58) (Fig. 1C).

Recipients of allografts from *KIR2DS1*-positive donors with *HLA-C1/C1* or *C1/C2* had lower mortality than recipients of allografts from *KIR2DS1*-negative donors (60.3% vs. 67.0%; hazard ratio, 0.85; 95% CI, 0.73 to 1.00; P = 0.04), whereas recipients of allografts from *KIR2DS1*-positive donors with *HLA-C2/C2* and recipients of allografts from *KIR2DS1*-negative donors had similar mortality (57.7% and 67.0%, respectively; hazard ratio, 1.01; 95% CI, 0.69 to 1.46; P = 0.98) (Table 2). The findings with respect to disease-free survival (i.e., relapse or death) were similar (Table 2). There was no association between allografts from *KIR2DS1*-positive donors and the incidence of grade II to IV acute GVHD (51.0%, vs. 51.4% for allografts from *KIR2DS1*-negative donors; odds ratio, 0.97; 95% CI, 0.77 to 1.24; P = 0.83) or death without relapse (32.6% vs. 34.0%; hazard ratio, 0.99; 95% CI, 0.80 to 1.21; P = 0.90). Among patients with ALL, the *KIR2DS1* status of donors was not associated with relapse or survival, a finding that is consistent with reports that NK reactivity is strongest against myeloid leukemias.[1,24,25]

Recipient *HLA-C* and AML Relapse

Patients who are homozygous for *HLA-C2* represent 13 to 19% of the HSCT population, and in studies of smaller cohorts, such patients have been reported to have high relapse rates.[26-28] We hypothesized that a lack of *KIR2DS1*-induced NK alloreactivity from donors with *HLA-C2/C2* is responsible for this observation. In our cohort, transplant recipients with *HLA-C2/C2* indeed had an increased risk of relapse, as compared with recipients with *HLA-C1/C1* or *HLA-C1/C2* (38.4% vs. 29.3%; hazard ratio, 1.33; 95% CI, 1.01 to 1.75; P = 0.05) (Fig. 2A). In recipients with *HLA-C2/C2*, allografts from *KIR2DS1*-positive donors did not provide protection from relapse (relapse rate, 37.7%, vs. 38.7% with allografts from *KIR2DS1*-negative donors; hazard ratio, 0.98; 95% CI, 0.56 to 1.73; P = 0.95) (Fig. 2B). In contrast, patients with *HLA-C1/C1* or *C1/C2* benefited significantly from receiving an allograft from a *KIR2DS1*-positive donor (relapse rate, 24.8%, vs. 31.5% with allografts from *KIR2DS1*-negative donors; hazard ratio, 0.72; 95% CI, 0.56 to 0.93; P = 0.01) (Fig. 2B). The increased rates of relapse associated with allografts from donors with *HLA-C2/C2*, both *KIR2DS1*-positive and *KIR2DS1*-negative (Fig. 1C and 2B), however, indicate that in addition to tolerizing KIR2DS1-bearing NK cells in the donor, HLA-C2/C2 homozygosity is associated with an increased rate of relapse owing to causes that are unrelated to KIR2DS1.

HLA-C Mismatch and Donor *KIR2DS1* Status

We sought to determine whether the association of donor *KIR2DS1* and a reduced rate of relapse was more prominent in the *HLA*-matched or *HLA*-mismatched combinations, particularly because the latter may also promote inhibitory KIR-mediated NK alloreactivity.[1,2] Although the relapse rate was not significantly lower among patients with allografts from *KIR2DS1*-positive donors, as compared with recipients of allografts from *KIR2DS1*-negative donors, when the allograft was matched for 10 of 10 alleles (29.3% vs. 33.5%; hazard ratio, 0.85; 95% CI, 0.63 to 1.16; P = 0.31) (Fig. 3A) or was mismatched at loci other than *HLA-C* (26.8% vs. 29.0%; hazard ratio, 0.84; 95% CI, 0.55 to 1.28; P = 0.42) (Fig. 3B), there was a significant effect of donor *KIR2DS1* positivity for allografts with a single-allele mismatch at the *HLA-C* locus (relapse rate, 17.1%, vs. 35.6% for donor *KIR2DS1* negativity; hazard ratio, 0.40; 95% CI, 0.20 to 0.78; P = 0.007) (Fig. 3C). Of patients with *HLA-C2/C2*, the 11 patients with a *KIR2DS1*-positive *HLA-C*–mismatched donor had a lower relapse rate than the 50 patients with a *KIR2DS1*-negative donor matched for *HLA-C* (hazard ratio, 0.38).

We therefore examined whether NK alloreactivity due to inhibitory KIRs contributed to these effects. Of the 216 *HLA-C*–mismatched pairs for which relapse data were available, 56 had the potential for donor-derived inhibitory KIR-mediated NK alloreactivity, with a fairly even distribution among the *KIR2DS1*-negative pairs (25%) and *KIR2DS1*-positive

pairs (27%). Patients who had a relapse after receiving an HLA-C–mismatched transplant were evenly distributed between recipients of allografts from donors with the potential for inhibitory KIR-mediated NK alloreactivity (29%) and recipients of allografts from donors without this potential (30%). In aggregate, inhibitory KIR-mediated NK alloreactivity did not appear to contribute to *KIR2DS1*-related protection from relapse.

Effect of Donor *KIR2DS1* versus Other *KIR* Genes on Relapse

KIR2DS1 is in positive genetic linkage disequilibrium with other activating *KIR* genes[22] — in particular, *KIR3DS1* ($r^2 = 0.56$ in this cohort). Although donor *KIR3DS1* positivity was associated with a decreased rate of relapse (28.9%, vs. 31.3% with *KIR3DS1* negativity; hazard ratio, 0.86; 95% CI, 0.69 to 1.07; P = 0.17), this protective effect was not sustained when donors were stratified according to *KIR2DS1* status (Table 2). The association of donor *KIR2DS1* positivity with a decreased rate of relapse, on the other hand, was similar regardless of donor status with regard to *KIR3DS1* (Table 2, and Fig. S1A in the Supplementary Appendix). Others have reported a favorable, dose-dependent effect of the *KIR2DS2*-containing centromeric *KIR* B-partial haplotype (*Cen-B*) on the risk of relapse among patients with AML.[24,25] We evaluated homozygosity for donor *Cen-B* positivity versus donor *Cen-B* negativity in this cohort and observed an association of *Cen-B* homozygosity with a reduced rate of relapse, although the association was not significant (28.1% vs. 33.7%; hazard ratio, 0.77; 95% CI, 0.52 to 1.13; P = 0.18). Adjustment for the presence of *Cen-B* did not change the association between donor *KIR2DS1* and a decreased rate of AML relapse (hazard ratio, 0.76 and 0.77, before and after adjustment for *Cen-B*).

Donor *KIR3DS1* and Overall Mortality

The previous observation that allografts from *KIR3DS1*-positive donors were associated with improved transplant-related and overall survival indicates that NK cell populations that express individual activating KIRs may play nonoverlapping roles in HSCT from unrelated donors.[20] In the current study, the presence of donor *KIR3DS1* was associated with decreased overall mortality (60.1%, vs. 66.9% in the absence of *KIR3DS1*; hazard ratio, 0.83; 95% CI, 0.71 to 0.96; P = 0.01) (Table 2, and Fig. S1B in the Supplementary Appendix), largely owing to reduced rates of death without relapse (Table S2 in the Supplementary Appendix). These reductions in mortality were influenced little by the presence of donor *KIR2DS1* (Table 2, and Table S2 and Fig. S1C in the Supplementary Appendix).

Discussion

In a large cohort, we found that specific activating *KIR* genes in donors were associated with distinct clinical outcomes of allogeneic HSCT for the treatment of AML. A *KIR2DS1*-dependent graft-versus-leukemia effect was modified by donor *HLA-C2* in a manner consistent with in vitro findings of KIR2DS1-mediated NK function, in which the interaction of KIR2DS1 with high levels of HLA-C2 in persons with *HLA-C2/C2* reduces NK reactivity.[11-13] Thus, although *KIR2DS1* was present in 33% of donors, the *KIR2DS1*-associated reduction in the rate of AML relapse was restricted to donors with *HLA-C1/C1* or *C1/C2*, and the benefit was eliminated in transplants from donors with *HLA-C2/C2*. Capturing NK alloreactivity in HSCT from unrelated donors is therefore more complex than selecting donors with multiple activating *KIR* genes.[24,25]

Induction of tolerance in NK cells that express activating receptors through chronic exposure to the ligand has been described in mice[14-16]; we now show an association between clinical outcomes and NK tolerance in HSCT from unrelated donors. An interesting finding in this study is that *KIR2DS1*-positive donors heterozygous for *HLA-C2* did not

have evidence of diminished function, as assessed by control of leukemic relapse. This clinical observation is consistent with recent findings from our group (unpublished data) and others[13] that in vitro–derived NK clones from *KIR2DS1*-positive donors with *HLA-C1/C1* or *C1/C2* genotypes have similarly high frequencies of cytotoxic activity against target cells, in contrast to NK clones from donors with *HLA-C2/C2*. To reduce the risk of AML relapse, the data support preferential selection of a *KIR2DS1*-positive donor if the donor has *HLA-C1/C1* or *C1/C2*. Because of the strong positive linkage dysequilibrium between *KIR2DS1* and *KIR3DS1*, the large majority of *KIR2DS1*-positive donors will also be positive for *KIR3DS1*, a favorable genetic marker for survival whose ligand and biologic function remain elusive.

Current practice dictates preferential selection of *HLA*-matched donors in order to minimize the risk of GVHD; however, the increased vulnerability of recipients with *HLA-C2/C2* to relapse challenges the clinician to consider an *HLA-C* KIR ligand–mismatched donor in order to capture KIR2DS1-mediated NK alloreactivity and NK alloreactivity due to inhibitory KIR-mediated mechanisms, even in the face of a potentially increased risk of GVHD.[29]

An increased understanding of how KIR–HLA interactions dictate NK function could lead to more informed selection of stem-cell donors. We found that the potential benefit of *KIR2DS1* is not simply predicted by the presence of the gene in the donor, but rather is modified by the presence of its ligand in the donor. We also found that donor *KIR3DS1* may confer a survival advantage by reducing the risk of death without relapse. The effect of these and other activating KIR associations should be examined in a prospective manner in ethnically diverse cohorts, in which *HLA* and *KIR* genotype frequencies may vary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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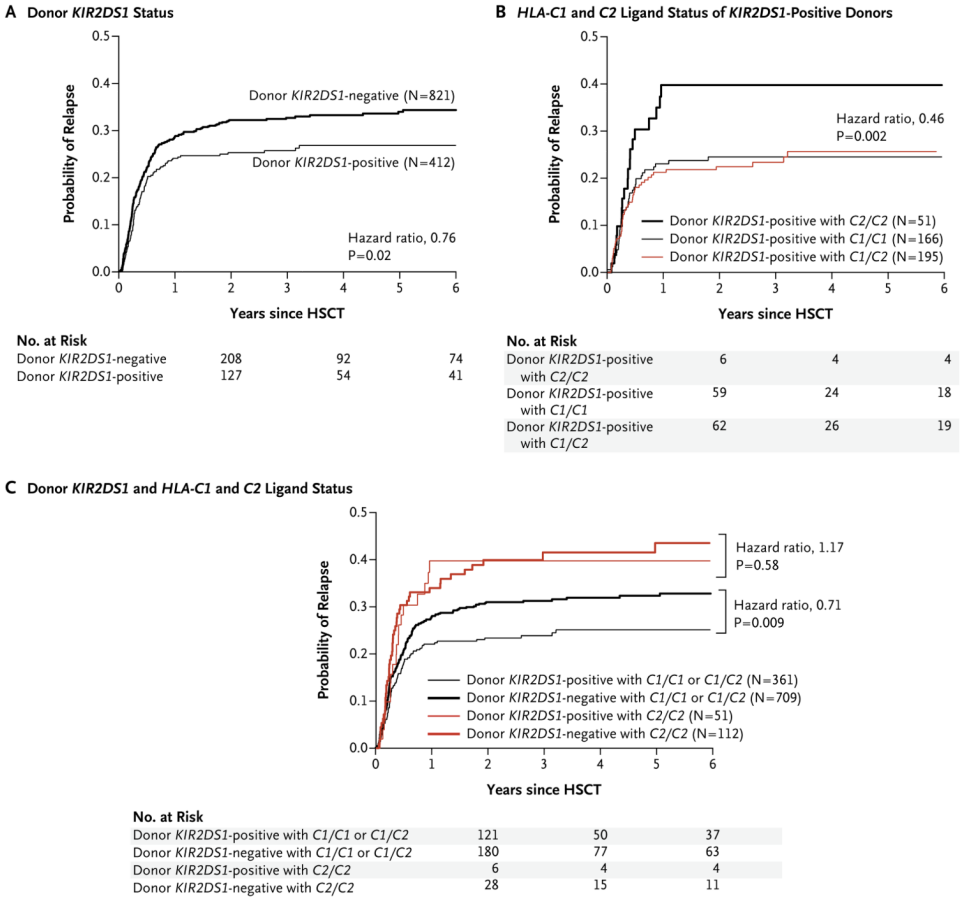

Figure 1. Effect of *KIR2DS1* and *HLA-C* Ligand in Stem-Cell Donors on Relapse in Patients with Acute Myeloid Leukemia (AML)

The cumulative incidence of AML relapse is shown for patients with *KIR2DS1*-negative versus *KIR2DS1*-positive donors (Panel A), patients with *KIR2DS1*-positive donors stratified according to *HLA-C1* and *C2* ligands (Panel B), and patients with donors stratified according to *HLA-C1* and *C2* ligands and *KIR2DS1* status (Panel C). HSCT denotes hematopoietic stem-cell transplantation.

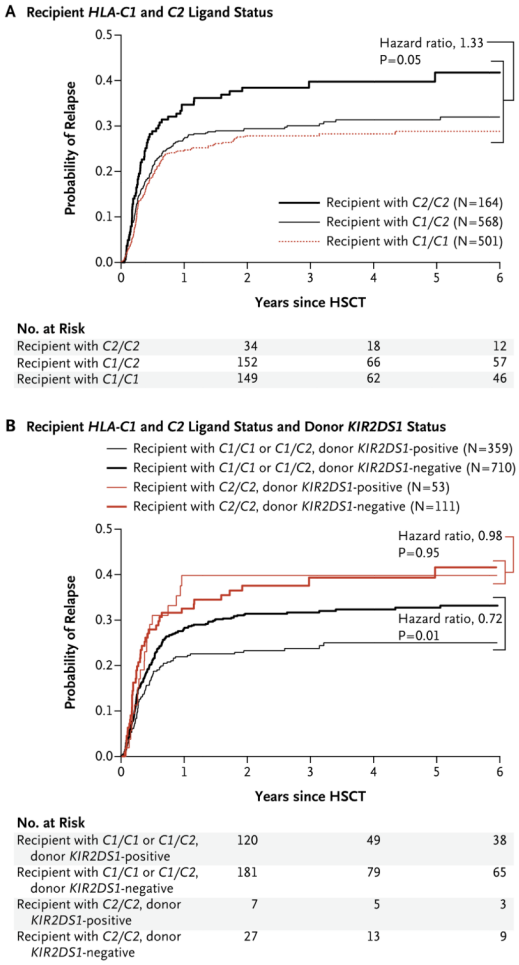

Figure 2. Association between Rate of Relapse after HSCT and Homozygosity for *HLA-C2* Ligand in Transplant Recipients

The cumulative incidence of AML relapse is shown for patients stratified according to status with respect to *HLA-C KIR* ligand (Panel A) and status with respect to both *HLA-C KIR* ligand and donor *KIR2DS1* (Panel B).

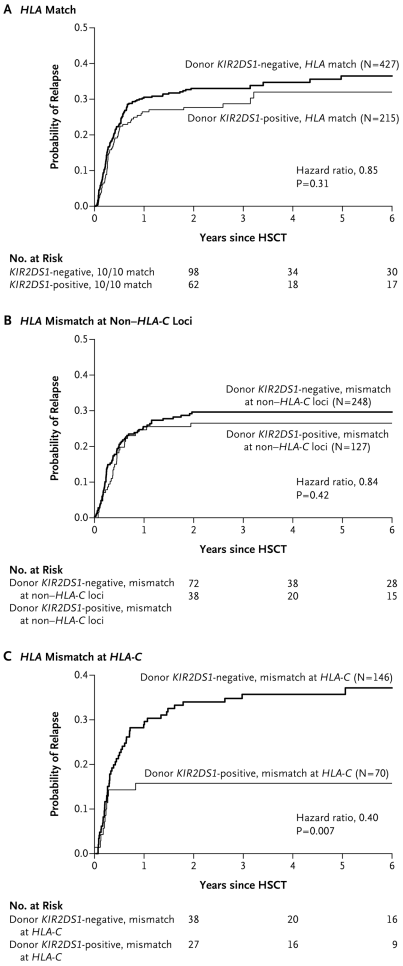

Figure 3. *KIR2DS1*-Mediated Graft-versus-Leukemia Effect in *HLA-C*–Mismatched HSCT

The cumulative incidence of AML relapse is shown for recipients of transplants from *KIR2DS1*-positive or *KIR2DS1*-negative donors with 10 of 10 *HLA* alleles matched (Panel A), with a single-allele mismatch at loci other than *HLA-C* (Panel B), or with a single-allele mismatch at the *HLA-C* locus (Panel C).

Table 1

Characteristics of Patients with AML and Stem-Cell Donors, According to Donor *KIR* Genotype.*

Characteristic	Donor *KIR2DS1*-Negative (N = 855)	Donor *KIR2DS1*-Positive (N = 422)
Patient's age — yr		
Median	41.7	40.5
Range	0.8–73.9	0.7–75.0
Risk level at time of transplantation — no. (%)†		
High	302 (35)	151 (36)
Intermediate	244 (29)	125 (30)
Low	304 (36)	143 (34)
Missing data	5 (<1)	3 (<1)
Year of transplantation — no. (%)		
1988–1994	30 (4)	15 (4)
1995–2000	208 (24)	94 (22)
2001–2005	287 (34)	132 (31)
2006–2008	330 (39)	181 (43)
Degree of *HLA* matching — no. (%)		
10 of 10 alleles matched	442 (52)	222 (53)
9 of 10 alleles matched	413 (48)	200 (47)
HLA-A mismatch	115 (13)	57 (14)
HLA-B mismatch	58 (7)	20 (5)
HLA-C mismatch	153 (18)	73 (17)
HLA-DRB1 mismatch	21 (2)	11 (3)
HLA-DQB1 mismatch	66 (8)	39 (9)
Conditioning regimen — no. (%)		
Ablative without total-body irradiation	284 (33)	154 (36)
Ablative with total-body irradiation	432 (51)	199 (47)
Nonablative or reduced intensity	126 (15)	63 (15)
Missing data	13 (2)	6 (1)
GVHD prophylaxis — no. (%)		
Cyclosporine and methotrexate	238 (28)	108 (26)
Tacrolimus	279 (33)	149 (35)
T-cell depletion	236 (28)	113 (27)
Other	102 (12)	52 (12)
Sex of patient–donor pairs — no. (%)		
Patient and donor female	160 (19)	89 (21)
Patient female, donor male	257 (30)	105 (25)
Patient male, donor female	142 (17)	68 (16)
Patient and donor male	295 (35)	160 (38)

Characteristic	Donor *KIR2DS1*-Negative (N = 855)	Donor *KIR2DS1*-Positive (N = 422)
Missing data	1 (<1)	0
Patient's race or ethnic group — no. (%)‡		
Black	26 (3)	7 (2)
Asian or Pacific Islander	11 (1)	2 (<1)
White	765 (89)	390 (92)
Hispanic	39 (5)	19 (5)
Native American	1 (<1)	0
Other or unknown	13 (2)	4 (<1)
Source of stem cells — no. (%)		
Bone marrow	471 (55)	218 (52)
Peripheral blood	384 (45)	204 (48)
CMV status of patient–donor pairs — no. (%)		
Donor and patient negative	258 (30)	134 (32)
Donor negative, patient positive	103 (12)	49 (12)
Donor positive, patient negative	296 (35)	147 (35)
Donor and patient positive	178 (21)	85 (20)
Missing data	20 (2)	7 (2)

*There were no significant differences between the two study groups. AML denotes acute myeloid leukemia, CMV cytomegalovirus, and GVHD graft-versus-host disease.

†Low risk indicates first complete remission, intermediate risk second or higher complete remission, and high risk primary induction failure or relapse.

‡Race and ethnic group were self-reported.

Table 2

Association of *KIR* and *HLA* Genotypes with the Outcome of Hematopoietic Stem-Cell Transplantation.*

Outcome	No./Total No. (%)	Hazard Ratio (95% CI)†	P Value
Relapse			
KIR2DS1			
Donor *KIR2DS1*-negative	267/821 (32.5)	1.00	
Donor *KIR2DS1*-positive	109/412 (26.5)	0.76 (0.61–0.96)	0.02
KIR2DS1 and *HLA-C*			
Donor *KIR2DS1*-negative	267/821 (32.5)	1.00	
Donor *KIR2DS1*-positive with *HLA-C1/C1*	41/166 (24.7)	0.71 (0.51–0.99)	0.05
Donor *KIR2DS1*-positive with *HLA-C1/C2*	49/195 (25.1)	0.67 (0.49–0.92)	0.01
Donor *KIR2DS1*-positive with *HLA-C2/C2*	19/51 (37.3)	1.51 (0.94–2.41)	0.09
Donor *KIR2DS1*-negative	267/821 (32.5)	1.00	
Donor *KIR2DS1*-positive with *HLA-C1/C1* or *C1/C2*	90/361 (24.9)	0.69 (0.54–0.88)	0.003
Donor *KIR2DS1*-positive with *HLA-C2/C2*	19/51 (37.3)	1.51 (0.94–2.42)	0.09
Donor *KIR2DS1*-positive with *HLA-C2/C2*	19/51 (37.3)	1.00	
Donor *KIR2DS1*-positive with *HLA-C1/C1* or *C1/C2*	90/361 (24.9)	0.46 (0.28–0.75)	0.002
Donor *KIR2DS1*-negative	267/821 (32.5)	0.66 (0.41–1.06)	0.09
Patient with *HLA-C1/C1* or *C1C2*‡	313/1069 (29.3)	1.00	
Patient with *HLA-C2/C2*	63/164 (38.4)	1.33 (1.01–1.75)	0.05
KIR3DS1 and *KIR2DS1*			
Donor *KIR3DS1*-negative	254/811 (31.3)	1.00	
Donor *KIR3DS1*-positive	122/422 (28.9)	0.86 (0.69–1.07)	0.17
Donor *KIR2DS1*-negative and *KIR3DS1*-negative	239/747 (32.0)	1.00	
Donor *KIR2DS1*-positive and *KIR3DS1*-positive	94/348 (27.0)	0.78 (0.61–1.00)	0.05
Donor *KIR2DS1*-positive and *KIR3DS1*-negative	15/64 (23.4)	0.68 (0.40–1.16)	0.16
Donor *KIR2DS1*-negative and *KIR3DS1*-positive	28/74 (37.8)	1.04 (0.70–1.55)	0.84
Partial *KIR* haplotype			
Donor with *Cen-A/A*	138/409 (33.7)	1.00	
Donor with *Cen-B/B*	34/121 (28.1)	0.77 (0.52–1.13)	0.18
HLA-match status			
10 of 10 alleles matched			
Donor *2DS1*-negative	143/427 (33.5)	1.00	
Donor *2DS1*-positive	63/215 (29.3)	0.85 (0.63–1.16)	0.31
Single-allele mismatch at loci other than *HLA-C*			
Donor *2DS1*-negative	72/248 (29.0)	1.00	
Donor *2DS1*-positive	34/127 (26.8)	0.84 (0.55–1.28)	0.42

Outcome	No./Total No. (%)	Hazard Ratio (95% CI)†	P Value
Single-allele mismatch at *HLA-C* locus			
Donor *2DS1*-negative	52/146 (35.6)	1.00	
Donor *2DS1*-positive	12/70 (17.1)	0.40 (0.20–0.78)	0.007
Relapse or death			
KIR2DS1			
Donor *KIR2DS1*-negative	591/850 (69.5)	1.00	
Donor *KIR2DS1*-positive	257/421 (61.0)	0.85 (0.73–0.99)	0.03
KIR2DS1 and *HLA-C*			
Donor *KIR2DS1*-negative	591/850 (69.5)	1.00	
Donor *KIR2DS1*-positive with *HLA-C1/C1* or *C1/C2*	225/370 (60.8)	0.82 (0.70–0.96)	0.01
Donor *KIR2DS1*-positive with *HLA-C2/C2*	32/51 (62.7)	1.18 (0.83–1.69)	0.36
Donor *KIR2DS1*-positive with *HLA-C2/C2*	32/51 (62.7)	1.00	
Donor *KIR2DS1*-positive with *HLA-C1/C1* or *C1/C2*	225/370 (60.8)	0.68 (0.47–0.98)	0.05
Donor KIR2DS1-negative	591/850 (69.5)	0.85 (0.59–1.21)	0.36
Death from any cause			
KIR2DS1 and *HLA-C*			
Donor *KIR2DS1*-negative	572/854 (67.0)	1.00	
Donor *KIR2DS1*-positive	253/422, (60.0)	0.87 (0.75–1.01)	0.06
Donor *KIR2DS1*-negative	572/854 (67.0)	1.00	
Donor *KIR2DS1*-positive with *HLA-C1/C1* or *C1/C2*	223/370 (60.3)	0.85 (0.73–1.00)	0.04
Donor *KIR2DS1*-positive with *HLA-C2/C2*	30/52 (57.7)	1.01 (0.69–1.46)	0.98
KIR3DS1 and *KIR2DS1*			
Donor *KIR3DS1*-negative	567/847 (66.9)	1.00	
Donor *KIR3DS1*-positive	258/429 (60.1)	0.83 (0.71–0.96)	0.01
Donor *KIR2DS1*-negative and *KIR3DS1*-negative	525/780 (67.3)	1.00	
Donor *KIR2DS1*-positive and *KIR3DS1*-positive	211/355 (59.4)	0.84 (0.71–0.99)	0.03
Donor *KIR2DS1*-positive and *KIR3DS1*-negative	42/67 (62.7)	0.87 (0.64–1.20)	0.40
Donor *KIR2DS1*-negative and *KIR3DS1*-positive	47/74 (63.5)	0.74 (0.55–1.00)	0.05
Grade II–IV acute GVHD			
KIR2DS1			
Donor *KIR2DS1*-negative	434/844 (51.4)	1.00	
Donor *KIR2DS1*-positive	213/418 (51.0)	0.97 (0.77–1.24)	0.83

*All models were adjusted for the patient's age, level of risk (low, intermediate, or high), cytomegalovirus (CMV) serostatus (positive or negative), and cytogenetic profile (no abnormalities, good risk, intermediate risk, or poor risk); use of T-cell depletion (yes or no); conditioning regimen (ablative with total-body irradiation, ablative without total-body irradiation, or nonablative); and *HLA* match (10 of 10 alleles vs. 9 of 10 alleles).

†Odds ratios are shown for grade II, III, or IV acute GVHD.

‡The hazard ratio was additionally adjusted for the presence of donor *KIR2DS1*.