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Donor *KIR B* Genotype Improves Progression-Free Survival of Non-Hodgkin Lymphoma Patients Receiving Unrelated Donor Transplantation

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Donor killer immunoglobulin-like receptor (*KIR*) genotypes are associated with relapse protection and survival after allotransplantation for acute myelogenous leukemia. We examined the possibility of a similar effect in a cohort of 614 non-Hodgkin lymphoma (NHL) patients receiving unrelated donor (URD) T cell–replete marrow or peripheral blood grafts. Sixty-four percent (n = 396) of donor-recipient pairs were 10/10 allele HLA matched and 26% were 9/10 allele matched. Seventy percent of donors had *KIR B/x* genotype; the others had *KIR A/A* genotype. NHL patients receiving 10/10 HLA–matched URD grafts with *KIR B/x* donors experienced significantly lower relapse at 5 years (26%; 95% confidence interval [CI], 21% to 32% versus 37%; 95% CI, 27% to 46%; $P = .05$) compared with *KIR A/A* donors, resulting in improved 5-year progression-free survival (PFS) (35%; 95% CI, 26% to 44% versus 22%; 95% CI, 11% to 35%; $P = .007$). In multivariate analysis, use of *KIR B/x* donors was associated with significantly reduced relapse risk (relative risk [RR], .63, $P = .02$) and improved PFS (RR, .71, $P = .008$). The relapse protection afforded by *KIR B/x* donors was not observed in HLA-mismatched transplantations and was not specific to any particular *KIR-B* gene. Selecting 10/10 HLA–matched and *KIR B/x* donors should benefit patients with NHL receiving URD allogeneic transplantation.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) can cure non-Hodgkin lymphoma (NHL) through the combination of chemotherapy and immune-mediated graft-versus-lymphoma (GVL) responses [1]. Long-term survival ranges from 30% to 70%, relapse being the major cause of treatment failure for all NHL histologic subtypes [2,3]. The mechanisms of tumor escape from GVL are poorly understood, but analyses of patients with acute myeloid leukemia (AML) after unrelated donor (URD) HCT reveal the importance of donor killer cell immunoglobulin-like receptor *(KIR)* genotype in effective GVL responses [4-6]. Natural killer (NK) cells reconstitute promptly after HCT and express inhibitory KIRs that interact with class I HLA-C1 (ligand for KIR2DL2/3), HLA-C2 (ligand for 2DL1), and HLA-Bw4 epitopes (ligand for 3DL1) to regulate NK cell education and function [7]. NK cells also can express activating KIRs 2DS1, 2DS2, 2DS3, and 2DS5 to coregulate antitumor effects by binding to HLA-C2 (2DS1) or neo-ligands on tumor cells. Individuals vary in the number of *KIR* genes contained in their genome. *KIR* genes are closely linked on chromosome 19q and inherited as haplotype A or B from each parent. The main difference between group A and B haplotypes is that group B contains variable numbers of activating *KIR* genes, whereas group A has a fixed gene content of inhibitory but no activating *KIR*. About 70% of the population has at least 1 *KIR B* haplotype. The haplotypes combine to give the *A/A* and *B/x* (*A/B* or *B/B*) genotypes [8]. The *KIR B* genotype can be further defined by a *KIR B* content

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score determined by the number of centromeric and telomeric motifs containing B haplotype–defining genes (permissible values 0 to 4). HLA and KIR genes segregate on different chromosomes (6 and 19) and are inherited independently. Although donor selection is guided by HLA matching, we hypothesized that donor *KIR* interactions with recipient HLA might influence clinical outcomes. Our previous studies showed that *KIR B/x* donors, and not *KIR A/A* donors, improve leukemia-free survival in recipients with AML [4-6]. The impact of *KIR* polymorphism on relapse and survival of patients with NHL after allo-grafting is unknown. In the current study, we investigated NHL patients receiving allogeneic URD HCT to determine the influence of donor *KIR* genotype and individual *KIR B* genes on clinical outcomes.

PATIENTS AND METHODS

We studied 614 adults (age >18 years) with NHL who underwent T cell–replete URD HCT between 1990 and 2009 facilitated by the National Marrow Donor Program. The outcome data were collected at the Center for International Blood and Marrow Transplant Research. The study protocol was approved by the institutional review board of the National Marrow Donor Program in accordance with the Declaration of Helsinki. Stored donor samples were obtained from the Center for International Blood and Marrow Transplant Research repository and genotyped for *KIR* [9]. *KIR* gene content was assessed, allowing each donor to be designated as either *KIR A/A* or *B/x* genotype.

Statistical Analysis

Progression-free survival (PFS) and overall survival (OS) were evaluated with Kaplan-Meier estimates [10]. Relapse, nonrelapse mortality, and acute graft-versus-host disease (GVHD) were evaluated using the cumulative incidence function. Clinical variables were tested for the proportional hazard assumption and were adjusted as needed through stratification. Stepwise forward-backward selection was performed to build multivariate Cox proportional hazards models with a threshold of .05 for model entry. Donor *KIR* genotype, the primary variable of interest, was forced into the model and adjusted for clinical variables. Other clinical variables analyzed were donor source, GVHD prophylaxis, conditioning regimen, HLA match, time from diagnosis to transplantation, histology group, disease status, in vivo T cell depletion, age, and Karnofsky performance score. To adjust for multiple testing, variable with $P < .01$ were considered statistically significant.

RESULTS

Patients, Disease, and Transplantation Characteristics

The ages of the 614 NHL patients ranged from 19 to 72 with a median of 50 years. Follicular lymphoma was the most common histology, followed by mantle cell lymphoma, diffuse large B cell lymphoma, and T cell NHL; patients with Burkitt/lymphoblastic lymphomas were excluded (Table 1). Almost all patients were Caucasians and 62% had chemosensitive lymphoma before transplantation. Most patients were at least 1.5 years from diagnosis to transplantation, 41% received myeloablative conditioning regimens, and 63% received filgrastim-mobilized peripheral blood stem cell grafts. The donor *KIR* genotype frequencies reflected those of a general Caucasian population; 30% were *KIR A/A* (n = 183) and 70% were *KIR B/x* (n = 431) with *KIR-B* content scores of 1 (n = 243), 2 (n = 140), or ≥ 3 (n = 48). We found no correlation between KIR *B/x* and donor ethnicity (Caucasian versus other 71% versus 68%, $P = .40$). Two-thirds of the donor-recipient pairs were 10/10 allele matched at *HLA-A, -B, -C, -DRB1*, and *-DQB1* (n = 396); the rest were 1 (n = 158) or ≥ 2 HLA allele (n = 60) mismatched. Fully matched recipients were older (52 versus 48 years, $P = .0053$), and more of them received reduced-intensity conditioning (RIC) (62% versus 52%, $P = .011$) and peripheral blood stem cell grafts (69% versus 53%, $P = .0003$) than HLA-mismatched transplant recipients. There were no significant differences for other clinical variables (Table 1). We then compared 10/10 HLA–matched donor-recipient pairs by donor *KIR* genotype and found similar patient and graft characteristics in patients with *KIR A/A* versus *KIR B/x* donors (Table 1).

Impact of KIR Genetics on Transplantation Outcomes

In the 10/10 HLA–matched HCT cohort (n = 396), *KIR B/x* donor grafts resulted in less relapse at 5 years after transplantation (26%; 95% confidence interval [CI], 21% to 32%) compared with *KIR A/A* donors (37%; 95% CI, 27% to 46%; $P = .05$). This relapse protection translated into improved PFS (*KIR B/x*, 35%; 95% CI, 26% to 44% versus *KIR A/A*, 22%; 95% CI, 11% to 35%; $P = .007$) (Figure 1A,B). After adjusting for important clinical variables, *KIR B/x* donors conferred significant protection against relapse (hazard ratio [HR], .63; 95% CI, .43 to .92; $P = .02$) and improved PFS (HR, .71; 95% CI, .55 to .91; $P = .008$) compared with *KIR A/A* donors. In evaluating the protection conferred by individual genes of the *KIR B* haplotype (*KIR2DS2, 2DS5, 2DL2, 2DS1, 3DS1, 2DS3*, and *2DL5*), we found that each *KIR* gene was associated with a similar degree of protection against relapse (relative risk [RR], .68 to .79; Figure 1C). Thus, individual centromeric and telomeric *KIR B* genes had similar influences on transplantation outcomes and donor with ≥ 3 *KIR B* genes conferred the best PFS compared with *KIR A/A* donors (RR, .47; 95% CI, .27 to .81; $P = .007$). The protective effect of *KIR B/x* donors was not observed for our cohort of HLA-mismatched transplantations (RR, 1.49; 95% CI, .87 to 2.55; $P =$ not significant). Donor *KIR* genotypes had no effect on 1-year nonrelapse mortality (*KIR B/x* versus *KIR A/A* HR, .8; 95% CI, .55 to 1.11; $P = .17$), grades II to IV acute GVHD (HR, 1.06; 95% CI, .82 to 1.38; $P = .67$), or chronic GVHD (HR, .91; 95% CI, .71 to 1.15; $P = .42$). Despite the effect on PFS, HCT recipients had similar OS when they underwent transplantation with *KIR B/x* versus *KIR A/A* donors (10/10 HLA–matched cohort: HR, .8; 95% CI, .61 to 1.06; $P = .12$; entire population: HR, .9; 95% CI, .74 to 1.1; $P = .40$). This likely reflects the growing number of immune options available to patients after receipt of an allograft.

Clinical Factors Affecting Transplantation Outcomes

The main factor associated with improved OS of entire population (n = 614) in adjusted multivariate regression was RIC conditioning (HR, .57; 95% CI, .42 to .77; $P = .0008$). Shorter OS was associated with chemotherapy-resistant disease (HR, 1.6; 95% CI, 1.08 to 2.40; $P = .02$), histology other than follicular lymphoma (HR, 1.74 to 2.06; $P = .0001$), and using ≥ 2-locus HLA-mismatched donors (≤8/10 match HR, 1.46; 95% CI, 1.06 to 2.01; $P = .02$; 9/10 match HR, 1.09; 95% CI, .81 to 1.47; $P = .57$). Transplantation-related mortality (TRM) was better with RIC conditioning (HR, .6; 95% CI, .5 to .8; $P = .001$) and follicular lymphoma histology (HR, .5; $P = .03$) and was not influenced by GVHD prophylaxis and *KIR* status (*KIR B/x* HR, .97; 95% CI, .74 to 1.27; $P = .81$). HCT using donors with ≥ 2-locus HLA mismatch had increased TRM (HR, 1.5; 95% CI, .99 to 2.26; $P = .056$). Factors associated with increased relapse were chemotherapy resistance (HR, 1.57; $P = .001$), in vivo T cell depletion (HR, 1.53; $P = .006$), histology other that follicular lymphoma (HR, 1.66 to 1.88; $P = .02$), and ≥ 2-locus HLA mismatch (≤8/10 match HR, 1.8; $P = .016$; 9/10 match HR, 1.19; $P = .3$). There were no interactions between the in vivo T cell depletion and < 10/10 HLA mismatch. Adjusted incidence of grades III to IV acute GVHD was reduced with tacrolimus/other (mostly methotrexate) GVHD prophylaxis (HR, .64; 95% CI, .38 to 1.07) compared to