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The Optimal Killer Cell Immunoglobulin-Like Receptor Donor—We Can Recognize, but Can We Search?

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The role of natural killer (NK) cells in relapse protection after hematopoietic cell transplantation (HCT) for patients with acute myelogenous leukemia (AML) is well recognized and has been extensively studied using various models of NK cell alloreactivity [1]. Among numerous NK cell receptors, the most extensively studied are the killer cell immunoglobulin-like receptors (KIRs), which can be either inhibitory or activating. The binding of inhibitory KIRs to their ligands (major histocompatibility complex class I molecules) protects the cell from NK cell cytotoxicity. However, as defined by the "missing self" hypothesis, if this recognition is lost or dampened, as is the case with many tumor cells that downregulate HLA molecules, NK cells exhibit cytotoxicity against the target cell [2].

Another perspective of defining NK alloreactivity focuses on the composition and location of the activating and the inhibitory KIRs. Based on this, all individuals can be broadly classified as carrying 1 of the 2 haplotypes with distinct KIR gene-content motifs located at centromeric (Cen) or telomeric (Tel) regions. Haplotype A is characterized by a predominance of inhibitory KIR genes, whereas haplotype B is characterized by a predominance of activating KIR genes [3-5]. Cooley et al. [6] showed that AML patients who underwent unrelated donor (URD) HCT from a KIR haplotype B/x donor had a significantly lower risk of relapse and superior survival, especially if the KIR B genes were homozygous and located in the Cen region (Cen-B/B), as compared to other donors [5]. Based on these results, the authors classified URD as "neutral" (none or 1 KIR B-motifs), "better" (2 or more B motifs without Cen-B/B), or "best" (2 or more B motifs with Cen-B/B) [4] [Table I] and showed that HCT in HLA C1/x recipients with the better/best URD was associated with a lower risk of relapse and improved survival than the neutral donors [4].

In the article accompanying this editorial, Weisdorf et al. [7] tested the generalizability of this concept in a multicenter prospective trial and assessed whether the KIR genotype information could be integrated with the URD search in an attempt to enhance the chances of selecting the "best" or the "better" donor for patients with AML. The study enrolled 535 patients at 14 centers, for whom 2080 potential donors were identified, who were then contacted by the Center for International Blood and Marrow Transplant Research for additional KIR genotyping. The donors then sent their buccal swabs to a central laboratory for KIR typing. A total of 916 donor were KIR genotyped; of the 247 patients who finally underwent URD HCT, 76% (n = 189) received a KIR-genotyped donor. Among these, about 12% (n = 23) had the "best" donor and about 25% (n = 48) had the "better" donor, which are roughly similar to the frequencies expected with a randomly selected donor (about 11% and 20%, respectively).

This study highlights several crucial challenges of any large clinical trial, especially those that require practice change. First, over the 5-year study period, 7359 URD searches were conducted at the 14 participating centers for 2839 patients; however, only 19% (n = 535) were enrolled in this trial. One of the reasons for low accrual could be the hesitation of treating physicians and concerns about potential delays in HCT. However, as shown in the study, the KIR genotyping was completed at a median of 14 days from the time of donor request and did not delay the transplantations. The median time from donor search to HCT was similar in patients who received a KIR-genotyped donor and those whose donors were not genotyped (median 84 versus 92 days, respectively). The low accrual rate noted in this study is actually harmonious with prior studies of general oncology clinical trial participation [8,9]. In addition, physicians' preference has been recognized as one of the major reasons for not enrolling even eligible patients on clinical trials [10,11].

Next, even for the enrolled patients, 56% of the donors were not KIR genotyped either because the donor center was not participating or the donor declined the KIR typing. Considering that the random probability of a donor being the "better" or the "best" donor is about 30%, at least 4 donors per patient

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Table 1
KIR haplotype group nomenclature.

KIR Genotype	*KIR B* Motif Content	Centromeric Haplotypes	Telomeric Haplotypes	KIR Donor Group[a]	
A/A	0	*A/A*	*A/A*	Neutral	*KIR-Neutral* (zero or one B motif)
B/x	1	*A/A*	*A/B*	Neutral	*KIR-Neutral* (zero or one B motif)
B/x	1	*A/B*	*A/A*	Neutral	*KIR-Neutral* (zero or one B motif)
B/x	2	*A/A*	*B/B*	Better	*KIR-Better/Best* (two or more B motifs)
B/x	2	*A/B*	*A/B*	Better	*KIR-Better/Best* (two or more B motifs)
B/x	2	*B/B*	*A/A*	Best	*KIR-Better/Best* (two or more B motifs)
B/x	3	*A/B*	*B/B*	Better	*KIR-Better/Best* (two or more B motifs)
B/x	3	*B/B*	*A/B*	Best	*KIR-Better/Best* (two or more B motifs)
B/x	4	*B/B*	*B/B*	Best	*KIR-Better/Best* (two or more B motifs)

[a]Better *KIR* donors have two or more B motifs without *Cen-B/B*, and Best *KIR* donors have two or more B motifs with *Cen-B/B*.

would need to be KIR genotyped to significantly increase the likelihood of finding the "better" or the "best" donor. The study was unsuccessful in reaching this target because only a median of 1.6 (range 0 to 5) donors were KIR genotyped per individual patient search.

Another perspective that needs further evaluation is whether the concept of KIR-based donor hierarchy applies across racial and ethnic groups, which was not described in the article. Human KIRs recognize 4 epitopes of HLA-A, -B, and -C, the distribution of which varies considerably among people from different parts of the world, and by racial and ethnic groups [12]. It is conceivable that white patients, especially those of European descent, would benefit the most from donor KIR genotyping because the probability of finding a matched URD is the highest in this group [13]. Conversely, minority groups, such as the blacks of South or Central American descent, who have very low probability of finding a matched URD [13], may not be as fortunate to have multiple potential donors.

Over time, if this evidence-based concept is to be generalized, this will require not only strategic recruitment but also increased education of care providers on both the recipient and donor sides. Moreover, measures to implement large-scale efforts to collect and integrate KIR genotype data up front into the HLA database may further expedite the search process and minimize the hesitancies of treating physicians. The cost-effectiveness of this approach is a matter of further investigation.

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