Choosing the Alternative

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Since the fundamental impact of HLA compatibility on the outcome of allogeneic hematopoietic stem cell transplantation (HSCT) was first demonstrated, efforts from the worldwide transplant community have been focused on 2 challenging and somewhat contradictory tasks: on the one hand, increasing the pool of volunteer stem cell donors to increase the chance of finding an acceptable match for patients in need of a transplant, and on the other hand, devising strategies to improve the feasibility and safety of HSCT from partially HLA-incompatible donors for all those patients that still do not find a match.

In particular, the last few decades have witnessed galloping advances in the development of strategies to modulate T cell alloreactivity in vivo, in the biotechnological possibilities for graft processing, and in the efficacy of anti-infectious supportive care. Altogether, these advances have turned HSCT from "alternative" donor sources (namely HLA-haploidentical family members and umbilical cord blood units) into an option that is not only feasible but also has outcomes that are at least not inferior to those of HSCT from HLA-matched donors [1-4].

The article by Imus et al published in this issue of *Biology of Blood and Marrow Transplantation* [5] makes an intriguing and provocative step forward in this direction. The authors report clinical evidence suggesting that, at least for some patients who relapse after a previous allogeneic HSCT, an HLA-mismatched second donor might actually be a better choice than an HLA-matched donor.

Because of the development of less toxic conditioning regimens and the improved control of late post-transplantation effects, including chronic graft-versus-host-disease, second allogeneic HSCTs have become a feasible option for patients experiencing disease relapse after a first transplant. A number of retrospective studies, mainly focused on HLA-matched related or unrelated HSCT, have convincingly shown that "fit" patients who relapse at least after 6 months from the first transplant can benefit from a second transplant, achieving long-term disease-free survival in a sizable proportion of cases [6].

In the studies that addressed this specific issue, changing the stem cell donor for the second transplant (which in most cases meant switching from a sibling to an HLA-matched unrelated donor, or between 2 HLA-matched unrelated donors), did not provide a significant advantage for disease recurrence or long-term survival, compared with selecting the original donor for the second transplant [7].

Imus et al. report the experience collected over the last 10 years at the Sidney Kimmel Comprehensive Cancer Centre at Johns Hopkins, Baltimore, where patients who relapsed after HLA-matched transplants were systematically offered haploidentical HSCT, and those who relapsed after a first haploidentical HSCT were retransplanted from a different haploidentical donor matched with the patient for the other HLA haplotype.

Intriguingly, the authors observe that the exposure to a new donor-derived immune system mismatched for a previously unencountered HLA haplotype, conferred to the patients a significant advantage in terms of both event-free and overall survival.

From a biological standpoint, switching from an HLA-matched to a mismatched donor means that the antileukemic response will no longer depend only on T cells specific for tumor antigens or minor histocompatibility antigens with generally limited precursor frequencies but also on T cells directly alloreactive to the mismatched HLA molecules, which are known to be far more numerous [8]. In a large retrospective study on haploidentical transplants, the higher magnitude of antihost alloreactivity did not translate into a lower incidence of disease relapse compared with HLA-matched HSCT [9]. However, the evidence provided here suggests that the picture is different in the context of second transplants, when leukemia has further increased its aggressiveness and possibly devised mechanisms to evade conventional antigen-specific T cell responses.

Even more biologically solid is the rationale for changing the stem cell donor after a first haploidentical HSCT. We and others have demonstrated that up to one third of relapses after haploidentical HSCT are characterized by leukemic variants that have undergone genomic loss of the HLA haplotype targeted by donor-derived alloreactive T cells [10-13]. By this loss of heterozygosity, leukemic cells render themselves "invisible" to the T cells of the original donor. Therefore, the presence of an "HLA loss" relapse represents a contraindication against donor lymphocyte infusions or a second transplantation from the original stem cell donor [14]. Conversely, choosing a different haploidentical donor matched with the patient for the other HLA haplotype entangles a unique immunogenetic situation in which donor T cells will still be haploidentical to the patient healthy tissues but 100% HLA mismatched with the relapsed leukemia (Figure 1). This is likely to be the biological basis for the clinical observation that, in the largest series of HLA loss relapses reported to date [15], a second transplant from a donor mismatched for the HLA alleles present on the relapsed leukemia, was the

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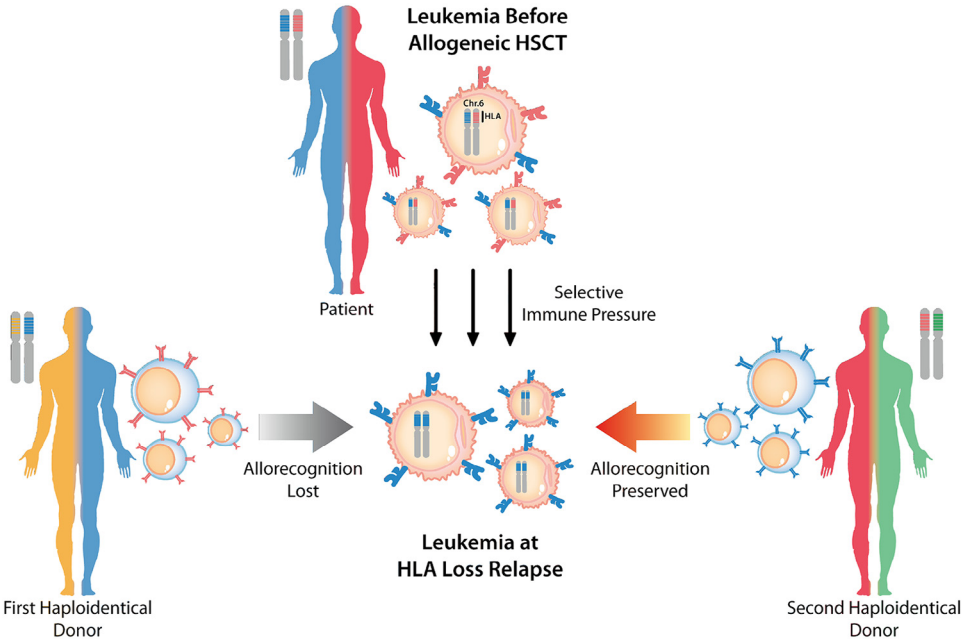

Figure 1. Second haploidentical HSCT for HLA loss relapses. Schematic model of the rationale supporting the change of haploidentical donor for second HSCT in patients who experience an "HLA loss" post-transplantation relapse after the first transplant. Leukemic cells, originally heterozygous, are exposed to an intense immunologic pressure after haploidentical HSCT, mostly mediated by donor T cells alloreactive against the mismatched HLA haplotype (in red). This selective pressure favors the emergence of mutant variants that lack the red HLA haplotype and are therefore no longer recognized by the first donor T lymphocytes. Conversely, a different haploidentical donor, matched to the patient for the other HLA haplotype, will carry T cells that are alloreactive against the blue HLA haplotype, conserved by the leukemic blasts. (This figure is available in color online at www.bbmt.org.)

treatment associated with the longest overall survival against these peculiar relapse variants. Of notice, HLA loss relapses tend to occur later than their "classical" counterparts [15], when most of the patients have recovered from the toxicities of the first transplant.

The series reported by Imus et al. is rather small and retrospective and needs confirmation in properly statistically powered prospective studies. Nonetheless, it provides new support to the growing evidence on the clinical potential of HSCT from "alternative" donors and provocatively suggests that the "best" donor might not always be synonymous with the "best-matched" donor, as already suggested several years ago by the high incidence of relapse observed after HSCT from syngeneic twins [16,17]. Finally, the report by Imus et al. offers a salutary reminder that a deeper understanding of the biology underlying the graft-versus-leukemia effect and post-transplantation relapse might rapidly translate into new rationales for clinical HSCT practice.

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Conflicts of interest statement:

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