TRANSPLANTATION

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Unrelated donor selection with PTCy

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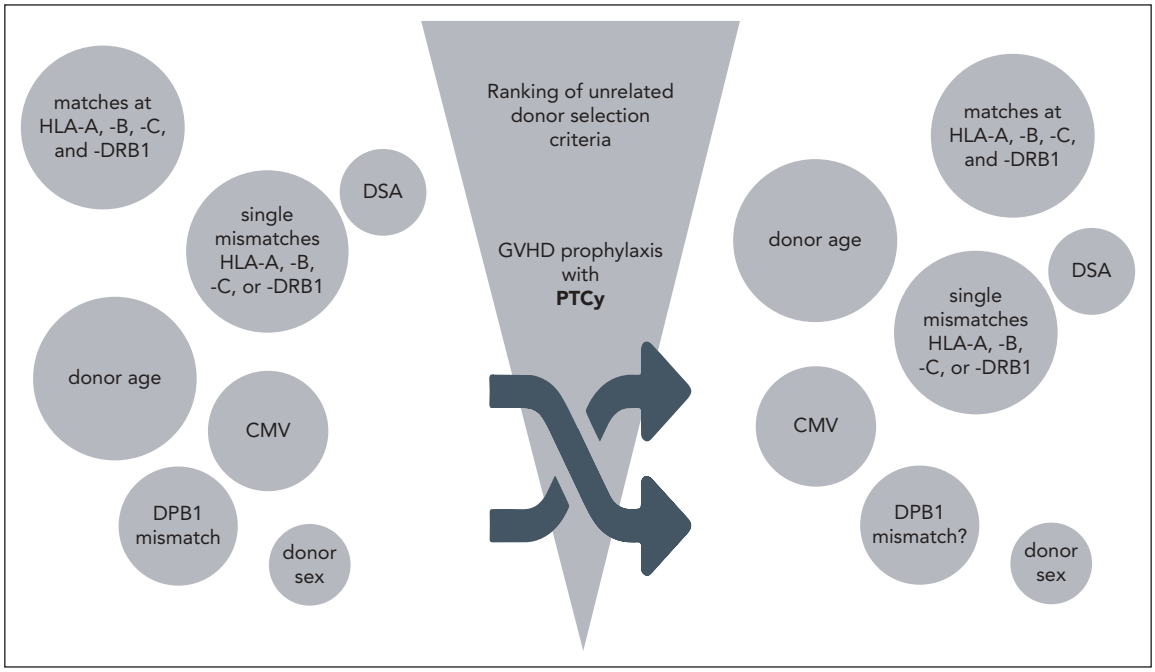
In this issue of *Blood*, Sanz et al retrospectively analyze data on patients with acute myeloid leukemia in complete remission who received allogeneic hematopoietic stem cells from matched (10 of 10) or partially mismatched (9 of 10) unrelated donors (MMUDs) with graft-versus-host disease (GVHD) prophylaxis built on posttransplant cyclophosphamide (PTCy).[1] The study addresses the important issue of whether donor selection should be informed by the type of GVHD prophylaxis, specifically PTCy (see figure). Using HLA matching for *HLA-A, -B, -C; -DRB1*; and *-DQB1*, the study shows, surprisingly, that donor age and not HLA disparity was the most important predictor for survival after transplantation in PTCy-treated patients.

Why is this observation intriguing? At the molecular level, neither the effect of donor age nor permissiveness of certain HLA mismatches is fully understood. Donor selection algorithms are based on predictive models, which work well when patients and treatments resemble those of the original data sets. The current guidelines for the selection of unrelated donors date from 2019 and are not based on studies with large numbers of patients who received PTCy as GVHD prophylaxis.[2] PTCy was formally established as a new standard for GVHD prophylaxis for patients with matched or partially matched related or unrelated donors who received reduced-intensity conditioning regimens in 2023 based on results of a randomized controlled trial. This trial demonstrated superior GVHD-free and relapse-free survival with PTCy after transplantation compared with tacrolimus plus methotrexate.[3] Further randomized, controlled trials are now underway comparing PTCy with alternative standard regimens for GVHD prophylaxis (eg, NCT05153226 and NCT04888741). The current data suggest that PTCy induces tolerance in the context of HLA disparity more effectively than alternative approaches.[4,5]

Genetic variation in the peptide-binding pocket of an HLA molecule may change the peptide-binding motif (PBM) to a lesser or greater extent. HLA disparity can thus be quantified experimentally by the degree of overlap of the immunopeptidome of HLA molecules. This functional classification allows for the assignment of HLA class I mismatches into PBM matches and mismatches. In an elegant proof-of-concept study, Crivello et al demonstrated that the degree of overlap between PBMs of mismatched donor-recipient pairs defined the risk of



This figure visualizes possible shuffling of unrelated donor selection criteria by posttransplant cyclophosphamide (PTCy)–based GVHD prophylaxis. The current evidence is not yet robust enough for PTCy-specific recommendations. CMV, cytomegalovirus; DSA, donor-specific antibodies.

GVHD and nonrelapse mortality with non–PTCy-based GVHD prophylaxis.[6]

Superior fitness of hematopoietic stem cells from younger individuals to reconstitute hematopoiesis was demonstrated decades ago.[7] Nevertheless, age-related changes of stem cell products are multifaceted. These changes may affect stem, immune effector, and regulatory cell populations, and some have been described at the molecular level. The favorable impact of young donor age on patient survival was first described in a large retrospective 2001 study from the Center for International Blood and Marrow Transplant Research and was confirmed in several subsequent studies.[8,9] To harness the beneficial impact of young hematopoietic stem cell grafts, a large pool of young donors is critical and, consequently, donor registries worldwide have been enrolling young volunteers preferentially. Several recent studies have described pronounced age effects, possibly related to the more recent ability to choose ever-younger unrelated donors. Mechanistically it is still unclear which aging-related cellular or subcellular changes are responsible for the negative effect of older donor age.

Sanz et al describe how young donor age retains its beneficial impact with PTCy-based GVHD prophylaxis. Notably, the impact of HLA class I and II mismatches appeared to be smaller with PTCy than in earlier studies with non–PTCy-based GVHD prophylaxis. This is an interesting observation and, if confirmed, may have consequences for future donor selection.

Certain caveats remain. First, owing to the nature of this retrospective analysis the dose of PTCy, coadministration of antithymocyte globulin/alemtuzumab, or the adjunct immunosuppression (calcineurin or mammalian target-of-rapamycin inhibitors with or without mycophenolate mofetil) was *not* standardized. It is unclear whether tolerance induction, especially with class I and II HLA mismatches, works similar across all possible variations. Second, in this retrospective study balanced acute myeloid leukemia risks cannot be assumed for all subgroups because major risk factors, e.g. mutations in *TP53*, *RUNX1*, or *ASXL1* genes, have not been evaluated. Finally, the fact that the impact of concurrent HLA DPB1 mismatches could not be analyzed in this study due to incomplete data and the moderate sample size add to the remaining uncertainty.

Sanz et al's data suggest that the relevance of single HLA mismatches may decrease and the relevance of donor age may increase with PTCy-based GVHD prophylaxis. Because the study does not show superior survival for a young, mismatched, unrelated donor over an older, matched, unrelated donor, donor age still should not trump HLA compatibility.[10] However, young MMUDs represent an alternative when HLA-matched related or unrelated donors are not available.

Given the excellent results of mismatched unrelated donor transplantation with PTCy in this study, the practical question arises whether young MMUDs or young haploidentical donors should be preferred. This question is being addressed in prospective, randomized trials (NCT03275636) and retrospective registry-based studies. Notably, both options may be limited by donor-specific HLA antibodies. Yet, the consideration of mismatched unrelated donors broadens the number of alternatives.

More research is needed to better understand mechanistically the impact of immunological donor factors in the context of PTCy and to provide empirical justification for PTCy-specific donor selection algorithms.

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