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The Bottom Line Identifying the Best Haploidentical Donor: Are We There?

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In this issue of *Biology of Blood and Marrow Transplantation*, Solomon et al. [1] report a study on how to select the optimal donor for an unmanipulated HLA-haploidentical transplant (HAPLO), using post-transplant cyclophosphamide (PT-CY) for graft-versus-host disease (GVHD) prophylaxis. The issue is of importance given the rapidly increasing number of HAPLO transplants worldwide [2], and has been the object of several previous studies [3-10].

First of all, let us look at the patient population (n = 208) in Solomon et al. [1]: 66% received unmanipulated peripheral blood and 34% bone marrow; the ethnic origin (race is a term that should be abandoned) was non-Caucasian in 41% of the patients; the intensity of the conditioning regimen was nonmyeloablative in 59%, and 33% of patients had a high disease risk index; 46% of patients had a hematopoietic cell transplantation-comorbidity index >2; HLA-DP nonpermissive mismatch was present in 23% of patients; the diagnosis was acute leukemia in 51%, myelodysplastic syndrome/myeloproliferative neoplasm in 20%, and lymphoma in 25%. The conclusions of Solomon et al. are as follows:

1) HLA-DR mismatch has a positive effect on survival, due to a reduced risk of nonrelapse mortality (NRM).
2) HL DP nonpermissive mismatch is associated with reduced risk of relapse.
3) Killer cell immunoglobulin-like receptor (KIR)–ligand mismatching and a KIR B/x genotype protect patients against relapse.
4) Increased HLA disparity protects against relapse.
6) Inferior survival is seen with parental donors and cytomegalovirus (CMV)-negative donors in CMV-positive recipients

Finally, a donor risk score is constructed, to identify the best possible HAPLO donor: overall survival is predicted by the donor score, both in patients with low/intermediate disease score index as well as in patients with high/very high disease score index.

Why DR mismatch in the GVHD direction should ameliorate NRM is a mystery, as the authors themselves admit: this result is counterintuitive to what is expected, and it may be just a question of chance in this particular population, which would not be reproduced on larger numbers. In addition, the role of mismatch for single HLA loci has been studied in unrelated donors by matching all other HLA loci [11]. When multiple mismatches are present, this becomes very difficult, because one would have to stratify DR matched or mismatched pairs, according to HLA-A, -B, -C, -DQ, and -DP mismatching, and of course this would require thousands of patients. As to HLA-DP nonpermissive mismatch, this is the first report on DP mismatching in HAPLO grafts, in keeping with other studies in unrelated donor transplants [12]. However, the same criticism as for DR holds true: we do not know the degree of mismatching in other HLA loci, for DP nonpermissive matched or mismatched pairs, but this result is interesting and needs to be looked at in larger cohorts of patients. KIR-ligand mismatching and a KIR B/x genotype have been shown to protect patients against relapse in several settings [13-15]: we have looked at 86 patients with leukemia, undergoing a HAPLO transplants with PT-CY, and have failed to find an association of KIR mismatching with relapse (unpublished data).

As to HLA disparity, we have recently studied 318 patients receiving a HAPLO graft with PT-CY [7]: we looked at

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the vector of mismatch (GVHD or host versus graft) and at the number of mismatched antigens, stratifying patients as low (0 to 2 HLA antigens) or high (3 to 4 HLA antigens) mismatches. We failed to show any correlation of mismatching and outcome. The European Group for Blood and Marrow Transplantation has studied 559 unmanipulated HAPLO grafts: the number of HLA mismatches did not influence outcome; however, a DR mismatch was an independent risk factor for GVHD and a B mismatch was an independent risk factor for NRM [6]. Other negative factors affecting GVHD were the use of peripheral blood as a stem cell source, a myaloablative regimen, and a negative CMV donor [6]

Wang et al. [3] also see no effect of HLA mismatching on relapse or survival: they report a negative effect of female-to-male combination and worse outcome for a mother compared with father with offspring grafts. In the large Baltimore experience donor age was not predictive, whereas there was a trend for a higher mortality in female-to-male combinations [10]. We have looked at 469 HAPLO grafts with PT-CY and NRM was 15% in female-to-male grafts, versus 18% for other combinations, and we see more NRM in minor ABO-mismatched grafts compared with matched or major-mismatched grafts (32% versus 18%; $P = .03$) (unpublished data).

In conclusion, there is really no consensus on how to select the optimal HAPLO donor for an unmanipulated graft: possibly younger age, CMV status, donor gender, and ABO matching are general characteristics we can all agree on, because they make donation and transplantation easier. HLA mismatch does not seem to play a major role, when either PT-CY or antithymocyte globulin is used for GVHD prophylaxis, whereas DP mismatch should be looked at, possibly with comparable degrees of mismatch on the other HLA loci. One reason for these discrepant results is that mortality is actually low, and we have a relatively small number of events to work with; in addition, the number of variables is such that it is very hard to compare different platforms: stem cell source, intensity of the conditioning regimen, GVHD prophylaxis, patients age, and of course disease phase. All play crucial roles, and may be stronger predictors of survival as compared with donor characteristics.

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