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HLA matching in the PTCy era: the locus still matters. Comment on: Selection of unrelated donors for allogeneic transplantation using post-transplant cyclophosphamide in acute lymphoblastic leukemia: an analysis by the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

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To the Editor

We read with interest the study by Sanz *et al.,* reporting comparable outcomes for patients with acute lymphoblastic leukemia (ALL) undergoing allogeneic hematopoietic cell transplantation (HCT) from 7/8 mismatched unrelated donors (MMUD) and 8/8 matched unrelated donors (MUD) in the context of post-transplant cyclophosphamide (PTCy) prophylaxis (1). While this work is thought-provoking, we respectfully caution against broad extrapolation of equivalence between MMUD and MUD.

Not all HLA mismatches carry the same immunologic risk (2). Petersdorf *et al.* demonstrated that HLA-B leader mismatch was associated with inferior survival in patients receiving 1-allele MMUD (2). Although this was observed in the pre-PTCy era, subsequent data from the Japanese Society for Transplantation and Cellular Therapy showed that HLA-B leader mismatch continued to negatively impact outcomes even with PTCy, being associated with significantly worse overall survival and a trend toward higher relapse in patients with ALL and lymphoma (3). In our retrospective cohort receiving PTCy in combination with ATG, MMUD with HLA-A or

HLA-B mismatches was associated with markedly worse outcomes, whereas mismatches at other loci yielded survival comparable to 10/10 MUD. On multivariable analysis, HLA-A and HLA-B mismatches remained independent predictors of inferior survival and higher non-relapse mortality (4).

These findings highlight that mismatches differ in their impact, and combining all 7/8 donors into a single group may obscure important locus-specific risks, even within a uniform disease population. Until larger studies provide detailed analyses by specific antigen- or allele-level mismatches, caution is warranted before assuming full equivalence between 7/8 MMUD and 8/8 MUD.

We therefore advocate for more nuanced reporting, ideally distinguishing HLA-A vs. HLA-B vs. HLA-C vs. HLA-DRB1 mismatches, and further research to determine whether particular mismatches could be “permissible” in the PTCy era. This granularity will be crucial to inform donor selection accurately and safely.

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