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"

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 (PT-Cy) 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 one-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 *versus* HLA-B *versus* HLA-C *versus* 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.

Authors

Nihar Desai[1,2] and Jonas Mattsson[1,2]

[1]Hans Messner Allogeneic Blood and Marrow Transplant Program, Princess Margaret Cancer Center, University Health Network and [2]Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

Correspondence:
J. MATTSSON - jonas.mattsson@uhn.ca

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Contributions

ND wrote the first draft of the manuscript. JM revised the manuscript and provided critical inputs.

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