Not all mismatches are equal: importance of alloreactivity direction

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Allogeneic stem cell transplant (allo-HCT) remains the only curative therapy for numerous haematological malignant and benign conditions. This comes with significant morbidity and mortality risk related to the transplant, graft versus host disease (GVHD) and relapse. The art of medicine in allo-HCT lies in walking the tight rope between relapse risk and graft-versus-host disease (GVHD). We have come a long way in minimising the risks of GVHD with rates in clinically significant (Grade 2-4) acute GVHD and moderate to severe chronic GVHD reported as low as 50% and 30% respectively.[1],[2] This is, no doubt, related to more widespread use of T-cell depletion methods and better HLA typing.[3] Optimal donor selection in the absence of a matched relative relies on an assessment of the relative risk, and selection of the donor most genetically suitable based on HLA matching at HLA-A, -B, -C, DR and DQ. Human-leukocyte-antigen DPB1 (HLA-DPB1) mismatch is known to be broadly associated with decreased relapse at the cost of increased rates of acute GVHD (aGVHD).[4] HLA-DPB1 mismatch in otherwise matched donors is common, yet our ability to predict GVHD severity based on this mismatch is limited. In this issue, Zou et al[5] present data supporting HLA-DPB1 mismatch associated risks of acute graft versus host disease whilst using clinical correlation to investigate the clinical impact of HLA-DPB1 molecular mismatch.

In the last two decades, donor selection algorithms have classified HLA-DPB1 mismatches as permissive or non-permissive, based on functional toxicity assays and T cell epitope (TCE) analysis.[6],[7] While these methods assess the qualitative character of a mismatch, they do not evaluate direction or anticipate immunogenicity of a given mismatch. This poorly characterised potential risk represents a limitation of current donor selection algorithms.
By contrast, molecular matching techniques assess structural components of epitopes, called eplets, allowing quantification of donor and recipient mismatched eplets (ME). This quantification, when combined with the PIRCHE score (PS), a predictor of TCE alloreactivity, has been shown to predict immunogenicity and clinical outcomes in haploidentical transplant recipients.[8] Zou et al[5] present novel data on the use of molecular algorithms for HLA-DPB1 mismatch, in a cohort of over 1500 patients who underwent unrelated donor transplant between 2005-2018 at The University of Texas MD Anderson Cancer Center. The primary question in this study is whether molecular matching offers superior prognostic guidance than the traditional TCE model. The group reports concordance testing of bidirectional ME and PS as well as the TCE model, with aGVHD outcomes. The central finding is that high levels of GVH-direction ME are the strongest single predictor of aGVHD. The authors propose use of molecular algorithms to guide the choice of or augmentation of aGVHD prophylaxis.

Another crucial finding is the importance of direction of alloreactivity. Bidirectional high ME or PS mismatch is universally associated with high rates of aGVHD and relapse, suggesting a synergistic effect. The reduced relapse risk purported to arise from HLA-DPB1 permissive mismatch was only observed amongst those with high GVH-direction ME or PS, and not those with isolated high-HVG direction PE or MS, who in fact had an increased rate of relapse. This is a clinically important outcome as it forces re-evaluation of the rationale for tolerating increased GVHD in HLA-DPB1 permissive mismatch recipients.

Building on the existing TCE model for HLA-DPB1 mismatch classification, there are several findings offering refined stratification. Amongst the permissive mismatch group, high HVG ME and PS are associated with high risk of GVHD, yet amongst non-permissive mismatched cases, an isolated high HVG ME is associated with low GVHD risk. The empirical inconsistency of these results highlights the persisting incomplete understanding of HVG pathophysiology.

While the outcomes reported here have potential to alter practice in the future, the authors acknowledge the need for significant further study. Involvement of only a single centre is a significant limitation. The retrospective nature of this research is not problematic in itself given the correlative nature of the analyses performed. However, one of the great challenges in allo-HCT transplant is the rapidly evolving landscape across which research is...
performed. Since the commencement of this study, the adoption of T cell depleting therapies has rapidly expanded. Across the trial period, anti-thymocyte globulin (ATG) use significantly increased (23.7% to 41.2%). It is unknown whether, and if so how, this has augmented results. Confirmatory investigations will be important to validate current findings and confirm them as enduring in the setting of routine T cell depletion.

Another important development has been the use of post-transplant cyclophosphamide in haploidentical allo-HCT. The associated rapid improvement in clinical outcomes has shifted the donor selection paradigm. If anything, the uptake of haploidentical transplant reinforces the importance of this trial. With increased availability of alternative donors, the imperative to refine outcome prediction in HLA-DPB1 mismatch is all the more relevant.

A further potentially significant development relates to the evolution of therapies for GVHD.[2],[9] More efficacious treatment and prevention strategies for GVHD may redefine donor selection algorithms, permitting mismatches that were previously prohibitive.

Zou et al[5] present an important novel approach to assessment of HLA-DPB1 mismatch permissibility. The authors acknowledge that confirmation of their findings with multi-centre data is needed before refinement of algorithms can be considered. One of the great challenges for the field of HCT moving forward is access to progressively more specialised molecular testing. There is also the need to embrace international research collaborations to allow real-time outcome reporting in a rapidly progressing field.
References


Figure 1. Competing risks regression for acute GVHD grade 2-4

Figure 2. Competing risks regression for non-relapse mortality

Figure 3. Competing risks regression for relapse
Competing-risks regression for acute GVHD grade 2-4

- HR 1.73, P value 0.008
- HR 1.06, P value 0.723
- HR 0.98, P value 0.928

Cumulative Incidence

Months after transplantation

Low ME GVH + Low ME HVG
Low ME GVH + High ME HVG
High ME GVH + Low ME HVG
High ME GVH + High ME HVG
Competing-risks regression for non-relapse mortality

HR 1.90, P value 0.008

Cumulative Incidence

Months after transplantation

Low ME GVH

High ME GVH
Competing-risks regression for relapse

HR 1.49, P value 0.042
HR 1.38, P value 0.192
HR 1.12, P value 0.574

Cumulative Incidence

Months after transplantation

Low ME GVH + Low ME HVG
Low ME GVH + High ME HVG
High ME GVH + Low ME HVG
High ME GVH + High ME HVG