Donor dilemmas in hereditary hematopoietic malignancies

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In this issue of *Haematologica*, Roloff and colleagues[1] present an approach to timely evaluation for hereditary hematopoietic malignancies (HHM) in the allogeneic stem cell transplant (alloSCT) setting, with a focus on minimizing harm arising from use of a matched related stem cell donor harboring a deleterious germline variant. Twenty-two patients were grouped into four categories based on personal and family history and initial tumor sequencing, with differing strategies applied to optimize stem cell donor selection. Several key issues relating to the HHM and alloSCT setting are presented, along with suggested management strategies specific to the clinical situation.

Central to the importance of the work by Roloff and colleagues is the relatively recent recognition of the significant prevalence (~5-10%) of germline predisposition conditions in adults with myelodysplastic syndrome (MDS)[2] and acute myeloid leukemia (AML),[3] with higher rates in children.[4,5] Adding to the challenge of the sheer weight of numbers of HHM diagnoses is the fact that, in many cases, a clinical suspicion of an underlying HHM may not be roused from the personal or family history alone. The most important example of this is *DDX41*-related hematologic malignancy predisposition syndrome, now recognized to be the most commonly implicated gene in HHM.[6] Typical features of this disease include a median age of malignancy onset being the same as that of sporadic MDS or AML, along with a normal physical examination and an often unremarkable family history reflecting incomplete disease penetrance, which taken together provide the rationale for routine assessment of *DDX41* in all newly presenting patients with MDS/AML,[6] most particularly for those who may be considered for alloSCT.

Looking beyond *DDX41*-HHM and considering HHM more broadly, it has been suggested that the prevalence of deleterious germline variants in the MDS/AML population provides the rationale to undertake comprehensive germline assessment for all patients regardless of their age at diagnosis.[2,7] The ability to undertake this will depend on test accessibility, funding and patients' consent; however, one of the very appealing things about this 'broad brush' approach is that applying a uniform strategy would aid simplification of complex clinical decision-making. The complexity of alloSCT donor selection in proven or suspected HHM is demonstrated by the four different approaches in the work by Roloff and colleagues.

Also highlighted in this work is the importance of attaining a non-hematologic germline sample, such as DNA extracted from cultured skin fibroblasts, upon which to undertake HHM testing, a process that adds several weeks to the HHM assessment process. Commencing germline work-up at the time of diagnosis of the hematologic malignancy, perhaps even attaining a skin biopsy (or hair follicle) sample at the time of diagnostic bone marrow biopsy, rather than deferring this consideration until further along the diagnostic work-up pathway or closer to the time when allograft is deemed indicated or imminent, would alleviate some of the significant time pressures which formed part of the rationale for the authors undertaking their study.

A significant and controversial issue highlighted in the work of Roloff and colleagues, worthy of careful consideration and discussion, is that of the safety or otherwise of using healthy heterozygous carriers of pathogenic variants in DNA repair genes as stem cell donors. In the setting of Fanconi anemia (FA), the majority of genes implicated in the FA context are associated with autosomal recessive inheritance, but it is also known that some FA genes (such as *BRCA1/2* and *PALB2*) convey cancer predisposition with autosomal dominant inheritance. Robust data to inform about stem cell donor appropriateness in this setting are lacking. No differences in clinical outcomes were observed in a cohort of patients with MDS undergoing alloSCT from donors who were carriers of an autosomal recessive condition.[2] Long experience in the FA alloSCT setting has proven the safety of healthy carrier siblings as donors, with a long-held and current recommendation to exclude FA by genetic testing

where possible in all full siblings of patients with FA along with HLA typing in order to inform donor suitability.[8] It has also recently been demonstrated that there is insufficient evidence of cancer risk for healthy carriers of FA mutations in genes associated with autosomal recessive inheritance.[9] Looking more specifically at this question in the setting of donors who harbor cancer predisposition mutations in *BRCA1/2*, it has been asserted that there is neither 'evidence to firmly support or discourage' the use of *BRCA1/2* mutation carriers as stem cell donors,[10] a statement demonstrative of the need for more data. Roloff *et al.* describe theoretical but unproven concerns about stem cell mobilization in donors who are carriers of DNA repair conditions, but these must be balanced against the risk of deferring healthy and motivated matched related donors and denying patients the benefits of an alloSCT from such donors without clear evidence that this is the best course of action. Clinical data evidencing poor donor or allograft outcomes in these settings is lacking. In their cohort, Roloff and colleagues describe the use of a matched related donor harboring the same heterozygous pathogenic *PALB2* mutation as their proband sibling with AML. To date, the clinical outcome has been good, with engraftment as expected and without donor-derived complications more than 4 years after the transplant. Larger datasets detailing long-term outcomes of cases such as these, alongside carefully annotated clinical features and mutational status of both donor and recipient, are required to inform this issue.

Roloff and colleagues have suggested a framework to apply in the complex and time-pressured setting of alloSCT donor selection for treatment of possible or proven HHM. Given the clear rationale for consideration of whether a HHM exists in all patients being evaluated for alloSCT, it behoves us to consider whether uniform application of germline testing at diagnosis should be performed and, by doing so, relieve some of the challenges elicited in this work on optimal donor selection. This increased genetic knowledge does, however, come with the accompanying challenge of the potential need for clinical decision-making in areas in which data are currently lacking.

Disclosures

No conflicts of interest to discloses.

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