Debate II: Should Individuals with an MDS Germline Mutation be Proactively Treated?

Yes

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Inherited genetic traits are mostly suspected and identified in pediatric patients with bone marrow failure syndromes, myeloid neoplasia and particularly myelodysplastic syndromes/neoplasms (MDS).[1] Conversely, BMF and MDS diagnosed in adults have been historically assumed not to be driven by deleterious germline (GL) variants, except in cases presenting at a young age or with a strong family history. The recent application of techniques able to screen the whole exome/genome unveiled GL variants in several myeloid disorders, emphasizing how also adults may carry such predisposing traits.[2] The precise estimation of the etiologic fraction of hereditary gene alterations in the pathogenesis of MDS in adults is hampered by difficulties deriving from differences in disease latency and phenotypes, reduced penetrance, and heterogeneous application of genetic testing, absent or incomplete family history and issues of competing mortality. However, we can estimate that about 10% of all comers MDS can carry inherited traits.[3]

In this debate, I will emphasize the importance of recognizing germline mutations in MDS and its clinical actionability with regards to management of patients and their families. Indeed, in such cases special attention must be given to indication for treatment, identification and follow-up of gene-specific extra-hematological conditions, and allogeneic hematopoietic stem cell transplant (HSCT), particularly concerning the use of familiar donors, genetic counselling for relatives, and adoption of dedicated conditioning strategies.[4,5]

By illustrating exemplificative cases of patients with MDS carrying *GATA2* and *DDX41* mutations, I will review how the identification of such mutation and the specific molecular makeup were crucial factors in the decision algorithm for treating these patients and proceeding to allo-HSCT.

References

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No

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The range of germline mutations associated with a predisposition for developing myeloid neoplasms has broadened considerably in the past several years. No longer are these variants restricted to individuals with young age of onset, associated syndromic effects, or extremely high risk of developing a myeloid malignancy. More recently discovered gene mutations are associated with an older age of disease onset, variable penetrance, and fewer clinically significant non-malignant consequences of these variants. Even in for mutations in genes presumed to have high penetrance, hypomorphic variants previously considered variants of undetermined significant are increasingly recognized and can cause milder or less penetrant phenotypes. Therefore, there should be no one-size-fits all approach to proactively treating all persons with myeloid malignancy predisposition mutations as most therapies we have are either not curative, not known to delay disease onset, or in the case of a potentially curative stem cell transplantation, associated with significant morbidity and mortality risk. Just as the phenotypes of germline DDX41 mutations are very different from those caused by mutations in GATA2 or RUNX1, proactive therapy must be considered on an individual basis taking not only the involved gene into account, but the specific variant, the patient's personal and family history, and their overall likelihood of a favorable outcome.