Be aware of the X: *BCOR* mutations in myeloid neoplasms

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In this issue of *Haematologica*, Baranwal *et al.*[1] analyze the clinical and biological features of myeloid neoplasms carrying mutations in the BCL6 corepressor (*BCOR*) gene.

The introduction of next-generation sequencing (NGS) to the diagnosis of myeloid neoplasms such as acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) has shed light on the molecular pathogenesis of these disorders, especially for those cases without recurrent chromosomal alterations. Over the past decade, numerous somatic single-nucleotide variants (SNV) have been recognized as driver mutations and prognostic biomarkers in myeloid neoplasms.[2] This growing evidence has been incorporated into AML and MDS classifications and predictive scores, including new molecularly-defined diagnostic categories and several mutations in risk stratification models.

The recent WHO and International Consensus classifications[3,4] have proposed a new group called "AML with myelodysplasia-related gene mutations," defined by somatic mutations in a set of genes, including *BCOR*. This category has also been incorporated into the European LeukemiaNet (ELN) 2022 AML classification[5] within the adverse risk group. Along these lines, the Molecular International Prognostic Scoring System (IPSS-M) risk score for MDS has considered *BCOR*, among other genes, a predictor of poor prognosis for MDS patients.[6]

BCL6 corepressor (*BCOR*) is a gene located in chromosome X encoding for a transcriptional repressor that participates in one form of the Polycomb repressive complex 1. This multi-protein complex regulates gene expression through histone modification, and its function is crucial for hematopoiesis and lymphoid differentiation.[7] *BCOR* gene alterations have been recurrently found in various human cancers, supporting its role as a tumor suppressor gene.[8] In hematologic malignancies, somatic mutations in *BCOR* have been reported in myeloid and lymphoid neoplasms,[9,10] and other non-malignant disorders like aplastic anemia.[11]

Baranwal *et al.*[1] sought to characterize *BCOR*-mutated (m*BCOR*) myeloid neoplasms. To investigate their incidence, they screened for *BCOR* mutations through NGS in a consecutive cohort of 6,887 adults treated at the Mayo Clinic from 2015 to 2017. They detected 138 (2%) patients carrying any SNV in *BCOR*. The authors describe the clinical features and outcomes of m*BCOR* patients compared to a wild-type cohort, and report that *BCOR* mutations are enriched in high-risk MDS and AML with an increasing incidence with age.

Interestingly, m*BCOR* MDS and AML display a distinct genetic signature, with a solid association to *RUNX1* and *U2AF1* mutations and mutual exclusion to other common mutations such as *NPM1* or *TP53*. Regarding cytogenetics, most patients had a normal karyotype, with a minority having complex karyotypes or other high-risk abnormalities. Mutations in *BCOR* were distributed along the coding sequence with no particular hotspot and were mostly frameshift.

The prognosis of m*BCOR* AML and MDS in this study was poor, with a median overall survival (OS) of 15 months, irrespective of blast count or initial diagnosis. While only 52.8% of AML patients in this study were initially assigned to the ELN 2017 adverse risk category, the results of the AML cohort are comparable to the ELN adverse group.[5] These data validate the inclusion of m*BCOR* AML into the adverse risk category of the ELN 2022 classification. Patients with complex karyotypes had the worst survival rates, while other co-occurring mutations made no substantial negative impact.

The authors demonstrate the beneficial effect of allogeneic stem cell transplant (alloSCT) in this group of myeloid neoplasms, suggesting that all m*BCOR* AML/MDS patients should be evaluated for upfront alloSCT when possible, given that the OS rate for alloSCT recipients was 61.1% at three years. Factors that worsened post-transplant outcomes in this cohort were *RUNX1* mutations and the presence of complex karyotypes.

The results published in this paper support the view that *BCOR* mutations identify a high-risk subgroup of myeloid neoplasms with a unique genetic signature and unfavorable prognosis that can be partially modified with alloSCT. Further research is needed to elucidate the impact of BCOR mutations on the survival of AML/MDS patients treated with venetoclax-based regimens or other target therapies.

Disclosures

No conflicts of interest to disclose.

Contributions

All authors discussed the results of the paper and wrote the editorial.

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