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Opinion Article

The Predictive Significance of Mutational Subgroups in Patients with AML

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DESCRIPTION

Common genetic changes in Acute Myeloid Leukemia (AML) include mutations of the gene encoding the transcription factor CCAAT-Enhancer Binding Protein Alpha (*CEBPA*). Numerous groups have looked into *CEBPA* mutations in AML since they were originally reported. Subsequent investigations have consistently shown that the enhanced prognosis associated with *CEBPA* mutations are limited to biallelic or double mutations, contrary to previous research that claimed all patients with these mutations would have a more favorable result. While single allele mutations were thought to be prognostically inconsequential, *CEBPA* was revealed to be associated with a different biology and to offer a more favourable clinical outcome, including greater rates of Complete Remission (CR), lower relapse risk, and increased Overall Survival (OS).

Nevertheless, a number of recent studies that examined the effects of individual *CEBPA* mutations in greater detail suggested that the favorable prognosis and unique clinical and molecular characteristics were limited to mutations occurring within the basic leucine zipper region of *CEBPA*, whether they occurred as a single or double mutation. Additional evidence for the distinct biology of *CEBPA* bZIP mutations in AML comes from gene expression research. Nevertheless, there is evidence that, depending on the specific type of *CEBPA* bZIP mutation, biological variations may exist even within this mutational grouping. When comparing patients with in-frame *CEBPA* bZIP mutations (either in-frame insertions/deletions or single base pair missense mutations) to patients with frameshift or nonsense mutations, our research found substantial differences in both molecular profiles and outcome. A more accurate biochemical and clinical classification of *CEBPA* mutations has been made possible by these discoveries. The 2022 update of the European Leukemia Net (ELN) recommendations on genetic risk classification and the International Consensus Classification (ICC) now classify *CEBPA* bZIP in-frame mutations as favorable risk entities. Regardless of the specific type of mutation or precise DNA modification, the *CEBPA* mutational class is still defined by the 2022 WHO classification by the existence of a single mutant bZIP mutation or a double mutant allelic status. The reason for this ongoing uncertainty may be that there is now little evidence to support either of these adjustments because few studies have examined the effects of various *CEBPA* mutational constellations in greater depth.

More than 1000 *CEBPA* mutant AML patient's clinical characteristics, treatment outcomes, and comprehensive sequencing data were analyzed as part of a pooled primary data analysis to obtain more understanding of the effects of various mutational subtypes, particularly the spectrum of *CEBPA* bZIP mutations. The principal aim of this investigation was to explore possible distinctions between various forms of bZIP mutations and to assess the significance of the allelic status.

Our study's key discovery is that it unequivocally confirms earlier research on the distinct behavior of bZIP mutations in relation to other kinds of *CEBPA* mutations. The findings demonstrate that, independent of allelic state, CEBPA bZIPInDel mutations define a unique subgroup with younger age and a particular co-mutational profile, which includes a high frequency of *GATA2* and WT1 mutations and the mutual exclusion of other lesions that define subtypes, such as *NPM1* mutations. Furthermore, a highly positive outcome was linked to *CEBPA* bZIPInDel mutations. With a 5-year overall survival rate above 75%, individuals with bZIPInDel mutations—particularly those with double mutant *CEBPA* should be regarded as one of the AML categories that responds best to standard treatment.

On the other hand, regardless of their allelic status, patients with bZIPSTOP, bZIPms, or TAD mutations displayed a distinct biology and a worse prognosis. According to the current ELN and ICC criteria, we classified and examined bZIPms mutations as "bZIP in-frame" in our earlier analysis together with bZIPInDel. While bZIPms mutations were clinically and molecularly distinct from bZIPInDel mutations, they shared more characteristics with the other *CEBPA* subgroups. Nevertheless, in the current analysis of a larger cohort of patients, bZIPms mutations were unmistakably linked to a worse outcome when assessed individually.

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