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Letter to the Editor

Overview of Prognosis of FLT3 Mutations and Interactions with Other Genetic Alterations in Acute Myeloid Leukemia

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Acute Myeloid Leukemia (AML) is one of the most aggressive hematological malignancies. It has a highly heterogeneous genetic background and complex clonal evolution. In this letter, we emphasized the prognostic importance of a crucial biomarker in AML – the Fms - like tyrosine kinase 3 (FLT3). This receptor tyrosine kinase plays a significant role in several cellular signalling processes. FLT3 is found on hematopoietic stem cells and early progenitor cells. After binding to its ligand, activated FLT3 triggers intracellular kinase, leads to cellular proliferation, and inhibits differentiation and apoptosis.[1]

Almost 30% of newly diagnosed AML patients, including adults and children, have activating mutations in the FLT3 gene. FLT3 mutations fall into two main categories: internal tandem duplication (ITD) insertion in the juxtamembrane domain and point mutations in the tyrosine kinase domain (TKD), which mostly affect residue D835 (D835Y, D835H, D835V, e.g.). Rare FLT3 point mutations are also found in TKD. These include F594L, K663Q, N841I, and Y842C. FLT3-ITD occurs in almost 25% of AML cases, while TKD mutations occur in nearly 5%.[2]

FLT3 mutations, also associated with other recurrent mutations and cytogenetic abnormalities, are particularly associated with the nucleophosmin 1 (NPM1) gene mutation, found in 50-60% of cases.[3] According to the 2022 ELN criteria, FLT3wt - NPM1mut is favorable while FLT3-ITD - NPM1mut and FLT3-ITD - NPM1wt are intermediate prognosis markers.[4] FLT3 mutations have also been reported in approximately 16% of AML patients with t(8;21)(q22;q22) (RUNX1/RUNX1T1). Among patients with this combination, those with a high FLT3-ITDmut allele burden (>50%) have been reported to have a lower survival risk, while those with a high FLT3-TKDmut allele burden have a better prognosis; however, there are conflicting results in the literature.[5] FLT3-ITD mutations have been associated with a worse prognosis than TKD mutations. A direct correlation between the duplication size in FLT3-ITD mutations and chemotherapy resistance has been reported. However, the prognostic utility

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of high FLT3-ITD allele burden has been removed from the updated ELN 2022 guidelines. DNMT3A, TET2, PTPN11, NRAS gene mutations are also found together with FLT3 mutations, but there is not enough evidence to say whether they are prognostically favorable or unfavorable. FLT3 mutations and ASXL1, WT1, and RUNX1 mutations have been associated with poor prognosis. Most cytogenetic markers of good or poor prognosis have not been reported to be affected by FLT3 mutations.[3]

FLT3 inhibitors have now become pivotal in treating FLT3-mutated AML. Type I (midostaurin, gilteritinib, andcrenolanib) and type II inhibitors (quizartinib and sorafenib) targeting FLT3 have been developed.[2] Chemotherapy plus FLT3 inhibitor treatments in AML are ongoing in newly diagnosed patients. However, further studies are needed to clarify the algorithms, especially for patients with additional genetic alterations. We believe this letter will help clinicians in the evaluation of FLT3 mutations alone and combined with other genetic alterations in AML. Hopefully, it will be an inspiration for new studies in AML.

REFERENCES

1. Kennedy VE, Smith CC. FLT3 Mutations in Acute Myeloid Leukemia: Key Concepts and Emerging Controversies. Front Oncol. 2020 Dec 23;10:612880. doi: 10.3389/fonc.2020.612880. PMID: 33425766; PMCID: PMC7787101.
2. Negotei C, Colita A, Mitu I, Lupu AR, Lapadat ME, Popovici CE, et. al. A Review of FLT3 Kinase Inhibitors in AML. J Clin Med. 2023 Oct 10;12(20):6429. doi: 10.3390/jcm12206429. PMID: 37892567; PMCID: PMC10607239.
3. Reikvam H. Revisiting the prognostic role of FLT3 mutations in acute myelogenous leukemia. Expert Rev Hematol. 2023 May;16(5):317-323. doi: 10.1080/17474086.2023.2202849. Epub 2023 Apr 17. PMID: 37066885.
4. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et. al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345-1377. doi: 10.1182/blood.2022016867. PMID: 35797463.
5. Christen F, Hoyer K, Yoshida K, Hou HA, Waldhueter N, Heuser M, et. al. Genomic landscape and clonal evolution of acute myeloid leukemia with t(8;21): An international study on 331 patients. Blood. 2019 Mar 7;133(10):1140-1151. doi: 10.1182/blood-2018-05-852822. Epub 2019 Jan 4. PMID: 30610028.