Documents

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AML-234 Prognostic Value of FLT3-ITD Residual Disease in Acute Myeloid Leukemia

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Abstract
Context: FLT3-internal tandem duplications (FLT3-ITD) are among the most common genetic molecular abnormalities in acute myeloid leukemia (AML) patients. Here, the prognostic impact of the presence of minimal residual disease (MRD) of FLT3-ITD in AML patients is assessed by next-generation sequencing (NGS). Objective: The prognostic significance of FLT3-ITD in AML in relation to other concurrent gene mutations and allelic mutational burden has remained a subject of scientific controversy. Detection of FLT3-ITD MRD by RQ-PCR is restricted by patient-specific variables, such as sequence, position, and length. However, systematic studies analyzing the applicability of FLT3-ITD MRD detection with NGS techniques are currently lacking. Here, we evaluate the impact of the presence of FLT3-ITD MRD detected by NGS on treatment outcome in the context of current prognostic factors at diagnosis and MRD status measured by multiparameter flow cytometry (MFC) and mutant NPM1. Methods: In 161 de novo AML patients with an FLT3-ITD enrolled in the HOVON-SAKK clinical trials, NGS was performed at diagnosis and ultra-deep in CR after induction chemotherapy. Presence of FLT3-ITD MRD was correlated to incidence of relapse and overall survival (OS). Results: NGS-based FLT3-ITD MRD was present in 47 of 161 (29%) AML patients. Presence of FLT3-ITD MRD was associated with increased risk of relapse (4-year CIR, 75% FLT3-ITD MRD vs. 33% no FLT3-ITD MRD; P<0.001) and inferior OS (4-year OS, 31% FLT3-ITD MRD vs. 57% no FLT3-ITD MRD; P<0.001). In multivariate analysis, detection of FLT3-ITD MRD in CR confers independent prognostic significance for relapse (hazard ratio, 3.55; P<0.001) and OS (hazard ratio 2.51; P<0.001). Presence of FLT3-ITD MRD exceeds the prognostic value of most of the generally accepted clinical and molecular prognostic factors, including the FLT3-ITD allelic ratio at diagnosis and MRD status of mutant NPM1 and MFC. Conclusions: Presence of FLT3-ITD MRD in CR detected by NGS after induction chemotherapy identifies AML patients with an increased risk of relapse and inferior OS that outweighs the significance of currently accepted prognostic factors. This finding offers support for the use of FLT3-ITD MRD as a clinically relevant biomarker for dynamic disease risk assessment in AML. © 2022 Elsevier Inc.

Author Keywords
acute myeloid leukemia; AML; FLT3-ITD; minimal residual disease; MRD; next generation sequencing

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