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Acute Leukemias

BEYOND THE MUTATION: PROGNOSTIC ROLE OF FLT3-ITD LENGTH AND GENOMIC CONTEXT IN ACUTE MYELOID LEUKEMIA

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Acute Myeloid Leukemia (AML) is a genetically heterogeneous malignancy characterized by recurrent somatic mutations that influence disease biology and prognosis. Among these, internal tandem duplication (ITD) mutations in the *FLT3* gene are among the most frequent and clinically adverse alterations. However, the prognostic relevance of ITD length and insertion site remains controversial, highlighting the need for further investigation. We conducted a single-center observational study including 384 newly diagnosed adult AML patients (pts) over 5 years, analyzed both prospectively and retrospectively. The *FLT3*-ITD mutation was detected in 72 pts (19%) by NGS or RT-PCR. ITD length (base pairs, bp) was correlated with clinical and biological features, and an optimal threshold was determined by Maximally Selected Rank Statistics (MAXSTAT). For 37 pts (51%) evaluated by NGS, the precise genomic insertion site was defined its biological and clinical relevance.

The median age at diagnosis was 64 years. Co-mutations most frequently involved *NPM1* (59%) and *DNMT3A* (43%). Multiple ITDs were detected in 6 pts. The median ITD length was 48 bp (IQR 30-69). Most insertions affected exon 14 (95%), while exon 15 and intronic regions were less commonly affected (5 and 16%, respectively). MAXSTAT analysis defined 63 bp as the optimal cut-point (Figure 1A), defining two distinct prognostic groups with comparable baseline features.

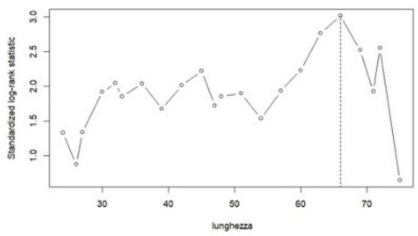
Pts who relapsed showed significantly longer ITDs (median 71 vs 42 bp; p=0.018) (Figure 1B). A higher 5-year Cumulative Incidence of Relapse was observed in pts with long ITD (≥63 bp) (sHR=3.57; 95% CI:1.21–10.56; p=0.0216) (Figure 1C), with a consistent trend toward worse Overall and Event Free Survival. The negative prognostic effect of longer ITDs persisted after adjustment for age (p=0.0003), supporting ITD length as an independent predictor of outcome.

Longer ITDs were more frequently associated with intronic involvement (p=0.001). No correlation was found between length and total number of co-mutations; however, *DNMT3A*-mutated pts displayed significantly longer ITDs and a fivefold higher likelihood of harboring ITDs ≥63 bp. Notably, pts harboring both *DNMT3A* mutation and long ITD (≥63 bp) (27%) had markedly reduced 5-year OS (p=0.02) (Figure 1D). Within the *DNMT3A*-mutated subgroup, longer ITDs also conferred inferior survival (p=0.03) (Figure 1E).

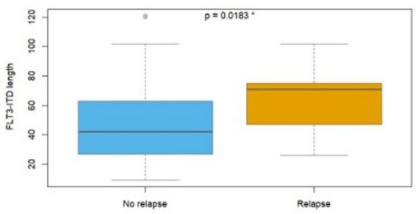
Our findings demonstrate that longer *FLT3*-ITDs are associated with higher relapse risk and poorer clinical outcomes. We also identify a prognostically adverse interaction between *DNMT3A* mutation and ITD length. The preferential intronic involvement of long ITDs may indicate functional diversity with biological impact. These findings support integrating of ITD length, insertion site, and co-mutational status, particularly *DNMT3A*, into prognostic algorithms to improve risk stratification and guide treatment choice, including therapy intensification and indication for allogenic stem cells transplantation.

ACUTE LEUKEMIAS

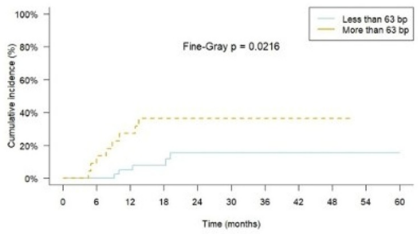
1A – Cut-point with MAXSTAT



1B – *FLT3*-ITD length vs relapse



1C – Cumulative Incidence of Relapse at 5 years



1B – *FLT3*-ITD length vs relapse