We read with great interest the paper by Stirewalt et al. analyzing the prognostic significance of different Fms-like tyrosine kinase (FLT3) gene internal tandem duplication (ITD) size in acute myeloid leukemia (AML). There is a considerable variability in ITD size, and Stirewalt et al. suggest that with increasing size of ITD there is a more significant loss of autoinhibitory function of FLT3/ITD mutation. We have found 18 (20.9%) patients with FLT3/ITD mutation. We have analyzed 86 consecutive patients with AML, 37 men and 49 women, with a median age of 57 years (range, 18-85 years), and 49 women, with a median age of 57 years (range, 18-85 years), by reverse transcriptase–polymerase chain reaction (RT-PCR) for FLT3/ITD mutation. We have found 18 (20.9%) patients with FLT3/ITD mutations, with the highest frequency (3/8; 37.5%) in acute promyelocytic leukemia (APL). ITD was associated with higher white blood cell (WBC) count (67 vs 26 × 10^9/L, P = 0.013) and somewhat inferior survival (hazard ratio [HR] = 1.98; confidence interval [CI] 1.11-6.11; P = .02, when we exclude patients with APL). There was no significant difference in age, sex, cytogenetic risk, and other hematologic parameters between FLT3/ITD-mutated and unmutated patients.

Median ITD size was 70 bp (range, 30-100 bp). ITD size was negatively correlated with age (R = −0.51; P < .05) and cytogenetic risk (R = −0.58; P < .05) and was not correlated with WBC count, sex, or other hematologic parameters. We have divided our patients’ FLT3/ITD mutations into long (>70 bp; 11/18, 61.1%) and short ITD (<70 bp; 7/18, 38.9%) subgroups. We found better survival in the long-ITD subgroup (HR 4.07, CI 2.28-66.32; P = .002) (Figure 1), even without patients with APL (HR 3.18, CI 1.51-6.47; P < .001). In the multivariate Cox proportional hazard model, with ITD size as continuous variable, in overall patients' FLT3/ITD mutations into long (≥70 bp; 11/18, 61.1%) and short ITD (<70 bp; 7/18, 38.9%) subgroups. We found better survival in the long-ITD subgroup (HR 4.07, CI 2.28-66.32; P = .002) (Figure 1), even without patients with APL (HR 3.18, CI 1.51-6.47; P = .001).

More on prognostic significance of FLT3/ITD size in acute myeloid leukemia (AML)

To the editor:

References

Response:

Does FLT3/ITD size matter?

In this issue of Blood, Kusec et al describe their results examining the potential prognostic significance of FMS-like tyrosine kinase 3 (FLT3) gene internal tandem duplication (ITD) size in 86 patients with acute myeloid leukemia (AML). Contrary to our recent publication,1 these investigators found that patients with AML and smaller FLT3/ITDs had a worse prognosis. The exact reason for the disparity between the 2 studies is uncertain. These investigators used a different screening technique, which may not be as sensitive as the method in our analyses (polymerase chain reaction/single-strand conformation polymorphism [PCR/SSCP]).2

Using a less sensitive screening method will reduce the detection of additional signaling pathways, including STAT5 pathway, by FLT3/ITD may suggest qualitative differences as the basis for different biologic effects of FLT3 mutations.4 Thus the observed different biologic effects of different FLT3/ITDs may relate to a different activation of these additional signaling pathways. FLT3 modeling and functional studies including signaling as well as further clinical studies are warranted to resolve these puzzling and conflicting results.

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References


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