中文題目：較低的 FLT3-ITD 突變比率急性骨髓性白血病具有獨特的基因突變與轉錄體

英文題目：Low allelic ratio FLT3-ITD is associated with distinct genetic and transcriptomic features in adult acute myeloid leukemia

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Background: The mutant burden of *FLT3*-ITD modulates its prognostic impact on patients with acute myeloid leukemia (AML). However, for patients with low allelic ratio *FLT3*-ITD (*FLT3*-ITD^{low}, AR < 0.5), clinical features as well as genomic and transcriptomic profiles remain unclear. This study aimed to elucidate the genomic and transcriptomic features, and clinical outcome of *FLT3*-ITD^{low} in AML patients with intermediate-risk cytogenetics.

Methods: This study enrolled 444 AML patients with intermediate-risk cytogenetics homogeneously treated with standard chemotherapy. Next generation sequencing on 26 targeted genes were performed at initial diagnosis and serial follow-up. Samples of patients were hybridized to HumanHT12 v4 Expression BeadChip (Illumina) for transcriptomic analysis. Gene Set Enrichment Analysis (GSEA) software was used to investigate systematic enrichments of *FLT3*-ITD governed expressional profiles in biological functions

Results: *FLT3*-ITD^{low} patients exhibited a marked enrichment of the RAS pathway, with higher frequencies of RAS pathway mutations, different from those with *FLT3*^{wt} or *FLT3*-ITD^{high}. *FLT3*-ITD^{low} transcriptome was also enriched for survival and inflammatory pathways, including TNFα, JAK-STAT, NOTCH, and TGFβ signaling. Concurrent *CEBPA* double mutations were favorable prognostic factors, whereas *MLL*/PTD, mutations in splicing factors, and *RUNX1* were unfavorable prognostic factors in *FLT3*-ITD^{low} patients. Higher *FLT3*-ITD AR correlated with increased relapse rate. Patients with *FLT3*-ITD^{low} had a shorter overall survival (OS) and disease-free survival (DFS) than those with *FLT3*^{wt}. Allogeneic stem cell transplantation (Allo-HSCT) in first complete remission (CR1) was associated with a longer OS and DFS compared with postremission chemotherapy in patients with *FLT3*-ITD^{low}.

Conclusion: Patients with *FLT3*-ITD^{low} had distinct mutational and transcriptomic profiles and poor outcome. Presence of concomitant poor-risk mutations exerted negative prognostic impacts in these patients, who markedly benefited from allo-HSCT in CR1.

Key words: acute myeloid leukemia, *FLT3*-ITD, allelic ratio, transplantation, postremission therapy