中文題目：較低的 *FLT3*-ITD 突變比率仍可預測急性骨髓性白血病之不良預後

英文題目：Low allelic ratio *FLT3*-ITD exerts negative prognostic impact on acute myeloid leukemia patients

作　　者：田豐銘[1,2]，蔡承宏[1,2]，侯信安[2]，唐季祿[1,2]，田蕙芬[2]

服務單位：[1]國立台灣大學台成幹細胞治療中心　[2]臺大醫院內科部血液腫瘤科

Background：The mutant burden of *FLT3*-ITD modulates its prognostic impact on acute myeloid leukemia (AML) patients. It is well known that high allelic ratio *FLT3*-ITD confers poor prognosis compared to the *FLT3* wild-type (*FLT3*^{WT}) group. However, the prognostic relevance of low allelic ratio *FLT3*-ITD (*FLT3*-ITD^{low}) (allelic ratio<0.5) remains unclear. In this study, we aimed to evaluate the prognosis and transplantation outcome in *FLT3*-ITD^{low} AML patients.

Methods：A cohort of 437 *de novo* AML patients with intermediate-risk cytogenetics diagnosed from 1994 to 2016 who had cryopreserved bone marrow cells for analysis were enrolled. Metaphase chromosomes were banded by the conventional trypsin-Giemsa banding technique. The mutation status of 11 relevant genes (*FLT3-TKD, CEBPA, RUNX1*, *ASXL1, TET2, DNMT3A, SF3B1, SRSF2, U2AF1, NPM1* and TP53) was determined by Sanger sequencing and/or next generation sequencing (NGS). *FLT3*-ITD allelic burden was determined by fragment analysis and capillary electrophoresis.

Results：*FLT3*-ITD^{high}, *FLT3*-ITD^{low}, F*LT3*^{WT} each represented 95, 54, and 288 patients. The WBC count has positive correlation with *FLT3*-ITD alleic ratio. Comparing *FLT3*-ITD^{low} and *FLT3*^{WT} patients, the frequencies of concurrent

gene mutations (*CEBPA, ASXL1, RUNX1, DNTM3A, TET2, TP53, SF3B1, SRSF2, U2AF1*) were similar except for a higher frequency of *NPM1* mutation in *FLT3*-ITD^{low} group. The CR rates were also similar. The median follow-up was 5.9 years (range, 0.3-19.2). *FLT3*-ITD^{low} patients had a shorter overall survival (OS) (5yr OS, 30% vs. 57%, P=0.036) and disease-free survival (DFS) (5yr, 29% vs. 46%, P=0.111) than *FLT3*^{WT} patients. To minimize selection bias, those who attained CR1 for at least 3 months were included in transplantation analyses. In *FLT3*-ITD^{low} patients, alloSCT in CR1 was associated with a lower relapse rate (41.2% vs. 73.9%, P=0.037), longer OS (5yr OS, 66% vs. 19%, P=0.011) and DFS (5yr DFS, 43% vs. 18%, P=0.021) compared with postremission chemotherapy. In contrast, the prognostic impact for alloSCT could not be shown in *FLT3*-ITD^{low} patients.

Conclusion：Our results provide evidence that *FLT3*-ITD^{low} exerts negative prognostic impacts despite its association with concurrent *NPM1* mutation. *FLT3*-ITD^{low} patients significantly benefit from alloSCT in first CR with respect to both DFS and OS.

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