



The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS**Only FLT3-ITD Mutation Did Not Have a Deleterious Effect on Acute Myeloid Leukemia Patients with NPM1 Mutation, but Concomitant with DNMT3A Mutation or a <3log Reduction of MRD2 Predicted Poor Survival**

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Background Co-occurring mutations were observed in NPM1-mutated acute myeloid leukemia (AML) frequently, and the measurable residual disease (MRD) for NPM1 is effective for the prognosis of NPM1-mutated AML. However, the combined effects of co-occurring gene mutation at the baseline and MRD on survival are unclear. We investigated the impact of gene mutation status and NPM1 MRD on predictive value of AML patients with NPM1 mutation.

Method A single-center, retrospective cohort study was carried out in patients diagnosed as AML with NPM1 mutation in Peking University Peoples' hospital. Patients were treated by an anthracycline and cytarabine-based or homoharringtonine and cytarabine-based induction chemotherapy regimen and followed by high dose cytarabine as consolidation therapy. Patients who had the indications of allogeneic hematopoietic stem cell transplantation (allo-HSCT) underwent allo-HSCT. A small part of patients with FLT3-ITD mutation received FLT3 inhibitor. Targeted next-generation sequencing (NGS) were analyzed at diagnosis, and quantitative NPM1 mutation (A, B, and D type) were detected at diagnosis and each end of chemotherapy cycle. As MRD for NPM1 rare type (NPM1^{RT}) was not available, MRD, relapse free survival (RFS) or overall survival (OS) analysis were conducted in patients received chemotherapy only (NGS^{chemo}), excluding harboring NPM1^{RT}.

Results A total of 234 patients, with NGS results, diagnosed as NPM1-mutated AML were included. 68.4% (160/234) patients including 17 patients with NPM1^{RT} received chemotherapy only, and NGS^{chemo} patients were 143. After chemotherapy, 31.6% (74/234) patients underwent allo-HSCT. 1.7% (4/234) patients died of infection or hemorrhage during induction therapy. 15.8% (37/234) patients received FLT3 inhibitor, and 92.2% (212/230) patients achieved complete remission (CR) or incomplete hematologic recovery (CRi). During median follow-up time of 24.9 [interquartile range (IQR) 11.6-47.8] months, 40.6% (95/234) patients died. Median transcription of NPM1 at diagnosis was 31.13 (IQR 17.23-56.91)%, and would take a median time of 4.1 (IQR 2.6-5.6) months to converted to negativity. Reduction of MRD at the end of second cycle of consolidation (MRD2) $\geq 3\log$ associated with higher RFS (3-year RFS rate 66.3% vs. 11.1%, $p < 0.001$) and OS (3-year OS rate 78.4% vs. 32.4%, $p < 0.001$) than reduction $< 3\log$, and consistent negativity of MRD also predicted higher RFS (3-year RFS rate, 98.1% vs. 42.3%, $p < 0.001$) and OS (3-year OS rate, 100% vs. 67.7%, $p < 0.001$) than those whose MRD turned from negativity to positivity. 9 genes were mutated in $> 10\%$ in 234 patients, and DNMT3A and FLT3-ITD were the most prevalence (Figure 1). Univariate analysis showed FLT3-ITD, DNMT3A and reduction of MRD2 $< 3\log$ were associated with poorer RFS and OS in 143 NGS^{chemo} patients. But In multivariate analysis, only DNMT3A mutation [RFS, hazard ratio (HR)=1.9, $p = 0.023$; OS, HR=2.1, $p = 0.032$] and reduction of MRD2 $\geq 3\log$ (RFS, HR=0.1; OS, HR = 1.9, both $p < 0.001$) were independent prognostic factors for survival. Four subgroups were divided by different status of DNMT3A and FLT3-ITD, that were both FLT3-ITD and DNMT3A negative, FLT3-ITD positive and DNMT3A negative, FLT3-ITD negative and DNMT3A positive, and both FLT3-ITD and DNMT3A positive. The concurrence of FLT3-ITD and DNMT3A was associated with lowest RFS and OS (3-year RFS rate 29.2%, $p < 0.001$; 3-year OS rate 53.5%, $p < 0.001$). However, patients with only FLT3-ITD mutation did not contribute to poor survival compared with patients without FLT3-ITD mutation (3-year RFS rate 71.4% vs. 74.4%, $p < 0.843$; 3-year OS rate 74.5% vs. 75.8%, $p = 0.759$). Three risk group were re-stratified by the gene mutation and gene reduction of MRD2 (Figure 2), and the RFS and OS of the poor risk group,

defined by patients with <3log reduction of MRD2, or with both FLT3-ITD and DNMT3A mutation, could be improved by allo-HSCT(3-year RFS rate, 56.4% vs. 29.2%, $p = 0.015$; 3-year OS rate, 72.0% vs. 31.6%, $p = 0.001$).

Conclusion In AML patients with NPM1 mutation, the deleterious effect of FLT3-ITD could be pronounced in patients concomitant with DNMT3A mutation. A <3log reduction of MRD2 was also another independent poor prognostic factor for survival, which could be improved by allo-HSCT. Meanwhile, the conversion of MRD for NPM1 from negative to positive might be a poor prognostic factor, but it requires to be validated by multivariate analysis.

Disclosures No relevant conflicts of interest to declare.

Figure 1. Histogram showing the frequency of gene mutations detected in > 1% of patients.

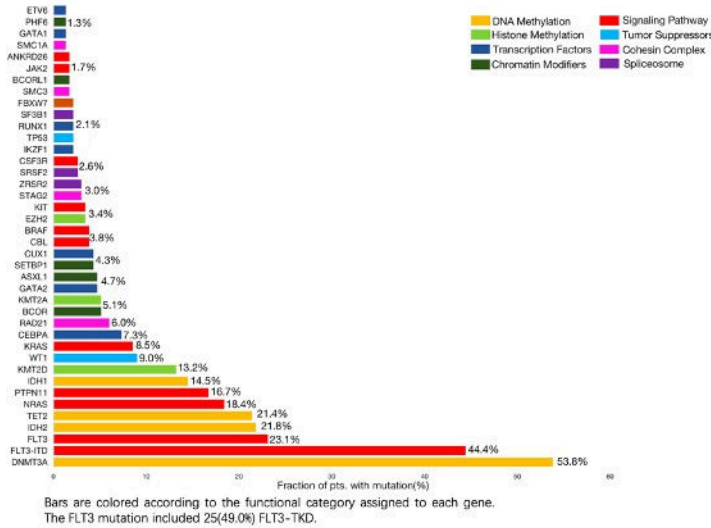
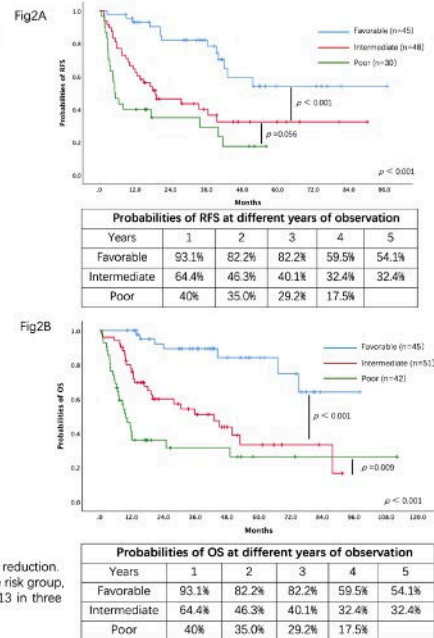


Figure 2. Survival of different risk groups re-stratified according to the status of FLT3-ITD and DNMT3A mutation and reduction of MRD2.



(A) RFS, (B) OS. Favorable risk group, both FLT3-ITD and DNMT3A negative, and MRD2 ≥ 3 log reduction. Poor risk group, both FLT3-ITD and DNMT3A positive or MRD2 < 3log reduction. Intermediate risk group, neither favorable nor poor risk group. In Fig 2A, patients received FLT3 inhibitor were 2, 2, 13 in three different risk groups, while 2, 2, 15 in Fig 2B.

Figure 1

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