The Impact of *DNMT3A/FLT3-ITD/NPM1* on Patients with Acute Myeloid Leukemia after Allogeneic Hematopoietic Stem Cell Transplantation

Akut Myeloid Lösemili Hastalarda *DNMT3A/FLT3-ITD/NPM1*'in Allojeneik Hematopoetik Kök Hücre Transplantasyonu Sonrası Etkisi

Long Su

Jilin University First Hospital, Clinic of Hematology, Changchun, China

To the Editor,

Recently, Ardestani et al. [1] published their excellent findings in this journal. They found that *DNMT3A* mutations alone do not affect the clinical outcomes of acute myeloid leukemia (AML) patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT), but when accompanied by *FLT3-ITD* mutations, the overall survival (OS) was significantly reduced and the relapse rate increased. *NPM1* mutations had no impact on either relapse-free survival or OS, but there was a significant difference between AML patients with and without *NPM1* mutations for relapse [1].

Integrative genomic analysis of de novo AML identified a subset of AML patients in which *DNMT3A*, FLT3, and *NPM1* mutations coexisted at a higher frequency than would be expected from chance occurrence [2]. Our unpublished data also showed that a close association could be observed among *DNMT3A*, *FLT3*, and *NPM1* mutations in patients with AML by factor analysis ($p<0.05$) based on 357 de novo AML patients analyzed by next-generation sequencing. A previous study demonstrated that younger (<60 years) patients with *DNMT3A/FLT3/NPM1* mutations had significantly shorter event-free survival ($p=0.047$) and a tendency towards shorter OS ($p=0.095$) compared to those in other mutation groups [3]. The adverse impact of *DNMT3A* mutations is more pronounced than that of *FLT3-ITD* among patients with *NPM1* mutations [3]. Accordingly, how did *DNMT3A/FLT3-ITD/NPM1* triple mutations influence the prognoses of AML patients who underwent allo-HSCT in this study? What about the impact of *DNMT3A* or *FLT3-ITD* on NPM1-mutated AML patients? Recent studies reported that variant allele frequencies of the *NPM1* and *FLT3-ITD* genes were closely related to long-term outcomes in patients with AML [4,5]. I wonder if there is information available on variant allele frequency in this subset of patients in order to re-analyze the impact of *NPM1* and *FLT3-ITD* on the prognoses of patients following allo-HSCT.

Address for Correspondence/Yazışma Adresi: Long SU, M.D.,
Department of Hematology, First Hospital of Jilin University, Changchun 130021, China
Phone : +86-0431-88782157
E-mail : sulongjdyy@163.com ORCID-ID: orcid.org/0000-0002-5360-468X

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Conflict of Interest: The author of this paper has no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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Reply to the Authors

To the Editor,

We appreciate Dr. Long Su for his interest in our study and his useful comments about our article published in Turkish Journal Hematology, entitled "The impact of *DNMT3A/FLT3-ITD/NPM1* on patients with acute myeloid leukemia after allogeneic hematopoietic stem cell transplantation" [1]. Our study demonstrated that *DNMT3A* R882 mutations are not related to inferior survival in AML patients after allogeneic HSCT. Regarding his comments, we analyzed impact of *DNMT3A* and *FLT3-ITD* on *NPM1* mutated AML patients. Our finding indicated that considering *NPM1* and *DNMT3A* mutations together, no significant difference in OS and DFS was revealed (Figure 1).

FLT3-ITD mutation had a negative impact on both RFS and OS of patients with mutated *NPM1*. DFS and OS were significantly more favorable in patients with *FLT3-ITD-/NPM1+* compared to patients with other mutation subgroups (Figure 2).

Also, patients with *DNMT3A/FLT3-ITD/NPM1* triple mutations demonstrated a significantly worse DFS (p=0.009) and OS (p=0.028) (Figure 3) compared to all other patients (Figure 3).

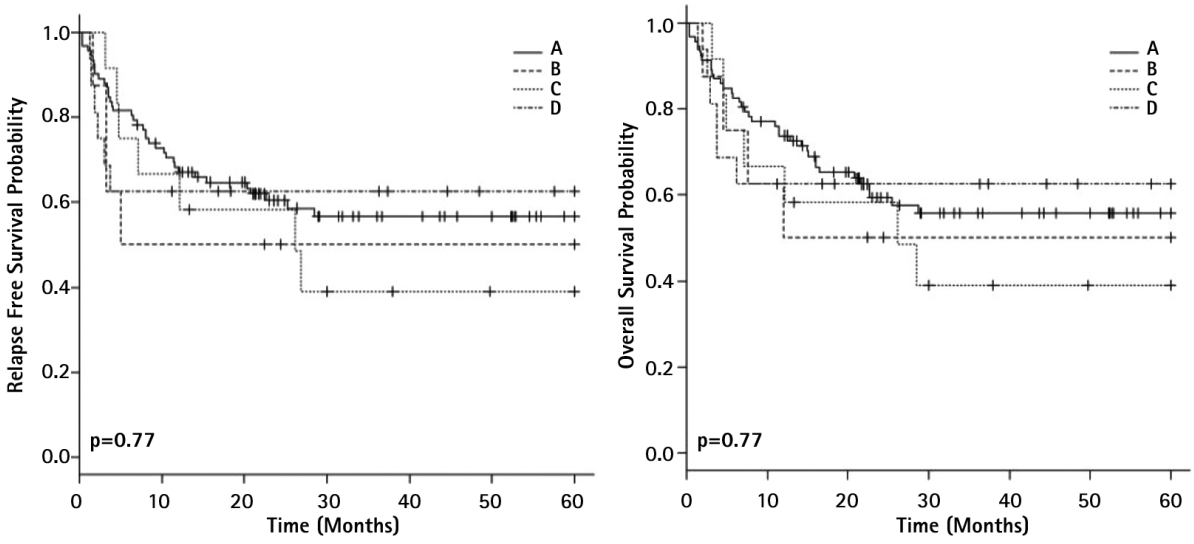

Figure 1. Survival curves of acute myeloid leukemia patients according to mutational status of *DNMT3A-/NPM1*: relapse free survival (left) and overall survival (right) (A=*DNMT3A-/NPM1-*, B=*DNMT3A+/NPM1+*, C=D*NMT3A+/NPM1-*, D=*DNMT3A-/NPM1-*).

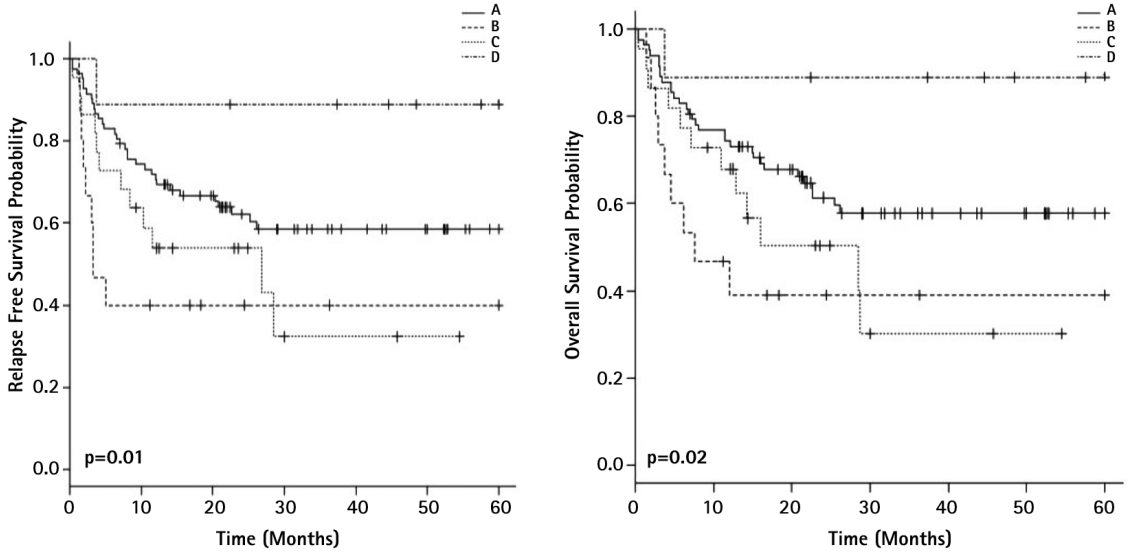

Figure 2. Survival curves of acute myeloid leukemia patients according to mutational status of *FLT3-ITD/NPM1*: relapse free survival (left) and overall survival (right) (A=*FLT3-ITD-/NPM1-*, B=*FLT3-ITD+/NPM1+*, C=*FLT3-ITD+/NPM1-*, D=*FLT3-ITD-/NPM1+*).

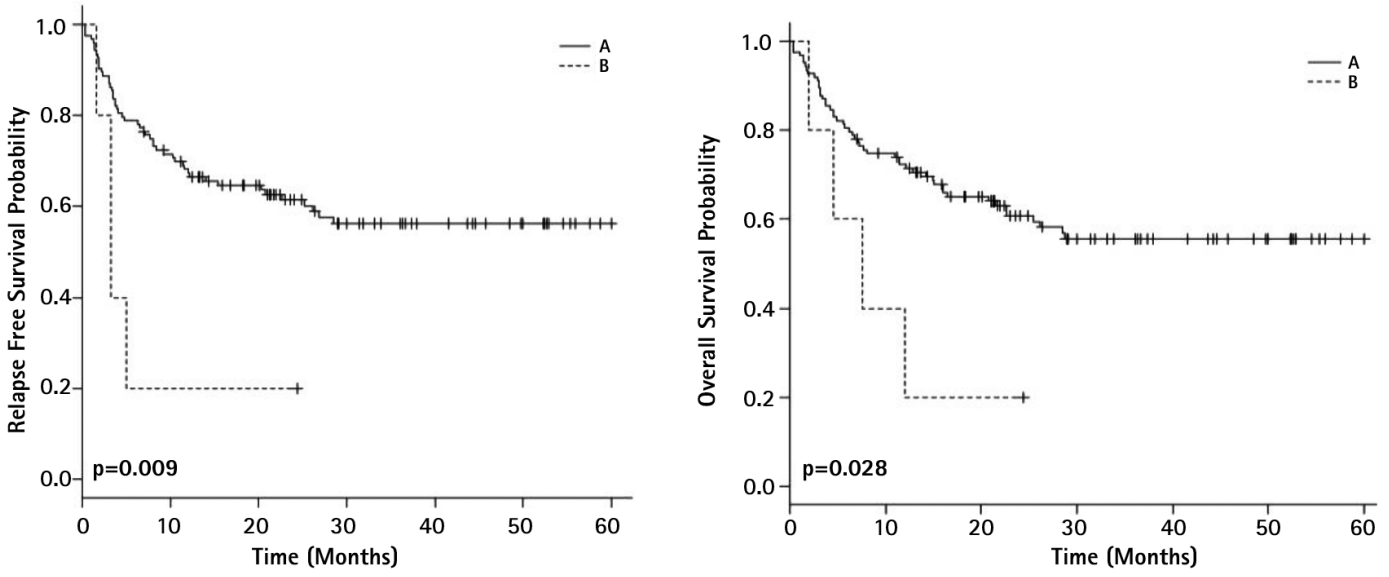

Figure 3. Survival curves of acute myeloid leukemia patients according to *DNMT3A/FLT3-ITD/NPM1* triple mutations: relapse free survival (left) and overall survival (right) (A=*DNMT3A/FLT3-ITD/NPM1*, B=others).

Unfortunately, in this study, information about the allele frequency of mutations was not available for most of patients, but in an ongoing prospective study, we are studying the effect of the allelic frequency of *FLT3-ITD* and NPM mutations on the clinical outcome of AML patients after HSCT.

Although there is more agreement on the poor prognostic role of DNMT3A mutations in AML patients [2], few studies have been conducted on the effect of these mutations on the clinical outcome of patients after allogeneic transplantation and there are disagreements over the results of these limited studies [3,4].

These differences can be due to coexistence of variable cytogenetic or molecular genetic aberrations in leukemia cells that could be effective in the clinical outcome of the patients. In the present study, only three genetic aberration were tested and additional genetic abnormality might impact the outcome of the patients.

Taken together, our findings indicated that *FLT3-ITD* may be a more powerful adverse prognostic biomarker than *NPM1* and *DNMT3A* in AML patients after HSCT. Although the comments have allowed us to add useful information to our previous paper, our conclusion remains the same as in our published work.

Best Regards,

Bahram Chahardouli, Saeed Mohammadi, Mohsen Nikbakht, Shahrbano Rostami

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