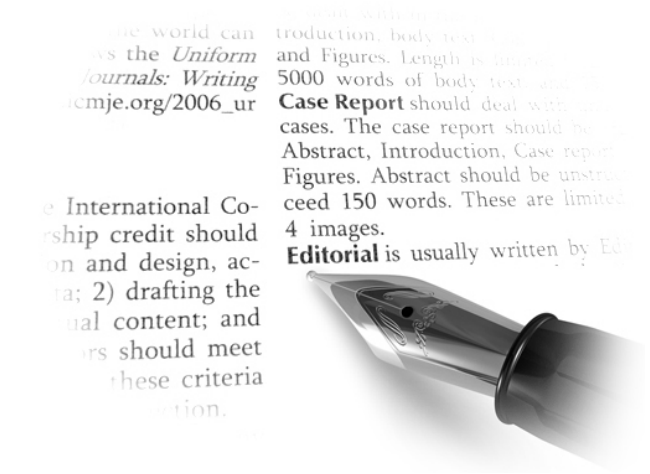

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Editorial

Mutations in AML with a normal karyotype: *NPM1* and *FLT3*-ITD, ready to use as a key prognosticator?

Hee-Je Kim, M.D.

Department of Internal Medicine, Division of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, Korea

Two well defined mutations, including the *NPM1* and CCAAT/enhancer-binding protein-alpha (CEBPA) genes, are generally accepted as a better prognosis in AML [1]. *NPM1*, one of frequent mutations in AML, have been described in association with several clinical features, including a normal karyotype and a significantly higher long-term survival benefit compared to those patients who are having other mutations. However, there have been many reports, although they are not confirmative yet, about the role of this specific mutation whether it is really positive or negative influential to the response after chemotherapy and/or hematopoietic stem cell transplantation (HSCT). Is the mutational state of *NPM1* alone or in combination with other defined mutations in AML matter when we treat the patients in any manner, i.e. either use of conventional chemotherapeutic agents or novel developmental agents introduced recently or even combination of sequential chemotherapies followed by HSCT? There is no clear answer yet unfortunately.

Furthermore, some studies showed that although *NPM1* mutation was a favorable factor for achieving complete remission (CR), it was even associated with a higher relapse rate and poorer disease-free survival (DFS) [2]. What is more interesting, the mutational state of *NPM1* alone had no significant effect on DFS and could not be a favorable prognostic factor for AML [3, 4]. Finally, no clinical significance for this mutation with respect to overall survival (OS) was described in any of these reports. Also, there is another recent Korean report that non-A subtype *NPM1* mutation predicts poor clinical outcome in *de novo* adult AML [5].

Because of the large variability of gene mutations or the heterogeneity of AML, it is basically understood as a very complex disease entity having diverse prognosticators. Therefore, many combinations of molecular markers in association with treatment outcome of AML have been introduced recently. Although there is not enough evidence to insist of positive impact on clinical outcome of *NPM1* mutation, it seems like that patients with isolated *NPM1* mutation (*NPM1*mut) generally had a better outcome in terms of either OS or DFS as compared to the group of *NPM1*mut+/*FLT3*-ITD+ patients [6, 7]. In contrast, most studies have reported that *FLT3*-ITD+ is an independent poor prognostic factor contributing to an increased risk of induction failure and finally poor survival.

Based on these concepts, Kim et al. [8] showed in previous issue of the Korean Journal of Hematology that adult patient with cytogenetically normal-AML (CN-AML) carrying isolated *NPM1*mut who performed allogeneic HSCT resulted in much higher 5-year relapse-free survival rate than those treated with high-dose cytarabine (HDAC) chemotherapy only as intensified consolidation therapy. Their results have profound meaning, but some critical limitations exist. This single institutional data of 121 adult CN-AML patients received the standard '3×7' induction chemotherapy using idarubicin plus cytosine arabinoside or BH-AC and then received 1-3 courses of HDAC consolidation chemotherapy (in total of 18 g/m^2 cytosine arabinoside per cycle). Among the patients carrying isolated *NPM1*mut, only 13 out of 35 patients received allogeneic HSCT with an extremely short median follow-up duration of 11.8 months. Most of all, all patients enrolled in this cohort showed the type

A mutation. Specifically, other subtype mutation of *NPM1* would be researchable in them. Like other studies published recently, they did not comprise any other complex set of mutations such as ERG, BAALC, *c-kit*, Ras, WT1, PRAME, MN1 etc [9]. Those numerous considerable parameters when treat AML would be also feasible if we can focus on the importance of molecular biogenetic characteristics of AML. Although this study is truly suggestive as a 1st comparison analysis in Korean *NPM1*mut CN-AML, it should be cautious not to consider any definite role of allogeneic HSCT for the subgroup of patients at the moment. This retrospective study is worth to reviewing with intermediate sample numbers of adult Korean AML in a single institution. However, it is not acceptable to take allogeneic HSCT for this subgroup of specific patient population, i.e. isolated *NPM1*mut CN-AML. Concerning *FLT3*-ITD mutation (*FLT3*-ITD+) in patients with CN-AML, isolated *FLT3*-ITD+ showed poor survivals, similar to those with poor-risk cytogenetics as shown in other previous reports [4, 10]. We need our own study to verify these foreign data performed absolutely with Caucasian. Most of all, we need a pharmacogenomic data for Korean by using various present (including HDAC strategy established by most Caucasian data) and/or future anti-leukemic agents. We then set the best therapeutic strategy for Korean AML based on those population genetics as well as our own clinical experiences.

There has been no study revealed the issue of appropriate treatment of *NPM1*mut-CN-AML with HDAC vs. HSCT. Although the NCCN guidelines for AML consider patients with isolated *NPM1*mut as a usual favorable-risk group, like in core-binding factor subgroup of AML, we should have definite answer for this interesting question in near future. As authors suggested, post-remission treatment for isolated *NPM1*mut could be investigated in a randomized study of allogeneic HSCT vs. repeated courses of HDAC vs. autologous HSCT. Further, more diligent work for finding other subtypes of *NPM1*/*FLT3*-ITD mutants together with more novel combinatorial molecular markers regarding expression of multiple genes in leukemogenesis will have a great impact on understanding of AML. The report by Kim et al. [8] should be a meaningful first step forward to enlighten these tough tasks we confront so far, and therefore more data in the context of more sample numbers with more fine analyses are further needed to shed light onto a basis of novel target therapy in AML. Let's get ready to use more arms!

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