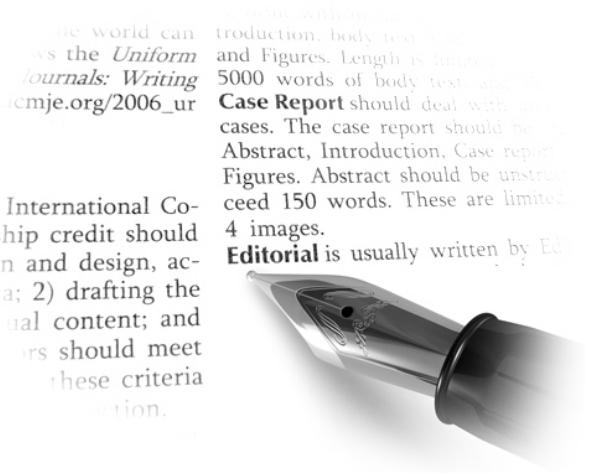

BLOOD RESEARCH
Volume 49 · Number 2 · June 2014
http://dx.doi.org/10.5045/br.2014.49.2.75

Editorial

How old is old: the beginning of a new era for therapeutic challenges for elderly patients with AML

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When patients with acute myeloid leukemia (AML) relapse, prognosis is considered dismal, even if the patient experiences a long period of complete remission (CR). Although we live in an era of genomic and epigenomic information, the management of elderly Korean patients with AML remains a challenge, given the patient's age, poor performance status, and various pre-existing comorbidities. As we know, the incidence of AML increases sharply with age, especially after the age of 55. According to the Surveillance, Epidemiology, and End Results (SEER) data (2006–2010), almost 70% of AML patients are >55 years old, with the peak incidence occurring at >75 years [1-3]. Unfortunately, most elderly AML patients do not receive intensive therapies, due to their age, a pattern that is based on the common misconception that elderly patients cannot tolerate chemotherapies. US SEER data from 2000–2007 revealed that only one third of elderly AML patients received early chemotherapy after initial diagnosis [2], although no Korean data exists to date. However, higher comorbidities and poor performance status, have a greater negative impact than age per se. Although there have been no large efficacy trials for these patients, large registry data, in addition to some positive retrospective studies, have shown that intensive induction therapy can improve survival [4-6]. There are currently many ongoing trials for selected elderly AML patients, including some with post-CR allogeneic hematopoietic stem cell transplantation (alloHSCT) approaches. However, a well designed treatment for elderly AML patients should be examined prospectively to determine whether patients who receive less toxic therapies achieve CR, whether post-CR alloHSCT may be avoided, and whether a true cure can be found with recent novel therapeutic agents.

In the present issue of **Blood Research**, Yi *et al.* [7] found that carefully selected elderly Korean AML patients (median age 70 years) experienced beneficial effects after treatment with either high-intensity regimens (HIR) or low-intensity regimens (LIR). The authors found that the median survival periods with HIR and LIR were 6.8 and 10.2 months, respectively, compared to just 1.6 months for patients who only received supportive care (SC). Multivariate analysis of the 168 patients, diagnosed in five institutes, identified age, ECOG performance status, Hb level, and serum creatinine at diagnosis as statistically significant prognostic factors for survival. Given the low sample numbers in the study, the authors suggested that further prospective trials would be necessary to identify specific prognostic factors, which could be used to precisely characterize elderly Korean AML patients.

However, some limitations in the study, and particularly some novel aspects that are presented should be noted. Firstly, the conclusion that HIR (N=76) provides an inferior median survival to LIR (N=18) (6.8 months vs. 10.2 months) is based on a very small sample size, and may not be supported by the study results. The CR rate in the LIR

group was just 5.6%, compared to 42.9% in the HIR group, which may suggest that the LIR group had been drawn from antiquated trials of uncertain design. Although LIR may contain various dose-intensity schedules, the overall median survival of 10.2 months for AML patients >65 years old is not a disappointing result, especially when compared with many older studies, or even recent therapeutic trials with novel agents [8]. Therefore, this dated treatment method should be amended, so as not to create confusion in a field clouded by lack of consensus. The authors also state that CR rates in the favorable, intermediate, and unfavorable groups were 20.0%, 22.6%, and 21.8% respectively. However, it is useless to comment on the risk grouping in this study, if the categorization was solely dependent on conventional cytogenetics, without molecular parameters. Although elderly AML patients receiving only SC (N=66) had a survival of 1.6 months, there was a prolonged survival for patients who received either HIR or LIR. However, these patients did not receive further intensive stem cell transplantation after achieving CR, since the extremely elderly patient (>65 years) were considered unable to maintain continuous CR and were unable to obtain reimbursement for alloHSCT in Korea.

Secondly, the 168 patients diagnosed at Gyeonggi area hospitals did not accurately represent elderly Korean patients with AML. As well, the four parameters from the analytic prognostic factors in this study do not accurately represent Korean patients either. Lastly, the continuous improvements of treatment regimens, through the introduction of epigenetic modulators in the 21st century, along with post-CR alloHSCT with reduced toxicity conditioning, should have been investigated, since even patients aged 65–75 years have exhibited encouraging results.

Instead of the multivariate analyses performed on all patients, or on the HIR, I recommend other productive conclusions after examining the data. The study included only 168 patients, diagnosed at local Korean institutes, where there are simply too many confounding variables to be considered in each facility. However, recent therapeutic reports for elderly Korean AML patients note that regimens containing low-dose cytosine arabinoside or mylotarg had similar superior outcomes, when compared to conventional intensive care patients [9, 10]. These results are especially notable for low-risk groups after considering multiple parameters, including comorbidity score, ECOG performance status, and age. Similarly, Yi *et al.* [7] found that age, ECOG performance status, Hb level, creatinine level, and C-reactive protein (CRP) level at initial diagnosis were considered prognostic factors. Although their study, as a pilot retrospective investigation, contains weaknesses, further prospective studies with well-selected patients could result in much improved outcomes for elderly Korean AML patients. I suggest that reliable prognostic and/or predictive factors should be used for approaching intensive therapies, including the use of elective alloHSCT after CR.

Although age has been considered one of the most important risk factors in most historical studies, tailor-made therapies, based on well-designed clinical trials with quality of life considerations, should be used to define the appropriate multimodality for current therapeutic options. The concept that AML patients older than 65 or 70 years cannot achieve CR should be rejected, since some patients possess favorable molecular cytogenetic profiles, allowing them to maintain continuous CR through treatment with only low-dose cytosine arabinoside or hypomethylating agents in outpatient clinic. We are still faced with the unresolved old-age AML management hurdles, especially for true elderly patients aged over 70–75 years. Therefore, it is imperative that we develop more reasonable treatment strategies for aging Korean AML patients in the near future. Again, how old is old?

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