Bone marrow blast elimination by the fifth day of 7 + 3 induction is the strongest predictor of potential cure in patients with acute myeloid leukemia younger than 61 years of age: A long-term follow-up of a multi-center prospective study

To the Editor:

Multiple clinical and genomic factors have been shown to be associated with improved prognosis in acute myeloid leukemia (AML). Nevertheless, based on the recent European LeukemiaNet (ELN) guidelines, incorporating these features, a significant portion of younger patients presenting with de-novo AML are still categorized in the intermediate-risk group. Refined precision of the outcome prediction is essential for the assignment of such patients to treatment, particularly allogeneic stem cell transplantation (allo-SCT).

Rapid eradication of blasts from the peripheral blood during induction therapy for AML is associated with a good response to initial treatment. Our previously conducted prospective observational study has aimed to identify the subgroup of leukemic patients in whom a prompt response to therapy would be a surrogate for a superior outcome. The findings of the study have demonstrated that early bone marrow (BM) response, defined as reduction in the number of BM blasts to less than 5% by the fifth day of induction is a strong predictor of remission and improved OS in patients younger than 61 years old and/or those with non-adverse cytogenetics, receiving the 3 + 7 induction regimen. Notably, our
multivariate analysis of OS has shown that rapid BM response supersedes all other outcome predictors, including cytogenetics.

The study was planned to include all AML patients who were assigned for intensive chemotherapy at the participating centers. One hundred and twenty-seven patients were recruited, including 18 patients of older age who received induction with clofarabine only. Data analysis revealed that the kinetics of the BM response in the latter patients was significantly different and slower than in similar patients treated with 3 + 7 induction. Thus, these 18 patients were excluded from further analysis. Included in this analysis were 109 adult AML patients treated with the 3 + 7 induction regimen, with a daunorubicin dose of either 60 or 90 mg/m². Patient median age was 58 (range 22-78) years. Patient characteristics were previously described.5 The majority of patients had de novo AML [75/109 (69%)] of standard or intermediate risk [72/109 (66%)]. The NPM1 and FLT3 mutations were present in 13/109 (12%) and 16/109 (14.7%) patients, respectively. Poor cytogenetics was found to be the only factor that was significantly associated with reduction in the early BM response rate (14% vs 39% for poor vs all other cytogenetic groups, respectively; P = .04). As the study was observational, treatment decisions were not made according to day five BM results but were rather based on day 14 BM evaluation that was performed at the discretion of the treating physician in the majority of patients [92/109 (84%)]. Yet, none of the patients who had a good response by day five had residual disease (>10% blasts) by day 14 that required re-induction. Overall, 70 (64.5%) patients achieved remission (CR1). Post-remission therapies varied according to patient’s age and risk factors.

At a long-term follow-up, data on a total of 103 patients were available, since six patients were excluded from the final analysis because of a mismatch between the blast counts in the day five BM aspiration, assessed morphologically and by flow cytometry.

The superior OS, observed in rapid compared to slow responders within the entire patient population, remained significant even after more than 5 years of follow-up (Figure 1A). As previously reported, this benefit was marked in patients younger than 61 years old. The predicted five-year OS of young rapid responders was as high as 79% compared to 38% in slow responders (Figure 1B). Among 24 promptly responding patients younger than 61 years old, an excellent outcome was demonstrated both in individuals undergoing allo-SCT and those receiving consolidation therapy only (Figure 1C). Notably, 11/15 (73%) young rapid responders who received consolidation chemotherapy without allo-SCT, while in CR1, are alive at a follow-up of more than 5 years.

Since BM samples derived in remission have not been assessed for the presence of minimal residual disease (MRD), we cannot determine whether an association of such results with rapid and deep response exists.

Out of the 92 patients for whom both day 5 and day 14 BM evaluation results have been available, a superior long-term survival has been observed in rapid responders by day 5 compared to all other patients, regardless of day 14 BM results. Given that none of the rapid responders has presented with unfavorable cytogenetics, we suggest that rapid response by day five of therapy may point to the patients with non-adverse cytogenetics, in whom allo-SCT may not be required to achieve cure.

The prognostic value of early BM evaluation has also been demonstrated by the Polish Adult Leukemia Group.6

We are approaching the era when effective non-intensive anti-AML regimens are becoming available. In the upcoming time, chemotherapy will be just one of multiple tools in the treatment armamentarium and the identification of AML patients, for whom chemotherapy could have a curative potential will be essential.

**FIGURE 1** Overall survival of patients at a long-term follow-up. OS comparison in rapid and slow responders: A, in the entire patient group; B, in patients younger than 61 years old. C, OS comparison in rapid responders younger than 61 years old treated with and without allo-SCT.
The current report of a long-term follow-up of a prospective trial is the first to suggest that early BM blast clearance after intensive induction may identify patients who have a disease that can be cured with chemotherapy alone.

For patients younger than 61 years of age who present with standard- or intermediate-risk AML, larger studies are warranted to confirm the significance of rapid response, its association with deeper remissions and its use as a clinical discriminator for the assignment to post-remission therapy.

CONFLICT OF INTEREST

The authors have no conflicts to declare.

AUTHOR CONTRIBUTIONS


REFERENCES


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Methodological aspects of the oxygenscan in sickle cell disease: A need for standardization

To the Editor:

Recently a method has been developed to assess red blood cell (RBC) deformability as a function of oxygen tension (pO₂).1 This method, called oxygen gradient ektacytometry or the oxygenscan, is particularly useful for evaluating individuals affected by sickle cell disease (SCD). Sickle cell disease is caused by a single point mutation in the β-globin gene (p.Glu7Val) leading to the production of an abnormal hemoglobin S (HbS). Abnormal hemoglobin S polymerizes under deoxygenation, which causes RBCs to take on a sickle shape. These sickled RBCs have impaired deformability and are therefore more vulnerable to damage during shear. The oxygenscan measures the ability of RBCs to deform in a gradient of oxygen tension, providing a quantitative measure of RBC deformability. This method can help identify individuals at risk of complications such as stroke or heart failure, and may be used to monitor response to treatments that target RBC deformability. Further research is needed to establish the clinical utility of the oxygenscan in the management of sickle cell disease.

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