Novel prognostic factors for patients with acute myeloid leukemia

Several criteria are now available for defining the prognosis of the individual patient with acute myeloid leukemia (AML). First of all, distinct karyotypic categories have been identified:

i) acute promyelocytic leukemia (APL) and AML with rearrangements involving the core binding factor (CBF), i.e., AML associated with t(8;21) and with inv(16) or t(16;16). Most of these patients achieve long lasting remissions and many of them can be cured;

ii) AML with normal karyotype or with rare aberrations that are associated with an intermediate prognosis;

iii) AML with abnormalities of chromosomes 5 and 7 and/or with complex aberrant karyotypes (i.e. ≥3 chromosomes involved) in which the median survival may be even less than six months;

Additional prognostic factors are represented by age and history of preceding hematologic diseases, mainly myelodysplastic syndromes. Recently, internal tandem duplications (ITD) and D835 mutations in FLT3 tyrosine kinase receptor have been shown to confer a bad prognosis in AML.

Despite this, it is known that pre-treatment prognostic factors explain only a minority of the variability in outcome following treatment of newly-diagnosed AML. Therefore, several studies have tried to improve the individual risk assignment by the quantification of minimal residual disease (MRD) using immunological or molecular markers. However, it is quite plausible that assessment of the initial response to treatment will improve prognostic accuracy.

The study by Haferlach and co-workers in this issue suggests that this hypothesis is correct. These authors recently demonstrated that early quantification of therapy-induced cytoreduction in leukemic bone marrow highly correlated not only with the response to induction therapy but also with long-term outcome in a cohort of 449 adult patients with newly diagnosed AML. The present analysis in the first step aimed at improving the prognostic model based on the cytogenetic risk stratification: a) by including the level of bone marrow blasts one week after the end of the first course of induction therapy and b) by defining AML with complex aberrant karyotype as a distinct group. Haferlach and co-workers defined this model based on 321 patients with de novo AML treated within the AMLCG 1992 trial. In the second step they validated this new risk score prospectively in 680 patients treated within the AMLCG 1999 trial. The German authors were able to clearly separate five prognostic subgroups for both studies using the pre-therapeutic parameter cytogenetics and the therapy-dependent early blast clearance (Figure 1). In fact, they demonstrate that the proportion of blasts in the marrow one week after completing the first course of chemotherapy adds information to that provided by the knowledge that pretreatment karyotype conveys intermediate risk. They also show that the unfavorable karyotype group can itself be divided into 2 prognostically distinct groups. This article will allow more individualized assessment of risk since 5 prognostic groups now replace the usual three.

As underlined by Elihu Estey in his comment, the paper by Haferlach and co-workers should spark interest in prediction of risk based on post-treatment response. For example, day 21 cytogenetics and detection of aberrant immunophenotypes on day 16 may eventually be incorporated with residual blasts as predictors of subsequent outcome. Molecular biology approaches may provide additional information. Schnittger and co-worker have recently evaluated the prognostic significance of quantitative PML–RARα, AML1–ETO, and CBFβ–MYH11 fusion transcript expression. AML patients at high risk for treatment failure...
could be identified by high levels of fusion gene expression at diagnosis or less than 3 logs of tumor reduction during the first 3 to 4 months of therapy. By combining the transcription ratios at these two checkpoints, a new powerful prognostic score has thus been established.

References


