

Optimal Post-Remission Therapy for Flow-Cytometry Minimal Residual Disease Positive Adult Patients with Acute Myeloid Leukemia

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We read with interest the brief report by Edward Laane and co-workers published into Haematologica/ The Hematology Journal, June 2006.¹ By multiparametric flow-cytometry (MPFC), the authors determined the levels of minimal residual disease (MRD) in 45 younger adult patients with acute myeloid leukemia (AML) in complete remission after induction therapy. They observed that receiving or not allogeneic stem cell transplant (SCT) was the only variable affecting significantly overall survival (OS) and relapse free survival (RFS) of patients MRD positive at the end of consolidation therapy. They concluded that *“the prognostic significance of MRD differs depending on the therapy applied and that autologous SCT may be an alternative for patients not eligible for allogeneic SCT. We wish to contribute to this issue presenting our experience.”*² By MPFC, we monitored the MRD levels in 100 adult patients with AML in complete remission after induction therapy. We found that the threshold of 3.5×10^{-4} residual leukemic cells discriminated between categories with different risk and that the assessment of MRD at the post-consolidation time-point was critical to predict disease outcome. At a variance with Laane experience, by multivariate analysis we demonstrated that MRD status at the end of consolidation was an independent factor influencing significantly the duration of OS and RFS. We believe two potential biases emerge from the report by Laane explaining such a difference: on one side, the series of patients may be too small to allow a statistical significance to be reached in multivariate analysis. On the other hand, in only five cases $100-500 \times 10^3$ events have been acquired whereas in the remainders 30×10^3 events have been: this poses a serious problem of sensitivity in order to pick up events which are present at very low frequency in the bone marrow samples. This topic has been addressed by several authors for MRD detection in acute lymphoblastic leukemia;^{3,4} by definition no less than 10-20 clustered cells/ 10^5 total events are considered MRD. This issue appears even more relevant in the AML scenario due to the intrinsic heterogeneity of the population under study and the natural fluorescence background of myeloid cells. In order to overcome this major flaw, we use to acquire 10^6 events. As to the role of allogeneic SCT, we certainly agree that this procedure may be the best option for MRD positive patients; this is confirmed by our data (Figure 1) (ASH 2006, oral communication). As for the role of autologous SCT, it may be an option when no other chances of allogeneic SCT are available, but with few possibility to prolong DFS. We addressed this issue in a previous report,⁵ demonstrating that the outcome of patients MRD positive at the end of consolidation, is not improved by autologous SCT (we are surprised the authors state that there is not literature on this matter). Finally, we find questionable the assumption of the authors that *“the prognostic significance of MRD differs depending on the therapy applied: prognostic determinants such as MRD or cytogenetics dictate prognosis and, as a consequence, they dictate therapy to improve the prognosis. The efficacy of a given therapeutic strategy requires to be measured against specific prognostic*

Figure 1. Disease Free Survival for 34 patients MRD positive at the end of consolidation, according to the post remissional therapy received (autologous vs. allogeneic SCT).

determinants; in this view, the authors are in keeping with us when they observe that allogeneic SCT achieves better results compared to autologous SCT in a poor risk categories such as MRD positive patients. This does not attenuate the prognostic role of MRD determination, rather highlights it since MRD positive patients can be rescued to a more favorable outcome only applying risk-adapted therapies.

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