Letter To Editor

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We read with great interest the letter by Buccisano *et al*, Optimal Post-Remission Therapy for Flow-Cytometry Minimal Residual Disease Positive Adult Patients with Acute Myeloid Leukemia". Although the first large study on the prognostic significance of minimal residual disease (MRD) detected by flow cytometry (FCM) in AML was published in 1997 by San Miguel *et al*,[1] there are so far no guidelines on how to integrate the results of MRD analysis in the treatment planning. Furthermore, the published literature on predicting prognosis in AML patients treated by allogeneic stem cell transplantation (allo-SCT) or autologous stem cell transplantation (auto-SCT) using MRD detection is still limited.[2] Therefore, the previously published study by Buccisano et al makes a significant contribution to this important field.[3]

We definitely agree that allo-SCT is the overall best post-remission therapeutic option for MRD positive, younger AML patients. In concordance with our study, Feller *et al.*[2] also demonstrated that MRD positive patients can be cured by allo-SCT only.

The efficacy of auto-SCT in AML patients is less clear. In our study, MRD positive patients who underwent auto-SCT had an improved outcome as compared to MRD positive patients treated only with conventional chemotherapy. Therefore auto-SCT may be considered as an option for younger AML patients who are not eligible for allo-SCT. Feller *et al.*[4] reported that CD34 positive cell levels >0.8% in autologous peripheral blood stem cell (PBSC) products were associated with a higher relapse rate and decreased disease-free survival (DFS). Venditti *et al*.[5] demonstrated that the pre-transplant MRD status predicted outcome in patients subjected to auto-SCT. All high-risk patients (MRD levels $\geq 3.5\times10^{-4}$ leukemic cells) in that study had a recurrent disease at a median time of 7 months. However, 26% of low-risk group patients also relapsed after a median time of 11 months. Our data is in concordance with the results of these two studies, as we also observed that patients who were MRD negative before auto-SCT had a better outcome by comparison to patients who were MRD positive. However, we would not recommend to tailor treatment of AML patients according to the MRD cut-off level of $\geq 3.5\times10^{-4}$ leukemic cells, since this level of diligence may be difficult to standardize between various laboratories and due to relatively high fraction of low-risk patients who suffered recurrence. In the study of San Miguel *et al.*[1] patients with MRD above 0.01% after induction had higher relapse risk by comparison to those with no detectable MRD. We would like to point out that our results have been obtained using MRD analyses, which started as a part of BIOMED 1 Concerted Action on MRD and were performed during 1994-2001 with three-color FCM. We agree that using four-color FCM with aqcuisition 0.5-1 $\times10^6$ cells per tube gives much higher sensitivity and it has been applied as a standard in our laboratory since year 2001. The application of polychromatic FCM with six or eight fluorochromes may further improve the sensitivity of detecting cells with aberrant phenotypes but there are as yet no published MRD studies using this approach.

In our study, MRD status was not a significant predictor of prognosis in the group of younger AML patients. This could be explained by a relatively high fraction of younger AML patients treated by SCT (30% of CR patients underwent allo-SCT and 28% of patients auto-SCT). MRD levels after induction and after consolidation treatment were significantly predicitive for both DFS and overall survival when the whole cohort of adult AML patients treated during this period was analyzed ($p<0.01$; data not shown). However, due to differences in post-induction therapy we did not want to analyze the results in older and younger AML patients together. By comparison, in the study by Buccisano et al,[3] only 11% patients underwent allo-SCT and the outcome of auto-SCT patients (44%) was relatively poor. Also, in the study by Buccisano et al younger and older patients were analyzed together.

Our study, although based on limited numbers of patients, clearly indicated that MRD status defined outcome in younger adult AML patients who were not allografted. However, our data also indicated that MRD status might not be critical for the outcome of AML patients who underwent allo-SCT. Therefore, the prognostic signifcance of MRD may depend on applied post-remission therapy. It is abundantly clear that the value of prognostic factors depends on applied therapy, which may be exemplified by the observation that with modern treatment protocols, childhood T-ALL patients seem to have lower risk of recurrence than B-precursor ALL patients.[6]

Taken together, the accumulating data highlight the importance of MRD dectection in directing post-remission therapy in AML. To further improve our knowledge in risk-adapted management of patients with AML, large prospective studies are needed where several issues should be addressed:

1) the standardization of the FCM methodology
2) clinically relevant MRD levels,
3) the most relevant time-points for MRD detection
4) relationship of MRD to other known prognostic factors.

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