PROCEEDINGS ARTICLE

Minimal residual disease

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The aim of minimal residual disease (MRD) studies in patients with acute leukemia is to measure initial treatment response accurately, provide an assessment of the residual leukemic burden throughout therapy and detect relapse early. Therefore, information resulting from MRD monitoring can substantially improve many facets of clinical management. Methods for MRD detection, namely flow cytometry and PCR, have been applied to study the remission status of thousands of patients with acute lymphoblastic leukemia and acute myeloid leukemia. Collectively, the data indicate that MRD is a powerful prognostic indicator and an indispensable parameter for risk-adapted therapy. The current status of MRD in acute leukemia is briefly reviewed in this paper.

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Tracking residual leukemic cells beyond the resolution of morphological methods, that is, 'minimal residual disease' (MRD), provides powerful prognostic information. Therefore, MRD is increasingly used to guide the clinical management of patients with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML).

Leukemic cells have unique genetic and immunophenotypic signatures, which can be detected by using real-time PCR or flow cytometry. In ALL, the main targets for PCR are clonal antigen-receptor (immunoglobulin and/or T-cell receptor) gene rearrangements and gene fusion transcripts (for example, BCR-ABL1, MLL-AFF1, TCF3-PBX1 and ETV6-RUNX1), which are present in about 90% and 40% of cases, respectively; they allow a sensitivity of detection of 0.001%.¹ In AML, antigen-receptor gene rearrangements are normally in a germline configuration and hence cannot be used for MRD studies. The fusion transcripts most extensively used to monitor MRD in AML (in addition to PML-RARA for acute promyelocytic leukemia (APL)) are AML1-ETO, CBFbeta-MYH11 and MLL-AF9, which are present in approximately one-third of non-APL AML cases.² In most cases of ALL and AML, cells also express marker combinations that are sufficiently distinct to allow MRD studies by flow cytometry. In the St Jude Total XV study for pediatric ALL, we could monitor MRD by flow cytometry with a 0.01% sensitivity in 482 of the 492 patients (98%),³ whereas in the St Jude AML02 trial for pediatric AML, we found aberrant immunophenotypes that allow a sensitivity of at least 0.1% in 200 of the 210 (95%) patients.⁴

MRD tests provide unique and important prognostic information in patients with newly diagnosed ALL, which often abolishes the prognostic weight of presenting clinical and biologic features.^{3,5–8} MRD is also prognostic in subgroups of ALL patients, such as infants,⁹ those with T-ALL¹⁰ and those with specific genetic abnormalities.⁷ Poorer early clearance of ALL reflected by higher MRD levels during remission induction therapy is generally associated with a higher risk of relapse.^{6,11,12} Even very low levels of MRD (that is, <0.01%) at the end of remission-induction therapy are associated with an increased risk of relapse,¹³ whereas high levels (that is, ≥1%) predict a particularly poor outcome.^{3,5} Moreover, MRD is a strong prognostic factor for children

and adolescents with first-relapse ALL who achieve a second remission¹⁴ and for those undergoing allogeneic hematopoietic stem cell transplantation.^{15,16} There is also evidence that MRD is clinically important in adult ALL. In studies of the GMALL, MRD on days 11 and 24 of treatments predicted outcome in adult patients with 'standard-risk' ALL,¹⁷ and sequential studies of MRD were also informative.¹⁸ Other studies also demonstrated the predictive value of MRD in different subgroups of adult ALL.^{19–21}

In pediatric AML, flow cytometry has been widely used for correlative studies of MRD and outcome.^{22–25} In the St Jude AML02 study, MRD remained a predictive prognostic factor despite treatment intensification for MRD-positive patients.⁴ The prognostic significance of MRD was also demonstrated in adult patients with AML.^{26,27} Maurillo *et al.*²⁸ found that levels of MRD after consolidation therapy were particularly informative: MRD-negative patients had a significantly more favorable outcome, regardless of whether they received autologous or allogeneic stem cell transplantation. In summary, evidence for the prognostic importance of MRD in both ALL and AML is extraordinarily strong; arguably, it is more compelling than that supporting any other prognostic factors used in the past for risk stratification.

The prevalence of MRD varies among different genetic subtypes of ALL and AML,^{3,4,29–31} it is associated with gene profiles of leukemic cells,^{32,33} as well as germline- or leukemia-associated gene polymorphisms.³⁴ Nevertheless, the predictive information provided by MRD testing is independent of these associations, as MRD measurements reflect the composite influence of multiple factors, including variables related to drug interactions, dosage, pharmacokinetics and compliance. Moreover, besides its use for prognostication, MRD monitoring can also recognize leukemia relapse before it is morphologically overt, assess the leukemia burden before transplant and measure the efficacy of a treatment regimen in relation to that of its predecessor. Therefore, it is likely that MRD measurements will be increasingly used in risk stratification algorithms for patients with acute leukemia, and as an end point for the assessment of novel therapeutic agents. The widening application of MRD testing is supported by novel methodologies that promise to further improve its sensitivity and reliability.^{35–37}

CONFLICT OF INTEREST

The author declares no conflict of interest.

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