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MYELOID NEOPLASIA

Comment on Schuurhuis et al, page 1275

Consensus on MRD in AML?

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The European LeukemiaNet (ELN) Working Party publishes its consensus document on minimal/measurable residual disease (MRD) in acute myeloid leukemia (AML) in this issue of *Blood*; Schuurhuis et al's article reports the status of existing methodologies for MRD assessments, provides guidelines for standardized approaches, and recommends future directions.[1]

Dependent on age, approximately half of AML patients in morphologic complete remission relapse. This has led generations of scientists to study ways of detecting the trace levels of leukemic cells that remain after therapy and, presumably, eventually cause leukemia recurrence. Initially called "minimal," these remnants of disease are now preferably termed "measurable" residual disease. There are ample, though mostly retrospective, studies that suggest that MRD has a decisive role in risk stratification of AML. Why then is MRD testing not yet used routinely to dictate postremission therapy? One answer is that MRD assessment is plagued by a large variety of available test methods to measure it, difficulties in comparing MRD measurements among laboratories or across clinical trials, and (possibly underestimated) the detrimental effects of sample quality. In other words, the amount of residual disease measured depends on who measured it (ie, method used, experience of the operator), how MRD levels are reported (percentage of total white blood cells, nucleated cells, CD45-positive cells, or mononuclear cells), and what the degree of hemodilution of the marrow aspirate was, given that MRD levels are significantly lower in blood than in marrow. Of great potential importance is the apparently heterogeneous distribution of the leukemic burden after treatment of AML throughout the pelvic region, as is evidenced by positron emission tomography.[2]

Faced with this plethora of drawbacks with MRD assessment, the ELN MRD Working Party report is a valid attempt to introduce some level of standardization. A couple of suggestions, however, deserve discussion. The authors propose combining the 2 philosophies of flow-cytometric MRD detection, the one based on diagnostic leukemia-associated immunophenotypes (LAIP) with the different-from-normal (DfN) strategy, into the "LAIP-based DfN approach." One cannot help but sense in this proposal an attempt to settle this controversy semantically rather than through experimentation. For instance, by analyzing MRD specimens by both methodologies in parallel, particularly in AML cases with monocytic components, which remain a huge challenge, especially for LAIP proponents. Given the listed advantages of DfN, why not agree on DfN and the creation of fixed antibody panels for all to use? Furthermore, while recognizing the need for reporting MRD levels in a clinically interpretable fashion and providing several recommendations for how to achieve that, the ELN report advocates keeping the commonly used 0.1% threshold level, derived from retrospective studies, to distinguish MRD-positive from MRD-negative AML patients, with the caveat that MRD levels below 0.1% may still be of prognostic significance. Although the level of quantifiable MRD changes with the methodology used, the level of clinically relevant MRD changes with the choice of therapy. There is evidence that clinically relevant thresholds of MRD may differ with the intensity of therapy.[3] Furthermore, improvements in outcome by novel therapeutic interventions are not invariably associated with lower MRD levels.[4] In any MRD-driven prospective trial comparing a novel agent with standard treatment, therefore, the clinically most relevant MRD threshold for the novel agent will have to be retrospectively redefined. No doubt, this requirement will complicate the introduction of MRD-guided prospective trials. It may indeed be premature to introduce as a novel response category "CR without MRD," defined by any method and target of choice.[5]

The question is whether harmonization of currently used MRD detection methods is the only or best solution to the MRD challenge in AML. After all, MRD status has been significantly associated with clinical outcome irrespective of methodology and despite the lack of standardization. This suggests that the concept of MRD, that not having disease is better than having disease, is robust and not easily swayed by technical aspects. What about the 25% to 30% of patients, however, in whom MRD status, defined by currently available MRD assays, defies clinical response? It is unlikely that assay standardization alone will be sufficient to overcome this conundrum. Standard pretreatment prognostic features, including cytogenetics, gene mutations, and immunophenotypic characteristics, have segregated patients into favorable, intermediate, and unfavorable risk classes. Within each of those categories, MRD appears to add independently to prognosis, though patients deemed unfavorable may benefit the least.[6] Ivey et al reported that the molecular heterogeneity of standard-risk AML with mutated *NPM1* precluded outcome prediction in this subset of patients on the basis of this pretreatment risk factor alone.[7] Measuring the remaining *NPM1*-mutant transcripts at the end of induction therapy on the NCRI AML17 trial, however, provided powerful

prognostic information, in that 82% of patients with detectable *NPM1*-MRD relapsed. But so did one-third of patients without detectable *NPM1*-MRD. This raises the question as to whether gene mutations other than *NPM1* were present in those cells that survived chemotherapy, leading to relapse in the *NPM1*-MRD-negative cohort. In a comparison of flow-cytometric MRD with gene mutation status, only mutations of *DNMT3A*^{R882}, a gene mutation frequently found in *NPM1*-mutated AML, significantly predicted the presence of flow-cytometric MRD following induction chemotherapy.[8] In fact, *DNMT3A* gene mutations have been identified in preleukemic hematopoietic stem cells, whereas *NPM1* mutations arise later, beyond the preleukemic state, in leukemogenesis.[9] Is it clinically relevant to detect MRD at the level of preleukemic stem cells to account for the 30% of AML patients in whom conventional MRD is not informative? Monitoring mutational clearance after therapy by testing for as many combinations of mutations throughout the AML genome as is feasible has been suggested as a beginning to defining a genomic posttreatment risk stratification.[10] Does the heterogeneous make-up of any myeloid leukemia population, both at the genetic and the epigenetic levels, add a potentially insurmountable complexity to the monitoring of MRD? Without question, the clinically most useful MRD test and targets are yet to be determined, and both will most likely depend on the individual patient's characteristics and the therapy administered.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Shapiro et al, page 1301

Woody eyes, be gone!

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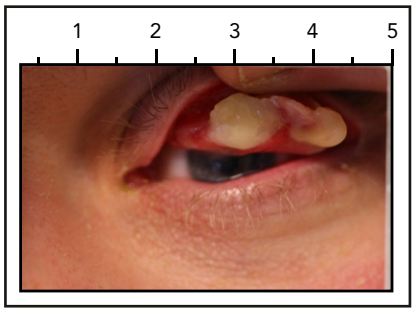
In this issue of *Blood*, Shapiro et al describe the first-in-class experience of infusing plasma-derived Glu-plasminogen to 14 patients with congenital deficiency of plasminogen as part of an ongoing, phase 2/3, open-label clinical trial, reporting encouraging results.[1] Congenital plasminogen deficiency is caused by homozygous or compound-heterozygous mutations in the plasminogen (*PLG*) gene, located on chromosome 6q26. It is, in the words of the authors, "ultra-rare," predicted to affect ~1 to 2 per million people.[2] Plasminogen is activated to plasmin and is critical for intravascular and extravascular fibrinolysis. Other functions include wound healing, cell migration, tissue remodeling, angiogenesis, and embryogenesis. Glu-plasminogen has a glutamic acid residue at its N-terminus, as opposed to Lys-plasminogen, which has a lysine. Glu-plasminogen is the predominant form found in circulation and has a half-life of 2 to 2.5 days, whereas the half-life of Lys-plasminogen is 0.8 days.[3]

Patients lacking plasminogen suffer from abnormal growth of fibrin-rich, woodlike ("ligneous") pseudomembranes on mucous membranes, such as conjunctiva, gingiva, airways, and the vaginal tract, typically within the first year of life.[4] Ligneous conjunctiva is the pathognomonic manifestation of congenital plasminogen deficiency (see figure). If left untreated, these woody growths over time severely affect quality of life and eventually lead to organ dysfunction, including blindness.



Ligneous conjunctiva. See Figure 3A in the article by Shapiro et al that begins on page 1301.

Historically, local therapy was the only available treatment. Topical eye drops containing plasminogen only treated conjunctival lesions, and surgery to remove the pseudomembranes predisposed to scar tissue and regrowth of lesions. The first publication reporting the successful use of IV infusions of unlicensed Lys-plasminogen to treat

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