Measure for measure: minimal residual disease in CLL

Richard F. Little and Lisa M. McShane

In this issue of Blood, Kwok and colleagues have provided a wealth of retrospective clinical data that greatly expands our appreciation for the prognostic importance of flow-cytometric residual disease measurement across a spectrum of clinical presentations in chronic lymphocytic leukemia (CLL).1

Measuring minimal residual disease (MRD) to detect 1 or fewer CLL cells in 10,000 normal leukocytes has consistently shown correlation with long-term clinical outcomes when examined in the context of prospective clinical trials.2-4 Substantial international effort has provided a sound scientific foundation establishing valid and reproducible methods in flow cytometry and polymerase chain reaction–based molecular assays.5 The excitement for CLL MRD is justified both by the impressive methods science and the remarkable therapeutic advances in CLL unfolding with each contemporary major clinical trial. Each new achievement is revolutionizing the principles and practice of CLL medicine.6 In the current study, Kwok and colleagues have shown that the long-term prognostic value of MRD is valid with up to 18 years of follow-up across a spectrum of therapeutic approaches both in the up-front setting and for previously treated patients.1 Doubts about the prognostic validity of MRD in various settings should now be put to rest. The clinical utility of MRD must now be understood so that it can be properly applied.

MRD as a clinical tool rests on its powerful prognostic capacity. There is interest in using MRD to guide therapy and for the design of clinical trials, including as end points. Improving clinical outcomes for those living with CLL entails improving survival and quality of life while minimizing toxicity, including financial burden. MRD assessment will play an important role in achieving these goals.

In order to learn how to apply MRD toward these goals, randomized controlled clinical trials (RCTs) asking specific questions concerning the use of MRD must be conducted. For example, should MRD status support treatment decisions for shortening or intensifying therapy? Can MRD assessments be used to define treatment duration? Only through RCTs can answers to these types of critically important questions be ascertained. The essential clinical trial end points required for this work, progression-free survival (PFS) and overall survival (OS), require long-term follow-up. The work is daunting yet essential. There is interest in shorter-term clinical trial end points, such as MRD status, in hopes of more rapidly achieving these goals to improve the lives of those living with CLL. However, to confidently use a shorter-term end point in place of an accepted longer-term clinical benefit end point demands that key evidentiary requirements be met.

The strong association of MRD status with prognosis has raised the prospect that MRD may be suitable for use as a surrogate for the true clinical benefit end points PFS and OS.7 Indeed, if the treatment effect on MRD were able to reliably predict the treatment effect on PFS and OS—this is termed the trial-level effect—the ability to complete clinical trials could potentially be substantially shortened. One might ask if the current data already support the use of MRD as a surrogate for longer-term clinical benefit end points. Unfortunately, the answer to this is no, not yet. The analyses so far have evaluated MRD by pooling patients who have undetectable MRD levels and comparing them to those pooled on the basis of positive MRD detection—such an analysis reflects an amalgamation of varied patient-level effects. In this situation the improved outcomes in the undetectable MRD group are pooled over specific therapies at the patient level, and therefore, it is impossible to assign a causal effect or magnitude of effect on MRD to any given therapy. In other words, trial-level effects of treatment are not demonstrated. One way to think of such an analysis is that MRD serves as a tumor sensitivity assay for each patient, and so MRD results forecast on an individual patient level whether clinical outcome is likely to be favorable or not. We can only conclude that an individual patient with undetectable MRD status has a more favorable prognosis compared with a patient with detectable MRD.

For MRD to serve as a surrogate end point in RCTs, we need to establish that the trial-level effect of a specific treatment causes the MRD effect and that the MRD effect reliably predicts the true clinical benefit effect. To establish the desired trial-level surrogate, a collection of RCTs is required in order to show how the experimental treatment affects MRD compared with how the control treatment effects MRD and whether the magnitude of effect on MRD enables one to reliably predict the magnitude of effect on PFS or OS.8,9 This is a formidable task. Many
factors can confound the assessment. If patient clinical care is changed based on MRD knowledge outside of the protocol-directed approach, then the potential surrogacy relationship is uninterpretable. Further complicating the use of MRD as a surrogate is the fact that MRD dynamics vary incredibly by type of treatment. For example, compared with chemoimmunotherapy, novel biologic therapies such as ibrutinib have a much slower response time and often do not result in undetectable MRD status, yet they may improve PFS.5,10 This introduces uncertainty for timing of MRD assessment for various therapies in the quest toward establishing surrogacy. Establishment of surrogacy for one type of therapy does not necessarily support a claim of surrogacy for another therapeutic agent. Surrogacy has to be constantly verified with new therapeutic agents.

Importantly, surrogacy is not required for immediate incorporation of MRD assessment into clinical trials designed to improve clinical outcome for the individual patient and to address important individual and public health concerns. As novel therapies for CLL involve chronic administration of expensive medicines, trials focused on duration, intensification, or deintensification of therapy can provide precision in determining who will benefit from different treatment strategies. Provided such studies measure the true clinical benefit end points, they will also provide the necessary data to evaluate claims for potential surrogacy of MRD.

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REFERENCES

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Metformin: treating the cause of Fanconi anemia?

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In this issue of Blood, Zhang et al have uncovered that metformin, a first-line treatment for type 2 diabetes, can improve hematopoietic stem cell (HSC) function and reduce cancer risk in a mouse model of Fanconi anemia (FA).1

FA is a rare genetic disease that leads to bone marrow failure and an extreme predisposition to cancer. Cells from these patients are unable to repair a particular kind of DNA damage, and this defect is thought to be the basis of the observed pathologies. At the molecular level, 21 gene products act in a common pathway to repair damage caused by DNA interstrand crosslinking agents (eg, cisplatinum). Although we understand quite a considerable amount about how these proteins cooperate to repair damaged DNA, we have very little understanding of why this should lead to bone marrow failure or why cancer predisposition is worse in certain tissues. One explanation could be that certain tissues have greater exposure to damage, but until recently, we had very little idea of the physiological sources of DNA damage that precipitate FA. A recently identified source of damage may be simple aldehydes.2,4 Alternatively, it has been proposed that when HSCs leave their quiescent state, they accumulate DNA damage, necessitating FA-mediated repair.4 Building on these foundations, Zhang et al reveal that metformin may be the first agent that targets the source of DNA damage in FA.

Mice deficient in the key Fanconi protein FANCD2 were fed a diet supplemented with metformin. In FA-deficient mice, this treatment attenuated the blood cytopenias, and improved, but did not fully correct, the reduced frequency of HSCs and restored them to a quiescent state. Finally, treatment with metformin resulted in a small but significant reduction in the tumor predisposition of Fancd2+/−/p53+/− mice. The magnitudes of these effects are relatively small but this may in part be due to the fact that the HSC loss in FA begins during embryonic development, however the metformin treatment was only initiated in adults (see figure).5

Despite this, metformin is the first example of a pharmacological intervention that both improves hematopoietic function and suppresses tumor predisposition. As the effect of metformin is restricted to Fanconi-deficient mice, it is plausible that metformin could be attenuating the source of damage that drives the FA phenotype.

The mechanism(s) of metformin’s effect remains to be fully uncovered. The authors go some way to address this by using a poly(I:C) treatment that mimics viral infection and induces a type I interferon response. This treatment has been shown to drive HSCs to
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