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CLINICAL TRIALS AND OBSERVATIONS

Comment on Dimier et al, page 955

MRD negativity as a surrogate for PFS in CLL?

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In this issue of *Blood*, Dimier et al, for the first time, quantitate the relationship between minimal residual disease (MRD) negativity and progression-free survival (PFS) in patients receiving chemoimmunotherapy as first-line treatment of chronic lymphocytic leukemia (CLL), establishing its validity as a surrogate marker for PFS.[1]

Prolonged PFS is possible after first-line treatment of CLL with chemoimmunotherapy, particularly in patients with favorable biological risk features. An important open question is whether novel oral therapies alone or in combination will be superior to chemoimmunotherapy. However, as CLL researchers, we are victims of our success; the prolonged PFS achieved after first-line chemoimmunotherapy necessitates prolonged follow-up to ascertain differences in PFS between treatment groups. This delays regulatory approval of novel regimens that, in CLL, is generally based on demonstration of improvement in PFS in a phase 3 study.

This conundrum led to interest in developing surrogates for PFS that can be assessed more rapidly. MRD in CLL is assessed quantitatively by a method with the sensitivity to detect <1 CLL cell in 10 000 leukocytes, most commonly multiparameter flow cytometry[2]; achievement of MRD negativity (<1 CLL cell in 10 000 leukocytes) in either blood or bone marrow strongly correlates with longer PFS in patients treated with chemoimmunotherapy in the first-line setting.[3-6] The importance of using MRD negativity as a primary end point in clinical trial design is that differences in the rate of MRD negativity between treatment arms can be assessed after only 9 to 15 months (depending on treatment duration), thus potentially allowing more rapid regulatory approval of novel therapies. For these reasons, MRD negativity has been accepted by the European Medicines Agency (EMA) as a surrogate marker for PFS.[7] However, the EMA raised several important caveats, including noting that "The validation of MRD response rate (undetectable MRD + CR) as a surrogate endpoint requires that the treatment effect on this marker can explain quantitatively the treatment effect in terms of PFS." Although the EMA guidelines accept MRD negativity as an interim end point, they require that PFS benefit be confirmed with longer-term follow-up.

The current study mathematically models and quantitates the relationship between the effect of treatment on MRD and the effect of treatment on PFS. The model is based on 3 German CLL Study Group studies of first-line chemoimmunotherapy: CLL8 (fludarabine and cyclophosphamide [FC] vs fludarabine, cyclophosphamide, and rituximab [FCR]), CLL10 (FCR vs bendamustine and rituximab), and CLL11 (chlorambucil vs chlorambucil plus rituximab vs chlorambucil plus obinutuzumab). External validation was performed with data from the REACH trial of FC vs FCR in relapsed patients. They developed a weighted linear regression model in which patients were grouped according to geographical region in order to create enough data points to fit the model. This model demonstrated that approximately one-third of the variability in PFS hazard ratio could be explained by whether patients were or were not MRD negative at the completion of therapy. This knowledge allows statisticians to infer the expected PFS hazard ratio from the expected ratio of MRD-negative rates for 2 treatment arms and thus allow design of future phase 3 studies with MRD negativity as the primary end point.

However, although these results demonstrate the robustness of MRD negativity as a surrogate marker for PFS, they also demonstrate that a significant amount of variability in PFS was accounted for by factors other than MRD negativity. This is likely due to 2 factors: First, the testing methodology has limited sensitivity (1:10^4) and cannot directly assess residual disease in lymph nodes and other tissue sites; thus, some patients are categorized as being MRD negative who have clinically significant residual disease either below the level of detection or in unassessed sites, which subsequently leads to relapse. This may also explain the fact that there was a residual difference in PFS between treatment groups, even when MRD negativity was taken into account. Second, time to clinical progression is determined by both residual tumor burden and the growth kinetics of any low-level residual tumor cells; in turn, growth kinetics are determined by the biological characteristics of the tumor, such as *IGHV* somatic hypermutation status. Thus, biological tumor characteristics affect PFS even when MRD results are factored in. The latter point is important when designing future studies, as these current data were derived from clinical trials that included patients with heterogeneous tumor biological features. If future studies are performed in patient populations that are more homogeneous (eg, patients who have unmutated *IGHV* only), the amount of variability in the PFS

hazard ratio explained by the difference in MRD-negative rates could potentially be higher.

So, how can this model be used in future clinical trials? Clearly, the model will not be useful for comparing a chemoimmunotherapy regimen with a targeted therapy, such as ibrutinib, which rarely achieves MRD negativity and is given indefinitely as maintenance therapy. In contrast, it may have usefulness in informing sample-size calculations based on MRD negativity end points for studies comparing chemoimmunotherapy with novel regimens that have significant potential to achieve MRD negativity. In particular, venetoclax plus obinutuzumab,[8] venetoclax plus ibrutinib,[9] and venetoclax plus ibrutinib and obinutuzumab[10] in the first-line setting have been shown to achieve high rates of MRD negativity. Three venetoclax-based regimens are currently being compared with chemoimmunotherapy in the ongoing first-line CLL13 trial (NCT02950051). This study uses MRD negativity at 15 months as the primary end point to compare the venetoclax plus obinutuzumab (which is given for 1 year) and chemoimmunotherapy arms. One caveat is that the model discussed here is based entirely on studies of chemoimmunotherapy. It is unknown whether the relationship between treatment effect on MRD negativity and treatment effect on PFS will be quantitatively similar in patients receiving venetoclax-based regimens given for a finite duration. For this reason, it will be important to repeat the analyses performed by Dimier et al when sufficient data on venetoclax-based regimens are available. Finally, as more sensitive technologies for MRD detection (eg, high-throughput sequencing) are adopted, the quantitative impact of MRD negativity on PFS hazard ratio will need to be reassessed.

We now possess an array of therapeutic options able to achieve deep responses; the ability to rapidly determine significant differences between treatment arms, through quantitative detection of MRD, is essential to accelerate the regulatory approval of novel regimens and make them widely available for the benefit of our patients.

Conflict-of-interest disclosure: P.A.T. has served as an advisory board member for Pharmacyclics and Genentech and as a consultant for AbbVie. ■

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Comment on Rowczenio et al, page 974

The elusive pathogenesis of Schnitzler syndrome

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In this issue of *Blood*, Rowczenio et al investigate the role of genetic factors, inflammasome activation, and proinflammatory cytokines in the pathogenesis of Schnitzler syndrome.[1]

Schnitzler syndrome is a rare disorder characterized by recurrent or chronic urticaria associated with a monoclonal gammopathy and persistent inflammation.[2] This disorder often goes undiagnosed.[3] The rash is typically resistant to antihistamines, and histologically, it is a neutrophilic urticarial dermatosis. The monoclonal protein is an immunoglobulin Mκ (IgMκ) in 80% to 90% of cases. In the remaining patients, IgMλ and IgG monoclonal proteins have been reported. The invariable presence of the monoclonal protein suggests a possible pathogenic role, which has remained elusive. Additional features, which are minor diagnostic criteria, include intermittent fever, arthralgia, bone pain, liver or spleen enlargement, palpable adenopathy, elevated markers of inflammation, and bone abnormalities on radiological investigations. Fatigue is frequent, and the clinical manifestations are often disabling. Schnitzler syndrome can progress to Waldenström macroglobulinemia or other lymphoproliferative disorders, with a frequency comparable to that of patients with IgM monoclonal gammopathy of undetermined significance. Moreover, systemic amyloid A (AA) amyloidosis that occurs as a consequence of chronic inflammation may develop (see figure). To prevent this, treatment should be aimed at