clonal progression. Indeed, clonal progression is a major cause of morbidity and mortality among patients with hematopoietic neoplasms. Among the most important research directions we could foster is the development of agents that can stabilize minimally deviated neoplastic clones (see figure). The use of (putative) demethylating agents in clonal cytopenias and oligoblastic leukemia is a rudimentary effort to stabilize a chronic or subacute myeloid neoplasm. Therapists hope that by reversing methylation the result may be the reexpression of normal genes previously silenced.

In the management of myeloid malignancies, we are often confronted with the battle between the neoplastic clone and polyclonal normal hematopoiesis. The remission-relapse pattern of acute myelogenous leukemia is a classic example of such competition. The good guys lose too often. It is unclear, in specific biologic terms, how a single mutated cell can gain hegemony over the multiple normal clones that constitute polyclonal hematopoiesis. Stem cell niches are a focus of attention. Although some work has been conducted on this process, we are largely in the dark, and it should be a major direction of our research. Today, ablation should be read by hematologists who want to be

(see figure). That approach could provide the greatest potential for progress. Developing models to study stable, metastable, and progressive clonal hematopoietic neoplasms and the ability to prevent their progression is an important research direction.

The paper by Steensma et al has several virtues. It raises an important consideration, the diagnosis of CHIP, at a time when genetic profiles of hematopoietic cells are becoming de rigueur and cautions us against the misinterpretation of a clonal somatic mutation in the absence of a phenotype sufficient to make an accurate diagnosis. It provides an opportunity to reinvigorate the concept of developing a reversible reaction: converting severely or moderately deviated neoplasms back to minimally deviated neoplasms or stabilizing a minimally deviated neoplasm. The latter action could be equivalent to a cure. Not an easy task, but worthy of the application of someone’s genius. It also provides an economical discussion and review of important recent genetic findings in the clonal myeloid neoplasms, and it provides insights into the diagnosis of myelodysplastic syndromes. It should be read by hematologists who want to be informed on these matters.

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**REFERENCES**


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**CLINICAL TRIALS AND OBSERVATIONS**

Comment on Saußele et al, page 42

**Living with CML: is death no longer the end (point)?**

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In this issue of *Blood*, Saußele et al demonstrate, in a study based on 1519 chronic myeloid leukemia (CML) patients, that death may be a flawed end point for the assessment of tyrosine kinase inhibitor (TKI) efficacy because, in the current era, CML patients more often die with their disease than because of it.

The basic tenet of trial design when evaluating new cancer therapies is that having surrogate markers of good response that correlate with favorable long-term outcomes is appropriate and pragmatic, but that the ultimate test for a new therapy is to establish improved survival. This study suggests that survival may not be the gold standard end point, at least when it comes to trials of TKIs in CML. Because, for the majority of patients, CML is now a chronic condition maintained by regular TKI therapy, improvements in survival have become increasingly difficult to demonstrate, requiring large studies and very long follow-up. This study found that the most powerful predictor of survival for CML patients in the large German CML Study IV trial3 was a composite measure of comorbidities (the Charlson comorbidity index)4 at diagnosis rather than
the disease-specific Sokal or EUTOS prognostic scores (see figure).

Saußele et al demonstrate that there is a strong negative association between comorbidities at diagnosis and overall survival, but that comorbidities have no effect on response (ie, complete cytogenetic response and major molecular response), remission rates, and progression to advanced phases in CML. The negative association is also not due to adverse drug-related events, either hematologic or nonhematologic. They indicate therefore that survival may be an inappropriate outcome measure for specific CML treatments, as the overall survival of CML patients is now determined more by comorbidities than by their CML. With a number of different TKIs available for therapy, and patients often switching to a second- or third-line therapy, overall survival is becoming more difficult to assess, and comorbidities may indeed be the major influence.

It follows then that survival may not be the ideal end point for CML trials, because it is so strongly influenced by comorbidities that may mask real differences in disease-related outcomes. In this case, is there a better end point we could use? One obvious candidate would be to use CML-related deaths as the key end point. This would allow us to identify new therapies that actually reduced the risk of disease progression, the overwhelming cause of CML-related deaths. There are 2 potential drawbacks here. First, it is not always straightforward to determine whether a death is CML related. For instance, how do you classify the patient who does not achieve good disease control, proceeds to an allograft while still in the chronic phase, and subsequently dies of complications, or a case of sudden unexplained death? Any subjectivity in the assessment of this end point would make the analysis potentially open to influence and bias. However, a more substantial concern is that by focusing exclusively on CML-related deaths, a subtle increase in non–CML-related deaths induced by a new therapy could be overlooked. Both the Evaluating Nilotinib Efficacy and Safety in Clinical Trials—newly diagnosed patients (ENESTnd)\(^5\) and the Dasatinib versus Imatinib Study in Treatment–Naïve CML Patients (DASISION)\(^6\) demonstrated lower rates of progression in patients randomized to the nilotinib and dasatinib arms compared with the imatinib arms; however, both studies failed to show a significant difference in overall survival for those patients on second-generation TKIs. This was surprising because the outcome for patients who progress to blast crisis has not improved greatly in the TKI era. Therefore, why didn’t the lower transformation rate translate into improved survival for the nilotinib and dasatinib arms of these trials? Some would argue that the high background rate of non–CML-related deaths dilutes this difference in CML-related deaths, but it is also quite plausible that the lower rate of progression and consequent CML-related deaths seen with the more potent TKIs is counterbalanced by a slightly higher rate of death from other causes. Higher rates of infection and pulmonary toxicity with dasatinib and vascular toxicity with nilotinib could potentially underlie this increase in non–CML-related deaths.

A possible shortfall of this study is the restricted definition of comorbidities. The Charlson index does not take into account things such as hypertension, angina, and obesity. It is, however, a commonly used index that has been validated in numerous settings. Furthermore, because this study was based on a clinical trial, it is reasonable to assume that various trial entry criteria around comorbidities would have restricted trial access for some patients and may have also meant that the age group studied was not truly representative of clinical practice. Although this is likely to be true, one could speculate that the inclusion of these patients would have actually increased the power of these study findings rather than reduced them.

Consideration of end points such as overall survival or freedom from CML-related death may become less relevant now that the focus of CML therapy is increasingly the achievement of a stable deep molecular response, which can provide the platform for a trial of cessation. The success of the next generation of therapies for CML will likely be judged by the capacity to achieve treatment-free remission in a greater number of patients than the current approaches, rather than measuring subtle differences in survival.

This timely study by Saußele et al reminds us that the greatest danger for most patients with CML is not their leukemia but their preexisting comorbidities. Clinicians would be wise to pay just as much attention to these comorbidities as they do to the patient’s leukemic disease risk score when selecting the optimal TKI therapy and when managing CML patients in the long term.

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In this issue of Blood, Bonzheim et al have reported the diagnostic value of the assessment of MYD88 L265P (MYD88) mutations in vitreoretinal lymphoma. In general terms, the diagnosis of lymphoma classically requires standard histopathologic, immunophenotypical, genetic, and molecular criteria that are combined to a variable extent to define individual clinicopathologic entities recognized by World Health Organization classification. These gold standard requisites may not be fulfilled in some rare particular instances, resulting in diagnostic difficulties. One challenging example of this latter occurrence is represented by vitreoretinal diffuse large B-cell lymphoma. The identification of vitreoretinal diffuse large B-cell lymphoma is crucial for 2 main reasons. First, this type of lymphoma is particularly aggressive and must be distinguished from low-grade marginal-zone B-cell lymphomas of the choroid, and second, vitreoretinal diffuse large B-cell lymphoma could represent the intraocular dissemination of a concomitant diffuse large B-cell lymphoma of the central nervous system (PCNSL). PCNSL is another and more frequent type of aggressive B-cell lymphoma that needs to be promptly recognized and treated.

Easy morphologic diagnosis is not the rule in vitreoretinal diffuse large B-cell lymphoma; in fact, the evaluable material is usually obtained by vitreous body aspirate, and this implies that cytologic instead of histologic assessment is often performed in routine practice. Moreover, the diagnosis is further hampered by the low number of cells, the poor conservative status of these free-floating elements in the vitreous, and the prevalent admixture of non-neoplastic components, including smaller lymphocytes. Clearly enough, the most difficult differential diagnosis arises with uveitis and infections. Useful diagnostic tools mainly used in systemic lymphomas, such as flow cytometry and molecular biology, have a limited value in vitreoretinal diffuse large B-cell lymphoma. This is mainly a result of the overall limited amount of material in the case of flow cytometry and the risk of detecting pseudoclonal/oligoclonal B-cell populations by polymerase chain reaction owing to the few cells occurring in the vitreous. Importantly, this latter occurrence may be encountered also in benign/reactive conditions, thus increasing the difficulty in diagnosing vitreoretinal diffuse large B-cell lymphoma. A significant achievement has been reached with the demonstration that increased IL–10 levels are associated with vitreoretinal diffuse large B-cell lymphoma, but not all diagnostic laboratories are equipped to measure these levels.

On these grounds, Bonzheim et al introduce a new strategy able to improve the diagnostic accuracy of vitreoretinal diffuse large B-cell lymphoma, through the detection of MYD88 mutations in vitreous aspirates of patients suspected of having vitreoretinal diffuse large B-cell lymphoma. Some cases interpreted as reactive with currently available techniques were reclassified as neoplastic on the basis of the presence of MYD88 mutations and, most importantly, their malignant nature was confirmed by clinical follow-up. Although comparative studies on the diagnostic accuracy between IL–10 levels and MYD88 mutations deserve to be tested in a prospective study, the strategy of the detection of MYD88 mutations is particularly attractive. In fact, it should be taken into account that these molecular assessments are usually already in use within well-equipped diagnostic hematopathology laboratories, because they are equally useful for the recognition of some lymphoproliferative disorders such as lymphoplasmacytic lymphomas often associated with Waldenström macroglobulinemia and diffuse large B-cell neoplasms of activated B-cell-like type, mostly represented by testicular lymphomas, PCNSL, and “leg-type” entities of the skin. Therefore, no additional technical efforts would be required to better diagnose vitreoretinal diffuse large B-cell lymphoma.

The results herein provided have further implications. In fact, 65% to 90% of patients with vitreoretinal diffuse large B-cell lymphoma eventually progress to PCNSL, and it appears critical to assess lymphomatous involvement of the vitreous to properly treat these patients. Another critical feature is that this concept could be extended also to vitreoretinal involvement by systemic or extranodal lymphomas, as confirmed by the experience of Bonzheim et al, who reported the intraocular dissemination by 2 cases of primary testicular lymphomas without a concomitant PCNSL. Because one of these patients developed mutated MYD88 vitreoretinal diffuse large B-cell lymphoma 10 years after the diagnosis of a testicular lymphoma carrying the identical mutation, these results show that this molecular approach also deserves to be tested as a powerful method to detect late relapses and assess the prognostic implications of the occurrence of MYD88 mutations in the vitreous of patients with testicular lymphomas.
Living with CML: is death no longer the end (point)?

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