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● ● ● **CLINICAL TRIALS**

Predicting response in CML

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Predicting response in chronic myeloid leukemia (CML) patients who are offered tyrosine kinase inhibitor (TKI) second-line therapy is vitally important. For younger patients, allogeneic transplantation is still a therapeutic option Thus, physicians need new models to predict the outcome of their patients.

In this issue of *Blood*, Jabbour et al propose a simple scoring system easily applicable in the clinic.[1] The analysis was based on a group of 123 patients with chronic-phase CML who failed imatinib therapy and who were switched to dasatinib or nilotinib. Their model identified 2 variables that were significantly associated with event-free survival. In a multivariate analysis, the lack of any cytogenetic response to previous imatinib therapy and Eastern Cooperative Oncology Group performance status of 1 or more at the start of second-generation TKI therapy were identified as independent adverse factors associated with poor event-free survival. The model thus subdivides patients into 3 categories: good risk (0 factor), intermediate risk (1 factor), and poor risk (factors) associated with 2-year, event-free survival of 78%, 49%, and 20%. Of note, the 2-year overall survival was also significantly associated with the risk categories. Moreover, Jabbour et al performed additional multivariate analyses using a 12-month landmark. They stated that the lack of major cytogenetic response at 12 months after the onset of the second TKI is an adverse independent factor for event-free survival. Although the definition of "event"-free survival has to be carefully considered, the general finding is in accordance with the definition of the response to the second-generation TKIs dasatinib and nilotinib as second-line therapy of patients with imatinib-resistant CML–chronic phase (CML-CP) which was proposed by the new European Leukemia Net recommendation.[2]

Less-than–major molecular response at 12 months was considered (at least provisionally) a suboptimal response and less-than–partial cytogenetic response as failure. Using this approach, the authors confirmed that a performance status of 1 or more is a poor prognosis factor for the survival. However, other clinical and/or biological parameters could still be of interest. First, prognostic scores, such as the Sokal score, which relates to the pathophysiology of the disease at diagnosis, may still be of some value even later on the course of their disease. For example, intermediate- and high-risk patients are at higher risk of molecular relapse after cessation of imatinib.[3] The Hammersmith group recently proposed a score including 3 factors associated with the achievement of responses after second TKI therapy: that is, the best cytogenetic response on imatinib, the occurrence of neutropenia, and the Sokal score at diagnosis.[4] Second, mechanisms of resistance to imatinib are not unique. Consequently, some parameters may be predictive of resistance to second generation of TKIs in specific subgroups of patients and not in others.

Early retrospective data showed a high incidence of imatinib noncompliance in CML patients which could lead to undesired clinical outcomes. The ADAGIO (adherence assessment with gleevec: indicators and outcomes) study[5] evaluated adherence to imatinib in 169 CML patients and found that during the initial 90-day period of imatinib treatment, one-third of patients were considered to be non adherent. Only 14.2% of patients were compliant with all prescribed doses of imatinib. Thus, nonadherences could be an issue with second TKI. Chronic adverse events of even grade 1 or 2 must also to be considered,

essentially because these side effects may explain non adherence to treatment. In these 2 situations, predictors of response to second TKI may be somewhat different from those of patients who received imatinib using prescribed dosages.

Point mutations in the BCR–ABL kinase domain, which are frequently involved in TKI resistance, may be an important determinant in clinical decisions. Several recent reports suggested that routine mutation screening could provide valuable information regarding the selection of the optimal TKI and could also identify patients at high risk of disease progression.[6] Thus, such biologic abnormalities should be considered in parallel with the new score.

Clonal cytogenetic abnormalities and elevation in BCR–ABL transcript levels could be investigated for further models because some studies showed that elevations in BCR–ABL transcript levels might indicate a potential for BCR–ABL gene mutations and emergence of TKI resistance.[7]

Identification of biomarkers to predict resistance to TKIs is currently in progress. For example, gene array data on blast cells or the CD34-enriched cell population from chronic phase have provided interesting information.[8,9] Although a pretreatment molecular signature has been identified for imatinib-treated patients, such a signature could serve as a molecular biomarker for stratifying patients treated with any other TKI into risk group. Moreover, recent data provided evidence that BCR–ABL mutation leads to kinase activation, suggesting that this mechanism may extend beyond activation loop mutations.[10] Finally, it would be helpful if several international CML groups could select a large independent cohort of patients to validate these new scoring systems and select the one that would produce the most accurate information for the monitoring of CML patients.

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Comment on Fehniger et al, page 1828

The times they are a-changin'

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The article by Fehniger et al in this issue of *Blood* suggests that lenalidomide at 50 mg daily is a qualitatively different, and potentially useful, therapy for AML.[1]

To date the drug, at 10 mg daily, has found its greatest use in reducing red cell transfusion requirements in patients with low-grade myelodysplasia (< 10% blasts) and a deletion of the long arm of chromosome 5 (del 5q).[2] Treating 33 acute myeloid leukemia (AML) patients age 60 years or older, none of whom had del 5q, Fehniger et al noted 6 complete remissions (CRs) and 4 CRs with incomplete count recovery (CRi). In contrast to remissions seen after daunorubicin and cytarabine ("conventional treatment"), remissions after lenalidomide occurred without marrow hypoplasia (cellularity < 10%), and there was no apparent relation between achievement of remission and lenalidomide-induced neutropenia. Also, unlike conventional treatment, cytogenetics (ie, intermediate vs "unfavorable" using Southwest Oncology Group/Eastern Cooperative Oncology Group criteria) were not the principal predictor of response. Response was unrelated to age (60-64 years, 65-69 years, or older than 69 years). Rather, there was a striking inverse relation between response and extent of disease, quantified by marrow blast percentage or number of circulating blasts. Extent of disease is typically not a major predictor of response to

3 + 7 but was found by Ades et al to be such in a trial administering lenalidomide to patients with "high-risk" myelodysplastic syndrome (MDS), or AML with up to 30% marrow blasts.[3] Specifically, Ades et al reported a CR in 6 of 29 in patients with less than 20% marrow blasts but only 1 of 18 in patients with 20%-29% blasts who achieved a CR. Because all of these patients had a del 5q and a similar median age to the Fehniger et al study, the higher response rate in the latter (5 of 8 in patients with 20%-30% marrow blasts) likely results from use of a 50-mg rather than the conventional 10-mg dose used by Ades et al.[3] Because more myelosuppression did not seem to translate into a higher response rate, the reason for the dose-response relationship is not immediately obvious. However, the lenalidomide dose-response relation does appear steeper than that seen with conventional treatment; for example, 10 mg vs 50 mg of lenalidomide is comparable to the dose-response relationship of 100 vs 3000 mg/m^{2} cytarabine.

Perhaps the most striking difference with conventional treatment is the seeming lack of a relation ($P = .37$) between survival and re-

sponse category (CR vs CRi). For many years response to induction therapy for AML was considered CR or no CR, based on 50-year-old data suggesting that only CR increased survival.[4] Walter et al have reported that with conventional treatment, CR was associated with longer survival than CRp (CR with a platelet count < 100 000/μL).[5] Although it seems reasonable to hypothesize that CRi will be associated with shorter survival than CRp given that it appears a lesser response requiring no recovery of neutrophils, large databases are not readily equipped to address the relative value of CRi. And certainly, what is found regarding survival in patients with CR versus CRi receiving conventional treatment may not apply with other therapies, as has been suggested with azacitidine.[6] Fehniger et al are careful to note that their ability to detect longer survival with CR than with CRi was limited by patient numbers, and indeed the data in their Table 3 indicate that the median survival for CRi was 8.5 months versus at least 16 months for CR. Because patients are interested in "response" primarily as it affects survival, the survival value of responses less than CR will undoubtedly be further elucidated in the future.

Although lenalidomide is probably qualitatively distinct from conventional therapy, outcomes after its use—as noted by Fehniger et al—do not appear obviously better. While agreeing with the authors that lack of randomization hinders comparison, the CR rate was plausibly lower than might be expected had some of these patients (for example, those age 60-65 years with a normal karyotype) received conventional therapy[7] (or, more recently, escalated doses of daunorubicin[8]). However, as widely recognized, it is important to move to a more "personalized" approach. In particular, it may be possible to identify patients (eg, those with low blast counts and other, to be discovered, markers) whose survival with 50 mg of lenalidomide is superior to that seen with more conventional therapy.

Lenalidomide's future in AML almost certainly lies in combination with other agents such as azacitidine[9] or conventional treatment. Indeed, many new anti-AML drugs appear promising in single-arm phase 2 trials such as that reported by Fehniger et al. A very incomplete list includes plerixafor, sapacitabine, voreloxin, suberoylanilide hydroxamic acid (SAHA), AT-406, and