CORRESPONDENCE

Telomerase Inhibitor Imetelstat in Essential Thrombocythemia and Myelofibrosis

TO THE EDITOR: Baerlocher et al. (Sept. 3 issue)[1] report on telomere-targeted treatment with imetelstat in 18 patients with essential thrombocythemia. The drug was effective in controlling platelet levels in all patients, albeit often at the expense of hemoglobin and neutrophil levels. However, the other main treatment goals in essential thrombocythemia[2] — controlling symptoms and preventing both disease progression and thromboembolic complications — were definitely not achieved. Fatigue, diarrhea, and nausea were all reported by more than 70% of the patients. A total of 3 patients had progression to myelofibrosis, and 2 patients had a thromboembolic event. Thus, treatment with imetelstat does not seem to be promising in this relatively benign disease.

Only 4 patients had received interferon before undergoing this experimental therapy. Pegylated interferon alfa-2 is effective in controlling thrombocytosis in most patients, and it is not associated with myelofibrotic transformation, leukemogenicity, or other adverse long-term events.[3] Furthermore, interferon may induce a deep molecular remission (i.e., a very low *JAK2* V617F mutation level) and normalization of bone marrow changes, effects that in some patients may be maintained years after treatment cessation.[3,4] In Denmark, interferon is suggested as first-line treatment in patients with essential thrombocythemia.[5]

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TO THE EDITOR: In their editorial on the findings of Baerlocher et al. and Tefferi et al. (Sept. 3 issue),[1] Armanios and Greider[2] suggest that the experimental drug imetelstat may change the natural course of myeloproliferative neoplasms, possibly by binding to cell-surface receptors such as toll-like receptor 9 (TLR9). Since TLR9 induces the production of type I interferons by plasmacytoid dendritic cells,[3] it is tempting to speculate that the effect may be mediated through interferon alfa-2, which in several studies during the past 25 years has proved to be highly effective and safe in the treatment of myeloproliferative neoplasms with the induction of complete hema-

tologic remission.[4] In a subgroup of patients, deep molecular remissions with a reduction in *JAK2* V617F mutant alleles and normalization of the bone marrow were sustained even years after the discontinuation of interferon alfa-2, findings that are compatible with "minimal residual disease."[5] Thus, interferon alfa-2 may change the natural course of myeloproliferative neoplasms if the drug is initiated at the time of diagnosis.[4] Given the toxic side effects and modest treatment response associated with imetelstat, we do not think this drug can be considered as an alternative to interferon alfa-2, which in addition to its immune-modulating effects is a telomerase inhibitor as well.[6]

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DR. BAERLOCHER AND COLLEAGUES REPLY: Our phase 2 study of imetelstat enrolled 18 patients with essential thrombocythemia with a median interval of 7 years since initial diagnosis. All the patients had received a median of two previous therapies, including hydroxyurea, anagrelide, and interferon. Although interferon is used in patients with essential thrombocythemia, this disorder is not an approved indication. A total of 4 patients in our study were previously treated with interferon; 1 had resistance, and 3 had unacceptable side effects. All 4 of these patients had a hematologic response to imetelstat, and 2 of the 3 patients with mutations had a molecular response.

Rapid, substantial hematologic and molecular responses that were observed in such patients provided evidence of anticlonal activity and proof-of-concept data for further investigation of imetelstat in patients with advanced myeloid cancers. The interpretation of data with respect to progression to myelofibrosis and thromboembolic events in patients with long treatment histories is difficult from this single-group study. Randomized clinical studies are required to compare such end points. Furthermore, complete and partial remissions, including reversal of bone marrow fibrosis and molecular responses, were recently reported in the study by Tefferi et al.

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DR. TEFFERI REPLIES: It is true that imetelstat may not have the side-effect profile that justifies its further consideration for the treatment of essential thrombocythemia, as reported by Baerlocher et al. However, drug benefit–risk assessment is best accomplished in the context of randomized studies and should not be surmised from the results of a small proof-of-concept study. The same holds true for other drugs for the treatment of essential thrombocythemia, including interferon alfa. Treatment-induced reduction in the *JAK2* or *CALR* mutant allele burden in patients with essential thrombocythemia has been observed with imetelstat, interferon alfa,[1] and busulfan.[2] Such observations do not necessarily imply that each of these drugs has the same effect on coexistent disease clones with different mutations[3] or an advantage in terms of meaningful health outcome; the latter requires evidence from controlled studies and not conjecture based on local treat-

ment practices. The observations from our pilot study of imetelstat support a unique mechanism of action that deserves further laboratory-based investigation.

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Since publication of his article, the author reports no further potential conflict of interest.

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Cell-free DNA Analysis for Noninvasive Examination of Trisomy

TO THE EDITOR: Norton et al. (April 23 issue)[1] report near-perfect accuracy of detection for trisomy 21 (Down's syndrome) with the use of cell-free DNA (cfDNA) (sensitivity, 100% [38 of 38 cases of trisomy 21]; false positive rate, 0.06% [9 false positives among 15,841 women]) in the Noninvasive Examination of Trisomy (NEXT) study. These seemingly promising results may be misleading because they excluded 488 patients (3% of their sample) with indeterminate cfDNA results. The prevalence of aneuploidy was higher among these patients than in the overall cohort (2.7% vs. 0.4%); thus, their exclusion may introduce bias.[2] Estimates of accuracy should consider indeterminate results to be either positives or negatives according to how they would be handled in clinical practice.[2]

Given their increased risk of aneuploidy, patients with indeterminate results would probably undergo additional testing. Thus, it may be appropriate to classify their cfDNA results as positives. This classification would result in a false positive rate of 3.0% and a positive predictive value of 7.6%, much lower than the reported positive predictive value of 80.9%. Alternatively, if indeterminate results were classified as negatives, sensitivity would be reduced to 38 of 41 cases (93%) (95% confidence interval [CI], 80 to 98). Assuming that no patients with indeterminate results on standard screening had trisomy 21, the sensitivity of cfDNA testing and standard screening (33 of 41 cases [81%]; 95% CI, 66 to 90) would not be significantly different ($P=0.22$ by McNemar's test).

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TO THE EDITOR: Norton and colleagues found that cfDNA testing for trisomy 21, as compared with standard screening, had a better global performance during the first trimester of pregnancy. However, they did not provide information about the 14 fetal chromosomal abnormalities in the 15,841 screened pregnancies, other than for trisomies 13, 18, and 21.

Were these 14 aneuploidies diagnosed prenatally because of abnormal features on follow-up ultrasonography or because of stillbirths or miscarriages? Or were they detected by standard screening or postnatally? The answers to these questions may help to determine whether a routine policy of general screening for aneuploidy with the use of ultrasonography and cfDNA testing rather than standard screening is the best strategy.

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