To the Editor:

Methylation of the proximal promoter of the c-ABL oncogene is a specific epigenetic alteration associated with progression of chronic phase chronic myelogenous leukemia (CML) to accelerated and blastic phases. A recent report by Issa et al published in Blood concludes that c-ABL methylation “is associated with disease progression” but “lacks prognostic significance.” Our previous work is in full agreement with the investigators’ conclusion that c-ABL methylation is a reliable marker for disease progression. However, we find it hard to reconcile to the proposed dissociation of prognosis from malignant progression. Therefore, we were surprised by the categorical finality imbued in the title of the article and the strongly negative conclusions on the prognostic value of the marker which, in our opinion, are not warranted by the methodology and the data presented.

Issa et al have tested the prognostic significance of c-ABL methylation by correlating solitary determinations of methylation status at diagnosis with survival at 5 to 7 years. This approach may prove to be of limited informative potential because it disregards the fact that c-ABL methylation is a dynamic variable that can be modulated by treatment. We have shown that the majority of patients with positive evidence for methylation at diagnosis who were subsequently treated with interferon-α (IFN-α) underwent reversal of the methylation status within an average of 10.8 months under treatment. This phenomenon was totally independent of cytogenetic response and, therefore, cannot be argued to constitute a substitute index for cytogenetic remission. Therefore, to properly ascertain the prognostic significance of c-ABL methylation, treatment outcomes and survival should be correlated with response of methylation to therapeutic modulation as determined by multiple assessments. In other words, it is important to use methylation as a dynamic parameter to monitor disease activity and/or the kinetics of aggressive subclones of cells, because these factors will eventually determine the rate of clinical progression and prognosis. It is notable that the investigators did show a palpable (albeit not statistically significant) difference in survival rates between high- and low-methylation groups when they used c-ABL methylation as a static parameter, despite the problems inherent in this type of analysis. These data do not unequivocally exclude a prognostic role for c-ABL methylation in CML and, in our opinion, call for a fuller study.

We further believe that a number of additional issues need to be addressed before a candid assessment of prognostic value can be made. First, the outlook of patients with no evidence of methylation in diagnosis who subsequently undergo de novo methylation must be ascertained. If methylation is indeed a marker for disease progression, its emergence in these patients, especially when under treatment, is likely to carry a dismal prognosis. Second, rates of relapse between high- and low-methylation groups after treatment should be compared. Third, the degree of c-ABL methylation before bone marrow transplantation in chronic phase has to be correlated with outcome. Answers to these questions were not sought in the report by Issa et al.

The issue of which method to use to detect methylation also remains open. By using restriction endonuclease–based assays, Issa et al find a significantly high proportion of cases with methylated c-ABL in early chronic phase compared with other studies using similar methods. The investigators note this discrepancy and attribute it to patient selection and/or methodology bias. We have also used restriction-enzyme based techniques and are fully aware that the use of restriction endonucleases to detect methylation may be marred with a high number of false-positive results that may render subsequent analyses problematic. We have attempted to circumvent these problems by developing methods based on polymerase chain reaction of sodium bisulfite-modified DNA. Our data suggest that determination of methylation status of colonies derived from single hematopoietic progenitors appears to have a good correlation with clinical course and it may deserve full comparison with traditional methods.

The premise that c-ABL methylation is associated with CML progression appears to enjoy a wide consensus in the literature. This epigenetic change may represent either a stochastic mutation or a time-dependent consequence of the BCR-ABL translocation event. Recent data from our laboratory suggest that c-ABL promoter methylation is a necessary (but probably not sufficient) event for CML clonal evolution. It is probable that the chronic phase of CML is maintained by a balance of BCR-ABL and cytoplasmic ABL proteins exerting opposite and antagonistic functions at the level of apoptosis, cell-cycle progression, and genetic instability. The disease may evolve when this balance is lost as the result of reduced transcription from the internal c-ABL promoter. Through its effects on methylation, interferon treatment appears to be capable of reestablishing the status quo, leading to prolongation of the chronic phase of disease. The potential prognostic value of modulation of these molecular events by interferon treatment cannot be overstated and merits further investigation.

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REFERENCES

Prognostic Significance of c-ABL Methylation in Chronic Myelogenous Leukemia: Still an Open Question

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