The Indolent Natural History of Essential Thrombocythemia: A Challenge to New Drug Development

AYALEW TEFFERI, MD

Essential thrombocythemia (ET) is a diagnosis to be considered when neither reactive thrombocytosis nor an otherwise defined myeloid malignancy explains a persistently increased platelet count. The disease was first described in 1934 and subsequently classified as a myeloproliferative disorder (MPD) in 1951. Over the years, remarkably little has been accomplished by way of controlled treatment trials in ET. Physicians, therefore, have relied mostly on carefully conducted prospective cohort studies and large retrospective studies to guide them in patient management. Accordingly, evidence-based management currently dictates the use of hydroxyurea in high-risk patients (age ≥60 years or positive history of thrombosis) while drug therapy has not been shown, in a controlled setting, to have an advantage over observation alone in either low-risk (age <60 years and negative history of thrombosis and platelet count <1500 × 10⁹/L and absence of cardiovascular risk factors) or indeterminate-risk (neither high- nor low-risk) patients. This, however, has not stopped the pervasive use of alternative cytoreductive agents including anagrelide, interferon alfa, and pipobroman (not available in the United States) across all risk categories in ET, based on demonstration of “treatment efficacy” from uncontrolled single arm studies. Such a noncritical approach to drug therapy becomes particularly unnerving considering the potential occurrence of serious adverse effects associated with some of these drugs including anagrelide-associated cardiomyopathy and interferon alfa–associated neuropathy. An equally important issue from the patient’s perspective is that both anagrelide and interferon alfa are substantially more toxic as well as more expensive than hydroxyurea.

What then is the impetus to use drugs other than hydroxyurea in patients with ET and how can one best determine their efficacy? This analysis is problematic in that median survival in ET exceeds 2 decades and might not be inferior to that of an age- and sex-matched control population. Therefore, it is next to impossible to show a survival advantage attached to a “new” drug. It is equally statistically challenging to demonstrate the value of a new drug in the control of disease-related complications because of the low baseline rates seen with conventional therapy. For example, in a recent large retrospective study of 435 patients with ET, the 15-year cumulative risks of thrombosis and clonal evolution into either acute myeloid leukemia (AML) or myelofibrosis with myeloid metaplasia (MMM) were 17%, 2%, and 4%, respectively. Furthermore, the risk of both thrombosis and bleeding in low-risk patients who are not receiving any cytoreductive therapy may not be significantly different from that of the age- and sex-matched control population. On the other hand, the antithrombotic value of cytoreductive therapy for high- or intermediate-risk ET has been addressed by 2 randomized treatment trials, both of which clearly documented the therapeutic superiority of hydroxyurea over both observation alone or anagrelide therapy. What about the impact of new drugs on the issue of clonal progression as well as possible drug leukemogenicity associated with hydroxyurea use? In the aforementioned large retrospective study of ET (N=435), the 15-year cumulative risk of either AML (2%) or MMM (4%) was not significantly influenced by single-agent chemotherapy of any kind including hydroxyurea. In addition, the fact that these episodes of clonal evolution occurred at a median of 14.5 and 10.9 years, respectively, again underscores the magnitude of the problem of sample size and duration of follow-up necessary for a controlled study to allow statistically valid conclusions. Two other smaller retrospective studies involving 25 and 35 patients reported no cases of leukemia after 5-14 years and 2-12 years.

From the Department of Internal Medicine and Division of Hematology, Mayo Clinic College of Medicine, Rochester, Minn.

Individual reprints of this article are not available. Address correspondence to Ayalew Tefferi, MD, Division of Hematology, Mayo Clinic College of Medicine, 200 First St SW, Rochester, MN 55905 (e-mail: tefferi.ayalew@mayo.edu).

© 2005 Mayo Foundation for Medical Education and Research
respectively, of treatment with hydroxyurea. Consistent with the observation from these retrospective studies, the risk of leukemic transformation in the aforementioned randomized treatment trials was not adversely affected by the use of hydroxyurea alone, whereas patients treated with anagrelide experienced a significantly higher rate of transformation into MMM (16 vs 5 events on the hydroxyurea arm after a median follow-up of 39 months). Similarly, another recent communiqué, involving 90 patients with ET, suggested a substantial increase in bone marrow fibrosis after treatment with interferon alfa. Therefore, at this juncture, there is no hard evidence to implicate hydroxyurea use in ET as being leukemogenic, whereas new information suggests that both anagrelide and interferon alfa may increase the risk of transformation into MMM.7,30

Where do we go from here? Based on the aforementioned discussions, it is reasonable to question the practical impact as well as return value of additional randomized treatment trials in ET. Instead, it might be more cost-effective to direct resources and effort toward basic and translational research that focuses on disease pathogenesis and leads to curative therapy. In this regard, the National Institutes of Health recently sent out a request for applications (expiration date, February 17, 2005) for MPD research that focuses on the cellular and genetic characteristics of these disorders (http://grants1.nih.gov/grants/guide/rfa-files/rfa-hl-04-034.html). In the meantime, current evidence continues to support the use of hydroxyurea as the preferred drug of choice for high-risk patients with ET. The remarkably low incidence of AML in hydroxyurea-treated patients with either ET or polycythemia vera, despite the fact that it is usually administered to patients who are vulnerable to clonal evolution because of either aggressive disease phenotype or advanced age, should dispel the unsubstantiated fear of drug leukemogenicity and provides much-needed comfort to physicians who practice evidence-based medicine and use this particular agent for the treatment of young women with essential thrombocythemia [letter]. In fact, there is no hard evidence to implicate hydroxyurea use in ET as being leukemogenic, whereas new information suggests that both anagrelide and interferon alfa may increase the risk of transformation into MMM.7,30

Finally, the experience in ET should serve as a lesson in discouraging the blanket use of new drugs in polycythemia vera before their value is properly evaluated in a randomized setting.

REFERENCES