Commentary (Haire): Diagnosis and Treatment of Thrombocythemia in Myeloproliferative Disorders

By William D. Haire, MD

Myeloproliferative disorders originate in the clonal expansion of a transformed pluripotent hematopoietic progenitor cell. This results in a group of syndromes that include polycythemia vera, essential thrombocythemia,

Dr. Gilbert has succinctly summarized much of the recently published literature on the diagnosis and treatment of thrombocytosis caused by polycythemia vera and essential thrombocythemia. Many of her recommendations reflect the opinions of most investigators and practitioners in the field. However, there is a body of literature and interpretations of cited studies that are not included in her article.

Diagnostic Dilemmas

From a diagnostic point of view, the 1997 revision of the Polycythemia Vera Study Group’s (PVSG’s) diagnostic criteria for essential thrombocythemia is often not particularly helpful in clinical practice. Of the seven criteria, five (items 2 through 6 in Dr. Gilbert’s Table 3) are directed at differentiating essential thrombocythemia from other primary marrow disorders such as polycythemia vera, chronic myelocytic leukemia, primary myelofibrosis, or one of the myelodysplastic syndromes. Although this is important in defining the disorder in a clinical research setting, its usefulness in determining the requirements of patient care is debatable.

In clinical practice, thrombocytosis of all myeloproliferative diseases has similar therapeutic implications, as attested to by inclusion of all disorders in a large therapeutic trial of anagrelide (Agrylin).[1] Criterion 1, the requirement of a platelet count greater than 600,000/µL, may be insensitive—excluding many patients with true myeloproliferative disorders, some of whom are destined to develop vaso-occlusive symptoms or overt organ infarction.[2,3]

Criterion 7, “no cause for reactive thrombocytosis,” is also problematic because it fails to define any standard evaluation that will rule out such a problem in a specific patient. For example, it is fairly simple to conclude that a patient with stage IIIB Hodgkin’s disease at 1 month post-staging splenectomy probably has a "reactive thrombocytosis." However, it is more difficult to be sure that a patient with chronic bronchitis, stable angina pectoris, and an erythrocyte sedimentation rate of 78 mm/h with a stable platelet count of 620 to 670,000/µL does not have thrombocytosis due to the effects of systemic inflammation.

These two criteria pose the greatest diagnostic problems for practicing clinicians. If they hold dogmatically to the 1997 PVSG criteria, they may withhold cytoreductive therapy from patients who might benefit from it, because they feel these patients do not have essential thrombocythemia if their platelet count never exceeds 600,000/µL or if there is the remote possibility of a cause for reactive thrombocytosis. In fact, these patients may require additional testing, such as platelet aggregation studies, looking for lack of epinephrine-induced aggregation,[4] or marrow morphology, looking for megakaryocytic dyspoiesis.[5] However, the absence of these findings does not rule out essential thrombocythemia.

These patients may need cytoreductive therapy even if they do not fulfill the PVSG criteria for the diagnosis of essential thrombocythemia. Lack of such a standard is not only a problem in clinical practice, but also makes it impossible to determine whether patients from different clinical research studies are comparable—the threshold for ruling out causes for a reactive thrombocytosis may well vary between institutions, investigators, geographic locations, and over time.
Hydroxyurea Controversy

From a therapeutic point of view, Dr. Gilbert states unequivocally that one widely used medication for the treatment of thrombocytosis, hydroxyurea, is leukemogenic and that its use is "inappropriate for young patients, low-risk patients..." These two statements are made with a degree of conviction that is not held by all investigators in this field. To support the contention that hydroxyurea is leukemogenic, the author cites uncontrolled observational studies, which show that patients taking hydroxyurea developed leukemia.[6-8]

When interpreting these studies, it must be remembered that correlation and causation are not synonymous. Essential thrombocythemia and polycythemia vera are clonal myeloproliferative disorders with an inherent tendency to evolve into acute leukemia and other myelodysplastic disorders,[9] even in the absence of any cytoreductive therapy. The patient-specific factors, beyond type of therapy, that are associated with progression to leukemia are unknown. Therefore, in a nonrandomized therapeutic trial, patient-specific variables may influence the observed rate of leukemic conversion.

This is especially true in series in which patients were given hydroxyurea only if their disease progressed, often after being treated with another therapy.[7,10] These patients may have an intrinsically more aggressive disease process with a greater propensity for leukemic conversion. In the only randomized trial cited, the rate of leukemic conversion was similar whether hydroxyurea or pipobroman was administered—suggesting that both were equally leukemogenic or that there was an intrinsically high rate of leukemic conversion in this group of patients with progressive polycythemia vera.[11]

None of the studies purporting to show that hydroxyurea is leukemogenic did so using the modern standard for such evaluations—the randomized clinical trial. Consequently, variations in the observed rate of leukemic transformation in different groups of patients may reflect intrinsic differences in the biology of the disease among the groups of patients rather than their treatments. Because of this, not all investigators are convinced of the inherent leukemogenicity of hydroxyurea,[9] and many feel that hydroxyurea has a role in the management of patients of all ages.[12]

High-Risk vs Low-Risk Patients

Another problem with extending Dr. Gilbert’s statements about hydroxyurea into practice is the concept that there is a readily defined group of patients at "low risk." As she points out, the risk of adverse outcome (mainly from vascular occlusive events) is not proportional to the platelet count. The most widely quoted risk factors are a history of prior thrombosis and advanced age.[9] In practice, the first requires that a patient wait until he has suffered the morbidity of a thrombotic event before using cytoreductive therapy to prevent a subsequent event—ie, closing the barn door after the horses have escaped. And youth does not uniformly protect against thrombosis in all series.[13,14] Indeed, the thrombosis-free survival curves for patients with essential thrombocythemia younger and older than age 55 years are comparable.[15]

Moreover, none of the studies of prognostic factors have tested variables prospectively, to determine their positive and negative predictive values for thrombotic complications in any cohort of patients. Consequently, in clinical practice, accurately determining the prognosis for a given patient is problematic.

The Argument for Anagrelide

As counterpoint to hydroxyurea, Dr. Gilbert states that anagrelide has shown no evidence of leukemogenicity, and hence, is a safe choice for young patients. The greatest risk of acute leukemia in patients treated with hydroxyurea did not become apparent until after 5 years of therapy.[8] In a cohort of 262 patients with essential thrombocythemia, Storen et al identified 37 consecutive young patients with a median age of 40 years who were seen at the Mayo Clinic to assess long-term toxicity and drug tolerance. Six of these patients discontinued treatment due to toxicity (four patients) or
personal preference (two patients). The 31 remaining patients were treated with anagrelide for a mean of 10.7 years, and none developed acute leukemia,[16] suggesting that, in the absence of randomized trial data, it may be reasonable to infer that it has a low leukemogenic potential.

On further analysis, however, this cohort of patients was found to have a 20% incidence of thrombosis and a 26% incidence of bleeding prior to initiation of anagrelide therapy. During anagrelide therapy, these complication rates were essentially unchanged at 20% and 20%, respectively,[17] calling into question its safety relative to the overall health of these young patients.

This point is important because of data from a randomized, prospective, placebo-controlled trial of essential thrombocythemia therapy, wherein hydroxyurea was associated with a significant reduction in thrombotic episodes—from 24% in the placebo group to 3.6% in the treated group—and no major hemorrhagic complications.[18] In these studies of hydroxyurea and anagrelide, thrombotic and major hemorrhagic complications that occurred during therapy were associated with platelet counts exceeding 400,000/µL, suggesting (but not proving) that complete normalization of the platelet count may be necessary to minimize the residual thrombohemorrhagic risk during treatment—indeed, to determine the type of treatment used. Whether this is more likely to occur with anagrelide or hydroxyurea cannot be determined without comparative clinical trials.

This information underscores the fact that contemporary therapy for myeloproliferative thrombocytosis continues to require weighing the potential risk of leukemogenicity against the risk of death or disability from thrombotic events—just as it did 15 years ago.[19]

**Conclusions**

Clinically, Dr. Gilbert’s recommendations are useful if they are viewed as basic guidelines to be tempered with clinical judgment. However, it is clear that, despite a quarter century of study, we have not answered some basic questions about the treatment of myeloproliferative thrombocytosis:

1. What are the risk factors for thrombotic complications and, quantitatively, what are their predictive values?

2. What are the risk factors for leukemic conversion, and is one of them treatment-related?

Experience from the last 25 years or so of investigation has shown that more uncontrolled treatment registries, no matter how large, are unlikely to answer these questions. The time has come for a systematic approach to these problems using currently accepted methods of clinical research based on blinded, controlled clinical trials with long-term observation and clearly defined end points as well as the inception cohort/validation cohort methodology for risk-factor determination. Although this will not be easily accomplished, experience with anagrelide[1] shows that when enough resources are brought to bear, the required patient volume can be achieved, and the end points are detectable. All that is needed is a demand by practicing physicians for accurate information to use in clinical decision-making.

**References:**


