

Essential Thrombocytosis: Diagnostic and Treatment Dilemmas

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Essential thrombocytosis is one of the chronic myeloproliferative disorders that includes polycythemia vera, chronic myelogenous leukemia, and agnogenic myeloid metaplasia. Despite established diagnostic criteria and greater than a quarter century of study, there are still several diagnostic and management dilemmas that plague researchers and clinicians alike. We present a case of essential thrombocytosis in a patient with multiple sequelae.

A 57-year-old black man presented with a 3-day history of painful right thigh swelling. The swelling and pain became progressively more intense. On the second day, he noticed purple skin-color changes in the areas of swelling. The patient denied any history of trauma to his right lower extremity.

The patient's medical history was significant for a stroke in 1999 with some residual right-sided weakness that resulted in the use of a cane for ambulation. The patient had a history of significant alcohol intake history and an 80-pack-year tobacco history, but denied any HIV risk-factors. Pertinent physical exam findings included extensive right anterior thigh ecchymoses superimposed on a 4x10 cm area of induration. No hepatosplenomegaly or

lymphadenopathy was detected. The patient's platelet counts the previous year ranged from 918-1870 x 10³/μL (normal 130-400 x 10³/μL). One month prior to admission, normal iron studies, a negative Coombs test, a normal hemoglobin electrophoresis, and a reticulocyte count of 1.9% with an absolute flow reticulocyte count of 71 x 10³/μL (normal 50-165 x 10³/μL) were demonstrated. On admission, the patient's hematocrit was 24.8% (normal 40% to 51%); platelet count was 1874 x 10³/uL; and WBC was 28 x 10³/uL (normal 4.5–11.0 x 10³/μL) with a 20% bands.

A gadolinium-enhanced MRI of the affected thigh suggested a hematoma between the fascial planes with surrounding edema. Additionally, bone marrow replacement in both femurs and the coccyx was noted. A bone marrow

CME INFORMATION

TARGET AUDIENCE

The November/December Clinical Case of the Month is intended for family physicians, general internists, medicine subspecialists, general practitioners, emergency medicine physicians, and pathologists.

EDUCATIONAL OBJECTIVES

The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University in New Orleans. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be able to 1) understand possible mechanisms underlying essential thrombocytosis, 2) recognize diagnostic dilemmas of thrombocytosis, 3) understand therapeutic options for patients with essential thrombocytosis.

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

DISCLOSURE

Dr. Dugan has nothing to disclose.
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biopsy revealed an increased number of megakaryocytes with clustering. Erythroid and myeloid cells were normal in number and morphology. Iron stores were normal. Cytogenetic studies including fluorescence *in situ* hybridization (FISH) revealed a normal male karyotype with no Philadelphia chromosome or BCR-ABL rearrangement. A ristocetin cofactor, von Willebrand factor antigen level, and factor VIII activity level were within normal limits.

The patient's hospital course was complicated by expansion of the hematoma, with a fall in hematocrit requiring a total of 6 units of packed red blood cells and the concurrent discovery of superficial venous thrombosis, prompting the placement of an inferior vena caval filter. The patient was, therefore, experiencing simultaneous thrombotic and hemorrhagic complications. Because of the patient's bleeding diathesis due to his dysfunctional platelets, plateletpheresis was performed with lowering of the platelet count to $426 \times 10^3/\mu\text{L}$. The patient's thigh swelling reduced dramatically, and he was discharged on aspirin and hydroxyurea.

DISCUSSION

Essential thrombocytosis (ET) is one of the chronic myeloproliferative disorders (MPD) that also includes polycythemia vera, chronic myelogenous leukemia, and myeloid metaplasia with or without myelofibrosis. ET is characterized by peripheral thrombocytosis (sustained platelet counts greater than $600 \times 10^3/\mu\text{L}$) and megakaryocytic hyperplasia. Epidemiologic studies demonstrate an incidence of 2.5-cases/100,000 population per year.¹ The average age at presentation is 50 to 60 years with a nearly equal sex distribution. In women, however, there is an additional peak in incidence that occurs around age 30 and may account for a slight female preponderance of cases. ET has the potential to evolve into myelofibrosis, and rarely into acute leukemia.²

ETIOLOGY AND PATHOGENESIS

Clonality

No single specific molecular aberration or cellular regulatory dysfunction has yet been implicated in the pathogenesis of ET. Rather several points along the evolution of the platelet have been implicated. Although ET is primarily characterized by sustained peripheral thrombocytosis and megakaryocytic hyperplasia, glucose-6-phosphate dehydrogenase enzyme-based clonal assays have demonstrated that the disease is most likely a clonal disorder, originating at the level of the pluripotent hematopoietic stem cell.³ Trilineage clonal myeloproliferation has been demonstrated in the majority of patients with ET by X chromosome-linked DNA or gene-product analysis.⁴ The particular clonal assay involved is based on the alteration of the X chromosome inactivation pattern (XCIP). Such assays, however, have revealed polyclonal hematopoiesis in

a substantial minority of patients with ET and also in some patients with polycythemia vera. The interpretation of these observations is further confounded by the frequent occurrence of "monoclonal" XCIP in normal elderly controls.⁵ The clonal proliferation in some patients with ET may encompass lymphocytes or be restricted to megakaryocytes. Taken together, the aforementioned studies suggest clonal heterogeneity in ET. This heterogeneity is clinically relevant in that there may be a lower incidence of thrombotic complications in patients with "polyclonal" ET compared to those with "monoclonal" ET.⁴

Abnormal Megakaryocytopoiesis

The concept of "polyclonal" ET may reflect an abnormality in megakaryocyte production. As one of the chronic myeloproliferative disorders, ET may originate from a defect in a pluripotent hematopoietic stem cell or clone, as discussed above. Some of the specific MPD tends to be phenotypically expressed as preferential proliferation of only a single cell lineage: the megakaryocyte line being the one expressed in ET. Thrombopoietin (TPO) is the cytokine that acts on the megakaryocyte growth factor receptor, *c-mpl*, and is thus the major humoral regulator of megakaryocytopoiesis and platelet production.

Normally, TPO levels are inversely correlated with circulating platelet and marrow megakaryocyte mass. TPO levels are regulated by the expression of *c-mpl* on platelet surfaces. This receptor binds free TPO and removes it from circulation. There is also an added feedback regulation of TPO occurring at the level of TPO gene expression in bone marrow stromal cells. These modulatory mechanisms are designed to restore steady-state platelet production in quantitative platelet disorders. In other MPD like polycythemia vera or CML, proliferation of a specific hematopoietic cell line leads to a physiologic feedback suppression of the specific growth factors that control their proliferation and differentiation. In ET, however, this reciprocal relationship between platelet count and TPO does not occur. Serum TPO levels are usually elevated or 'inappropriately' normal, despite thrombocytosis and increased megakaryocyte mass.² This dysregulation of TPO has been considered to be due to reduced or abnormal *c-mpl* expression on the surfaces of clonally-defective platelets and megakaryocytes, resulting in impaired binding and impaired clearance of free TPO from the circulation.²

It is unlikely that decreased surface expression of *c-mpl* is the sole reason for high or normal circulating levels of TPO in ET. It has been suggested that platelet progenitors in ET are also hypersensitive to existing levels of TPO. Axelrad et al and Kawasaki et al each found that circulating progenitors from patients with ET, grown in strictly serum-free culture conditions, were markedly hypersensitive to a form of modified TPO as well as to human recombinant TPO.⁶ The proliferation of this cell line, as measured in colony forming units of megakaryocytes (CFU-MK), demonstrated an increase in sensitivity to TPO that was 50-80 fold greater in ET patients than the prolifera-

tion of CFU-MK seen in a normal population. Demonstration of spontaneous CFU-MK observed in serum-deprived cultures of non-adherent mononuclear cells that disappeared in cultures of CD34+ cells was also noted. Kawasaki et al suggest that spontaneous megakaryocyte formation may be due to a very low concentration of TPO released from residual accessory cells or contained in the culture system, despite attempts to provide a strict serum-free culture.⁶

DIAGNOSIS

Currently no test is diagnostic of ET, and the disease remains largely one of exclusion. Reactive thrombocytosis may be responsible for more than 85% of cases of thrombocytosis seen in routine clinical practice. Since the distinction of ET from reactive thrombocytosis has critical therapeutic implications, the major causes of secondary thrombocytosis must first be excluded. Common causes of secondary thrombocytosis include iron deficiency anemia, hyposplenism, malignancy, infection, inflammatory bowel disease, collagen vascular disease, hemolysis, hemorrhage, polycythemia vera, and chronic myeloid leukemia, among others. An exhaustive differential should be explored before the diagnosis of ET is made.⁴

The Polycythemia Vera Study Group (PVSG) initially developed diagnostic criteria for ET in 1986. To diagnose ET, one must demonstrate all of the primary criteria and three or more of the secondary criteria. Primary diagnostic criteria include a platelet count in excess of $600 \times 10^3/L$ on two occasions separated by 1 month; erythrocyte mass of less than 125% of the predicted normal for the individual; minimal bone marrow fibrosis; and absence of the Philadelphia chromosome, the fusion BCR-ABL gene, and clonal cytogenetic abnormalities associated with myelodysplastic disorders. Secondary diagnostic criteria include splenomegaly; a bone marrow profile consisting of hypercellularity with megakaryocyte hyperplasia and clusters of multi-

lobulated large megakaryocytes (Figures 1 and 2); absence of iron deficiency as demonstrated by stainable marrow iron and/or normal serum ferritin; presence of abnormal hematopoietic progenitor cells that form erythroid or megakaryocytic colonies in vitro in the absence of cytokines; normal plasma levels of C-reactive protein and interleukin-6; and the presence of clonal hematopoiesis by means of genetic analysis of the X chromosome in female patients only. Despite this established form, there still remains a number of diagnostic dilemmas.³

Differentiation from chronic myelogenous leukemia is particularly important for prognosis and specific therapy. Some patients whose clinical diagnosis is most consistent with ET may actually have a variant form of CML with Philadelphia chromosome or BCR-ABL positivity. There are several largely contradicting studies detailing the varying degree and significance of BCR-ABL transcript positivity among patients with ET. One study found 63% BCR-ABL positivity while another found less than 1% positivity among their 112 patients diagnosed with ET. The discrepancies between these reports may be attributable to the different patient populations studied, different effects of treatment, or possible acquisition of the Philadelphia chromosome or BCR-ABL rearrangement as a result of the natural history of the disorder in some ET patients. Larger groups of patients with ET will have to be studied by sequential marrow samples in order to resolve this uncertainty.⁷

Examination of a patient's previous laboratory records is essential during the initial evaluation of thrombocytosis and may help distinguish ET from reactive thrombocytosis. In general, however, the degree of thrombocytosis, platelet morphology, size distribution, and platelet function tests are of limited value because of overlap between ET and reactive thrombocytosis. The clinician must be sure to exclude iron-deficiency anemia. Even this holds its own diagnostic dilemma in that the bone marrow aspirate of patients with ET, or related disorders, may lack stainable

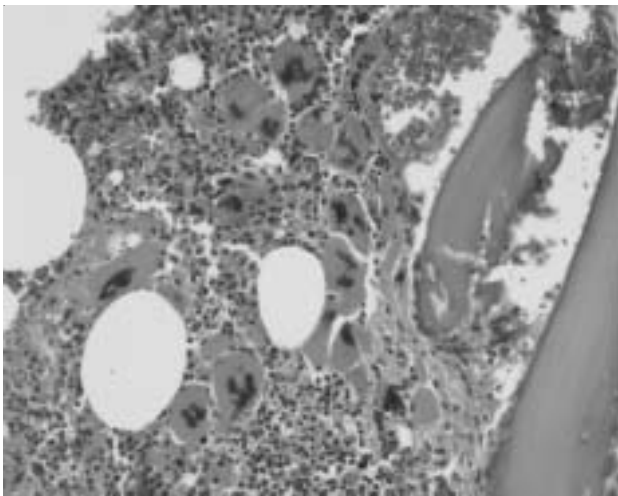


Figure 1. Bone marrow biopsy with megakaryocytic hyperplasia and clustering of megakaryocytes.

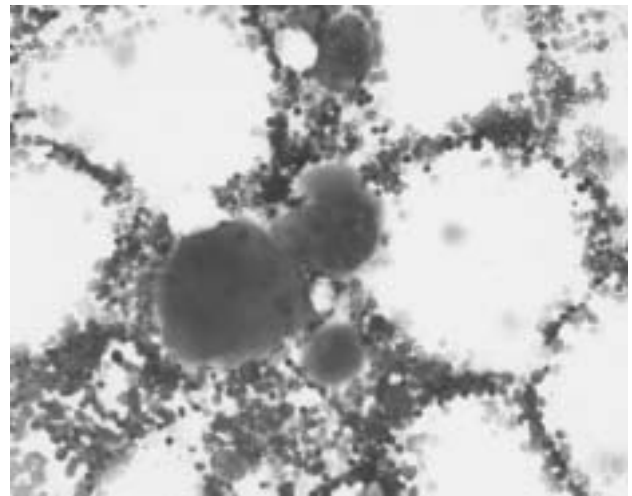


Figure 2. Bone marrow aspirate smear showing clustering of megakaryocytes.

iron stores in the absence of true iron deficiency. The patient's history helps to rule out several other causes of reactive thrombocytosis, and the additional absence of Howell-Jolly bodies may help to rule out functional hyposplenism. A normal C-reactive protein may help rule out an occult inflammatory or malignant process.

Unfortunately, there is currently no positive test for ET that is reliable. Mesa et al demonstrated that histologic stratifying criteria incorporating increased bone marrow angiogenesis, decreased megakaryocyte *c-mpl* expression, and marked megakaryocyte proliferation in the bone marrow was highly sensitive (97%) and specific (95%) for distinguishing ET from reactive thrombocytosis. However, because of the short duration of follow-up available on the patients in that study, none of the histologic features evaluated have yet demonstrated prognostic value for subsequent clinical course.⁸ Teofili et al, in a study of 88 patients with ET, showed that a heterogeneous-weak staining pattern of *c-mpl* expression was associated with a 6-fold increased risk of thrombosis compared with that of patients with a uniform staining pattern in bone marrow megakaryocytes. They concluded that by using immunohistochemistry, a bone marrow biopsy specimen could be a useful tool for identifying patients with ET who may have a higher risk of thrombosis.⁹ However, both *c-mpl* immunohistochemistry and in vitro myeloid/megakaryocyte colony assays are available only in research laboratories and may not be suitable for widespread use.

CLINICAL MANIFESTATIONS

Essential thrombocytosis is largely a disorder of individuals 60 years of age or older. The risk of complications is both age-related and influenced by the length of a patient's survival. Most patients with ET either are asymptomatic or suffer from inconsequential vasomotor disturbances that are effectively treated with low-dose aspirin. Those who are symptomatic carry the principle risks from ET, including thrombosis, major hemorrhage requiring hospitalization or transfusion, conversion to leukemia, or conversion to myelofibrosis. In one small retrospective study, the most common cause of death in ET patients was sudden cardiac death or myocardial infarction, followed by acute leukemia. Other causes of death were bowel infarction caused by mesenteric thrombosis, pulmonary embolism, renal insufficiency, and stroke. The sequelae of ET can be classified into three categories: primary sequelae, such as thrombosis and hemorrhage; secondary sequelae determined by the natural progression of the disorder; and finally, secondary sequelae that are treatment-related.

Primary Sequelae

The most common primary sequelae are a spectrum of vasomotor disturbances such as headache, light-headedness, atypical chest pain, acral dysesthesia, and erythromelalgia. Erythromelalgia and these other vasomotor symptoms of microvasculature occlusion can be trou-

bling, but do not carry an added risk of thrombosis. Erythromelalgia is described as an intense burning or throbbing pain in a patchy distribution in the extremities, most prominently involving the plantar surfaces of the feet and sometimes one or more toes or fingers.¹⁰ Untreated, it can progress to frank gangrene and necrosis of the digits, particularly the toes, although these signs of digital microvascular ischemia may develop in ET independently of erythromelalgia.¹¹

Other common vasomotor symptoms experienced in these patients are a varying range of cerebrovascular ischemia. More common neurologic complications may bear striking similarities to migraine headaches. Patients can present with brief episodes of acute cerebral or visual dysfunction, which may be localized or diffuse and quite non-specific. A dull throbbing headache frequently accompanies the neurologic symptoms. These symptoms are usually transient and rarely result in ischemic strokes, although the risk for progression to strokes in higher risk patients is present.¹¹ These microvasculature ischemic manifestations of ET are usually quite responsive to low-dose aspirin and/or cytoreductive therapy, as will be discussed further in this article.

The most concerning complications of this disease are thrombohemorrhagic. The overall incidence of thrombosis (superficial or deep) is 20% to 40% at diagnosis or during follow-up. Arterial thrombotic complications occur more frequently than venous thromboses in ET, although about 10% to 25% of all thrombotic events are deep vein thrombosis of the lower extremities. Arterial thromboses may occur in larger arteries such as the femoral, coronary or renal arteries, or may occur in the microvasculature as described above.⁴ Hepatic vein (Budd-Chiari syndrome) and portal vein thrombosis are more commonly associated with polycythemia vera than with ET, but these myeloproliferative disorders, in general, represent the most common identifiable underlying etiologies in patients who present with these thrombotic problems.¹¹

Hemorrhagic events are less common than thrombotic, occurring in <10% of patients at or after diagnosis.⁴ These events are generally associated with platelet counts in excess of $1,000 \times 10^3/\mu\text{L}$. Major bleeding has been defined as a drop of hemoglobin concentration or bleeding occurring in a critical organ. When bleeding manifestations occur, they are similar in nature to those encountered in platelet and vascular disorders, such as von Willebrand disease. They tend to involve superficial locations, most commonly at nasopharyngeal, oral, genitourinary tract, and cutaneous sites. Gastrointestinal sites are common, especially the upper intestine, where duodenal arcade thrombosis can result in mucosal sloughing that simulates a bleeding duodenal ulcer. Postoperative bleeding is also common.¹²

In a retrospective study, Cortelazzo et al determined the factors associated with increased risk of thrombotic complications in a group of 100 consecutive and unselected patients with ET who had been treated with busulfan for platelet counts of $1,000 \times 10^3/\mu\text{L}$ and/or a major throm-

botic or hemorrhagic event. The frequency of events was compared with 200 historical age/sex-matched patients without evidence of a myeloproliferative disorder.¹³ The authors were able to show that the incidence of events increased with age with 15.1% events-per-patient year in patients older than 40 years of age contrasted with 1.7% events-per-patient year in those patients less than 40 years of age. This study also showed that among patients with previous thrombosis, the incidence rate for recurrent events was 31.4% per patient year contrasted with an incidence rate of 3.4% among patients without a prior history of thrombus. This, therefore, established age and prior thrombotic experience as the primary risk factors for thrombosis in ET.¹⁴

There are also multiple risk factors for thromboembolic events that are not specific to ET but which may increase the thrombotic risk in patients with this disorder. These include peripheral vascular disease, hypertension, diabetes mellitus, obesity, smoking and hypercholesterolemia. It is important to investigate thoroughly all patients who present with thrombosis. This may include search for congenital or acquired prothrombotic states if a high clinical suspicion exists.¹⁴

Retrospective studies generally have been unable to establish a clear and consistent correlation between the platelet count and hemostatic complications in any of the myeloproliferative disorders. Studies in the past have attempted to make theories based on qualitative platelet abnormalities, but none have been definitive. One study, based on 65 patients, suggests that subnormal plasma erythropoietin levels in newly diagnosed ET patients may be a risk factor for vascular complications.¹⁵ While qualitative platelet abnormalities are likely to contribute to the pathogenesis of hemostatic complications in ET, the disappointing lack of clinical correlations raises the possibility that other, unknown, hemostatic defects play a role that is not yet recognized.¹¹

Secondary Sequelae (Progression-Related)

Many people have a chronic indolent form of the disorder that goes on for many years with minimal complications. Untreated patients face the risk of secondary sequelae that occur with the natural progression of ET over time.¹⁵ These sequelae can include progression into myeloid metaplasia, myelofibrosis, acute myelogenous leukemia and myelodysplastic syndrome. In any of these disease states, splenomegaly can be the presenting symptom or cause of extensive morbidity. The incidence of spontaneous transformation of ET into acute leukemia is very low: <5% in one series and a range of 1% to 20% described in others.^{4,11}

A notable sequela related to the progression of ET is an acquired von Willebrand disease. In this acquired form, there is selective reduction of the large multimers of von Willebrand factor (vWF) in plasma (similar to that found in inherited type II von Willebrand disease), presumably caused by adsorption of these plasma multimers by the abnormal thrombocytic platelets.¹¹ This defect can pre-

dispose to a significant hemorrhagic tendency in patients with platelet counts in excess of $1,500 \times 10^3/\mu\text{L}$ who have low Factor VIII activity and abnormal vWF ristocetin cofactor activity.¹² An historically noted association of extreme thrombocytosis and increased gastrointestinal bleeding may be attributable to occult acquired von Willebrand disease.⁴

TREATMENT

The therapeutic approach to patients with ET has been tempered by the recognition that their life expectancy is comparable to that of age-matched cohorts. Nevertheless, there is substantial impact from thrombohemorrhagic complications, and thrombosis-free survival may be increased in some patients if treatment is given. Since potentially serious adverse effects accompany most therapeutic interventions offered for ET, attempts are made to risk stratify patients by indications for treatment and types of treatment.¹¹ A caveat to this, and any decision to treat, is that specific therapy in ET has never been shown to influence either overall survival or the risk of leukemic transformation.⁴ Also, lab findings, like bleeding time and platelet aggregation are generally not predictive of complications. Therefore, the decision to initiate treatment in ET should be based on clinical parameters. The two main treatment objectives are to prevent thrombohemorrhagic events and to prevent progression of the disease or progression-related sequelae.

Preventing Thrombohemorrhagic Events

In ET, the traditional primary treatment objective has been to maintain a platelet count of $<600 \times 10^3/\mu\text{L}$. While the degree of platelet elevation is not consistently correlated with thrombotic incidence, there is substantial evidence that controlling the platelet count reduces the occurrence of thrombosis.¹⁴ This number of $<600 \times 10^3/\mu\text{L}$ was dictated in part by the historical capabilities of the treatment options once available. In general, hydroxyurea would have more intolerable side effects at doses that would maintain a lower platelet count. As new agents offer the prospect of lower platelet counts without significant increases in toxicity, clinicians are looking more toward maintenance levels of $400 \times 10^3/\mu\text{L}$ or even the upper limits of normal platelet counts.¹⁶ A recent study showed that thrombotic complications occurred most often among young ET patients on cytoreductive therapy when their platelet counts exceeded $400 \times 10^3/\mu\text{L}$. This and other studies suggest that the traditional point of cytoreductive intervention may be dangerously high and that the treatment goal should be at the high end of the normal range.¹⁵ A less aggressive control of platelets with a cytoreductive drug may be indicated in patients who have either aspirin-resistant vasomotor symptoms or symptomatic acquired von Willebrand disease.⁴

Patients of any age whose platelet counts are greater than $1,500 \times 10^3/\mu\text{L}$ are at increased risk for major bleeding. Aspirin aggravates this risk, particularly if patients

have acquired von Willebrand disease. Therefore, aspirin and NSAIDs should be avoided in these patients so that treatment to reduce platelet counts can be started.¹⁰ Patients should also be advised to improve cardiovascular risk factors and to treat any potential areas at risk for GI bleeding, such as peptic ulcer disease.

Preventing Progression-Related Sequelae

Secondary treatment goals deal mainly with preventing splenomegaly or reducing splenic mass. Other goals include eliminating monoclonal stem cells, promoting polyclonal hematopoiesis and preventing both myelofibrosis and leukemic conversion. Obviously, these are optimal goals still being targeted with research into new medications or hematopoietic stem cell transplantation.

Treatment by Risk Stratification

Treatment strategies remain empirical. The most reasonable approach is risk-based therapy, which individualizes treatment. Low risk ET patients are less than 60 years old, have not had thromboses, and have platelet counts $< 1,500 \times 10^3/\mu\text{L}$. These patients may be observed or placed on low-dose aspirin. Intermediate risk ET patients include those less than 60-years-old who have not had thromboses, but whose platelet counts are $\geq 1,500 \times 10^3/\mu\text{L}$ and those who have significant cardiovascular risk factors, regardless of platelet count. This group of patients should be given low-dose aspirin and should also have their cardiovascular risk factors treated. Some of these patients may ultimately require hydroxyurea, anagrelide, or Interferon-alpha. High-risk patients with ET, defined as those 60-years-old or older or those of any age who have had a thrombosis, should be treated with hydroxyurea. If hydroxyurea cannot be tolerated, anagrelide and interferon-alpha are alternatives. All risk groups are recommended to reduce cardiovascular risk factors, and all groups can use low-dose aspirin to reduce vasomotor symptoms, unless they are actively bleeding or have a known contraindication.¹⁰

Pearson performed a review of the literature and suggested that patients under 40-years-old without thrombotic complications can be observed and cytoreductive therapy avoided. An intermediate group, defined as those 40-60 years old without prior sequelae may be at an increased risk for complications. The Medical Research Council Polycythemia Vera Trial No. 1, in which these intermediate risk patients were randomized to cytoreductive therapy or no treatment, is currently ongoing, and its results will answer some of these questions directly.¹⁴

SPECIFIC TREATMENT OPTIONS

Aspirin

Although aspirin is known to reduce platelet aggregation, its specific role in ET is uncertain. Aspirin is particularly efficacious for vasomotor symptoms including eryth-

romelalgia for both neurologic and visual manifestations of ET and for microvascular occlusions. Specifically, increased platelet turnover and consumption in erythromelalgia has been reported to be corrected by aspirin, but not by warfarin.¹¹ One retrospective study using low-dose (100 mg/day) aspirin, alone or in combination, showed a reduced incidence of thrombosis. Low dose aspirin may not increase the bleeding diathesis of some patients with ET and is recommended as a supplement to cytoreductive therapy in high-risk, and as an optional consideration in most patients.¹⁷ Pilot studies of low-dose aspirin, 40-100 mg/day doses, have not shown an increase in severe hemorrhage and have pointed toward a reduction in thrombosis risk. Platelet cyclooxygenase levels are inhibited at the 40-mg/d dose. A prospective randomized controlled trial comparing low-dose aspirin to placebo in asymptomatic patients is currently underway.¹⁵

The benefit of aspirin's antithrombotic properties must be balanced against the risk of hemorrhage. The main contraindications to aspirin are patients with acquired von Willebrand disease and platelet counts exceeding $1,500 \times 10^3/\mu\text{L}$ or a history of significant bleeding.¹⁵

Hydroxyurea

Hydroxyurea, a nonalkylating antimetabolite, inhibits ribonucleotide diphosphate reductase. Hydroxyurea's effects are dose-dependent and have been shown to reduce hematopoietic progenitor growth and CD34+ cells in patients with ET. Historically, hydroxyurea has been the treatment of choice for ET following publication of evidence that alkylating chemotherapeutic agents, such as chlorambucil and busulphan, were leukemogenic.¹⁵

In a prospective study by Cortelazzo et al, 114 patients with ET at high risk of thrombosis were randomized to hydroxyurea or no myelosuppressive therapy. The two groups were matched for age, sex, and platelet count at the time of randomization. During the 27-month follow-up period, two patients (3.6%) treated with hydroxyurea had thrombotic episodes. In contrast, 14 patients (24%), among the untreated controls, experienced thrombotic events that included one stroke, five transient ischemic attacks, five peripheral arterial occlusions, one deep venous thrombosis, and two cases of superficial thrombophlebitis. These data were interpreted as incidence rates of 8% per patient-years in the untreated group and 1.5% in the hydroxyurea treated group. This 1.5% rate is statistically equivalent to a control group of patients in the general population without evidence of a myeloproliferative disorder.¹⁸ Only hydroxyurea has been proven in a randomized controlled trial to reduce the risk of thrombosis in high-risk patients. In terms of targeting progression-related sequelae, hydroxyurea has not proven effective. It may shrink the spleen on a short-term basis, but subsequent growth renewal is the norm during chronic therapy.¹⁵ Patients treated for long periods with hydroxyurea may evolve to a spent phase characterized in part by myeloid metaplasia.

Anagrelide

Anagrelide, an orally administered quinazolone derivative that inhibits prostaglandin synthetase, is platelet-specific and appears to affect platelet proliferation in post-mitotic megakaryocytes by interfering with megakaryocytic maturation.¹⁵ It produces a dose-dependent response usually capable of reducing thrombocytosis in >80% of patients to a maintenance count of $400 \times 10^3/\mu\text{L}$ or less. The usual time to achieve 50% platelet reduction is 11 days. Anagrelide is not leukemogenic and is a reasonable alternative to hydroxyurea as first line therapy in young patients with ET who require long-term platelet cytoreduction.¹¹ It can be used both in the patients less than 60 years old and in those older than 60 who are free of symptomatic cardiovascular disease.¹⁰

About 15% of patients are not able to tolerate anagrelide. Because it is a prostaglandin inhibitor and vasodilator, anagrelide causes headaches and dizziness and can change renal blood flow and induce fluid retention.¹⁰ The vehicle of the drug is lactose, so bloating, nausea, diarrhea and vomiting, some of which is caused by lactose sensitivity, may be experienced. Anagrelide is also an inotrope and can induce palpitations or cardiac arrhythmias. Patients who have borderline or poor cardiac function may experience congestive heart failure, including pulmonary edema after ingesting anagrelide.¹⁵

Interferon-alpha

Interferon-alpha, a biologic-response-modifying cytokine, is both myelosuppressive and immunomodulatory. Interferon alpha can take 3 months to produce its maximum response. Treatment can be suspended following titration and attainment of the platelet count goal. Many patients achieve stable remission for a few months up to 2 years or more before requiring the resumption of interferon-alpha therapy. It is indicated in patients who cannot tolerate hydroxyurea or anagrelide. It is the preferred treatment during pregnancy.¹⁵

Of these three medications only interferon-alpha effectively reduces splenomegaly. After 2 months of treatment, the spleen begins to shrink, and the decrease in size continues for a period of 6 to 12 months. The reduction often persists after withdrawal of the agent and patients respond quickly to subsequent treatment courses following detection of renewed growth. It has been studied more extensively in splenomegaly associated with polycythemia vera.¹⁵

About 20% to 30% of patients will not be able to tolerate the side effects of interferon-alpha. The most common side effects are flu-like symptoms including chills and fever, mild alopecia and diarrhea. Patients complain of myalgias, fatigue, anorexia, headache, depression, and neuropathy. Common hematologic side effects are neutropenia and anemia. As an immunomodulatory agent, interferon may cause symptomatic episodes of autoimmune disease including hypothyroidism.¹⁵

Other Options

Alkylating agents of the past such as melphelan and chlorambucil have been abandoned secondary to leukemogenic side effects. Radioactive phosphorus has been used in the past and may rarely play a role in the treatment of an older patient who cannot tolerate oral medications. Hemopoietic stem cell transplantation may provide curative therapy for patients with ET, as well as the other myeloproliferative disorders, but it is reserved for highly selected, young patients with advanced disease complicated by myelofibrosis with cytopenias or transformation into acute leukemia or myelodysplasia.¹¹ Stem cell transplantation is still considered experimental and is undergoing current research.

CONCLUSION

Despite a quarter century of study, we are still attempting to answer some basic questions about the treatment of myeloproliferative thrombocytosis. What are the risk factors for thrombotic complications and, quantitatively, what are their predictive values? What are the risk factors for leukemic conversion, and is one of them treatment-related? As these questions are still being studied, focus has appropriately been directed toward optimizing the patient's quality of life with the therapeutic options that are available.

REFERENCES

1. Mesa, RA, Silverstein MN, Jacobson SJ et al. Population-based incidence and survival figures in essential thrombocythemia and agnogenic myeloid metaplasia: an Olmsted County Study, 1976-1995. *Am J Hematol* 1999; 61:10-12.
2. Wright CA, Tefferi A. A single institutional experience with 43 pregnancies in essential thrombocythemia. *Eur J Haematol* 2001; 66:152-159.
3. Fialkow PJ, Fajuet GB, Jacobson RJ et al. Evidence that essential thrombocythemia is a clonal disorder with origin in a multipotent stem cell. *Blood* 1981; 58:916-919.
4. Tefferi A, Murphy S. Current opinion in essential thrombocythemia: pathogenesis, diagnosis, and management. *Blood Rev.* 2001; 15:121-131.
5. Champion, KM, Gilbert JG, Asimakopoulos FA et al. Clonal haemopoiesis in normal elderly women: Implications for the myeloproliferative disorders and myelodysplastic syndromes. *Br J Haematol* 1997; 97:920-923.
6. Kawasaki H, Nakano T, Kohdera U et al. Hypersensitivity of megakaryocyte progenitors to thrombopoietin in essential thrombocythemia. *Am J Hematol* 2001; 68:194-197.
7. Emilia G, Marasca R, Zucchini P et al. BCR-ABL rearrangement is not detectable in essential thrombocythemia. *Blood* 2001; 97:2187-2189.
8. Mesa RA, Hanson CA, Li CY et al. Diagnostic and prognostic value of bone marrow angiogenesis and megakaryocyte c-Mpl expression in essential thrombocythemia. *Blood* 2002; 99:4131-4137.

9. Teofili L, Pierconti F, Di Febo A et al. The expression pattern of c-mpl in megakaryocytes correlates with thrombotic risk in essential thrombocythemia. *Blood* 2002; 100:714-717.
10. Solberg LA Jr. Therapeutic options for essential thrombocythemia and polycythemia vera. *Semin Oncol* 2002; 29:10-15.
11. Schafer AI. Thrombocytosis and thrombocythemia. *Blood Rev* 2001; 15:159-166.
12. Hoffman R. Quality of life issues in patients with essential thrombocythemia and polycythemia vera. *Semin Oncol* 2002; 29:2-9.
13. Cortelazzo S, Viero P, Finazzi G et al. Incidence and risk factors for thrombotic complications in a historical cohort of 100 patients with essential thrombocythemia. *J Clin Oncol* 1990; 8:886-862.
14. Pearson TC. The risk of thrombosis in essential thrombocythemia and polycythemia vera. *Semin Oncol* 2002; 29:16-21.
15. Gilbert HS. Other secondary sequelae of treatments for myeloproliferative disorders. *Semin Oncol* 2002; 29:10-15.
16. Storen ED, Tefferi A. Long-term use of anagrelide in young patients with essential thrombocythemia. *Blood* 2001; 97:863-866.
17. Van Genderen PJ, Mulder PG, Waleboer M et al. Prevention and treatment of thrombotic complications in essential thrombocythaemia: efficacy and safety of aspirin. *Br J Haematol* 1997; 97:179-184.
18. Cortelazzo S, Finazzi G, Ruggeri M et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. *N Engl J Med* 1995; 332:1132-1136.

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CME QUESTIONS

To earn CME credit, read the preceding CME article and complete the registration, evaluation, and answer form on page 351. Mail or fax the registration, evaluation, and answer form to the Educational and Research Foundation. Answers must be postmarked or faxed prior to December 31, 2004. Participants must attain a minimum score of 75% to receive credit.

For each question, choose the one answer that is most correct.

1. The modulation of thrombopoietin by the megakaryocyte growth factor receptor, *c-mpl*, is normal in all of the following diseases except
 - a) essential thrombocytosis
 - b) chronic myelogenous leukemia
 - c) iron deficiency anemia
 - d) hemolysis
2. A 33-year-old woman presents with an intense throbbing pain in a patchy distribution in the extremities involving the plantar surfaces of the feet usually accompanied by a headache. Labs showed a platelet count of $626 \times 10^3/\mu\text{L}$ and an otherwise normal blood count. What is the best treatment option?
 - a) Melphelan
 - b) Prednisone
 - c) aspirin
 - d) Sumatriptan
3. The most common cause of death in a 64-year-old man with a diagnosis of ET is
 - a) acute leukemia
 - b) renal insufficiency
 - c) myocardial infarction
 - d) major postoperative bleeding
4. A 65-year-old man with a prior history of coronary artery disease was recently diagnosed with ET after presenting with a femoral vein thrombosis. The best option for treatment is
 - a) aspirin alone
 - b) hydroxyurea
 - c) anagrelide
 - d) interferon-alpha
5. Which is the best treatment option for a pregnant woman with essential thrombocytosis and recurring thrombotic events?
 - a) Anagrelide
 - b) Hydroxyurea
 - c) Interferon-alpha
 - d) Stem cell transplantation