

Essential Thrombocytosis

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Updates: Proposed WHO new criteria for essential thrombocytosis (ET)

Introduction

Essential thrombocytosis (ET) is a rare myeloproliferative disorder with a predisposition to development of thrombosis, bleeding, polycythemia vera, primary myelofibrosis and myelodysplasia/acute leukemia [1]. Approximately half of all patients with ET have a clonal stem cell defect, and these patients are at higher risk of thrombosis, when compared to those without clonal hematopoiesis [2]. A mutation of Janus Kinase 2 is present in over half of patients with ET [3].

The treatment of thrombocytosis has been summarized in a CCO evidence-based guideline written by Dr. John Matthews (www.cancercare.on.ca). Much of the data included here on thrombotic/bleeding risk comes from this excellent overview.

Diagnosis

The *proposed* WHO criteria for ET, requires all 4 of the following criteria [4]:

1. Sustained platelet count in excess of $450 \times 10^9/L$
2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes; no significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis. The histologic criteria described in the WHO classification for pre-fibrotic PMF may be difficult to apply reproducibly and some question the validity of distinguishing true ET from prefibrotic PMF [5].
3. Not meeting WHO criteria for PV, † PMF, ‡ CML, § MDS, ¶ or other myeloid neoplasm
4. Demonstration of JAK2 V617F or other clonal marker, or in the absence of a clonal marker, no evidence for reactive thrombocytosis (includes iron deficiency, splenectomy, surgery, infection, inflammation, connective tissue disease, metastatic cancer, and lymphoproliferative disorders)

† Requires the failure of iron replacement therapy to increase hemoglobin level to the PV range in the presence of decreased serum ferritin. Exclusion of PV is based on hemoglobin and hematocrit levels, and red cell mass measurement is not required.

‡ Requires the absence of relevant reticulin fibrosis, collagen fibrosis, peripheral blood leukoerythroblastosis, or markedly hypercellular marrow for age accompanied by megakaryocyte morphology that is typical for PMF, small to large with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous or irregularly folded nuclei and dense clustering.

§ Requires the absence of *BCR-ABL*.

¶ Requires absence of dyserythropoiesis and dysgranulopoiesis.

These criteria are expected to supersede the PV study group criteria listed below [6]:

Criteria A	Criteria B
<ol style="list-style-type: none">1. Raised RBC mass (male > 36 ml/kg; females > 32 ml/kg)2. Absence of any secondary cause of erythrocytosis3. Bone marrow biopsy – increased cellularity, enlarged megakaryocytes with hyperploid nuclei or clusters of megakaryocytes, increase reticulin (optional)	<ol style="list-style-type: none">1. Platelet count > 4002. Granulocytes > 103. Splenomegaly by palpation or ultrasound4. Spontaneous EEC in absence of EPO

A123 – early PV, A123 + any B – overt PV, A3 + B1 – Essential thrombocythemia



Baseline Investigations

- ❖ CBC, differential, blood film
- ❖ Serum ferritin
- ❖ Peripheral blood or bone marrow PCR for BCR/ABL and JAK2, and FISH for 5q minus
- ❖ Bone marrow aspirate and biopsy with cytogenetics
- ❖ Outside of a clinical trial, it is reasonable to omit the bone marrow examination for patients without anemia, abnormal findings in the peripheral blood other than thrombocytosis and large platelets, or other unusual clinical or laboratory findings
- ❖ Ultrasound for spleen size if physical exam deemed unreliable due to obesity

Staging & Prognosis

It is difficult to estimate the risk of bleeding or thrombosis from the published literature due to differing definitions and differing lengths of follow up in the various series. One estimate from a series of 100 consecutive patients followed for a median of 33 months reported a thrombosis rate of 6.6%/patient-year and a major bleeding rate of 0.33%/patient-year [7]. Most thrombotic events do not lead to long-term sequelae, as most episodes were transient and few patients experienced stroke, myocardial infarction or pulmonary embolism. One report of 322 patients with ET followed at the Mayo Clinic [8] (median age, 54 years; median follow-up, 13.6 years), the median survival time was 18.9 years. The survival in the first decade of disease was similar to that of the control population (risk ratio, 0.72; 95% confidence interval, 0.50-0.99), but became significantly worse thereafter (risk ratio, 2.21; 95% confidence interval, 1.74-2.76). Multivariable analysis identified age at diagnosis of 60 years or older, leukocytosis, tobacco use, and diabetes mellitus as independent predictors of poor survival. Age at diagnosis of 60 years or older, leukocytosis, and history of thrombosis were independent predictors of major thrombotic events. The risk of leukemic or any myeloid disease transformation was low in the first 10 years (1.4% and 9.1%, respectively) but increased substantially in the second (8.1% and 28.3%, respectively) and third (24.0% and 58.5%, respectively) decades of the disease.

The following factors have been reported to be predictive of higher rates of thrombosis or bleeding [6]:

- (a) **History of thrombosis or bleeding:** in most studies that considered the issue, the presence of thrombotic symptoms was predictive of higher rates of subsequent thrombosis. Only 1/3 of studies reported that bleeding symptoms at inception predicted for higher rates of hemorrhage.
- (b) **Platelet count:** The height of the platelet count did **not** predict thrombosis in 14/14 studies. In one report, patients who spent > 70% of the time with a platelet count < 600 x10⁹/L had fewer thromboses than those who did not. The *height of the platelet count was predictive of higher rates of hemorrhage* in 5/9 studies.
- (c) **Age:** Advancing age was predictive of thrombosis in 2/7 studies.
- (d) **Anemia:** A hemoglobin level less than the normal laboratory range at diagnosis predicts a higher rate of transformation to leukemia or PMF [9].
- (e) **Leukocytosis:** Leukocytosis in excess of 10 x 10⁹/L predicts a higher rate of thrombotic events [8].
- (f) **Other risks:** General vascular risk factors have not consistently been found to be predictive of thrombosis. Smoking was predictive in 2/5 studies and obesity in 1/5. Thrombosis may be more common in patients with the V617F mutation [10].



Treatment

The following options are available for patients with ET:

- (a) **Observation:** Complication rates without treatment are low, particularly for patients without risk factors. Most patients who are asymptomatic and do not have a history of thrombotic or bleeding symptoms can be observed without treatment regardless of the platelet count or age of the patient [11].
- (b) **Aspirin:** The benefit of ASA in ET remains unproven. Low-dose aspirin has been shown to safely reduce the incidence of thrombotic complications in patients with *polycythemia vera* by 50% in one large randomized control trial [12]. Patients with ET and a history of thromboembolic complications, one or more cardiovascular risk factors, and no contraindications to ASA are likely to benefit from low dose ASA (81 mg). The current role of ASA in ET patients lacking a history of thromboembolic complications or cardiovascular risk factors has not been evaluated, although it is a near universal practice and is recommended.
- (c) **Hydroxyurea (HU):** HU is the only agent that has been shown to reduce the rates of thrombosis in ET [13]. In a randomized trial comparing HU given to keep the platelet count $< 600 \times 10^9/L$ to no cytoreductive therapy, a lower rate of minor thrombosis was observed in the HU arm. There was no difference in major thrombosis (stroke, MI, DVT). Survival in both groups was identical. HU may be associated with an increased risk of developing MDS/acute leukemia [14, 15]. This risk appears greatest in patients who also receive other cytoreductive agents such as busulfan or p32. In one study, MDS/AML developed in 5/15 (33%) of patients who received HU and busulfan, 3/77 (3.9%) who received HU alone and 0/20 (0%) patients who were left untreated. Hydroxyurea is typically started at 500 mg - 1000 mg daily and is titrated to keep platelet count $< 600 \times 10^9/L$. Hydroxyurea is generally well tolerated. Major toxicities include myelosuppression, mucositis, and leg ulcers. JAK2 V617F mutated patients are more sensitive to hydroxyurea, requiring lower doses to control platelet counts than JAK2 V617F negative patients [16].
- (d) **Anagrelide:** Anagrelide is an antiplatelet agent, which lowers platelet counts in the majority of patients with myeloproliferative disorders [17]. Anagrelide does not appear to be leukemogenic. Anagrelide is started at a dose of 0.5 mg four times daily and increased to a maximum of 1 mg four times daily. A randomized trial in 809 patients with ET at high risk for vascular events compared low-dose aspirin plus either anagrelide or hydroxyurea. At a median follow-up of 39 months, patients in the anagrelide group were significantly more likely than those in the hydroxyurea group to have reached the primary endpoint of arterial thrombosis, venous thrombosis, serious hemorrhage, or death from thrombotic or hemorrhagic causes (OR, 1.57; $P=0.03$). As compared with hydroxyurea plus aspirin, anagrelide plus aspirin was associated with increased rates of arterial thrombosis ($P= 0.004$), serious hemorrhage ($P=0.008$), and transformation to myelofibrosis ($P=0.01$) but with a decreased rate of venous thromboembolism ($P=0.006$). Patients receiving anagrelide were more likely to withdraw from their assigned treatment ($P<0.001$). Equivalent long-term control of the platelet count was achieved in both groups. Thus, hydroxyurea is the preferred treatment for high risk patients with ET [18].
- (e) **Interferon:** Interferon is effective at controlling platelet counts in ET and improving disease-associated symptoms [19]. There is no randomized data evaluating its effect on thrombotic complications, however, one cohort study reported lower rates of thrombotic events after initiating interferon [20]. Interferon is a toxic agent. 17-20% of patients discontinue the agent due to toxicity. Common side effects include fatigue, nausea, anorexia, increased liver transaminases, and depression. Interferon is typically started at a dose of 1 million units three times weekly and increased to control platelet counts to $< 600 \times 10^9/L$. The average maintenance dose required is 3 million units three times weekly.



Odette Cancer Centre Policy

- ❖ Patients who are asymptomatic with no prior history of thrombosis or bleeding generally will not be given cytoreductive treatment regardless of age or platelet count.
- ❖ Patients with 1 or more cardiovascular risk factors (hypertension, smoking, diabetes, hypercholesterolemia, or family history), erythromelalgia, leukocytosis, and a prior history of thrombosis should be given ASA 81 mg daily. ASA may be reasonable treatment option for all patients with ET, given the low risk of adverse events.
- ❖ Patients with thrombotic symptoms or a history of thrombosis should receive cytoreductive treatment. The preferred agent is hydroxyurea, as it is the only agent shown to reduce thrombosis, but patients must be counseled about the possible increased risk of leukemia.
- ❖ Younger patients with a history of thrombosis who are felt to be at high-risk of MDS/AML due to an expected longer treatment period and those who refuse hydroxyurea should be treated with interferon.
- ❖ Anagrelide may be used for patients failing or intolerant to HU and interferon.

Monitoring

Patients who are stable off treatment should be assessed every 6 to 12 months. Patients on cytoreductive therapy should have a CBC performed q8 weeks and should be assessed clinically at least every 6-12 months. The target platelet count on cytoreductive therapy is $< 600 \times 10^9/L$. A reduction of platelet count to $< 400 \times 10^9/L$ can be considered if patients are tolerating treatment well or symptomatic disease with platelet count between 400 and $600 \times 10^9/L$.

Special Considerations

(a) Perioperative Management

Elective surgery: Patients should have good hematologic control (platelet count $< 600 \times 10^9/L$) for at least 6 weeks preoperatively if possible.

Urgent surgery: Patients should have platelet counts lowered to $< 600 \times 10^9/L$ using HU 500 mg - 3500 mg orally. Patients should receive appropriate thromboprophylaxis, should be monitored for DVT/PE, and surgeons should be informed of the increased risks of perioperative bleeding.

(b) Thrombocytosis in Pregnancy

Most young women with ET are at low risk of complications. For this reason, most do not require cytoreductive therapy [21]. If cytoreductive treatment is needed, interferon is the only agent, which has been used in pregnancy and is not felt to be teratogenic or to cross the placenta. Patients should be monitored in concert with a high-risk obstetrical unit. Pregnant patients with ET have a fetal loss rate 3.4-fold higher (95% confidence interval [CI]: 3-3.9; $P < .001$) than in the general population [22, 23].



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