

# Current Challenges in the Management of Essential Thrombocythemia

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**Abstract:** Essential thrombocythemia (ET), an uncommon blood cancer, is one of the classic myeloproliferative neoplasms, a category that also includes polycythemia vera and primary myelofibrosis. All 3 diseases are clonal hematopoietic stem cell disorders. Since 2005, when scientists discovered a molecular aberration driving clonal hematopoiesis in polycythemia vera, our understanding of the genomic underpinnings of these conditions has increased rapidly. Over the last decades, primary prevention of thrombotic and hemorrhagic complications has improved the lives of patients with ET, and the ability to characterize the disease by the presence or absence of molecular mutations has lent precision to our prognostic models. This review outlines a modern approach to the diagnosis and treatment of ET. It highlights the 2016 World Health Organization standards for differentiating the disease from primary myelofibrosis, which is key for an accurate prognosis. It also describes the current risk stratification models and discusses the vascular and hemorrhagic risks that affect patients with this chronic condition, including younger individuals and pregnant women. Finally, it outlines a simple-to-follow treatment algorithm that is based on an understanding of the vascular risks and provides a foundation for discussing treatment choices with patients.

## Introduction

Essential thrombocythemia (ET) is a rare blood cancer. The disease is one of the Philadelphia chromosome–negative myeloproliferative neoplasms (MPNs), a category that also includes polycythemia vera (PV) and primary myelofibrosis (PMF). All 3 diseases are clonal hematopoietic stem cell disorders; ET is characterized by abnormal megakaryocytic morphology. The hallmark phenotype is a persistent, nonreactive thrombocytosis and an increased risk for arterial and venous vascular events.

Given the overlap in disease characteristics in addition to the genomic and phenotypic similarities observed in the MPNs,<sup>1</sup> the characterization of ET has been challenging. The discovery of associated genetic mutations has facilitated a delineation of the differences among these conditions, and recently, therapeutic decision making

## Keywords

Essential thrombocythemia, myeloproliferative neoplasms, thrombocytosis

**Table 1.** 2016 World Health Organization Diagnostic Criteria for Essential Thrombocythemia

Major Criteria	Minor Criterion
1. Platelet count $\geq 450 \times 10^9/L$	1. Presence of a clonal marker or absence of evidence of reactive thrombocytosis
2. Bone marrow biopsy showing proliferation, mainly of the megakaryocyte lineage, with increased numbers of enlarged, mature megakaryocytes that have hyperlobulated nuclei; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers	
3. Not meeting WHO criteria for <i>BCR-ABL1</i> -positive CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms	
4. Presence of <i>JAK2</i> , <i>CALR</i> , or <i>MPL</i> mutation	

*CALR*, calreticulin gene; CML, chronic myeloid leukemia; *JAK2*, Janus kinase 2 gene; *MPL*, myeloproliferative leukemia gene; PMF, primary myelofibrosis; PV, polycythemia vera; WHO, World Health Organization.

Source: Arber DA et al. *Blood*. 2016;127(20):2391-2405.<sup>1</sup>

has been adjusted according to the genetic profile.

ET often has an indolent course. Age older than 60 years, previous thrombotic events, driver mutations, and very high platelet counts indicate an increased risk for complications and guide treatment strategies.<sup>1-3</sup> Major complications include thrombotic and hemorrhagic events; therapy is aimed at reducing the rate of these events and alleviating vasomotor symptoms.

This article summarizes current knowledge regarding the treatment of ET, discusses the management of complex presentations of the disease, and describes areas of concern in which future research is especially needed.

## Epidemiology

ET most commonly occurs in adults. The median age at diagnosis is 60 years, but the condition can occur throughout the life cycle, including, rarely, in childhood.<sup>4</sup> The estimated annual incidence according to pooled data from the United States and Europe is 1.03 per 100,000 people, with a female-to-male ratio of approximately 2:1.<sup>5</sup>

Survival has improved over the last 50 years as

both primary prevention and the treatment of thrombotic, hemorrhagic, and infectious complications have improved. The International Prognostic Scoring System for Essential Thrombocythemia is a tool for predicting survival. In this model, patients receive points for the following: (1) leukocyte count equal to or greater than  $11 \times 10^9/L$  (1 point), (2) age of 60 years or older (2 points), and (3) history of thrombosis (1 point). Patients are then stratified into low- (0 points), intermediate- (1-2 points), and high-risk ( $\geq 3$  points) categories. This model has not been used to estimate survival for low-risk patients. Intermediate risk portends a median survival of approximately 25 years, whereas high risk carries a median overall survival of 15 years.<sup>6</sup>

## Diagnostic Criteria

Establishing diagnostic criteria for ET has proved to be a challenge given that the presentation and phenotype of the disease can mimic those of other benign or malignant hematologic disorders.<sup>7</sup> For example, both PV and PMF can present with an isolated thrombocytosis.<sup>8,9</sup> The World Health Organization (WHO) attempted to address the definition of ET in 2002, characterizing it as part of a group of chronic myeloproliferative diseases that included PV, ET, PMF, chronic myelogenous leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia, and hypereosinophilic syndrome.<sup>10</sup> The definitions were revised in 2008 and again in 2016 as additional research revealed that these entities were clonal neoplastic diseases of the hematopoietic stem cell with several features in common. The shared features include survival that often is measured in decades, low rates of disease transformation into acute leukemia, and genotypic and phenotypic characteristics.<sup>1,7</sup>

According to the 2016 WHO update, ET is diagnosed after 4 major criteria, or the first 3 major criteria and 1 minor criterion, have been met (Table 1). The disease can also be diagnosed if the patient does not have any of the 3 known driver mutations but meets the first 3 major criteria and has another clonal marker with no signs of reactive thrombocytosis.<sup>1</sup>

The Janus kinase 2 gene (*JAK2*) mutation was the first driver mutation to be discovered in ET and is present in roughly 50% of cases. Although the presence of a *JAK2* V617F mutation supports the diagnosis, it is not specific to ET and can be present in other MPNs.<sup>11,12</sup> In large, retrospective studies, the *JAK2* mutation has been linked to an increased frequency of disease complications, especially thrombosis. This finding can assist in classifying disease risk and discussing treatment strategies.<sup>3,13</sup>

Mutations in the calreticulin gene (*CALR*) on chromosome 19p13.2 and the myeloproliferative leukemia gene

(*MPL*) on chromosome 1p34 were subsequently identified as additional driver mutations associated with MPNs.<sup>11,14</sup> They also can present rarely in other MPNs, with the *CALR* mutation present in approximately 25% and the *MPL* mutation in 4% of patients with ET.<sup>12</sup> Approximately 10% to 15% of patients have triple-negative disease, in which none of these 3 driver mutations is expressed.<sup>15</sup>

It is essential that all patients be tested for the *BCR-ABL* translocation, which defines chronic myeloid leukemia (CML) and allows uniquely effective therapy in the form of targeted tyrosine kinase inhibitors.<sup>16</sup> To exclude PV, the hemoglobin level must be lower than 16.5 g/dL in men or lower than 16.0 g/dL in women.<sup>1</sup> Additionally, causes of reactive thrombosis must be ruled out. Reactive thrombocytosis can commonly occur, for example, in settings of iron deficiency, autoimmune disorders, or trauma.<sup>7</sup>

## Pathology

Both bone marrow biopsy and genetic testing are important in the diagnosis and risk stratification of ET. The 2016 revised guidelines from the WHO specify that bone marrow biopsy is critical for a diagnosis of ET, to differentiate it from prefibrotic PMF. The bone marrow in ET is characteristically normocellular to mildly hypercellular with signs of increased proliferation and enlarged megakaryocytes. If the findings include an increase in neutrophil granulopoiesis or erythropoiesis, alternative diagnoses should be considered.<sup>1,16</sup>

Prefibrotic PMF is a distinct entity that can present with isolated thrombocytosis, and the only way to distinguish it from ET is by bone marrow biopsy. In contrast to ET, PMF shows hypercellular bone marrow with increased granulocytes and enlarged megakaryocytes that have atypical bulbous nuclei.<sup>16,17</sup> Of note, the natural history of prefibrotic PMF differs significantly from that of ET, underscoring the importance of these diagnostic strategies.<sup>18-20</sup>

## Presentation

### Symptoms

In keeping with the relatively indolent course of ET, approximately half of cases are discovered incidentally on the basis of laboratory findings. Sometimes, after the diagnosis has been made, patients report that they have experienced nonspecific symptoms, such as fatigue and bone pain, that did not trigger an evaluation.<sup>21</sup> Fatigue is the most common presentation and affects approximately 80% of patients.<sup>22</sup> This ubiquitous feature of ET and other MPNs affects patients' quality of life and is multifactorial in etiology.<sup>23-25</sup>

Vasomotor symptoms, including headaches, erythromelalgia, acroparesthesias, livedo reticularis, transient ischemic attacks, peripheral ischemia, scotomas, and amaurosis fugax, are also common.<sup>26</sup> The pathophysiology of these symptoms may consist largely of abnormal platelet-endothelium interactions and small-vessel inflammation. Thromboxane formation, which is increased in ET, has been shown to increase arterial microvascular thrombosis and cause erythromelalgia.<sup>27</sup> These symptoms can often be managed or even eradicated with once- or twice-daily low-dose aspirin.<sup>28,29</sup>

### Thrombosis

Venous thrombosis can present as a clot in the deep venous system, pelvis, portal vein, or mesenteric system. Arterial events can involve the coronary, cerebral, ophthalmic, or distal vessels. The risk for arterial or venous thrombosis can be as low as 1% to 3% per patient-year, but with the *JAK2* mutation, the risk increases to 7.7%.<sup>13,30</sup> The presence of the *JAK2* mutation or cardiovascular risk factors has been shown in several studies to increase the rate of thrombosis independently.<sup>3,13,31</sup>

These complications are main drivers of morbidity and mortality in ET. Guidelines for risk stratification and treatment strategies are focused on decreasing the risk for thrombotic events. Several models for assessing risk for thrombosis exist and are presented below.<sup>3,16,32,33</sup>

### Hemorrhage

There is less consensus about the overall rate of hemorrhage, with estimates ranging widely—from 0.79% to 30%. Differences in these numbers can likely be attributed to differences in definitions of bleeding events. The risk increases with a platelet count above 1000 to  $1500 \times 10^9/L$ .<sup>34,35</sup> Hemorrhage can be related to acquired von Willebrand syndrome (AVWS) with extreme thrombocytopenia.<sup>36</sup>

## Risk Stratification and Treatment

The treatment of ET is focused on reducing the risk for disease complications, including bleeding and thrombosis, and on relieving the symptom burden. Treatment decision making begins with risk stratification (Table 2). Traditionally, patients were categorized as at low risk if they were younger than 60 years and had never had an arterial or venous clot. In 2011, the European LeukemiaNet (ELN) classification system was articulated.<sup>37</sup> In this simple system, patients are categorized on the basis of 3 major risk factors: (1) age 60 years or older, (2) personal history of thrombosis or major hemorrhage, and (3) platelet count above  $1500 \times 10^9/L$ . If any of these criteria are met, the patient is considered at high risk. If none of these criteria are met, the patient is

**Table 2.** Risk Stratification Models for Essential Thrombocythemia

	<b>ELN Criteria</b>	<b>IPSET-Thrombosis*</b>	<b>Revised IPSET-Thrombosis</b>
<b>High risk</b>	Age $\geq 60$ y or Prior history of thrombosis or bleeding or Platelet count $>1500 \times 10^9/L$	3-6 points	Prior history of thrombosis or Age $>60$ y and Positivity for the <i>JAK2</i> V617F mutation
<b>Intermediate risk</b>	NA	2 points	No prior thrombosis history and Age $>60$ y and Negativity for the <i>JAK2</i> V617F mutation
<b>Low risk</b>	Age $<60$ y and No prior history of thrombosis or bleeding and Platelet count $<1500 \times 10^9/L$	0-1 point	No prior thrombosis history and Age $<61$ y and Positivity for the <i>JAK2</i> V617F mutation
<b>Very low risk</b>	NA	NA	No prior thrombosis history and Age $<61$ y and Negativity for the <i>JAK2</i> V617F mutation

ELN, European LeukemiaNet; IPSET-Thrombosis, International Prognostic Score of Thrombosis in World Health Organization–Essential Thrombocythemia; *JAK2*, Janus kinase 2 gene; NA, not applicable.

\*IPSET-Thrombosis: age  $>60$  y (1 point); prior thrombotic event (2 points); presence of cardiovascular risk factors: diabetes, hypertension, smoking (1 point); detection of *JAK2* V617F mutation (2 points)

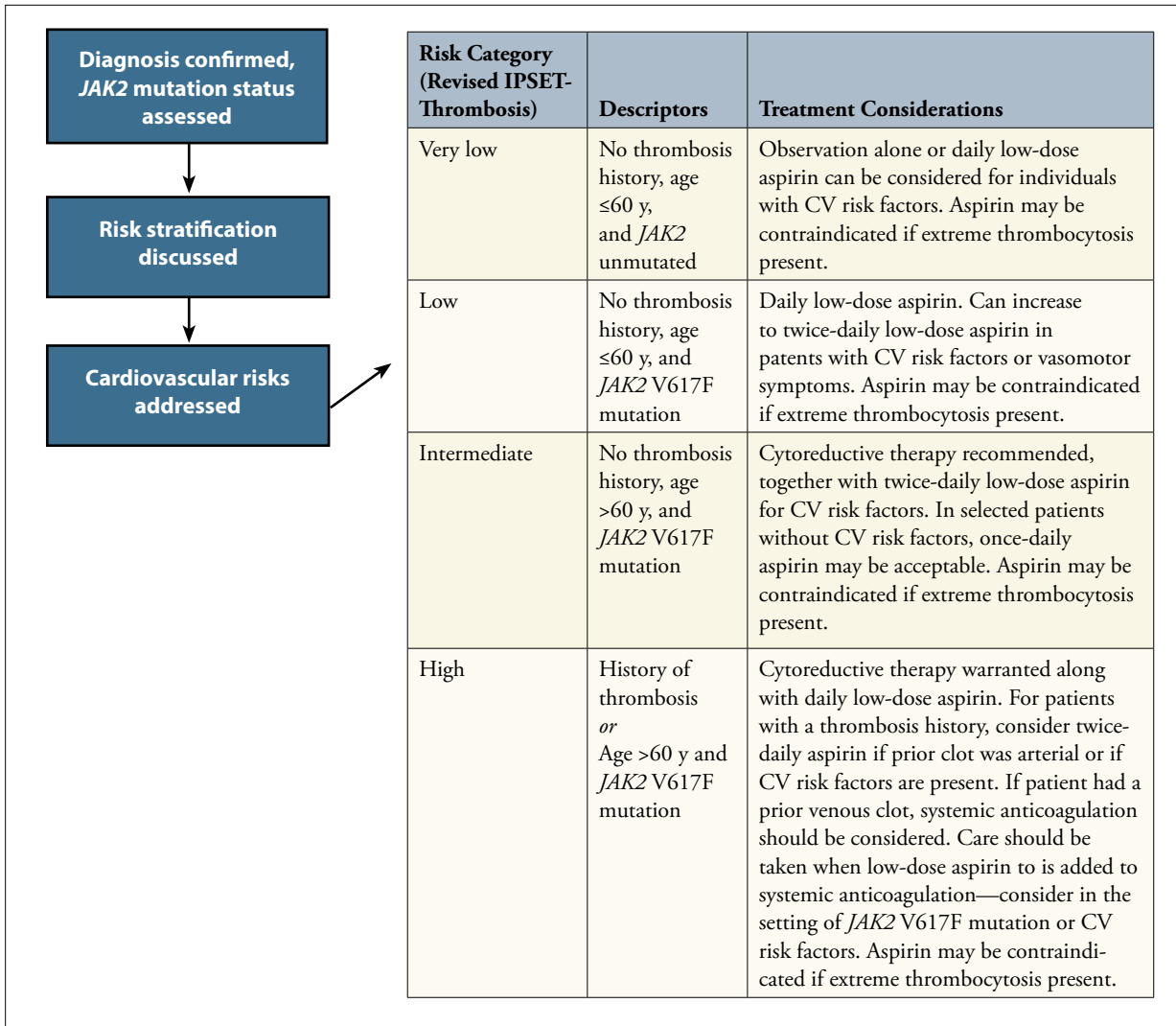
Sources: Rumi E, Cazzola M. *Blood*. 2017;129(6):680-692<sup>16</sup>; Tefferi A, Barbui T. *Am J Hematol*. 2017;92(1):94-108<sup>33</sup>; Barbui T et al. *J Clin Oncol*. 2011;29(6):761-770<sup>37</sup>; Haider M et al. *Am J Hematol*. 2016;91(4):390-394<sup>41</sup>; Passamonti F et al. *Leukemia*. 2017. doi:10.1038/leu.2017.169.<sup>86</sup>

considered at low risk. Of note, this system places patients with extreme thrombocytosis in the high-risk category and makes them eligible for cytoreductive therapy.<sup>32</sup> Whether the finding of a platelet count above  $1500 \times 10^9/L$ , absent of any other clinical findings, should be a rationale for starting cytoreductive therapy has been debated.<sup>34</sup> As noted (Figure), when a patient in this situation is encountered, an in-depth discussion of risk vs benefit is warranted.

Given that the risk is largely centered on thrombosis, some physicians use the International Prognostic Score of Thrombosis in World Health Organization–Essential Thrombocythemia (IPSET-Thrombosis). This model considers the presence of the *JAK2* V617F mutation as well as cardiovascular risk factors.<sup>38</sup> In retrospective studies of patients with ET, a *JAK2* mutation and cardiovascular risk factors have been shown to increase the risk for thrombosis independently. IPSET-Thrombosis scores are based on age older than 60 years (1 point), a history of thrombosis (2 points), presence of cardiovascular risk factors (1 point), and presence of the *JAK2* V617F mutation

(2 points). This 3-tiered model—in which patients are categorized as at low (0-1 points), intermediate (2 points), or high risk ( $\geq 3$  points)—has been shown to predict the risk for vascular events more accurately than a model categorizing patients only as at low or high risk. Investigators demonstrated that with these criteria, one can estimate thrombosis risks of 1.03%, 2.35%, and 3.56% per year for patients in the low-, intermediate-, and high-risk categories, respectively.<sup>38</sup> This method has been further validated in secondary populations.<sup>39,40</sup>

A revision to the above system has been published and validated in a retrospective cohort.<sup>3,41</sup> This model considers 4 risk categories: high (prior thrombosis or age  $>60$  years and the presence of a *JAK2* mutation); intermediate (no thrombosis history, age  $>60$  years, and no *JAK2* mutation); low (no thrombosis history, age  $\leq 60$  years, and *JAK2* mutation); and very low (no thrombosis history, age  $\leq 60$  years, and no *JAK2* mutation). Notably, cardiovascular risk factors are not part of the risk stratification here but can be used in treatment decision making.



**Figure.** Treatment considerations according to risk stratification. Not universally supported by randomized studies at this time. CV, cardiovascular; IPSET-Thrombosis, International Prognostic Score of Thrombosis in World Health Organization–Essential Thrombocythemia; *JAK2*, Janus kinase 2 gene; y, years.

Sources: Adapted from Rumi E, Cazzola M. *Blood*. 2017;129(6):680-692<sup>16</sup>; Rumi E, Cazzola M. *Blood*. 2016;128(20):2403-2414<sup>32</sup>; Tefferi A, Barbui T. *Am J Hematol*. 2017;92(1):94-108.<sup>33</sup>

There is no universal consensus about which risk stratification system is optimal. Treatment recommendations for each of these risk groups need to be established in controlled studies.<sup>3,32,33</sup> The discussion with a patient should emphasize that most morbidity from this disease arises from vascular events, so avoiding them is the goal of therapy. Importantly, every clinical consultation starts with a review of cardiac risk factors. All patients require aggressive management of diabetes, hypertension, and hypercholesterolemia. A thorough history should be undertaken of vascular events, such as lower-extremity venous thromboembolism (VTE), pulmonary embolism, cerebrovascular events, sinus venous thrombosis,

and myocardial infarction. A history of bleeding should be obtained, including any recent peripartum events in young women. Finally, one needs to verify the presence or absence of the *JAK2* V617F mutation. When clinicians make treatment recommendations (Figure), they should use the revised IPSET-Thrombosis model to predict risks for future events.

**Very Low-Risk Disease**

Patients who have no thrombosis history, are 60 years of age or younger, and do not have a *JAK2* V617F mutation are considered to have very low-risk disease. These patients may be managed with observation or with low-

dose aspirin. There is insufficient evidence to insist on aspirin use by patients in this group who do not have any cardiac risk factors or symptoms.<sup>33,33</sup> Patients should be followed for disease progression or transformation. One observational study suggested that in low-risk patients who lack all 3 high-risk characteristics according to the ELN criteria, thrombotic and hemorrhagic event rates were the same as those in a disease-free age- and sex-matched population.<sup>42</sup> If vasomotor symptoms are present, once- or twice-daily low-dose aspirin may be started if AVWS or extreme thrombocytosis is not a concern.<sup>33,43</sup>

#### **Low-Risk Disease**

Patients who have no thrombosis history, are 60 years of age or younger, and have a *JAK2* V617F mutation are considered to have low-risk disease. These patients may be managed with a daily low dose of aspirin. Some experts recommend twice-daily aspirin in those with cardiovascular risk factors.<sup>33</sup> If vasomotor symptoms are present, once- or twice-daily low-dose aspirin may be started if the patient does not have AVWS or extreme thrombocytosis.<sup>33,43</sup>

#### **Intermediate-Risk Disease**

Patients who have no thrombosis history, are older than 60 years, and do not have a *JAK2* V617F mutation are considered to have intermediate-risk disease. A thorough history should be obtained to look for concurrent cardiovascular risk factors, with appropriate interventions adopted. According to the ELN criteria, these patients are at high risk because of their age, and cytoreductive therapy should be initiated. However, in selected patients, twice-daily aspirin may be an acceptable alternative, or even once-daily aspirin if no cardiovascular risk factors are present.<sup>16,32,33</sup> Given the need to start aspirin in this patient cohort, the practitioner must be aware of the risks for bleeding in patients with extreme thrombocytosis or AVWS.

#### **High-Risk Disease**

Patients who either have a history of thrombosis or are older than 60 years and who have a *JAK2* V617F mutation are considered to have high-risk disease. Patients with a *JAK2* mutation, cardiovascular risk factors such as hypertension and hyperlipidemia, or known coronary artery disease should receive low-dose aspirin to decrease the risk for thrombosis.<sup>35</sup> Patients should also receive a cytoreductive agent.<sup>32,33</sup> The first-line agent for treatment is hydroxyurea, although some may wish to consider interferon in appropriate patients for the initial intervention.<sup>18,44</sup> Some experts recommend twice-daily aspirin for patients in this category who are not on systemic anticoagulation.<sup>33</sup>

#### **Extreme Thrombocytosis**

A high platelet count—above 1000 to 1500 × 10<sup>9</sup>/L—can be associated with increased thrombosis but can also lead to the development of AVWS and subsequent bleeding events. AVWS can be due to dysfunction or an inadequate amount of von Willebrand factor.<sup>36,45</sup> ET is characterized by a decrease in large von Willebrand factor multimers. The exact mechanism is unclear, but this feature has been shown to prolong bleeding time and increase risk for hemorrhage.<sup>46</sup> As mentioned earlier, the decision to start cytoreduction in a patient with extreme thrombocytosis but without any history of bleeding or symptoms is not straightforward, and this point is controversial.<sup>32,34</sup> Testing for the serum ristocetin level may be clinically helpful.

The best strategy for aspirin use in extreme thrombocytosis is not known.<sup>34</sup> In our practice, we carefully discuss the risks and benefits of cytoreduction in patients with evidence of AVWS and withhold aspirin until the platelet count is lowered. In a patient with a history of bleeding or a platelet count above approximately 1500 × 10<sup>9</sup>/L, we typically withhold aspirin therapy and discuss the option of cytoreduction. Prospective studies on this issue are particularly necessary. Practitioners should be aware of the reasons for the lack of clarity on this issue, which can help with clinic discussions.<sup>32-34</sup>

#### **Treatment Options**

Treatment options include aspirin, a cytoreductive agent, or a combination of aspirin and a cytoreductive agent. The choice of agent may be influenced by the patient's age, desire for fertility, and experience with prior cytoreductive agents. No prospective trials have determined the ideal platelet count to decrease the risk for thrombosis; once cytoreduction is started, experts generally recommend a goal platelet count below 400 to 450 × 10<sup>9</sup>/L. In the pivotal study comparing hydroxyurea with anagrelide in patients who had high-risk disease, the hydroxyurea was titrated according to a platelet goal below 400 × 10<sup>9</sup>/L.<sup>12,32,47</sup>

#### **Aspirin**

Low-dose aspirin has been extensively studied and shown to decrease thrombotic events, likely by inhibiting platelet thromboxane A<sub>2</sub> (TXA<sub>2</sub>).<sup>38</sup> In cases of symptomatic ET, low-dose aspirin can reduce symptoms of acral paresthesias and erythromelalgia.<sup>29,48</sup> Biochemical studies of thromboxane synthesis have indicated that a trial of twice-daily aspirin can be used if once-daily aspirin does not adequately control symptoms.<sup>49</sup>

Patients who have a *JAK2* mutation should be treated with aspirin, which has been shown to reduce the risk for venous thrombosis and has the additional benefit of



decreasing arterial thrombosis in patients with concurrent cardiovascular risks.<sup>50</sup> *CALR* mutations have not been associated with increased thrombotic events; therefore, for patients who are at low risk and asymptomatic, aspirin therapy is not imperative and can be discussed on a case-by-case basis.<sup>51</sup>

In cases of ET with platelet counts above 1000 to  $1500 \times 10^9/L$ , aspirin therapy may be contraindicated owing to the concern about the development of AVWS and the increased risk for hemorrhage. AVWS is diagnosed with a thorough patient history, along with measurement of a contemporary von Willebrand antigen level and ristocetin cofactor activity.

### **Hydroxyurea**

Hydroxyurea works by inhibiting the enzyme ribonucleotide reductase, thereby decreasing the production of deoxyribonucleotides. Hydroxyurea has long been considered first-line treatment for ET, given its favorable toxicity profile. The most common side effects, which are generally mild, include oral ulcers and skin hyperpigmentation or rashes.<sup>52</sup> There is no universal consensus regarding dosing. In the 1995 randomized study of patients with ET that demonstrated a reduction in vascular events with hydroxyurea vs placebo, subjects received 15 mg/kg daily with a goal of keeping platelet counts below  $600 \times 10^9/L$ .<sup>53</sup> Other experts recommend a starting dose of 1 g/d and modifications to correct leukocytosis; the platelet count endpoint is relatively permissive, although generally between  $400$  and  $600 \times 10^9/L$ .<sup>32</sup>

In a study of 114 patients, the combined use of hydroxyurea and aspirin decreased the rate of thrombotic events by 20.4% compared with aspirin alone.<sup>53</sup> Leukocytosis has also been suggested to increase the risk for thrombosis. Therefore, although neutropenia must be avoided, it may be beneficial to target the correction of leukocytosis of at least  $11 \times 10^9/L$ .<sup>44,54</sup> No solid evidence indicates that hydroxyurea is leukemogenic in this patient population, although the possibility is a common concern among patients.<sup>55</sup>

Notably, hydroxyurea is teratogenic. A 3- to 6-month washout period is recommended for patients wishing to conceive. Although the use of interferon in this situation is off label, interferon is an appropriate alternative for patients who wish to maintain their fertility or who are younger. In our practice, we routinely discuss the option of interferon therapy with patients younger than 50 years who require cytoreductive therapy.<sup>32</sup>

### **Anagrelide**

At higher doses, anagrelide acts through anticyclic adenosine monophosphate (AMP) phosphodiesterase to inhibit platelet aggregation. At lower doses, it also works by

decreasing platelet counts.<sup>56</sup> This agent is generally considered for patients in whom hydroxyurea or interferon fails or causes unacceptable toxicities. Its use has been examined in 2 major studies.

The prospective, randomized trial ANAHYDRET (Anagrelide vs. Hydroxyurea - Efficacy and Tolerability Study in Patients With Essential Thrombocythaemia) enrolled 259 patients, 122 of whom were randomly assigned to the anagrelide arm and 137 to the hydroxyurea arm. It was designed as a noninferiority study of the prevention of thrombohemorrhagic events in high-risk ET. Results showed no significance differences between platelet counts, hemoglobin levels, or leukocyte counts and indicated that anagrelide is noninferior to hydroxyurea in preventing thrombosis in the setting of ET.<sup>57</sup>

The PT-1 (Primary Thrombocythaemia 1) trial randomly assigned patients with high-risk ET, as defined by the Polycythemia Vera Study Group, to anagrelide or hydroxyurea.<sup>47</sup> Although anagrelide was equally as efficacious at reducing platelet counts, the rate of occurrence of a composite endpoint—which included arterial thrombosis, significant hemorrhage, and transformation to myelofibrosis—was higher in the anagrelide arm. Anagrelide outperformed hydroxyurea in decreasing rates of venous thrombosis.

Anagrelide has a significant side effect profile related to its vasodilator action. The risks include fluid retention, headaches, and heart palpitations. Anagrelide also has been associated with acute cardiomyopathy.<sup>58,59</sup> Cardiac evaluation is recommended before treatment.

### **Interferon Alfa**

Interferon alfa targets the malignant clone to reduce the colony-forming capabilities of erythroid, granulocytic, and megakaryocytic progenitors,<sup>48</sup> so that it is an effective agent for treating both ET and PV. It has been shown to induce a good molecular response in MPNs. In a phase 2 trial that enrolled 77 patients with either ET or PV, the response rate was 80% after a median follow-up of 21 months.<sup>49</sup> Interferon alfa is not associated with gonadal toxicity and has no teratogenic effects, and therefore it is not contraindicated in pregnancy. It is available only in intravenous forms, so that it is more difficult to administer than other agents.

The most common side effects include malaise, fevers, chills, myalgia, and joint pain, although these are less common with the pegylated forms. Depression can occur or, if it is present at baseline, be significantly worsened, so it is challenging to administer this drug in the setting of prior depressive symptomatology. Traditionally, the average rate of discontinuation due to side effects is approximately 25%.<sup>48</sup> Patients younger than 60 years tend to tolerate this agent better than older patients.<sup>3</sup> A randomized clinical

trial, conducted by the Myeloproliferative Disorders Research Consortium (MPD-RC), is currently evaluating pegylated interferon alfa-2a vs hydroxyurea as first-line therapy in high-risk PV and ET.<sup>60</sup> The endpoint is either complete or partial hematologic remission after 1 year of therapy. In an interim analysis of 75 patients, presented in December 2016, no difference in the primary endpoint was found among 44 patients with ET. The patients in the interferon arm initially demonstrated a reduction in the symptom burden (fatigue, early satiety, abdominal discomfort). However, by 9 and 12 months, symptoms were less severe in the hydroxyurea arm.<sup>61</sup> Surprisingly, patients in either arm who achieved a complete hematologic remission reported worsening sad mood and decreased sexuality. In our practice, pegylated interferon is discussed alongside hydroxyurea as a possible option for patients who are younger or desire to maintain fertility and who have no significant history of depression.<sup>18,44</sup>

### **Ruxolitinib**

Ruxolitinib (Jakafi, Incyte Corporation), a JAK1/JAK2-targeted inhibitor, is the only treatment approved by the US Food and Drug Administration (FDA) that is specific for myelofibrosis; it is also indicated for the treatment of PV after failure of hydroxyurea. Interest has been shown in testing ruxolitinib in patients with ET. The largest study to date is a phase 2 trial called MAJIC (A Randomised Study of Best Available Therapy versus JAK Inhibition in Patients With High Risk Polycythaemia Vera or Essential Thrombocythaemia Who Are Resistant or Intolerant to Hydroxycarbamide), which randomly assigned patients who had ET that was not well controlled with hydroxyurea to either ruxolitinib or best available therapy. A preliminary analysis of 110 patients, presented in June 2016, demonstrated no difference between the rates of complete hematologic remission and partial hematologic remission with ruxolitinib and the rates with best available therapy. The rates of thrombosis and hemorrhage were also similar; however, the symptom scores for early satiety, itching, and weight loss were improved in the ruxolitinib arm. A further analysis, presented in December 2016, included molecular response and clinical outcomes. There was some suggestion from these data that molecular response or symptom reduction may not correlate with progression.<sup>44,62,63</sup> The use of ruxolitinib in this population remains investigational.

### **Other Agents**

Busulfan and 32P are agents historically used to control platelet count in ET, but both have been shown to increase rates of acute myeloid leukemia following treatment. These agents are now typically used in patients with an expected lifespan of 3 to 5 years.<sup>33</sup>

Pipobroman is an oral alkylating agent that is not currently used in the United States but is used in Europe. Most of its common side effects are gastrointestinal, such as nausea, diarrhea, and cramping. It been associated with an increase in acute myeloid leukemia, especially when given in conjunction with other platelet-lowering agents.<sup>18</sup>

## **Special Circumstances**

### **Pregnancy**

ET is not an absolute contraindication for pregnancy and in fact is the most common MPN in women of reproductive age. Pregnancy outcome data for patients with ET are largely retrospective and have demonstrated mixed results. Historically, the risks for maternal and fetal complications were thought to be increased, including spontaneous abortion (25%-50%, mostly in the first trimester), fewer live births (50%-70%), pre-eclampsia, placental dysfunction, intrauterine growth restriction, postpartum hemorrhage, and thrombosis.<sup>64,65</sup> Recently, however, Alimam and colleagues published results of a prospective cohort study of pregnancy outcomes over a 3-year period in the United Kingdom in patients with MPNs, and these indicate that in the modern era, pregnancy outcomes may be better than those in retrospective studies.<sup>66</sup> Of the 58 women with MPN in the cohort, 81% had confirmed ET, with 58 live births, 1 stillbirth, and 1 miscarriage (miscarriage rate of 1.7/100; 95% CI, 0.04-9.24). Of the patients with ET, 6% experienced pre-eclampsia, and 9% of all patients had postpartum hemorrhage. There are no clear predictors of adverse outcomes, including age, parity, mutational status, white cell count, platelet count, and hemoglobin levels.

Pregnancy in these patients should be planned and managed while they are under the care of a multidisciplinary team, including an experienced hematologist and obstetrician. Before pregnancy, a 3- to 6-month washout period is recommended for both men and women treated with teratogenic agents.<sup>64-66</sup> Preconception planning to assess risk factors and formulate an individual plan is ideal. A number of reviews on this subject have been published.<sup>64,67-71</sup>

### **Splanchnic Vein Thrombosis**

The prevalence of splanchnic vein thrombosis (SVT)—which includes Budd-Chiari syndrome and portal vein thrombosis—ranges from 5.5% to 10% in patients with ET.<sup>72</sup> MPNs are the leading nonmalignant and non-cirrhotic cause of SVT, responsible for 15% to 50% of cases.<sup>73</sup> Budd-Chiari syndrome is a result of the obstruction of hepatic venous outflow when thrombosis develops in the hepatic veins or inferior vena cava.



In the absence of a known diagnosis of MPN, patients with idiopathic SVT should be screened for the *JAK2* V617F mutation, particularly given the recent evidence of its role in thrombosis via possible site-specific endothelial dysfunction in splanchnic vessels.<sup>74</sup> In a meta-analysis of 831 patients, Dentali and colleagues detected the *JAK2* mutation in 32.7% of those with SVT.<sup>75</sup> Among the patients without overt MPN at the time of SVT, MPN was eventually diagnosed in 52.4% of those with the *JAK2* V617F mutation.

Data regarding the *CALR* mutation are not as robust; however, experts still recommend that an assessment for this mutation be included in the workup of patients with SVT who do not have the *JAK2* V617F mutation.<sup>32,74</sup> In 2 large studies, the presence of a *CALR* mutation was demonstrated in 1.9% (4/209)<sup>76</sup> and 1.6% (5/308)<sup>78</sup> of the patients with SVT; however, MPN was subsequently diagnosed in all 9 patients.<sup>74</sup>

Unless contraindicated, indefinite oral anticoagulation is recommended for all patients who have SVT in the setting of ET, owing to the high rates of recurrence.<sup>78</sup> A majority of studies have used vitamin K antagonists (VKAs); however, small reports used direct factor Xa inhibitors.<sup>74</sup> One retrospective study demonstrated a reduced risk for recurrence (hazard ratio [HR], 0.53; 95% CI, 0.38-0.73) in patients on cytoreductive therapy, especially when it was combined with antiplatelet or anticoagulant agents.<sup>79</sup>

Like all patients with SVT, these patients should have close follow-up for sequelae, including portal hypertension and esophageal varices, which can be particularly dangerous in patients with poorly controlled thrombocytosis.

### **Long-term Anticoagulation**

The cumulative incidence of cardiovascular events in patients with ET is 1.75% per year, whereas the cumulative incidence of thromboembolic events is 1.9% to 3.0% per patient-year.<sup>72</sup> In the acute setting, standard treatment options include, but are not limited to, heparin, low-molecular-weight heparin (LMWH), and direct oral anticoagulants. There are limited reports of heparin-induced thrombocytopenia in patients with MPNs,<sup>80</sup> so therapies associated with a smaller risk should be used when possible. Although the CLOT trial (Comparison of Low Molecular Weight Heparin Versus Oral Anticoagulant Therapy for Long Term Anticoagulation in Cancer Patients With Venous Thromboembolism) demonstrated significant benefit in patients who had a malignancy treated with LMWH vs a VKA, patients with MPN were not included in the trial.<sup>81</sup> However, many experts still recommend the use of LMWH over a VKA in patients with ET, given its superiority in the setting of malignancy.

The duration of treatment remains controversial. The rate of recurrent thrombosis in MPN has been reported to be 7.6%, with higher rates in patients who are older than 60 years or have another hereditary thrombophilia.<sup>79</sup> In the same study, rates of serious bleeding with a VKA were 0.9% per year and increased to 2.8% per year when a VKA was taken concurrently with a platelet inhibitor. The patients who completed VKA treatment and continued platelet inhibition did have reduced rates of recurrence (HR, 0.42; 95% CI, 0.22-0.77), similar to the rates during VKA therapy.

Prolonged or indefinite anticoagulation should be considered for patients with a high risk for VTE and a low risk for bleeding—those with recurrent VTE, SVT (discussed previously), life-threatening VTE, or progressing MPN.<sup>72</sup> It should also be considered for patients in whom VTE develops while they are on aspirin and cytoreductive therapy.

### **Young Patients**

ET is not as clearly defined or well studied in the pediatric population, and the percentage of patients with *JAK2* or *MPL* mutations is much lower.<sup>4,82</sup> More commonly, children have transient or reactive thrombocytosis. Multiple small studies and case series of pediatric ET have been reported. The rate of complications of ET—including thrombosis and hemorrhage—appears to be significantly lower in children than in adults. Some studies have demonstrated mutations in the *JAK2*, *ASXL1*, and *cMPL* genes.<sup>83,84</sup>

No consensus guidelines are available for the treatment of pediatric ET. Close observation is recommended for asymptomatic patients. Low-dose aspirin is recommended for patients with symptoms or additional risk factors for thrombosis, although aspirin in children younger than 12 years of age may be contraindicated because of the risk for Reye syndrome.<sup>82</sup> Cytoreductive therapy can be used, but only as a last resort. According to experts from the ELN,<sup>85</sup> there are insufficient data to recommend a specific agent in children, so careful discussion should be undertaken and consent obtained. This is an additional situation in which specialized expertise may be warranted.

### **Conclusions**

ET is an uncommon hematologic malignancy in which patients and physicians must be aware of the risks of both the disease and the therapies. Life-shortening morbidities are largely due to vascular events—both arterial and venous clotting as well as hemorrhage. Risk stratification models exist and are continually being refined. The presence of a *JAK2* V617F mutation can help determine, in an asymptomatic person, whether treatment should be

initiated. Therapeutic interventions have not changed much in the last decade, with hydroxyurea and at times interferon used for first-line cytoreduction. The National Comprehensive Cancer Network guidelines are anticipated to be released in the near future. Life events such as pregnancy require special attention but can be safely managed. We await novel agents for this disease and a better understanding of the interactions among molecular events, symptomatology, and outcomes.

### Disclosures

*Dr Michaelis has served on advisory boards for Novartis, Celgene, and Incyte, and owns equity in Pfizer. Drs Kleman and Singavi have no disclosures.*

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