Polycythemia Vera and Essential Thrombocythemia

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ABSTRACT

Objective: To review the clinical aspects and current practices in the management of polycythemia vera (PV) and essential thrombocythemia (ET).

Methods: Review of the literature.

Results: PV and ET are rare chronic myeloid disorders. The 2 most important life-limiting complications of PV and ET are thrombohemorrhagic events and myelofibrosis/acute myeloid leukemia (AML) transformation. Vascular events are at least in part preventable with counseling on risk factors, phlebotomy (for patients with PV), antiplatelet therapy, and cytoreduction with hydroxyurea, interferons, or anagrelide (for patients with ET). Ruxolitinib was recently approved for PV after hydroxyurea failure. PV/ET transformation into myelofibrosis or AML is part of the natural history of the disease and no therapy has been shown to prevent it. Treatment of leukemic transformation of myeloproliferative neoplasms (MPN LT) follows recommendations set forth for primary myelofibrosis and AML.

Conclusion: With appropriate management, patients with PV and ET typically enjoy a long survival and near-normal quality of life. Transformation into myelofibrosis or AML cannot be prevented by current therapies, however. Treatment results with MPN LT are generally poor and novel strategies are needed to improve outcomes.

Key words: myeloproliferative neoplasms; myelofibrosis; leukemic transformation.

Polycythemia vera (PV) and essential thrombocythemia (ET), along with primary myelofibrosis (PMF), belong to the group of Philadelphia-negative myeloproliferative neoplasms (MPN). All these malignancies arise from the clonal proliferation of an aberrant hematopoietic stem cell, but are characterized by distinct clinical phenotypes [1,2]. Although the clinical course of PV and ET is indolent, it can be complicated by thrombohemorrhagic episodes and/or evolution into myelofibrosis and/or acute myeloid leukemia (AML) [3]. Since vascular events are the most frequent life-threatening complications of PV and ET, therapeutic strategies are aimed at reducing this risk. Treatment may also help control other symptoms associated with the disease [4]. No therapy has been shown to prevent evolution of PV or ET into myelofibrosis or AML. The discovery of the Janus kinase 2 (*JAK2*)/V617F mutation in most patients with PV and over half of those with ET (and PMF) [5,6] has opened new avenues of research and led to the development of targeted therapies, such as the JAK1/2 inhibitor ruxolitinib, for patients with MPN [7,8].

Epidemiology

PV and ET are typically diagnosed in the fifth to seventh decade of life [9]. Although these disorders are generally associated with a long clinical course, survival of patients with PV or ET may be shorter than that of the general population [10–13]. Estimating the incidence and prevalence of MPN is a challenge because most patients remain asymptomatic for long periods of time and do not seek medical attention [13]. The annual incidence rates of PV and ET are estimated at 0.01 to 2.61 and 0.21 to 2.53 per 100,000, respectively. PV occurs slightly more frequently in males, whereas ET has a predilection for females [14]. Given the long course and low mortality associated with these disorders, the prevalence rates of PV and ET are significantly higher than the respective incidence rates: up to 47 and 57 per 100,000, respectively [15–17].

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Molecular Pathogenesis

In 2005 researchers discovered a gain-of-function mutation of the *JAK2* gene in nearly all patients with PV and more than half of those with ET and PMF [5,6,18,19]. JAK2 is a non-receptor tyrosine kinase that plays a central role in normal hematopoiesis. Substitution of a valine for a phenylalanine at codon 617 (ie, V617F) leads to its constitutive activation and signaling through the JAK-STAT pathway [5,6,18,19]. More rarely (and exclusively in patients with PV), *JAK2* mutations involve exon 12 [20–22]. The vast majority of *JAK2*-negative ET patients harbor mutations in either the myeloproliferative leukemia (*MPL*) gene, which encodes the thrombopoietin receptor [23–25], or the calreticulin (*CALR*) gene [26,27], which encodes for a chaperone protein that plays a role in cellular proliferation, differentiation, and apoptosis [28]. Both the *MPL* and *CALR* mutations ultimately result in the constitutive activation of the JAK-STAT pathway. Thus, *JAK2*, *MPL*, and *CALR* alterations are collectively referred to as driver mutations. Moreover, because these mutations affect the same oncogenic pathway (ie, JAK-STAT), they are almost always mutually exclusive in a given patient. Patients with ET (or myelofibrosis) who are wild-type for *JAK2*, *MPL*, and *CALR* are referred to as having "triple-negative" disease. Many recurrent non-driver mutations are also found in patients with MPN. These are not exclusive of each other (ie, patients may have many at the same time) and involve for example ten-eleven translocation-2 (*TET2*), additional sex combs like 1 (*ASXL1*), enhancer of zeste homolog 2 (*EZH2*), isocitrate dehydrogenase 1 and isocitrate dehydrogenase 2 (*IDH1/2*), and DNA methyltransferase 3A (*DNMT3A*) genes, among others [29]. The biologic and prognostic significance of these non-driver alterations remain to be fully defined in ET and PV.

Diagnostic Criteria

Diagnostic criteria for PV and ET according to the World Health Organization (WHO) classification [30] are summarized in **Table 1**. Criteria for the diagnosis of prefibrotic myelofibrosis are included as well since this entity was formally recognized as separate from ET and part of the PMF spectrum in the 2016 WHO classification of myeloid tumors [30]. Clinically, both PV and ET generally remain asymptomatic for a long time. PV tends to be more symptomatic than ET and can present with debilitating constitutional symptoms (fatigue, night sweats, and weight loss), microvascular symptoms (headache, lightheadedness, acral paresthesias, erythromelalgia, atypical chest pain, and pruritus) [31], or macrovascular accidents (larger vein thrombosis, stroke, or myocardial ischemia) [32]. ET is often diagnosed incidentally, but patients can suffer from similar general symptoms and vascular complications. Causes of secondary absolute erythrocytosis (altitude, chronic hypoxemia, heavy smoking, cardiomyopathy, use of corticosteroids, erythropoietin, or other anabolic hormones, familial or congenital forms) or thrombocytosis (iron deficiency, acute blood loss, trauma or injury, acute coronary syndrome, systemic autoimmune disorders, chronic kidney failure, other malignancies, splenectomy) should be considered and appropriately excluded. Once the diagnosis is made, symptom assessment tools such as the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) [33] or the abbreviated version, the MPN-SAF Total Symptom Score (MPN-SAF TSS) [34], are generally used to assess patients' symptom burden and response to treatment in everyday practice.

Risk Stratification

Thrombohemorrhagic events, evolution into myelofibrosis, and leukemic transformation (LT) are the most serious complications in the course of PV or ET. Only thrombohemorrhagic events are, at least partially, preventable. Arterial or venous thrombotic complications are observed at rates of 1.8 to 10.9 per 100 patient-years in PV (arterial thrombosis being more common than venous) and 0.74 to 7.7 per 100 patient-years in ET, depending on the risk group [35] and the presence of other factors (see below).

The risk stratification of patients with PV is based on 2 factors: age ≥ 60 years and prior history of thrombosis. If either is present, the patient is assigned to the high-risk category, whereas if none is present the patient is considered at low risk [36]. In addition, high hematocrit [37] and high white blood cell (WBC) count [38], but not thrombocytosis, have been associated with the development of vascular complications. In one study, the risk of new arterial thrombosis was increased by the presence of leukoerythroblastosis, hypertension, and prior arterial thrombosis, while karyotypic abnormalities

Table 1. **World Health Organization Diagnostic Criteria for Polycythemia Vera, Essential Thrombocythemia, and Prefibrotic Myelofibrosis**

	Polycythemia Vera	Essential Thrombocythemia	Prefibrotic Myelofibrosis
Major criteria	1. Hemoglobin > 16.5 g/dL (men) or 16.0 g/dL (women) or hematocrit > 49% (men) or 48% (women), or increased red cell mass 2. Bone marrow hypercellular for age with trilineage growth including pleomorphic, mature megakaryocytes 3. Presence of the *JAK2*V617F or *JAK2* exon 12 mutation	1. Elevated platelet count (ie, ≥ 450 x 10^3/μL) 2. Bone marrow showing proliferation, mainly of the megakaryocyte lineage, without increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers 3. Lack of diagnostic criteria for any other myeloid neoplasm 4. Presence of clonal markers, such as the *JAK2*, *CALR,* or *MPL* mutations	1. Megakaryocytic proliferation and atypia, without reticulin fibrosis > grade 1, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and often decreased erythropoiesis 2. Does not meet WHO criteria for BCR-ABL1+ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms 3. Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker,* or absence of minor reactive bone marrow reticulin fibrosis†
Minor criteria	Subnormal serum erythropoietin level	Presence of a clonal marker or exclusion of reactive thrombocytosis	Presence confirmed in 2 consecutive determinations of: a. Anemia not attributed to comorbid conditions b. Leukocytosis ≥ 11,000/μL c. Palpable splenomegaly d. LDH increased above the upper limit of institutional reference range
Diagnosis	3 major criteria or 2 major criteria + minor criterion	4 major criteria or the first 3 major criteria + minor criterion	3 major criteria and at least 1 minor criterion

Adapted from Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391–405.

CML, chronic myeloid leukemia; ET, essential thrombocythemia; LDH, lactate dehydrogenase; PV, polycythemia vera.

*Either a driver mutation or another recurrent mutation (eg, *ASXL1*, *EXH2*, *TET2*, I*DH1/2*, *SRSF2*, *SF3B1*).

†Minor (grade 1) reticulin fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

and prior venous thrombosis were predictors of new venous thrombosis [39]. Another emerging risk factor for thrombosis in patients with PV is high *JAK2* allele burden (ie, the normal-to-mutated gene product ratio), although the evidence supporting this conclusion is equivocal [40].

Traditionally, in ET patients, the thrombotic risk was assessed using the same 2 factors (age ≥ 60 years and prior history of thrombosis), separating patients into low- and high-risk groups. However, the prognostication of ET patients has been refined recently with the identification of new relevant factors. In particular, the impact of *JAK2* mutations on thrombotic risk has been thoroughly studied. Clinically, the presence of *JAK2*V617F is associated with older age, higher hemoglobin and hematocrit, lower platelet counts, more frequent need for cytoreductive treatment, and greater tendency to evolve into PV (a rare event) [41,42]. Many [41,43–46], but not all [47–51], studies suggested a correlation between *JAK2* mutation and risk of both arterial and venous thrombosis. Although infrequent, a *JAK2*V617F homozygous state (ie, the mutation is

Table 2. **Revised International Prognostic Score of Thrombosis for Essential Thrombocythemia (IPSET-thrombosis)**

Risk factors	Age > 60 yr
	Prior thrombosis
	*JAK2*V617F mutation
Risk groups	Very low-risk: no prior thrombosis, age ≤ 60 yr, wild-type *JAK2*
	Low-risk: no prior thrombosis, age ≤ 60 yr, *JAK2*-mutated
	Intermediate-risk: no prior thrombosis, age > 60 yr, wild-type *JAK2*
	High-risk: prior thrombosis or age > 60 yr and *JAK2*-mutated

Adapted from Barbui T, Vannucchi AM, Buxhofer-Ausch V, et al. Practice-relevant revision of IPSET-thrombosis based on 1019 patients with WHO-defined essential thrombocythemia. Blood Cancer J 2015;5:e369.

present in both alleles) might confer an even higher thrombotic risk [52]. Moreover, the impact of the *JAK2* mutation on vascular events persists over time [53], particularly in patients with high or unstable mutation burden [54]. Based on *JAK2*V617F's influence on the thrombotic risk of ET patients, a new prognostic score was proposed, the International Prognostic Score for ET (IPSET)-thrombosis (**Table 2**). The revised version of this model is currently endorsed by the National Comprehensive Cancer Network and divides patients into 4 risk groups: high, intermediate, low, and very low. Treatment recommendations vary according to the risk group (as described below) [55].

Other thrombotic risk factors have been identified, but deemed not significant enough to be included in the model. Cardiovascular risk factors (hypercholesterolemia, hypertension, smoking, diabetes mellitus) can increase the risk of vascular events [56–59], as can splenomegaly [60] and baseline or persistent leukocytosis [61–63]. Thrombocytosis has been correlated with thrombotic risk in some studies [64–68], whereas others did not support this conclusion and/or suggested a lower rate of thrombosis and, in some cases, increased risk of bleeding in ET patients with platelet counts greater than 1000 × 10^3/μL (due to acquired von Willebrand syndrome) [51,61,63,68,69].

CALR mutations tend to occur in younger males with lower hemoglobin and WBC count, higher platelet count, and greater marrow megakaryocytic predominance, as compared to *JAK2* mutations [26,27,70–72]. The associated incidence of thrombosis was less than 10% at 15 years in patients with *CALR* mutations, lower than the incidence reported for ET patients with *JAK2*V617F mutations [73]. The presence of the mutation per se does not appear to affect the thrombotic risk [74–76]. Information on the thrombotic risk associated with *MPL* mutations or a triple-negative state is scarce. In both instances, however, the risk appears to be lower than with the *JAK2* mutation [73,77–79].

Venous thromboembolism (VTE) in patients with PV or ET may occur at unusual sites, such as the splanchnic or cerebral venous systems [80]. Risk factors for unusual VTE include younger age [81], female gender (especially with concomitant use of oral contraceptive pills) [82], and splenomegaly/splenectomy [83]. *JAK2* mutation has also been associated with thrombosis at unusual sites. However, the prevalence of MPN or *JAK2*V617F in patients presenting with splanchnic VTE has varied [80]. In addition, MPN may be occult (ie, no clinical or laboratory abnormalities) in around 15% of patients [84]. Screening for *JAK2*V617F and underlying MPN is recommended in patients presenting with isolated unexplained splanchnic VTE. Treatment entails long-term anticoagulation therapy. *JAK2*V617F screening in patients with nonsplanchnic VTE is not recommended, as its prevalence in this group is low (< 3%) [85,86].

Risk-Adapted Therapy

Low-Risk PV

All patients with PV should receive counseling to mitigate cardiovascular risk factors, including smoking cessation, lifestyle modifications, and lipid-lowering therapy, as indicated. Furthermore, all PV patients should receive acetyl-

salicylic acid (ASA) to decrease their risk for thrombosis and control vasomotor symptoms [55,87]. Aspirin 81 to 100 mg daily is the preferred regimen because it provides adequate antithrombotic effect without the associated bleeding risk of higher-dose aspirin [88]. Low-risk PV patients should also receive periodic phlebotomies to reduce and maintain their hematocrit below 45%. This recommendation is based on the results of the Cytoreductive Therapy in Polycythemia Vera (CYTO PV) randomized controlled trial. In that study, patients receiving more intense therapy to maintain the hematocrit below 45% had a lower incidence of cardiovascular-related deaths or major thrombotic events than those with hematocrit goals of 45% to 50% (2.7% versus 9.8%) [89]. Cytoreduction is an option for low-risk patients who do not tolerate phlebotomy or require frequent phlebotomy, or who have disease-related bleeding, severe symptoms, symptomatic splenomegaly, or progressive leukocytosis [38].

High-Risk PV

Patients older than 60 years and/or with a history of thrombosis should be considered for cytoreductive therapy in addition to the above measures. Frontline cytoreductive therapies include hydroxyurea or interferon (IFN)-alfa [87]. Hydroxyurea is a potent ribonucleotide reductase inhibitor that interferes with DNA repair and is the treatment of choice for most high-risk patients with PV [90]. In a small trial, hydroxyurea reduced the risk of thrombosis compared with historical controls treated with phlebotomy alone [91]. Hydroxyurea is generally well tolerated; common side effects include cytopenias, nail changes, and mucosal and/or skin ulcers. Although never formally proven to be leukemogenic, this agent should be used with caution in younger patients [87]. Indeed, in the original study, the rates of transformation were 5.9% and 1.5% for patients receiving hydroxyurea and phlebotomy alone [92], respectively, although an independent role for hydroxyurea in LT was not supported in the much larger European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) study [93]. Approximately 70% of patients will have a sustained response to hydroxyurea [94], while the remaining patients become resistant to or intolerant of the drug. Resistant individuals have a higher risk of progression to acute leukemia and death [95].

IFN-alfa is a pleiotropic antitumor agent that has found application in many types of malignancies [96] and is sometimes employed as treatment for patients with newly diagnosed high-risk PV. Early studies showed responses in up to 100% of cases [97,98], albeit at the expense of a high discontinuation rate due to adverse events, such as flu-like symptoms, fatigue, and neuropsychiatric manifestations [99]. A newer formulation of the drug obtained by adding a polyethylene glycol (PEG) moiety to the native IFN-alfa molecule (PEG-IFN alfa) was shown to have a longer half-life, greater stability, less immunogenicity, and, potentially, better tolerability [100]. Pilot phase 2 trials of PEG-IFN-alfa-2a demonstrated its remarkable activity, with symptomatic and hematologic responses seen in most patients (which, in some cases, persisted beyond discontinuation), and reasonable tolerability, with long-term discontinuation rates of 20% to 30% [101–103]. In some patients, *JAK2*V617F became undetectable over time [104]. Results of 2 ongoing trials, MDP-RC111 (single-arm study, PEG-IFN-alfa-2a in high-risk PV or ET [NCT01259817]) and MPD-RC112 (randomized controlled trial, PEG-IFN-alfa-2a versus hydroxyurea in the same population [NCT01258856]), will shed light on the role of PEG-IFN-alfa in the management of patients with high-risk PV or ET. In two phase 2 studies of PEG-IFN-alfa-2b, complete responses were seen in 70% to 100% of patients and discontinuation occurred in around a third of cases [105,106]. A new, longer-acting formulation of PEG-IFN-alfa-2a (peg-proline INF-alfa-2b, AOP2014) is also undergoing clinical development [107,108].

The approach to treatment of PV based on thrombotic risk level is illustrated in **Figure 1**.

Very Low- and Low-Risk ET

Individuals with ET should undergo rigorous cardiovascular risk management and generally receive ASA to decrease their thrombotic risk and improve symptom control. Antiplatelet therapy may not be warranted in patients with documented acquired von Willebrand syndrome, with or without extreme thrombocytosis, or in those in the very low-risk category according to the IPSET-thrombosis model [55,87]. The risk/benefit ratio of antiplatelet agents in patients with ET at different thrombotic risk levels was assessed in poor-quality studies and thus remains highly

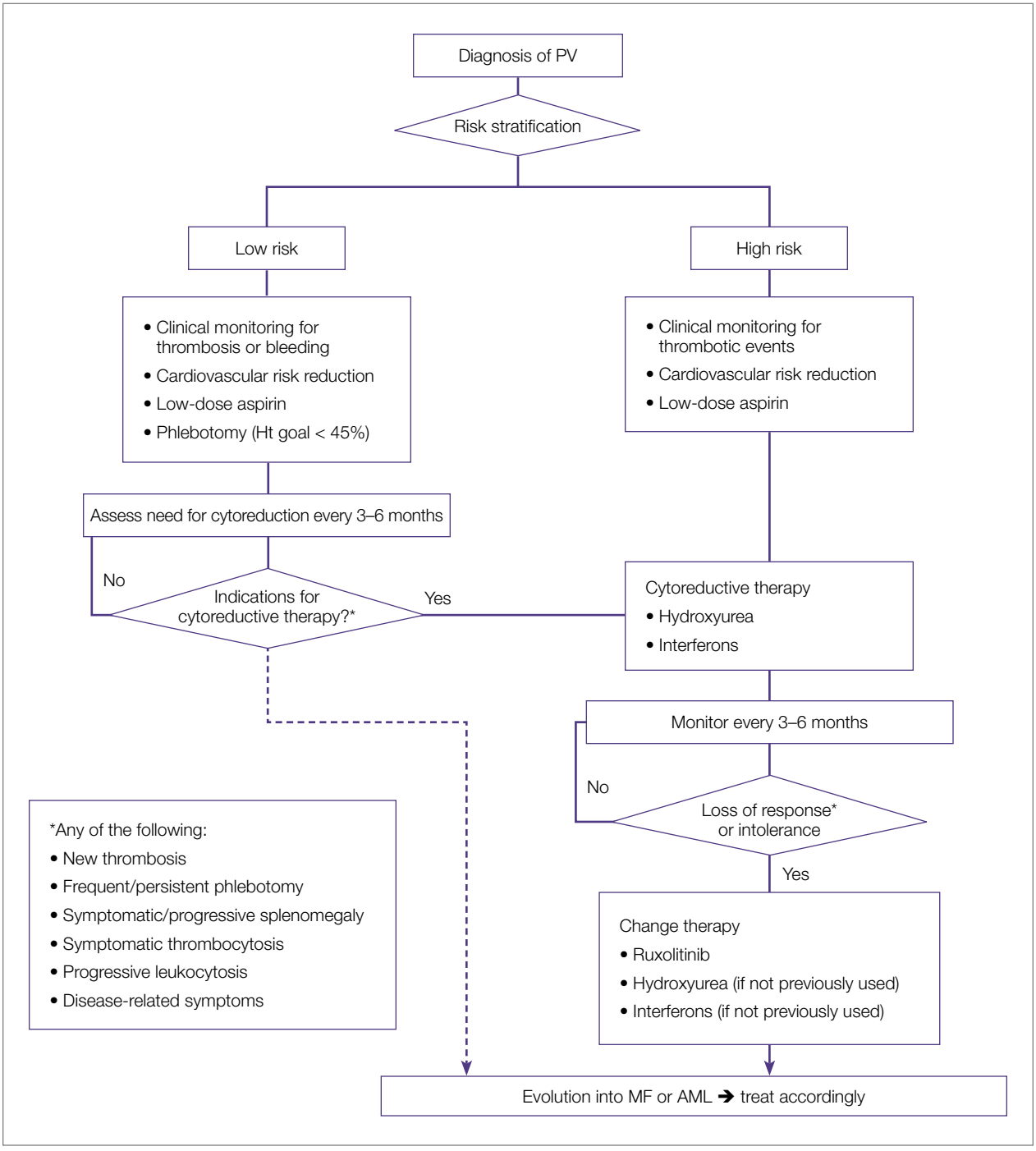

Figure 1. Polycythemia vera (PV) treatment algorithm. AML, acute myeloid leukemia; MF, myelofibrosis.

uncertain. Platelet-lowering agents are sometimes recommended in patients with low-risk disease who have platelet counts ≥ 1500 × 10^3/μL, due to the potential risk of acquired von Willebrand syndrome and a risk of bleeding (this would require stopping ASA) [109]. Cytoreduction may also be used in low-risk patients with progressive symptoms despite ASA, symptomatic or progressive splenomegaly, and progressive leukocytosis.

Intermediate-Risk ET

This category includes patients older than 60 years, but without thrombosis or *JAK2* mutations. These individuals

would have been considered high risk (and thus candidates for cytoreductive therapy) according to the traditional risk stratification. Guidelines currently recommend ASA as the sole therapy for these patients, while reserving cytoreduction for those who experience thrombosis (ie, become high-risk) or have uncontrolled vasomotor or general symptoms, symptomatic splenomegaly, symptomatic thrombocytosis, or progressive leukocytosis.

High-Risk ET

For patients with ET in need of cytoreductive therapy (ie, those with prior thrombosis or older than 60 years with a *JAK2*V617F mutation), first-line options include hydroxyurea, IFN, and anagrelide. Hydroxyurea remains the treatment of choice in most patients [110]. In a seminal study, 114 patients with ET were randomly assigned to either observation or hydroxyurea treatment with the goal of maintaining the platelet count below 600×10^3/μL. At a median follow-up of 27 months, patients in the hydroxyurea group had a lower thrombosis rate (3.6% versus 24%, $P = 0.003$) and longer thrombosis-free survival, regardless of the use of antiplatelet drugs [64].

Anagrelide, a selective inhibitor of megakaryocytic differentiation and proliferation, was compared with hydroxyurea in patients with ET in 2 randomized trials. In the first (n = 809), the group receiving anagrelide had a higher risk of arterial thrombosis, major bleeding, and fibrotic evolution, but lower incidence of venous thrombosis. Hydroxyurea was better tolerated, mainly due to anagrelide-related cardiovascular adverse events [111]. As a result of this study, hydroxyurea is often preferred to anagrelide as frontline therapy for patients with newly diagnosed high-risk ET. In the second, more recent study (n = 259), however, the 2 agents proved equivalent in terms of major or minor arterial or venous thrombosis, as well as discontinuation rate [112]. The discrepancy between the 2 trials may be partly explained by the different ET diagnostic criteria used, with the latter only enrolling patients with WHO-defined true ET and the former utilizing Polycythemia Vera Study Group-ET diagnostic criteria that included patients with increases in other blood counts or varying degrees of marrow fibrosis.

Interferons were studied in ET in parallel with PV. PEG-IFN-alfa-2a proved effective in patients with ET, with responses observed in 80% of patients [103]. PEG-IFN-alfa-2b produced similar results, with responses in 70% to 90% of patients in small studies and discontinuation observed in 20% to 38% of cases [105,106,113]. Because the very long-term leukemogenic potential of hydroxyurea has remained somewhat uncertain, anagrelide or IFN might be preferable choices in younger patients.

The approach to treatment of ET based on thrombotic risk level is illustrated in **Figure 2**.

Assessing Response to Therapy

For both patients with PV and ET the endpoint of treatment set forth for clinical trials has been the achievement of a clinicohematologic response. However, studies have failed to show a correlation between response and reduction of the thrombohemorrhagic risk [114]. Therefore, proposed clinical trial response criteria were revised to include absence of hemorrhagic or thrombotic events as part of the definition of response (**Table 3**) [94].

Approach to Patients Refractory to or Intolerant of First-line Therapy

According to the European LeukemiaNet recommendations, an inadequate response to hydroxyurea in patients with PV (or myelofibrosis) is defined as a need for phlebotomy to maintain the hematocrit below < 45%, the platelet count > 400×10^3/μL, and a WBC count > 10,000/μL, or failure to reduce splenomegaly > 10 cm by > 50% at a dose of ≥ 2 g/day or maximum tolerated dose. Historically, treatment options for patients with PV or ET who failed first-line therapy (most commonly hydroxyurea) have included alkylating agents, such as busulfan, chlorambucil, pipobroman, and phosphorus (P)-32. However, the use of these drugs is limited by the associated risk of LT [93,115,116]. IFN (or anagrelide for ET) is often considered in patients previously treated with hydroxyurea, and vice versa.

Ruxolitinib is a JAK1 and JAK2 inhibitor currently approved for the treatment of PV patients refractory to or intolerant of hydroxyurea [7]. Following promising results of a phase 2 trial [117], ruxolitinib 10 mg twice daily was compared with best available therapy in the pivotal RESPONSE trial (n = 222). Ruxolitinib proved superior in achieving hematocrit control, reduction of spleen volume, and improvement of symptoms. Grade 3-4 hematologic

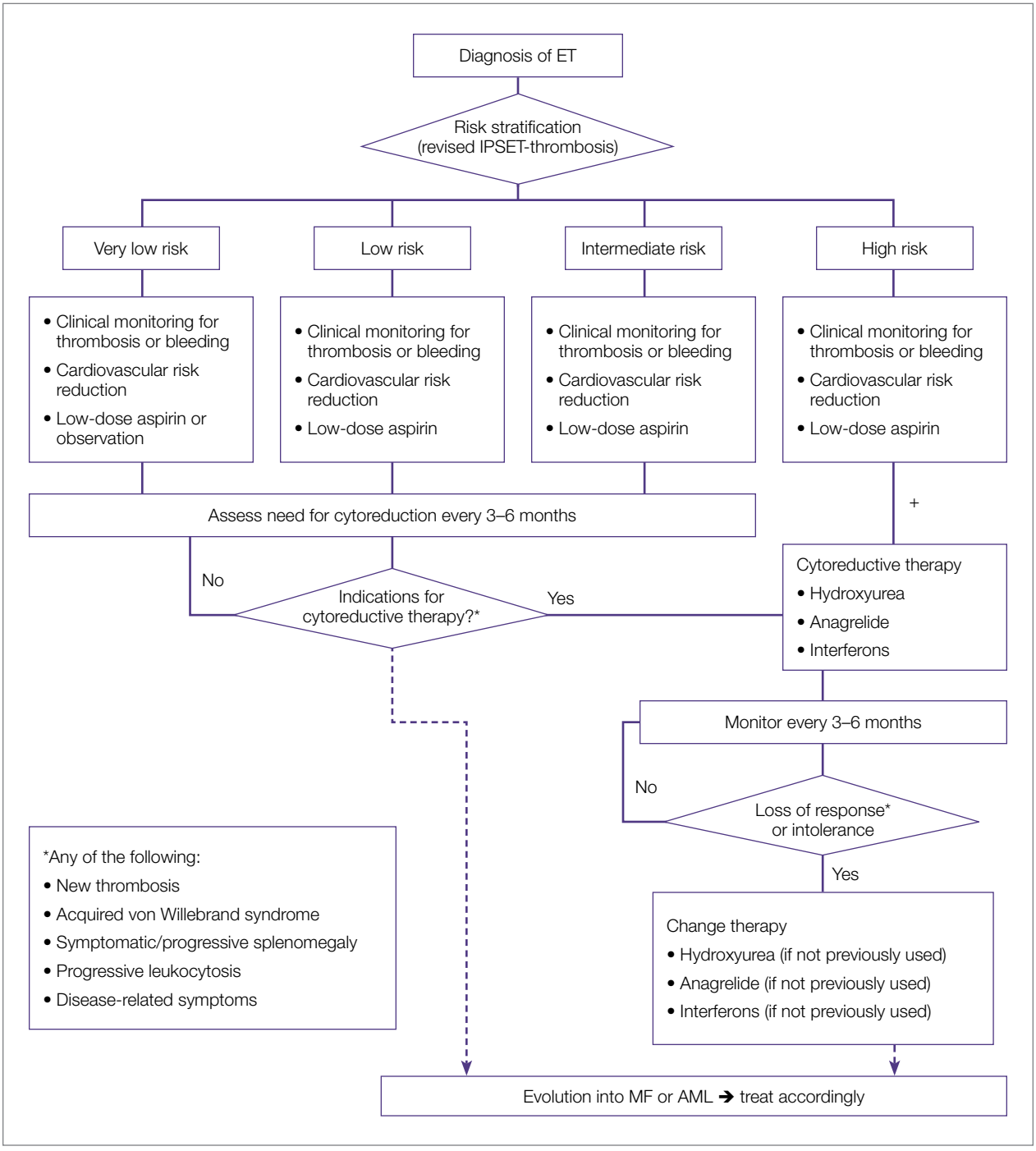

Figure 2. Essential thrombocythemia (ET) treatment algorithm. AML, acute myeloid leukemia; MF, myelofibrosis.

toxicity was infrequent and similar in the 2 arms [118]. In addition, longer follow-up of that study suggested a lower rate of thrombotic events in patients receiving ruxolitinib (1.8 versus 8.2 per 100 patient-years) [119]. In a similarly designed randomized phase 3 study in PV patients without splenomegaly (RESPONSE-2), more patients in the ruxolitinib arm had hematocrit reduction without an increase in toxicity. Based on the results of these studies, ruxolitinib can be considered a standard of care for second-line therapy in this post-hydroxyurea patient population [120]. Ruxolitinib is also being tested in patients with high-risk ET who have become resistant

Table 3. **ELN and IWG-MNRT Treatment Response Criteria (2013)**

Type of Response	Essential Thrombocythemia	Polycythemia Vera
Complete remission	Resolution of disease-related signs, including palpable hepatosplenomegaly for ≥ 12 wk, ≥ 10-point decrease in the MPN-SAF TSS, plus Durable peripheral blood count remission defined as: platelet count ≤ 400 x 10^3/μL, WBC count < 10,000/μL, absence of leukoerythroblastosis, plus No signs of progressive disease, and absence of any hemorrhagic or thrombotic events plus Bone marrow histological remission defined as disappearance of megakaryocyte hyperplasia and absence of > grade 1 reticulin fibrosis	Resolution of disease-related signs, including palpable hepatosplenomegaly for ≥ 12 wk, ≥ 10-point decrease in the MPN-SAF TSS, plus Durable peripheral blood count remission defined as: hematocrit < 45%, platelet count ≤ 400 x 10^3/μL, WBC count < 10,000/μL, absence of leukoerythroblastosis, plus No signs of progressive disease, and absence of any hemorrhagic or thrombotic events plus Bone marrow histological remission defined as the presence of age-adjusted normocellularity and disappearance of trilineage hyperplasia, and absence of > grade 1 reticulin fibrosis
Partial remission	Resolution of disease-related signs, including palpable hepatosplenomegaly for ≥ 12 wk, ≥ 10-point decrease in the MPN-SAF TSS, plus Durable peripheral blood count remission defined as: platelet count ≤ 400 x 10^3/μL, WBC count < 10,000/μL, absence of leukoerythroblastosis, plus No signs of progressive disease, and absence of any hemorrhagic or thrombotic events plus Without bone marrow histological remission, defined as the persistence of megakaryocyte hyperplasia	Resolution of disease-related signs, including palpable hepatosplenomegaly for ≥ 12 wk, ≥ 10-point decrease in the MPN-SAF TSS, plus Durable peripheral blood count remission defined as: hematocrit < 45%, platelet count ≤ 400 x 10^3/μL, WBC count < 10,000/μL , absence of leukoerythroblastosis, plus No signs of progressive disease, and absence of any hemorrhagic or thrombotic events plus Without bone marrow histological remission, defined as persistence of trilineage hyperplasia
No response	Any response that does not fit partial remission	Any response that does not fit partial remission
Progressive disease	Transformation into PV, post-ET myelofibrosis,* or MDS/acute leukemia [30]	Transformation into post-ET myelofibrosis,* MDS, or acute leukemia [30]

Adapted from et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood 2013;121:4778–81.

ELN, European LeukemiaNet; ET, essential thrombocythemia; IWG-MNRT, International Working Group–Myeloproliferative Neoplasms Research and Treatment; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; PV, polycythemia vera.

*Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: consensus statement from the International Working Group for Myelofibrosis Research and Treatment. Leukemia 2008;22:437–8.

to, or were intolerant of hydroxyurea, but currently has no approved indication in this setting [121,122]. Common side effects of ruxolitinib include cytopenias (especially anemia), increased risk of infections, hyperlipidemia, and increased risk of non-melanoma skin cancer.

Novel agents that have been studied in patients with PV and ET are histone deacetylase inhibitors, murine double minute 2 (MDM2, or HDM2 for their human counterpart) inhibitors (which restore the function of p53), Bcl-2 homology domain 3 mimetics such as navitoclax and venetoclax, and, for patients with ET, the telomerase inhibitor imetelstat [123].

Disease Evolution

Post-PV/Post-ET Myelofibrosis

Diagnostic criteria for post-PV and post-ET myelofibrosis are outlined in **Table 4**. Fibrotic transformation represents a natural evolution of the clinical course of PV or ET. It occurs in up to 15% and 9% of patients with PV and ET, respectively, in western countries [124]. The true percentage of ET patients who develop myelofibrosis is confounded by the inclusion of prefibrotic myelofibrosis cases in earlier series. The survival of patients who develop myelofibrosis is shortened compared to those who do not. In patients with PV, risk factors for

Table 4. **Diagnostic Criteria for Post-Polycythemia Vera and Post-Essential Thrombocythemia Myelofibrosis**

	Post-PV MF	Post-ET MF
Required criteria	Documentation of preexisting WHO-defined PV	Documentation of preexisting WHO-defined ET
	Bone marrow fibrosis grade 2 or 3 (on the European 0–3 scale) or grade 3 or 4 (on the standard 0–4 scale)	Bone marrow fibrosis grade 2 or 3 (on the European 0–3 scale) or grade 3 or 4 (on the standard 0–4 scale)
Additional criteria (at least 2)	Anemia or sustained loss of requirement for phlebotomy (without cytoreductive therapy) or cytoreductive treatment for erythrocytosis	Anemia and a 2 g/dL loss in hemoglobin from baseline
	Peripheral blood leukoerythroblastosis	Peripheral blood leukoerythroblastosis
	Splenomegaly ≥ 5 cm below the costal margin or new palpable splenomegaly	Splenomegaly ≥ 5 cm below the costal margin or new palpable splenomegaly
	At least 1 of: ≥ 10% weight loss, night sweats, unexplained fever > 37.5°C	At least 1 of: ≥ 10% weight loss, night sweats, unexplained fever > 37.5°C

Adapted from Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. Leukemia 2008;22:437–8.

ET, essential thrombocythemia; MF, myelofibrosis; PV, polycythemia vera; WHO, World Health Organization.

myelofibrosis evolution include advanced age, leukocytosis, *JAK2*V617F homozygosity or higher allele burden, and hydroxyurea therapy. Once post-PV myelofibrosis has occurred, hemoglobin < 10 g/dL, platelet count < 100 × 10^3/μL, and WBC count > 30,000/μL are associated with worse outcomes [125]. In patients with ET, risk factors for myelofibrosis transformation include age, anemia, bone marrow hypercellularity and increased reticulin, increased lactate dehydrogenase, leukocytosis, and male gender. The management of post-PV/post-ET myelofibrosis recapitulates that of PMF.

Leukemic Transformation

The presence of more than 20% blasts in peripheral blood or bone marrow in a patient with MPN defines LT. This occurs in up to 5% to 10% of patients and may or may not be preceded by a myelofibrosis phase [126]. In cases of extramedullary transformation, a lower percentage of blasts can be seen in the bone marrow compared to the peripheral blood. The pathogenesis of LT has remained elusive, but it is believed to be associated with genetic instability, which facilitates the acquisition of additional mutations, including those of *TET2*, *ASXL1*, *EZH2 DNMT3*, *IDH1/2*, and *TP53* [127].

Clinical risk factors for LT include advanced age, karyotypic abnormalities, prior therapy with alkylating agents or P-32, splenectomy, increased peripheral blood or bone marrow blasts, leukocytosis, anemia, thrombocytopenia, and cytogenetic abnormalities. Hydroxyurea, IFN, and ruxolitinib have not been shown to have leukemogenic potential thus far. Prognosis of LT is uniformly poor and patient survival rarely exceeds 6 months.

There is no standard of care for MPN LT. Treatment options range from low-intensity regimens to more aggressive AML-type induction chemotherapy. No strategy appears clearly superior to others [128]. Hematopoietic stem cell transplantation is the only therapy that provides clinically meaningful benefit to patients [129], but it is applicable only to a minority of patients with chemosensitive disease and good performance status [130]. Notable experimental approaches to MPN LT include hypomethylating agents, such as decitabine [131] or azacytidine [132], with or without ruxolitinib [133–135].

Conclusion

PV and ET are rare, chronic myeloid disorders. Patients typically experience a long clinical course and enjoy near-normal quality of life if properly managed. The 2 most important life-limiting complications of PV and ET are thrombohemorrhagic events and myelofibrosis/AML transformation. Vascular events are at least in part preventable with counseling on risk factors, phlebotomy (for

patients with PV), antiplatelet therapy, and cytoreduction with hydroxyurea, IFNs, or anagrelide (for patients with ET). In addition, ruxolitinib was recently approved for PV patients after hydroxyurea failure. PV/ET transformation in myelofibrosis or AML is part of the natural history of the disease and no therapy has been shown to prevent it. Treatment follows recommendations set forth for PMF and AML, but results are generally poorer and novel strategies are needed to improve outcomes.

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