Received: 24 September 2018 | Accepted: 26 September 2018
DOI: 10.1002/ajh.25303

WILEY AJH

ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES

Polycythemia vera and essential thrombocythemia: 2019 update on diagnosis, risk-stratification and management

Ayalew Tefferi[1] | Tiziano Barbui[2]

[1]Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, Minnesota

[2]Research Foundation, Papa Giovanni XXIII Hospital, Bergamo, Italy

Correspondence
Ayalew Tefferi, Division of Hematology, Department of Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905.
Email: tefferi.ayalew@mayo.edu

Abstract

Disease Overview: Polycythemia vera (PV) and essential thrombocythemia (ET) are myeloproliferative neoplasms respectively characterized by erythrocytosis and thrombocytosis; other disease features include leukocytosis, splenomegaly, thrombosis, bleeding, microcirculatory symptoms, pruritus, and risk of leukemic or fibrotic transformation.

Diagnosis: Bone marrow morphology remains the cornerstone of diagnosis. In addition, the presence of *JAK2* mutation is expected in PV while approximately 90% of patients with ET express mutually exclusive *JAK2*, *CALR*, or **m**yeloproliferative leukemia mutations. In ET, it is most important to exclude the possibility of prefibrotic myelofibrosis.

Survival: Median survivals are 14 years for PV and 20 years for ET; the corresponding values for younger patients are 24 and 33 years. Certain mutations (mostly spliceosome) and abnormal karyotype might compromise survival in PV and ET. Life-expectancy in ET is inferior to the control population. Driver mutations have not been shown to affect survival in ET. Risk of thrombosis is higher in *JAK2*-mutated ET. Leukemic transformation rates at 10 years are estimated at <1% for ET and 3% for PV.

Thrombosis Risk: In PV, 2 risk categories are considered: high (age > 60 years or thrombosis history present) and low (absence of both risk factors); in ET, 4 risk categories are considered: very low (age ≤ 60 years, no thrombosis history, *JAK2* wild-type), low (same as very low but *JAK2* mutation present), intermediate (age > 60 years, no thrombosis history, *JAK2* wild-type) and high (thrombosis history present *or* age > 60 years with *JAK2* mutation).

Risk-Adapted Therapy: The main goal of therapy in both PV and ET is to prevent thrombohemorrhagic complications. All patients with PV require phlebotomy to keep hematocrit below 45% and once- or twice-daily aspirin (81 mg), in the absence of contraindications. Very low-risk ET might not require therapy while aspirin therapy is advised for low-risk disease. Cytoreductive therapy is recommended for high-risk ET and PV but it is not mandatory for intermediate-risk ET. First-line drug of choice for cytoreductive therapy, in both ET and PV, is hydroxyurea and second-line drugs of choice are interferon-α and busulfan. We do not recommend treatment with ruxolutinib in PV, unless in the presence of severe and protracted pruritus or marked splenomegaly that is not responding to the aforementioned drugs.

1 | DISEASE OVERVIEW

The World Health Organization (WHO) classification system for hematopoietic tumors was recently revised and the 2016 document recognizes myeloproliferative neoplasms (MPNs) as one of several myeloid malignancies (Table 1).[1,2] In routine clinical practice, MPN refers to polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), the latter including prefibrotic PMF[2]; these disorders are characterized by stem cell-derived clonal myeloproliferation with mutually exclusive *JAK2*, *CALR*, and myeloproliferative leukemia *(MPL)* mutations.[3]

Almost all patients with PV harbor a *JAK2* (Janus kinase 2; 9p24) mutation; approximately 96% and 3% displaying somatic activating mutations in exon 14 (*JAK2*V617F) and exon 12 of *JAK2*, respectively.[4,5] *JAK2*V617F also occurs in ET and PMF, with respective

mutational frequencies of 55% and 65%. *JAK2* exon 12 mutations are rare in ET or PMF. Calreticulin (*CALR*: 19p13.2) mutations are rare in PV but occur in 25-35% of patients with PMF and 15%-24% with ET.[6–8] CALR is a multi-functional Ca^{2+} binding protein chaperone mostly localized in the endoplasmic reticulum. *MPL* (virus oncogene; 1p34) mutations occur in approximately 4% of ET patients, 8% of PMF patients, and rarely in PV. *MPL* mutations cluster in exon 10, the most frequent being *MPL*W515L/K.[9–11] *MPL*S505 N is both a germline (hereditary thrombocythemia)[12,13] and somatic (ET) mutation.[11] Hereditary thrombocytosis has also been reported with germline *JAK2* mutation (*JAK2*V617I) and associated with vascular events but not fibrotic/leukemic progression.[14] Both *JAK2*V617F and *MPL* mutations also occur infrequently in other myeloid malignancies.

*JAK2*V617F presence or increased allele burden does not appear to affect survival or leukemic transformation in PV or ET. In ET, the presence of *JAK2*V617F has been associated with an increased risk of thrombosis and a lower risk of postET MF.[15] In PV, a higher *JAK2*V617F mutant allele burden has been associated with pruritus and fibrotic transformation.[16] In general, *JAK2*V617F clusters with older age, higher hemoglobin level, leukocytosis, and lower platelet count.[5] *JAK2* exon 12 mutation-positive patients usually present with predominantly erythroid myelopoiesis, subnormal serum erythropoietin level and younger age at diagnosis, but were prognostically similar to *JAK2*V617F.[17] In ET, mutant *CALR* (vs *JAK2*) was associated with younger age, male sex, higher platelet count, lower hemoglobin level, lower leukocyte count, and lower incidence of thrombotic events; type 2 vs type 1 *CALR* mutations were associated with higher platelet count.[18] In PMF, *CALR*-mutated patients were younger and presented with higher platelet count, better risk profile and lower frequencies of anemia, leukocytosis, and spliceosome mutations.*MPL* mutations have been inconsistently associated with older age, female gender, lower hemoglobin level and higher platelet count,[11,19,20] while no associations with survival or leukemic transformation have been reported.[11,19]

2 | DIAGNOSIS

Diagnosis of PV and ET is currently according to the 2016 WHO criteria and based on a composite assessment of clinical and laboratory features (Table 2).[1] Figure 1 provides a practical diagnostic algorithm that begins with peripheral blood mutation screening for *JAK2*V617F. The laboratory detection of *JAK2*V617F is highly sensitive (97% sensitivity) and virtually 100% specific for distinguishing PV from other causes of increased hematocrit, the possibility of false positive or false negative mutation test result is effectively addressed by the concomitant measurement of serum erythropoietin (Epo) level, which is expected to be subnormal in more than 85% of patients with PV.[21] A subnormal serum Epo level in the absence of *JAK2*V617F mandates additional mutational analysis for *JAK2* exon 12 mutation in order to capture some of the approximately 3% of PV patients who are *JAK2*V617F-negative.[4] Figure 2 provides a diagnostic approach for erythrocytosis caused by conditions other than PV, including acquired and congenital polycythemia.

When evaluating thrombocytosis, the detection of *JAK2*V617F, *CALR*, or *MPL* mutations confirms the presence of an underlying MPN but their absence does not rule out the possibility since up to 20% of patients with ET might be triple-negative (ie, negative for all 3 mutations) (Figure 1). It is also important to note that other *JAK2*/*CALR*/*MPL*-mutated MPN (or myelodysplastic syndrome [MDS]/MPN) can mimic ET in their presentation; these include prefibrotic PMF and MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN).[22] Therefore, bone marrow examination is often necessary to make an accurate morphologic diagnosis of ET and distinguish it from other myeloid neoplasms, especially from prefibrotic PMF; megakaryocytes in ET are large and mature-appearing and form loose clusters whereas those in prefibrotic PMF display abnormal maturation with hyperchromatic and irregularly folded nuclei and form tight clusters. A large international study confirmed the prognostic relevance of distinguishing ET from prefibrotic PMF. In the absence of *JAK2*/*CALR*/*MPL* mutations, the possibility of CML is readily addressed by *BCR-ABL1* mutation screening. The diagnosis of postPV or -ET MF should adhere to criteria published by the International Working Group for MPN Research and Treatment (IWG-MRT) (Table 3).[23]

3 | RISK FACTORS FOR SURVIVAL AND LEUKEMIC OR FIBROTIC TRANSFORMATION

Among 826 Mayo Clinic patients with ET, PV or PMF, the respective median survivals were approximately 20 years for ET, 14 years for PV and 6 years for PMF;[24] the corresponding values for patients younger than age 60 years were 33, 24, and 15 years. The particular study also showed that life-expectancy in ET was inferior to that of the sex- and age-matched US population and that survival in ET was superior to that of PV, regardless of mutational status.[24] *JAK2*/*CALR*/*MPL* mutational status does not affect survival in ET. Risk factors for survival in ET and PV include advanced age, leukocytosis and thrombosis history.[25,26] Leukemic transformation rate at 20 years is estimated at <10% for PV and 5% for ET; fibrotic transformation rates are slightly higher.

In a study of over 1500 patients with PV, risk factors for survival included advanced age, leukocytosis, venous thrombosis and abnormal

TABLE 1 2016 WHO classification of myeloid malignancies (*see text for references*)

AML and related neoplasms	Chronic myeloid neoplasms
AML with recurrent genetic abnormalities AML with myelodysplasia-related changes Therapy-related myeloid neoplasms AML, not otherwise specified Myeloid sarcoma Down associated myeloid proliferations	MPNs 1. *Chronic myeloid leukemia, BCR-ABL1+* 2. *Chronic neutrophilic leukemia, often CSF3R mutated* 3. *Chronic eosinophilic leukemia, not otherwise specified* 4. *MPN, unclassifiable* 5. *PV* 6. *ET* 7. *PMF*
	Mastocytosis
	Myeloid/lymphoid neoplasms with eosinophilia and *PDGFRA*, *PDGFRB*, *FGFR1*, or *PCM1-JAK2* mutations
	MDS/MPNs
	MDS
	Myeloid neoplasms with germ line predisposition

TABLE 2 2016 revised WHO diagnostic criteria for PV and ET (*see text for references*)

PV (diagnosis requires all 3 major criteria or the first 2 major and the minor criterion)	ET (diagnosis requires all 4 major criteria or the first 3 major and the minor criterion)
Major criteria: 1. Hemoglobin >16.5 g/dL in men or > 16 g/dL in women; **or** hematocrit >49% in men or > 48% in women **or** increased red blood cell mass 2. Bone marrow tri-lineage proliferation with Pleomorphic mature megakaryocytes[a] 3. Presence of *JAK2* mutation	*Major criteria:* 1. Platelets ≥450 × 10^9/L 2. Bone marrow megakaryocyte proliferation and loose clusters 3. Not meeting WHO criteria for other myeloid neoplasms 4. *JAK2*/*CALR*/*MPL* mutated
Minor criterion: *Subnormal serum erythropoietin level*	*Minor criterion:* *Other clonal marker present or no evidence of reactive thrombocytosis*

[a] Bone marrow biopsy might not be needed in the presence of hemoglobin >18.5 g/dL (hematocrit 55.5%) in men or >16.5 g/dL (hematocrit 49.5%) in women.

karyotype.[25] Risk factors for leukemic transformation in PV include advanced age, leukocytosis, and abnormal karyotype.[25] In addition, *JAK2*V617F allele burden of >50% has been associated with fibrotic transformation.[16] In a study of over 1100 patients with ET or prefibrotic PMF, risk factors for overall survival were prefibrotic PMF morphology, advanced age, thrombosis history, leukocytosis and anemia; and for leukemia-free survival were prefibrotic PMF morphology, thrombosis and extreme thrombocytosis (platelets >1 million/μL). In the same study, risk factors for fibrotic transformation included prefibrotic PMF morphology, advanced age and anemia while the presence of *JAK2*V617F was associated with a lower risk of fibrotic transformation.

Most recently, we described the occurrence and prognostic relevance of DNA sequence variants/mutations other than *JAK2*/*CALR*/*MPL* in both PV and ET.[27] Next-generation sequencing (NGS) revealed 53% percent of 133 Mayo Clinic patients with PV and 53% of 183 with ET harbored one or more sequence variants/mutations, other than *JAK2*/*CALR*/*MPL*; the most frequent were *TET2* and *ASXL1*. "Adverse variants/mutations", in terms of overall, leukemia-free or fibrosis-free survival, in PV included *ASXL1*, *SRSF2*, and *IDH2* and in ET *SH2B3*, *SF3B1*, *U2AF1*, *TP53*, *IDH2*, and *EZH2*; combined prevalence was 15% and 15%, respectively. Adverse variants/mutations were associated with inferior survival in both PV and ET and the effect was independent of conventional prognostic models; these observations were validated in 215 Italian patients with PV and 174 with ET. In both Mayo Clinic and Italian cohorts, leukemic or fibrotic progression was also predicted by adverse variants/mutations. Number of mutations did not provide additional prognostic information.[27]

In an even more recent report, we have identified male sex as an independent risk factor for overall survival in ET but not in PV.[28] Furthermore, the above-mentioned collaboration between the Mayo Clinic, Rochester, Minnesota and University of Florence, Florence, Italy is currently ongoing with the objective of developing integrated clinical and genetic survival risk models for both ET and PV.

4 | RISK FACTORS FOR THROMBOSIS AND BLEEDING

Current risk stratification in PV and ET is designed to estimate the likelihood of recurrent thrombosis (Figures 3 and 4). Accordingly, PV includes 2 risk categories: high-risk (age > 60 years or thrombosis history) and low-risk (absence of both risk factors) (Figure 3). In ET, risk stratification includes 4 categories (Figure 4): very low risk (age ≤ 60 years, no thrombosis history, *JAK2* wild-type), low risk (age ≤ 60 years, no thrombosis history, *JAK2* mutated), intermediate risk (age > 60 years, no thrombosis history, *JAK2* wild-type) and high risk (thrombosis history *or* age > 60 years with *JAK2* mutation). In addition, presence of extreme thrombocytosis (platelets >1000 × 10^9/L) might be associated with acquired von Willebrand syndrome (AvWS) and, therefore, risk of bleeding.

Thrombosis risk stratification in ET and PV was based on a number of seminal studies. In 891 patients with WHO-defined ET, after a median follow-up of 6.2 years, 109 (12%) patients experienced arterial (n = 79) or venous (n = 37) thrombosis. In multivariable analysis, predictors of arterial thrombosis included age > 60 years, thrombosis history, cardiovascular (CV) risk factors including tobacco use, hypertension, or diabetes mellitus, leukocytosis (>11 × 10^9/L), and presence of *JAK2*V617F.[29] In contrast, only male gender predicted venous thrombosis. Interestingly, platelet count more than 1000 × 10^9/L was associated with a lower risk of arterial thrombosis. Mutant *CALR* (vs *JAK2*) was associated with lower incidence of thrombotic events without necessarily affecting the international prognostic scoring system for thrombosis in ET. In PV, arterial and venous thromboses were the main risk factors for recurrent arterial or venous vascular events, respectively. In addition, history of hypertension predicted arterial thrombosis and advanced age venous thrombosis.

The above-discussed new risk stratification systems in PV and ET help refine our treatment approach as outlined in Figures 3 and 4.[30] In addition, because of the potential risk for bleeding, low-risk patients with extreme thrombocytosis (platelet count >1000 × 10^9/L) are considered separately.[31]

5 | RISK-ADAPTED THERAPY

5.1 | Low-risk PV or ET, in the absence of extreme thrombocytosis

Controlled studies have confirmed the anti-thrombotic value of low-dose aspirin in PV, among all risk categories, including low-risk disease.[32] Aspirin therapy has also been reported, in a retrospective study, to be beneficial in *JAK2*V617F-mutated low-risk ET, in

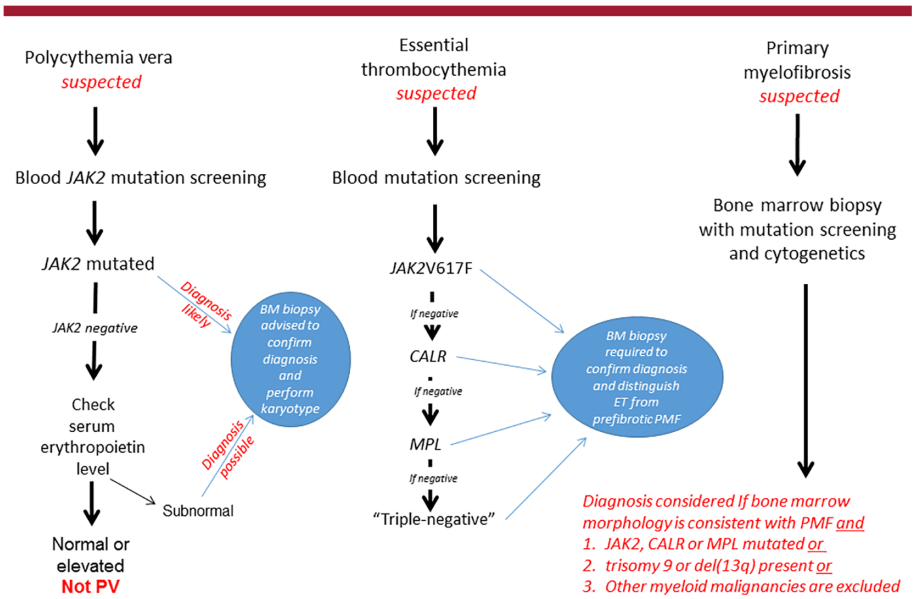

FIGURE 1 Practical diagnostic algorithm for MPNs [Color figure can be viewed at wileyonlinelibrary.com]

preventing venous thrombosis, and also in patients with CV risk factors, in preventing arterial thrombosis.[33] There is now both controlled[34] and uncontrolled[35] evidence that supports phlebotomy for all patients with PV. In a recent randomized study, 365 adult patients with PV were treated with a target hematocrit of <45% or 45 to 50%,[34] after a median follow-up of 31 months, the primary end point of thrombotic events or deaths from CV causes was recorded in 5 of 182 patients in the low-hematocrit group (2.7%) and 18 of 183 patients in the high-hematocrit group (9.8%) (P = .007), supporting the current practice of keeping the hematocrit below 45% in patients with PV.

Low-dose aspirin therapy has also been shown to be effective in alleviating vasomotor (microvascular) disturbances associated with ET or PV.[36] Vasomotor symptoms in ET constitute headaches, lightheadedness, transient neurologic or ocular disturbances, tinnitus, atypical chest discomfort, paresthesias, and erythromelalgia (painful and burning sensation of the feet or hands associated with erythema and warmth). These symptoms are believed to stem from small vessel-based abnormal platelet–endothelial interactions.[37] Histopathological studies in erythromelalgia have revealed platelet-rich arteriolar microthrombi with endothelial inflammation and intimal proliferation accompanied by increased platelet consumption that is coupled with abundant VW factor deposition.[37–39] In regards to aspirin therapy in PV or ET, a recent report suggested that twice-daily aspirin may work better than once daily dose in certain cases.[40] Accordingly, we sometimes consider such a

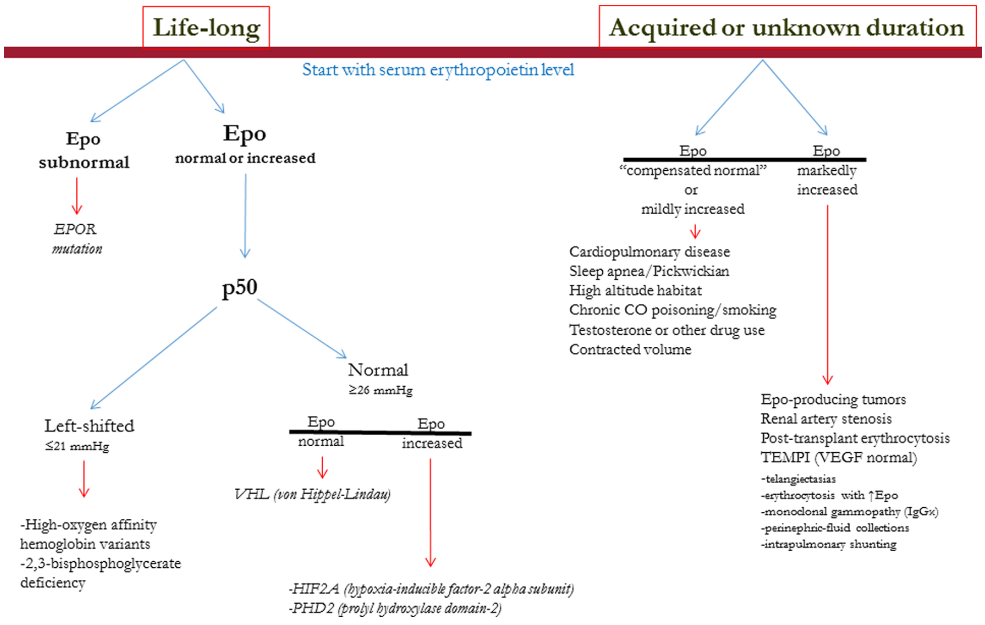

FIGURE 2 Practical work up for erythrocytosis that is not PV [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 IWG-MRT recommended criteria for postPV and postET MF (*see text for references*)

PostPV MF	postET MF
Required: 1. Prior documentation of WHO[a]-defined PV 2. Bone marrow fibrosis grade ≥ 2[b]	*Required:* 1. Prior documentation of WHO[a]-defined ET 2. Bone marrow fibrosis grade ≥ 2[b]
Additional criteria (2 required) *Anemia or loss of phlebotomy requirement* *A leukoerythroblastic blood smear* *Increasing splenomegaly* *Development of constitutional symptoms*	*Additional criteria (2 required)* *Anemia and ≥ 2 g/dL decrease in hemoglobin level* *A leukoerythroblastic blood smear* *Increasing splenomegaly* *Development of constitutional symptoms* *Increased serum lactate dehydrogenase*

[a] WHO, world health organization.
[b] Diffuse often coarse fiber network with or without evidence of collagenization (trichrome stain).

therapeutic approach in patients who seem to be resistant to once daily dosing or considered to be at a higher risk of arterial thrombosis (Figures 3 and 4).

Aspirin therapy is also considered to be adequate, and potentially useful in preventing complications during pregnancy, especially in *JAK2*V617F-positive cases.[41–43] First-trimester spontaneous miscarriage rate in ET or PV (>30%) is significantly higher than the 15% rate expected in the control population and does not appear to be influenced by specific treatment.[44] Late obstetric complications as well as maternal thrombohemorrhagic events are relatively infrequent and platelet count usually decreases substantially during the second and third trimesters. Neither platelet count nor cytoreductive therapy appears to affect either maternal morbidity or pregnancy outcome. Therefore, cytoreductive treatment is currently not recommended for low-risk women with ET that are either pregnant or wish to be pregnant.

Pruritus occurs in the majority of patients with PV (and a substantial number with PMF) and is often exacerbated by hot bath.[45] In the low-risk disease setting, management should start with simple non-drug measures, such as avoidance of precipitating conditions, dry skin, and temperature control of one's environment and water used for bathing. Etiology of PV-associated pruritus remains to be determined and treatment responses to antihistamines have been both unpredictable and variable.[45] In contrast, recent studies have suggested a >50% response rate in PV-associated pruritus treated with paroxetine (20 mg/d), which is a selective serotonin reuptake inhibitor.[46] Other treatment modalities that have been reported to be useful in PV-associated pruritus include JAK inhibitors,[47] interferon-α (IFN-α)[48] and narrow-band ultraviolet B phototherapy.[49]

5.1.1 | Recommendations in the management of low-risk ET or PV without extreme thrombocytosis

We recommend the use of low-dose aspirin (81 mg/d; range 40-100 mg/d) in all patients with low-risk PV or JAK2-mutated ET, provided there are no major contraindications; the latter include clinically significant (ristocetin cofactor activity of <20%-30%) AvWS that might be associated with extreme thrombocytosis (ie, platelet count over 1 million/μL) (Figures 3 and 4). In the presence of aspirin-resistant symptoms, it is reasonable to utilize a twice-daily rather than once-daily regimen of low dose aspirin or alternative anti-platelet agents such as clopidogrel (75 mg/d) alone or in combination with aspirin,[50] as long as patients are monitored closely for drug side effects. One might also consider platelet-lowering agents (eg, hydroxyurea) in aspirin-refractory cases, but the target platelet count in this instance should be the level at which relief of symptoms is observed, and not necessarily 400 × 10^9/L. Twice-daily aspirin use in low-risk patients might also be reasonable in JAK2-mutated patients with CV risk factors. In PV patients, we prefer a hematocrit target of <45%. We manage,

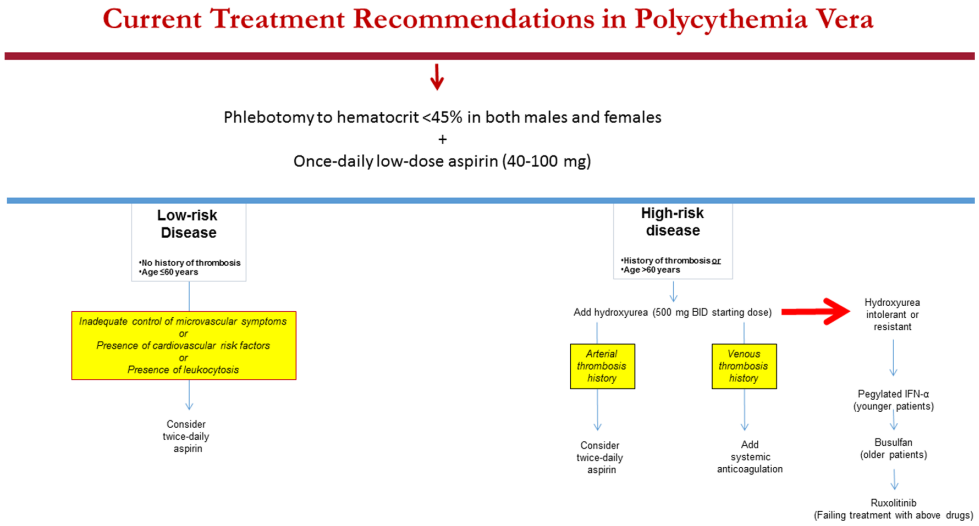

FIGURE 3 Current treatment recommendation in PV [Color figure can be viewed at wileyonlinelibrary.com]

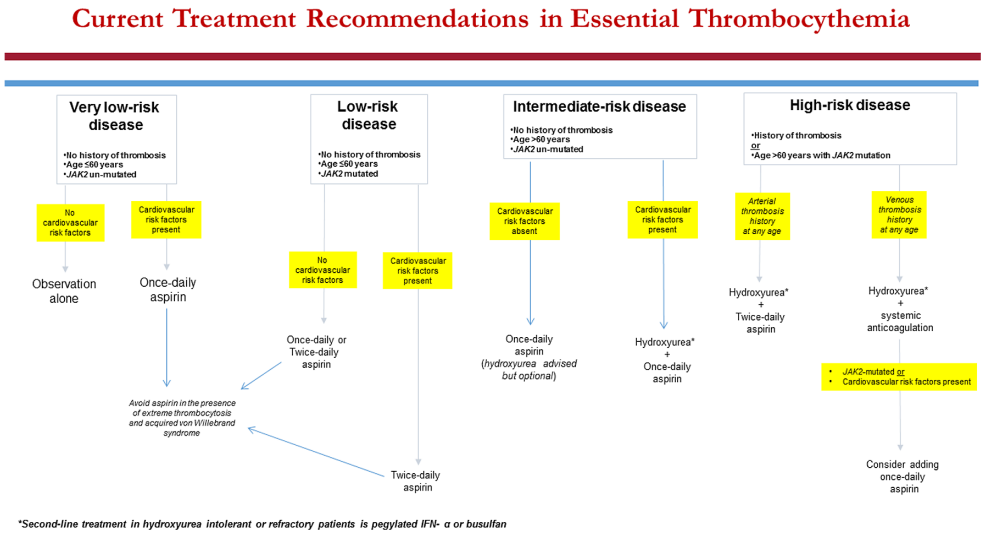

FIGURE 4 Current treatment recommendation in ET [Color figure can be viewed at wileyonlinelibrary.com]

pregnant patients or women of child-bearing potential, in the same general manner and we do not use platelet-lowering agents or heparin therapy in the setting of low-risk disease.

6 | RISK-ADAPTED THERAPY

6.1 | Low-risk PV or ET, in the presence of extreme thrombocytosis

Bleeding diathesis in ET or PV is currently believed to be multifactorial in etiology.[51] Laboratory evidence of AvWS occurs in the majority of patients with ET or PV and is characterized by the loss of large von Willebrand factor multimers, linked to their increased proteolysis by the ADAMTS13 cleaving protease, in a platelet count-dependent fashion. This results in a functionally more relevant defect that may not be apparent when measuring VWF:Ag and FVIII levels alone and requires the use of assays that assess VWF function (eg, ristocetin cofactor activity; VWF:RCoA). Other causes of platelet dysfunction in ET or PV include acquired storage pool deficiency, increased platelet activation, decreased adrenergic receptor expression, impaired response to epinephrine, and decreased platelet membrane glycoprotein receptor expression.[51]

Based on the above, the use of aspirin in both PV and ET requires caution, especially in the presence of extreme thrombocytosis (platelet count >1000 × 10^9/L), which promotes the development of AvWS. However, clinically relevant AvWS can occur even when the platelet count is well below 1000 × 10^9/L, and that laboratory evaluation of AvWS must be performed in the presence of abnormal bleeding, regardless of platelet count.[52]

6.1.1 | Recommendations in the management of low-risk ET or PV with extreme thrombocytosis

In patients with PV or ET and extreme thrombocytosis, the use of aspirin can lead to bleeding complications because of AvWS; therefore, in the presence of platelets > 1000 × 10^9/L, screening for ristocetin cofactor activity is advised and consideration be given to withhold aspirin therapy if the result shows < 20% activity. On the other hand, extreme thrombocytosis neither defines high-risk disease nor warrants the use of cytoreductive therapy (Figures 3 and 4).

7 | RISK-ADAPTED THERAPY

7.1 | High-risk PV or ET

7.1.1 | Summary of randomized studies in PV

In the first controlled study in PV, the PV study group (PVSG) randomized 431 patients, between 1967 and 1974, to treatment with either phlebotomy alone or phlebotomy with either oral chlorambucil or intravenous radioactive phosphorus (P32).[53] The results significantly favored treatment with phlebotomy alone with a median survival of 12.6 years compared with 10.9 and 9.1 years for treatment with radiophosphorus and chlorambucil, respectively. The difference in survival was attributed to an increased incidence of acute myeloid leukemia (AML) in patients treated with chlorambucil or radiophosphorus compared with those treated with phlebotomy alone (13.2% vs 9.6% vs1.5% over a period of 13-19 years).[54] Furthermore, 3.5% of the patients treated with chlorambucil developed large cell lymphoma and the incidence of gastrointestinal and skin cancer was increased in those patients treated with either chlorambucil or radiophosphorus.

The European Organization for Research on Treatment of Cancer randomized 293 patients between 1967 and 1978 to treatment with either radiophosphorus or oral busulfan.[55] The results favored busulfan in terms of both first remission duration (median, 4 years vs 2 years) and overall survival (10-year survival rates of 70% vs 55%). At a median follow-up period of 8 years, there was not significant difference in the risk of leukemic transformation (2% vs 1.4%), nonhematologic malignancy (2.8% vs 5%), vascular complications (27% vs 37%), or transformation into postPV MF (4.8% vs 4.1%) between the 2 arms.

Other randomized studies in PV have compared hydroxyurea against pipobroman (the first report showed a significant difference favoring pipobroman in the incidence of transformation into postPV

MF but no difference in survival, incidence of thrombosis, or the rate of leukemic conversion; however, a longer-term follow-up revealed a shorter survival, an increased risk of leukemic transformation, and a lower risk of postPV MF, associated with pipobroman therapy),[56,57] radiophosphorus alone or with HU (no difference in survival, incidence of thrombosis, or risk of transformation into postPV MF but radiophosphorus alone was associated with significantly less incidences of both acute leukemia and other cancers),[58] and radiophosphorus plus phlebotomy against phlebotomy plus high-dose aspirin (900 mg/d) in combination with dipyridamole (225 mg/d) (the addition of antiplatelet agents provided no benefit in terms of thrombosis prevention but increased the risk of gastrointestinal bleeding).[59] Ruxolitinib, a JAK1/2 inhibitor, was also compared with hydroxyurea, in a phase 3 study in PV patients intolerant or not-responding to hydroxyurea[60]; the study showed hematocrit control of 60% for ruxolitinib vs 20% for standard therapy; in addition, as expected, spleen and symptom control was better with ruxolitinib. Unfortunately, the particular study did not address issues of meaningful health outcome in PV, such as prevalence of thrombotic complications, survival and leukemic or fibrotic transformation rates. There are currently ongoing controlled studies in PV and ET that are comparing hydroxyurea to IFN-α.[61]

The lack of antithrombotic value from anti-platelet agents in the above-mentioned PVSG-aspirin study may have been influenced by the fact that 27% of the patients randomized to the phlebotomy-aspirin-dipyridamole arm had a prior history of thrombosis compared with 13% in the other arm. This contention was confirmed by the most recent study from the European collaboration study on low-dose aspirin in polycythemia.[32] The study enrolled 518 patients with PV in a double-blind randomized trial to low-dose aspirin (100 mg daily) or placebo. Treatment with aspirin did not increase the incidence of major bleeding and instead reduced the risk of combined endpoints for "nonfatal myocardial infarction, nonfatal stroke, or death from CV causes" and "nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from CV causes".[62] Most recently, a randomized study comparing hematocrit targets of <45% or 45%-50%, using phlebotomy with or without hydroxyurea, was published and revealed decreased thrombotic events with the lower hematocrit target[34]; the particular study confirmed the prudence of aggressive phlebotomy in all patients with PV and provided additional evidence to support current practice.

7.1.2 | Summary of randomized studies in ET

In one of the very few controlled studies in ET, Cortelazzo et al.[63] randomized 114 mostly high-risk patients to hydroxyurea (n = 56) or not (n = 58). After 27 months of follow-up, the incidences of thrombotic complications were 3.6% for hydroxyurea and 24% for no hydroxyurea, although the "thrombotic" episodes in 2 patients in the nonhydroxyurea arm constituted superficial thrombophlebitis. This is the only study, to-date, which randomized patients with ET to a drug vs no drug.

Two randomized studies in ET compared hydroxyurea with anagrelide. In the earlier study,[64] 809 high-risk patients with were given low-dose aspirin plus either anagrelide or hydroxyurea. Hydroxyurea was better in terms of reducing the risk of arterial thrombosis, major bleeding and fibrotic progression. Anagrelide performed better in preventing venous thrombosis. In addition, adverse dropout rate was significantly higher in the anagrelide arm. In the second study,[65] anagrelide was compared with hydroxyurea in in 259 high-risk ET patients; during the total observation time of 730 patient-years, there was no significant difference between the anagrelide and hydroxyurea group regarding incidences of major arterial (7 vs 8) and venous (2 vs6) thrombosis, severe bleeding events (5 vs 2), minor arterial (24 vs 20) and venous (3 vs 3) thrombosis and minor bleeding events (18 vs 15), or discontinuation rates (adverse events 12 vs 15 or lack of response 5 vs 2); incidences of leukemic or fibrotic transformations were not reported. It should be noted that WHO diagnostic criteria were strictly adhered to in the latter study,[65] and not in the former.[64]

Most recently, ruxolitinib (JAK1/2 inhibitor) was compared with best available therapy in hydroxyurea unresponsive/intolerant high-risk ET, in a randomized phase-2 study.[66] The 1-year complete response rates, which were not associated with molecular responses, were similar in the 2 study arms as were the 2-year rates of thrombosis, hemorrhage and leukemic/fibrotic transformation.

7.1.3 | Overview of single arm alkylating therapy in PV and ET

Hydroxyurea

In a nonrandomized study by the PVSG, treatment with hydroxyurea was associated with a lower incidence of early thrombosis compared with a historical cohort treated with phlebotomy alone (6.6% vs 14% at 2 years). Similarly, the incidence of AML in patients treated with hydroxyurea, compared with a historical control treated with either chlorambucil or radiophosphorus, was significantly lower (5.9% vs 10.6% vs 8.3%, respectively, in the first 11 years of treatment).[67] Other studies have confirmed the low incidence of AML in PV patients treated with hydroxyurea (1%-5.6%).[68–70]

Pipobroman

Many studies have reported on the use of pipobroman as a single agent in PV.[71,72] In one of these studies involving 163 patients, the drug was effective in more than 90% of the patients and median survival exceeded 17 years.[71] In the first 10 years, the incidences of thrombotic events, acute leukemia, postPV MF, and other malignancies were 16%, 5%, 4%, and 8%, respectively. A similar retrospective study in 164 patients with ET treated with pipobroman as first-line therapy (starting dose 1 mg/kg/d) and followed for a median of 100 months, AML occurred in 5.5% of the cases.[73] In another study of 33 young patients (<50 years of age) with ET treated with pipobroman only and followed for a median of almost 16 years, the complete remission rate was 94% and only 1 patient (3%) developed AML whereas no patient experienced thrombotic complications.[74] However, as mentioned earlier, the final analysis of a French PV study comparing hydroxyurea to pipobroman has revealed a shorter survival, an increased risk of leukemic transformation, and a lower risk of postPV MF, associated with pipobroman therapy.[56,57] The association between pipobroman therapy and increased risk of leukemic transformation in PV was confirmed by a more recent international study.[25]

Busulfan

Favorable outcome has also been reported in single arm studies using oral busulfan.[75,76] In 65 busulfan-treated patients with PV followed between 1962 and 1983, median survival was 19 years in patients whose disease was diagnosed before age 60 years.[75] Only 2 patients (3.5%) treated with busulfan alone developed acute leukemia. A similar percentage (3%) developed the complication in another study involving ET patients.[77] These figures were well within the baseline risk that is intrinsic to the diseases and no different than those seen with hydroxyurea.[77] The safety and efficacy of busulfan treatment in ET was recently underlined by a long-term study of 36 patients above age 60 years of age;[78] no instances of AML or other malignancies were documented after a median follow-up of 72 months. In a more recent study of over 1500 patients with PV, use of busulfan was not correlated with leukemic transformation.[25] Most recently, the use of busulfan in hydroxyurea-resistant PV produced over 80% complete hematologic response and molecular remission in about a third of the patients.[79]

Interferon-α

It is now well established that IFN-α can control erythrocytosis or thrombocytosis in the majority patients with PV or ET (usual dose is 3 million units SC 3 times-a-week). A similar degree of benefit is appreciated in terms of reduction in spleen size or relief from pruritus. Two recent studies of pegylated INF-α (~90 μg SC weekly) in PV and ET reported hematologic remissions of ~80% accompanied by decreases in *JAK2*V617F allele burden (complete molecular remission rate of 5%-10%).[80,81] In 1 of the 2 studies,[80] 77 cases were evaluable after a median follow up of 21 months and 76% and 70% of patients with ET or PV, respectively, achieved a complete hematologic remission, mostly in the first 3 months; side effects were recorded in 96% of the patients and 22% had discontinued treatment. Controlled studies are needed to clarify the advantage (or disadvantage) of IFN therapy in PV, compared with hydroxyurea therapy. IFN therapy was also associated with significant reduction in mutant *CALR* allele burden in ET[82] whereas drug-induced *JAK2*V617F allele burden reduction has also been demonstrated with busulfan use in PV.[83]

The issue of drug leukemogenicity

There are, to date, no controlled studies that implicate either hydroxyurea or busulfan as being leukemogenic in either ET or PV. Similarly, the 2 largest noncontrolled studies in ET[84] and PV[70] do not support the concern that leukemia might arise from the use of hydroxyurea and there is additional evidence to that effect from long-term studies of patients receiving hydroxyurea for sickle cell disease.[85] The evidence for busulfan leukemogenicity in the context of treatment for PV or ET is equally weak and inappropriately extrapolated from older patients with advanced phase disease and exposed to multiple cytoreductive drugs. The recurrent flaw in data interpretation, when it comes to examining the relationship between leukemic drugs and leukemic transformation, is best illustrated by the largest prospective/retrospective study, to date, in PV (n = 1638).[70] At a median follow-up of 8.4 years from diagnosis, only 1.3% of the patients developed AML. When the authors compared the patients who transformed to those who did not, the former were older and more likely to have leukocytosis (known risk factor for leukemic transformation) at time of diagnosis or registration to the central database. They also had significantly longer disease duration and were more likely to have been treated with multiple drugs. In other words, exposure to alkylating agents other than hydroxyurea probably selects patients who are at a higher risk of leukemic transformation because of older age, longer disease duration and intrinsic aggressive disease biology. This, in our opinion, is the reason for the apparent association in some studies between leukemic transformation and drug therapy in PV or ET. Our impression is further supported by a recent International Working Group study of 1545 PV patients where cumulative hazard of leukemic transformation, with death as a competing risk, was 2.3% at 10 years and 5.5% at 15 years;[25] risk factors for leukemic transformation were older age, abnormal karyotype and leukocytes ≥15 × 10^9/L. Leukemic transformation was associated with treatment with pipobroman, P32 or chlorambucil but not with hydroxyurea or busulfan.[25]

7.1.4 | Recommendations in the management of high-risk patients with PV or ET

In addition to low-dose aspirin and phlebotomy to a hematocrit target of 45%, in case of PV, high-risk patients with PV or ET should receive hydroxyurea, as first-line cytoreductive drug of choice, in order to minimize their risk of thrombosis (starting dose 500 mg BID) (Figures 3 and 4). The dose of hydroxyurea is titrated to keep platelet count in the normal range. However, it is to be noted that the recommended platelet target is not based on controlled evidence. PV or ET patients who are either intolerant or resistant to hydroxyurea are effectively managed by INF-α (pegylated preparations preferred) or busulfan. Among these 2 second-line drugs, we prefer the use of INF-α for patients younger than age 65 years and busulfan in the older age group, although there is no controlled evidence to support or refute such a strategy. Busulfan is started at 2-4 mg/d, withheld in the presence of platelets < 200 × 10^9/L or WBC < 3 × 10^9/L, and the dose is reduced to 2 mg/d when treatment is resumed after withholding. We usually start subcutaneous pegylated IFN-α at 45 mcg once-a- week and titrate up to 180 mcg once-a-week if tolerated. In PV patients not responding to hydroxyurea, INF-α or busulfan, and in the presence of intractable pruritus or drug-refractory symptomatic splenomegaly, it is reasonable to try JAK2 inhibitor therapy (Figure 3). Finally, we believe it is reasonable to use twice-daily aspirin in patients with arterial thrombosis if they are older or harbor JAK2 mutations or in the presence of CV risk factors (Figures 3 and 4). In patients with venous thrombosis, systemic anticoagulation is advised and the addition of once-daily low dose aspirin, in the presence of JAK2 mutation or CV risk factors, is reasonable. Cytoreductive therapy is not mandatory in intermediate-risk patients with ET (age > 60 years but without JAK2 mutation and without history of thrombosis) and treatment approach in such cases should be individualized.

8 | CONCLUDING REMARKS

Median survival in young patients with PV and ET might exceed 30 years and is not that much worse for older patients.[86] Therefore, it is very important to avoid nonevidence-based therapeutic adventures in PV or ET that might shorten life-expectancy and increase the rate

of fibrotic or leukemic transformations, as has been previously documented for chlorambucil,[53] radiophosphorus,[54] pipobroman,[87] and most recently for anagrelide.[64] To date, drug therapy has not been shown to improve survival or prevent leukemic/fibrotic transformation in either ET or PV and treatment is primarily directed at preventing thrombotic complications. In this regard, lower risk patients are effectively managed by aspirin therapy or observation alone while cytoreductive therapy is reserved for high risk disease.

In high-risk patients with PV or ET, first-line cytoreductive drug of choice is currently hydroxyurea, a practice based on the results of randomized[63,64] and carefully designed single arm cohort studies.[63,88–90] Efforts to improve upon hydroxyurea as first-line therapy for PV or ET have not materialized as yet and instead have suggested harmful effects for some of the alternative drugs.[64] Second-line drugs of choice in high risk ET or PV, based on single-arm cohort studies with adequate follow-up and documentation of long-term safety, are pegylated IFN-α and busulfan. Concerns about drug leukemogenicity involving hydroxyurea or busulfan, which we do not share, are largely based on anecdotes rather than properly executed controlled studies and their safety in this regard has been affirmed by large retrospective studies.[15,25] There are no controlled studies that compared new drugs against currently established second-line drugs including and busulfan and IFN-α, in hydroxyurea non-responsive or intolerant patients; instead, ruxolitinib, JAK1/2 inhibitor, was compared with hydroxyurea, in such a setting and showed superior response in control of hematocrit, splenomegaly and symptoms[60]; however, the particular study did not target the appropriate health outcome as study endpoints, such as thrombosis, survival, and leukemic/fibrotic disease transformation rates.

In our opinion, the following 2 things are required in order to justify the risk of unknown long-term health effects of nonconventional drug therapy for PV or ET, such as with IFN-α or JAK2 inhibitors (eg, ruxolitinib): i) experimental or *in vivo* demonstration of disease-modifying activity and ii) controlled studies against hydroxyurea (for first-line therapy) or IFN-α/busulfan (for second-line therapy) to show added value. In other words, there is currently no compelling evidence to support the need for JAK2 inhibitor therapy (eg, ruxolitinib) in the majority of patients with hydroxyurea-refractory PV; such treatment should be reserved for patients not responding to hydroxyurea, busulfan and IFN-α and in the presence of intractable pruritus, severe constitutional symptoms, marked splenomegaly or evidence of disease transformation into postPV MF.[47]

ORCID

Ayalew Tefferi https://orcid.org/0000-0003-4605-3821
Tiziano Barbui https://orcid.org/0000-0003-2747-6327

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How to cite this article: Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2019 update on diagnosis, risk-stratification and management. *Am J Hematol*. 2019;94:133–143. https://doi.org/10.1002/ajh.25303