What are the current treatment approaches for patients with polycythemia vera and essential thrombocythemia?

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Polycythemia vera (PV) and essential thrombocythemia (ET) are chronic myeloproliferative neoplasms that are characterized by thrombohemorrhagic complications, symptom burden, and impaired survival mainly due to thrombosis, progression to myelofibrosis, and transformation to acute leukemia. In this manuscript, we will review the most recent changes in diagnostic criteria, the improvements in risk stratification, and the "state of the art" in the daily management of these disorders. The role of conventional therapies and novel agents, interferon α and the JAK2 inhibitor ruxolitinib, is critically discussed based on the results of a few basic randomized clinical studies. Several unmet needs remain, above all, the lack of a curative approach that might overcome the still burdensome morbidity and mortality of these hematologic neoplasms, as well as the toxicities associated with therapeutic agents.

Learning Objectives

- To become familiar with the revised 2016 World Health Organization (WHO) classification of PV and ET and the International Working Group for Myeloproliferative neoplasms Research and Treatment (IWG-MRT) criteria for myelofibrotic transformation of these diseases
- To understand the criteria for risk-based stratification of patients with PV and ET
- To understand the rationale for risk-adapted therapy in patients with PV and ET
- To realize how to manage special situations

Polycythemia vera (PV) and essential thrombocythemia (ET) are myeloproliferative neoplasms (MPNs) whose hallmarks are, respectively, erythrocytosis and thrombocytosis; in PV, expanded red cell mass is associated with leukocytosis and/or thrombocytosis in at least half of the cases, whereas isolated thrombocytosis is the only hematologic abnormality in most patients with ET. The main clinical features of PV and ET are an increased rate of major cardiovascular events (CEs; arterial and venous thrombosis) compared with a reference population, bleeding episodes, microcirculatory symptoms (such as headache, vertigo, dizziness, tinnitus, erythromelalgia, and paresthesia), systemic manifestations (ie, night sweats, body weight loss, and fever not related to infections), pruritus (typically aquagenic), and splenomegaly. Both diseases can transform to myelofibrosis (MF), called post-PV MF (PPV-MF) and post-ET MF (PET-MF), at estimated rates of 20% and 10%, respectively, 15 years after initial diagnosis, whereas transformation to acute leukemia (AL) occurs in <10% and <5% of PV and ET, respectively, 20 years from diagnosis.

In a large series of molecularly annotated patients with mature follow-up data, median survival was overall reduced compared with the general population and approximated 14 years in PV and 20 years in ET[1]; when referred to patients younger than 60 years of age, median survival was 24 years and 33 years for PV and ET, respectively. However, in another study, survival of ET patients was similar to a reference European population.[2] According to a population-based study from the Swedish Cancer Registry, which considered patients diagnosed between 1993 and 2000, the 10-year probability of cause-related death was 25% and 21% for cardiovascular and cerebrovascular disease, 7% and 13% for hematological malignancies, 10% and 9% for solid tumors, in PV and ET, respectively.[3] There was also a nonnegligible risk of death due to infections (5% and 2% for PV and ET).

The molecular hallmark of PV and ET is a recurrent point mutation (V617F) in *JAK2* that is detected in 95% of PV and 60% of ET patients. The remaining few patients with PV may harbor mutation in *JAK2* exon 12 (missense mutation, deletion, insertion). In the case of ET, 3% to 5% of the patients present point mutation at codon 515 (W515L/K/A are the most frequent) of the *MPL* gene, which encodes the receptor for thrombopoietin; furthermore, mutations in *CALR*, the gene that encodes the endoplasmic reticulum–associated chaperone calreticulin, can be detected in 20% to 25% (the most common variants are del52/type1 and ins5/type2).[4] The remaining 10% to 15% of patients with ET who lack any of the above mutated "driver" genes are usually referred to as "triple negative"; this is a heterogeneous category of subjects, some of whom may have rare noncanonical mutations in *JAK2* and *MPL*, but the large majority remain molecularly not characterized, possibly representing familial forms and otherwise unexplained both clonal and nonclonal thrombocytosis.[4-6]

Despite the renewed interest in MPNs that accompanied discovery of those mutations and the development of JAK2 inhibitors, there is still great heterogeneity in the way PV and ET are diagnosed and managed in the community and in academic centers, as well as in different

Conflict-of-interest disclosure: A.M.V. is on the board of directors or an advisory committee for Novartis, has received research funding from Novartis, and has been affiliated with the speakers bureaus for Novartis, Shire, and Gilead. P.G. declares no competing financial interests.

Off-label drug use: Interferon.

Table 1. Diagnostic criteria for the chronic phase of PV and ET and for prefibrotic PMF: revised 2016 WHO criteria

2016 WHO Criteria	PV	ET	Early/Pre-PMF
Major	1. Hb (>16.5 g/dL in men; >16.0 g/dL in women) or hematocrit (>49% in men; >48% in women) or increased RCM* 2. BM biopsy† showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size) 3. Presence of *JAK2*V617F or *JAK2* exon 12 mutation	1. Platelet count ≥450 × 10^9/L 2. BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with 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 BCR-ABL11 CML, PV, PMF, MDSs, or other myeloid neoplasms 4. Presence of *JAK2*, *CALR*, or *MPL* mutation.	1. Megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis 2. Not meeting the WHO criteria for BCR-ABL + CML, PV, ET, MDS, 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 BM reticulin fibrosis§
Minor	Subnormal serum erythropoietin level	Presence of a clonal marker or absence of evidence for reactive thrombocytosis	a. Anemia not attributed to a comorbid condition b. Leukocytosis ≥11 × 10^9/L c. Palpable splenomegaly d. LDH increased to above upper normal range
Criteria required for diagnosis	All 3 major or the first 2 major and the minor criterion	All 4 major criteria or the first 3 major and the minor criterion	All 3 major criteria, and at least 1 minor criterion

BM, bone marrow; CML, chronic myeloid leukemia; ET, essential thrombocythemia; Hb, hemoglobin; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; MF, myelofibrosis; PMF, primary myelofibrosis; PV, polycythemia vera; RCM, red cell mass; WHO, World Health Organization.

*More than 25% above mean normal predicted value.

†BM biopsy may not be required in cases with sustained absolute erythrocytosis defined as hemoglobin levels >18.5 g/dL in men (hematocrit, 55.5%) or >16.5 g/dL in women (hematocrit, 49.5%) if major criterion 3 and the minor criterion are present. However, initial MF can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt MF (post-PV MF).

‡In the absence of any of the 3 driver mutations, the search for the most frequent accompanying mutations (eg, *ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1*) are of help in determining the clonal nature of the disease.

§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.

countries. For example, in a survey involving members of the MPN Research Foundation who were asked about their approach to PV, use of the single diagnostic variables included in World Health Organization (WHO) criteria ranged from 95% (*JAK2*V617F testing) to 86% (serum erythropoietin [sEPO] levels) to 59% (bone marrow [BM] biopsy) in the academic setting; the corresponding figures in private practice were 67%, 67%, and 42%.[7] Also, in a retrospective analysis of 1476 PV patients from 34 centers in Germany, mainly from private physicians and primary care centers, a notable 23% of patients had unknown *JAK2* mutation status and sEPO was determined in 40% only.[8] Such variability is also reflected in several guidelines and consensus statements for diagnosis and treatment developed by national scientific societies (British, Italian, Canadian, Swedish, Japanese, Czech, to name a few) and scientific groups, such as European LeukemiaNet (ELN)[9] and the International Working Group for Myeloproliferative neoplasms Research and Treatment (IWG-MRT). In the United States, National Comprehensive Cancer Network (NCCN) guidelines have been developed for MF,[10] whereas those for PV and ET are due. In this manuscript, we will outline the current approach to the management of PV and ET commonly used and the one to which we adhere (see Boxes 1-3); however, we acknowledge that different expert opinions and practice patterns may exist, as already discussed and as illustrated in the following sections.

Diagnostic criteria

The WHO revised the diagnostic criteria for MPN in 2016 (Table 1).[11] There was no substantial change in the diagnostic criteria of ET compared with the previous (2008) version, except for including *CALR* mutations among the major criteria. However, a remarkable action was the identification of a prefibrotic/early form of MF (pre-primary MF [pre-PMF]) as a distinct entity with respect to ET and overt fibrotic MF. Although a reticulin fibrosis not greater than grade 1 may be found in both ET and pre-PMF, the 2 entities may be distinguished by morphologic evaluation of BM biopsy. Increased numbers of large and mature-appearing megakaryocytes, with hyperlobulated nuclei, in the context of normal, age-adjusted BM cellularity, are typical of ET, whereas, in pre-MF, megakaryocytes display abnormal maturation with hyperchromatic and irregularly folded nuclei, form clusters, and are surrounded by increased cellularity with granulocytic proliferation and often decreased eythropoiesis.[11] Other minor criteria may also help in the differential diagnosis between ET and pre-PMF (Table 1). The prognostic relevance of distinguishing ET from pre-PMF is supported by several studies.[2,12] In a series of 278 patients with pre-PMF and 421 with ET, respective median survival was 14.7 years and 30.2 years, accounting for a hazard ratio of 2.7 (95% confidence interval [CI], 1.9-3.7).[12] BM histopathology is also useful to exclude myelodysplastic syndrome (MDS)/MPN with ring sideroblasts and thrombocytosis, which is characterized by anemia with ≥15% ring sideroblasts in the BM, thrombocytosis, and a *SF3B1* mutation usually associated with *JAK2*V617F (>70% of cases), *MPL*, or *CALR* mutations.

As concerns PV, remarkable changes were introduced in the 2016 WHO revision of the diagnostic criteria (Table 1). These consist of

Table 2. Diagnostic criteria for PPV-MF and PET MF: IWG-MRT criteria

IWG-MRT criteria	PPV-MF	PET-MF
Required	1. Documentation of a previous diagnosis of PV as defined by the WHO criteria 2. BM fibrosis grade 2-3 (on 0-3 scale) or grade 3-4 (on 0-4 scale)‖	1. Documentation of a previous diagnosis of ET as defined by the WHO criteria 2. BM fibrosis grade 2-3 (on 0-3 scale) or grade 3-4 (on 0-4 scale)‖
Additional	1. Anemia¶ or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment of erythrocytosis 2. A leukoerythroblastic peripheral blood picture 3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly 4. Development of ≥1 of 3 constitutional symptoms: >10% weight loss in 6 mo, night sweats, unexplained fever (>37.5°C)	1. Anemia¶ and a ≥2 mg/mL decrease from baseline Hb level 2. A leukoerythroblastic peripheral blood picture 3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly 4. Increased LDH (above reference level) 5. Development of ≥1 of 3 constitutional symptoms: >10% weight loss in 6 mo, night sweats, unexplained fever (>37.5°C)
Criteria required for diagnosis	All 2 required criteria and at least 2 additional criterion	All 2 required criteria and at least 2 additional criterion

Abbreviations are explained in Table 1.
‖Grade 2-3 according to the European classification or grade 3-4 according to the standard classification.
¶Below the reference range for appropriate age, sex, gender, and altitude considerations.

the inclusion of BM biopsy as a major criterion, the dismissal of the erythropoietin-independent erythroid colony test, and, most importantly, the lowering of the hemoglobin threshold to 16.5 g/dL (hematocrit, 49%) and 16.0 g/dL (hematocrit, 48%) for men and women, respectively, compared with 18.5 g/dL and 16.5 g/dL in the 2008 version. Detection of *JAK2*V617F mutation in the presence of raised hemoglobin/hematocrit is virtually specific for PV; in case the mutation is absent, analysis for *JAK2* exon 12 mutations should be done in the presence of subnormal sEPO levels. Of note, however, in up to 15% of patients with *JAK2*-mutated PV, the sEPO levels may fall within the normal range.[13] The WHO criteria do not mandate BM biopsy for patients with hemoglobin levels >18.5 g/dL (men) and 16.5 g/dL (women) because these levels are invariably equivalent to an expanded red cell mass; however, BM biopsy is recommended to assess BM fibrosis because a grade ≥1 fibrosis at diagnosis of PV is associated with worse outcome.[14]

Criteria for diagnosing transformation to PPV-MF and PET-MF were developed by the IWG-MRT through expert consensus methodology and are outlined in Table 2.[15]

Goals of therapy and risk stratification

The obvious goal of treatment in PV and ET would be the cure, which is not a realistic end point with current therapies, or at best prolongation of survival; the latter has indeed improved in the last decades mainly because of the reduction of major thrombotic events. On the other hand, there is scant evidence that any treatment, including interferon and the JAK1/2 inhibitor ruxolitinib, might delay progression to PPV-MF and PET-MF or prevent leukemic transformation. Conversely, treatments that increase the risk of AL, namely radioactive phosphorus, chlorambucil, and pipobroman as well as the use of sequential chemotherapeutics including hydroxyurea, have been highlighted. Concerning the treatment needs and goals, it is interesting to appreciate the different perceptions expressed by physicians and patients who took part in a MPN landmark survey, conducted in the United States among 457 physicians and 813 patients, including 380 with PV and 226 with ET.[16] Slowing/delaying progression of the hematologic disease was rated as the most important treatment goal by 25% of PV patients vs 6% of physicians, who conversely identified prevention of CE in 43% of responders vs 21% of the patients; similarly, in ET, delaying disease progression was underscored by 21% and 4% of the patients and physicians, respectively, and prevention of CE by 35% vs 57%. We interpret these different opinions as reflecting, on the physicians' side, the awareness of the shortage of disease-modifying agents contrasting with the benefits obtained with risk-adapted therapy in reducing thrombosis rate and, on the patients' side, the anxiety about the relentless deterioration of the underlying hematologic neoplasm. Finally, physicians apparently overvalued, as compared with patients, symptom improvement as one of the most important treatment goals (20% and 14% for PV and ET, respectively, compared with 9% only of the patients), whereas patients were more concerned about abnormal blood counts.

The goals of treatment of PV and ET, according to the ELN recommendations,[9] are the prevention of first occurrence and/or recurrence of thrombotic and bleeding complications in addition to minimizing the risk of progression to MF or AL, the control of systemic symptoms, and the appropriate management of complications and risk situations.[9] Criteria for standardized assessment of response to treatment were first developed in 2009 and revised in 2013 by the ELN and IWG-MRT,[17] and include improvement of blood cell counts, splenomegaly, symptoms, and histology, resulting overall in different degrees of response (complete response, partial response, no response, progressive disease); of note, molecular response is not required for adjudicating complete or partial response.[17] However, the aim of these criteria was to create uniformity in clinical trial reporting results, but they are not appropriate instruments to judge the efficacy of conventional treatments in the practice and have not been validated prospectively against hard clinical end points. For example, whether attainment of a complete hematologic response directly translates into clinical benefits in patients with ET is debated.[18]

The criteria used in the clinical practice for therapeutic decisions are tailored to the assessment of the individual's risk of suffering from thrombosis and bleeding. Although a number of clinical, hematologic, and molecular variables have been associated with shortened survival in PV and ET, the resulting predictive scores do not find immediate

Table 3. Criteria used for risk-stratifying patients with PV and ET according to the conventional 2-tiered score and the revised IPSET-thrombosis for ET

Risk category	PV	ET	
	2-tiered score	2-tiered score	Revised IPSET
Very low	—	—	No thrombosis history, age ≤60 y and *JAK2*-unmutated
Low	≤60 y of age, and no history of thrombosis	≤60 y of age, and no history of thrombosis	No thrombosis history, age ≤60 y and *JAK2*V617F-mutated
Intermediate	—	As low risk, but with cardiovascular risk factor	No thrombosis history, age >60 y and *JAK2*-unmutated
High	>60 y of age and/or with history of thrombosis	>60 y of age and/or with history of thrombosis	Thrombosis history or age >60 y with *JAK2*V617 mutation

—, not applicable.

clinical applicability.[19] The 2 strongest variables associated with thrombosis risk in PV and ET are older age (>60 years) and history of CEs, resulting in a 2-tiered risk stratification. Conventionally defined "high-risk" patients present either of the 2 variables, whereas "low-risk" patients are younger and had not suffered from thrombosis. Although the intuitive additional role of generic cardiovascular risk factors, particularly hypertension,[20] smoking, and leukocytosis, is supported by several epidemiologic studies, these characteristics are not yet included in conventional risk-scoring systems; however, some experts delineated an "intermediate-risk" category in ET based on their presence (Table 3). In patients with ET, the revised International Prognostics Score System (IPSET)-thrombosis, which incorporates the *JAK2*V617F mutation status, allows more accurate prediction of thrombosis risk compared with the 2-tiered score. Four categories are considered: a very low risk (no risk variables), low risk (presence of *JAK2*V617F mutation), intermediate risk (age >60 years, no thrombosis history, *JAK2* unmutated), and high-risk (history of thrombosis and/or age >60 years and *JAK2*V617F mutation)[21] (Table 3). Patients with ET harboring *CALR* mutation are at a reduced risk of thrombotic events when compared with *JAK2*V617F mutated, but introduction of this variable did not appreciably modify the predictive power of the IPSET-thrombosis score; a similar low rate of CEs was observed in triple-negative patients.[22] Although it remains to be prospectively validated, the use of IPSET score might allow more tailored use of antiplatelet agents[21]; in this regard, a recent systematic review concluded that the risk-benefit ratio of antiplatelet therapy in ET patients is highly uncertain.[23] However, in daily practice, the decision to use cytoreductive therapy still relies on 2-tiered risk stratification. The presence of extreme thrombocytosis (in excess of 1000×10^9/L platelets) may be associated with an acquired von Willebrand syndrome, and therefore predicts for an increased risk of bleeding (Box 1).

Therapies for PV

There are 2 evidence-based recommendations for patients with PV. The first recommendation is to guarantee a steady hematocrit level <45%; it derives from the results of the phase 3 randomized CYTO-PV trial, where PV patients maintained at <45% with either phlebotomy alone (that is recommended in low-risk patients) or/plus cytoreduction (that is recommended in high-risk patients) had fourfold less major thrombotic events compared with patients whose hematocrit level was between 45% and 50%.[24] The second is the use of low-dose aspirin (81-100 mg per day), which, in the placebo-controlled European Collaboration on Low-dose Aspirin in PV (ECLAP) trial, reduced the combined risk of nonfatal CE events (myocardial infarction, stroke, pulmonary embolism, major venous thrombosis) or cardiovascular death by 60%.[25] In patients with high-risk disease, the use of cytotoxic drugs is recommended to maintain the target hematocrit level, and hydroxyurea is the drug recommended upfront.[9,26] Although there is no randomized study comparing hydroxyurea to phlebotomy in high-risk patients with PV, the results of a randomized study in high-risk ET[27] and a phase 2 study of the Polycythemia Vera Study Group (PVSG) present arguments for a beneficial effect of hydroxyurea in reduction of thrombosis rate.[28] The potential leukemogenic risk of hydroxyurea has been long debated, and long-term follow-up studies and registry data suggest that this drug is not associated with an appreciably increased rate of AL.[19,29] In 1 long-term randomized study that compared hydroxyurea to pipobroman, the cumulative incidence of AL/MDS was significantly higher in the pipobroman arm (52% vs 24% in the hydroxyurea arm at 20 years).[30] This study highlighted the leukemogenic potential of pipobroman, and provided an estimate of the expected rate of AL/MDS also in patients receiving hydroxyurea; it remains to be assessed whether the non-negligible observed rate of leukemia should be attributed to the natural history of PV rather than a cumulative leukemogenic effect of hydroxyurea over prolonged treatment. However, a conservative approach using the nonleukemogenic interferon-α might be appropriate in younger patients, although no formulation of interferon is licensed with this indication. In several small phase 2 trials, interferon induced a high rate of hematologic response, improved clinical manifestations, and reduced the neoplastic clone, as shown by the decreasing V617F allele burden, whereas other funder mutations (ie, *TET2*) were unaffected.[31] Long-term follow-up of a phase 2 trial with pegylated interferon alfa-2a that enrolled 43 patients with PV and 40 with ET confirmed sustained hematologic (median, 65 months) and molecular (median, 58 months) responses in 79% and 63% of the patients with PV, respectively; however, interferon did not prevent major thromboembolic events, which overall involved 10% of the patients (including ET), although 3 of the 8 vascular events occurred in the settings of surgical or vascular procedures. Interferon did not prevent progression to MF (6 cases; 7%) and AL (1 case); the rate of these transformation events was comparable to the historical matched cohort of patients not treated with interferon.[32] There are 2 phase 3 studies ongoing with different formulations of interferon in high-risk patients with PV. The first of these, the PROUD study, preliminarily reported that ropeginterferon alfa-2b, a new interferon with longer half-life, was not inferior to hydroxyurea with regard to hematologic control, and the number of adverse events, including skin cancers, was generally lower than hydroxyurea.[33] Conversely, interim analysis of a randomized study of pegasys vs hydroxyurea in 72 patients with high-risk PV and ET did not disclose any benefit of interferon in terms of hematologic control, *JAK2*V617F allele burden reduction, and BM morphology changes; tolerability was inferior.[34] In summary, pending final results

Box 1. How we diagnose, communicate diagnosis, and risk-stratify patients with PV and ET

- We adhere to the 2016 WHO guidelines for all patients with suspected PV and ET (Table 1). We routinely perform BM biopsy in patients with hemoglobin levels >18.5 g/dL (men) and 16.5 g/dL (women) in order to grade BM fibrosis; exceptions are older patients in whom biopsy may be contraindicated or not accepted.
- In cases of suspected PV, we routinely search (in order until selecting the winner) the *JAK2*V617F mutation and *JAK2* exon 12 mutations; *LNK* mutations and all *JAK2* exon mutations are reserved for exceptional cases in research centers. In cases of suspected ET, we routinely search (in order) *JAK2*V617F mutation, *CALR* mutations, *MPL* mutations; all *MPL* exon mutations may be searched in rare instances. We do not routinely perform karyotype or extensive mutation analysis by next-generation sequencing; conversely, these tests are usually performed in younger patients who progressed to PPV-MF/PET-MF and are potential candidates for stem cell transplantation.
- We adopt the IWG-MRT criteria for diagnosing PPV-MF and PET-MF (Table 2).
- We use the 2-tiered thrombotic-risk score for risk-stratifying patients with PV (Table 3).
- We use the revised ISPET-thrombosis risk score for risk-stratifying patients with ET (Table 3), although decision about cytoreductive therapy still relies on the 2-tiered thrombotic risk score.
- We discuss with the patient the diagnosis, nature, and course of the disease, the individual risk category; we clarify the noninherited nature of the disease and explore the familiarity of MPN; we inform of the need to be followed lifelong by expert physicians.
- We underscore the relevance of generic cardiovascular risk factors, and eventually refer to specialists for the appropriate management of hypertension, diabetes, obesity, abnormally elevated levels of cholesterol and/or triglycerides, or for counseling about the use of oral contraceptives, which are generally discouraged.
- We aggressively pursue stoppage of smoking in all patients, and eventually refer to counseling.
- We do not routinely perform laboratory assays for thrombophilia, except in younger patients with unusual or recurrent thrombosis, before pregnancy, or when a family history is reported.

of these phase 3 trials, at present there is no hard evidence that interferon is superior to hydroxyurea in preventing CEs or halting disease progression in high-risk PV, whereas tolerability might be an issue; however, tolerability might improve with the newest formulations and the final safety profile might eventually be better than hydroxyurea. Of note, in the US physician survey,[7] 45% of the doctors believed that interferon has the potential to modify the course of PV but only 20% actually used it as the upfront cytoreductive agent; almost 80% preferred hydroxyurea. Similarly, in the German survey, only 3.9% of 1476 PV patients had received interferon as first-line therapy vs 64% for hydroxyurea.[8] Finally, we were quite surprised noticing that, notwithstanding the favorable results of the ECLAP study, aspirin was recommended by only 75% and 66% of the US and German physicians.

Around 10% of the PV patients receiving hydroxyurea develop manifestations of intolerance or respond poorly to the drug; ad hoc criteria for defining intolerance/refractoriness to hydroxyurea were developed through consensus by the ELN[35] (Table 4). Intolerance is represented by mucosal and cutaneous toxicity, such as mouth, genital, and leg ulcers; older subjects may present actinic keratosis and the development of nonmelanoma skin cancers might be facilitated by hydroxyurea. Hydroxyurea-related fever and interstitial pneumonitis are rare events, but require stoppage of treatment. Hematologic intolerance manifests with leukopenia and/or thrombocytopenia at the lowest drug dose required to control hematocrit. Development of cytopenias under hydroxyurea has been associated with risk of transformation to MF and AL and an overall adverse outcome in a retrospective study.[36] According to the ELN/IWG-MRT response criteria,[17] patients who require occasional phlebotomies while receiving an optimally tolerated dose of hydroxyurea should be considered as "resistant" to the drug. However, it has been shown that maintaining some phlebotomy requirement under hydroxyurea, in an otherwise well-controlled disease, is not predictive of increased rate of thrombosis and may not require, in the clinical practice, a shift to second-line options.[37] On the other hand, patients who, in spite of adequate hydroxyurea dose, complain of severe disease manifestations, particularly devastating pruritus, develop severe skin and mucosal toxicities, present progressive and symptomatic spleen enlargement, or poorly tolerate a sustained high rate of phlebotomy should be considered for second-line therapy.

Conventional second-line alternatives are interferon for patients on hydroxyurea, and vice versa, or busulfan; there is no firm demonstration of a leukemogenic effect of this alkylating agent, but its use after long-term hydroxyurea has been correlated with increased rate of transformation, and it should be avoided in younger subjects.[28] Recently, the JAK1 and JAK2 inhibitor ruxolitinib was approved for the treatment of PV patients with refractoriness or intolerance to hydroxyurea, based on the ELN criteria. Two randomized studies, RESPONSE[38] and RESPONSE 2,[39] showed that ruxolitinib was superior to best-available therapy (BAT) in maintaining the target hematocrit level without need of phlebotomy (at a median of 111 weeks of follow-up in the RESPONSE study, this response was maintained in 89% of the responders, ie, 60% of those originally randomized to ruxolitinib).[40] Ruxolitinib also induced complete hematologic responses, that is, normalization of leukocytosis and thrombocytosis, which occurred in 24% of the patients at primary end point assessment (32 weeks) and was maintained in 69%; furthermore, in patients with splenomegaly enrolled in the RESPONSE study, a sustained reduction of spleen volume occurred in 40%. Ruxolitinib was very effective in reducing the symptomatic burden of the patients and ameliorating quality of life[41]; the symptom burden, as assessed by the MPN symptom-assessment form, improved by >50% in 49% of the patients receiving ruxolitinib compared with 5% in the BAT arm. Most patients had impressive improvements of their intractable pruritus with ruxolitinib. Treatment was usually well tolerated, and hematologic toxicity was negligible; however, patients in the ruxolitinib arm suffered from episodes of herpes zoster reactivation (≈5 events per 100 patient-years of exposure, mostly low grade, as compared with none in the control arm). An increase in skin tumors was reported (4.4 vs 2.7 per 100 patient-years in the BAT group), usually in patients with prior history of nonmelanoma skin cancers; the potential increase of skin cancers with ruxolitinib requires careful surveillance of the patients under treatment and long-term safety data. Ruxolitinib did not prevent transformation to PPV-MF and AL in a few cases, with rates consistent with expectations based on historical data. Long-term treatment of up to 4 years induced progressive reductions in *JAK2*V617F

Table 4. Definition of resistance and intolerance to hydroxyurea in patients with PV, according to the ELN consensus

Resistance and intolerance to hydroxyurea in patients with PV: ELN consensus
1. Need for phlebotomy to keep hematocrit <45% after 3 mo of at least 2 g per day of hydroxycarbamide, OR
2. Uncontrolled myeloproliferation, ie, platelet count >400 × 10^9/L AND white blood cell count >10 × 10^9/L after 3 mo of at least 2 g per day of hydroxycarbamide, OR
3. Failure to reduce massive splenomegaly (ie, extending >10 cm from the left costal margin) by >50% as measured by palpation, OR failure to completely relieve symptoms related to splenomegaly, after 3 mo of at least 2 g per day of hydroxycarbamide, OR
4. Absolute neutrophil count <1.0 × 10^9/L OR platelet count <100 × 10^9/L or hemoglobin <100 g/L at the lowest dose of hydroxycarbamide required to achieve a complete or partial clinicohematological response,* OR
5. Presence of leg ulcers or other unacceptable hydroxycarbamide-related nonhematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever at any dose of hydroxycarbamide

*Complete response was defined as: hematocrit <45% without phlebotomy, platelet count <400 × 10^9/L, white blood cell count <10 × 10^9/L, and no disease-related symptoms. Partial response was defined as: hematocrit <45% without phlebotomy, or response in 3 or more of the other criteria.

allele burden, but very few patients obtained complete molecular remission[42] (Box 2).

Therapies for ET

Therapy for conventionally defined high-risk patients with ET is informed by 3 randomized studies. In the Bergamo trial, hydroxyurea vs no cytoreduction significantly reduced the rate of thrombosis from 24% to 3.6% at 27 months.[27] Hydroxyurea was also superior to anagrelide in reducing arterial thrombosis, major bleeding, and progression to MF in the PT-1 study, whereas anagrelide performed better for prevention of venous events.[43] Conversely, in the ANAHYDRET study, anagrelide was not inferior to hydroxyurea for arterial and venous thrombosis, disease progression, or hemorrhage. These differences might be in part related to different enrollment criteria, with the use of the more selective WHO criteria in the ANAHYDRET study as compared with PT-1 study.[44]

Interferon has been shown to induce hematologic and molecular remissions in a subset of ET patients, particularly those with *CALR* mutation, provided there are no additional nondriver mutations.[45] In the long-term phase 2 study mentioned in the previous section (which, however, included mostly patients with advanced refractory disease), thrombosis and myelofibrotic transformation were seen; the ultimate impact of treatment on the natural history of disease remains uncertain. Long-term follow-up of the randomized study of the Myeloproliferative Disease-Research Consortium will help to better position interferon in the treatment of ET. Results of a phase 2 study with ruxolitinib in hydroxyurea-resistant or refractory patients have been reported.[46]

No prospective study has addressed the safety and antithrombotic efficacy of low-dose aspirin in patients with ET, and its use is based on indirect evidence and expert recommendations. A retrospective study highlighted an excess of hemorrhage, and no advantage to thrombosis rate, in low-risk *CALR*-mutated patients receiving antiplatelet agents,[47] whereas some benefit was seen in patients with *JAK2*V617F mutation or cardiovascular risk factors.[48] On the other hand, there is preclinical evidence supporting the need for twice-daily doses of aspirin, due to accelerated renewal of platelet cyclooxygenase-1 owing to the rapid platelet production from megakaryocytes; however, until randomized trials prove the safety and added value of a higher aspirin dose, we prefer to use the single pill, if not otherwise indicated.[49] Low-dose aspirin usually resolves or mitigates microvascular symptoms, whereas a higher dose may occasionally be needed for painful erythromelalgia attacks (Box 3).

Special situations

Pregnancy

Information about pregnancy rate, risk factors, and outcome in PV and ET derive from small studies, often with conflicting results; however, because the number of young patients diagnosed with PV and ET is exponentially rising, the issue of managing a pregnancy might become much more common than in the past. Maternal morbidity is rare, but unsuccessful pregnancy occurs in up to 30% of the instances.

Box 2. How we treat patients with PV

- We discuss with the patient the rationale and goals of treatment, choice of drugs, and the potential side effects and how to report them.
- We advise about the importance of maintaining a hematocrit <45% with phlebotomy and/or cytoreductive drugs. Generally, we use the same hematocrit target irrespective of sex, although some experts indicate 42% as the optimal target for women.
- At diagnosis, or in cases of coincident thrombotic event, phlebotomy rate should be intensive, even at alternate days, in order to quickly reach the target hematocrit level.
- In low-risk patients, we use phlebotomy as the only cytoreductive approach.
- We use hydroxyurea as first-line drug in high-risk patients, adjusted to maintain the hematocrit level to <45%, eventually supplemented with phlebotomies as needed. In younger subjects, interferon is an off-label alternative. Busulfan is very effective, but should be reserved to older subjects. We do not use pipobroman or radioactive phosphorus any longer.
- Hydroxyurea or interferon also may be indicated in occasional low-risk patients who need, and poorly tolerate, frequent phlebotomies, have unmanageable disease-related symptoms, present extensive thrombocytosis or progressively increasing leukocyte count, or suffer from symptomatic splenomegaly (all are indeed quite rare instances).
- We use low-dose aspirin in all PV patients, unless it is clearly contraindicated. In cases of poor tolerance, we prefer to add anti-H2 agents rather than switching to another antiplatelet agent. We do not routinely use long-life prophylaxis with anti-H2 in patients who tolerate aspirin well.
- We use ruxolitinib as second-line therapy in selected patients with clinically relevant toxicities due to hydroxyurea, or when the maximum tolerated dose of hydroxyurea does not produce a satisfactory hematocrit control and the patient does not tolerate a persistently high phlebotomy rate, or presents large, symptomatic splenomegaly, refractory disease-associated symptoms, or incoercible pruritus. We advise patients about possible herpes zoster reactivation and skin tumors.

Box 3. How we treat patients with ET

- In high-risk ET patients, we use hydroxyurea as first-line agent; in younger patients, interferon (preferentially pegylated preparation; off-label use) is an alternative. We use anagrelide as second line when thrombocytosis is refractory to the maximum tolerated dose of hydroxyurea or interferon, or when the patient develops not-otherwise-manageable toxicities to first-line agent. Busulfan as second line is reserved for older subjects. We do not use pipobroman.
- In low-risk patients, we watch-and-wait. We do not consider isolated thrombocytosis (up to 1500×10^9/L), if asymptomatic, to require cytoreduction.
- In high-risk ET patients, we prescribe aspirin, irrespective of mutation status, whereas in low risk, we prefer to reserve aspirin for those who are *JAK2*V617F or *MPL* mutated. Provided no cardiovascular risk factor is present, we tend to avoid aspirin in younger *CALR*-mutated patients.
- We do not routinely assay for von Willebrand factor activity, if there is no evidence of hemorrhagic manifestations, but we do interrupt aspirin in patients with platelet count in excess of 1000×10^9/L.

Pregnancy should be planned, as long as possible, and disease management should be optimized before conception. The criteria commonly used for defining a high-risk pregnancy are reported in Table 5.[26] For a low-risk pregnancy, there is no need to modify the standard treatment, including phlebotomy in a low-risk PV patient, taking care to maintain hematocrit levels within a gestation-appropriate target range; for women with high-risk disease, hydroxyurea and anagrelide should be stopped in advance (at least 3-6 months) and eventually interferon might be prescribed. For the case of a high-risk pregnancy in an otherwise low-risk patient, interferon might be considered. Low-dose aspirin is used during the entire pregnancy up to about 2 weeks before planned delivery, followed by heparin that is maintained for an additional 6 to 8 weeks after delivery. In the case of a high-risk pregnancy, heparin should be used for the entire duration of pregnancy. Strict collaboration with an expert gynecologist/obstetrician is mandatory.

Anticoagulation

In patients with major venous thrombosis who have very high-risk features (recurrent events, splanchnic and cerebral sinus vein thrombosis, thrombophilia), we advise maintaining permanent anticoagulation. Although there is no controlled study to support this practice, a retrospective study in 206 patients with MPN-related venous thromboembolism showed an incidence rate of recurrence of 5.3 (95% CI, 3.2-8.4) per 100 patient-years in those on continuous vitamin K antagonist compared with 12.8 (95% CI, 7.3-20.7) in those who discontinued anticoagulation.[50] There was a slightly higher, not significant, increase of bleeding with continuous anticoagulation. However, this study also suggests that, in spite of prolonged anticoagulation, the rate of recurrent venous thrombosis remains high, representing a still unmet need. We routinely use vitamin K antagonists, but we anticipate that the use of new direct oral anticoagulants will rise in the near future. A recent report of 25 patients with PV and ET treated with direct oral anticoagulants preliminarily suggests efficacy and safety of these drugs.[51] The combined use of anticoagulation and aspirin should be reserved for patients with recurrent arterial and venous thrombosis and multiple cardiovascular risk factors, after carefully weighting individual potential benefit and risk.

Table 5. Criteria for "high-risk pregnancy" in a woman with PV or ET

High-risk pregnancy criteria for PV or ET
Sustained rise in platelet count to $>1500 \times 10^9$/L
Previous venous or arterial thrombosis
Previous hemorrhage attributed to the underlying PV or ET
Previous pregnancy complication, including any of the following:
• ≥1 unexplained deaths of a morphologically normal fetus ≥10 wk of gestation
• ≥1 premature delivery of a morphologically normal fetus <34 wk gestation because of:
(i) Severe preeclampsia or eclampsia defined according to standard definitions
(ii) Recognized features of placental insufficiency
• ≥3 consecutive otherwise unexplained miscarriages <10 wk gestation,
• Otherwise unexplained intrauterine growth restriction
• Significant antepartum or postpartum hemorrhage requiring transfusion
• Abnormal uterine artery Doppler at 20 wk (mean pulsatility index >1.4)

Extreme thrombocytosis

In low-risk asymptomatic patients with platelet counts even up to 1500×10^9/L, we do not routinely use cytoreduction, and we avoid aspirin when platelets are above 1 million; however, in this regard, there are different opinions. In case of newly diagnosed, extreme thrombocytosis ($>2000 \times 10^9$/L), we promptly institute cytoreductive therapy with full-dose (2 g per day) hydroxyurea. In selected cases where rapid reduction of such extremely elevated platelet count is desirable because of ongoing hemorrhage, recent thrombosis, or severe neurologic symptoms due to microvascular disturbances, plateletpheresis might be used. While waiting for interferon to effectively control a recently discovered extreme thrombocytosis, plateletpheresis might be used exceptionally during pregnancy.

Conclusions

The last 2 decades have seen significant improvements in diagnosing PV and ET earlier and more accurately, identifying the variables associated with risk of complications and dying, delivering more tailored therapeutic approaches, and developing novel agents, all resulting overall in improved survival and quality of life. Such improvements resulted mainly from application of molecular biology tools, epidemiologic studies, and few, but basic, controlled clinical trials. Yet, these disorders remain the orphan of curative options, and it is not yet clear how much the novel agents are meeting the expectations of being disease-modifiers. Therefore, it is recommended that physicians support patients with PV and ET in their willingness to participate in novel studies, wherever there are basic and translational science studies, epidemiologic studies, or intervention trials; additionally, companies are urged to continue to invest in pharmacologic research and clinical trials in this area.

Acknowledgments

This work was supported by a grant from Associazione Italiana per la Ricerca sul Cancro (AIRC; Milan, Italy), Special Program Molecular Clinical Oncology 5x1000 to AIRC–Gruppo Italiano Malattie Mieloproliferative (AGIMM) project 1005.

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