Polycythemia Vera Management and Challenges in the Community Health Setting

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Abstract

Patients with polycythemia vera (PV) experience shortened survival, increased risk of thromboembolic and hemorrhagic events, and burdensome symptoms. For all patients with PV, treatment with aspirin and hematocrit control with phlebotomy are recommended. In addition, patients with high-risk status or poor hematocrit control benefit from cytoreductive therapy with hydroxyurea, although approximately 1 in 4 patients develops resistance or intolerance. For patients who are resistant to or intolerant of hydroxyurea, studies have shown that ruxolitinib, a Janus kinase 1/2 inhibitor, provides hematocrit control, reduces spleen size, normalizes blood counts, and improves PV-related symptoms. For many patients, PV is managed in a community health setting, and it is important that community hematologists, oncologists, and internists are familiar with the contemporary management of PV to improve patient outcomes, including management for patients who present with unique health-care needs. This review provides an overview of current treatment options for patients with PV and discusses challenging

circumstances encountered by community providers in the management of PV, including symptom assessment, identification of hydroxyurea resistance/intolerance, pregnancy, elective surgeries, concomitant immunosuppressants, and managing patients in areas with limited access to specialized hematologic care.

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Introduction

The World Health Organization distinguishes polycythemia vera (PV) from other myeloproliferative neoplasms (MPNs) primarily on erythrocytosis and activating mutations in *Janus kinase 2 (JAK2)*, and updated criteria include marrow trilineage myeloproliferation as assessed by bone marrow biopsy and lower hemoglobin thresholds for erythrocytosis [1]. Patients with PV, including the estimated 100,000 with PV in the US [2], experience burdensome symptoms [3] and have an increased risk of mortality compared with age- and sex-matched individuals in the general population [4]. Thromboembolic and hemorrhagic events are the most common complications and the leading causes of disease-related death, with disease transformation to myelofibro-

sis (MF) or acute myeloid leukemia (AML) being a less common contributor to patient mortality [5, 6]. Symptoms often experienced by patients with PV include fatigue, concentration problems, itching, and inactivity, as well as splenomegaly-associated symptoms (e.g., early satiety and abdominal discomfort or pain) [3]. Nearly all patients with PV have activating mutations in *JAK2*, most often *JAK2*V617F in exon 14, and less frequently *JAK2* exon 12 or other mutations [5]. Constitutively active *JAK2* signaling is the driver for PV disease features, including elevated hematocrit and blood counts, pruritus, splenomegaly, thrombotic risk, risk of fibrotic transformation [7], and systemic inflammation [8].

Community-based oncologists often take a leading role in managing patients with PV, and optimal care requires up-to-date knowledge of management strategies, treatment guidelines, and approved therapies. Community-based providers also face challenging circumstances beyond the “textbook” patient with PV, such as patients with limited access to hematologic care, a lack of tools to assess PV-related symptoms, hydroxyurea resistance or intolerance, pregnancy, elective surgery, and concomitant treatment with immunosuppressants. This review summarizes the use of traditional treatment options for patients with PV, clinical trial evidence for the use of ruxolitinib in PV, disease management challenges (including those unique to community providers), and potential future treatment options.

PV Management

Risk Factors and Traditional Treatment Options

The management of patients with PV is primarily guided by risk of thromboembolic events. Risk factors in patients with PV traditionally include age ≥ 60 years, history of thrombosis [9], and hematocrit level $\geq 45\%$ [10]. In addition, nonconventional risk factors requiring further validation include white blood cell count $\geq 11 \times 10^9/L$ [11], female sex [12], molecular markers such as mutant *JAK2* allele burden [13], and traditional cardiovascular risk factors (i.e., diabetes mellitus, current smoking status, elevated cholesterol, and high systolic blood pressure) [14]. Combined, these varied risk factors suggest that current risk stratification systems based solely on age and thrombosis history [9] may be insufficient to identify all high-risk patients. All patients, regardless of risk stratification, are treated with low-dose aspirin [15] and phlebotomy leading to iron deficiency that maintains hematocrit levels $<45\%$ [10]. Moreover, some experts advocate

for hematocrit levels $<42\%$ in women because this would be more in line with the normal physiologic range [16]. In addition, some patients, including those identified by the aforementioned risk factors, derive additional clinical benefit from cytoreductive treatment [17]. Hydroxyurea is recommended as first-line cytoreductive therapy by European LeukemiaNet (ELN) guidelines [18] and is the most common cytoreductive therapy for patients with PV [19]. However, approximately one quarter of patients will become resistant or intolerant [20]. Treatment with conventional interferon (IFN)- α is associated with clinical benefit, including normalized blood counts and improved pruritus for some patients [21]. However, IFN- α -associated toxicity, especially at high doses, and inconvenience as an injectable drug negatively affect long-term tolerability and adherence for some patients [21]. Pegylated (PEG) variants of IFN- α with improved safety and tolerability profiles are currently in phase 3 clinical development (see the Potential Future Treatment Options section below). Busulfan or pipobroman may be considered after failure of first-line treatment options, but limited to patients with a short life expectancy because of leukemogenic potential [9, 18]. Neither hydroxyurea, IFN- α , nor busulfan have been approved by the US Food and Drug Administration (FDA) for patients with PV.

It remains unclear if these traditional treatment options significantly improve PV-related symptoms or quality of life (QoL) [22]. In a retrospective analysis of patients with PV ($n = 538$), hydroxyurea, IFN- α , aspirin, and/or phlebotomy were not associated with significant improvement in patient-reported symptom severity. Furthermore, in a prospective analysis, patients with PV ($n = 1,334$) treated with phlebotomy and/or hydroxyurea continued to experience more severe symptoms compared with untreated patients [23]. Considered together, these findings emphasize an unmet treatment need for some patients with PV.

Ruxolitinib

Ruxolitinib is a potent *JAK1/JAK2* inhibitor that is approved by the FDA for patients with PV who have had an inadequate response to or are intolerant of hydroxyurea [24]. Ruxolitinib is also indicated by the FDA for the treatment of patients with intermediate or high-risk MF, including primary MF, post-PV MF, and postessential thrombocythemia (ET) MF [24]. Regulatory approval of ruxolitinib for PV was based on the ongoing, randomized, open-label, multicenter phase 3 RESPONSE trial, which evaluated the efficacy and safety of ruxolitinib ver-

sus best available therapy (BAT) in patients with PV who were hydroxyurea-resistant/intolerant (ClinicalTrials.gov identifier, NCT01243944) [8]. Eligible patients required phlebotomy to achieve hematocrit control and had splenomegaly. Crossover to ruxolitinib was permitted starting at week 32 following failure to meet the primary composite endpoint (hematocrit control without phlebotomy and $\geq 35\%$ reduction in spleen volume at week 32) or disease progression (phlebotomy eligibility and/or progression of splenomegaly).

Overall, ruxolitinib provided superior clinical benefit compared with BAT in a number of domains. At week 32, larger proportions of patients in the ruxolitinib group, compared with BAT, experienced both spleen reduction and hematocrit control (23 vs. 1%; $p < 0.001$) [8, 25] and complete hematologic remission (defined as hematocrit control, platelet count $\leq 400 \times 10^9/L$, and white blood cell count $\leq 10 \times 10^9/L$; 24 vs. 8%; $p = 0.0016$).

A preplanned analysis after all patients had reached the 80-week visit or had discontinued treatment indicated that responses with ruxolitinib were durable. Patients who achieved the primary endpoint had a 92% probability of maintaining response for 80 weeks and a 69% probability of maintaining complete hematologic remission [25]. Importantly, most patients (71%) who did not achieve the protocol-defined hematocrit control endpoint at week 32 responded with extended treatment duration in the 80-week analysis [26].

In an exploratory analysis from the RESPONSE trial, more patients treated with ruxolitinib versus BAT achieved $\geq 50\%$ reductions in symptom scores for the MPN Symptom Assessment Form (MPN-SAF) total symptom score (49 vs. 5%), cytokine symptom cluster (64 vs. 11%), hyperviscosity symptom cluster (37 vs. 13%), and the splenomegaly symptom cluster (62 vs. 17%) [8]. Ruxolitinib was also associated with greater improvements in the severity of individual MPN-SAF symptoms (Table 1) [8]. Patient-reported results from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and Pruritus Symptom Impact Scale similarly favored ruxolitinib. Finally, more patients receiving ruxolitinib reported their condition was “very much improved” or “much improved” using the Patient Global Impression of Change (68%) compared with those receiving BAT (13%).

Eighty-three percent of patients in the ruxolitinib arm continued treatment through the 80-week analysis of the RESPONSE trial. None of the patients in the BAT arm continued randomized treatment long-term [25],

Table 1. Median percentage change from baseline in MPN-SAF symptom scores at week 32 in the RESPONSE trial

Symptom	Ruxolitinib (n = 110)	Best available therapy (n = 112)
Cytokine symptom cluster		
Sweating while awake	−100	−4.4
Itching	−94.9	−2.1
Muscle ache	−61.1	0.4
Night sweats	−99.5	3.9
Tiredness	−49.6	−4.2
Hyperviscosity symptom cluster		
Dizziness	−80.2	7.9
Skin redness	−64.1	5.0
Headache	−51.5	11.1
Concentration problems	−44.0	16.7
Vision problems	−41.8	10.9
Numbness/tingling in hands/feet	−37.1	15.7
Ringing in ears	0	17.2
Splenomegaly symptom cluster		
Early satiety	−93.9	0
Abdominal discomfort	−65.9	1.4

Data from Vannucchi et al. [8]. Negative values indicate an improvement in symptom severity. MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form.

with most crossing over to ruxolitinib at or shortly after week 32 [8].

In the primary analysis of the RESPONSE trial, adverse events (AEs) in both treatment arms were primarily grade 1 or 2, and the incidence of grade 3 or 4 AEs was lower with ruxolitinib compared with BAT (28.8 vs. 44.0 per 100 patient-years of exposure) (Table 2) [8]. Grade 1 or 2 herpes zoster infections occurred only in patients receiving ruxolitinib (6.4%) [8]. Infections of any grade occurred in 42 versus 37% of patients in the ruxolitinib and BAT arms, respectively; grade 3 or 4 infections occurred in 4 versus 3% of patients. Nonmelanoma skin cancer was observed in 4 patients receiving ruxolitinib and 2 patients receiving BAT [8]; however, all but 1 patient in the BAT arm had a history of nonmelanoma skin cancer. Thromboembolic events occurred in 1 patient in the ruxolitinib arm and 6 patients in the BAT arm through week 32, before crossover was permitted [8].

At data cutoff for the 80-week analysis, 6 patients treated with ruxolitinib had progressed to MF (rate/100 patient-years of exposure: ruxolitinib arm, 1.3; ruxolitinib crossover group, 2.0), and there were 2 cases of AML (ruxolitinib arm, 0.4; ruxolitinib crossover group, 0.7)

Table 2. Adverse events regardless of causality in the primary analysis of the RESPONSE trial

Adverse events	Ruxolitinib (n = 110)		Best available therapy (n = 111) ^c	
	all grades	grades 3 or 4	all grades	grades 3 or 4
Nonhematologic ^a				
Headache	16.4	0.9	18.9	0.9
Diarrhea	14.5	0	7.2	0.9
Fatigue	14.5	0	15.3	2.7
Pruritus	13.6	0.9	22.5	3.6
Dizziness	11.8	0	9.9	0
Muscle spasms	11.8	0.9	4.5	0
Dyspnea	10.0	2.7	1.8	0
Abdominal pain	9.1	0.9	11.7	0
Asthenia	7.3	1.8	10.8	0
Hematologic ^b				
Anemia	43.6	1.8	30.6	0
Lymphopenia	43.6	16.4	50.5	18.0
Thrombocytopenia	24.5	5.5	18.9	3.6
Leukopenia	9.1	0.9	12.6	1.8
Neutropenia	1.8	0.9	8.1	0.9

From Vannucchi et al. [8]. Reprinted with permission from Massachusetts Medical Society. Values indicate percentages.

^a Events occurring in ≥10% of patients in either treatment group.

^b These were new or worsening abnormalities as assessed on the basis of laboratory values. ^c One patient withdrew consent and did not receive study treatment.

[25]. No patients died during the randomized phase; however, there were 2 deaths unrelated to study drug after crossover to ruxolitinib.

Two limitations of RESPONSE should be considered further. First, eligible patients were hydroxyurea-resistant/intolerant; however, 59% in the BAT group continued hydroxyurea treatment [8]. This management approach was consistent with real-world practice before regulatory approval of ruxolitinib, in which some physicians continued hydroxyurea despite diminished benefit because of limited alternative treatment options [8, 27]. Furthermore, in subgroup analyses by treatment type in the BAT arm, ruxolitinib was associated with greater clinical benefit at week 32 versus nonhydroxyurea treatment options for achievement of a ≥35% reduction from baseline in spleen volume (40 vs. 0%, respectively), hematocrit control without phlebotomy (60 vs. 16%) [8, 25], and a ≥50% improvement from baseline in MPN-SAF TSS (49 vs. 6%) [28]. Second, patients were required to have spleen volume ≥450 cm³, potentially recruiting some patients with MF inappropriately diagnosed with PV. All

patients were required to be diagnosed per the 2008 WHO criteria to minimize misdiagnosis. In addition, the ongoing phase 3b RESPONSE 2 trial is evaluating ruxolitinib versus BAT in patients with PV who are hydroxyurea-resistant/intolerant and have a nonpalpable spleen. Early results indicate that ruxolitinib is superior to BAT at week 28 for achievement of hematocrit control without phlebotomy (62 vs. 19%; *p* < 0.0001) and a ≥50% improvement from baseline in MPN-SAF TSS (45 vs. 23%) [29].

Implications for Practice

The FDA and European Medicines Agency approval of ruxolitinib for patients with PV who are hydroxyurea-resistant/intolerant [30] has provided an important treatment option for patients with PV. The cornerstone of therapy continues to be low-dose aspirin [15] and phlebotomy to maintain hematocrit levels <45% to reduce the risk of cardiovascular events and related death [10]. Moreover, it is important to identify those with high-risk features (e.g., age ≥60 years, thrombotic events) or poor hematocrit control with phlebotomy to determine if cytoreductive therapy with hydroxyurea or IFN-α should be added [18]. Of equal importance is the regular assessment of patients for signs of disease resistance, progression (e.g., changing blood counts, escalating symptoms, spleen growth) [18], or intolerance as defined by ELN criteria (Table 3) [31, 32], at which point they should be considered for an alternative therapy such as ruxolitinib.

Challenges and Special Considerations for Community-Based Hematologists, Oncologists, and Primary Care Physicians

Patient Management in Areas with Limited Access to Hematologic Care

Continuous appraisal of the medical literature and application of clinical advances, often synthesized in reviews and guidelines, is needed to develop optimal treatment plans [9, 18]. In rural or underserved areas, patients with PV may not have local access to hematology/oncology specialty care. In such cases, primary care physicians may be tasked with managing PV and may be unaware of current treatment guidelines and goals (e.g., maintaining hematocrit level <45% [10]) and PV-specific complications (e.g., acquired von Willebrand disease in some patients with PV, in the presence or absence of excessively elevated platelet counts [33]). Moreover, patients may not have access to health-care providers with experience in performing or facilities that routinely perform phlebotomy.

Table 3. European LeukemiaNet criteria for hydroxyurea resistance/intolerance in patients with polycythemia vera

- 1 Need for phlebotomy to keep hematocrit <45% after 3 months of ≥ 2 g/day of hydroxyurea OR
- 2 Uncontrolled myeloproliferation (i.e., platelet count $>400 \times 10^9/L$ AND white blood cell count $>10 \times 10^9/L$) after 3 months of ≥ 2 g/day of hydroxyurea OR
- 3 Failure to reduce massive^a splenomegaly by >50% as measured by palpation OR failure to completely relieve symptoms related to splenomegaly after 3 months of ≥ 2 g/day of hydroxyurea OR
- 4 Absolute neutrophil count $<1.0 \times 10^9/L$ OR platelet count $<100 \times 10^9/L$ OR hemoglobin <100 g/L at the lowest dose of hydroxyurea required to achieve a complete or partial clinicohematologic response^b OR
- 5 Presence of leg ulcers or other unacceptable hydroxyurea-related nonhematologic toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever at any dose of hydroxyurea

Adapted with permission from Barosi et al. [32]. ^a Organ extending by >10 cm from the costal margin. ^b Complete response was defined as hematocrit <45% without phlebotomy, platelet count $\leq 400 \times 10^9/L$, white blood cell count $\leq 10 \times 10^9/L$, and no disease-related symptoms. Partial response was defined as hematocrit <45% without phlebotomy or response in ≥ 3 of the other criteria [31].

mies; in such cases, managing clinicians may need to develop an alternative treatment plan for their patient's PV. In these instances, even a single visit with a specialist with a focus on MPNs, followed by a care partnership between consultant and referring physician, can extend expertise into areas with limited access to specialized care.

Symptom Assessments

Patients with PV are often burdened with symptoms that negatively affect QoL [3], and routine evaluation with validated instruments is critical to adequately assess patients for the presence of, severity of, and changes in PV-related symptoms. This focus on patient reported outcomes (PROs) as part of disease treatment monitoring is a somewhat unique approach in cancer medicine. Of new oncology medications approved by the FDA between 2010 and 2014, only 3 (7.5%; ruxolitinib, abiraterone acetate, and crizotinib) had PRO-related labeling [34].

The MPN-SAF is a validated objective tool that evaluates the severity of key symptoms experienced by patients with PV and other MPNs [35]. PROs with the MPN-SAF are strongly correlated with patient responses on the

EORTC QLQ-C30, as well as physician perceptions of patient symptoms, and are consistent between serial administrations. The shorter, 10-question version of the MPN-SAF (Table 4) [3] is used to track a patient's symptoms over time while on treatment and can be a useful tool to identify new or worsening trends in PV-related symptoms. Patients treated at the Mayo Clinic complete the MPN-SAF when checking in or during vital sign measurements, so the results are available for the physician visit, whereas patients at the Cleveland Clinic review the 10-question MPN-SAF with the physician or nurse at every visit.

Identification of Hydroxyurea-Resistant/Intolerant Patients

Retrospective analysis has noted that patients who develop hydroxyurea resistance have a 7-fold increased risk of disease transformation to MF and/or AML and a 6-fold increased risk of death over a median follow-up period of 7.2 years [20]. Therefore, these high-risk patients treated with hydroxyurea should be assessed at regular intervals for resistance or intolerance based on the ELN criteria (Table 3) [31, 32] to minimize delays in treatment changes when needed. There are also other circumstances when the treating physician should use clinical judgment beyond published criteria to determine whether hydroxyurea may be inappropriate. For example, discontinuation of hydroxyurea is required to promote healing of leg ulcers [36]. Although it has not been evaluated in a clinical trial, physicians could consider interruption of hydroxyurea in situations where poor wound healing not explicitly included in the ELN criteria may affect clinical outcome. Furthermore, some concomitant therapies may increase hydroxyurea toxicity [37], such as methotrexate and psoralen plus ultraviolet light treatment for autoimmune disorders or atopic dermatitis. As outlined elsewhere in this review, second-line treatment options for patients with PV who are hydroxyurea-resistant/intolerant include primarily IFN- α [18] and ruxolitinib [30].

Pregnancy

Pregnancy is relatively rare among patients with PV because disease onset is often later in life, with only 10% of patients diagnosed at <40 years of age [5]. A review of 36 pregnancies in 18 patients with PV reported increased risks for both the fetus and mother [38]. Pregnancy ended in miscarriage in 15 of 21 cases, 8 of which occurred in the first trimester, and an additional 3 resulted in neonatal deaths. Maternal outcomes included preeclampsia

Table 4. The 10-question MPN-SAF

Symptom											
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 h*. ^a	0	1	2	3	4	5	6	7	8	9	10
Circle the one number that describes, during the past week, how much difficulty you have had with each of the following symptoms											
Filling up quickly when you eat (early satiety) ^b	0	1	2	3	4	5	6	7	8	9	10
Abdominal discomfort ^b	0	1	2	3	4	5	6	7	8	9	10
Inactivity ^b	0	1	2	3	4	5	6	7	8	9	10
Problems with concentration – compared to prior to my MPD ^b	0	1	2	3	4	5	6	7	8	9	10
Numbness/tingling (in my hands and feet) ^b	0	1	2	3	4	5	6	7	8	9	10
Night sweats ^b	0	1	2	3	4	5	6	7	8	9	10
Itching (pruritus) ^b	0	1	2	3	4	5	6	7	8	9	10
Bone pain (diffuse not joint pain or arthritis) ^b	0	1	2	3	4	5	6	7	8	9	10
Fever (>100°F) ^c	0	1	2	3	4	5	6	7	8	9	10
Unintentional weight loss last 6 months ^b	0	1	2	3	4	5	6	7	8	9	10

Reproduced with permission from Emanuel et al. [3]. * Question used with permission from the MD Anderson Cancer Center Brief Fatigue Inventory[®]. 1 to 10 (0 if absent) ranking. 1 is most favorable and 10 least favorable. ^a “No fatigue” (0) to “worst imaginable” (10); ^b “absent” (0) to “worst imaginable” (10); ^c “absent” (0) to “daily” (10). MPD, myeloproliferative disease; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form.

($n = 4$), pulmonary emboli ($n = 2$), postpartum hemorrhage ($n = 1$), and death ($n = 1$). Importantly, all 36 cases occurred before the identification of JAK2-activating mutations and current treatment recommendations regarding low-dose aspirin and hematocrit control <45%. A more recent retrospective study of 48 patients with PV reviewed the outcomes of 39 pregnancies that occurred before and 70 evaluable pregnancies that occurred after PV diagnosis [39]. Median age (range) at delivery was 32 years (21–43 years). Following diagnosis of PV, patients were treated with low-dose aspirin during pregnancy and low-molecular-weight heparin from delivery to 6 weeks postpartum; a target hematocrit of 40% was maintained with phlebotomy. The live birth rate was significantly higher in pregnancies that occurred after versus before diagnosis (77 vs. 49%; $p = 0.002$). Pregnancies that occurred before PV diagnosis ended in spontaneous abortion (23%), still birth (21%), and late fetal loss (8%); after PV diagnosis, 17% ended in spontaneous abortion, 4% in still birth, and 1% with an ectopic pregnancy. Severe maternal thromboembolic event rates were similar between pregnancies that occurred before (2.6%) and after (2.8%) PV diagnosis, whereas the maternal bleeding rate was lower in pregnancies that occurred before PV diagnosis ($p = 0.036$). There were no maternal deaths.

The ELN guidelines recommend that treatment during pregnancy be limited to anticoagulation with aspirin or low-molecular-weight heparin, phlebotomy, and IFN- α , stratified by pregnancy risk (Table 5) [18]; however, this recommendation is not based on prospective clinical evidence. Ruxolitinib has not been evaluated in pregnant patients who have PV and should be avoided.

Elective Surgeries

Surgery may increase the risk of morbidity and mortality among patients with PV. A retrospective study of patients with PV ($n = 105$) or ET ($n = 150$) who underwent surgery ($n = 311$ procedures) reported 12 arterial thromboses, 12 venous thromboses, 23 major hemorrhages, 7 minor hemorrhages, and 5 deaths during a 3-month follow-up period [40]. Treatment with heparin or antiplatelet drugs was not significantly associated with patient outcomes [40]. Risk for postsurgical complications may be lower among patients with hematologic control compared with uncontrolled patients, based on an older retrospective study [41]. However, current prospective data are lacking and will be required to better inform management strategy. We recommend hematocrit maintenance <45% and normalization of blood counts for ≥ 3 months before elective surgery [42]. Low-

Table 5. European LeukemiaNet treatment strategy for patients with polycythemia vera during pregnancy

Pregnancy risk	Therapy
Low-risk pregnancy	Target hematocrit <45% OR mid-gestation-specific range, whichever is lower PLUS Low-dose aspirin PLUS Prophylactic dose low-molecular-weight heparin after delivery until 6th week postpartum
High-risk pregnancy ^a	Low-risk pregnancy therapy PLUS If previous major thrombosis or severe pregnancy complications: low-molecular-weight heparin throughout pregnancy (stop aspirin if bleeding complications) If platelet count >1,500 × 10 ⁹ /L: consider interferon-α If previous major bleeding: avoid aspirin and consider interferon-α to reduce thrombocytosis

Adapted with permission from Barbui et al. [18]. ^a Features consistent with high-risk myeloproliferative neoplasm pregnancy include: previous venous or arterial thrombosis (whether pregnant or not); previous hemorrhage attributed to myeloproliferative neoplasm (whether pregnant or not); previous pregnancy complication that may have been caused by myeloproliferative neoplasm, such as unexplained recurrent first-trimester loss (3 unexplained first-trimester losses), intrauterine growth restriction (birth weight less than 5th percentile for gestation), intrauterine death or stillbirth (with no obvious other cause, evidence of placental dysfunction, and growth restricted fetus), severe pre-eclampsia (necessitating preterm delivery before 34 weeks), or development of any such complication in the index pregnancy; placental abruption; significant ante- or postpartum hemorrhage; and marked sustained increase in platelet count to >1,500 × 10⁹/L.

molecular-weight heparin should be delivered at a prophylactic dose starting a minimum of 12 h before surgery because of high thrombotic risk in this patient population [42]. Guidelines for the specific surgical intervention should guide the application of additional treatments for thrombosis prophylaxis. Most patients are required to stop aspirin typically 5 days ahead of surgeries or major procedures. This period without antiplatelet therapy may increase PV patients' risk for thrombotic events [15] and may be best managed temporarily with low-molecular-weight heparin, especially those with high-risk clinical characteristics as described. Ruxolitinib has not been evaluated in patients with PV undergoing surgical procedures, and each case must be examined for individual risks and benefits. In general, with the concern for a potential rebound of symptoms following discontinuation

of ruxolitinib, we recommend continuing treatment through surgery, although the current ruxolitinib prescribing information does not provide guidance regarding use during surgery. If ruxolitinib is to be discontinued, a taper can be considered, and ruxolitinib should be discontinued within 1–2 weeks before the procedure to assess for rebound of symptoms.

Concomitant Immunosuppressants

Patients with other illnesses or comorbidities requiring treatment with high-dose prednisone or other steroids [43] or other immunosuppressants [44], especially for extended periods, may be at increased risk of infections, although this has not been evaluated in prospective clinical trials in patients with PV. Concomitant treatment with ruxolitinib should be used with caution, with regular monitoring for signs of infection, notably herpes zoster [8]. Prophylaxis with acyclovir is suggested by the authors if ruxolitinib is combined with other immunosuppressive agents, although there is no clinical study to support this specific recommendation. We provide this recommendation based on clinical experience and anecdotal cases, while also considering the low toxicity profile of acyclovir used at prophylactic doses (e.g., 800 mg daily), which is a common practice in the treatment of lymphoid and myeloid malignancies [45]. Patients on ruxolitinib should also avoid live-attenuated vaccines such as the intranasal flu vaccine and zoster vaccine.

Potential Future Treatment Options

Several potential new treatment options are currently in phase 3 clinical trials for patients with PV or post-PV MF, including PEG-IFN-α variants, other JAK inhibitors, and the telomerase inhibitor imetelstat.

Pegylated IFN-α

To address toxicity and tolerability challenges associated with conventional IFN-α treatments, PEG-IFN-α variants have been developed that have longer plasma half-lives compared with conventional IFN-α, and therefore may be administered weekly rather than daily [21].

The PEG-IFN-α₂ variants in clinical development for patients with PV include PEG-IFN-α_{2a} (Genentech, San Francisco, CA, USA), PEG-IFN-α_{2b} (Merck, Whitehouse Station, NJ, USA), and AOP2014/P1101 (Merck). AOP2014 is a variant of PEG-IFN-α_{2b} in which PEG is attached to IFN-α_{2b} by a stable bond to an N-terminal proline residue that is not present in the comparatively less

stable PEG-IFN- α_{2b} , resulting in a longer half-life [46]. In phase 2 clinical trials with PEG-IFN- α_{2a} (ClinicalTrials.gov identifiers, NCT00241241 and NCT00452023) and AOP2014 (ClinicalTrials.gov identifier, NCT01193699), hematologic response rates ranged from 80 to 100%, with complete hematologic response achieved by 53–95% of patients after median follow-up ranges of 18–31 months [47–49]. Molecular response rates based on reductions in *JAK2* allele burden ranged from 46 to 72%. A phase 2 clinical trial with PEG-IFN- α_{2b} (unregistered) reported hematocrit control <45% without phlebotomy for 4 of 9 patients (44%) who required phlebotomy $\leq$ 6 months before starting study treatment [50]. AEs were generally grade 1 or 2 with PEG-IFN- α_{2a} and PEG-IFN- α_{2b} [47, 48, 50]; 88% of patients treated with AOP2014 reported an AE, but a breakdown of AEs by grade was not provided [46]. Overall, 10–38% of patients discontinued because of PEG-IFN- α_2 -related toxicity.

Based on the results of the phase 2 clinical trials, PEG-IFN- α variants are under evaluation in patients with PV in 5 ongoing phase 3 trials (ClinicalTrials.gov identifiers, NCT01259856, NCT01387763, NCT02218047, NCT02523638, and NCT01949805).

An ongoing phase 2 clinical trial aims to evaluate the combination of PEG-IFN- α_{2a} and ruxolitinib for patients with PV or MF (EudraCT identifier, 2013-003295-12) [51]. A key limitation of IFN- α therapy is intolerable toxicity, which may include flu-like symptoms, gastrointestinal toxicity, and weight loss [21]. IFN- α activates *JAK1*/*STAT* pathways that promote inflammatory signaling normally initiated by viral infection [52]. Given the similarities between IFN- α -related toxicity and symptoms of the flu, it is reasonable to speculate that *JAK1*/*STAT* signaling may contribute to IFN- α -related toxicity. The addition of ruxolitinib may improve IFN- α tolerability by inhibiting *JAK1* and therefore *JAK1*-dependent symptoms, while providing clinical efficacy that is mechanistically distinct from IFN- α (i.e., *JAK1*/*JAK2* inhibition). An interim analysis included 30 patients (PV, $n = 20$), 27 of whom were previously intolerant or unresponsive to IFN- α [51]. Overall, 19 patients (63%) achieved complete response as best response, 8 (27%) achieved partial response, and 3 (10%) had no response [51]. Cytopenias were the most common AEs and were managed by dose reductions [51]. Serious AEs occurred in 9 patients (30%), most frequently pneumonia ($n = 3$) and fever ($n = 2$) [51]. These early results suggest that PEG-IFN- α_{2a} plus ruxolitinib combination therapy may be feasible for patients with PV; however, definitive conclusions are dependent on the final results of this trial [51].

Other Treatments in Clinical Development

Several additional potential treatment options for PV are in phase 2 or 3 clinical development. The *JAK* inhibitors momelotinib and pacritinib are currently in phase 3 clinical trials for PV and/or post-PV MF (ClinicalTrials.gov identifiers NCT01594723, NCT02124746, NCT01969838, and NCT01773187). The telomerase inhibitor imetelstat has been associated with clinical efficacy in patients with post-PV MF, post-ET MF, or primary MF [53] and is currently being investigated in a phase 2 trial in patients with PV or ET who require cytoreductive therapy and are resistant to or intolerant of previous therapy or who refused standard therapy (ClinicalTrials.gov identifier, NCT01243073). Finally, the recombinant pentraxin-2 protein (PRM-151) was associated with improvements in bone marrow fibrosis and stabilized or improved cytopenias in patients with post-PV MF, post-ET MF, or primary MF [54]. Currently, there are no planned clinical trials to evaluate PRM-151 in patients with PV; however, preclinical evaluation of pentraxin-2 in various fibrotic disease models – including pulmonary [55], cardiac [56], and kidney fibrosis [57] – suggests that it may inhibit or delay fibrosis. Combined with the clinical benefit observed in patients with post-PV MF [54], there may be value in exploring the ability of PRM-151 to potentially prevent or delay fibrotic transformation in this population.

Conclusions

Patients with PV have an increased risk of mortality compared with the general population [4] and experience a broad range of symptoms that reduce QoL [3]. Aspirin [15], phlebotomy [10], and cytoreduction with hydroxyurea [17] provide clinical benefit; however, approximately 1 in 4 patients becomes intolerant of or resistant to hydroxyurea [20]. The *JAK1*/*JAK2* inhibitor ruxolitinib is approved by the FDA for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea [24]. Treatment with ruxolitinib provides hematocrit control, reduces spleen size, normalizes blood counts, and improves PV-related symptoms and QoL [8]. In addition, numerous other potential treatment options are also in development. Those taking care of patients with PV – including community hematologists, oncologists, and internists – should monitor for signs of disease progression, including hydroxyurea resistance or intolerance and

changes in symptom severity based on routine assessments with a validated objective tool such as the MPN-SAF. Community clinicians should also be familiar with current management guidelines and special considerations for patients with PV during pregnancy, those undergoing elective surgery, and those treated with concomitant immunosuppressants. Routine patient monitoring and optimized management of patients who present special challenges will help improve patient outcomes.

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