Optimizing Treatment Strategies in Patients With Polycythemia Vera Who Develop a Thrombotic Event on Frontline Therapy

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Advanced practitioners are ideal advocates for their patients with polycythemia vera who have had a thrombotic event to ensure that secondary prevention measures are in place, including the implementation of close monitoring and tailoring therapy to meet individual needs. Being equipped with the medical knowledge to identify patients who are displaying signs and symptoms of resistance or intolerance is key to minimizing disease- or therapy-related complications and ultimately provide personalized therapy for each patient.

CASE STUDY

Mr. W, a 62-year-old man with a history of hypertension and type II diabetes, and a 20-pack-year smoking history, presented to his primary care physician with complaints of periodic headaches, fatigue, and pruritis for the past 6 months. A complete blood count revealed a white blood cell count within normal limits (6.3×10^9/L [4.5–11.0 $\times 10^9$/L]), erythrocytosis as evidenced by an elevated hemoglobin (18.2 g/dL [13.5–17.5 g/dL]), and elevated hematocrit (58% [41%–53%]; Table 1), thrombocytosis (platelet count, 885×10^9/L [150–400 $\times 10^9$/L]; Dean et al., 2005), and low erythropoietin (3.3 mU/mL [3.7–31.5 mU/mL]; Lupak et al., 2020). Physical examination revealed an overweight ambulatory older gentleman in no acute distress with a blood pressure of 165/89 mmHg, pulse 75 beats/min, temperature 98.5°F, height 69 inches, and weight 88.9 kg (body mass index of 28.9). A cardiac exam revealed a regular rate and rhythm and a II/VI murmur, his lungs were clear to auscultation bilaterally, and no hepatosplenomegaly was appreciated (see Table 2 for secondary causes of erythrocytosis).

Mr. W was referred to the hematology clinic for a more thorough evaluation. A bone marrow biopsy revealed hypercellular bone marrow

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Table 1. Mr. W's Lab Values During Weekly Phlebotomy Treatment

Week	Values
1	WBC 9.3 × 10^9/L, hemoglobin 14.8 g/dL, hematocrit 48%, platelet count, 447 × 10^9
2	WBC 13.8 × 10^9/L, hemoglobin 16.9 g/dL, hematocrit 53.5%, platelet count, 557 × 10^9
3	WBC 12.9 × 10^9/L, hemoglobin 16.4 g/dL, hematocrit 52.4%, platelet count, 543 × 10^9
4	WBC 9.6 × 10^9/L, hemoglobin 15.1 g/dL, hematocrit 49.3%, platelet count, 490 × 10^9

(90%) with trilineage hyperplasia, including marked atypical megakaryocytic hyperplasia, and *JAK2* mutation analysis was positive for the *JAK2*V617F mutation. Mr. W was diagnosed with polycythemia vera with a high risk for thrombosis based on his age (> 60 years old).

Although age and previous history of thrombosis are the most substantiated clinical risk factors for thrombosis, other factors should be considered by the oncology providers in determining thrombosis risk as well.

ADDITIONAL RISK FACTORS FOR THROMBOSIS

Cardiovascular Risk Factors

In the European Collaboration on Low-dose Aspirin (ECLAP) study—the largest epidemiologic study in polycythemia vera (PV)—cardiovascular mortality accounted for 41% of all deaths, primarily due to coronary artery disease (15%), congestive heart failure (8%), nonhemorrhagic stroke (8%), and pulmonary embolism (8%; Marchioli et al., 2005). Management of cardiovascular risk factors such as diabetes, hypertension, smoking, and dyslipidemia through lifestyle changes and secondary prevention is critical for minimizing cardiovascular complications. Mr. W's hypertension, type II diabetes, smoking history, and weight should be proactively addressed and managed by his care team, including advanced practitioners in hematology and other subspecialties.

Leukocytosis

Another potential risk factor for thrombosis is leukocytosis. The pathophysiology of PV inherently increases neutrophil and platelet activation, thereby triggering a pathway leading to increased platelet–leukocyte aggregates, endothelial damage, and eventually increased levels of blood hypercoagulability markers (Stefano et al., 2010). In the prospective, randomized CYTO-PV study, patients in the high-hematocrit group (receiving less aggressive therapy for a hematocrit target of 45% to 50%) had significantly higher leukocyte counts than patients in the low-hematocrit group (with a more aggressive hematocrit goal of < 45%), but platelet counts were similar in the two groups. Thus, in the high-hematocrit cohort, the persistence of leukocytosis may have contributed to the higher rates of thrombosis observed in this group of patients (Marchioli et al., 2013). Interestingly, research found that the presence of leukocytosis at the time of first thrombosis doubled the risk for arterial, but not venous, recurrence. This is thought to be secondary to increased neutrophil and platelet activation, increased platelet-leukocyte aggregates, endothelial damage, and increased levels of hypercoagulable markers in the blood (Stefano et al., 2010).

Leukocytosis at time of diagnosis has also been identified as a main prognostic risk factor of survival in patients with PV. In a population-based study of 327 patients, those older than 70 with hyperleukocytosis (WBC > 13,000 × 10^9/L) and/or thrombosis at diagnosis were found to have worse relative survival than those without these risk fac-

Table 2. Secondary Causes of Erythrocytosis

Sleep apnea
Gaisbock's disease
Smoking or lung disease
Obesity
Performance-enhancing drugs (EPO, testosterone)
Kidney disease
Living at high altitude
EPO-secreting tumor

tors (Bonicelli et al., 2013). Finally, an association between leukemic transformation and the risk factors of advanced age and leukocytosis (WBC > $15{,}000 \times 10^9$/L) has been confirmed (Gangat et al., 2007; Tefferi et al., 2013). In a study of 459 patients with PV at the Mayo Clinic, a multivariate analysis identified advanced age ($p < .0001$), leukocytosis (leucocyte count $\geq 15 \times 10^9$/L; $p = .0006$), and arterial thrombosis at diagnosis ($p = .01$) as independent predictors of inferior survival. In the absence of the first two risk factors, median survival was projected at 272 months as opposed to 108 months in the presence of both risk factors ($p < .0001$; Gangat et al., 2007).

ACHIEVING TREATMENT GOALS

Goals of treatment for PV include reducing the incidence of thrombotic events by controlling cellular hyperproliferation, strict hematocrit control < 45%, and symptom control. Low-risk patients should be started on aspirin and phlebotomized to obtain a hematocrit below 45% (Barbui et al., 2018); however, cytoreductive therapy is not typically required for this group. First-line management strategies for high-risk patients include a combination of low-dose aspirin, phlebotomy, and cytoreductive therapy.

Aspirin

Low-dose aspirin has played an essential role in PV management since the double-blind, placebo-controlled ECLAP study showed that daily aspirin significantly reduced (60% decrease) the risk of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes in patients with PV, regardless of history of previous thrombosis (Landolfi et al., 2004). This impressive decrease in thrombosis risk is likely related to aspirin's effect on thromboxane in platelets. The synthesis of thromboxane in patients with PV is reportedly 10-fold higher than the general population, suggesting that thromboxane-dependent platelet activation is a major contributor to the increased risk of thrombosis among patients with the disease (Landolfi et al., 1992). After Mr. W's lab work and medical history for contraindications was reviewed, Mr. W was instructed by the advanced practitioner to begin taking aspirin at 81 mg daily.

Phlebotomy

Therapeutic phlebotomy is often the first treatment utilized for PV. Aspirin and phlebotomy are both recommended for all patients, both low and high risk, to maintain a hematocrit of less than 45%. By removing excess cellular elements, mainly red blood cells, circulation of blood is improved by decreasing blood viscosity. In newly diagnosed patients like Mr. W, phlebotomy should be used to bring hematocrit to goal and then as needed to maintain the hematocrit target (National Comprehensive Cancer Network, 2020). A recent analysis of several prospective trials found that the frequency of phlebotomies in PV patients on hydroxyurea does not represent a risk factor for future thrombosis, reinforcing that low hematocrit is the key variable to reduce thrombotic risk in PV patients and providing reassurance for patients requiring more consistent phlebotomies (Barbui et al., 2017).

Phlebotomy can reduce hematocrit as well as help maintain a hematocrit of less than 45%, another treatment goal. As previously mentioned, patients enrolled in the CYTO-PV study who were treated with phlebotomy, hydroxyurea, or both (plus aspirin) were assigned to one of two groups: strict control of hematocrit (< 45%) or less aggressive control of hematocrit (45% to 50%). The results revealed that a hematocrit of 45 to 50% was associated with four times the rate of death from cardiovascular causes or major thrombosis compared with maintaining a hematocrit less than 45% (Marchioli et al., 2013). Because Mr. W's hematocrit at presentation was 58%, reduction to below 45% will be a priority for initial management of his disease.

CYTOREDUCTIVE THERAPY

For high-risk patients, cytoreductive therapy is recommended for disease management. Hydroxyurea and recombinant interferon-α are preferred first-line agents (Barbui et al., 2017, 2018).

Hydroxyurea

Hydroxyurea is an oral chemotherapy that causes inhibition of DNA synthesis by blocking an enzyme called ribonucleotide reductase. This interruption of DNA synthesis reduces the growth of cancer cells (Bristol Myers Squibb, 2016). After decades of use in PV, hydroxyurea is still the most widely prescribed cytoreductive agent for treatment of high-

risk patients. The results of a large systemic review and meta-analysis of the use of hydroxyurea in PV "underline the value of an old, cheap, and safe molecule as a reliable and accessible resource for those settings where there is need to reconcile economic sustainability" (Ferrari et al., 2019).

An association between treatment with hydroxyurea and an increased risk of transformation to acute myeloid leukemia (AML) was reported in some studies (Kiladjian et al., 2011; Nielsen & Hasselbalch, 2003), but these findings were not confirmed in subsequent reports. A large cohort analysis found that the use of alkylating agents or a combination of two or more cytoreductive agents in patients with MPN was significantly associated with an increased risk of transformation to AML or myelodysplastic syndrome; treatment with hydroxyurea, however, was not an independent risk factor for this leukemic transformation (Björkholm et al., 2011). See Table 3 for a list of adverse events associated with hydroxyurea treatment.

Pegylated Interferon

Pegylated interferon, a form of recombinant interferon, is a biological agent that has antiproliferative, proapoptotic, antiangiogenic, and immunomodulatory properties. It inhibits the growth of abnormal clonal cells, leading to a reduction of the clinical and laboratory signs of PV (Hasselbalch & Holmström, 2019). Pegylated interferon is often the treatment of choice for younger patients, pregnant patients requiring cytoreductive therapy, or patients requiring cytoreductive therapy that defer hydroxyurea (National Comprehensive Cancer Network, 2020). It is given by subcutaneous injection and can be administered weekly to start.

In two smaller studies, interferon alfa-2b resulted in a greater molecular response rate and 5-year progression-free survival rate than patients with *JAK2*-mutated PV who were treated with hydroxyurea (Huang, Zeng, Zhao, Li, & Chen, 2014; Kiladjian et al., 2008). Pegylated interferon offers lower rates of toxicity than standard interferon alfa-2b, making it a more appealing option. However, larger prospective studies directly comparing pegylated interferon to hydroxyurea for initial treatment of high-risk PV are needed before it can be recommended over hydroxyurea as first-line treatment of all high-risk patients (Barbui et al., 2013; Kiladjian et al., 2008).

Table 3. Adverse Events Associated With Hydroxyurea

Hematologic
Myelosuppression (anemia, leukopenia, thrombocytopenia)
Cutaneous vasculitic toxicity
Macrocytosis
Nonhematologic
Gastrointestinal: Mucositis, nausea, vomiting, diarrhea, constipation
Dermatologic: Skin ulcers, rash, erythema, alopecia, dry skin
Pulmonary: Interstitial pneumonitis
Renal and urinary: Dysuria, elevated serum uric acid, blood urea nitrogen, and creatinine
Hepatobiliary: Elevated hepatic enzymes, cholestasis, hepatitis
Nervous system: Headache, dizziness, drowsiness
General: Fever, chills, malaise, edema, asthenia, anorexia

MR. W'S CASE CONTINUES

Mr. W was started on hydroxyurea at 500 mg daily and aspirin at 81 mg daily, and therapeutic phlebotomy was initiated. His labs were checked once a week, and he had a follow-up appointment at the hematology clinic 4 weeks later to assess his response. After 1 month, his hematocrit was still elevated despite weekly phlebotomies (see Table 1).

Hydroxyurea should be titrated as needed, depending on continued phlebotomy requirements. Once a patient is on a stable dose and at goal hematocrit without the need for phlebotomies, the time between blood draws and follow-ups can be extended to up to 6 months. Because Mr. W's hematocrit was still elevated, the clinical team increased his dose of hydroxyurea to 500 mg twice daily. One month later, he returned to the clinic. Upon review of his weekly labs, his hematocrit was near goal (WBC 8.3×10^9/L, hemoglobin 15.1 g/dL, hematocrit 45.6%, platelet count 327×10^9), and he only required one phlebotomy during the month. He was advised to continue hydroxyurea at 500 mg twice daily.

Mr. W continued to do well for 2 years with minimal phlebotomy needs. However, he called the clinic to schedule an office visit due to concerns about a new leg wound that developed and had become larger over the past 2 weeks. Upon

presenting to clinic, Mr. W was found to have a 2 × 2 cm right lower extremity ulceration near the medial malleolus that was painful with erythematous borders, yet not draining. More importantly, he also reported new-onset chest pressure and nausea that had begun 24 hours prior.

A stat EKG revealed ST elevation, and he was immediately transported by ambulance to the closest emergency department. There, elevated cardiac markers and a repeat EKG confirmed an ST elevation myocardial infarction. A CBC revealed a WBC at 12.2×10^9/L, hemoglobin at 17.3 g/dL, hematocrit at 52%, and platelet count at 520×10^9.

HYDROXYUREA RESISTANCE OR INTOLERANCE

Approximately 25% of patients with PV who are treated with hydroxyurea have unacceptable side effects or an inadequate response, including 10% of patients who fail to reach any degree of hematologic response (Alvarez-Larrán et al., 2012). A Spanish study revealed that resistance to hydroxyurea was associated with a 5.6-fold increase in the risk of death and increased leukemic transformation after adjustment for other relevant prognostic factors (Alvarez-Larrán et al., 2012). The European LeukemiaNet (ELN) criteria (Barosi et al., 2010) provides a guideline for determining if hydroxyurea resistance or intolerance is present (Table 4); patients are considered intolerant of or resistant to hydroxyurea by fulfilling just one of the criteria. A study found that a higher phlebotomy requirement—three or more phlebotomies per year—under hydroxyurea therapy identified a subset of patients with increased proliferation of polycythemia vera. Accordingly, these patients also required higher doses of hydroxyurea and were more likely to fulfill the ELN criteria for hydroxyurea resistance or intolerance, mainly due to extrahematologic toxicities (Alvarez-Larrán et al., 2017).

TREATMENT OF HYDROXYUREA-RESISTANT PV

According to the National Comprehensive Cancer Network Guideline for Myeloproliferative Disease (Version 1.2020), the preferred treatment for hydroxyurea resistance or intolerance is either ruxolitinib (Jakafi) or enrollment in a clinical trial. Ruxolitinib is an oral kinase inhibitor that inhibits Janus associated kinases (JAKs) JAK1 and JAK2, enzymes that mediate the signaling of several cytokines and growth factors that are important for hematopoiesis and immune function.

Ruxolitinib

The RESPONSE trial, a prospective, randomized, phase III study, investigated the use of ruxolitinib vs. standard therapy in phlebotomy-dependent patients with splenomegaly (Vannucchi et al., 2015). The primary end point—hematocrit control through week 32 and at least a 35% reduction in spleen volume at week 32—was achieved in 21% of patients in the ruxolitinib group compared with 1% of patients in the standard-therapy group ($p < .001$). A complete hematologic remission was achieved in 24% of patients in the ruxolitinib group and 9% of those in the standard-therapy group ($p = .003$); 49% vs. 5%, respectively, had at

Table 4. European LeukemiaNet (ELN) Criteria for Determining if Hydroxyurea Resistance or Intolerance Is Present

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

least a 50% reduction in the total symptom score at week 32 (Vannucchi et al., 2015).

The rate of thromboembolic events in the ruxolitinib group was lower than expected in this high-risk population compared with patients who respond to hydroxyurea and with those without a response, respectively (1.2 vs. 2.8 vs. 3.5 events per 100 patient-years). Ruxolitinib was also successful at controlling hematocrit and reducing spleen volume, as well as reducing symptoms in those who had an inadequate response to or had unacceptable side effects from hydroxyurea (Vannucchi et al., 2015).

The US Optum database study in polycythemia vera also reported a reduction in the annual incidence of thromboembolic events in patients switching to ruxolitinib compared with those who continued treatment with hydroxyurea (Verstovsek et al., 2019). Based on the findings from this study, phlebotomy dependency and red cell distribution width were indicated as predictors of hydroxyurea treatment failure within 3 months, whereas lymphocyte percentage plus platelet count and lymphocyte percentage (> 13%) plus red cell distribution width were predictors of incidence of thromboembolic events in patients with and without a history of thromboembolic events, respectively.

FOLLOWING UP WITH MR. W

The decision was made to transition Mr. W from hydroxyurea to ruxolitinib due to his intolerance—the development of a leg ulcer while taking hydroxyurea—and resistance, indicated by persistent elevation of hematocrit > 45% despite 2 grams of hydroxyurea a day complicated by a thrombotic event. He recovered from his acute myocardial infarction and was placed on antiplatelet therapy with clopidogrel post stent placement. Mr. W returned to the clinic after picking up his ruxolitinib from the pharmacy and was started on the standard dose for PV: ruxolitinib at 10 mg by mouth twice daily. A CBC revealed WBC 9.3×10^9/L, hemoglobin 16.3 g/dL, hematocrit 49%, platelet count, 415×10^9.

Mr. W was phlebotomized, and hydroxyurea 500 mg twice daily was continued at ruxolitinib initiation to reduce the risk of rapid hyperproliferation before the ruxolitinib took effect. Labs were drawn every 2 weeks to monitor for the development of cytopenia and to ensure that counts were controlled. At the first 2-week follow-up, hydroxyurea was safely discontinued based on improvement in his CBC (WBC 6.5×10^9/L, hemoglobin 14.3 g/dL, hematocrit 43%, platelet count, 300×10^9). Mr. W returned every 2 weeks for another month and then, with continued control of his cell counts, proceeded with monthly follow-up.

DISCUSSION

Collaborative practice and coordination of care with cardiology to ensure appropriate management of cardiovascular risks factors will be a critical component of reducing risk for additional thrombotic events and maintaining a good quality of life for Mr. W. Advanced practitioners are ideal advocates for their patients with polycythemia vera who have had a thrombotic event to ensure that secondary prevention measures are in place, including the implementation of close monitoring and tailoring therapy to meet individual needs. Being equipped with the medical knowledge to identify patients who are displaying signs and symptoms of resistance or intolerance is key to minimizing disease- or therapy-related complications and ultimately provide personalized therapy for each patient.

Disclosure

Ms. Lyle has served on advisory boards for AbbVie, Agios, Bristol Myers Squibb, Celgene, and Incyte. Ms. Huynh-Lu has served on the speakers bureau and advisory board for Incyte.

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