Risk-adapted Therapy for PV

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Learning Objective:
Devise treatment plans for patients with PV based on risk of thromboembolic events and patient-specific features

Introduction
Join Dr. Spivak as he discusses risk stratification and management strategies for polycythemia vera (PV). Topics include the pathophysiology and mutational foundation of PV, predicting risk and PV prognosis, current treatment strategies and controversies, and the role of targeted therapies in managing PV.

What is polycythemia vera (PV) and what risk does it pose?

Polycythemia vera (PV) is one of three myeloproliferative disorders (the others are essential thrombocytosis [ET] and primary myelofibrosis [PMF]) that share mutations that activate the physiologic signal-transduction pathways involved in hematopoiesis. PV results primarily from gain-of-functions mutations in *JAK2*, although *CALR or LNK* mutations may also be involved. *JAK2* acts as the cognate tyrosine kinase for the erythropoietin and thrombopoietin receptors, but may also be utilized by the granulocyte colony-stimulating factor receptor. Unlike ET and PMF, PV is characterized by erythrocytosis, as well as increases in granulopoiesis and thrombopoiesis. However, the phenotype of PV is often indistinguishable from ET and PMF, and the shared driver mutations can make a specific diagnosis a 'moving target;' For example, *JAK2*^{v617F}-positive ET and PMF can transform into PV.[1] This behavior can reflect a number of factors, including involvement of a different hematopoietic stem cell (HSC) clone, clonal expansion due to *JAK*^{V61F} homozygosity, or lack of clinical recognition of 'masked' PV due to plasma volume expansion.[1-3]

Importantly, it is now understood that variability of the *JAK2*^{V61F} allele burden has both diagnostic and prognostic implications. Furthermore, sex, age at diagnosis, and disease duration all independently influence *JAK2*^{V61F} behavior, with females having a lower *JAK2*^{V61F} allele burden than males.[4] *JAK2*^{V61F} expression is age-independent, but has been found to occur at a younger age in women compared with men, and increases in frequency after the age of 60

years.[1,5,6] PV disease complications also vary by sex; women with a myeloproliferative neoplasm (MPN) have been found to have higher rates of certain vascular complications such ocular migraine and hepatic vein thrombois.[7]

PV is a relatively indolent (although progressive) blood neoplasm, but it is associated with certain risks, including risk of thrombosis and bleeding events. About 10% of patients develop post-PV myelofibrosis (PPMF). Leukemic transformation of PV to acute myeloid leukemia (AML) is the most serious consequence of PV. Transformative risk factors include PPMF stage (versus chronic PV stage), age 60 years or older, and exposure to chemotherapy; neither *JAK2*^{V61F} expression nor its allele burden appear to correlate with conversion to AML unless mutational homozygosity is present.[1]

How is risk assessed in PV and how does this risk inform treatment decisions?

Current recommendations for PV advise that risk stratification should be based on age and thrombosis history.[8] Patients under age 60 years are recommended to receive phlebotomy and aspirin, while those age 60 or older should receive hydroxyurea for cytoreduction and prevention of thrombosis. However, the evidence supporting these recommendations is weak, and fails to acknowledge 1) the impact of age on survival, which is independent of disease, 2) the very high risk of thrombosis in older adults, and 3) important differences in hematocrit phlebotomy targets for men versus women.[1] Also, most such recommendations are based on retrospective data or data obtained from a mixture of treated and treatment-naïve patients.

More recently, a genomic-based MPN prognostic calculator was developed.[9] This calculator defines eight genomic subgroups derived from 63 clinical and genomic variables; each of these subgroups is associated with a unique distinct clinical phenotype, including blood counts, risk of leukemic transformation, and event-free survival. This calculator was able to accurately predict patient outcomes and may support the provision of personalized treatment of patients with an MPN, but this has not been validated clinically and may not reflect the behavior of indolent PV or ET.

What are the goals of care when managing patients with PV and how are these goals achieved?

While not curative, therapy for PV can relieve symptoms and prolong survival. The goals of care are to reduce the risk of first and/or recurrent thrombosis, prevent bleeding events and intractable splenomegaly, minimize the symptom burden, and reduce the risk of evolution to PPMF and AML. The most immediate health threat in patients diagnosed with PV is thrombosis, and phlebotomy is the primary method of mitigating this risk. Many clinicians utilize hydroxyurea as the therapy of choice in PV together with phlebotomy.[1,10] However, evidence from the PVSG-01 study comparing chemotherapy or radiophosphorus (^{32}P) supplemented by phlebotomy in treatment-naïve PV patients, demonstrated that thrombosis risk was equal between phlebotomy and chemotherapy arms (despite an initially flawed phlebotomy control study design which appeared to favor the chemotherapy and ^{32}P arms with respect to thrombosis incidence) and that phlebotomy was superior to chemotherapy in terms of survival. Moreover, the chemotherapy treatment group experienced a greater rate of skin cancer, gastrointestinal tumors, lymphomas, and nonhematologic malignancies.[11] Hydroxyurea is

known to cause therapy-related AML (tAML) through the facilitation of clonal expansion of harmful HSC-bearing mutations such as *TP53*. Long-term follow-up of randomized controlled trials in PV have shown a 24% rate of AML development in hydroxyurea-treated patients.[12]

Phlebotomy, therefore, should remain a foundational treatment in PV. This treatment can successfully alleviate symptoms related to hyperviscosity by reducing the red cell mass (RCM) and expanding the plasma volume. Phlebotomy does not cause myelofibrosis, thrombosis, or stimulate hematopoiesis due to the fact that in PV, hematopoiesis is autonomous. It is important to remember that PV patients absorb iron in excess, and an increase in phlebotomy is in indication of excess body iron, rather than disease acceleration. To ensure adequate response, a hematocrit of ≥45% for men or ≥42% for women should be targeted. The lower hematocrit target for women is designed to account for significantly lower testosterone levels and red cell mass (RCM) in female versus male patients; a hematocrit target of 45% in female patients will result in an excess of ~600 mL of blood or more, especially with hepatic vein thrombosis (HVT), which is common in women PV patients, often with an apparently normal hematocrit due to plasma volume expansion.[1,13-15] Phlebotomy is therefore necessary in the presence of HVT, even in the presence of normal hematocrit, as plasma volume expansion masks the elevated RCM and anticoagulation alone will be inadequate.

Other symptomatic management strategies for PV include thrombocytosis control for migraine or transient ischemic attack (TIA), preferably with a peg-interferon (pegINF) rather than anagrelide. Management of aquagenic pruritus can be achieved with ruxolitinib, pegINF, psoralen, ultraviolet A, or hydroxyurea (depending on the severity). Surgical management of thrombocytosis-induced von Willebrand syndrome should include tranexamic acid or epsilon-aminocaproic acid (for minor surgery) or platelet count reduction (for major surgery).

What role does targeted therapy play in PV treatment?

There are now two nonmyelotoxic, target-specific agents available to treat PV: pegINF and ruxolitinib. PegINF is an HSC-specific therapy that can be offered to newly diagnosed PV patients, particularly those under age 60 years. The effects of pegINF are durable, even if complete remission is not achieved, and there is evidence that patients who lose a hematologic response continue to experience the symptomatic benefit of pegINF.[16] It is important to remember that continuous pegINF exposure can drive normal HSCs into cell cycle, and is associated with arrhythmias, hypothyroidism, and autoimmune events.[1] Moreover, this agent stimulates erythropoiesis, and phlebotomy often remains necessary despite pegINF treatment.[1]

Ruxolitinib has been shown to be effective for PPMF and chronic-phase PV, providing durable symptom relief, blood count control, and reduction in splenomegaly.[1] In the RESPONSE-2 phase 3b study, ruxolitinib was superior to best standard care (ie, hydroxyurea, interferon, or pegINF) in terms of hematocrit control in patients with inadequately controlled PV without splenomegaly.[17] However, ongoing questions remain about the effect of this agent on long-term safety with respect to immunosuppression.[1] Ruxolitinib treatment is associated with side effects such as fatigue, weight gain, immunosuppression, herpes zoster and opportunistic infection, skin cancer, and lymphomas, but drug holidays due to toxicity do not preclude

response on rechallenge.[1] Those with advanced PPMF can be treated with combined ruxolitinib and azacitidine,[18] or thalidomide and prednisone ± ruxolitinib, which can improve blood counts and reduce circulating blasts and resultant splenomegaly.[1]

What final thoughts do you have regarding the treatment of PV?

Much of what is recommended for PV management – particularly regarding the use of hydroxyurea – is based on mostly retrospective or observational evidence without adequate phlebotomy control. Hydroxyurea is inferior to ruxolitinib or pegINF and has been demonstrated to cause acute leukemia in PV (like other forms of chemotherapy) in a randomized, control clinical trial.[12] Although approaching PV as a malignant neoplasm that requires chemotherapy may be the first instinct of clinicians, they should remember that management with phlebotomy with an appropriate, gender-specific hematocrit target is typically adequate to achieve most of PV treatment goals. Additionally, although we now have two non-myelotoxic target-specific drugs for PV, more research is necessary to determine how to best implement these agents within care strategies. Finally, based on more recent literature, the role of aspirin should be limited to patients with cardiovascular risk factors, TIA or ocular migraine, particularly in older patients where the risk of bleeding is greatest.[19]

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Provided by MediCom Worldwide, Inc.
This activity is supported by educational grants from Bristol-Myers Squibb and Incyte Corporation.

