This article, sponsored by Incyte Corporation, is based on a paid interview with Rami S. Komrokji, MD, of Moffitt Cancer Center, Tampa, Florida, conducted on May 4, 2015.

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Polycythemia vera: Emerging diagnostic and risk stratification criteria

According to Rami S. Komrokji, MD, motivation is high for refining diagnostic and risk stratification criteria for polycythemia vera (PV), as conventional models do not provide hematologists and oncologists the ability to predict disease progression, hematologic transformation, or overall survival. Dr Komrokji reports that new models are being developed to reflect contemporary understanding of risk factors, integrate more molecular data, and account for symptom burden.

Diagnosis

Polycythemia vera is a Philadelphia chromosome–negative myeloproliferative neoplasm (MPN).[1,2] Erythrocytosis is the hallmark of PV and is associated with its most common serious complications.[3-8] Uncontrolled erythrocytosis can increase the risk for thrombotic events, systemic and pulmonary hypertension, and impaired renal and cerebral blood flow through several mechanisms.[4] The hyperviscosity caused by red cell expansion plays a major role in the pathogenesis of thromboses and microcirculatory disturbances, generating platelet microparticles, enhancing platelet reactivity and interactions with leukocytes at the vessel wall, and damaging endothelial cells. Furthermore, uncontrolled erythrocytosis is associated with increased infarction size.[4]

However, PV involves more than red cells.[7,9-11] Excessive proliferation of not only erythroid but also myeloid and megakaryocytic components of the bone marrow produces elevated white blood cell (WBC) and platelet counts as well. Erythrocytosis with leukocytosis and/or thrombocytosis is more consistent with PV than isolated erythrocytosis.[12] In one large study (N = 1,545), 49% of patients with PV presented with leukocytosis and 53% presented with thrombocytosis.[13] Most patients with PV are diagnosed by chance during routine blood testing, after a thrombotic event, or upon presenting with a disease-related symptom.[12]

The Polycythemia Vera Study Group (PVSG) was the first to develop a widely accepted set of specific criteria for the diagnosis of PV.[14] Those criteria were significantly modified by the British Committee for Standards in Haematology (BCSH)[15] and the World Health Organization (WHO).[16] After the identification of *JAK2*V617F and functionally similar mutations—found in approximately 95% of patients with PV[17-23]—the BCSH and WHO criteria were revised to their present forms and are now the most widely used diagnostic criteria for MPNs.[24]

BCSH diagnostic criteria for PV are based primarily on hematocrit (Hct) levels >52% in men and >48% in women,[25] whereas WHO criteria rely on hemoglobin (Hb) levels >18.5 g/dL in men and >16.5 g/dL in women.[1,2] Table 1 presents the complete 2008 WHO diagnostic criteria for PV. Diagnosis requires meeting both major criteria and 1 minor criterion or the first major criterion and 2 minor criteria.[2]

Table 1: The 2008 WHO Diagnostic Criteria for PV[2]

Major criteria	1. Hb >18.5 g/dL in men and >16.5 g/dL in women *or* Hb or Hct >99th percentile of reference range for age, sex, or altitude of residence *or* Hb levels >17 g/dL in men and >15 g/dL in women if associated with a sustained increase of ≥2 g/dL from baseline *or* Elevated red cell mass >25% above mean normal predicted value 2. Presence of *JAK2*V617F or similar mutation
Minor criteria	1. Bone marrow trilineage myeloproliferation 2. Subnormal serum erythropoietin level 3. Endogenous erythroid colony growth

Adapted from Tefferi et al.[2]

Abbreviations: Hb, hemoglobin; Hct, hematocrit; JAK, Janus-associated kinase; PV, polycythemia vera; WHO, World Health Organization.

Both Hb and Hct are surrogates for red cell mass (RCM), the true determinant of absolute erythrocytosis, although the relationship between these surrogates and RCM is uncertain.[24,26,27] Because the RCM and plasma volume can vary independently of each other, an elevated plasma volume could cause observed Hb

and Hct levels to appear normal despite an elevated RCM, obscuring the diagnosis of PV.[28] Table 2 lists several investigational studies that explored the correlations of the Hb, Hct, and RCM parameters. In these studies, an elevated RCM was present in a large subset of patients with normal Hb and Hct levels. Patients with elevated RCM but normal Hb and Hct levels would not meet the current WHO and BCSH diagnostic criteria without assessment of the RCM.[28-32] Many of these patients might be erroneously diagnosed with essential thrombocythemia (ET), since approximately half the patients with PV present with thrombocytosis.[13]

Table 2: Patients With Hb or Hct Below Criteria Threshold for PV but RCM 25% Higher Than Mean Predicted Value

Johansson et al, 2005[29]	Hb	37 of 77 patients (48%)
Cassinat et al, 2008[30]	Hb	33 of 71 patients (46%)
Alvarez-Larrán et al, 2012[32]	Hb Hct	53 of 114 patients (46%) 21 of 114 patients (18%)
Silver et al, 2013[31]	Hb or Hct	8 of 28 patients (29%)

Adapted from Stein et al.[33]
Abbreviations: Hb, hemoglobin; Hct, hematocrit; PV, polycythemia vera; RCM, red cell mass.

Lamy et al introduced the concept of masked PV (mPV) (also known as occult, latent, smoldering, subclinical, or inapparent PV) in 1997.[28] Both the existence of mPV and its outcomes are unsettled. Several researchers have described a subset of patients with clinical correlates of PV but an Hb and/or Hct level below current WHO diagnostic thresholds.[27,29-32,34] Barbui et al found outcomes for these patients poorer compared with overt PV. This was primarily driven by inferior survival associated with significantly higher rates of progression to myelofibrosis and acute leukemia.[27] Other studies, however, demonstrated clinical outcomes similar to those of patients with overt PV when all patients were managed according to PV guidelines.[34,35] The increased rates of transformation seen by Barbui et al could be explained by patient selection criteria, which relied on histologic findings.[34,36] The similar outcomes of PV and mPV seen in the other studies emphasized the need to maintain all patients at an Hct level <45% as suggested in the Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) randomized clinical trial.[34,35]

Investigators have proposed revision to the WHO 2008 diagnostic criteria for PV that includes lower Hb thresholds (>16.5 g/dL in men, >16 g/dL in women) and lower Hct thresholds (>49% in men, >48% in women) in addition to *JAK2* mutation. Furthermore, these researchers propose that bone marrow trilineage myeloproliferation be elevated from a minor criterion to a major criterion and that endogenous

Lowering red cell parameters has been proposed for the prospective revision of the 2008 WHO criteria.[37]

erythroid colony growth be removed because of limited practical use and redundant value. The only minor criterion that would remain would be a subnormal serum erythropoietin level.[37] Although the diagnostic impact of bone marrow morphology has been questioned and the diagnosis of PV usually can be established by the presence of erythrocytosis and a *JAK2* mutation, bone marrow histology could potentially identify cytogenetic abnormalities and might provide valuable support to diagnosis in borderline Hct.[38] The presence of only mild to moderate marrow fibrosis in PV also allows separation from ET (absence of fibrosis) and from fibrotic cases of primary myelofibrosis. Additionally, marrow biopsy specimens obtained at the time of diagnosis are useful in establishing reticulin and collagen content, serving as a basis for subsequent analysis of potential disease progression. In addition, obtaining a bone marrow biopsy at time of diagnosis could allow clinicians to establish a baseline to track the progression of fibrosis, which would be particularly useful in patients younger than 40 or 50 years of age.

In patients with the JAK mutation, the proposed Hb and Hct criteria would potentially identify patients with borderline red cell parameters who may be at increased risk for thrombotic events.[37]

Risk stratification to guide disease management

The conventional risk factors of age >60 years and a previous thrombotic event estimate the risk for thrombosis to help determine the therapeutic approach.[39,40] A more comprehensive model might help predict or assess outcomes, overall survival, disease progression, and risk for hematologic transformation (Table 3).[39,40] Published scientific literature supports that age >60 years at diagnosis and presence of vascular events in patients' history are the most relevant prognostic factors used to classify patients into low-risk (no risk factors) or high-risk groups (1 or 2 risk factors) regarding thrombosis in PV.[39-42] In the landmark European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) observational study, age ≥65 years and a thrombotic event before recruitment each doubled the rate of thrombotic cardiovascular events; the rate of events was approximately 4-fold higher in patients with both criteria.[43]

The conventional risk stratification model has an impact on the therapeutic approach,[42] helping clinicians tailor treatment for individual patients according to their risk for thrombohemorrhagic events.[6] According to this model, low-risk patients with PV should be treated with phlebotomy to maintain Hct levels <45% or with low-dose aspirin

(100 mg/day) in the absence of major complications, such as extreme thrombocytosis (platelet count ≥1,500 × 10^9/L), which can be associated with bleeding due to acquired von Willebrand disease.[6,12,42] The use of cytoreductive agents is not warranted in low-risk patients with no or optimally managed cardiovascular risk factors.[42] However, these agents may be appropriate (1) when phlebotomy is poorly tolerated or required frequently, (2) in cases of symptomatic or progressive splenomegaly, or (3) in the presence of severe disease-related symptoms, progressive leukocytosis, or extreme thrombocytosis. Recommendations vary on the use of cytoreductive therapy in low-risk patients with extreme thrombocytosis.[6,12,42]

Table 3: Risk Factors That May Predict Outcomes in PV

Erythrocytosis	Marchioli 2013[3]
Leukocytosis	Landolfi et al, 2007[9] Gangat et al, 2007[44] Chou et al, 2013[45] Lim et al, 2015[46] Bonicelli et al, 2013[47] Marchioli et al, 2013[3]
Thrombocytosis	Alvarez-Larrán et al, 2012[48]
Mutational profile	Vannucchi et al, 2007[49] Passamonti et al, 2010[50]
Hydroxyurea resistance	Alvarez-Larrán et al, 2012[48]

Abbreviation: PV, polycythemia vera.

Recommendations for high-risk patients, in addition to low-dose aspirin and phlebotomy to maintain Hct levels <45%, include cytoreductive therapy with the goal of reducing the risk for thrombosis.[6,42,51] Hydroxyurea (HU) is a widely used cytoreductive agent in the United States. This classic, 2-tiered risk stratification model is useful in guiding therapy but has its limitations. Clearly, thrombotic events occur in younger patients (<60 years), and risk factors have emerged that may result in the development of improved and more personalized risk stratification.[33] Recent studies have examined factors that may predict not only thrombosis but also other outcomes, including disease complications, hematologic transformation, and overall survival. These investigational risk factors raise the issues of whether thrombosis per se is the only relevant outcome in PV and whether we now have the tools to construct models that can reliably predict survival as well.[10,13,40]

Risk stratification to predict outcomes

Erythrocytosis

Because erythrocytosis is the source of the most common serious complications in PV,[5,7,52] failure to maintain hematocrit at an appropriate level (<45%) constitutes a serious risk for thrombosis and death.[3] Uncontrolled erythrocytosis also causes systemic and pulmonary hypertension and splenomegaly and impairs renal and cerebral blood flow.[4] Results of the randomized controlled CYTO-PV trial showed that maintaining the Hct level <45% reduced the rate of death from cardiovascular causes or major thrombotic events. This firmly established the Hct level of <45% as a dynamic prognostic factor in PV.[3]

Leukocytosis

Current research indicates that leukocytosis is a common marker of aggressive disease in myeloid malignancies.[13] In addition to age and the presence of a prior thrombotic event, many investigators have associated leukocytosis with poor prognosis in PV.[5,9,44,45] Patients with leukocytosis appear to be at increased risk for incident and recurrent thrombosis and shortened survival.[48] In 261 patients with PV who were treated with HU and followed for a median of 7.2 years, having no response in leukocyte count increased risk for death 2.7-fold after adjustment for age, sex, initial hematologic values, cardiovascular risk factors, and development of thrombosis or bleeding during follow-up. In the same trial, lack of sustained HU response in the leukocyte count increased the risk for hematologic transformation 3.2-fold ($P = 0.004$) after adjustment for age, sex, initial hematologic values, and exposure to ^{32}P or busulfan.[48]

A subanalysis of the ECLAP study identified a significant increase in the risk for thrombosis in patients having leukocyte counts >15 × 10^9/L compared with those with leukocyte counts <10 × 10^9/L ($P = 0.017$).[9] This finding was derived primarily from an increased risk for myocardial infarction, confirmed in multivariate analyses adjusted for age, sex, disease duration, prior thrombosis, prior hemorrhage, conventional risk factors, number of comorbidities, and cytoreductive or antithrombotic therapy.[9] A more recent study by the CYTO-PV Collaborative Group found that patients whose Hct levels were maintained at <45% had lower leukocyte counts, suggesting that the reduction in thrombotic risk might be associated with a lower leukocyte count as well as lower Hct levels.[3]

One group has developed a 3-tiered prognostic model and validated it in a cohort of 1,545 patients with PV. Variables included older age, leukocyte count ≥15 × 10^9/L, and history of venous thrombosis.[13] The model demonstrated excellent discrimination between low-risk, intermediate-risk, and high-risk patients (median survival of 27.8, 18.9, and 10.9 years, respectively).[13] The model was heavily weighted for age, with age ≥67 years assigned 5 adverse points, age 57 to 66 years assigned 2 points, and leukocytosis and venous thrombosis assigned 1 point each.[13] Another retrospective analysis of 101 patients with PV found leukocyte count ≥16 × 10^9/L to be an independent predictor of hemorrhage ($P = 0.010$), where hemorrhage was associated with significantly shorter survival ($P = 0.002$).[45]

Thrombocytosis

Because PV is a trilineage MPN, the role of platelets has also been investigated. While many studies have suggested a

link between erythrocytosis and leukocytosis and outcomes in PV, evidence for the involvement of thrombocytosis is more circumstantial. Some evidence for the risk associated with thrombocytosis is provided by studies in ET, where reducing the platelet count significantly reduced the incidence of vascular events. In the ECLAP trial, treatment with aspirin significantly lowered the risk for cardiovascular events, again suggesting a role for platelets in thromboembolic events.[43]

The European LeukemiaNet (ELN) definition of clinicohematologic response to therapy for PV includes a platelet count ≤400 × 10^9/L[42] and a leukocyte count ≤10 × 10^9/L. Platelet response was included in the revision of the ELN guidelines in conjunction with the International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT).[42] Therefore, formal guidelines acknowledge potential platelet involvement in the pathogenesis of PV.[53] In a recent study of 261 patients treated with HU, achieving the ELN-defined response in platelet count was predictive of significantly fewer thrombohemorrhagic complications.[48]

Mutational profile

Although the data are mixed, some study findings associate the *JAK2*V617F allele burden with thrombosis as well as splenomegaly, pruritus, leukocytosis, transformation to post–PV myelofibrosis, and disease duration.[49,50] Data suggest a trend for increased thrombosis in patients with the *JAK2*V617F mutation.[54] The effect of the allele burden may be even more prognostic in progression of PV to fibrosis.[50,55]

Studies have examined abnormal karyotype as an additional risk factor for leukemic transformation in PV.[13,37] The prognostic relevance of karyotype in PV is being explored with the hope of establishing differential prognostic effect associated with specific cytogenetic abnormalities. Although molecular profiling is an area of increasing focus in the MPNs, karyotype has yet to be incorporated into any risk stratification model in PV. Additional studies are needed to obtain cytogenetic information in patients who have PV to determine the clinical significance and prognostic value of an abnormal karyotype.

Hydroxyurea resistance

Investigators have noted that a large proportion of patients (20%-60%) remain on therapy with HU despite a lack of response.[56] HU resistance has been shown to be a highly significant risk factor in PV, increasing risk for death 5.6-fold and increasing transformation to acute myelogenous leukemia or myelofibrosis 6.8-fold.[48] Resistance may take the form of failure to maintain an Hct level of <45% after at least 3 months of 2 g/d of HU or uncontrolled myeloproliferation including platelet count >400 × 10^9/L and WBC count >10 × 10^9/L. ELN criteria for HU resistance in PV also include failure to reduce massive splenomegaly (>10 cm from the costal margin) by more than 50% or failure to completely relieve symptoms related to splenomegaly, also after 3 months of at least 2 g/d of HU. HU intolerance manifests as cytopenias necessitating discontinuation of therapy or the presence of leg ulcers or other HU-related toxicities at any dose, which can include mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever.[42,57] These patients should be recognized promptly so that timely decisions may be made about options for alternative therapies.[42,58]

Conclusion

Revised diagnostic criteria—to lower thresholds for Hb and Hct levels and to elevate bone marrow trilineage myeloproliferation to a major criterion—may help identify PV in patients who present with Hb or Hct levels below the current criteria despite the presence of qualifying *JAK* mutations and bone marrow morphology. Identification of PV in these patients could impact disease management and potentially identify patients whose borderline red cell parameters may put them at increased risk for thrombotic events.

Investigators continue to explore the associations of various potential risk factors associated with outcomes in PV. Standard risk factors (age >60 years and history of thrombosis) will maintain their significance but do not incorporate the latest advances in understanding the disease and may by themselves be inadequate to guide disease management. Recent years have seen a proliferation of studies investigating novel risk factors for PV, which can lead to a refinement of conventional risk stratification and the development of more-comprehensive risk models. The development of the 3-tiered model incorporating leukocytosis is a good start, although the strong emphasis on age may mask the effect of other relevant factors. It may be that more than a single model is needed to capture thrombotic risk, disease progression, and overall survival. Risk assessment has become an active area of focus in PV, and it is hoped that developments will improve patient care and outcomes in this challenging cancer. Future developments towards incorporating molecular risk prognostic scores may further refine the understanding of the course and natural history of PV and its management, improving outcomes.

Dr Komrokji was compensated for his participation in this interview. He has also received clinical research funding from and served as a consultant for Incyte Corporation (Wilmington, DE).

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