



Editorial

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# Polycythemia Vera: Current Therapeutic Approaches



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## Abstract

The hemoglobin level threshold required to diagnose PV is now established at 16.5 g/dL for men and 16 g/dL for women by the 2016 WHO classification for MPNs. The clinical course of PV might be interrupted by thrombohemorrhagic complications and disease transformation to MF or acute myeloid leukemia. JAK2 oncogenes homozygosity may result in distinct tumorigenic consequences. Different therapeutic strategies and good candidates' patients for such therapies are illustrated.

**Keywords:** Polycythemia vera; Thrombohemorrhagic; Tumorigenic; Myeloid leukemia

**Abbreviations:** PV: Polycythemia Vera; STAT: Signal Transducer and Activator of Transcription; AML: Acute myeloid leukemia; MF: Myelofibrosis; MPNs: Myeloproliferative neoplasms

## Introduction

PV is one of the lower-risk subtypes of MPNs [1] that is characterized primarily by clonal erythrocytosis [2]. It has an annual incidence of 0.21-2.27 per 100,000. Median age at diagnosis is estimated at 71 years. A male preponderance is noted. JAK2 V617F is found in >95% of PV patients and JAK2 exon 12 mutations in ~4% [3]. JAK2 exon 12 mutations such as insertions or deletions are relatively specific to JAK2V617F-negative PV and not found in ET and PMF [4]. JAK2 homozygosity is neither necessary nor sufficient for a PV phenotype as indicated by presence of small or undetectable homozygous clones in some PV patients [5]. Heterozygous mutant erythroblasts of PV patients have distinct transcriptional profiles that precede acquisition of homozygosity and reflect differential activation of phosphorylated STAT1, which modulate erythropoiesis [5]. CALR and MPL have distribution frequency of 0 and 0% [6]. Other mutations (e.g., LNK) have been reported [2]. Co-occurrence of CALR mutation exon 9 with JAK2V617F, usually occurs in less than 1% of PV [4].

JAK2, MPL, and calreticulin mutations are driver mutations that activate the JAK2 pathway, but additional recurrent somatic mutations in several genes (TET2, ASXL1, DNMT3A, CBL, LNK, IDH1/2, IKF1, EZH2, TP53, and SRSF2), encoding transcriptional and epigenetic regulators and signaling proteins, modulate disease progression and can also occur as a primary mutation [3].

Clinical features of PV include mild-to moderate degree of splenomegaly, mild-to-moderate degree of constitutional symptoms, including fatigue and pruritus [6] (usually after bathing) [2], symptoms of hyperviscosity, leukocytosis, thrombocytosis, microvascular symptoms (e.g., headaches, lightheadedness,

visual disturbances [6] e.g., blurry vision [2], atypical chest pain, acral paresthesia and erythromelalgia [6] i.e., erythema, warmth, and pain in distal extremities) [2], and thrombotic and bleeding complications [6].

The risk of thrombosis exceeds 20% [7]. History of hypertension predicted arterial thrombosis and advanced age venous thrombosis [7]. Hepatic and portal vein thrombosis is a well-recognized phenotypic association with JAK2 V617F and is often observed in younger women, with either a masked phenotype, or lower leukocyte counts and lower allelic burdens. The affected patients present a unique exception with regard to demographics, clinical phenotype, and allelic burden [8]. Some patients may develop AvWS, especially in the presence of extreme thrombocytosis (platelets >1000 x 10<sup>9</sup>/L) and are at risk for aspirin associated bleeding [7].

JAK2 oncogenes homozygosity may result in distinct tumorigenic consequences, but direct evidence has been elusive (5). JAK2V617F homozygosity was associated with reduced platelet survival that is likely to reflect increased platelet apoptosis and/or clearance. Moreover, homozygosity results in reduced platelets numbers, consistent with the lower platelet levels seen in PV compared with ET [5]. Increased JAK2V617F signaling may enhance (or reduce) platelet reactivity, a concept that may be relevant to thrombotic (or hemorrhagic) complications in PV patients [5].

JAK2 V617F homozygous allele burden has been associated with older age, male sex, pruritus, and splenomegaly; associations between homozygous or increasing allelic burdens and thrombosis

(arterial and venous), as well as MF transformation have also been suggested [8]. JAK2 exon 12e mutated PV, is more likely to be associated with younger age and [2] may have higher hemoglobin, and lower platelet and leukocyte counts compared with those with JAK2 V617F mutated PV, clinical outcomes do not differ, with similar incidences of thrombosis, MF, AML, and death [8].

PV may present with thrombocytosis and because hydroxyurea suppresses erythropoiesis, misdiagnosis of PV patients with prominent thrombocytosis as having ET may have occurred. Iron deficiency may mask the polycythemia [9].

Estimated median survivals for PV are 14 years; the corresponding median survivals in younger patients were 33 and 24 years [2]. In WHO-defined PV, the 10- year projected rates for survival, leukemic transformation and fibrotic progression were >75%, <5%, and <10%, respectively [7]. Patients who developed MF (post-PV MF) had a higher rate of leukemic transformation [9].

The goal of therapy in PV is primarily to prevent thrombohemorrhagic complications, without increasing bleeding risk, and secondarily to control the microcirculatory symptoms. Treatment is tailored to individual patients according to their risk for thrombosis or bleeding [7]. The presence of hypertension and leukocytosis is taken into consideration, when deciding treatment in certain circumstances [6].

Low-risk patients (i.e., those <60 years and without a history of thrombosis) are commonly treated with phlebotomy [10] (to a hematocrit target of 45%) [7] and antiplatelet therapy [10]. Hydroxyurea or interferon may be indicated in low-risk patients in quite rare instances such as those who need, and poorly tolerate, frequent phlebotomies, unmanageable disease-related symptoms, extensive thrombocytosis or progressively increasing leukocyte count, or symptomatic splenomegaly [11].

High-risk patients (i.e., presence of any thrombosis history or advanced age with JAK2 mutation) receive cytoreductive treatment in addition to low-dose aspirin (depending on the type and date of the previous thrombotic event, oral anticoagulation may be indicated instead of low-dose aspirin) [10]. Twice-daily aspirin is used in arterial thrombosis in older patients or harbor JAK2 mutations or in the presence of CV risk factors. In patients with venous thrombosis, systemic anticoagulation is advised and the addition of once-daily low dose aspirin, in the presence of JAK2 mutation or CV risk factors, is reasonable [7].

High-risk patients should receive hydroxyurea (starting dose 500 mg BID) as first-line drug to minimize their risk of thrombosis. The dose of hydroxyurea is titrated to keep the platelet count in the normal range [7]. Complete response was defined as: hematocrit <45% without phlebotomy, platelet count <400 x 10<sup>9</sup>/L, white blood cell count <10 x 10<sup>9</sup>/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 [11].

Hydroxyurea resistance and intolerance in PV patients is defined by ELN consensus as

1. Need for phlebotomy to keep hematocrit <45% or

2. Uncontrolled myeloproliferation, i.e., platelet count >400 x 10<sup>9</sup>/L AND white blood cell count >10 x 10<sup>9</sup>/L, or

3. Failure to reduce massive splenomegaly (i.e., extending >10 cm from the left costal margin) by >50% as measured by palpation, OR failure to completely relieve symptoms related to splenomegaly, or

4. All these first 3 criteria after 3 mo of at least 2 g per day of hydroxycarbamide, or

5. Absolute neutrophil count <1.0 x 10<sup>9</sup>/L OR platelet count <100 x 10<sup>9</sup>/L or hemoglobin <100 g/L at the lowest dose of hydroxycarbamide required to achieve a complete or partial clinicohematological response, or

6. Presence of leg ulcers or other unacceptable hydroxycarbamide-related non-hematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever at any dose of hydroxycarbamide [11].

The three drugs, pegylated IFN- $\alpha$ , busulfan and ruxolitinib are currently considered as second-line therapy for PV [6]. PV patients who are either intolerant or resistant to hydroxyurea are effectively managed by INF-  $\alpha$  (pegylated preparations preferred) or busulfan [7]. The use of INF- $\alpha$  is preferred for patients younger than age 65 years and busulfan in the older age group. There is no controlled evidence to support or refute such a strategy. Busulfan is started at 4 mg/day, withheld in the presence of platelets <200 x 10<sup>9</sup>/L or WBC <3 x 10<sup>9</sup>/L, and the dose is reduced to 2 mg/day when treatment is resumed after withholding. Pegylated IFN- $\alpha$  is usually started at 45 mcg once-a- week and titrate up to 180 mcg once-a-week if tolerated [7].

Long-term safety data are considered acceptable for pegylated IFN- $\alpha$  and busulfan. Both drugs display broader activity against clonal myeloproliferation and display better quality of response, including the ability to induce molecular remission compared to ruxolitinib [6]. There are no controlled studies that implicate either hydroxyurea or busulfan as being leukemogenic in PV [7]. The risk of acute leukemia was not significantly increased until after 8 years of hydroxyurea exposure [9].

Ruxolitinib is recommended only in PV if there is severe protracted pruritis [12], severe constitutional symptoms [7] or marked splenomegaly that is not responding to interferon alpha or busulfan [12]. Advise patients about possible herpes zoster reactivation and skin tumors [11].

### Conclusion

High-risk patients should receive hydroxyurea. The risk of acute leukemia was not significantly increased after hydroxyurea exposure Long-term safety data are considered acceptable for pegylated IFN- $\alpha$  and busulfan as second line. Use of ruxolitinib is limited to certain indications.

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