Evolving Therapeutic Options for Polycythemia Vera: Perspectives of the Canadian Myeloproliferative Neoplasms Group

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Abstract

Polycythemia vera (PV) is a clonal stem cell disorder characterized by erythrocytosis and associated with burdensome symptoms, reduced quality of life, risk of thrombohemorrhagic complications, and risk of transformation to myelofibrosis and acute myeloid leukemia. The discovery of the *JAK2 V617* mutation marked a significant milestone in understanding the pathophysiology of the disease and subsequently the diagnostic and therapeutic approaches. The current diagnostic criteria for PV are based on hemoglobin level and presence of the *JAK2 V617* mutation. The treatment is geared toward prevention of thrombotic events, normalization of blood counts, control of disease-related symptoms, and potential prolongation of survival. Cytoreductive therapy is indicated in patients at increased risk of thrombosis. Hydroxyurea (HU) remains the most commonly used first-line cytoreductive therapy and is superior to phlebotomy in reducing risk of arterial and venous thrombosis. Interferon (IFN) is used either at failure of HU or in selected patients as first-line therapy. The results of pegylated IFN in phase 2 studies appear encouraging, with molecular responses occurring in some patients. Ongoing phase 3 studies of HU versus pegylated IFN will define the optimal first-line cytoreductive therapy for PV. A recent phase 3 trial has shown the superiority of the *JAK1/2* inhibitor ruxolitinib in comparison to best available treatment in HU-intolerant or -resistant patients. The therapeutic landscape of PV is likely to change in the near future. In this report, we assess the potential impact of the changing landscape of PV management on daily practice.

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Introduction

Polycythemia vera (PV) is a clonal stem cell disorder characterized by overproduction of red blood cells, often accompanied by leukocytosis and/or thrombocytosis.[1] In 1951, Dameshek[1] speculated that the manifestations of proliferative activity of bone marrow (BM) cells was due to an undiscovered myelostimulatory factor, which later was discovered to be the *JAK2 V617F* mutation. Overactivity of *JAK* signaling caused by the unique *V617F* mutation within exon 14 (~95% of PV)[2] and by different mutations within exon 12 of the *JAK2* gene (~4% of PV)[3] has been implicated in the pathogenesis of PV. Erythrocytosis is the most prominent clinical feature of PV and distinguishes it from other myeloproliferative

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neoplasms (MPNs). Similar to other MPNs, individuals with PV often have splenomegaly and significant burden of disease-related symptoms, including pruritus, night sweats, fatigue, and bone pain. Patients are also at risk of thrombotic complications and transformation to secondary myelofibrosis (MF), also known as post-PV MF (PPV-MF) or acute myeloid leukemia (AML).

The estimated incidence of PV worldwide is approximately 0.84 per 100,000, with slightly higher reported rates in Europe than in North America.[4,5] Recent data from 2 large health plans in the United States indicate the prevalence rates of 44 to 57 cases per 100,000.[5] However, there is a wide variation in both prevalence and incidence estimates observed across data sources. The median age at presentation is in the sixth decade, and approximately 10% of patients are under 40 years, with an equitable gender distribution.[6]

The clinical presentation of PV usually involves the following 3 common scenarios: (1) an incidental discovery of elevated hemoglobin or hematocrit (Hct); (2) diagnosis after a thrombotic event; and (3) diagnosis after investigating disease-related symptoms.[7] These may be nonspecific complaints, such as headache, weakness, dizziness, and excessive sweating, which are present in 30% to 50% of PV patients; acute gouty arthritis has been described in 5% to 20%. Symptoms more specific to PV include pruritus, especially after warm baths or showers (aquagenic pruritus; reported by 70% of patients),[8] and erythromelalgia, or a burning pain in the feet or hands accompanied by erythema (seen in 28% of patients).[9]

The most common abnormal findings on physical examination in PV include splenomegaly (present in approximately 30% to 40% of patients), facial plethora (67% of patients), and hepatomegaly (40% of patients). Laboratory findings include an elevated hemoglobin/Hct in most patients, platelet count $> 450 \times 10^9$/L, and a white blood cell count of $> 10.5 \times 10^9$/L in approximately 50% of patients.[6]

Diagnostic Approaches

Current diagnosis of PV is based on the 2008 World Health Organization (WHO) criteria and requires the composite assessment of clinical and laboratory features, as summarized in Table 1.[10] Although the WHO criteria are widely applied in clinical practice, consensus for the optimal diagnostic criteria for PV has not yet been achieved.[11] Furthermore, the current WHO criteria are undergoing revisions; proposed changes are also outlined in Table 1.[12]

The rational for the proposed changes is based on recent observations that some *JAK2 V617F*–positive PV patients present with hemoglobin levels lower than the current WHO criteria of 185 g/L for men and 165 g/L for women.[13,14] Compared with other PV patients, masked PV (mPV) patients have increased risk of thrombosis, perhaps resulting from late diagnosis, and inadequate disease control. Because mPV patients are missed by current WHO criteria, a retrospective analysis of a large cohort of patients with MPN has suggested that lowering the hemoglobin threshold to 165 g/L for men and 160 g/L for women would capture most of these mPV cases.[14]

The Canadian Myeloproliferative Neoplasms Group (Appendix) acknowledges the necessity of appropriately diagnosing mPV but has concerns about potential misuse of these criteria for screening for PV, as large numbers of individuals would be subjected to unnecessary further testing to rule out mPV. To that end, 2 large

Table 1 Current and Proposed WHO Criteria for Diagnosis of PV

2008 WHO Diagnostic Criteria for PV[10]	2014 Proposed Revision of WHO Diagnostic Criteria for PV[12]
Major Criteria	
1. Hemoglobin >185 g/L (men), >165 g/L (women), or evidence of increased red cell volume[a]	1. Hemoglobin >165 g/L (men), >160 g/L (women) or hematocrit >49% (men), >48% (women)
2. Presence of *JAK2 V617F* or other functionally similar mutation (eg, *JAK2* exon 12 mutation)	2. BM findings consistent with WHO criteria with pleomorphic megakaryocytes
	3. Presence of *JAK2* mutation
Minor Criteria	
1. BM biopsy showing hypercellularity for age with trilineage myeloproliferation	1. Subnormal serum erythropoietin level
2. Serum erythropoietin level below the normal reference range	
3. Endogenous erythroid colony formation in vitro	
Diagnosis of PV requires meeting either both major criteria and 1 minor criterion or the first major criterion and 2 minor criteria.	*Diagnosis of PV requires meeting either all 3 major criteria or the first 2 major criteria and 1 minor criterion.*

Abbreviations: BM = bone marrow; PV = polycythemia vera; WHO = World Health Organization.

[a]Hemoglobin or hematocrit > 99th percentile of method-specific reference range for age, sex, altitude of residence; or hemoglobin > 170 g/L in men or 150 g/L in women if associated with a documented and sustained increase of at least 20 g/L from a person's baseline value that cannot be attributed to correction of iron deficiency; or elevated red cell mass > 25% above mean normal predicted value.

Adapted from Tefferi et al, Leukemia *2014; 28:1407-13, and Thiele et al, Lyon, France: IARC Press; 2008:40-3.*

Montreal hospitals (Centre Hospitalier de l'Université de Montréal and Maisonneuve-Rosemont Hospital) performed an analysis (unpublished results, manuscript in preparation) that showed that close to 4.4% of all complete blood count analyses from unselected male (non-hematology-oncology clinic) patients had hemoglobin levels higher than 165 g/L versus only 0.29% that met the current criteria (hemoglobin > 185 g/L). This indicates that close to 15 times more men will be suspected as having PV and will be subjected to further investigation. The proposed change to the WHO criteria has less impact in women, as only 0.39% had hemoglobin levels greater than 160 g/L. This is only 5 times more frequent than the current cutoff of 165 g/L, which accounts for 0.07% of unselected women. Therefore, it is important that the cost-effectiveness of the new proposed criteria be carefully evaluated before they are adapted in routine clinical practice. In addition, hemoglobin levels above the suggested threshold should not be taken in isolation but rather in the context of other potential signs and symptoms indicative of PV. It is important to emphasize that the intent of lowering the thresholds is to more accurately differentiate between *JAK2*-positive essential thrombocythemia and mPV rather than to serve as a basis for population screening.

For diagnostic purposes, a complete blood count is of particular relevance, as an increase in all 3 lineages (erythrocytosis with leukocytosis and/or thrombocytosis) is more indicative of PV than isolated erythrocytosis.[15] In patients with isolated erythrocytosis, causes of secondary polycythemia should be considered. The