Polycythemia Vera: Are Some Patients at Increased Risk?

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Overview

What Is Polycythemia Vera?

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) characterized by an overproduction of normal red blood cells, white blood cells and platelets that leads to an increased risk of thrombosis. Erythrocytosis (elevated red blood cell mass) is the most prominent clinical manifestation of PV, distinguishing it from other MPNs.

PV may occur at any age but often presents later in life, with a median age at diagnosis of 60 years. Approximately 100,000 patients in the United States are living with PV.

Clinical Presentation of PV Contributing to Its Diagnosis

Janus kinases (JAKs) mediate cytokine signaling and growth factors. An important genetic discovery about a point mutation in the Janus kinase 2 (JAK2) gene has enhanced the understanding of PV.

The specific JAK2V617F mutation is detected in >95% of patients with PV. Although the JAK2V617F mutation is the key driver of PV, an understanding of the clinical presentation of PV will help to facilitate a more accurate diagnosis.

PV is an elusive disease that may not be recognized for years. Diagnosis most frequently occurs by chance following a routine examination. Diagnosis may also occur after a thrombotic event or as a result of disease-related symptoms.

The following important signs and symptoms warrant a prompt evaluation and suggest PV:

- Elevated hemoglobin or hematocrit levels
- Thrombotic events
- Splenomegaly (with or without thrombocytosis and/or leukocytosis)

Clinical Considerations in Managing PV

Prognosis and Risk Factors

PV is a disease with no curative treatments at this time. In a large population-based study in more than 4,000 patients with PV, life expectancy was 36% lower than that of the general population.

Thrombotic and hemorrhagic complications are among the leading causes of morbidity and mortality associated with PV. Cancer and cardiovascular mortality are the frequent causes of deaths in PV.

When assessing risks for morbidity and mortality in patients, consider the following:

- Elevated hematocrit levels
- History of thrombosis
- Advanced age (≥60 years)
- Leukocytosis
- Cardiovascular risk factors such as high cholesterol levels, hypertension, diabetes, obesity and smoking

According to data from a large, randomized, controlled clinical trial, the rate of death due to cardiovascular events or major thrombosis was four times higher in patients with elevated hematocrit levels of 45% to 50% compared with those who maintained a hematocrit target of <45%.

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**CI = confidence interval; Hct = hematocrit.**

Figure 1. Kaplan-Meier curve for total cardiovascular events.


Thrombosis, Splenomegaly and Other Disease-related Symptoms

In PV, a wide spectrum of thrombotic manifestations exists that may occur before the disease is diagnosed. Palpable splenomegaly is an important physical finding because increased spleen size is present in 30% to 40% of patients with PV. Additional signs and symptoms of PV, which may contribute to a substantial quality-of-life burden in patients with PV, include:

- Fatigue
- Pruritus
- Night sweats
Clinical Need in PV

Therapeutic approaches to PV focus on:3,11;
- Controlling and maintaining hematocrit levels at <45%
- Treating complications of thrombosis and hemorrhage
- Reducing thrombotic risk and minimizing the risk of leukemogenic transformation
- Managing splenomegaly and other disease-related symptoms

Phlebotomy is usually the starting point of treatment in patients with PV, in addition to therapy with low-dose aspirin.2,11 Low-dose aspirin has been shown to prevent both arterial and venous thrombotic complications in patients with PV.18

Cytoreductive therapy with hydroxyurea or interferon-alpha may also be helpful in patients who have difficulty with phlebotomy, who have symptomatic or progressive splenomegaly or who experience severe symptoms.11 Although treatment with hydroxyurea may be tolerated by most patients, it is important to consider that approximately 25% of patients with PV develop resistance to or intolerance of hydroxyurea (Table 1).19,20

Table 1. Assessment of hydroxyurea (HU) resistance and intolerance

<table>
<thead>
<tr>
<th>HU Resistance</th>
<th>HU Intolerance</th>
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<tbody>
<tr>
<td>After 12 weeks of HU at a total dose of ≥2 g/day or at the maximum tolerated dose, if &lt;2 g/day</td>
<td>At least 1 of the following:</td>
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<tr>
<td>• Need for phlebotomy to maintain Hct level at &lt;45% or</td>
<td>• Neutropenia (absolute neutrophil count of &lt;1.0 x 109/L)</td>
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<tr>
<td>• Elevated platelet and white blood cell counts or</td>
<td>• Platelet count of &lt;100 x 109/L</td>
</tr>
<tr>
<td>• &lt;50% reduction in splenomegaly</td>
<td>• Hgb level of &lt;10 g/dL</td>
</tr>
</tbody>
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Hct, hematocrit; Hgb, hemoglobin.

Modified from Barosi et al.16

There are no FDA-approved drug treatments for PV (Figure 2). Despite current approaches, including phlebotomy, low-dose aspirin, interferon-alpha or cytoreductive therapy with hydroxyurea, some patients will not be able to gain and maintain hematocrit levels of <45%.19,20

For some patients whose hematocrit levels remain elevated, and for those who continue to experience clinical signs and symptoms such as fatigue, pruritus, night sweats or splenomegaly, PV remains uncontrolled.11,20 Recently, standardized criteria for monitoring and assessing response in PV have been developed for clinical research. Evaluation of response includes such parameters as resolution of splenomegaly and other disease-related signs, hematocrit of <45%, blood count remission, absence of thrombotic events and bone marrow histology.21

References

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