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Polycythemia Vera

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Overview

Practice Essentials

Polycythemia vera (PV) is a stem cell disorder characterized as a panhyperplastic, malignant, and neoplastic marrow disorder. Its most prominent feature is an elevated absolute red blood cell mass because of uncontrolled red blood cell production. This is accompanied by increased white blood cell (myeloid) and platelet (megakaryocytic) production, which is due to an abnormal clone of the hematopoietic stem cells with increased sensitivity to the different growth factors for maturation.[1,2,3,4]

Signs and symptoms of polycythemia vera

Impaired oxygen delivery due to sludging of blood may lead to the following symptoms:

- Headache
- Dizziness
- Vertigo
- Tinnitus
- Visual disturbances
- Angina pectoris
- Intermittent claudication

Bleeding complications, seen in approximately 1% of patients with PV, include epistaxis, gum bleeding, ecchymoses, and gastrointestinal bleeding. Thrombotic complications (1%) include venous thrombosis or thromboembolism and an increased rate of stroke and other arterial thromboses.

Physical examination findings may include the following:

- Splenomegaly (75% of patients)
- Hepatomegaly (30%)
- Plethora
- Hypertension

Diagnosis of polycythemia vera

According to 2022 revised World Health Organization (WHO) guidelines, diagnosis of PV requires requires the presence of either all three major criteria or the first two major criteria and the minor criterion.[5]

Major WHO criteria are as follows:

1. Hemoglobin > 16.5 g/dL in men and > 16 g/dL in women, or hematocrit > 49% in men and > 48% in women
2. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3. Presence of JAK2V617F or JAK2 exon 12 mutation

The minor WHO criterion is as follows:

- Serum erythropoietin level below the reference range for normal

Previous versions of the WHO guidelines included red cell mass > 25% above mean normal predicted value as a diagnostic criterion. The WHO removed this criterion from its 2022 guidelines because the determination of red cell mass with chromium-

51–labeled red cells has become uncommon in routine clinical practice.[5]

Management of polycythemia vera

Treatment measures are as follows:

- Phlebotomy – To keep hematocrit below 45%
- Aspirin – 81 mg daily
- Cytoreductive therapy – For patients at high risk for thrombosis
- Splenectomy – In patients with painful splenomegaly or repeated episodes of splenic infarction

Hydroxyurea is the most commonly used cytoreductive agent. If hydroxyurea is not effective or not tolerated, alternatives include the following:

- Ropeginterferon alfa 2b
- Busulfan – In patients older than 65 years
- Ruxolitinib (Jakafi)
- Fedratinib (Inrebic)

For discussion of polycythemia in children, see Pediatric Polycythemia vera.

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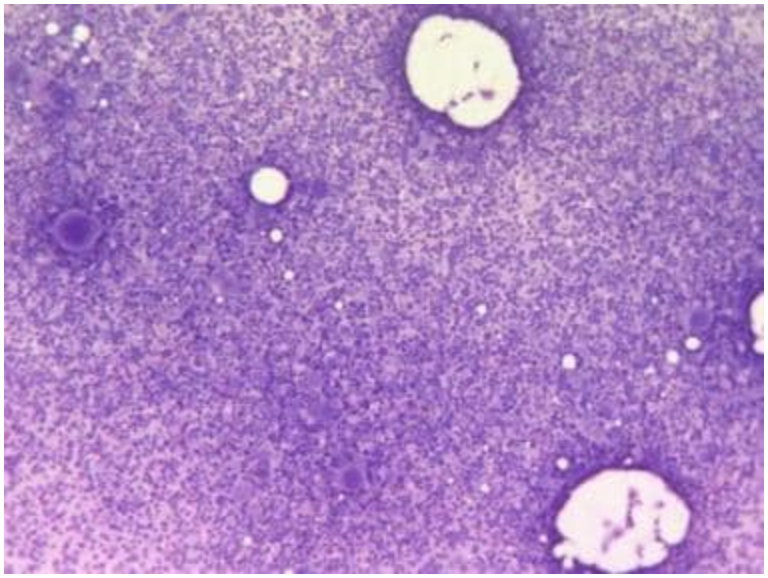
Pathophysiology

The bone marrow of patients with polycythemia vera (PV) contains normal stem cells but also contains abnormal clonal stem cells that interfere with or suppress normal stem cell growth and maturation. The panmyelosis in PV appears to result from unregulated neoplastic proliferation. The origin of the stem cell transformation remains unknown. See the image below.



Bone marrow film at 100X magnification demonstrating hypercellularity and increased number of megakaryocytes. Courtesy of U. Woermann, MD, Division of Instructional Media, Institute for Medical Education, University of Bern, Switzerland.

Progenitors of the blood cells in these patients display abnormal responses to growth factors, suggesting the presence of a defect in a signaling pathway common to different growth factors. The observation that in vitro erythroid colonies grow when no endogenous erythropoietin (Epo) is added to the culture and the presence of a truncated Epo receptor in familial erythrocytosis indicate that the defect is in the transmission of the signal. The sensitivity of PV progenitors to multiple cytokines suggests that the defect may lie in a common pathway downstream from multiple receptors. Increased expression of BCLX suggests an additional decrease in cellular apoptosis.

A mutation of the Janus kinase–2 gene (JAK2) is the most likely source of PV pathogenesis, as JAK2 is directly involved in the intracellular signaling following exposure to cytokines to which PV progenitor cells display hypersensitivity.[6] A recurrent unique acquired clonal mutation in JAK2 has been found in most patients with PV and other myeloproliferative diseases (MPDs), including essential thrombocythemia and idiopathic myelofibrosis.

A unique valine-to-phenylalanine substitution at position 617 (V617F) in the pseudokinase JAK2 domain has been identified. The substitution, called JAK2V617F, leads to a permanently turned-on signaling at the affected cytokine receptors.

[7,8,9,10] The JAK2V617F mutation is present in more than 95% of PV cases, but is also found in 50-60% of essential thrombocytosis and primary myelofibrosis cases.[11] How these mutations interact with the wild-type kinase genes and how they manifest into different forms of MPDs need to be elucidated.

At diagnosis of PV, a homozygous JAK2 genotype is found less often in women than in men (median, 61% vs 80%). JAK2 variant allele frequency, which is initially similar in men and women, over time becomes significantly higher in men than in women.[12]

Thrombosis and bleeding are frequent in persons with PV, as a result of the disruption of hemostatic mechanisms because of (1) increased numbers of red blood cells and (2) elevation of the platelet count. There are findings that indicate the additional roles of tissue factor and polymorphonuclear leukocytes (PMLs) in clotting, the platelet surface as a contributor to phospholipid-dependent coagulation reactions, and the entity of platelet microparticles. Tissue factor is also synthesized by blood leukocytes, the level of which is increased in persons with MPD, which can contribute to thrombosis.

PV tends to be milder in women than in men, with lower rates of myocardial infarction and peripheral arterial disease (although this may be related to lower rates of smoking in women). However, venous thrombosis is more common in females; in particular, the rate of splanchnic vein thrombosis is significantly higher in young women.[12]

Rusak et al evaluated the hemostatic balance in patients using thromboelastography and also studied the effect of isovolemic erythrocytapheresis on patients with PV. They concluded that thromboelastography may help to assess the thrombotic risk in these patients.[13]

Hyperhomocystinemia is a risk factor for thrombosis and is also widely prevalent in patients with MPD (35% in controls, 56% in persons with PV).

Acquired von Willebrand syndrome is an established cause of bleeding in persons with MPD, accounting for approximately 12-15% of all patients with this syndrome. von Willebrand syndrome is largely related to the absorption of von Willebrand factor onto the platelets; reducing the platelet count should alleviate the bleeding from the syndrome.

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Etiology

The causes of polycythemia vera (PV) are unknown, but a number of approaches are being studied to define the molecular lesion or lesions. The JAK2 V617F mutation can give rise to a turned-on cytokine receptor, leading to pancytosis similar to the PV phenotype. This is similar to the biologic properties of the BCR/ABL abnormality in that they both mimic cytokine signaling.

Clonality studies using a rare polymorphism in the G6PD gene demonstrate predominant expression of a single allele in all blood cell lines. X-chromosome inactivation studies have played a pivotal role in establishing current concepts of many hematologic malignancies. Approximately 90% of patients with PV show a skewed pattern of X inactivation in all their blood cell lines, indicating support for the concept of a transformed multipotential stem cell.

Cytogenetic studies show the presence of an abnormal karyotype in the hematopoietic progenitor cells in approximately 34% of patients with PV, depending on the stage of the disease in which the study was performed. Approximately 20% of patients have cytogenetic abnormalities at diagnosis, increasing to more than 80% for those with more than 10 years of follow-up care.

The following genetic abnormalities, which are similar to the abnormal karyotypes observed in patients with myelodysplastic syndromes and other MPDs, have been observed in patients with PV:

- Deletion of 20q (8.4%)
- Deletion of 13q (3%)
- Trisomy 8 (7%)
- Trisomy 9 (7%)
- Trisomy of 1q (4%)
- Deletion of 5q or monosomy 5 (3%)
- Deletion of 7q or monosomy 7 (1%)

Spivak and colleagues analyzed gene expression in CD34+ peripheral blood cells from 19 patients with PV and found twice as many up-regulated or down-regulated genes in men as in women. In addition, these researchers found 102 genes with differential regulation that was concordant in men and women and that could be used to divide patients into two phenotypical groups. The groups differed significantly with respect to disease duration, clinical manifestations, and prognosis.[14]

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Epidemiology

Frequency

United States

Polycythemia vera (PV) is relatively rare, occurring in 0.6-1.6 persons per million population.

Race-, sex-, and age-related demographics

Originally, Ashkenazi Jewish persons were thought to have a higher predilection for polycythemia vera than members of other ethnic groups. Subsequently, however, many studies have shown that this condition occurs in all ethnic groups.

Most studies have found the incidence of polycythemia vera to be slightly higher in males than females. However, a slightly higher incidence in females has also been reported, and one systematic review and meta-analysis showed no significant difference in the crude annual incidence between males and females.[12]

The peak incidence of polycythemia vera onset is age 50-70 years. However, this condition occurs in persons of all age groups, including early adulthood and childhood, albeit rarely.

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Prognosis

Median survival in patients with polycythemia vera (PV), which is 1.5-3 years in the absence of therapy, has been extended to approximately 14 years overall, and to 24 years for patients younger than 60 years of age, because of new therapeutic tools.[15] However, according to a study of Surveillance, Epidemiology and End Results (SEER) data, mortality in PV patients is higher than in an age- and sex-matched population. Five-year survival in the overall cohort was 79.5% but patients are at a high risk of second primary malignancies and leukemic transformation, which may compromise long-term survival.[16]

Morbidity and mortality

The major causes of morbidity and mortality are as follows:

- Thrombosis
- Hemorrhage
- Peptic ulcer disease
- Myelofibrosis
- Acute leukemia or myelodysplastic syndrome

Thrombosis

Venous and arterial thrombosis has been reported in 15-60% of patients, depending on the control of their disease. It is the major cause of death in 10-40% of patients. All of the following have been noted:

- Pulmonary embolism
- Kidney failure from renal vein or artery thrombosis
- Intestinal ischemia from mesenteric vein thromboses
- Peripheral arterial emboli

Hemorrhage

Hemorrhagic complications occur in 15-35% of patients and lead to death in 6-30% of these patients. Bleeding is usually the consequence of vascular compromise resulting from ischemic changes from thrombosis or hyperviscosity.

Peptic ulcer disease

Peptic ulcer disease is reported to be associated with PV at a 3- to 5-fold higher rate than that of the general population. This has been attributed to increased histamine serum levels.

Myelofibrosis

Myelofibrosis and pancytopenia occur in 3-10% of patients, usually late in the disease, which is considered the spent phase of PV. In these patients, infections and bleeding complications may be the most serious health threats, and red blood cell transfusions may be required to maintain adequate red blood cell counts and to improve fatigue and other anemia-related symptoms.

The US Food and Drug Administration (FDA) has approved two Janus kinase (JAK) inhibitors for treatment of post-PV myelofibrosis. The JAK1 and JAK2 inhibitor ruxolitinib (Jakafi) was approved in 2011; the highly selective JAK2 inhibitor fedratinib (Inrebic) was approved in 2019.[17]

Leukemia and myelodysplastic syndrome

Acute leukemia or a myelodysplastic syndrome develops in 1.5% of patients treated with phlebotomy alone. The transformation risks increase to 13.5% within 5 years with treatment using chlorambucil and to 10.2% within 6-10 years in patients treated with phosphorus-32. At 15 years, the transformation risk for patients treated with hydroxyurea is 5.9%, which, although not statistically significant, is a worrisome trend.

Abdulkarim et al studied the long-term (15 years) rate of transformation to acute myelogenous leukemia (AML) in Swedish and French patients with Philadelphia chromosome–negative MPD, including 317 patients with PV. The annual rate of AML transformation was 0.38% in patients with PV, and the average time from PV diagnosis to AML transformation was 88 +/- 56 months. Notably, 17 of the 18 patients with PV whose condition transformed to AML were females, despite the fact that almost half of the patients with PV were males.[18]

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Presentation

History

Clinical manifestations of polycythemia vera (PV) are often insidious in onset, and they are often related to blood hyperviscosity secondary to a marked increase in the cellular elements of blood. Subsequent sludging of blood flow and thrombosis lead to poor oxygen delivery, with symptoms that include the following:

- Headache
- Dizziness
- Vertigo
- Tinnitus
- Visual disturbances
- Angina pectoris
- Intermittent claudication

Bleeding complications, seen in approximately 1% of patients with PV, include epistaxis, gum bleeding, ecchymoses, and gastrointestinal (GI) bleeding. Thrombotic complications (1%) include venous thrombosis or thromboembolism and an increased rate of stroke and other arterial thromboses.

Abdominal pain due to peptic ulcer disease may be present because PV is associated with increased histamine levels and gastric acidity or possible Budd-Chiari syndrome (hepatic portal vein thrombosis) or mesenteric vein thrombosis. Early satiety can occur in patients with splenomegaly, because of gastric filling being impaired by the enlarged spleen or, rarely, as a symptom of splenic infarction. Weight loss may result from early satiety or from the increased myeloproliferative activity of the abnormal clone.

Pruritus results from increased levels of histamine, released from the increased numbers of basophils and mast cells, and can be exacerbated by a warm bath or shower. This occurs in up to 40% of patients with PV.

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Physical

Physical findings in patients with polycythemia vera (PV) are due to the myeloproliferative process and excess concentrations of the cellular elements of blood with extramedullary hematopoiesis. Splenomegaly is present in 75% of patients at the time of diagnosis. Hepatomegaly is present in approximately 30% of patients.

Plethora or a ruddy complexion is characteristic of PV and results from the marked increase in total red blood cell mass. This manifests in the face, palms, nailbeds, mucosa, and conjunctiva.

Hypertension is common in patients with PV. Measurement of the red blood cell mass should differentiate this condition from Gaisbock syndrome, which is hypertension and pseudopolycythemia (ie, high hemoglobin levels due to low plasma volume).

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Diagnostic Considerations

Polycythemia is characterized by increased cell counts in all cell lines in the myeloid series (ie, red blood cells [RBCs], white blood cells [preferentially granulocytes], and platelets). Thus, conditions that involve individual cell lines, such as the following, must be excluded:

- Erythrocytosis - Causes include secondary polycythemia (an increase in RBC counts, typically due to chronic hypoxemia), familial erythrocythemia, and relative polycythemia (a benign condition in which RBC numbers are normal but plasma volume is contracted, due to dehydration or to reduced venous compliance).
- Granulocytosis from infections or mobilization by secondary causes, as in leukemoid reactions
- Thrombocytosis from bleeding and iron deficiency

Diagnostic laboratory tests have been developed to increase the ability to identify primary myeloproliferative diseases (MPDs) and to differentiate them from reactive conditions associated with increased blood cell levels, which can mimic MPDs. Once an MPD (Philadelphia chromosome negative [Ph–]) is documented, it must be differentiated from the following conditions, which have manifestations that overlap with polycythemia vera (PV):

- Essential thrombocytosis (ET)
- Chronic myelogenous leukemia (CML)
- Primary myelofibrosis

Differential Diagnoses

- Chronic Myelogenous Leukemia (CML)
- Essential Thrombocytosis
- Primary Myelofibrosis
- Secondary Polycythemia

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Workup

Workup

Approach Considerations

The Polycythemia Vera Study Group (PVSG) was the first to set rigorous criteria for the diagnosis of polycythemia vera (PV) in the 1970s. With the establishment of polymerase chain reaction (PCR)–based methods for detecting the JAK2 V617F mutation, this may become the first molecular diagnostic marker for PV, similar to BCR/ABL for chronic myelogenous leukemia (CML). However, because of a paucity of centers doing red blood cell mass measurements, demonstrating an elevated red blood cell mass continues to become more difficult; indeed, the 5th edition of the World Health Organization (WHO) classification, published in 2022, removed elevated red blood cell mass as a criterion for PV diagnosis, because use of the assay has become uncommon in routine clinical practice.[5]

The diagnostic criteria set by the PVSG are organized into two categories, A and B. The diagnosis of PV is established if all three category A criteria are present, or if criteria A1 and A2 plus any two criteria from category B are present.

Category A criteria are as follows:

1. Total red blood cell mass ≥36 mL/kg in males or ≥32 mL/kg in females
2. Arterial oxygen saturation ≥92%
3. Splenomegaly

Category B criteria are as follows:

- Thrombocytosis, with platelet count > 400,000/µL
- Leukocytosis, with a white blood cell count > 12,000/µL

- Increased leukocyte alkaline phosphatase (ALP) > 100 U/L
- Serum vitamin B12 concentration > 900 pg/mL or binding capacity > 2200 pg/mL

Total red blood cell mass is measured by labeling the cells with chromium 51 (51Cr). Documentation of an elevated total red blood cell mass with 51Cr-labeled red blood cells and, ideally, an iodine-131 (131I) plasma volume dual technique differentiates true erythrocytosis from pseudoerythrocytosis (decreased plasma volume). However, the red blood cell mass is becoming difficult to obtain because the 51Cr isotope needed to perform the test is no longer readily available, and institutions willing to perform the test are few as a result of small demand and lack of profit in performing the test.

Diagnostic criteria for PV as per the 2022 revised WHO guidelines include three major criteria and a minor criterion. Diagnosis requires the presence of either all three major criteria or the first two major criteria and the minor criterion.[5]

Major WHO criteria are as follows:

1. Hemoglobin > 16.5 g/dL in men and > 16 g/dL in women, or hematocrit > 49% in men and > 48% in women
2. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3. Presence of JAK2V617F or JAK2 exon 12 mutation

The minor WHO criterion is as follows:

- Serum erythropoietin level below the reference range for normal

Criterion 2 (bone marrow biopsy) may not be required in patients who have sustained absolute erythrocytosis (in men, hemoglobin/hematocrit of > 18.5 g/dL/55.5% or in women, > 16.5 g/dL/49.5%) if major criterion 3 and the minor criterion are present. However, bone marrow biopsy is the only way to detect initial myelofibrosis, which is present in up to 20% of patients and may predict a more rapid progression to overt myelofibrosis.[5]

JAK2 mutations also occur in about 60% of patients with essential thrombocythemia. PV is mainly related to JAK2 mutations, whereas a wider mutational spectrum is detected in essential thrombocythemia (ET) with mutations in JAK2, the thrombopoietin (TPO) receptor (MPL), and the calreticulin (CALR) genes.[19]

In patients who are positive for JAK2 and whose hemoglobin/hematocrit level is diagnostically equivocal (as in "masked" PV), bone marrow examination is necessary to distinguish the two conditions.[20] Masked PV includes both early forms of PV as well as a distinct form marked by male predominance, a more frequent history of arterial thrombosis and thrombocytosis, and significantly higher rates of progression to myelofibrosis and acute leukemia and inferior survival.[21]

If the JAK2 V617F mutation is absent but the erythropoietin level is low, then testing for JAK2 exon 12 and 13 mutations would be helpful for making a diagnosis of PV in the 2-3% of PV patients who are negative for JAK2 V617F mutation. Patients who are negative for JAK2 mutations and have a normal or high erythropoietin level have secondary erythrocytosis.

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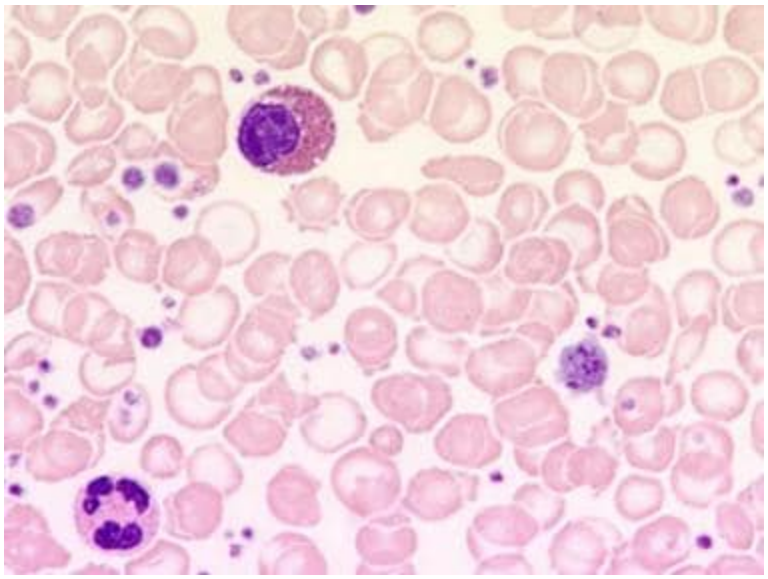
Laboratory Studies

Automated red blood cell counts and hematocrit values (including hemoglobin levels) may be deceptive with regard to the total red blood cell mass in patients with polycythemia vera (PV). Direct measurement of the red blood cell mass should show an increase with a normal or slightly decreased plasma volume. This is a nuclear medicine test that uses radiochromium-labeled red blood cells to measure actual red blood cell and plasma volume. However, patients with hemoglobin concentrations of at least 20 g/dL or hematocrit values of at least 60% in males and 56% in females always have an elevated red blood cell mass.

The red blood cells in patients with PV are usually normochromic and normocytic, unless the patient has been bleeding from underlying peptic ulcer disease or phlebotomy treatment (in which case the cells may be hypochromic and microcytic, reflecting low iron stores). See the image below.



This blood film at 10,000X magnification shows a giant platelet and an eosinophil. Erythrocytes show signs of hypochromia as a result of repeated phlebotomies. Courtesy of U. Woermann, MD, Division of Instructional Media, Institute for Medical Education, University of Bern, Switzerland.

Findings that are often present in patients with PV, but are not required for diagnosis, include the following[1]:

- Thrombocytosis (> 400,000 platelets/µL)
- Leukocytosis (>12,000/µL)
- Leukocyte alkaline phosphatase score >100 units/L in the absence of fever or infection

The platelet count is elevated to 400,000-800,000/µL in approximately 50% of patients. The release of potassium into the serum caused by the increased number of platelets during in vitro coagulation may cause a pseudohyperkalemia in the serum, whereas the true plasma potassium level in vivo is actually within the reference range, as shown by measuring plasma levels and by the lack of electrocardiography (ECG) changes. Morphologic abnormalities in platelets include macrothrombocytes and granule-deficient platelets.

An elevated white blood cell count (> 12,000/µL) occurs in approximately 60% of patients. It is mainly composed of neutrophils with a left shift and a few immature cells. Mild basophilia occurs in 60% of patients.

The leukocyte alkaline phosphatase (LAP) score is elevated (> 100 U/L) in 70% of patients. This technique is only semiquantitative and is susceptible to interobserver and laboratory errors unless it can be performed by flow cytometry, which is not routinely available.

Abnormal platelet function (as measured by platelet aggregation tests with epinephrine, adenosine diphosphate [ADP], or collagen) may be demonstrated, but bleeding time may be normal. Some patients' platelet-rich plasma spontaneously aggregates without the addition of any of the above substances. This indicates a propensity for thromboses.

Routine coagulation test results are normal, with a high turnover rate for fibrinogen. The prothrombin time (PT) and activated partial thromboplastin (aPTT) time may be artifactually prolonged, however, because the erythrocytosis results in the collection of a low amount of plasma in relation to the anticoagulant in the test tube. Thus, the volume of the ratio of anticoagulant to blood must be modified when drawing blood for coagulation tests in patients who are polycythemic.

Vitamin B12 levels are elevated to more than 900 pg/mL in approximately 30% of patients, and 75% of patients show an elevation in the unbound vitamin B12 binding capacity greater than 2200 pg/mL. This is because of increased transcobalamin III, a binding protein found in white blood cells, and it reflects the total white blood cell counts in the peripheral blood and bone marrow.

Hyperuricemia occurs in 40% of patients and reflects the high turnover rate of bone marrow cells releasing DNA metabolites.

The most important diagnostic tests are JAK2 mutation analysis and the serum erythropoietin (Epo) level. A positive JAK2 V617F mutation and a low Epo level confirms the diagnosis of PV.

A low serum Epo level, which is decreased in nearly all patients with PV who have experienced no recent hemorrhage, distinguishes polycythemia from secondary causes of polycythemia in which the serum Epo level is generally within the reference range or is elevated. Each laboratory has its own reference range for serum Epo levels.

Endogenous erythroid colony (EEC) formation had been a minor diagnostic criterion in the WHO classification of PV, but was dropped in 2016; the study requires bone marrow aspiration and sophisticated laboratory procedures. Wang et al proposed insulinlike growth factor 1 receptor (IGF-1R) measurement as a substitute for EEC. IGF-1R has proved responsible for the EEC formation in PV, and Wang et al found significantly elevated IGF-1R levels in the peripheral blood of 14 of 16 (87%) PV patients. In comparison, none of 33 patients with secondary polycythemia and 29 normal controls had elevated IGR-1R levels. In addition, IGF-1R levels were significantly higher in patients with PV who were treated with phlebotomy only, compared with those treated with hydroxyurea or ruxolinitinib.[22]

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Imaging Studies

An enlarged spleen is often palpable and in such cases, imaging studies are not required. In some patients with posteriorly enlarged spleens or in those who are obese, ultrasonography or computed tomography scans may be able to detect splenic enlargement that was not evident on physical examination.

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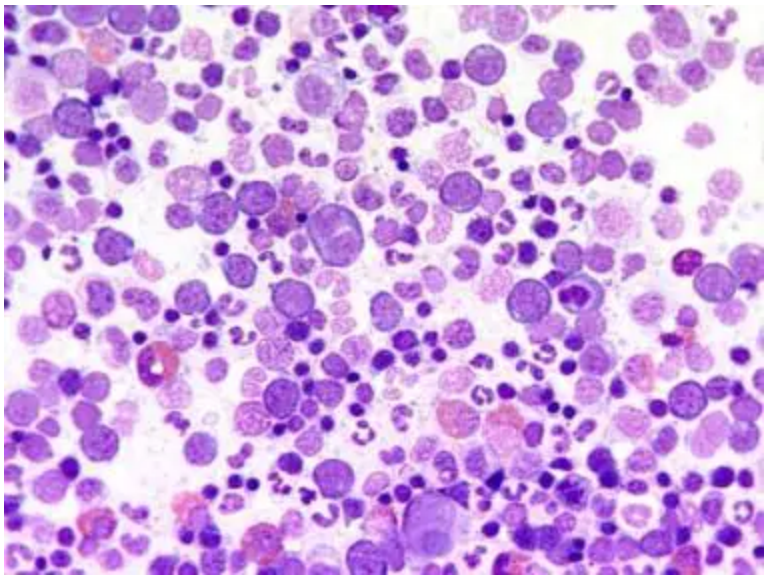
Other Tests

Measuring arterial oxygen saturation (SaO2) and carboxyhemoglobin (COHb) levels is important to rule out hypoxia as a secondary cause for erythrocytosis. Pulse oximetry is the most convenient method for measuring SaO2; however, in people who smoke cigarettes, the COHb must be determined directly and subtracted to give an accurate SaO2 value. A value below 92% indicates a causal relationship with erythrocytosis. If the fall is due to increased COHb, this is less likely to cause erythrocytosis.

Nocturnal oxygen desaturation due to sleep apnea is observed in 20% of patients.

Bone marrow studies are not necessary to establish the diagnosis of polycythemia vera. If such studies are performed, however, the finding of hypercellularity and hyperplasia of the erythroid, granulocytic, and megakaryocytic cell lines or myelofibrosis supports the diagnosis of a myeloproliferative process. See the image below.



Bone marrow film at 400X magnification demonstrating dominance of erythropoiesis. Courtesy of U. Woermann, MD, Division of Instructional Media, Institute for Medical Education, University of Bern, Switzerland.

Iron stores are decreased or absent because of the increased red blood cell mass, and macrophages may be masked in the myeloid hyperplasia that is present. Fibrosis is increased and detected early by silver stains for reticulin.

Cytogenetics of the bone marrow cells show a clonal abnormality in 30% of patients who are not treated and in 50% of patients who are treated with alkylating or myelosuppressive agents. These chromosomal abnormalities include deletions of the long arm of chromosome 5 or 20 (5q-, 20q-) and trisomy 8 (+8) or 9 (+9). Leukemic transformation is usually associated with multiple or complex abnormalities.

Measuring spontaneous growth of erythroid progenitors in cultures (burst-forming unit, erythroid [BFU-E]) in the absence of Epo is a very sensitive test for polycythemia vera (PV) or familial erythrocytosis. However, it is not routinely available for clinical use.

The hemoglobin-oxygen dissociation curve may be useful in rare cases to detect a congenital hemoglobinopathy with increased oxygen affinity. This condition can occur in families.

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Treatment

Approach Considerations

The goals of treatment of polycythemia vera (PV) are as follows:

- Reduce the risk of thrombosis
- Prevent bleeding events
- Minimize the risk of transformation to post–polycythemia vera myelofibrosis and acute myeloid leukemia
- Ameliorate the symptom burden

The optimal management remains elusive despite the findings of the Polycythemia Vera Study Group (PVSG).[23] However, general principles in the management of PV include the following:

- Tailor therapy to suit the clinical needs of the patient; consider the status of the formed elements of the blood, bone marrow, and organomegaly.
- Normalize red blood cell mass with phlebotomy as rapidly as clinically possible (250-500 mL every other day); patients who are elderly or have cardiovascular compromise should be phlebotomized cautiously, and smaller amounts should be removed.
- Suppress myeloproliferative activity with chemotherapy (hydroxyurea) in all patients older than 50 years.
- The JAK1/2 inhibitor ruxolitinib is approved by the US Food and Drug Administration (FDA) for treatment of PV in patients who have had an inadequate response to or are intolerant of hydroxyurea.[24] The JAK inhibitor fedratinib is approved treatment of adults with intermediate-2 or high-risk primary or secondary (post-PV or post–essential thrombocythemia) myelofibrosis.
- Ropeginterferon alfa-2b-njft (Besremi) is approved for treatment of adults with PV. It is the first FDA-approved medication for PV that patients can take regardless of their treatment history, and the first interferon therapy specifically approved for PV.[25]
- Patients with thrombotic tendencies or those who develop thrombocytosis after phlebotomy should be treated with marrow suppression; consider anagrelide in younger patients (aged 50-70 y).
- Phosphorus-32 (32 P) is rarely used. In general, 32P therapy should be reserved for patients older than 80 years or patients with comorbid conditions in whom life expectancy is less than 5-10 years and the convenience of 32P dosing outweighs the substantial risks of developing acute leukemia 5-15 years after 32P administration.
- Maintain blood values at reference range levels by regular examination and treatment.
- Avoid overtreatment and toxicity by careful and judicious use of chemotherapy and radiation; supplemental phlebotomy is preferred over excess marrow suppression.
- Postpone elective surgery until long-term control of the disease is established.
- Women of childbearing age should be treated with phlebotomy only.
- In young males, myelosuppressive therapy can lead to aspermia; thus, evaluate treatment carefully before using any chemotherapy or radiotherapy.
- The PVSG no longer recommends the use of alkylating agents because of the associated increased incidence of leukemia and certain types of cancer.
- Treat hyperuricemia with allopurinol (100-300 mg/d) until remission has been attained; for acute gouty attacks, colchicine or other anti-inflammatory agents are indicated (see Gout and Pseudogout)

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Medical Care

The long-term risks of polycythemia vera (PV) include leukemic and fibrotic transformation, which occur in fewer than 5% and 10% of patients, respectively, by 10 years. Current treatment modalities do not change these outcomes. Instead, treatment for PV is intended to decrease the risk of arterial and venous thrombotic events, which could be approximately 20%.

Patients can be risk-stratified for their risk of thrombosis according to their age and history of thrombosis. Patients older than 60 years or with a previous history of thrombosis are considered to be high risk. Patients younger than 60 years and with no prior history of thrombosis are considered low risk.

All patients with PV should undergo phlebotomy to keep their hematocrit below 45%. Lower hematocrit targets have been proposed for women with PV, but no empiric evidence supports that recommendation.[1]

All patients with PV should take aspirin, 81 mg daily, unless contraindicated by major bleeding or gastric intolerance.[1] A systematic review concluded that in patients with PV, use of low-dose aspirin is associated with a reduction in the risk of fatal thrombotic events and all-cause mortality; however, the reduction was statistically nonsignificant (P = 0.07). The review found no increased risk of major bleeding with low-dose aspirin therapy in PV.[26] The initial Polycythemia Vera Study Group (PVSG) study of antiplatelet drugs, which used aspirin at 300 mg 3 times a day plus dipyridamole at 75 mg 3 times a day, showed an increase in the incidence of hemorrhage.

If a patient is at high risk for thrombosis, cytoreductive therapy is added to the management plan. Hydroxyurea at a starting dose of 500 mg twice daily is the most commonly used cytoreductive agent. It can be titrated on the basis of blood counts. In patients whose PV is refractory to hydroxyurea or who cannot tolerate the drug, interferon alpha can be used as an alternative. Busulfan is also an option for patients older than 65 years.[27]

Alvarez-Larran et al reported resistance or intolerance to hydroxyurea in 137 of 890 (15.4%) patients with PV. With a median survival of 19 years, resistance or intolerance had no impact on survival, but patients who developed cytopenia had increased risk of death (hazard ratio [HR] 3.5, P = 0.003) and of myelofibrotic transformation (HR 5.1, P = 0.001). Cytopenia at the lowest dose required to achieve a response was also an independent risk factor for transformation to acute leukemia (HR 20.3, P < 0.001).[28]

Leukocytosis may be a risk factor for thrombosis. In a subanalysis of the Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) trial, risk of thrombosis was increased in patients whose WBC exceeded 7000/µL, and reached statistical significance at levels of 11,000/µL and above (HR 3.90, P = 0.02). An association between elevated WBC counts and thrombosis has also been found in studies of patients with essential thrombocythemia. These authors recommend including the WBC count when evaluating response to cytoreductive therapy.[29]

Ropeginterferon

Ropeginterferon alfa-2b, a long-acting pegylated interferon alfa-2b, is considered an alternative to hydroxyurea for certain patients, including the following[2]:

- Young women of reproductive age
- Patients with intolerance of or resistance to hydroxyurea therapy
- Patients requiring treatment to reduce their phlebotomy requirement rather than to prevent thrombosis

Research also supports a role for interferon as a first-line treatment. Although toxicity can be problematic, a systematic review and meta-analysis concluded that interferon can be a safe and effective long-term treatment for PV, with an annualized rate of thromboembolic complications of 0.5% and that of treatment discontinuation due to adverse events of 6.5%.[30] This review included studies of both interferon alfa (which was discontinued by the manufacturer in 2021 for business reasons) and pegylated interferon, but found that pegylated and non-pegylated formulations had comparable efficacy.

Unlike aspirin and hydroxyurea, which are purely symptomatic treatments, interferon therapy can reduce the allele burden of driver mutations and so may have a disease-modifying effect.[30] In a single-center retrospective study of 470 PV patients, longer duration of interferon alpha therapy was associated with a lower risk of myelofibrosis (HR 0.91) and lower mortality (HR 0.94) compared with hydroxyurea or phlebotomy-only treatment.[31]

In the phase III PROUD-PV trial and its extension study, CONTINUATION-PV, in patients with early PV, ropeginterferon alfa-2b did not show non-inferiority to hydroxyurea with respect to hematologic response and normal spleen size at 12 months. However, response to ropeginterferon alfa-2b increased over time, and by 36 months, responses were superior to those seen with hydroxyurea.[32] The European Medicine Agency has approved ropeginterferon alfa-2b for monotherapy in adults with PV without symptomatic splenomegaly.[33] In 2021, the US Food and Drug Administration approved ropeginterferon alfa-2b for treatment of adults with PV, regardless of their treatment history.[25]

Phlebotomy

Phlebotomy (bloodletting) has long been the mainstay of therapy for polycythemia vera (PV). The object is to remove excess cellular elements, mainly red blood cells, to improve the circulation of blood by lowering the blood viscosity. Because phlebotomy is the most efficient method of lowering the hemoglobin and hematocrit levels to the reference range, all newly diagnosed patients are initially phlebotomized to decrease the risk of complications.

Patients can be phlebotomized once or twice a week to reduce the hematocrit to less than 45%. A randomized trial demonstrated a significantly lower rate of thrombotic events and cardiovascular deaths (2.7% vs 9.8%) when the hematocrit goal was 45% versus 50%.[34] Patients with severe plethora who have altered mentation or associated vascular compromise can be bled more vigorously, with daily removal of 500 mL of whole blood.

Elderly patients with some cardiovascular compromise or cerebral vascular complications should have the volume replaced with saline solution after each procedure to avoid postural hypotension. The presence of elevated platelet counts, which may be exacerbated by phlebotomy, is an indication to use myelosuppressive agents to avoid thrombotic or hemorrhagic complications.

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Maintenance therapy

Once the patient's hemoglobin and hematocrit values are reduced to within the reference range, implement a maintenance program either by inducing iron deficiency by continuous phlebotomies (the frequency of the procedure depends on the rate of reaccumulation of the red blood cells) or by using a myelosuppressive agent. The choice depends on the risks of secondary leukemias and the rate of thrombosis or bleeding. Patients must be cautioned to not take iron supplements.

The risks for secondary leukemia depend on the type of therapy (eg, phlebotomy, chlorambucil) or the type of myelosuppressive agents (eg, hydroxyurea [HU], anagrelide, ropeginterferon alfa 2b) and duration of therapy.

The Polycythemia Vera Study Group (PVSG) demonstrated a decreased survival rate and increased mortality rate from acute leukemia in the first 5 years, and a total of 17% of patients had leukemia after 15 years with chlorambucil and with phosphorus-32.[35] Increased risk of leukemia was also found with use of phosphorus-32.

An increased incidence of thrombotic complications occurred in the phlebotomy arm. This indicates that phlebotomy is not ideal for patients with elevated platelet counts and previous thrombosis, as are observed in patients who are older. In this situation, using HU has decreased these complications.

HU has been the mainstay therapy for PV since the PVSG results indicated it is an effective agent for myelosuppression. In the PVSG trial, HU therapy reduced the risk of thrombosis compared with phlebotomy alone; the PVSG recommended that HU should be the drug of choice for patients older than 40 years.[36]

However, concerns have been raised regarding long-term risks for leukemic transformation.[37] The role of HU in leukemic transformation is not clear. Several nonrandomized studies have supported or refuted a significant rise in leukemic conversion with the long-term use of HU in patients with essential thrombocythemia (from 0% to 5.5%) and in patients with PV (from 2.1% to 10%).

The PVSG closed the chlorambucil arm because of increased rates of acute leukemia after 7 years. However, in the 15-year follow-up of the HU arm compared with the phlebotomy-alone arm, the trend for leukemic transformation was greater in the HU arm but the differences did not meet statistical significance. Followup for a median of 8.6 years and a maximum of 795 weeks showed that 5.4% of patients developed leukemia in the HU arm compared with 1.5% of patients treated with phlebotomy alone.

Other case series have reported secondary leukemia in 3-4% of patients, which is relatively low compared with the benefits of preventing thrombotic complications.

Do not administer alkylating agents to younger patients (< 40 y) who need long-term treatment. Alternative nonleukemogenic agents are needed for these patients

Low-dose aspirin suppresses thromboxane biosynthesis by platelets, which is increased in PV and essential thrombocythemia. The European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) found that low doses of aspirin (40 mg/d) were effective for preventing thrombosis and controlling microvascular painful symptoms (erythromelalgia), which result from spontaneous platelet aggregation, in patients with PV and essential thrombocythemia, without creating a bleeding diathesis.[38]

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JAK Inhibitors

Ruxolitinib (Jakafi), a Janus-associated kinase (JAK1/JAK2) inhibitor, was approved by the FDA in 2014 for the treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea. Approval was based

on data from the phase III RESPONSE trial. In this trial, patients treated with ruxolitinib demonstrated superior hematocrit control and reductions in spleen volume compared with best available therapy. A greater proportion of patients on the ruxolitinib treatment arm achieved complete hematologic remission (ie, hematocrit control and lowered platelet count and WBC). Hematologic adverse reactions are prevalent with ruxolitinib (incidence > 20%) and include thrombocytopenia and anemia.[39]

Ruxolitinib had initially been approved in the United States in 2011 for patients with intermediate- or high-risk myelofibrosis, including primary myelofibrosis, post–polycythemia vera myelofibrosis, and post–essential thrombocythemia myelofibrosis.

Another JAK inhibitor, fedratinib (Inrebic), was approved in 2019 for adults with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF). Efficacy of fedratinib was investigated in JAKARTA, a double-blind, randomized, placebo-controlled trial in 289 patients with intermediate-2 or high-risk MF, post-polycythemia vera MF, or post-essential thrombocythemia MF with splenomegaly. Patients were randomized to receive either fedratinib 500 mg (n=97), 400 mg (n=96), or placebo (n=96) once daily for at least 6 cycles.

The primary efficacy outcome was the proportion of patients achieving a reduction of 35% or greater from baseline in spleen volume at the end of cycle 6 measured by MRI or CT with a follow-up scan 4 weeks later. Of the 96 patients treated with the recommended dose (400 mg) of fedratinib, 35 (37%) achieved a 35% or greater reduction in spleen volume, compared with 1 of 96 patients who received placebo (P < 0.0001). The median duration of spleen response was 18.2 months for the fedratinib 400 mg group. In addition, 40% of patients who received 400 mg experienced a 50% or greater reduction in myelofibrosis-related symptoms, whereas only 9% of patients receiving placebo experienced a decline in these symptoms.[40]

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FGFR Inhibitors

Pemigatinib

Pemigatinib is an orally bioavailable inhibitor of the fibroblast growth factor receptor (FGFR) types 1, 2, and 3 (FGFR1/2/3). It inhibits FGFR 1/2/3 phosphorylation and signaling, and decreases cell viability in cancer cell lines with activating FGFR amplifications and fusions. It is indicated for relapsed or refractory myeloid-lymphoid neoplasms with FGFR1 rearrangement in adults.

Approval was based on the phase 2 FIGHT-203 clinical trial. Study participants included patients with documented MLNs with an 8p11 translocation on conventional cytogenetics and/or an FGFR1 rearrangement on break-apart FISH testing.

In patients with chronic phase in the marrow with or without extramedullary disease (EMD) (N = 18), the complete response (CR) rate was 78%. The median time to response of CR was 104 days (range, 44 to 435 days). The median duration of CR was not reached. In patients with blast phase in the marrow with or without EMD (N = 4), 2 patients achieved a CR. For all patients (N = 28 including 3 patients without evidence of morphologic disease) the complete cytogenetic response rate was 79% (22/28; 95% CI: 59, 92).[41]

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Surgical Care

Consider splenectomy in patients with painful splenomegaly or repeated episodes of thrombosis causing splenic infarction.

Budd-Chiari syndrome occurs in patients with myeloproliferative disease (MPD) and most frequently in young women. Surgical approaches to the management of Budd-Chiari syndrome are, therefore, relevant to patients with polycythemia vera.[42]

Budd-Chiari syndrome is a liver-related condition associated with large-vessel thromboses and outflow obstruction with inferior vena cava or portal vein thrombosis. This is associated with the development of ascites, hepatosplenomegaly, abdominal pain, and gastrointestinal bleeding, but 20% of patients are asymptomatic.

The diagnosis is made by using ultrasonography to identify portal vein patency. In addition to the standard computed tomography (CT) scan and magnetic resonance imaging (MRI), patients with Budd-Chiari syndrome may need invasive angiographic imaging to determine the hemodynamics of the liver and the intrahepatic and vena caval gradients to determine the best surgical procedure. The histology of the liver helps determine the acuteness of the problem, the presence of chronic changes, and the degree of cirrhosis. This determines whether a patient requires a shunt or a liver transplant.

The following procedures have been used in patients with Budd-Chiari syndrome:

- Transjugular intrahepatic portosystemic shunt (TIPS)
- Side-to-side portocaval shunt or mesocaval shunt, portocaval/cavoatrial shunt, or mesoatrial shunt

These procedures have been reported to be successful in 38-100% of patients, with follow-up ranging from 9-98 months.

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Consultations

Consultation with a hematologist is recommended in cases of polycythemia vera. Long-term follow-up care of these patients and managing complications of the disease and its treatment can be difficult.[24]

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Medication

Medication Summary

One objective of therapy for polycythemia vera (PV) is to control the myeloproliferative activity of this disease. Evidence of an increase in levels of white blood cells and/or platelets and organomegaly indicate uncontrolled myeloproliferative activity that requires a myelosuppressive agent.

Studies by the Polycythemia Vera Study Group (PVSG) have led to the near-abandonment of long-term therapy with phosphorus-32 (32P) and most alkylating agents (eg, busulfan, chlorambucil), and to the use of hydroxyurea (HU) instead. However, long-term data seem to indicate a possible slight late increase in cases of acute leukemia in patients with PV who are treated with HU for more than 15 years.

Ruxolitinib is a second-line therapy for patients in whom HU is ineffective or poorly tolerated. It is also approved for use in intermediate- or high-risk myelofibrosis, including primary myelofibrosis, post-PV myelofibrosis, and post–essential thrombocythemia myelofibrosis.

Another JAK inhibitor, fedratinib, is indicated for adults with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis.

Ropeginterferon alfa-2b-njft (Besremi) is indicated for treatment of adults with PV regardless of their treatment history.

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Antimetabolites

HU is a nonalkylating agent that inhibits DNA synthesis and cell replication by blocking the enzyme ribonucleoside diphosphate reductase.

Hydroxyurea (Droxia, Hydrea)

Inhibitor of deoxynucleotide synthesis and DOC for inducing hematologic remission in CML. Less leukemogenic than alkylating agents such as busulfan, melphalan, or chlorambucil. Myelosuppressive effects last a few days to a week and are easier to control than those of alkylating agents; busulfan has prolonged marrow suppression and can cause pulmonary fibrosis. Can be administered at higher doses in patients with extremely high WBC counts (>300,000/µL) and adjusted accordingly as counts fall and platelet counts drop. Dose can be administered as a single daily dose or divided into 2-3 doses at higher dose ranges. Droxia, available in smaller tabs of 200, 300, and 400 mg, is for patients with sickle cell disease.

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JAK Inhibitors

Myelofibrosis is a myeloproliferative neoplasm known to be associated with dysregulated Janus-associated kinase (JAK) signaling.

Ruxolitinib (Jakafi)

JAK1/JAK2 kinase inhibitor indicated for polycythemia vera in patients who have had an inadequate response to or are intolerant of hydroxyurea. Janus-associated kinases (JAKs) JAK1 and JAK2 mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function.

Fedratinib (Inrebic)

Fedratinib inhibits Janus-associated kinase-2 (JAK2), which mediates signaling of cytokines and growth factors that are important for hematopoiesis and immune function. It is indicated for adults with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis.

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FGFR Inhibitors

Consider for relapsed or refractory myeloid/lymphoid neoplasms (MLNs) with fibroblast growth factor receptor 1 (FGFR1) rearrangement.

Pemigatinib (Pemazyre)

Orally bioavailable inhibitor of the FGFR types 1, 2, and 3 (FGFR1/2/3). Pemigatinib inhibits FGFR 1/2/3 phosphorylation and signaling, and decreases cell viability in cancer cell lines with activating FGFR amplifications and fusions. It is indicated for relapsed or refractory MLNs in adults with FGFR1 rearrangement.

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Imidazole Quinazolines

Imidazole quinazolines have been demonstrated to have powerful anti-aggregating effects on platelets and to cause thrombocytopenia.

Anagrelide hydrochloride (Agrylin)

Primary activity is to lower platelet levels but shows slight decrease in mean hemoglobin and hematocrit while WBC counts maintained. Effective in polycythemia vera with elevated platelet counts. Adjust dosage to lowest effective dose to reduce and maintain platelet counts, WBC count, and hemoglobin levels within reference range.

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Interferons

Recombinant interferon alfa is a biologic response modifier with myelosuppressive activity.

Ropeginterferon alfa 2b (Besremi, Ropeginterferon alfa-2b-njft)

Long-acting pegylated interferon alfa-2b. Alfa interferons bind to and activates the human type 1 interferon receptor; signal transduction is initially mediated by the Janus kinase-2 gene (JAK2); polycythemia vera is caused by a JAK2 V617F mutation, that permanently turns of signaling at affected cytokine receptors; this results in overproduction of RBCs by the bone marrow.

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Questions & Answers

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