**Polycythemia Vera- an overview**

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**Abstract:**

Polycythemia Vera (PV) is a clonal myeloproliferative disorder involving a multipotent hematopoietic progenitor cell in which phenotypically normal blood cells proliferate in the absence of a known physiological stimulus. Patients with polycythemia may be asymptomatic or experience symptoms due to hyperviscosity. Venous and arterial thrombosis may be the presenting symptoms in some patients of this disorder. Aquagenic pruritis and erythromelalgia are some specific symptoms of polycythemia vera (PV). When a patient with polycythemia vera presents with features of panmyelosis (erythrocytosis, leucocytosis, thrombocytosis) and or splenomegaly the disease is obvious. Diagnostic criteria for PV as per 2016 revised WHO guidelines include three major criteria and one minor criterion. Diagnosis requires the presence of either all three major criteria or the first two major criteria and the minor criterion. PV patients are categorized into two groups for treatment: Low-risk patients and High-risk patients. Phlebotomy, low-dose aspirin, cytoreductive therapies, and JAK-2 inhibitors are the treatment options for this disorder.

**Introduction:**

Polycythemia is a clonal myeloproliferative disorder involving a multipotent hematopoietic progenitor cell in which phenotypically normal blood cells (RBCs, Granulocytes, platelets) proliferate in the absence of a known physiological stimulus. Etiology: The exact etiology of PV is not known. Although some nonrandom chromosome abnormalities have been documented in up to 30 % of nontreated PV patients. A mutation in the pseudokinase domain of the tyrosine kinase, JAK-2 appears to have a central role in the pathogenesis of PV Clinical features: Patients with polycythemia may be asymptomatic or experience symptoms due to hyperviscosity, which include neurological symptoms such as vertigo, tinnitus, headache, visual disturbance, TIA, and systolic hypertension. Venous and arterial thrombosis may be the presenting symptoms in some patients of this disorder. Aquagenic pruritis, epistaxis, digital ischemia, gastrointestinal hemorrhage, and easy bruisability may occur due to vascular stasis or thrombocytosis. Some patients may have erythromelalgia which is characterized by erythema and burning sensation in extremities due to severe thrombocytosis. Hyperuricemia which leads to secondary gout, and uric acid stones are the other manifestation of this disorder. Diagnosis: When a patient with polycythemia vera presents with features of panmyelosis (erythrocytosis, leucocytosis, and thrombocytosis) and or splenomegaly the disease is apparent. However, when patients present with an elevated hematocrit, hemoglobin, or red cell count alone than the diagnostic approach became more complex due to the possibilities of many differentials [1] (Figure 1)

Diagnostic criteria for PV : Diagnostic criteria for Polycythemia Vera (PV) as per 2016 revised WHO guidelines include 3 major criteria and 1 minor criterion. Diagnosis requires the presence of either all 3 major criteria or the first 2 major criteria and the minor criterion.[2] The major 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, or red cell mass >25% above mean normal predicted value 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 criterion is as follows: 1. 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 three and the minor criterion are present. 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.[2]  In patients who are positive for JAK2 and whose hemoglobin/hematocrit level is diagnostically equivocal (ie, as in "masked" PV), bone marrow examination is necessary to distinguish the PV and essential thrombocytosis. [3] If the JAK2 V617F mutation is negative but the erythropoietin (Epo) level is low, then testing for JAK2 exon 12 and 13 mutations would be helpful to reach the diagnosis of PV.

Treatment: After diagnosing the PV, patients are categorized in two groups for treatment: A. Low risk patients B. High risk patients.

1. **Low risk PV patients:** are defined as patients with an age 60 years or younger with no history of thrombosis. These patients are further divided into two groups: Group I: Asymptomatic Patients with low-risk PV: The cornerstone of treatment for these patients are : (1) Low-dose aspirin (2) Phlebotomy to maintain a hematocrit value of less than 45 % Group II: Low-risk patients with persistent symptoms or other complications ( Headache, pruritis, progressively enlarged spleen), having rising blood count, and/or intolerant to phlebotomy: These patients also require cytoreductive therapy ( Hydroxyurea) along with the low dose aspirin and phlebotomy.
2. **Polycythemia patients in the High-risk category**: are defined as (i) patients with an age of more than 60 years and (ii) Patients with a positive history of thrombotic/bleeding events Treatment options for these patients are: A. Cytoreductive therapy (Hydroxyurea) as an initial treatment B. Low dose aspirin C. Phlebotomy Hydroxyurea and interferon are recommended as frontline drug therapy for cytoreduction in this group of patients. The cytoreductive therapy effectively reduces the elevation in red cell count. It tends to be inadequate, however in the control of platelet count and WBC counts.

**Phlebotomy:**

One unit of phlebotomy (500 ml) should reduce the Hct by 3 % in a normal-sized adult. Men may tolerate removal of 1.5 to 2 units per week, whereas older adults, some women, and persons with low body weight (<50 kg) or underlying cardiovascular disease may only tolerate removal of 0.5 units per week. Post phlebotomy: The patient should be advised to maintain proper hydration and avoid vigorous exercise for at least 24 hours. Iron supplementation should not be given because phlebotomy controls polycythemia by producing a state of absolute iron deficiency.

**Low dose aspirin :**

For preventing thrombosis in PV low dose of aspirin (40-100 mg) should be given to all patients with PV unless there are some contraindications Polycythemic patients with platelet count more than 10 lakhs/mm3 should be tested for acquired Von Willebrand disease before starting aspirin. Aspirin should not be used in patients who developed acquired VWD.

**Monitoring of treatment :**

1. Regular assessment of hematocrit level to ensure it remains under 45 %.
2. Monitoring for thrombosis /bleeding and for complications from therapy.
3. Assessment of symptoms, such as pruritus, headache, and microvascular complications.
4. Monitor for changes in their WBC count or platelet count and spleen size

**Response assessment:**

Response to therapy should be monitored by following CBC and assessing the sign and symptoms. There is no need to routinely monitor molecular or bone marrow response Response criteria (ELN and international working group)- Myeloproliferative neoplasm response [4]

**Complete response :**

1. Resolution of disease signs and improved symptoms for at least 12 weeks

2. Normalisation of peripheral blood count for at least 12 weeks

- White blood cells less than 10000

- Platelets count- equal to or less than 400000/microlitre

- Hct- < 45 % ( without phlebotomy)

3. Absence of vascular events and disease progression

4. Disappearance of bone marrow hematological abnormalities

**Partial response:**

The first three criteria of complete response are achieved in the absence of bone marrow hematological remission. Failure to achieve these benchmarks is a sign of resistance to treatment. The criteria for intolerance include leg ulcerations, gastrointestinal disturbances, mucosal ulceration, and secondary skin cancers.

**Treatment of PV refractory/resistance/intolerance to initial hydroxyurea therapy :**

The available agents for the refractory cases of hydroxyurea are: Pegylated IFN, Busulfan, Ruxolitinib and pacritinib.[5,6]

**Ruxolitinib:**

This JAK-2 inhibitor is the cornerstone of second-line therapy for patients who are resistant or intolerant to hydroxyurea. The JAK signal transducer and activator of the transcription (STAT) pathway and the JAK-2 protein are overly active in all patients with polycythemia vera due to mutation in JAK-2 V617F and JAK-2 exon 12. The RESPONSE trial has shown a significant decrease in spleen size and improvement in clinical symptoms along with a decrease in the need for phlebotomy. The toxicities are a slight increase in herpes zoster infection or reactivation.[ 6] Ruxolitinib is used as a second-line treatment in the case of polycythemia vera. This drug is offered to patients with polycythemia Vera in the following conditions:

1. Marked symptomatic splenomegaly that failed to respond to Hydroxyurea, IFN, and Busulfan

2. Severe protracted pruritis that failed to respond to other cytoreductive therapies

3. Post PV Myelofibrosis

Data related to the long-term effect of Ruxolitinib in PV are not available. There is no evidence that Ruxolitinib reduces the malignant clone or changes the natural course of this disorder. Discontinuation of ruxolitinib can be associated with relapse of the symptoms.

**Pacritinib:**

Pacritinib which is also a JAK-2 inhibitor, is also approved by US-FDA for treatment of post polycythemic myelofibrosis with platelet counts less than 50000/μL

**Specific conditions related to PV**

1. Thrombotic complications: Phlebotomy to maintain hematocrit (Hct) less than 45 % , low dose aspirin and or cytoreductive agents are used to prevent the thrombotic complications. Patient with PV and venous thrombosis should be treated by anticoagulants. The optimal duration for anticoagulation is uncertain.

2. Bleeding : Bleeding episode may be associated with very high platelet count (more than 10 lakhs) due to aquired VwD, Use of aspirin dose more than 100 mg/day and or C. Use of anticoagulant or antiplatelet agents

3. Pregnancy:

There is an increased risk of spontaneous abortion, abruptio placenta,pre eclampsia,IUGR in patient with PV. Aspirin and INF are associated with reduced rate of pregnancy loss and other complications in these patients.

These patients should be closely monitored for pregnancy induced hypertension. IFN alfa is prefered cytoreductive therapy in pregnant female with PV and in those with childbearing potential due to the risk of teratogenicity of hydroxyurea, ruxolitinib and other alkylating agents. [7]

**Prognosis:**

Median survival of untreated symptomatic patients with PV has been estimated as 18 months. The overall survival of treated patients with PV is inferior to that of an age-matched normal population. Survival is at least 13 years in patients who are treated.[8]

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**Figure-I: Illustrates a diagnostic approach for the evaluation of suspected erythrocytosis (Polycythemia)**

Increased hct or hgb

Measure RBC mass

Measure serum EPO levels

Smoker?

Measure arterial O2 saturation

Measure carboxyhemoglobin level

Dx : Smoker’s polycythemia

Dx : Relative erythrocytosis

Dx: Polycythemia vera

Diagnostic evaluation for heart or lung disease.

e.g. COPD, high altiutude, AV or ontracardiac shunt.

Measure hemoglobin O2 affinity

Dx: ↑O2 affinity hemoglobinopathy

Search for tumor as source of EPO

Renal ultrasound ( renal ca or cyst)

CT of head (cerebellar hemangioma)

CT of pelvis (uterine leiomyoma)

CT of abdomen (hepatoma)

Confirm JAK2 mutation

normal

low

low

No

normal

Yes

elevated

Increased

normal

elevated

elevated

normal

*Source: Harrison’s Principles of Internal Medicine, 20th Edition, pp. 393*