Approaches in Hematology

Hematology Made Easy

Polycythemia Rubra Vera

- ✓ **Polycythemia Rubra Vera (PRV)** or Primary Polycythemia Vera is a chronic myeloproliferative disorder characterized by an increase in RBC mass, which often manifests as an increased hematocrit (Hct). There is a malignant transformation of the multipotential stem cell with excess production of red cells. PRV involves increased production of all cell lines, including RBCs, WBCs, and platelets.

- ✓ **Pathophysiology & consequences:** Polycythemia Rubra Vera is characterized by overproduction of red cells in the bone marrow, without any identifiable cause. These cells accumulate in the bone marrow and in the bloodstream where they increase the blood volume and cause the blood to become thicker, or more 'viscous' than normal. In many people with polycythemia rubra vera, too many platelets and white cells are also produced. Extramedullary hematopoiesis may occur in the spleen, liver, and other sites that have the potential for blood cell formation.

- ✓ **Age of the onset:** PRV is the most common of the myeloproliferative disorders; with incidence increasing with age. PRV may be slightly more common in men. The mean age at diagnosis is around 60 years. The disease is very rare in children.

- ✓ **Clinical Features:** Develop gradually and include:

A. Symptoms related to increased viscosity & hemoconcentration:
   - Headaches
   - Dizziness
   - Tinnitus
   - Visual problems

B. Signs might be seen in PRV:
   - The face may be red (plethoric) and the retinal veins engorged.
   - The palms and feet may be red, warm, and painful.
   - Generalized pruritus, particularly after a hot bath.
   - Hepatomegaly is common, and splenomegaly is present in 75% of cases.
   - One-third of patients are hypertensive.
   - Hypermetabolism can cause low-grade fevers and weight loss and suggests disease progression.

C. Complications
- Thrombotic episodes e.g. (neurologic deficits with stroke or transient ischemic attack, DVTs, unilateral vision loss with retinal vascular occlusion, and portal vein & hepatic vein thromboses (Budd Chiari Syndrome)
- Bleeding episodes especially peptic ulcers.
- Hyperuricemia and Gout: Patients may come with Acute gouty arthritis.

✓ **Investigations:**

❖ CBC looking for:
- Raised Hb & Raised Hematocrit: Raised red cell mass. This is essential for the diagnosis to differentiate it from pseudo-polycythemia due to a low plasma volume.
- White cell count is usually raised.
- Platelet count is often raised.

❖ Other important labs
- NAP score is raised.
- JAK2 V617F mutation (positive in approximately 95 - 97 % of cases) If JAK2 V617F is negative --> do JAK2 exon 12 mutation.

❖ Imaging
- CXR to exclude Chronic lung diseases.
- Abdominal US to confirm splenomegaly.

❖ In some cases, the diagnosis of PRV must be made by careful exclusion of Secondary Polycythemia. This includes a CXR, IV urogram, blood gases, Hb electrophoresis and O2 dissociation curve.

✓ **Causes of secondary polycythemia:**

- The most common causes of secondary polycythemia include:
  - Obstructive sleep apnea
  - Obesity hypoventilation syndrome
  - Chronic obstructive pulmonary disease (COPD).
  - Testosterone replacement therapy
  - Heavy cigarette smoking.
  - Patients who have arteriovenous or intracardiac shunting can present with polycythemia without hypoxemia.
  - Erythropoietin-secreting tumors (e.g., hepatocellular carcinoma, renal cell carcinoma, adrenal adenoma)
  - Polycystic kidney disease & obstructive uropathy
  - Patients living at high altitudes.

- Secondary polycythemia must be differentiated from primary polycythemia and relative polycythemia (in which RBC numbers are normal but plasma volume is contracted).

- The reduction in plasma volume may be due to dehydration or reduced venous compliance; the latter is also termed stress polycythemia or Gaisböck syndrome and is typically seen in obese middle-aged men who are receiving a diuretic for treatment of hypertension.

✓ **Diagnosis of polycythemia vera**

- According to 2016 revised World Health Organization (WHO) guidelines, diagnosis of PV requires the presence of either all three major criteria or the first two major criteria and the minor criterion.

❖ 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, 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 WHO criterion is as follows:

1) Serum erythropoietin level below the reference range for normal

- N.B: JAK2 V617F mutation and erythropoietin (EPO) level are key in the diagnosis of erythrocytosis.
- If the JAK2 V617F mutation is positive and EPO level is low, then it confirms the diagnosis of PRV (JAK2 V617F mutation is positive in 97% of PRV patients).
- Important Notes:
  A. JAK2 mutations also occur in about 60% of patients with essential thrombocythemia. In patients who are positive for JAK2 and whose hemoglobin/hematocrit level is diagnostically equivocal, a bone marrow examination is necessary to distinguish the two conditions.
  B. If the JAK2 V617F mutation is absent but the EPO level is low, then testing for JAK2 exon 12 and 13 mutations would be helpful for making a diagnosis of PRV in the 2-3% of PRV patients who are negative for JAK2 V617F mutation.
  C. Patients who are negative for JAK2 mutations and have a normal or high EPO level have secondary polycythemia.

✓ **Treatment:**

- 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.

- Optimal management remains elusive despite the findings of the Polycythemia Vera Study Group (PVSG). However, general principles in the management of PV include the following.
- Tailor therapy to suit the clinical needs of the patient.

Non-pharmacological treatment

ℛ Venesections (phlebotomy)

- 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.

- 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 empirical evidence supports that recommendation.

- Target hematocrit: Repeated phlebotomies (venesections) aiming to keep Hct < 0.45

Pharmacological treatment

❖ Cytoreductive therapy (drugs that lower Hb & ↓ complications)

ℛ Myelosuppressive therapy (hydroxyurea)

- Suppress myeloproliferative activity with chemotherapy (hydroxyurea) in all patients older than 50 years.

- 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.

ℛ JAK2 inhibitors

- A recent advance in the treatment of PV is the development of JAK inhibitors.
- The JAK1/2 inhibitor Ruxolitinib (JAKAFI) is approved for treatment of PV in patients who have had an inadequate response to or are intolerant of hydroxyurea.
- N.B 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.

ℛ Interferon therapy

- Pegylated interferon is considered an alternative to hydroxyurea for certain patients, including the following:
  - 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.

- Ropeginterferon alfa-2b-njft (Besremi) is approved by the US Food and Drug Administration (FDA) 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.

℟ Phosphorus 32 therapy (Radiotherapy)

- Radioactive phosphorus (rarely used).
- In general, phosphorus-32 (32 P) 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.

✓ **Risk stratification and choice of therapy based on the degree of the patient's risk.**

- Patients can be risk-stratified for their risk of thrombosis according to their age and history of thrombosis.
  i. Patients older than 60 years or with a previous history of thrombosis are considered to be high risk.
     ↳ If a patient is at high risk for thrombosis, cytoreductive therapy is added to the management plan.

  ii. Patients younger than 60 years and with no prior history of thrombosis are considered low risk.
     ↳ Low-risk patients can be managed by regular phlebotomies with follow-up hematocrit.

- In patients whose PV is refractory to hydroxyurea or who cannot tolerate the drug, interferon alpha can be used as an alternative. Also, JAK2 inhibitors would be alternative (expensive)

✓ **Treatment & prevention of complications**

❖ Hyperuricemia & gout
  - 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.

❖ Prevention of thrombosis
  - Aspirin, 75 - 81 mg daily, unless contraindicated by major bleeding or gastric intolerance.

❖ Control of blood pressure if raised.

✓ **Important Notes**

- Avoid overtreatment and toxicity by careful and judicious use of chemotherapy and radiation; supplemental phlebotomy is preferred over excess marrow suppression.

- 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.

✓ **Summary of the Management of polycythemia vera**

- Treatment measures are as follows:

ℛ Phlebotomy – To keep hematocrit below 45%

ℛ Aspirin 75 - 81 mg daily

ℛ Cytoreductive therapy: For patients at high risk for thrombosis only

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

- Interferon alfa
- Ruxolitinib (Jakafi)
- Fedratinib (Inrebic)

ℛ Treatment of complications such as hyperuricemia & high BP.

ℛ Splenectomy in patients with painful splenomegaly or repeated episodes of splenic infarction