BCR-ABL Negative MPN - Classic

UpToDate: 1. Ruxolitinib (Jakafi): approved for myelofibrosis, intermediate to high risk, as well as polycythemia vera who can not tolerate to or progressed on hydroxyurea.

Introduction: 1. Myeloproliferative neoplasms (MPNs):
   - BCR-ABL positive: CML
   - BCR-ABL negative: polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis.
   - Incurable;
   - PV diagnosed before age 40 has aggressive course.

Risk Factors: Unclear, has familial clustering tendency

Biology: JAK2 is downstream to EPO and TPO signaling.
1) PV: * JAK2V617F (>90%, somatic activating mutation) → erythrocytosis a/w thrombocytosis or leukocytosis. * √ Exon 12 mutation of JAK2 → erythrocytosis w/o thrombocytosis or leukocytosis.

2) ET: * JAK2 V617F (40-50%); * TPO receptor (MPL) mutation (3-5%)

3) PMF: * JAK2 V617F (50%); * del 13 (q); * Trisomy 9

Symptoms:
A. PV: 80% symptomatic at diagnosis → ↑ risk for Budd-Chiari syndrome, splenomegaly, pulmonary HTN (once occur, median survival <18 months)

B. ET: 50% asymptomatic at diagnosis → ↑ risk for thrombosis or secondary VWD.
   - LAP: ↑ in ET and PV, ↓CML. ET → (+) giant platelet on blood smear.
   - Diff Dx for atypical CML(isolated thrombocytosis): √ BCR-ABL.

C. PMF: → Hypercatabolic sx (fever, fatigue, night sweat, weight loss) + prominent extramedullary hematopoiesis.

D. Major complications for all MPN: thrombosis, bleeding, or evolution to acute myeloid leukemia (AML) or a fibrotic phase of the disease.

Diagnosis: A. Tefferi Approach:
1) Are there any blasts? * > 20% → AML.
   * if <20%, → then ask
2) Is there any dysplasia in morphology? * if yes, → MDS.
   * if no, → then ask (MPN? or MPN/MDS?)
3) Is there any cytosis? * If yes, → MPN.

B. Algorithm for Polycythemia:
1) PV: Hb > 18.5 in man, >16.5 in woman, → r/o relative polycythemia (↓ plasma volume) or 2nd erythrocytosis (due to hypoxia or inappropriate EPO production), then → √ EPO and JAK2 V617F.
- If JAK2 V617F pos → PV diagnosed
- If JAK2 V617F neg and EPO high → PV excluded.
- If JAK2 V617F neg and low or nl EPO → √ JAK2 exon 12 mutation.
- If both JAK2 V617F and exon 12 mutation neg → √ BM and/or red cell mass (RCM).

**Diff Dx: "Absolute Polycythemia" (↑RCM) vs Relative Polycythemia (↓plasma volume). But PV with iron deficiency can have normal RCM.

2) Acquired Secondary Polycythemia:
- Hypoxia (O2 Sat <92%) → ↑ EPO production
- Malignancy (kidney, liver) → inappropriate EPO production

3) Inherited Polycythemia other than PV:
- Low EPO: EPO receptor mutation (activating), AD
- ↑ or nl EPO: √p50 (Hb affinity for O2) for functional hyoxia
  * if p50 nl → VHL mutation (Chuvash-type congenital polycythemia) → abnormal oxygen sensing (as if hypoxia) → ↑ EPO → AR (↑ risk for thrombotic and hemorrhagic complications).
  * if p50 ↓ → High oxygen-affinity hemoglobinopathy or 2,3 BPF deficiency

C. Algorithm for ET: Isolated thrombocytosis (>450,000) → can be ET or any MPN
- √BM for diagnosis: megakaryocyte (large, mature, w/o cytogenetic abnormalities).
JAK2 VF pos in 50% pt.

D. Algorithm for PMF:
- Blood smear: leukoerythroblastic immature myeloid cells, nuclear red, tear drop, large platelet
- √ BM: Bulky megakaryocyte, ↑reticulin, cytogenetic changes (del 13q, trisomy 9).
JAK2 VF-pos in 50% pt.

Pathology:
A. WHO Classification:
  BCR-ABL negative MPN (WHO 2008):
  1) Classic: * Polycythemia Vera (PV), * Essential Thrombocythemia (ET), * Primary Myelofibrosis (PMF)

Prognosis:
A. DIPSS-plus scoring for PMF: Unfavorable factors (8-point)
  - Age >65; Constitutional sx; Hb<10, WBC >25k, Blood blast >1%, Transfusion need, Platelet <100k, Cytogenetics.
  - Risk: low (0), intermediate-1 (1), intermediate-2 (2-3), high (>4)

Tx Principle:
A. Management of PV and ET:
  1) Complications: ↑ risk for thrombosis; ↑ risk of AML or PMF transformation
  2) Goal of therapy: ↓ thrombotic risk, but there is no tx to ↓ AML or PMF risk.
- Tx for PV and ET are identical except phlebotomy for PV (see algorithm)

<table>
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<tr>
<th>Risk</th>
<th>Phlebotomy</th>
<th>Aspirin</th>
<th>Cytoreduction</th>
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Low with plt<1million  Yes  Yes  No  
High Risk*  Yes  Yes  Yes  
Low with plt>1million  Yes  Yes*  No  

- Phlebotomy (for PV): → Hct <45% or @ Hb level pts feel comfortable.
- Cytoreduction → ↓Thrombotic risk:
  * Low-risk: "age <60yrs + neg thrombosis h/o + plt < 1 million" → no cytoreduction
  * Low-risk with platelet >1million: → low thrombosis risk instead ↑ bleeding risk due to 2nd VWD → √ VWF:Rco assay → if >30%, Rx ASA, otherwise (<30%), hold ASA.
  * High risk: "age > 60 OR pos thrombosis history" → cytoreduction.
    1st line: Hydroxyurea → achive platelet < 400k.
    2nd line: IFN-α (for pregnant woman or pts intolerate hydroxyurea).
    For hydroxyurea-refractory: → IFN-α (age <65) or Busulfan or JAK2 inhibitor (age >65)
- Pruritus: phlebotomy ineffective; try antihistamine, cholestyramine, SSRI.
- Painful splenomegaly: hydroxyurea, IFN-α, splenectomy
- SCT: potential curable.

B. Myelofibrosis
1) Complication: ↑ CD34+ cells and ↑ PDGF →↑ risk of AML transformation
2) Treatment:
   - Low-risk and asymptomatic: observe
   - Low-risk symptomatic:
     * If pos for 5q del, → lenalidomide, especially for anemia
     * If neg for 5q del, → manage symptoms
   - Anemia: ESA, cortisosterosid, androgen, etc. * Pomalidomide (0.5mg daily)
      indicated for anemia with JAK2 VF (+) and splenomegaly <10cm (phase I in Myo Clinic)
   - Splenomegaly: Hydroxyurea, splenectomy (RT is not a good choice for splenomegaly)
   - Extramedullary hematopoiesis: low dose irradiation
   - High-risk: allo-SCT

Follow-Up:
- ET →AML transformation: rare in first year, but ↑ in subsequent yrs
- ET →PV transformation (5%): ↑ in ET with pos JAK2 V617F mutation

Pharmacology:
A. COMFORT trials: Ruxolitinib
   - Ruxo vs Placebo (COMFORT-1): → ↓ spleen size (41% vs <1%).
   - Ruxo vs Conventional (COMFORT-2): → ↓spleen size (28.5% vs 0%)
   - SE: anemia, thrombocytopenia
   - JAK2 inhibitors controls constitutional symptoms and splenomegaly, but unable to control blood counts or induce molecular remission.
   - Ruxolitinib discontinuation syndrome: Acute relapse → rapid ↑ spleen size, profound weight loss, worsening cytopenia.

C. Pomalidomide 0.5mg/day: for anemia in pts with JAK2V617F pos PMF and spleen size <10cm. NO effect on splenomegaly.