MYELOPROLIFERATIVE DISORDERS

Gina C. Guzman, MD, DBIM, FALU, ALMI
Triennial
2nd VP & Medical Director
October 2012

Normal Blood Cell Development

Myeloproliferative Disorders
^ RBCs
^ PLTs
^ WBCs
^ fibroblasts
Myeloproliferative vs. Myelodysplastic

- **Myeloproliferative disorders** (MPDs) or neoplasms (MPNs)
  - A group of blood diseases characterized by abnormal over-proliferation of morphologically “normal” blood cells in the bone marrow
  - Erythrocytosis/polycythemia, thrombocytosis, leukocytosis

- **Myelodysplastic syndromes** (MDSs)
  - A group of blood diseases characterized by dysplastic bone marrow hyperplasia
  - Poorly formed or dysfunctional cells
  - Variable degrees of peripheral cytopenia

“Classic” vs. “Atypical” Myeloproliferative Disorders (MPDs)

<table>
<thead>
<tr>
<th>Comparison of FAB and WHO Classifications of Chronic Myeloproliferative Diseases.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FAB</strong></td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
</tr>
<tr>
<td>Polycythemia vera</td>
</tr>
<tr>
<td>Essential thrombocytosis</td>
</tr>
<tr>
<td>Agnogenic myelodysplasia/myeleephalis</td>
</tr>
<tr>
<td>...</td>
</tr>
<tr>
<td>...</td>
</tr>
<tr>
<td>...</td>
</tr>
</tbody>
</table>

French-American-British Classification 2002 World Health Organization

Atypical MPNs: chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, atypical CML, unclassifiable MDS/MPN
Features Common to all MPDs

- Origin in a pluripotent hematopoietic stem cell
- ABNORMAL UNSTIMULATED OVERPRODUCTION of one or more of the formed elements of the blood
- HYPERCELLULAR bone marrow
- ^ Risk for Thrombosis and Bleeding (esp. with PV and ET)
- ^ Risk for Transformation to acute leukemia (AML) and/or marrow fibrosis/myelodysplastic syndrome (MDS)
- Associated genetic mutations of many different tyrosine kinases

Presenting Signs and Symptoms

- Incidental finding in an asymptomatic person with an abnormal CBC
- Fatigue (81%), Pruritis (52%), Night sweats (49%)

- Secondary causes for abnormal elevations much more common than MPDs
  - Erythrocytosis
    - Only 5% of patients with persistent erythrocytosis will have PV
    - Dehydration, hypoxia (smoker, altitude, OSA), renal disease
    - Steroids (testosterone for hypogonadism)
  - Reactive thrombocytosis much more common than ET
    - Acute phase reactant, infections, inflammatory disease, *anemia
Value of Erythropoietin (EPO)

- Hormone produced by the kidney that promotes the formation of red blood cells (RBCs) in the bone marrow
- Prime regulator of RBC production

- Measurement of serum EPO can be useful in differentiating RBC disorders
  - Normal or $^\wedge$ in secondary causes of polycythemia
  - Normal or Decreased in Polycythemia Vera

- Normal levels 0 – 19 mU/mL

JAK2 (V617F) Mutation

- JAK2 (identified in 1993) is the tyrosine kinase protein involved in normal blood cell development
- JAK2 mutation – JAK2 (V617F) – point mutation (discovered in 2005) allows continuous activation of cell proliferation and resistance to cell death – the most important advance in MPD in 30 years!
- Highly sensitive for MPDs since NOT found in healthy persons, secondary polycythemia, or a reactive blood count elevation
- Diagnostic only for the presence of a MPD, not its type
  - 97% of patients with polycythemia vera (PV)
  - 57% of patients with essential thrombocythemia (ET)
  - 50% of patients with primary myelofibrosis (PMF)

Polycythemia Vera (PV)
Primary Polycythemia, Polycythemia Rubra Vera

- Most common Myeloproliferative Disorder
- Elevated RBC parameter (RBC, Hgb, Hct, or RBC mass)
- The number of WBCs and Platelets may also increase
- Relatively rare – 5 to 20 cases/100,000 in US
  - PCP will make the dx once or twice during his/her career
- Peak incidence 50-70 years old, but may occur at any age
- M:F ratio 2:1
- 97% JAK2 mutation+
- 75% have splenomegaly; pruritis is common
Diagnostic criteria for Polycythemia Vera (PV)

**Major criteria**
- Hemoglobin >18.5g/dl in men or >18.5g/dl in women (or other evidence of ↑ RBC volume)
- JAK2(V617F) mutation or other functionally similar mutation such as JAK2 exon 12 mutation

**Minor criteria**
- Bone marrow biopsy showing hypercellularity with myeloid, erythroid, granulocytic and megakaryocytic proliferation
- Low serum erythropoietin level
- Endogenous erythroid colony formation (in vitro)

**PV Diagnosis**
- Both major criteria and one minor criterion or
- First major and two minor criteria

Revised WHO Criteria 2008 (from 2001)
Hematology/Oncology Clinics Aug 2009

---

**High Risk PV**

- Age > 60
- Previous h/o thrombotic events
- CV risk factors – Smoking, HTN, Diabetes
- Leukocytosis – WBC > 12,000/uL (60%) at diagnosis
- Platelets > 400,000/uL (50%) at diagnosis
Treatment of PV

- **Regular Phlebotomy** to lower blood viscosity
  - Goal HCT < 45% in men, < 42% in women
  - ^ risk of thromboses and vascular events with HCT > 44%
  - Yields the best overall survival

- **Low dose Aspirin**

- **CV Risk Factor Modification** – stop smoking!

- **Cytoreductive therapy** for High Risk RV (hydroxyurea, etc) can decrease the incidence of thromboses

- Goal of therapy – normalize CBC and prevent thrombohemorrhagic complications

PV – Mortality/Morbidity

- Median survival for untreated symptomatic patients is 6 to 18 months

- **Thromboses account for the majority of morbidity/mortality**
  - Thrombotic complications – 15-60 % - depends on control of disease
  - Major cause of death in 10-40% of patients
  - Both venous and arterial thromboses
  - DVT/PE, Stroke, MI, Renal artery/vein thromboses, intestinal ischemia
  - Transformation to AML/MDS ~1.5%
  - Bleeding complications – 15-35%
  - With treatment, medial survival is more than 10 years
Essential Thrombocytopenia (ET)

- A diagnosis of exclusion, first described in 1934
- Chronic *nonreactive* elevated platelets without evidence of any other MPD
- Megakaryocyte hyperplasia in the bone marrow
- Prevalence 24 cases/100,000 in US
- Median age at diagnosis 60, up to 20% < 40 years old, extremely rare in kids
- F:M ratio 2:1
- 50% JAK-2 mutation+
- ~50% totally asymptomatic at presentation
Diagnostic Criteria for ET

- A diagnosis of EXCLUSION
  - Sustained Platelet Count $\geq$ 450 X 10^9/L
  - Megakaryocytic Hyperplasia on Bone Marrow Biopsy
  - Does not meet WHO criteria for PV, PMF, CML, MDS, or any other myeloid neoplasm  (Diagnosis of exclusion)
  - +JAK-2 mutation OR no evidence for reactive thrombocytosis
  - All four criteria must be met

Revised WHO Criteria 2008 (from 2001)
Hematology/Oncology Clinics Aug 2009

High Risk ET

- Age of onset $\geq$ 60 years old
- History of thromboses
- Platelet count $\geq$ 1.5 million x 10^9/L
  - Paradoxically ^ risk of bleeding
- WBC count $> 15 \times 10^3$/uL at diagnosis
- Low hemoglobin level (<12 g/dL in females; < 13.5 g/dL in males)
- CV risk factors: Smoking, Hypertension, Hyperlipidemia, Obesity, Diabetes
- Markers for Hypercoagulability (e.g. Factor V Leiden, Antiphospholipid Ab)
- Increased risk of thromboses, poorer survival
Low Risk ET

- Age at dx < 60 years old
- No history of bleeding or thrombotic events
- WBC < 15,000/microL
- Well followed with stable platelet counts < 1 million/microL
- Good CV profile

Treatment for ET

- Consider observation for low risk patients
- Low dose aspirin
- CV risk factor modification - Stop smoking!
- Coumadin for venous thromboses
- Cytoreductive therapy (hydroxyurea, etc) for high risk ET
  - Hydroxyurea vs Anagrelide
    - HU + ASA superior to Anagrelide + ASA (*rate of arterial thromboses, bleeding, transformation, but decreased venous thromboses) (NEJM 2005;353:33-45)
  - In emergencies, plateletpheresis for acute thrombosis and/or marked thrombocytosis
Goal Platelet Count

- There is no established target platelet count
- No correlation between platelet count and thrombosis risk
- Goal platelet count:
  - Level where the patient is FREE from symptoms or from the risk of bleeding
  - Generally, less than 900K

ET – Mortality/Morbidity

- Related to thrombotic and bleeding complications
- Platelet count is elevated but function is impaired
- ^ Bleeding risk when PLT > 1.5 million
- Transformation Risk < 5% @ 15 years
  - Acute Leukemia (AML) < 5%
  - Myelodysplastic syndrome 4%
  - More common with +JAK 2

- Life expectancy for the low risk group is nearly that of the healthy population
Chronic Myelogenous Leukemia (CML)
Chronic Myeloid Leukemia, Chronic Myelocytic Leukemia

- Expansion of a clone of cells that carry the Philadelphia Chromosome
- t(9,22) translocation \(\Rightarrow\) forms the BCR-ABL cancer gene (discovered 1960)
- 3 phases

<table>
<thead>
<tr>
<th>Chronic stable</th>
<th>&lt; 5% blasts</th>
<th>Mild sx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerated</td>
<td>5-30%</td>
<td>^ sx</td>
</tr>
<tr>
<td>Blast crisis</td>
<td>&gt; 30%</td>
<td>Aggressive</td>
</tr>
</tbody>
</table>

- Goals of therapy
  - Complete *hematologic* response (NL WBCs, PLTs, no splenomegaly)
  - Complete *cytogenetic* response (No Ph-positive cells in BM)

Imatinib mesylate (Gleevec, Novartis)

- Currently recommended for *first-line therapy* of CML
- Well tolerated oral medication - SPECIFIC *tyrosine kinase inhibitor* of the protein made by the BCR-ABL cancer gene (first approved TKI)
- FDA-approved since May 2001, 400 mg/day for chronic-phase CML ($32K/yr)
- Sustained remissions with impressive response rates
  - 2003 NEJM 76% complete cytogenetic response @ 18 months
  - Overall survival 89% at 5 years, cumulative response 83%
- Responses occur quickly (within 2 weeks, almost all by 6 months)
- CML likely to return if drug treatment stopped, follow-up has been short (7 years)
- Main concerns: relapse, progression of disease, development of drug resistance
Second and Third generation TKIs

- dasatinib (SPRYCEL®) Initial US Approval 2006
- nilotinib (TASIGNA®) (2007) **WARNING: QT prolongation and sudden deaths
- bosutinib – third generation – undergoing clinical trials

- Valuable treatment options for subgroup of patients intolerant or resistant to imatinib
- In the first line-setting - lower rates of transformation, comparable or superior complete cytogenetic response compared to imatinib by 2-year f/u.


Allogeneic Stem-Cell Transplantation

- Only proven curative treatment for CML, potential toxicity, early mortality risk
- Leading causes of premature death
  - Relapse of primary disease (29%)
  - Chronic graft-vs-host disease (22%)
    - Up to 70% transplant patients develop some degree of GVHD
    - Prevention/treatment with immunosuppressives
  - Risk for secondary malignancies (treatment related) lymphomas
  - Endocrine abnormalities (premature menopause, hypothyroid)
  - Organ dysfunction (restrictive lung disease, CHF, infections, anemia)
  - Immunity begins to develop and be fully functional ~ 1-1.5 years in the absence of chronic GVHD
Mortality Risks after BMT

- Recurrence of primary disease – 29%
  - 67% occurred between 2 to 5 years
  - 27% occurred in the next 5 years
- cGVHD – 22% of deaths
- Late infection (in the absence of cGVHD) – 11%
- Treatment related causes – 25%
  - Second malignancy - 7%
  - Pulmonary complications - 5%
  - Cardiotoxicity - 3%
  - Other treatment related sequelae – 8.4%

Blood 2007; 110: 3784-3792

Primary Myelofibrosis (PMF)

- Least common MPD, most difficult to diagnose
- ^ collagen in bone marrow => bone marrow fibrosis
- Fever, night sweats, weight loss, fatigue
- 95% with palpable splenomegaly
- Anemia, thrombocytopenia with eventual complete bone marrow failure
- Average survival – 5 years
- Allogeneic stem cell transplant is the only possible curative therapy
- Generally considered an uninsurable condition
MPD Summary
Diagnosis, Risk, and Survival varies

<table>
<thead>
<tr>
<th></th>
<th>Diagnostic Criteria</th>
<th>Thrombotic Bleeding Risk</th>
<th>AML/MDS Transformation Risk</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV</td>
<td>^RBC parameter +JAK 2 Low EPO</td>
<td>&gt;20%</td>
<td>&lt;3% 10%</td>
<td>Untreated 6-8 months Treated &gt; 10 years</td>
</tr>
<tr>
<td>ET</td>
<td>^PLTs Dx of exclusion</td>
<td>&gt;20%</td>
<td>&lt;1% 1%</td>
<td>Near NL</td>
</tr>
<tr>
<td>CML</td>
<td>^WBCs Ph-chromosome</td>
<td></td>
<td></td>
<td>Untreated &gt; 90% Improving</td>
</tr>
<tr>
<td>PMF</td>
<td>Splenomegaly Bone marrow fibrosis</td>
<td></td>
<td>4%</td>
<td>&lt; 5 years</td>
</tr>
</tbody>
</table>

The Future for MPDs?
Cytogenetics?

Current research focuses on JAK2 inhibitors/TKIs, potential for targeted therapy

[Diagram showing timeline of research progress]
THANK YOU VERY MUCH
FOR YOUR ATTENTION

Gina C. Guzman, MD