Why do patients with polycythemia vera clot?

Kinsey McCormick
Hematology Fellows conference
August 10, 2012
Outline

• Case presentation
• Overview of PV
• Disease course
• Mechanisms of thrombosis
Case Presentation

- **CC/ID:** 56 yo M with no PMHx presented with acute abdominal pain
- **Exam:** AF, 86, 147/94. Voluntary guarding, diffuse abdominal tenderness
- **Labs:** WBC 26K (92% neutrophils), Hb 18.7, Hct 57, MCV 77, Plt 265K
- **CT abd/pelvis:**
  - Extensive thrombosis of portal vein, SMV, splenic vein
  - Small bowel wall thickening concerning for ischemia
  - No splenomegaly
Case, cont

- **Management:**
  - Hematology, surgery consulted
  - Started on IV heparin
  - Taken to OR

- **Work up:**
  - EPO 16 (range: 2-19)
  - JAK2 V617F mutation detected
  - Flow negative for PNH
  - Lupus anticoagulant negative, IgM anticardiolipin mildly elevated
Polycythemia vera

- Myeloproliferative neoplasm
- Acquired defect in pluripotent stem cell
- Majority with JAK2 mutation, causing constitutive activation of JAK2 kinase domain
  - 96% with JAK2 V617F
  - 3% with mutation in exon 12 of JAK2
- Elevated red cell mass in absence of causes for secondary erythrocytosis
- +/- increase in platelets, granulocytes
Diagnosis

2008 WHO Diagnostic Criteria

**Major**
- Hg >18.5 (men), >16.5 (women)
- Presence of JAK2 V617F, or JAK2 exon 12 mutation

**Minor**
- BM trilineage myeloproliferation
- Subnormal serum EPO
- Endogenous erythroid growth

Both major and 1 minor, or first major and 2 minor

Tefferi, et al. JCO 2011
Complications of PV

- Postpolycythemic myelofibrosis: <10% at 10y
- Secondary AML: <5% at 10y
- Bleeding: Present in 1.7-20% at diagnosis
- Thrombosis: 12-39% at diagnosis
## Main outcome events in ECLAP cohort

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes of mortality</td>
<td>164 (10.0)</td>
</tr>
<tr>
<td>Fatal thrombosis</td>
<td>67 (4.1)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>43 (2.6)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>13 (0.8)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>6 (0.4)</td>
</tr>
<tr>
<td>Other vascular death</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>Hemorrhagic death</td>
<td>7 (0.4)</td>
</tr>
<tr>
<td>Fatal cancer</td>
<td>54 (3.3)</td>
</tr>
<tr>
<td>Acute leukemia and myelofibrosis</td>
<td>22 (1.3)</td>
</tr>
<tr>
<td>Other cancers</td>
<td>32 (2.0)</td>
</tr>
<tr>
<td>Other cause of death</td>
<td>36 (2.2)</td>
</tr>
</tbody>
</table>

Fatal thrombosis accounted for 41% of all deaths

Thrombosis and PV

- Major cause of morbidity/mortality
- Arterial (2/3) > venous (1/3)
- Cerebral > coronary > peripheral arteries
- Increased incidence of venous thrombosis in unusual sites (e.g. mesenteric/portal veins, dural sinuses)
Timing of thrombotic events

Marchioli, et al. JCO, 2005
Why do patients with PV clot?*

*Disclaimer: We don’t know for sure.
I. Red cell mass matters

- Elevated hematocrit (>55%) associated with increased risk of thrombosis
  1. Hyperviscosity $\rightarrow$ slows blood flow
  2. Flow dynamics: At high shear flow rates $\rightarrow$ axial migration of RBCs $\rightarrow$ displace platelets $\rightarrow$ increase plt-endothelial, plt-plt interactions\(^1\)

\(^1\)Turitto, et al. Annals NY Acad Sci 1983
II. What do platelets have to do with it?

• Elevated platelet count *not* associated with increased thrombotic risk

• Numerous qualitative abnormalities identified
  – Abnormal platelet aggregation
  – Abnormalities of membrane proteins, receptors
  – Evidence for abnormal platelet activation

• Lack of correlation between qualitative abnormalities, risk of thrombosis
Platelets are activated in PV

- MPD patients have increased expression of activation-dependent membrane proteins

Jensen, et al. BJH 2000
More evidence for platelet activation

- PV patients have increased TXA₂ synthesis as evidenced by increased urinary excretion of metabolites
- TXA₂ made by activated platelets; induces platelet aggregation, vasoconstriction

What happens when you give aspirin?

- ASA inhibits TXA$_2$ synthesis via irreversible COX-1 inhibition
- Excess TXA$_2$ production suppressible with ASA
- Does this translate into reduced thrombotic risk?
• Double-blind, placebo-controlled trial
• n=518 patients with PV and no clear indication for anti-thrombotic therapy, randomized to ASA 100mg po q day vs. placebo
Efficacy of ASA in PV

RR 0.42, CI 0.24-0.74, p=0.002

Landolfi, et al. NEJM 2004
Role of platelets and treatment implications

- Evidence for abnormal platelet activation in patients with PV
- TXA₂ production suppressible with ASA
- ASA significantly reduces risk of first thrombosis in patients with PV
- ASA indicated in all patients with PV who do not have contraindication
III. Role of granulocytes

- Leukocytosis is risk factor for thrombosis
  - Patients with WBC ct >15,000 had increased risk of thrombosis, particularly MI, compared to those with WBC ct <10,000 (HR 1.71; 95% CI 1.1-2.65)\(^1\)

- Myelosuppressive therapy reduces risk of thrombosis

\(^1\)Landolfi, Blood 2007
Neutrophils are activated in PV

- Increased expression of activation-dependent membrane proteins in patients with PV/ET compared to controls

Activated neutrophils, cont

- Increased plasma levels of elastase, MPO (markers of neutrophil degranulation)

Mechanisms by which activated leukocytes may promote thrombosis

- Activate, damage endothelial cells
- Direct effects on coagulation system
- Cause inflammation
- Promote formation of platelet-leukocyte aggregates
Platelet-leukocyte aggregates

- Increased circulating platelet-leukocyte aggregates in patients with ET/PV\textsuperscript{1,2}
- Elevated levels of circulating aggregates found in other conditions associated with thrombosis\textsuperscript{2}
- Patients with MPN and h/o thrombosis have increased numbers of circulating aggregates compared to those with MPN and no h/o thrombosis\textsuperscript{1}

\textsuperscript{1}Jensen, Eur J Haematol 2001
\textsuperscript{2}Falanga, et al. Exp Hematol 2005
Summary: Cell activation, platelet-leukocyte aggregates

Neutrophils as target for antithrombotic activity of hydroxyurea?

Inhibition of tissue factor expression by hydroxyurea in polymorphonuclear leukocytes from patients with myeloproliferative disorders: a new effect for an old drug?

N. MAUGERI,* G. GIORDANO,† M. P. PETRILLI,† V. FRATICELLI,† G. DE GAETANO,* C. CERLETTI,* S. STORTI† and M. B. DONATI*

*Laboratory of Cell Biology and Pharmacology of Thrombosis, Research Laboratories; and †Onco Haematology Division, ‘John Paul II’ Centre for High Technology Research and Education in Biomedical Sciences, Catholic University, Campobasso, Italy
New effect for an old drug?

• 12 patients with ET/PV and healthy controls
• Measured:
  - P-selectin (expressed on activated platelets)
  - Intracellular content and membrane expression of tissue factor (neutrophils express TF after *in vitro* exposure to P-selectin)
  - Number of circulating platelet-leukocyte aggregates

What happens when you give hydroxyurea?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TF</th>
<th>CD11b</th>
<th>Fibrinogen</th>
<th>TF</th>
<th>Myeloperoxidase</th>
<th>P-selectin</th>
<th>Fibrinogen</th>
<th>Fibrinogen factor</th>
<th>Aggregates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before HU</td>
<td>6.3 ± 1.7</td>
<td>71.4 ± 3.7</td>
<td>23.4 ± 4.7</td>
<td>87.3 ± 6.1</td>
<td>54.3 ± 15.1</td>
<td>31.0 ± 4.5</td>
<td>14.9 ± 2.0</td>
<td>32.6 ± 10.2</td>
<td>42.0 ± 5.5</td>
</tr>
<tr>
<td>After HU</td>
<td>1.4 ± 0.2</td>
<td>61.6 ± 6.4</td>
<td>4.2 ± 3.0</td>
<td>41.8 ± 13.3</td>
<td>73.4 ± 12.0</td>
<td>35.3 ± 12.4</td>
<td>3.0 ± 0.9</td>
<td>58.4 ± 15.3</td>
<td>33.8 ± 9.3</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.05</td>
<td>n.s.</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>n.s.</td>
<td>n.s.</td>
<td>&lt; 0.01</td>
<td>n.s.</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

• **Conclusion:** Hydroxyurea prevents P-selectin induced platelet-leukocyte aggregate formation, TF expression
Role of leukocytes and treatment implications

• Evidence for leukocyte activation in PV
• Activated neutrophils promote thrombosis via variety of mechanisms
• Hydroxyurea decreases TF production/expression by neutrophils, inhibits formation of platelet-leukocyte aggregates
• Hydroxyurea indicated for patients at high risk for thrombosis
<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (age &lt;60, no h/o thrombosis)</td>
<td>• Phlebotomy (Hct &lt;45% men, &lt;42% women)</td>
</tr>
<tr>
<td></td>
<td>• Low dose ASA</td>
</tr>
<tr>
<td>Low with plt ct &gt;1,000 x 10^9/L</td>
<td>• Phlebotomy</td>
</tr>
<tr>
<td></td>
<td>• Low dose ASA (if ristocetin cofactor activity &gt;30%)</td>
</tr>
<tr>
<td>High (age ≥60 and/or h/o thrombosis)</td>
<td>• Phlebotomy</td>
</tr>
<tr>
<td></td>
<td>• Low dose ASA</td>
</tr>
<tr>
<td></td>
<td>• Hydroxyurea</td>
</tr>
<tr>
<td>Perioperative management</td>
<td>• Hold ASA 1 week prior</td>
</tr>
<tr>
<td></td>
<td>• Hct &lt; goal, Plt ct &lt;400,000</td>
</tr>
<tr>
<td></td>
<td>• Aggressive post-op DVT ppx</td>
</tr>
</tbody>
</table>

Adapted from Vanucchi, et al. CA Cancer J Clin 2009
Back to the case...

- Patient went to OR, 70cm of ischemic distal jejunum resected
- Long course in SICU
- Hct trended down to <45% with “phlebotomy”
- Plt ct increased to 752K
- Transitioned to therapeutic dalteparin
- Eventually started on ASA, Hydrea
Conclusions

- Due to acquired defect in pluripotent stem cell
- Majority with JAK2 mutation
- Thrombosis major cause of morbidity/mortality
- Mechanisms of thrombosis still being defined
  - Elevated red cell mass, abnormal platelet and neutrophil activation likely important
- Treatment according to risk of thrombosis (as determined by age, h/o thrombosis)
Thank you to Dr. Linenberger
References