PV Treatment in 2017: Is it curable?

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Outline

• What are we treating?
  • WHO Criteria 2016
  • Distinguishing between PV and JAK2(+) ET

• Treatment
  • Phlebotomy
  • Hydroxyurea
  • Interferon
  • Ruxolitinib

• Is PV curable?
WHO Criteria 2016

Major Criteria:

1. Presence of JAK2 mutation(s)

2. ♂ Hb > 16.5 g/dl     ♀ Hb > 16 g/dl     or
♂ Hct > 49%     ♀ Hct > 48%     or

Increased red cell volume > 125%

3. Marrow biopsy hypercellular for age with trilineage hyperplasia and megakaryocytic variability in size

Minor Criterion (in the case of JAK2 negativity):

Subnormal serum EPO level

Two main points regarding diagnosis of PV:

A single hematocrit or hemoglobin value is not a substitute for measuring red cell mass!!

EPO Levels may be normal (~15%).

B. Silver, Krichevsky, Gjoni. Lymph and Hem. 2016, in press.
Potential error when using hematocrit to distinguish JAK2+ ET and PV.

Barbui T et. al., “Masked polycythemia vera (mPV): Results of an international study.” Am. J. Hematol. 89:52-54
Bone Marrow Examination is Helpful

- Normal
- Cellular PMF
- PV
- ET
Outline

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Phlebotomy

All agree must phlebotomize patients

However, must adjust for gender difference

• Men: $\text{Hct} \leq 45\%$ ($\text{RBC} = 5.0 \times 10^6 / \text{mm}$)

• Women: $\text{Hct} \leq 42\%$ ($\text{RBC} = 4.5 \times 10^6 / \text{mm}$)

Phlebotomy: Important Form of Treatment

Effect of Hematocrit On Blood Viscosity

Based on Chien S, Gallik S. American Physiological Society 1984; 217-249

Initial Treatment

Must assess phlebotomy requirements first.
# Phlebotomy Requirements During the Year Prior to rIFNα: All Patients (Cornell Experience)

<table>
<thead>
<tr>
<th>Quartile</th>
<th># Patients</th>
<th># PHL during the year prior to rIFNα</th>
<th>Median</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>1-4</td>
<td>3</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>5-7</td>
<td>5.5</td>
<td>5.7</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>8-12</td>
<td>9.5</td>
<td>9.6</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>12-25</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Totals</td>
<td>34</td>
<td>Range: 1-25</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>
Myth of Phlebotomy Only: Phlebotomy Unacceptable as Sole Treatment

1. Poor clinical tolerance

2. Frequency of vascular complications

3. Development of iron-deficiency anemia

4. Risk of early progression to myelofibrosis (?)

5. Cardiac toxicity
The hematocrit value in polycythemia vera: caveat utilitor

With iron deficiency anemia, there is a poor correlation (right graph) between derived hematocrit and red cell count.

Silver and Gjoni, Leukemia Lymphoma, 2014
Effect of MCV on Derived HCT

Remember, simple arithmetic is still important!

Phlebotomy: low MCV
Chemotherapy: high MCV

<table>
<thead>
<tr>
<th>RBC</th>
<th>X</th>
<th>MCV</th>
<th>=</th>
<th>HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>X</td>
<td>90</td>
<td>=</td>
<td>45</td>
</tr>
<tr>
<td>5.0</td>
<td>X</td>
<td>110</td>
<td>=</td>
<td>55</td>
</tr>
<tr>
<td>5.0</td>
<td>X</td>
<td>75</td>
<td>=</td>
<td>37.5</td>
</tr>
<tr>
<td>6.4</td>
<td>X</td>
<td>70</td>
<td>=</td>
<td>45</td>
</tr>
</tbody>
</table>
Dangers of hematocrit values ignoring RBC

Myelosuppression is an important component of PV treatment PVSG

1. Control peripheral RBC, platelets, WBC
2. Diminish symptomatic splenomegaly
3. Relieves pruritis
4. Adjunct to phlebotomy

Hydroxyurea

• Worldwide, the majority of hematologists still use hydroxyurea (HU) as a cytoreductive agent

• Predisposition to cancers and leukemia?
## Comparative incidence of thrombosis (PVSG study)

*All events, first 378 weeks of study (7.3 years)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total patients</th>
<th>No. events</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrea + phlebotomy</td>
<td>51</td>
<td>7</td>
<td>13.7</td>
</tr>
<tr>
<td>Phlebotomy-only</td>
<td>134</td>
<td>51</td>
<td>38.1</td>
</tr>
</tbody>
</table>
Toxicities of hydroxyurea
Toxicities of hydroxyurea
Specific Activities of interferon-alpha (rIFN-α) of interest in PV

- rIFN specifically affects JAK2(+) stem cells in mice (Mullaly, et al. ASH, 2013)
- Affects intracellular signaling related to JAK-STAT and other pathways
- Inhibits early red cell and megakaryocyte development
- Inhibits blood vessel formation
Treatment of PV with low-dose rIFNa (N= 55)

According to the PVSG criteria (HCT < 45%, no phlebotomy requirements, and platelets < 600,000/μL):

- All 55 patients had clinical responses
- No thrombohemorrhagic episodes
- Previous treatment with HU in 30%

Start

\{rIFNα-2b 1 million unts 3 X wk
\{Peg rifn α-2b 45 mgm/wk

Silver RT. *Sem Hem.* 1997; 34:40-50
Silver RT. *Cancer.* 2006; 107:451-58
Change in Spleen Size

1 year after rIFN-α

• 27/30 (90%) patients with initial splenomegaly showed greater than 50% reduction in spleen size whether or not they received prior HU

2 years after rIFN-α

• In 23 (76.7%) patients, spleen became non-palpable

Silver, RT, Cancer, 2006
Effect of interferon treatment on spleen size
Progression-Free Survival from Thrombohemorrhagic Events, 55 PV Patients

All 55 patients had CR or PR

Silver, RT. Cancer 107:451-58, 2006
## Limitations of rIFN therapy

Side effects are mainly **dose dependent**; perhaps less with single isomer interferon, RO-PEG.

### Typically transient flu-like symptoms that occur shortly after injections

<table>
<thead>
<tr>
<th>Headache</th>
<th>Fever</th>
<th>Mild skin reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgia</td>
<td>Chills</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Back/joint pain</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Less common (resolve upon rIFN discontinuation or decrease in dose):

<table>
<thead>
<tr>
<th>Chronic fatigue</th>
<th>Confusion (elderly patients)</th>
<th>Pulmonary, cardiac, or renal dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Liver toxicity</td>
<td>Neurological (gait disturbance, frontal lobe dysfunction, bilateral lower extremity neuritis)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>Cytopenias</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>Autoimmune disease</td>
<td></td>
</tr>
<tr>
<td>GI toxicity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ropeginterferon alpha 2b (RoPEGα2b)

• 51 patients, treated every 2 weeks
  • 33% treated with hydroxyurea at time of screening
  • Prior to therapy, 22% of patients suffered major cardiovascular events

• Response rate: 90%
  • CR: 47%
  • PR: 43%
  • CMR: 31%

Gisslinger, et. al.; Blood, 2015
Significant Decreases in JAK2 Allele Burden After Peg-rIFNα
(a quantitative number from 0 – 100%)

• First reported by Kiladjian, then Quintas-Cardama, Verstovsek

• Not by Silver and Kuriakose

• May be related to dose, duration, degree of toxicity
Therapeutic Conundrum

Is it preferable to maintain complete hematologic response with lowest interferon dose rather than to aim for \textit{JAK2} negativity?
Interferon is effective in treating the fibrosis that occurs in polycythemia vera in the absence of leukoerythroblastosis.

This provided the basis for its use in treating “early” myelofibrosis.
2/11/2009: H&E section (20X): increased fibrosis and increased atypical megakaryocytes
2/11/2009: 20X reticulin special stain: Markedly increased fibrosis – diffuse thick reticulin fibers
7/27/2011: H&E, 20X: Megakaryocytes form focal clusters
7/27/2011: 20X, reticulin special stain: mild increase in fibers (1+)
Response to treatment in primary, post-PV, and post-ET myelofibrosis: all patients (N=30)

<table>
<thead>
<tr>
<th>Response</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2</td>
</tr>
<tr>
<td>PR</td>
<td>9</td>
</tr>
<tr>
<td>CI</td>
<td>4</td>
</tr>
<tr>
<td>Stable</td>
<td>7</td>
</tr>
<tr>
<td>PD</td>
<td>4</td>
</tr>
<tr>
<td>Death</td>
<td>4</td>
</tr>
</tbody>
</table>

73% improved or remained stable, with 50% achieving CI or better

Silver et al, Proceedings American Society of Hematology 2016
Silver et al, Cancer {In Press}
Ruxolitinib in PV
N=322

Patients: inadequate response/unacceptable toxicity after HU treatment

Results: 21% of patients in ruxolitinib group achieved end point of Hct control, 35% reduction in spleen size at 32 weeks

Rux + other drugs (rIFN, azacytadine) undergoing evaluation

Vannucchi et. al.; NEJM 2015
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Basis for Early Treatment

1) PV, JAK2^{V617} HSC clone is small

2) Minimum JAK2^{V617F} tumor burden preferentially sensitive to rIFNα → Preferential depletion of JAK2^{V617F} HS

3) Activate cell cycle within HSC compartment → Preferential depletion of JAK2^{V617F} HS

Conceptual models for drug-free remission (‘cure’)

- **Stem cell depletion**
- **Stem cell exhaustion**
- **Immunological control**

Diagnosis – TKI started

- Stem cells
- Mature progeny

Time

Melo, JV and Ross, DM, 2011
Model for Early Treatment of MPNs with rIFN

- **Early**: rIFN effective
- **Advanced**: rIFN less effective
- **Sclerotic**: rIFN not effective
## Myeloproliferative Neoplasms (MPNs)

<table>
<thead>
<tr>
<th>Mutation</th>
<th>PV (%)</th>
<th>ET (%)</th>
<th>MF (%)</th>
<th>post- MPN AML (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK2&lt;sup&gt;V617F&lt;/sup&gt;</td>
<td>95-99</td>
<td>50-70</td>
<td>40-50</td>
<td></td>
</tr>
<tr>
<td>JAK2 exon 12</td>
<td>Rare</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>MPL exon 10</td>
<td>Rare</td>
<td>4</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>TET2</td>
<td>15</td>
<td>4-11</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>CBL</td>
<td>Rare</td>
<td>Rare</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>IDH</td>
<td>1.9</td>
<td>0.8</td>
<td>4.2</td>
<td>21.6</td>
</tr>
<tr>
<td>IKZF1</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>21</td>
</tr>
<tr>
<td>EZH2</td>
<td>3</td>
<td>None</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>ASXL1 exon 12</td>
<td>&lt;7</td>
<td>&lt;7</td>
<td>19-40</td>
<td>19</td>
</tr>
</tbody>
</table>

PV: Polycythemia Vera, ET: Essential Thrombocythemia, MF: Myelofibrosis, AML: Acute Myeloid Leukemia

No apparent correlation between hematologic response, complete molecular response, and change in cellularity or fibrosis.
Is PV Curable?

• “Absolute” cure: Not now
• “Biologic” cure: Possible
• Hematologic/molecular remission: Most likely
Progress is impossible without change, and those who cannot change their minds cannot change anything.

- George Bernard Shaw