Issues I am concerned with regarding polycythemia vera, 2019

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Disclosures
(Past 12 months)

• Speaker’s Bureau
  AOP Orphan
  PharmEssentia

• No conflict of interest
Outline:

Diagnostic Criteria
  WHO 2016 criteria
  Distinguishing $ET^{JAKV617F}$ from PV

Treatment issues
  Risk categories
  Treatment with ruxolitinib
  Treatment with phlebotomy-only
Outline:

Diagnostic Criteria
- WHO 2016 criteria
- Distinguishing ET$^{JAKV617F}$ from PV
Polycythemia vera (PV) should be defined by an absolute increase in red blood cells. (red cell volume or red cell mass, RCM)

Should not be based on hemoglobin concentration since 95% of PV patients are iron-deficient at the time of diagnosis. Varying Hgb values are characteristic of PV.

Red cell mass (RCM) >125% of mean expected volume

Nearly always accompanied by other evidence of myeloproliferation (WBC, platelets, splenomegaly)

$JAK2^{V617F}$ or exon12 mutation virtually always present, thus excluding “secondary” polycythemias.

Silver RT, et. al. Blood. 2013
# Major Molecular Abnormalities in Myeloproliferative Neoplasms

<table>
<thead>
<tr>
<th>Molecular Abnormality</th>
<th>PV</th>
<th>ET</th>
<th>PM</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>JAK2\textsuperscript{V617F}</td>
<td>97</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>EXON12</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CALR</td>
<td>0</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>MPL</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Triple Neg</td>
<td>0</td>
<td>10</td>
<td>10</td>
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</tbody>
</table>
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

Initially, make the correct diagnosis

- In approximately 15% of patients, the diagnosis of JAK2+ ET, PV, or early MF may be incorrect.

- This has obvious therapeutic and prognostic implications.
Overlap Values for HCT in PV and ET^{JAKV617F}

Men

Women

- PV (n=45) ET (n=12) Proposed Threshold (HCT=49.3%)
- PV (n=38) ET (n=27) Proposed Threshold (HCT=47.9%)
Bone Marrow Examination is Helpful

Normal bone marrow

ET bone marrow

PV bone marrow
Polycythemia Vera: Bone Marrow Biopsy
PV, 81 year old male
Caveats

1. Not clear how many centers are performing at diagnosis a marrow biopsy or erythropoietin values.

2. Cannot rely only on peripheral counts to separate PV from ETJAKV617F

3. Serum erythropoietin values normal in 15% of PV patients.
Laboratory Investigation of Myeloproliferative Neoplasms
Recommendations of the Canadian MPN group


Cr-51 RBC – not available in Canada

“Although both hemoglobin and hematocrit levels have some limitations, they are accepted as reasonable surrogates and indicators of red cell mass”

“Bone marrow provides limited additional value for diagnostic purposes”

Only about 25% of PV patients have had bone marrow biopsy at diagnosis at MPN centers in the US (courtesy of Incyte Corporation)
Initial Treatment

All agree must phlebotomize patients
Adjust for gender difference

- Men: $Hct \leq 45\%$
- Women: $Hct \leq 42\%$
Outline of Lecture

1. DIAGNOSIS
   • Definitions
   • What are we treating?

2. ISSUES OF TREATMENT
   • Phlebotomy
   • Hydroxyurea
   • Ruxolitinib
   • Interferon
Phlebotomy: Initially, Important Form of Treatment

Effect of Hematocrit On Blood Viscosity

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

Treatment option in PV after initial phlebotomy to Hct ♂ 45%, ♀ 42%

Phlebotomy (continued)

Hydroxyurea

Interferon

Ruxolitinib after HU
Risk Assessment
(Italian-derived studies)

**Low Risk**
- Under 60 years of age
- No thrombotic events
- Treatment: Phlebotomy + Aspirin
  - HCT ≤ 45%

**High Risk**
- More than 60 years of age
- History of thrombotic events
- Treatment: Cytoreduction + Aspirin
  - HCT ≤ 45%
After Initial Phlebotomy Treatment

Must assess subsequent phlebotomy requirements first.
Those who cannot remember the past are condemned to repeat it.

George Santayana
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>
MPN Patients are highly symptomatic regardless of subset

- Fatigue: 61%
- Trouble concentrating: 61%
- Loss of appetite: 52%
- Inactivity: 52%
- Weight loss: 87%
- Itching: 62%

“Symptoms remain undermanaged in low risk patients not deemed candidates for cytoreductive therapy” (N=1334)
Low Risk Patient: Treatment

47 year old dentist

- Hgb: 23.3 g/dL
- HCT: 69%
- Platelets: 145,000 x10^9/L
- Low ferritin
- Phlebotomies
- Initial 13
- Maintenance: 6 per year

“Complaints of increasing weakness that limits some activities ascribed to severe iron deficiency…”

Vannucchi, AM. Blood 2014
Phlebotomy-Only (PHL-O) is Unacceptable as Sole Treatment in PV

1. Poor Clinical Tolerance

2. Frequency of Vascular Complications

3. Risk of Early Progression to Myelofibrosis (probably an association)

Consequences of Iron Deficiency (clinical)

1) More Frequent Falls
2) Cognitive impairment
3) Dementia
4) Poor Exercise Tolerance
5) Impaired Results after chemotherapy
6) Impaired Results after Myocardial Infarction
Koilonychia in iron-deficiency anemia

Ghaffari and Pourafkari, N Engl J Med 2018
Annual rate of thrombosis in contemporary patients with polycythemia vera and in general population

**Incidence rate (% pts/year)**

- **PV patients**: 2.23 (Low risk)
- **General population with multiple CV risk factors**: 0.6 (Low risk)
- **General population without risk factors**: 0.6 (Low risk)
- **High risk**: 3.14


Courtesy: T. Barbui, MD
“Myelosupression 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

Fruchtmann SM. Semin Hematol. 1997
Treatment

Worldwide, the majority of hematologists still use hydroxyurea (HU) for marrow suppression.
# 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>

Fruchtman S. PVSG Data. 1996
FAILURE, HU AT 1 YEAR, PVSG
(118 PTS)

Previously untreated: 27%
Previous myelosuppressives: 41%
Toxicities of hydroxyurea
Nail Changes during Chemotherapy
Ruxolitinib in PV
N=222

Patients: inadequate response or unacceptable toxicity after HU treatment

Phlebotomy dependant: 2 PHLs in prior 6 months

Control arm: resistant/intolerant to HU: 58.9%

Efficacy: 1. HCT \leq 45\% : 20\%
2. 35\% spleen size reduction,

HCT control only 60\%

Safety: H. zoster in (6.4\%) in the first 8 months

Vannucchi et. al.; NEJM 2015
Side effects of ruxolitinib

Anemia (43% vs. 31%) and thrombocytopenia
Initially, and usually mild

Infections
urinary tract, lungs
tuberculosis
Long-term use

Neoplasms
B-cell lymphoma
non-melanoma skin cancer
other second cancers
Long-term use

References:
Vannucchi et. al.; NEJM. 2015
Gisslinger et. al.; Blood. 2018
Pardanani, Tefferi; Blood 2018
When should ruxolitinib be used in PV? (RTS, 2019)

1. For symptomatic patients with:
   - pruritus
   - night sweats
   - early satiety, etc.

2. Symptomatic and/or persistent splenomealy

3. Patients resistant, refractory to HU, rIFNα

4. Frank myelofibrosis inappropriate for or not responsive to rIFN

5. Combination therapy with:
   - rIFNα – early stage (Hasselbach)
   - azacitidine – late stage (Verstovsek)
Specific activities of interferon-alpha (rIFN-a) of interest in PV

- Suppresses megakaryopoiesis (Wang)
- Antagonizes action of PDGF (Lin)
- Inhibits erythroid progenitors in vitro (Means, Krantz)
- Anti-angiogenic (Folkman)
- Involved in JAK-STAT signaling
- Affects PV stem cell (Mullaly)
- Safe to use during pregnancy
- Not leukemogenic
Basic principles for using IFN in PV (RTS et al.)

Most start with low dose

Increase dose slowly

End point: phlebotomy free
CHANGE IN SPLEEN SIZE

1 year after rIFN-a

- 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-a

- 27/30 (90%) patients with initial splenomegaly showed greater than 50% reduction in spleen size whether or not they received prior HU
- In 23 (76.7%) patients, spleen became non-palpable
Limitations of rIFN therapy

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

Typically transient flu-like symptoms that occur shortly after injections

- Headache
- Myalgia
- Back/joint pain
- Fever
- Chills
- Mild skin reaction
- Fatigue

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

- Chronic fatigue
- Depression
- Musculoskeletal pain
- Alopecia
- Gl toxicity
- Confusion (elderly patients)
- Liver toxicity
- Cytopenias
- Autoimmune disease
- Pulmonary, cardiac, or renal dysfunction
- Neurological (gait disturbance, frontal lobe dysfunction, bilateral lower extremity neuritis)

Summary: Drop-out rate 15-25% in reported studies depending on dose, enthusiasm of physician and patient.
Interferon is effective in treating the fibrosis that occurs in polycythemia vera in the absence of leukoerythroblastosis
2/11/2009: H&E section (20X): increased fibrosis and increased atypical megakaryocytes
7/27/2011: H&E, 20X: Megakaryocytes form focal clusters
PV: Myelofibrosis-free survival, by treatment

Abu-Zeinah G, Kirchevsky S, Sosner C, Savage N, Scandura JM, Silver RT. ASH 2018
Complete hematologic response (CHR)

<table>
<thead>
<tr>
<th>Study Month</th>
<th>Responder/N</th>
<th>Responder</th>
<th>Responder/N</th>
<th>Responder</th>
<th>P-value</th>
<th>RR [95% CI] (AOP2014/Control)</th>
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<tbody>
<tr>
<td>Ropeg (N=95)</td>
<td></td>
<td></td>
<td>Control (N=76)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONTH 12 (EOT in PR)</td>
<td>59/95</td>
<td>62.1</td>
<td>57/76</td>
<td>75.0</td>
<td>0.1201</td>
<td>0.85 [0.70-1.04]</td>
</tr>
<tr>
<td>MONTH 24</td>
<td>67/95</td>
<td>70.5</td>
<td>33/67</td>
<td>49.3</td>
<td>0.0111</td>
<td>1.42 [1.08-1.87]</td>
</tr>
<tr>
<td>MONTH 36</td>
<td>67/95</td>
<td>70.5</td>
<td>38/74</td>
<td>51.4</td>
<td>0.0122</td>
<td>1.38 [1.07-1.79]</td>
</tr>
</tbody>
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RR: Relative Risk

AOP2014
Control
AOP2014 (stat. significant RR)
Control (stat. significant RR)
# JAK2 (V617F) - Molecular response

## Study Month

<table>
<thead>
<tr>
<th>Study Month</th>
<th>Responder/N</th>
<th>Responder %</th>
<th>Responder/N</th>
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<td>Control (N=76)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONTH 12 (EOT in PR)</td>
<td>41/94</td>
<td>43.6</td>
<td>38/75</td>
<td>50.7</td>
<td>0.5001</td>
<td>0.84 [0.62-1.15]</td>
</tr>
<tr>
<td>MONTH 24 (LOCF)</td>
<td>64/94</td>
<td>68.1</td>
<td>25/75</td>
<td>33.3</td>
<td>0.0001</td>
<td>1.99 [1.40-2.84]</td>
</tr>
<tr>
<td>MONTH 36 (LOCF)</td>
<td>62/94</td>
<td>66.0</td>
<td>20/74</td>
<td>27.0</td>
<td>&lt;0.0001</td>
<td>2.31 [1.56-3.42]</td>
</tr>
</tbody>
</table>

*Courtesy of Gissinger H. ASH 2018*
Conclusions

Diagnosis of PV vs. ET$^{V617F}$ can be difficult, must have marrow

Phlebotomy only results in severe iron deficiency anemia; and allows the disease to progress unchecked.

Limitations in the use of ruxolitinib in PV

Interferon is probably the best treatment to control the proliferative aspects of polycythemia vera

- Biological basis for its use. Not leukemogenic.
- Able to induce clinical, hematological and some degree of molecular remission.
- Evidence of delayed onset of MF submitted

We use JAK2 allele burden and marrow biopsy to decide on discontinuing rIFN

JAK2 inhibitors in combination with interferon for symptomatic patients
Progress is impossible without change, and those who cannot change their minds cannot change anything.

- George Bernard Shaw