Managing Polycythemia Vera in 2021

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Disclosures

PharmaEssentia:  Speakers Bureau
                Consultant

Clinical Trials:  Multiple
PV patients have shortened survival


Initial Treatment of PV

All agree we must phlebotomize patients

However, we should adjust for gender difference

• Men: Hct ≤ 45%

• Women: Hct ≤ 42%
After Initial Phlebotomy Treatment

Must assess subsequent phlebotomy requirements first.
Phlebotomy requirements during the year prior to rIFNa, 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>

Silver RT, Cancer 2006
Second-line treatments and clinical trials in PV: PTG-300 hepcidin mimetic
Treatment option in PV after initial phlebotomy to Hct ♂ 45%, ♀ 42%

Phlebotomy (continued)

Hydroxyurea

Interferon

Ruxolitinib after HU
Risk Assessment
(NCCN, ELN)

**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%
PV initial treatment approach:
What do guidelines recommend? What do we recommend?

National Guidelines

<table>
<thead>
<tr>
<th>Initial Treatment by Risk Group</th>
<th>Weill Cornell practice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Risk</strong></td>
<td></td>
</tr>
<tr>
<td>• Assess for new blood clots and major bleeding</td>
<td></td>
</tr>
<tr>
<td>• Manage cardiovascular risk factors</td>
<td></td>
</tr>
<tr>
<td>• Aspirin</td>
<td></td>
</tr>
<tr>
<td>• Phlebotomy</td>
<td></td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td></td>
</tr>
<tr>
<td>• Assess for new blood clots and major bleeding</td>
<td></td>
</tr>
<tr>
<td>• Manage cardiovascular risk factors</td>
<td></td>
</tr>
<tr>
<td>• Aspirin</td>
<td></td>
</tr>
<tr>
<td>• Hydroxyurea or interferons</td>
<td></td>
</tr>
</tbody>
</table>

NCCN Guidelines for Patients, Myeloproliferative Neoplasms, 2019

+ INTERFERON (IFN)

IFN or Hydroxyurea (HU)
Related to Anemia

1) More frequent falls
2) Cognitive impairment
3) Dementia
4) Poor exercise tolerance
5) Impaired results after chemotherapy
6) Impaired results after myocardial infarction

Schrier S. Hem Onc. Jan 2015
DeLoughery, NEJM 2014
Myth of Phlebotomy-only: Phlebotomy is unacceptable as sole treatment

1. Poor Clinical Tolerance

2. Frequency of Vascular Complications

3. Risk of Early Progression to Myelofibrosis

MPN Patients are highly symptomatic regardless of subset

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

Geyer and Mesa, Blood 2015
Annual rate of thrombosis in general population and in contemporary patients with polycythemia vera % pts/year

General population without risk factors 0.6

General population with multiple risk factors 0.9

PV patients with low risk 2.23

PV patients with high risk 3.14

With permission and courtesy of T. Barbui MD 10th International Patient Symposium
### 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
“Approved” Treatment for HU Resistance or Toxicity

RESPONSE Trial: Ruxolitinib vs. “Standard therapy”

- P<0.001
- Odds ratio, 28.6
- (95% CI, 4.5–1206)

CHANGE IN SPLEEN SIZE

1 year after rIFN-a

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
Specific Activities of Interferon-alpha (rIFNa) 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
Does Interferon-alpha prolong survival of PV patients?

<table>
<thead>
<tr>
<th>Study Type</th>
<th>MPN-RC 112</th>
<th>DALIAH</th>
<th>CONTI-PV</th>
<th>Low-PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large study</td>
<td>☒ 85-254</td>
<td>☑ 470</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized, controlled</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long follow-up</td>
<td>☒ ~1-3 years</td>
<td>☒</td>
<td>☑ Median 10 years (up to 45)</td>
<td></td>
</tr>
</tbody>
</table>
Ropeg-IFN is possibly better than HU in a randomized trial of high-risk PV (CONTI-PV)

Ropeginterferon α-2b (Ropeg-FN) is a longer-acting, biweekly dosed form of Interferon-alpha

Complete hematologic response

Partial molecular response

Gisslinger H et al. Lancet Hematology 2020
Combined analysis of Hct<45% without phlebotomy AND molecular response

Barbui et al. Lancet Haematology 2021
IFN is associated with improved MFS in low-risk PV

MFS of low-risk patients by treatment group

- IFN
- HU
- PHL-O

Time (years)

MFS probability

p = 0.0011
IFN in PV is disease-modifying

Pretreatment | Posttreatment
---|---
Histologic response

Fibrosis reversion

Complete bone marrow responses

Probability of achieving BM - CR, %

Time [months]

Masarova L et al. Hematol Oncol. 2017
Longer time on IFN is associated with reduced MF

<table>
<thead>
<tr>
<th>Variable</th>
<th>Myelofibrosis (MF)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI, p-value)</td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.99-1.03, NS)</td>
</tr>
<tr>
<td>Sex (Female/Male)</td>
<td>0.70 (0.46-1.07, NS)</td>
</tr>
<tr>
<td>Thrombosis history (Y/N)</td>
<td>1.18 (0.63-2.20, NS)</td>
</tr>
<tr>
<td>CV risk factors (Y/N)</td>
<td>0.81 (0.47-1.38, NS)</td>
</tr>
<tr>
<td>IFN (time on therapy)</td>
<td>0.91 (0.87-0.95, p&lt;0.001)</td>
</tr>
<tr>
<td>HU (time on therapy)</td>
<td>0.98 (0.95-1.01, NS)</td>
</tr>
<tr>
<td>Other (time on therapy)</td>
<td>0.99 (0.94-1.05, NS)</td>
</tr>
</tbody>
</table>

9% MF risk reduction / year of IFN

IFN is associated with improved OS in high-risk PV

OS of high-risk patients by treatment group

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time (years)</th>
<th>OS probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN</td>
<td>22</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>0.8</td>
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<td></td>
<td>7</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0.8</td>
</tr>
<tr>
<td>HU</td>
<td>105</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>47</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.8</td>
</tr>
<tr>
<td>PHL–O</td>
<td>56</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>0.8</td>
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<tr>
<td></td>
<td>9</td>
<td>0.8</td>
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<tr>
<td></td>
<td>6</td>
<td>0.8</td>
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<tr>
<td></td>
<td>2</td>
<td>0.8</td>
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<tr>
<td></td>
<td>0</td>
<td>0.8</td>
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</table>

$p = 0.016$
Longer time on IFN is associated with reduced mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI, p-value)</td>
</tr>
<tr>
<td>Age</td>
<td>1.10 (1.07-1.12, p&lt;0.001)</td>
</tr>
<tr>
<td>Sex (Female/Male)</td>
<td>0.54 (0.36-0.83, p=0.005)</td>
</tr>
<tr>
<td>Thrombosis history (Y/N)</td>
<td>1.12 (0.61-2.04, NS)</td>
</tr>
<tr>
<td>CV risk factors (Y/N)</td>
<td>1.06 (0.67-1.68, NS)</td>
</tr>
<tr>
<td>IFN (time on therapy)</td>
<td>0.94 (0.90-0.99, p=0.012)</td>
</tr>
<tr>
<td>HU (time on therapy)</td>
<td>0.97 (0.94-1.00, NS)</td>
</tr>
<tr>
<td>Other (time on therapy)</td>
<td>1.00 (0.94-1.06, NS)</td>
</tr>
</tbody>
</table>

6% mortality risk reduction / year of IFN

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

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

- Chronic fatigue
- Confusion (elderly patients)
- Depression
- Liver toxicity
- Musculoskeletal pain
- Cytopenias
- Alopecia
- Autoimmune disease
- Back/joint pain
- GI toxicity
- Chronic fatigue
- Confusion (elderly patients)
- Depression
- Liver toxicity
- Musculoskeletal pain
- Cytopenias
- Alopecia
- Autoimmune disease
- Back/joint pain
- GI toxicity

### Summary: Drop-out rate 15-25% in reported studies depending on dose, enthusiasm of physician and patient.
IFN should be considered for both low and high risk patients

<table>
<thead>
<tr>
<th></th>
<th>Initial treatment by risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low risk</td>
</tr>
<tr>
<td>NCCN</td>
<td>PHL-O</td>
</tr>
<tr>
<td>ELN</td>
<td>PHL-O</td>
</tr>
<tr>
<td>WCM</td>
<td><strong>IFN &gt; PHL-O</strong></td>
</tr>
</tbody>
</table>
Climbing the PV rock

Interferon
Hydroxyurea
Ruxolitinib
Fedratinib
Transplantation
etc., etc...
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