### Disclosures

<table>
<thead>
<tr>
<th>Role</th>
<th>Companies/Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair, Data Safety Monitoring Board</td>
<td>PharmaEssentia</td>
</tr>
<tr>
<td>SURPASS study</td>
<td></td>
</tr>
<tr>
<td>Consultant</td>
<td>AbbVie, GSK</td>
</tr>
<tr>
<td>Multiple others:</td>
<td>Clinical trials</td>
</tr>
</tbody>
</table>
Conclusion
(Mayo Clinic 2013)

• Interferon may be the best treatment to control the proliferative aspects of polycythemia vera
  • Biological basis for its use
  • Able to induce clinical, hematological and some degree of molecular remission
  • Requires clinical trial
• Interferon in combination with JAK2 inhibitors and other drugs for symptomatic relief
• In the year 2012, treat for clinical response, not for molecular response to avoid toxicity (?)
“Five-year view: We believe that rIFN will become more widely used in the next 5 years.”
Diagnostic criteria for PV, 2022

1. We have confirmed WHO 2016, 2022 blood criteria for PV

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCT</td>
<td>&gt;49%</td>
<td>&gt;48%</td>
</tr>
<tr>
<td>Hgb</td>
<td>&gt;16.5 g/dL</td>
<td>&gt;16g/dL</td>
</tr>
<tr>
<td>Red Cell Mass</td>
<td>&gt;25%</td>
<td>&gt;25%</td>
</tr>
</tbody>
</table>


2. Some patients with $JAK2^{V617F}$ ET have similar values

3. Must have marrow biopsy (isotope studies not available in USA)

REVEAL study: only 25% of patients in US

Silver RT, Krichevsky S. *Haematologica*. 2019
Where we have been . . .

“PV patients have shortened survival . . .“

Where are we going?

---

*Modified from: Tefferi A et al. Blood 2014*

## ELN, NCCN
### Risk groups in PV

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>≤ 60, No</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 60, Yes or No</td>
</tr>
</tbody>
</table>
Initial Treatment of PV

All agree we must phlebotomize patients

Reminder: we should adjust for sex difference
  • Men: Hct ≤ 45%
  • Women: Hct ≤ 42%

Maintenance Therapy of PV
  • Phlebotomy
  • HU
  • rIFNα
Maintenance phlebotomy causes varying degrees of anemia

Clinical issues

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

DeLoughery, NEJM 2014
Consequences of Iron Deficiency
Laboratory issues

• Dysregulated iron metabolism

• DNA synthesis affected

• Mitochondrial electron transport impacted

• Muscle and cardiac function impaired

• Heme containing enzymes: altered function

Ginzburg Y, et al. Leukemia 2018
von Dygalski A and Adamson J. Blood 2011
**PROPOSITION:**
IFN should be considered for both low and high risk patients
Weill Cornell ...and others

<table>
<thead>
<tr>
<th>Initial treatment by risk group</th>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCCN</strong></td>
<td>PHL-O or IFN(^2)</td>
<td>HU or rIFN</td>
</tr>
<tr>
<td><strong>ELN</strong></td>
<td>PHL-O(^1)</td>
<td>HU or rIFN</td>
</tr>
<tr>
<td><strong>WCM</strong></td>
<td><strong>rIFN &gt; PHL-O</strong></td>
<td><strong>rIFN &gt; HU</strong></td>
</tr>
</tbody>
</table>

\(^1\)Barbui T. et al. *Lancet Haematology*, March 2021

\(^2\)NCCN, 2022
3 types of interferons
• TYPE 1 ($\alpha$, $\beta$) – “viral interferons”
• TYPE 2 (immune) – “antigens”
• TYPE 3 ($\lambda$, 1, 2, 3) – similar to type 1

Pegylation: polyethylene glycol: a “vehicle”

Clinical use:
Peg-recombinant-interferon $\alpha$-2a (“Pegasys”) – 11 isoforms of interferon
Ropeg-interferon $\alpha$-2b (“Besremi”) – 1 isoform of interferon

No qualitative difference between the interferons
Polycythemia Vera Treatment:
Many reasons to start rIFNα initially

• ELN/NCCN guidelines based on age/thrombosis risk are not adequate
  • do not account for symptoms
  • younger patients have more aggressive disease
  • long-term consequences: development of myelofibrosis

• HU satisfactory, but not disease modifying
  • second malignancies
  • ? 2nd Leukemia/MDS – long term

• rIFN – disease modifying
  • affects stem cells
  • LOW-PV: rIFN > PHLEB-O ← “low risk”
  • PROUD-CONTI study: rIFN > HU ← “high risk”
  • long-term survival study (WCM): rIFN > HU > PHLEB-O
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
Median JAK2V617F allele burden (LOCF)

Interferon yields superior results to PHL-O in low risk patients

Combined analysis of Hct<45% without phlebotomy AND molecular response

Barbui et al. Lancet Haematology 2021
Ropeginterferon-alpha-2b vs. Standard therapy for low-risk patients with PV followed for 2 yrs

Abstract 744

<table>
<thead>
<tr>
<th></th>
<th>Ropeg</th>
<th>Phl-O</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>Complete hematologic response</td>
<td>53 (83%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>0</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>48 (55%)</td>
<td>36 (28%)</td>
</tr>
</tbody>
</table>
ASH Abstract 744: Barbui et al. 2022

Disease progression

n = 8

All due to thrombocytosis

• Microvascular symptoms 6
• Cerebral TIA 1
• Splenic vein thrombosis 1
Does Interferon-alpha prolong survival of PV patients?

<table>
<thead>
<tr>
<th>Study size</th>
<th>Randomized, controlled</th>
<th>Long follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPN-RC 112 DALIAH CONTI-PV Low-PV</td>
<td>85-254 patients</td>
<td>✓</td>
</tr>
<tr>
<td>WCM (Cornell)</td>
<td>470 patients</td>
<td>✓</td>
</tr>
</tbody>
</table>
PV progression to MF: major contributor for late mortality?

Abu-Zeinah G et al. Leukemia 2021
Long term follow up: Weill Cornell (N=470)

IFN is associated with improved MFS in low-risk PV

Abu-Zeinah, G et al. Interferon-alpha for treating polycythemia vera yields improved myelofibrosis-free and overall survival. Leukemia 2021–03-02
Long term follow up: Weill Cornell (N=470)
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>0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.975</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>0.83</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time (years)</th>
<th>OS probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>HU</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>0.87</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time (years)</th>
<th>OS probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHL-O</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.975</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>0.83</td>
</tr>
</tbody>
</table>

p = 0.016

Abu-Zeinah, G et al. Interferon-alpha for treating polycythemia vera yields improved myelofibrosis-free and overall survival. *Leukemia* 2021–03-02
The longer a patient receives rIFNα, there is both reduced risk of MF and improved OS

• Myelofibrosis risk reduction / year of rIFNα  9%

• Mortality risk reduction / year of rIFNα  6%

PV event-free survival (EFS) by phlebotomy (PHL) alone or any cytoreductive therapy

- PHL\_Only=NO
- PHL\_Only=YES

EFS probability

Time (years)

p = 0.001

350 123
287 78
212 48
164 29
102 17
61 8
34 5
12 1
IFN in PV is disease-modifying

Pretreatment vs. Posttreatment

Histologic response

Fibrosis reversion

Silver RT et al. Blood 2011

Masarova et al. Hematol Oncol. 2017
"PV patients have shortened survival . . . "

Where we have been . . . .

Where are we going?


Overall survival (OS) of PV-WCM, PV-SEER, and matched population

WCM: HR 1.15, p=0.136
SEER: p<0.0001
OS of PV patients treated with IFNα

- Expected
- PV- rIFNα

p = 0.326

median OS = 28 yr

G. Abu-Zeinah et al. *Leukemia* 2022
Side effects (toxicity) of rIFNα therapy

Side effects are mainly dose dependent.

Typically transient flu-like symptoms that occur shortly after injections

- Fatigue
- Headache
- Fever
- Chills
- Myalgia
- Back/joint pain
- Mild skin reactions:
  - maculopapular

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

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

Summary: Drop-out rate 15-25% in reported studies depending on dose, enthusiasm of physician and patient.
Question: Should rIFN be discontinued after treatment success?

Cornell: Only with $JAK2^{V617}$ allele frequency <5%
Marrow biopsy “normal” cellularity, no fibrosis*
Allow some megakaryocyte atypia

French: More liberal approach

*Margolskee E, Krichevsky S, Orazi A, Silver RT. *Haematologica*. 2017
Is aiming for improved survival associated with cure?

Interferon most likely not curative

• Other mutations persist despite “eradication” of JAK2
• These mutations may precede JAK2
• 3 or more epigenetic mutations (ASXL-1, EZH2, etc.)
  associated with poor or no response

Kiladjian JJ et al. Leukemia 2010
Silver RT. Cancer 2017
Other drugs patients should know about for treating PV

1) JAK inhibitors
   - ruxolitinib
   - pacritinib
   - fedratinib
   - momelotinib (awaiting FDA approval)

2) MF drugs in development for primary MF will be used in PP-MF and MF

*3) Rusfertide – Hepcidin mimetic
   - Interferes with iron absorption, metabolism, distribution
   - Phase 3 trial net result:
     - No phlebotomies!
     - Does not affect JAK2, stem cells

The Future
Some ideas. . . (some ongoing)

1) Anti-inflammatory drugs
   • Ruxolitinib
     rIFNα may exacerbate inflammation
     Rux reduces rIFN toxicity, e.g., inflammation (DALIAH study)
   • Statin effects:
     Anti-inflammatory, anti-angiogenic, anti-proliferative, pro-optotic
     ↓ JAK-STAT signaling
   • Colchicine

2) Combination with rusfertide

3) Vaccine therapy
   Vaccines are immunogenic
   Peptic vaccination with JAK2, CALR epitopes

4) Treatment of CHIP (?)
   Modeling: early treatment is effective
   ? Colchicine

5) Identify poor-risk patients by “fitness” studies
Conclusion

• Evidence is accumulating that IFNs should be the treatment of choice for PV. May be used in combination with other drugs

• IFNs should be used in both low and high risk ELN/ NCCN patients

• IFNs have disease modifying effects by modifying stem cell activity

• IFNs have acceptable toxicity when properly used

• IFNs result in long clinical remissions

• We should revise ELN/NCCN recommendations for treatment
Acknowledgements

**WCM**
Ghaith Abu-Zeinah, MD  
Joseph Scandura, MD, PhD  
Andrew I Schafer, MD  
Ellen K Ritchie, MD  
Mara Sanderson, BA  
Katie Erdos, BA  
Neville Lee, BA

**International**
Jean-Jacques Kiladjian, MD, PhD (France)  
Hans Hasselbalch, MD, PhD (Denmark)  
Heinz Gisslinger, MD (Austria)  
Rüdiger Hehlmann, MD, PhD (Germany)

**USA**
Ruben Mesa, MD  
Srdan Verstovsek, MD, PhD  
Jerry Spivak, MD  
... and many others

**Research funding**

*Weill Cornell Medicine*
Clinical & Translational Science Center

*NIH*
National Center for Advancing Translational Sciences

*CR&T*
Cancer Research & Treatment Fund, Inc.  
Established 1908

*MPN Research Foundation*
Change Your Prognosis