Treatment of polycythemia vera with recombinant interferon alpha (rIFNα)

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Outline of Lecture

What are interferons?

Treatment options in PV

- Phlebotomy
- Hydroxyurea
- Interferon
- Ruxolitinib

Molecular response

Clinical response

Basis for early treatment

Conclusion
General Remarks About Interferons

- Discovered more than 50 years ago
- Interferons are a group of signaling proteins known as cytokines. They are released in response to viruses, parasites, protozoa, tumor cells etc.
- Interferons also activate NK cells, macrophages and STATs, upregulate histocompatibility complex antigens

3 types of interferons
- TYPE 1 (α, β) – “viral interferon”
- TYPE 2 – immune – “antigens”
- TYPE 3 (λ, l, 2, 3) [Similar to type I]
Pegylated IFNs (In Brief)

• **Peg-IFN\(\alpha\)-2b**: unstable urethane bond between Peg and IFN molecule; more likely to hydrolyze; more rapid release of IFN; shorter half-life (Merck)

• **Peg-IFN\(\alpha\)-2a**: more stable amide bond; longer half life; prolonged plasma concentration; prolonged efficacy; less toxicity (Roche)

• **Ropeginterferon**: proline-IFN\(\alpha\)-2b produced in E. coli (PharmaEssentia)  
  Single isoform

• No randomized controlled trials in Hep C.

• Similar results in one CML comparative trial between Peg-IFN\(\alpha\)-2b and rIFN\(\alpha\)-2b

• Safety profiles similar
Specific Activities of Interferons of Interest to Hematologists/Oncologists

- Induces expression of pro-apoptotic genes
- Inhibits angiogenesis and alters microenvironment
- Enhances immune response against malignant cells
- Promotes cycling of dormant malignant hematopoietic stem cells
- Affects megakaryopoiesis
- Affects JAK-STAT signaling
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• Phlebotomy
• Hydrea
• Ruxolitnib
• Interferon
Phlebotomy

All agree must initially phlebotomize patients

However, must adjust for gender difference

- Men: Hct ≤ 45% (RBC = 5.0x10⁶/mm)

- Women: Hct ≤ 42% (RBC = 4.5x10⁶/mm)

Phlebotomy: Important Initial Treatment

Effect of Hematocrit On Blood Viscosity

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

Subsequent 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>

Silver RT. Cancer. 2006; 107:451-58
Myth Of Phlebotomy-only:
Phlebotomy is unacceptable as sole treatment

1. Poor Clinical Tolerance
2. Frequency of Vascular Complications
3. Development of severe iron-deficiency anemia
4. Risk of early progression to myelofibrosis (?)
5. Cardiac toxicity

Consequences of Iron Deficiency (some)

• DNA synthesis affected

• Mitochondrial electron transport impacted

• Muscle and cardiac function impaired

• Cognitive decline

Dygaski A, Adamson J, Blood 2011
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

Hydroxyurea

- Worldwide, the majority of hematologists still use hydroxyurea (HU) as 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)

Start

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

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%

Silver RT. *Sem Hem.* 1997; 34:40-50
Silver RT. *Cancer.* 2006; 107:451-58
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
- Prior HU did not affect response
- 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, RHO-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
Some Reasons for Different Results

(1) More “advanced” cases. Much higher JAK2V617F allele burden (Silver)

(2) Higher does: more toxicity with better JAK2 results (Kiladjian, Quintas-Cardama)
Therapeutic Dilemma

Is it preferable to maintain complete hematologic response with lowest interferon dose rather than to aim for 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, ET JAK2$^{V617}$ HSC clone is small

2) Minimum JAK2$^{V617F}$ tumor burden preferentially sensitive to rIFNα

3) Activate cell cycle within HSC compartment

Preferential depletion of JAK2$^{V617F}$ HS

Suggested Hypotheses for “Cure” of PV 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\textsuperscript{V617F}</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 Thrombocytopenia, MF: Myelofibrosis, AML: Acute Myeloid Leukemia

No apparent correlation between hematologic response, complete molecular response, and change in cellularity or fibrosis.
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1. Interferon is probably 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

2. All interferons are qualitatively effective, but like all potent medications, have side effects.
   Peg-IFNs may have superior quantitative effect. RoPeg most promising.

3. Significance of molecular remission still not clear. Marrow fibrosis and hypercellularity persist even with low JAK2 allele burden.

4. MPNs should probably be treated earlier rather than later (Silver, Hasselbalch, Gisslinger, Kiladjian and probably others).

5. JAK2 inhibitors in combination with interferon for symptomatic relief, increased rate of molecular remission? Effect on fibrosis?
Progress is impossible without change, and those who cannot change their minds cannot change anything.

- George Bernard Shaw