Latest updates in Myeloproliferative Neoplasms

Elizabeth Hexner, MD, MSTR
Disclosures

Nothing to disclose
Agenda/Goals

- Treatment goals in PV
- Indications for cytoreduction in patients polycythemia vera
- Interferon: its evolution in the treatment of MPN
- Management issues for myelofibrosis in 2016
- What is new for myelofibrosis in 2016
Case presentation

- 49 year old woman referred for an elevated hemoglobin and hematocrit.
- Longstanding intermittent migraines
  - Recently increased in frequency
  - new visual symptoms (scotomata)
- Work-up identified hypothyroidism
- Despite thyroid replacement, headaches persisted.
Case presentation

- Medications: Excedrin migraine as needed; synthroid

- Past medical and family history otherwise unremarkable; nonsmoker.

- Exam: BP 166/86; oxygen saturation 99%, scleral injection and symmetric facial plethora; spleen - not palpable.
Case presentation

- **CBC:**
  - Wbc: 9.6 (80% PMNs)
  - Hemoglobin: 20.4 g/dL
  - Hematocrit: 61%
  - Mcv: 75
  - Platelets: 563
  - Ferritin: 19
Case presentation

- You recommend:
  - Echocardiogram for evaluation of right to left shunt
  - aspirin, hydroxyurea and immediate phlebotomy
  - sleep study and oral iron replacement
  - aspirin and immediate phlebotomy
  - hydroxyurea and immediate phlebotomy
  - aspirin and hydroxyurea
  - aspirin and pegylated interferon
Case presentation

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  - Echocardiogram for evaluation of right to left shunt
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  - **aspirin and immediate phlebotomy**
  - hydroxyurea and immediate phlebotomy
  - aspirin and hydroxyurea
  - aspirin and pegylated interferon
Case presentation

- Noting marked and symptomatic erythrocytosis with trilineage hyperproliferation, you are strongly suspicious that this represents polycythemia vera and recommend daily aspirin, 81 mg and immediate phlebotomy. Your goal hematocrit is:
  - titrate to comfort
  - \(<50\%\)
  - \(<42\%\)
Case presentation

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  - <50%
  - <42%
### Polycythemia vera: Risk Stratification and Treatment

#### PV risk stratification for thrombosis

<table>
<thead>
<tr>
<th>Risk</th>
<th>Phlebotomy</th>
<th>Aspirin</th>
<th>Cytoreduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>High-risk</td>
<td>+</td>
<td>+</td>
<td>+**</td>
</tr>
<tr>
<td>Low-risk with extreme thrombocytosis</td>
<td>+</td>
<td>+*</td>
<td>-</td>
</tr>
</tbody>
</table>

*After excluding clinically significant aVWS

**Hydroxyurea (IFNα in women of child-bearing age)
Polycythemia vera: clotting risk increases with hematocrit level

**Summary**

The relations between the incidence of vascular occlusive episodes and packed-cell volume (P.C.V.) and platelet-count in patients with primary proliferative polycythemia were determined retrospectively in patients treated by venesection with or without chemotherapy. The incidence of occlusive episodes correlated positively with P.C.V. level. The risk of vascular occlusive episodes was increased at moderately increased P.C.V. levels and the optimum P.C.V. level was rather lower than is often assumed. There was no statistically significant association between platelet-count, either alone or in combination with raised P.C.V., and incidence of vascular occlusion, though, episodes of occlusion were 1.5 times more common with platelet-counts above $400 \times 10^9$/l. The results of this study indicate that P.C.V. should be maintained at less than 0.45 and the platelet-count at less than $400 \times 10^9$/l in primary proliferative polycythemia.

Relation of P.C.V. range to number of vascular occlusive episodes per 10 patient-years in patients with primary proliferative polycythemia.
Eligible Patients
WHO-2008 diagnosis All adults

Standard arm
HCT<45%

Experimental arm
HCT 45-50%

5- year FOLLOW-UP
### RESULTS

#### Table

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<th>Low-HCT</th>
<th>High-HCT</th>
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<tr>
<td>182</td>
<td>183</td>
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<td>168</td>
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<td>144</td>
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<td>18</td>
<td>12</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
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</tbody>
</table>

#### Graphs

**A**
- Low-HCT: 5/182 (2.8%)
- High-HCT: 18/183 (9.8%)
- Log-Rank Test P=0.004
- HR (95%CI): 3.90 (1.45-10.5)

**B**
- Low-HCT: 8/182 (4.4%)
- High-HCT: 20/183 (10.9%)
- Log-Rank Test P=0.01
- HR (95%CI): 2.69 (1.18-6.10)
Case presentation

- You order additional diagnostic tests. She returns 2 weeks later. She is grateful because her symptoms have all resolved. She is normotensive. You have results:
  - JAK2 V617F mutation (peripheral blood) positive
  - Erythropoietin level: <1 MIU/L
Case presentation

- Diagnostically you can tell her:
  - She has polycythemia vera
  - You are strongly suspicious she has polycythemia vera, but only a bone marrow biopsy can confirm the diagnosis
  - She has masked polycythemia vera
Case presentation

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  - You are strongly suspicious she has polycythemia vera, but only a bone marrow biopsy can confirm the diagnosis
  - She has masked polycythemia vera
Case presentation

- You tell her the diagnosis of PV is confirmed, and that she is optimally managed currently with low dose aspirin and periodic therapeutic phlebotomy to maintain a hematocrit less than 42-45%
Case presentation

- At a routine follow-up visit 8 months later, spleen is palpable 13 cm below the left costal margin. She has had unintentional weight loss.

- Two months later she complains of left sided abdominal pain and headaches are back despite aspirin and adequate hematocrit control. WBC is 17, platelets are 835.
Case presentation

- You discuss additional treatments. Which of the following do you tell her:
  - You recommend hydroxyurea, since it can induce complete molecular remissions in patients with PV.
  - Pegylated interferon is difficult to tolerate for most patients.
  - Comparative efficacy between pegylated interferon and hydroxyurea is not yet established, and is the subject of a multicenter international study.
Case presentation

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Case presentation

She opts against participation in a clinical trial. You recommend pegylated interferon (peginterferon alfa-2a), which she starts at 45 μg weekly for several weeks without untoward effects, then escalates to 90 μg weekly. Headaches resolve, spleen and blood counts revert to normal.
Interferon in the treatment of polycythemia vera

**RECOMBINANT INTERFERON-ALPHA FOR TREATMENT OF POLYCYthaEMIA VERA**

**HAEMATOLOGICAL FINDINGS IN THREE PATIENTS WITH POLYCYthaEMIA VERA BEFORE (A) AND DURING (B) PHLEBOTOMY AND 1 YEAR AFTER START OF TIFN-α (C)**

<table>
<thead>
<tr>
<th></th>
<th>Patient 1 (64, F)</th>
<th>Patient 2 (52, M)</th>
<th>Patient 3 (46, M)</th>
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<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>RBC</td>
<td>8.0</td>
<td>5.1</td>
<td>4.6</td>
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<tr>
<td>Hct</td>
<td>72</td>
<td>47</td>
<td>36</td>
</tr>
<tr>
<td>WBC</td>
<td>13.5</td>
<td>7.7</td>
<td>7.5</td>
</tr>
<tr>
<td>Plt</td>
<td>276</td>
<td>300</td>
<td>225</td>
</tr>
<tr>
<td>Spl</td>
<td>2.0</td>
<td>.</td>
<td>0.5</td>
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</table>

For A and B results are medians.
RBC = red blood-cells (10⁶/μl); Hct = haematocrit (%); WBC = white blood-cells (10⁶/μl);
Plt = platelets (1000s/μl); Spl = spleen size (cm below left costal margin).

Silver, RTLancet, 1988
Long acting IFN: what is the difference?

- **Pegylated IFN-α-2b\(^1\)**
  - Allowed for weekly administration
  - Active
  - Equivalent toxicity to IFN-α

- **Pegylated IFN-α-2a\(^2\)**
  - Allowed for weekly administration
  - Highly active
  - Well tolerated
  - Disease modifying

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Pegylated IFN-α-2a: highly active in early PV

Hematologic responses and treatment discontinuations.

Pegylated IFN-α-2a: highly active in early PV

Boxplots of %V617F over time.

Pegylated IFN-α-2a: highly active

Alfonso Quintás-Cardama et al. Blood 2013;122:893-901
Case presentation

After two years of treatment, quantitative JAK2 V617F transcript level is 0. She asks, “am I cured? Can I stop?” You answer:

- Yes
- Complete molecular response is an established surrogate for survival in PV
- Optimal duration of treatment with pegylated interferon is not established
Case presentation

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Response: Mutations matter

Serial mutational analysis of genes outside of JAK2 during therapy with PEG-IFN-α-2a in patients with PV and ET.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Days between serial samples</th>
<th>JAK2V617F allele-burden</th>
<th>TET2</th>
<th>DNMT3A</th>
<th>ASXL1</th>
<th>IDH1/2</th>
<th>EZH2</th>
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<tr>
<td></td>
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<td>Initial</td>
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<td>7</td>
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<td>8</td>
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<td>9</td>
<td>2,554</td>
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<tr>
<td>10</td>
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<td>11</td>
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<td>363</td>
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<td>55%</td>
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<td>18</td>
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<tr>
<td>23</td>
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</tbody>
</table>

<sup>1</sup> All CMR patients found to have sustained undetectable quantitative JAK2V617F allele burden coincident or following these values.

Alfonso Quintás-Cardama et al. Blood 2013;122:893-901
Case presentation

- After you discuss the uncertainty in the field regarding clinical utility of minimal residual disease monitoring and duration of treatment, you decide together to decrease the frequency of pegylated interferon to every 2 weeks and then every 3 weeks, and continue to monitor blood counts and JAK2 V617F PCR periodically.
“I heard that interferon can make my disease go away”
Hi Elizabeth,

I have a 63 yo woman who has Jak2 positive MF with B symptoms, and transfusion dependent anemia. Only required a couple of blood transfusions but anemia worse on Jakafi 15 bid despite improvement in B-symptoms. When was on 20 mg daily had return of symptoms and more spleen pain...
Subject: ? On MF pt

- Dosing: TWICE DAILY

- Anemia
  - Tends to plateau
  - Equivalent symptom benefit (COMFORT)
  - Anemia in treated patients doesn’t adversely affect outcomes
  - I’d keep her on 15 BID and transfuse PRN

- Any “anemia-sparing” drugs coming to studies here soon?

- Ever give Procrit and Jakafi simultaneously?
What’s new?
Investigational options

- Imetelstat (phase 2)
- Decitabine and ruxolitinib
- Prm-151
- Pacritinib
Thank You