What are myeloproliferative neoplasms?

1. Myeloproliferative disorders in which a clonal marker is not identified
2. A category of myeloid malignancies that consists of PV, ET, PMF and CML only
3. A category of myeloid malignancies that were previously known as “myeloproliferative disorders”
4. Myeloid malignancies that are associated with a JAK2 mutation

Presentation includes discussion of the following off-label use of a drug or medical device:
Hydroxyurea, interferon-alpha, imatinib mesylate, 2-CdA, busulfan, anagrelide, thalidomide, lenalidomide, prednisone, androgens, erythropoiesis stimulating agents, camphath
 Audience Response Question

Which one of the following statements about JAK2 mutations is inaccurate?

1. JAK2 exon 12 mutation is the most frequent in PV
2. JAK2 exon 14 mutation (i.e. JAK2V617F) induces PV-like disease in mice
3. JAK2V617F is found in PV, ET and PMF but not in secondary polycythemia or reactive thrombocytosis
4. JAK2V617F is not necessarily the initial disease-causing mutation in myeloproliferative neoplasms

Levine et al. Nat Rev Cancer. 2007;7:673


Wernig et al. Blood 2006;107:4274

JAK2V617F and JAK2 exon 12 mutation induce a PV-like phenotype in mice

MPLW515L induces a PMF-like phenotype in mice
What are the initial tests you would order when you suspect PV, in the modern era?

1. Peripheral blood JAK2V617F mutation analysis and serum erythropoietin level
2. Bone marrow JAK2V617F mutation analysis and serum erythropoietin level
3. Red cell mass measurement and JAK2V617F mutation analysis
4. Red cell mass measurement, JAK2V617F mutation analysis and serum erythropoietin level

Clinical manifestations of myeloproliferative neoplasms

- Splenomegaly from extramedullary hematopoiesis
- Bone marrow myeloproliferation
- Myelofibrosis
- Anemia
- Cachexia
- Leukocytosis
- Erythrocytosis
- Thrombocytosis
- Thrombocytopenia
- Angiogenesis
- Osteosclerosis

Audience Response Question?

32 y/o woman with ET; asymptomatic and no history of thrombosis; platelet count 1.6 million; ristocetin co-factor activity 50%; wants to be pregnant. How would you manage?

1. Interferon alfa only
2. Interferon alfa plus aspirin
3. Aspirin only
4. Hydroxyurea and aspirin
Microvascular symptoms in ET/PV include erythromelalgia, headache, and transient visual disturbances.

Aspirin 81 mg PO daily.

Non-life-threatening complications in PV and ET

- Pruritus
- Paroxetine 20 mg/daily
  - in case of no response, try IFN-α 3 million units SC TIW
- Recurrent miscarriages
- Aspirin therapy may reduce risk
- Constitutional symptoms
- Cytoreductive therapy in the presence of marked splenomegaly

Life-threatening complications in PV and ET

- Thrombosis risk
  - At diagnosis 22%
  - At follow-up 36%
- ET
  - Thrombosis risk
  - At diagnosis 23%
  - At follow-up 29%

Thrombosis
- Blastic transformation
- Fibrotic transformation

AML risk
- 10-yr
- MF risk
- 10-yr
- 20-yr

MF risk

ET PV
- <2%
- <8%
- <5%
- <10%
- <15%
- <5%
- <20%
- <10%
- <30%

Risk stratification for thrombosis in ET and PV

<table>
<thead>
<tr>
<th>Low-risk</th>
<th>High-risk</th>
<th>Low-risk with extreme thrombocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 60 years and No history of thrombosis and Platelet count &lt; 1 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 60 years or Previous thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count ≥ 1 million/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thrombosis risk is not significantly increased compared to controls

Thrombosis risk is significantly increased

Thrombosis risk might be lower

Hydroxyurea n=56

Controls n=58

P=0.0001

Randomized study in high-risk ET

Does cytoreduction reduce the risk of thrombosis or bleeding in low-risk ET associated with extreme thrombocytosis?

A retrospective study of 99 consecutive low-risk patients with platelet count of 1000 x 10^9/L

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=99)</th>
<th>Treated (n=75)</th>
<th>Not treated (n=24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major thrombosis</td>
<td>23 (21%)</td>
<td>18 (24%)</td>
<td>3 (13%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>7 (7%)</td>
<td>6 (8%)</td>
<td>1 (4%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>46 (46%)</td>
<td>33 (44%)</td>
<td>13 (54%)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Harrison et al. NEJM 2005;353:33... median 6s 39 months...

HUU was better in terms of arterial thrombosis, serious hemorrhage, fibrotic transformation and treatment tolerance.

Anagrelide was better in venous thrombosis.

No difference in leukemic transformation.


Harrison et al. NEJM 2005;353:33
**vWF Multimer Analysis**

ET or PV patients with platelet counts over 1 million might display acquired VWS

**Treatment Algorithm in ET**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Phlebotomy</th>
<th>Aspirin</th>
<th>Cytoreduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>High</td>
<td>Yes</td>
<td>Yes**</td>
<td></td>
</tr>
<tr>
<td>Low with extreme thrombocytosis</td>
<td>Yes*</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

*After ruling out clinically significant VWS (ristocetin co-factor activity < 30%)
**At present, my drug of choice is hydroxyurea except in case of childbearing women where I prefer IFN-alpha

---

**Treatment Algorithm in PV**

<table>
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<th>Cytoreduction</th>
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<td>No</td>
</tr>
<tr>
<td>High</td>
<td>Yes</td>
<td>Yes**</td>
<td></td>
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<td>No</td>
<td></td>
</tr>
</tbody>
</table>

*After ruling out clinically significant VWS (ristocetin co-factor activity < 30%)
**At present, my drug of choice is hydroxyurea except in case of childbearing women where I prefer IFN-alpha

---

**Efficacy and Safety of Low Dose Aspirin In PV**

Landolfi et al.


Non-fatal arterial and venous thrombotic events and cardiovascular deaths p=0.08

---

**Mayo Clinic series of 322 ET patients followed for a median of 13.6 years**

Survival

Median survival 18.8 years
Older age and leukocytosis predicted poor survival
Thrombosis history predicted recurrent thrombosis
Leukemia risk not influenced by hydroxyurea
JAK2V617F status was prognostically irrelevant

---

**Weeks**

Cumulative survival

Thrombosis risk (%)

1yr 2yr 3yr

Phlebotomy
HU
134 51 141 42 156 93

Breslow X² = 3.60 P=0.0515

Logrank X² = 3.39 P=0.0692

---

**Risk Phlebotomy Aspirin Cytoreduction**

Low Yes Yes No

High Yes Yes Yes**

Low with extreme thrombocytosis Yes Yes* No

High-risk: no history of thrombosis or age < 60 years or PLT. ct. < 1 million

High-risk: history of thrombosis or age ≥ 60 years

Low-risk with extreme thrombocytosis: Neither low nor high-risk
Modern Natural History of PV

396 patients followed for a median of 9.5 years


Survival is inferior to controls

15-year leukemia risk = 7%
15-year myelofibrosis risk = 6%
15-year thrombosis risk = 27%

Leukemia risk not influenced by hydroxyurea

So what is the role of IFN-α or JAK2 inhibitor treatment for ET or PV?

- Low-risk patients without leukocytosis or anemia have a near-normal life expectancy with indolent clinical course and very low risk of thrombosis. I do not recommend that such patients be considered for either IFN-α or JAK2 inhibitor clinical trials.

- High-risk patients are currently well managed with hydroxyurea and aspirin. A major phase III trial is needed to show new drug advantage over this inexpensive and relatively well tolerated drug.

  One has to first demonstrate long-term safety as well as potential for inducing molecular remission.

- High-risk patients who do not tolerate hydroxyurea or are refractory to it. OK to use IFN here but equally OK to use pipobroman (in Europe) or busulfan.

Management of Myelofibrosis

- Transplant options
  - Myeloablative
    - Reduced-intensity
- Non-transplant options
  - Treatment for anemia
    - Erythropoietin
    - Corticosteroids
    - Androgens + Prednisone
    - Danazol
    - Thalidomide + Prednisone
    - Lenalidomide
  - Treatment for splenomegaly
    - Hydroxyurea
    - Splenectomy
  - Treatment for extramedullary hematopoiesis
    - Low-dose irradiation
    - Supportive care

42 y/o man with PMF; asymptomatic; spleen is palpable 10 cm below the costal margin; counts are normal.

How would you manage?

1. Observe only
2. Take the spleen out
3. Consider experimental therapy with JAK2 inhibitor
4. Consider RIC transplant

Clinical course in PMF based on 311 consecutive patients from Mayo followed for a median of 27 months; range 0-282

71% required some form of treatment
41% have died
9% developed AML
20% 10-year risk


ASH 2007 Abstract # 683

Dose-Reduced Conditioning Followed by Allogeneic Stem Cell Transplantation in Patients with Myelofibrosis. Results from a Multicenter Prospective Trial of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT)

Nicolaus Kroeger et al.

Prospective multicenter trial; 104 pts; med. age 55 (32-68); unrelated 71
Busulfan (10 mg/kg orally or 8mg/kg i.v.), fludarabine (180 mg/m2) and ATG (30–60 mg/kg)
Low risk with constitutional symptoms (18%) or intermediate risk (n= 58%) and high risk (n=19%)
Everybody but one engrafted in approximately 20 days
Treatment mortality at 1 year 19%; 27% if exclude low-risk; GVHD 32%
Relapse at 3 years 29%; 3-year OS 70%; EFS 55%
**Prognosis in Primary Myelofibrosis**

N=319

![Graph showing survival rates for different risk groups.](image)

**Mayo**

- Low-risk (n=152): Median survival 194 months
- Intermediate-risk (n=98): Median survival 81 months
- High-risk (n=71): Median survival 29 months

**MF conventional treatment**

- Anemia
  - Lenalidomide 10 mg/day is 5q- present
  - Thalidomide 50 mg/day
  - Fluoxymesterone 10 mg po bid
  - Prednisone 0.5 mg/kg/day
- Symptomatic splenomegaly
  - Danazol 400 mg po bid
  - Erythropoietin 40,000 U SC weekly

**MF treatment algorithm**

![Diagram showing MF treatment algorithm.](image)

Is 5q- present?

- No

- Yes
  - Observation
  - Favorable
  - Unfavorable

- Lenalidomide

**Audience Response Question?**

So what is new in the treatment of PMF?

1. JAK2 inhibitors and nothing else
2. Imatinib mesylate
3. Hypomethylating agents
4. All of the above
5. None of the above

**Janus Kinases (JAK1, JAK2, JAK3, TYK2)**

- ATP Binding Pocket
- V617F Mutation

**Anti-JAK2 drug therapy**

- Activation of genes important in proliferation and survival

**Levine et al.**

Nat Rev Cancer. 2007;7:673

**Tefferi et al.**

Cancer 109:2083-8, 2007
Anti-JAK2 ATP mimetics

<table>
<thead>
<tr>
<th>Compound</th>
<th>Primary Target</th>
<th>JAK Family Selectivity Profile (X-fold selectivity)</th>
<th>JAK2 IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG101348</td>
<td>JAK2 vs. JAK3</td>
<td>33x</td>
<td>4.5x</td>
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<tr>
<td></td>
<td>JAK2 vs. JAK1</td>
<td>35x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>JAK2 vs. TYK2</td>
<td>135x</td>
<td></td>
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<tr>
<td>XL019</td>
<td>JAK2 vs. JAK1</td>
<td>125x</td>
<td>2nM</td>
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<tr>
<td>INCB18424</td>
<td>JAK2 vs. JAK3</td>
<td>72x</td>
<td>4.5x IC50</td>
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<td></td>
<td>JAK2 vs. JAK1</td>
<td>60x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>JAK2 vs. TYK2</td>
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</tr>
<tr>
<td>CEP-701</td>
<td>JAK2 vs. JAK3</td>
<td>3x</td>
<td>1nM</td>
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<tr>
<td></td>
<td>JAK2 vs. JAK1</td>
<td>7x</td>
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A phase III study of INCB018424, an oral, selective JAK inhibitor, in patients with primary myelofibrosis (PMF) and post-polycythemia vera/essential thrombocythemia myelofibrosis (Post-PV/ET MP)

Verstovsek et al.
Leukemia Department, M.D. Anderson Cancer Center, Houston, TX,
Mayo Clinic, Rochester, MN
Incyte Corporation, Wilmington, DE

ASCO 2008 Abstract No: 7004
Citation: J Clin Oncol 26: 2008 (May 20 suppl; abstr 7004)

INCB18424-251
BID Dosing
N=12
Expansion
N=5
Maintenance
N=27
Switch
N=7

INCB18424-251
Once Daily Dosing
N=5

Data presented on 39 patients on the 10 or 25 mg BID doses

Improvement in Constitutional Symptoms-1

Responder Analysis-Spleen or Liver Size

INCB018424 Treatment (25 mg BID): Other Aspects of Myelofibrosis

- Bone Marrow
  - No significant changes in fibrosis or cellularity
  - No significant change in blasts

- Peripheral Blood
  - No significant change in LDH
  - No significant change in CD34+ cells
  - No significant change in leukoerythroblastosis
Acquired stem cell mutation(s)

Clonal myeloproliferation

Stromal reaction and tissue injury

Immunologic response

Ineffective hematopoiesis

Extramedullary hematopoiesis

Cachexia

Aberrant cytokine production

Altered bone marrow microenvironment

JAK2 inhibition

JAK2 and/or JAK1 inhibition

Pomalidomide

Tefferi et al. Blood 2006;108:1158

Currently ongoing

Anemia-22%

Splenomegaly-33%

Thrombocytopenia-50%

Anemia-20%

Splenomegaly-8%

Thrombocytopenia-80%

Elliott et al. BJH 2002;117:288

Thalidomide

Lenalidomide

Tefferi & Pardanani

Current Hematology Reports, 2004, 2004

Thank you for attending Master Class for Oncologists
Questions & Answers

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