The Diagnosis and Management of Myeloproliferative Neoplasms

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Impediments to the Understanding of the Chronic Myeloproliferative Neoplasms

• They are uncommon
• They have diverse clinical manifestations
• They are chronic and evolve over time
• They clinically mimic each other as well as other myeloid neoplasms and nonclonal hematologic disorders
• There is no specific diagnostic test for each of them
• Their natural history is not completely defined

• Clinical perspectives about these disorders continue to be driven by unproved assumptions made >50 years ago
“Primum Non Nocere”  
(Above all, do no harm)

• Diagnosis must be accurate

• Therapy must be safe as well as effective

• The treatment should not be worse than the disease
“What’s in a Name?”
(Romeo and Juliet II, ii, 1-2)

The Initial WHO Classification
of the Chronic MPD

Chronic myelogenous leukemia, *BCR-ABL*-positive
Chronic Neutrophilic leukemia
Chronic eosinophilic leukemia (and HES)
Polycythemia vera
Chronic idiopathic myelofibrosis (with extramedullary hematopoiesis)
Essential thrombocytosis
Chronic myeloproliferative disease, unclassifiable

The Revised WHO Classification
of the Chronic MPD

**MYELOPROLIFERATIVE NEOPLASMS (MPN)**

Chronic myelogenous leukemia, *BCR-ABL1*-positive
Chronic Neutrophilic leukemia
Polycythemia vera
Primary myelofibrosis
Essential thrombocytosis
Chronic eosinophilic leukemia, not otherwise specified
Mastocytosis
Myeloproliferative neoplasms, unclassifiable

Blood 100: 2292, 2002
Blood 114:937, 2009
The Chronic Myeloproliferative Neoplasms

- The MPN are a clonal stem cell disorders, which share a common set of driver mutations
- The MPN exhibit clonal dominance to varying degrees
- Hematopoiesis can be increased or decreased
- There can be hematopoiesis outside the bone marrow resulting in enlargement of the spleen and liver
- The MPN can spontaneously transform to a marrow failure syndrome with myelofibrosis
- The MPN can spontaneously transform to acute leukemia
- There are no specific diagnostic markers for any MPN
Evolution of a Clonal Hematopoietic Tumor and Clonal Dominance

Normal Stem Cells

Normal and Neoplastic Stem Cells

TRANSFORMATION

Clonal Dominance
Evolution of an MPN

"Receptive" HSC

Acquisition of JAK2, MPL or CALR mutation with or without earlier acquisition of other mutations

"MPN" HSC

Mutation - AML

Spontaneous transformation or chemotherapy for the MPN

Mutation + AML

MYELOFIBROSIS
Splenomegaly

Indolent phenotype

Acquisition of additional mutations, LOH or UPD
Increasing clonal burden

Spontaneous transformation or chemotherapy for the MPN

Spontaneous transformation or chemotherapy
The Hematopoietic Stem Cell Hierarchy

TPOR (Mpl)
(CALR)

HSC

Long term
Self-renewing cells

Short term

TPOR (Mpl)
EPOR
G-CSFR
(CALR)

Committed,
Nonrenewing
cells

Platelets
RBC

Dendritic cells
Myelomonocytic cells

T cells
B cells

BBMT 14:849, 2008
Polycythemia vera is the ultimate consequence of the JAK2 V617F mutation.
**JAK2, CALR and MPL Mutations in the Chronic Myeloproliferative Neoplasms**

<table>
<thead>
<tr>
<th></th>
<th>PV (92)</th>
<th>PMF (19)</th>
<th>ET (84)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>JAK2 V617F</strong></td>
<td>92%</td>
<td>~60%</td>
<td>~59%</td>
</tr>
<tr>
<td><strong>JAK2 Exon12</strong></td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>CALR</strong></td>
<td>1%</td>
<td>~25%</td>
<td>~25%</td>
</tr>
<tr>
<td><strong>MPL</strong></td>
<td>&lt;1%</td>
<td>~6%</td>
<td>~4%</td>
</tr>
<tr>
<td><strong>LNK and Unknown</strong></td>
<td>1%</td>
<td>~8%</td>
<td>~12%</td>
</tr>
</tbody>
</table>
Phenotypic Mimicry and “Anticipation” in the Chronic Myeloproliferative Neoplasms

Polycythemia Vera

“Essential Thrombocytosis”

Primary Myelofibrosis

27%

15%

10%

20%
Primary Myelofibrosis of 17 Years Duration Evolving into Polycythemia Vera

Time (Months)

Phlebotomies

RCM/PV study

Hydroxyurea therapy
Essential Thrombocytosis Evolving to Polycythemia Vera
in a 60 year old Man

JAK2 V617F

Phlebotomies

RCM/PV study
Are the Chronic Myeloproliferative Neoplasms Three Separate Diseases?

- Polycythemia Vera
- Primary Myelofibrosis
- Essential Thrombocythemia

Are they different Manifestations of the Same Disease?

- Polycythemia Vera
- Primary Myelofibrosis
- Essential Thrombocythemia

Or both?
Association between Sex, Disease Duration, Genotype, Allele Burden and MPD Type

Haematologica 95:1090, 2010
Survival for ET, PV and PMF - USA Patients

Blood 124:2057, 2014
# Failure to Distinguish MPN Phenotypes

## Table 1. Clinical characteristics of the MPN patients at diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>PV</th>
<th>ET</th>
<th>PMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>94</td>
<td>69</td>
<td>34</td>
</tr>
<tr>
<td>% female</td>
<td>51</td>
<td>67</td>
<td>26</td>
</tr>
<tr>
<td>Average age at diagnosis (range), y</td>
<td>58 (18-87)</td>
<td>51 (21-86)</td>
<td>61 (21-86)</td>
</tr>
<tr>
<td>Average time of follow-up, mo</td>
<td>92</td>
<td>56</td>
<td>49</td>
</tr>
<tr>
<td>Hemoglobin (g/L) average (range)</td>
<td><strong>181 (148-225)</strong></td>
<td><strong>141 (78-225)</strong></td>
<td><strong>126 (90-161)</strong></td>
</tr>
<tr>
<td>Platelets (10^9/L) average (range)</td>
<td>554 (90-1487)</td>
<td>994 (452-1983)</td>
<td>635 (16-1677)</td>
</tr>
<tr>
<td>Leukocytes (10^9/L) average (range)</td>
<td>12 (4-39)</td>
<td>9 (5-17)</td>
<td>11 (5-27)</td>
</tr>
<tr>
<td>Neutrophils (10^9/L) average (range)</td>
<td>9 (2-36)</td>
<td>6 (3-16)</td>
<td>8 (3-21)</td>
</tr>
<tr>
<td>Transformation to secondary myelofibrosis</td>
<td>4 (4%)</td>
<td>1 (1%)</td>
<td>NA</td>
</tr>
<tr>
<td>Transformation to AML</td>
<td>3 (3%)</td>
<td>2 (3%)</td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>

NA, not applicable.

## Table 2. Demographic, hematologic, and clinical features at diagnosis of patients with ET, subdivided according to JAK2 or CALR mutation status, and of patients with PV

<table>
<thead>
<tr>
<th>ET</th>
<th>CALR mutated (A)</th>
<th>JAK2 mutated (B)</th>
<th>PV (C)</th>
<th>(A) vs (B)</th>
<th>(B) vs (C)</th>
<th>(A) vs (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>176</td>
<td>466</td>
<td>468</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>90/86 (51%/49%)</td>
<td>167/299 (36%/64%)</td>
<td>233/235 (50%/50%)</td>
<td>.001</td>
<td>&lt;.001</td>
<td>.791</td>
</tr>
<tr>
<td>Age at onset, years, median (range)</td>
<td>45 (15-83)</td>
<td>50 (15-92)</td>
<td>57 (13-86)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL, median (range)</td>
<td><strong>13.8 (11.3-17.6)</strong></td>
<td><strong>14.4 (10-17.7)</strong></td>
<td><strong>18.2 (15.0-24.0)</strong></td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>WBC count, ×10^9/L, median (range)</td>
<td>8.0 (4.0-17.9)</td>
<td>9.0 (4.0-28.0)</td>
<td>10.0 (3.4-55.3)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PLT count, ×10^9/L, median (range)</td>
<td>883 (500-3000)</td>
<td>700 (456-2148)</td>
<td>464 (109-1472)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum erythropoietin, mU/mL, median (range)</td>
<td>9.4 (1.2-27)</td>
<td>4.7 (0-47)</td>
<td>2.7 (0-66)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Splenomegaly, no. (%)</td>
<td>4 (2.3%)</td>
<td>30 (6.4%)</td>
<td>105 (22.4%)</td>
<td>.046</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lactate dehydrogenase, mU/mL, median (range)</td>
<td>199 (78-472)</td>
<td>200 (77-540)</td>
<td>217 (104-758)</td>
<td>.83</td>
<td>&lt;.001</td>
<td>.003</td>
</tr>
<tr>
<td>Circulating CD34+ cells, ×10^9/L, median (range)</td>
<td>4.1 (0.6-18)</td>
<td>4 (0-15.3)</td>
<td>3.4 (0-261.3)</td>
<td>.50</td>
<td>.037</td>
<td>.039</td>
</tr>
<tr>
<td>Thrombosis at diagnosis, no. (%)</td>
<td>5 (2.8%)</td>
<td>33 (7.1%)</td>
<td>49 (10.5%)</td>
<td>.059</td>
<td>.082</td>
<td>.001</td>
</tr>
</tbody>
</table>

Blood 123: 2220, 2014
Features “Unique” to Specific “Chronic Myeloproliferative Disorders”

- Polycythemia vera  
- Primary Myelofibrosis
- “Essential Thrombocytosis”

- Erythrocytosis
- Elevated circulating CD34+ cells (early in the disease only)
- None
Polycythemia Vera

• Polycythemia vera is a chronic myeloproliferative disorder in which there is unregulated production of \textit{morphologically normal} red cells, white cells and platelets.

• Polycythemia vera is the commonest of the chronic myeloproliferative disorders with an incidence of \(~2.5/100,000\).

• \textit{Erythrocytosis} is the feature that distinguishes polycythemia vera from \textit{all} other chronic myeloproliferative disorders.

• There is currently no \textit{specific} clonal diagnostic marker for polycythemia vera.
### Causes of Absolute Erythrocytosis

<table>
<thead>
<tr>
<th>Hypoxia</th>
<th>Renal Disease</th>
<th>Tumors</th>
<th>Drugs</th>
<th>Polycythemia vera</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon monoxide intoxication (tobacco abuse, environmental)</td>
<td>Renal artery stenosis</td>
<td>Hypernephroma</td>
<td>Androgenic steroids</td>
<td>JAK2 V617F</td>
</tr>
<tr>
<td>High affinity hemoglobins</td>
<td>Focal sclerosing or membranous glomerulonephritis</td>
<td>Hepatoma</td>
<td>Recombinant erythropoietin</td>
<td>JAK2 exon 12 mutations</td>
</tr>
<tr>
<td>High altitude</td>
<td>Renal transplantation</td>
<td>Cerebellar hemangioblastoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td></td>
<td>Uterine fibromyoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right to left shunts</td>
<td></td>
<td>Adrenal tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep apnea syndrome</td>
<td></td>
<td>Meningioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic disease</td>
<td></td>
<td>Pheochromocytoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Causes of Relative Erythrocytosis

<table>
<thead>
<tr>
<th>Loss of Fluid from the Vascular Space</th>
<th>Chronic Plasma Volume Contraction</th>
<th>Only ~5% of erythrocytosis patients are likely to have polycythemia vera</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emesis, diarrhea, diuretics, sweating, polyuria, hypodipsia, hypoalbuminemia, capillary leak syndromes, burns, peritonitis</td>
<td>Hypoxia from any cause</td>
<td>Androgen therapy</td>
</tr>
<tr>
<td>Androgen therapy</td>
<td>Recombinant erythropoietin therapy</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Recombinant erythropoietin therapy</td>
<td>Tobacco use Pheochromocytoma</td>
<td>Ethanol abuse</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Sleep apnea</td>
<td>Sleep apnea</td>
</tr>
</tbody>
</table>

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*Causes of Absolute Erythrocytosis* and *Causes of Relative Erythrocytosis* are detailed in the table above. The table lists various conditions and factors that can lead to absolute (Causes of Absolute Erythrocytosis) or relative (Causes of Relative Erythrocytosis) erythrocytosis, which is an increase in the number of red blood cells in the blood. The mention of *Polycythemia vera* and its associated genetic mutations (JAK2 V617F, JAK2 exon 12 mutations) indicates a genetic form of the condition, which is typically diagnosed when only around 5% of erythrocytosis patients are likely to have the disease.
Diagnostic Questions Facing the Physician About Erythrocytosis

- Does my patient with a high hematocrit of hemoglobin level have polycythemia vera?

- If the hematocrit (or hemoglobin level) is high, does my patient have a true erythrocytosis?

- If my patient has a true erythrocytosis is it due to polycythemia vera or a benign cause of erythrocytosis?

- Does my patient with thrombocytosis or myelofibrosis have essential thrombocytosis, primary myelofibrosis or polycythemia vera?
The PVSG Diagnostic Criteria for Polycythemia Vera

Elevated red cell mass
Normal arterial oxygen saturation
Splenomegaly

Plus any two below if no splenomegaly
Leukocytosis > 12,000/mm³
Thrombocytosis > 400,000/mm³
LAP > 100
Elevated $B_{12} > 900 \text{ pg/ml}$ or $uB^{12}BC > 2200 \text{ pg/ml}$

Table 2. The presenting blood counts and prevalence of palpable splenomegaly in 2 series of polycythemia vera patients at the time of diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Polycythemia Vera Study Group, %</th>
<th>Malmo, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytosis alone</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td><strong>Erythrocytosis and</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>13</td>
<td>29</td>
</tr>
<tr>
<td>Thrombocytosis</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>Leukocytosis and thrombocytosis</td>
<td>57</td>
<td>38</td>
</tr>
<tr>
<td>Splenomegaly (palpable)</td>
<td>70</td>
<td>58</td>
</tr>
<tr>
<td><strong>Splenomegaly and</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>ND</td>
<td>66</td>
</tr>
<tr>
<td>Thrombocytosis</td>
<td>ND</td>
<td>54</td>
</tr>
</tbody>
</table>

ND indicates not determined.
Table 2. Proposed revised WHO criteria for polycythemia vera

<table>
<thead>
<tr>
<th>Proposed criteria for PV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major criteria</strong></td>
</tr>
<tr>
<td>1. Hemoglobin &gt; 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume*</td>
</tr>
<tr>
<td>2. Presence of JAK2V617F or other functionally similar mutation such as JAK2 exon 12 mutation</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
</tr>
</tbody>
</table>

Diagnosis requires the presence of both major criteria and 1 minor criterion or the presence of the first major criterion together with 2 minor criteria.

*Hemoglobin or hematocrit greater than 99th percentile of method-specific reference range for age, sex, altitude of residence or hemoglobin greater than 17 g/dL in men, 15 g/dL in women, if associated with a documented and sustained increase of at least 2 g/dL from an individual’s baseline value that can not be attributed to correction of iron deficiency, or elevated red cell mass greater than 25% above mean normal predicted value.

Splenomegaly has been omitted as a diagnostic criterion as have the leukocyte and platelet counts.
Diagnostic Issues in Polycythemia Vera

- Serum erythropoietin
  - Not sensitive; low negative predictive value

- Cytogenetics
  - Abnormal in less than 25% of patients at diagnosis; not specific

- Clonal Assays
  - Applicable only in informative women; not sensitive

- Bone marrow morphology
  - Can be normal; not specific; not cost-effective

- Erythroid progenitor cell (EEC) assays
  - Not usually available, not standardized, not sensitive

- CT scanning for spleen size
  - Not standardized, not specific
**WHO Hemoglobin Guidelines for True Erythrocytosis are Unsatisfactory**

<table>
<thead>
<tr>
<th>WHO Hemoglobin Guidelines (O)</th>
<th>Erythrocytosis (Hct &gt; 55 %)</th>
<th>No Erythrocytosis (Hgb &lt; 55 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytosis</td>
<td>35 %</td>
<td>65 %</td>
</tr>
<tr>
<td>No Erythrocytosis</td>
<td>14 %</td>
<td>76 %</td>
</tr>
</tbody>
</table>

Br J Haematol 129:701, 2005
Effect of Plasma Volume and Red Cell Mass Changes on the Venous Hematocrit

Normal

“High”

High

High

2° ERT

PV
## Masked Erythrocytosis in a 18 year old Patient with Hepatic Vein Thrombosis and Splenomegaly

Hct 36 %; MCV 88; White cell Count 5,700/mL; Platelet Count 371,000/mL; Reticulocyte Count 1.4 %; JAK2 V617F-positive

<table>
<thead>
<tr>
<th></th>
<th>Calculated</th>
<th>Observed</th>
<th>Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Cell Mass</td>
<td>2058 mL</td>
<td>3210 mL</td>
<td>+1152 mL</td>
</tr>
<tr>
<td>Plasma Volume</td>
<td>3061 mL</td>
<td>5674 mL</td>
<td>+2613 mL</td>
</tr>
<tr>
<td>Total Blood Volume</td>
<td>5119 mL</td>
<td>8884 mL</td>
<td>+3765 mL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>40 %</td>
<td>36 %</td>
<td></td>
</tr>
</tbody>
</table>
18 year old Patient with Hepatic Vein Thrombosis and Splenomegaly

The marrow is very cellular (>90%). Megakaryocytes are conspicuous, increased in number with significant cytological atypia. Some forms are large with widely spaced nuclei or otherwise abnormal nuclear chromatin distribution. These cluster in areas. In the background marrow, trilineage hematopoiesis is present with an erythroid predominance. The M:E ratio is inverted. Streaming fibrosis is not prominent by the H&E alone, though marrow sinuses are wide, and a reticulin stain shows 1+ fibrosis. CD34 and CD117 immunostains do not show an increase in blasts. **There is no stainable iron.**

This is a difficult case. The megakaryocyte histology raises the possibility of a primary marrow disorder and is most suggestive of a myeloproliferative process such as cellular phase of primary chronic idiopathic marrow fibrosis. Other types of myeloproliferative processes are less likely given the peripheral blood counts.
The Variable Presentations of Polycythemia Vera

<table>
<thead>
<tr>
<th>Reasons To Perform Red Blood Cell Volume In Patients with Inapparent Polycythemia Vera</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal vein thrombosis*</td>
</tr>
<tr>
<td>Isolated splenomegaly</td>
</tr>
<tr>
<td>Splenomegaly</td>
</tr>
<tr>
<td>+ (platelets $&gt;500 \times 10^9/L$)</td>
</tr>
<tr>
<td>+ (leucocytes $&gt;12 \times 10^9/L$)</td>
</tr>
<tr>
<td>+ Both increased platelets/leucocytes</td>
</tr>
<tr>
<td>Platelets $&gt;500 \times 10^9/L$ without enlarged spleen†</td>
</tr>
<tr>
<td>Both increased platelets $&gt;500 \times 10^9/L$ and leucocytes $&gt;12 \times 10^9/L$ without enlarged spleen‡</td>
</tr>
</tbody>
</table>

* All of these 5 patients had splenomegaly.
† Normal serum iron.
‡ Karyotype normal.

Spleen size was determined in each case by clinical examination and ultrasound: In the 15 cases in which a splenomegaly was detected, the spleen size was $>15$ cm.
Essential Thrombocytosis

(aka essential thrombocythemia, hemorrhagic thrombocytosis, idiopathic thrombocytosis or primary thrombocytosis) is a disorder of unknown etiology, whose principal clinical feature is the overproduction of platelets in the absence of a definable cause, and for which there is no specific diagnostic marker.
Causes of Thrombocytosis

Tissue Inflammation
  Collagen vascular disease, inflammatory bowel disease
Malignancy
Infection
Myeloproliferative Disorders
  Polycythemia vera, primary myelofibrosis, essential thrombocythemia, chronic myelogenous leukemia
Myelodysplastic Disorders
  5q-syndrome, idiopathic refractory sideroblastic anemia
Postsplenectomy or hyposplenism
Hemorrhage
Iron deficiency anemia
Surgery
Rebound
  Correction of vitamin B12 or folate deficiency, post ethanol abuse
Hemolysis
Familial
  Thrombopoietin overproduction, constitutive Mpl activation, K39N
In this series of unselected consecutive patients with isolated thrombocytosis referred for RCM determination, we found that 46.5% of cases would have been misdiagnosed as ET instead of PV in the absence of RCM measurement, this proportion reaching 64.5% in the group of JAK2 V617F patients. Those results suggest that RCM should be performed in JAK2 V617F patients with isolated thrombocytosis, for proper MPD classification and management.
What Disease Does This Patient Have?

An asymptomatic 61 year old woman is referred for evaluation of thrombocytosis

2003  The platelet count  =  480,000/μl

2004  The platelet count  =  600,000/μl

2005  The platelet count  =  799,000/ μl
Hemoglobin = 14.9 gm %; White cell count =12,700/μl
MCV = 93 fl; Reticulocyte count = 1.9 %

Bone marrow: Cellular with increased megakaryocytes
and decreased but present stainable iron
(serum ferritin = 33 ng/ml)

Bcr-Abl FISH is negative

Jak2 V617F + (heterozygote)

Red cell mass:  38.5 ml/kg (20-30 ml/kg)
Plasma volume:  47.1 ml/kg  (30-45 ml/kg)

She has polycythemia vera
Primary Myelofibrosis

(also known as agnogenic myeloid metaplasia, idiopathic myelofibrosis, myelofibrosis and myeloid metaplasia, or primary osteomyelofibrosis) is a clonal stem cell disorder involving a pluripotent hematopoietic stem cell resulting in disordered blood cell production, marrow fibrosis and extramedullary hematopoiesis, most prominently involving the spleen, with eventual bone marrow failure or transformation to acute leukemia in some patients.
Causes of Myelofibrosis

**Malignant**
- Acute leukemia (lymphocytic, myelogenous, megakaryocytic)
- Chronic myelogenous leukemia
- Hairy cell leukemia
- Hodgkin’s disease

**Primary Myelofibrosis**
- Lymphoma
- Multiple myeloma
- Myelodysplasia
- Metastatic carcinoma
- Polycythemia vera
- Systemic mastocytosis

**Non Malignant**
- HIV infection
- Hyperparathyroidism
- Renal osteodystrophy
- Systemic lupus erythematosus
- Tuberculosis
- Vitamin D deficiency
- Thorium dioxide exposure
- Gray platelet syndrome
- Thrombopoietin receptor agonists
Criteria for the Diagnosis of Primary Myelofibrosis

Table 7. Proposed revised WHO criteria for primary myelofibrosis

<table>
<thead>
<tr>
<th>Proposed criteria for PMF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major criteria</strong></td>
</tr>
<tr>
<td>1. Presence of megakaryocyte proliferation and atypia,* usually accompanied by either reticulin and/or collagen fibrosis, or, in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic cellular-phase disease)</td>
</tr>
<tr>
<td>2. Not meeting WHO criteria for PV,† CML,‡ MDS,§ or other myeloid neoplasm</td>
</tr>
<tr>
<td>3. Demonstration of JAK2617V&gt;F or other clonal marker (eg, MPL515W&gt;L/K), or in the absence of a clonal marker, no evidence of bone marrow fibrosis due to underlying inflammatory or other neoplastic diseases]</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
</tr>
<tr>
<td>1. Leukoerythroblastosis][</td>
</tr>
<tr>
<td>2. Increase in serum lactate dehydrogenase level][</td>
</tr>
<tr>
<td>3. Anemia][</td>
</tr>
<tr>
<td>4. Palpable splenomegaly][</td>
</tr>
</tbody>
</table>

Diagnosis requires meeting all 3 major criteria and 2 minor criteria.

* Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering.
† Requires the failure of iron replacement therapy to increase hemoglobin level to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels. **Red cell mass measurement is not required.**
‡ Requires the absence of BCR-ABL.
§ Requires the absence of dyserythropoiesis and dysgranulopoiesis.
¶ Secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies. It should be noted that patients with conditions associated with reactive myelofibrosis are not immune to primary myelofibrosis and the diagnosis should be considered in such cases if other criteria are met.
∥ Degree of abnormality could be borderline or marked.

Blood 112: 231, 2008

Blood 110:1092, 2007
A Myeloproliferative Masquerade

48 year old woman referred for evaluation of splenomegaly:

1985: Hgb = 13 gm %;
WBC = 6300/mm$^3$
Platelets = 400,000/mm$^3$

Spleen palpable (3 cm); Bone marrow biopsy = myelofibrosis

**Diagnosis:** Primary Myelofibrosis or Essential Thrombocytosis

1993: Hgb = 13 gm %;
WBC = 18,000/mm$^3$
Platelets = 840,000/mm$^3$

Asymptomatic but with massive splenomegaly

<table>
<thead>
<tr>
<th>Patient</th>
<th>Patient</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCM</td>
<td>52 ml/kg</td>
<td>20-30 ml/kg</td>
</tr>
<tr>
<td>PV</td>
<td>71 ml/kg</td>
<td>30-45 ml/kg</td>
</tr>
</tbody>
</table>

**Diagnosis:** Polycythemia vera
“There is a tendency in medical practice – by no means limited to hematologists – to treat almost any condition as vigorously as possible. In hematology, this consists in attempting to change an abnormal number – whether this number is ..........the hematocrit, white cell count or platelet count to get normal values, whether the patient needs it or not!”

William Dameshek, 1968
# The Consequences of Polycythemia Vera

<table>
<thead>
<tr>
<th>Consequence</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis, hemorrhage, hypertension</td>
<td>Elevated red cell mass, decreased vWF multimers</td>
</tr>
<tr>
<td>Organomegaly, pulmonary hypertension</td>
<td>Extramedullary hematopoiesis or elevated red cell mass</td>
</tr>
<tr>
<td>Pruritus, acid-peptic disease</td>
<td>Inflammatory mediators</td>
</tr>
<tr>
<td>Erythromelalgia</td>
<td>Thrombocytosis</td>
</tr>
<tr>
<td>Hyperuricemia, gout, renal stones</td>
<td>Increased cell turnover</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>Reaction to the neoplastic clone</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>Therapy-induced or clonal evolution (&quot;Richter’s syndrome&quot;)</td>
</tr>
</tbody>
</table>
Polycythemia Vera: Proliferative Behavior

Indolent

Aggressive
Incidence of the Major Complications of Polycythemia Vera in Phlebotomized Patients

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis</td>
<td>30%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>16%</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>83%</td>
</tr>
<tr>
<td>Pruritis</td>
<td>32%</td>
</tr>
<tr>
<td><strong>Myelofibrosis</strong></td>
<td><strong>12%</strong></td>
</tr>
<tr>
<td>Acute Leukemia</td>
<td>1.5%</td>
</tr>
</tbody>
</table>
Recommendations for Therapy in Polycythemia Vera

<table>
<thead>
<tr>
<th>Risk categories</th>
<th>Polycythemia vera</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk without extreme thrombocytosis (age &lt;60 years and no thrombosis history)</td>
<td>Low-dose aspirin + phlebotomy</td>
</tr>
<tr>
<td>Low-risk with extreme thrombocytosis (platelets &gt;1,000 $\times 10^9$/L)</td>
<td>Low-dose aspirin provided tislocitin cofactor activity &gt;30% + phlebotomy</td>
</tr>
<tr>
<td>High-risk (age ≥60 years and/or presence of thrombosis history)</td>
<td>Low-dose aspirin + phlebotomy + hydroxyurea</td>
</tr>
<tr>
<td>High-risk disease that is refractory or intolerant to hydroxyureas</td>
<td>Low-dose aspirin + phlebotomy + interferon-α (age &lt;65 years) or busulfan (age ≥65 years)</td>
</tr>
</tbody>
</table>

Figure 2. Complications by age group. Complications by age at diagnosis were statistically similar in prevalence between those diagnosed with polycythemia vera age ≤45 or age ≥65.
The Complications of Polycythemia Vera and their Management

- Erythrocytosis
- Pruritus
- Erythromelalgia; ocular migraine
- Thrombosis (arterial; venous)
- Thrombocytosis
- Hemorrhage
- Leukocytosis
- Hyperuricemia
- Splenomegaly

- Phlebotomy to a gender-correct level
- Antihistamines; ruxolitinib; pegylated interferon; PUVA; hydroxyurea
- Aspirin; anagrelide; pegylated interferon; ruxolitinib, hydroxyurea
- Aspirin; coumadin; hydroxyurea (TIA only)
- anagrelide; pegylated interferon; hydroxyurea
- EACA (Amicar)
- Ruxolitinib; pegylated interferon; hydroxyurea
- Allopurinol (uric acid ~10 mg %)
- Ruxolitinib; pegylated interferon; hydroxyurea; thalidomide; Gleevec; splenectomy;
Effect of Phlebotomy to a Hematocrit < 45 % on Cardiovascular Events in PV

NEJM 368:22, 2013
What to do if PV is suspected but you can’t do a red cell mass and plasma volume study

Relationship between the PCV (Hematocrit) and Thrombosis in Polycythemia Vera

[Graph showing the relationship between PCV and vascular occlusive episodes per patient-10 years across different PCV ranges for men and women.

(PVSG)]

Lancet 2:1219, 1978
Cancer-free survival was better with no chemotherapy for 1213 patients with polycythemia vera.

Kaplan-Meier survival analysis for death or major thrombosis, was better for no chemotherapy, for 1213 patients with polycythemia vera.
Hydroxyurea or Pi Therapy is Associated with A High Risk Of Leukemia in Polycythemia Vera, Often with a Late Onset
PEGYLATED INTERFERON-ALFA-2a INDUCES COMPLETE HEMATOLOGICAL AND MOLECULAR RESPONSES WITH LOW TOXICITY IN POLYCYTHEMIA VERA

Blood e-Pub, 2008
Ruxolitinib is Effective in the Treatment of Polycythemia Vera

Cancer 120:513, 2014
Complications of Essential Thrombocythaemia

• Microvascular ischemia
  (migraine, erythromelalgia, transient ischemic attacks)

• Thrombosis
  (stroke acute coronary syndrome, peripheral arterial occlusion, digital gangrene, deep venous thrombosis)

• Hemorrhage due to acquired von Willebrand disease

• Transformation to acute leukemia
Diagnosis of ET

History of presentation with thrombosis or major hemorrhagic complication or age > 60 years

Cytoreductive treatment:
- Hydroxyurea (HU) as first choice;
- Interferon in special situations (pregnancy);
- Anagrelide as second-line therapy in patients intolerant or refractory to HU
- Low-dose aspirin if major thrombosis or microvascular symptoms

No symptoms and platelet count < 1,500,000/ml and age < 60 years

No cytoreduction
- Re-consider if complications
- Low-dose aspirin if microvascular symptoms

Figure 2: Flowchart of therapeutic recommendations in essential thrombocythemia.
Hydroxyurea was Not More Protective Against Major Arterial Thrombosis than Anagrelide and was Less for Deep Venous Thrombosis in ET

<table>
<thead>
<tr>
<th></th>
<th>HU</th>
<th>Anagrelide</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial thrombosis</td>
<td>17</td>
<td>37</td>
<td>2.16 (1.27–3.69)</td>
<td>0.004</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7</td>
<td>13</td>
<td>1.84 (0.76–4.41)</td>
<td>NS</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>2</td>
<td>4</td>
<td>1.94 (0.39–9.63)</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke</td>
<td>7</td>
<td>9</td>
<td>1.30 (0.49–3.47)</td>
<td>NS</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1</td>
<td>14</td>
<td>5.72 (2.08–15.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other†</td>
<td>2</td>
<td>0</td>
<td></td>
<td>NE</td>
</tr>
</tbody>
</table>

| Venous thromboembolism   | 14       | 3          | 0.27 (0.11–0.71)             | 0.006   |
| Deep-vein thrombosis     | 9        | 1          | 0.20 (0.06–0.71)             | 0.009   |
| Pulmonary embolism       | 5        | 2          | 0.43 (0.01–1.87)             | NS      |
| Hepatic-vein thrombosis  | 1        | 0          |                              | NE      |

Hydroxyurea was Not More Protective Against Major Arterial Thrombosis than ASA

<table>
<thead>
<tr>
<th></th>
<th>HU</th>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient ischemic attacks</td>
<td>2 (100)</td>
<td>11 (79)</td>
</tr>
<tr>
<td>Digital microvascular ischemia</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

NEJM 353:39, 2005

NEJM 332:1132, 1995
Anagrelide vs Hydroxyurea in ET

Platelet Count

Hemoglobin

Leukocyte Count
Event-free Survival

Blood 121:1720, 2013
Effect of the CALR Mutation on Thrombosis and Overall Survival in ET

Blood 123: 1552, 2014
Age, gender, cardiovascular risk factors, except for smoking, hemoglobin, leukocytosis, thrombocytosis or JAK2 V617F expression at study entry was associated with arterial or venous thrombosis but there was more venous thrombosis in JAK2 V617F patients not on antiplatelet therapy.

Blood 116:1205, 2010
Transformation of ET to “High Risk” Does Not Impact on Overall Survival

Event-free Survival

Overall Survival

Blood 116:1205, 2010
Correlation Between Platelet Count and vWF Activity in Essential Thrombocythaemia
Management of Thrombocytosis in Essential Thrombocytosis

• Asymptomatic thrombocytosis requires no therapy in the absence of a thrombotic or significant hemorrhagic diathesis
• Platelet counts ≥ 1 x 10^6/µl can be associated with reduced vWF high MW multimers and ristocetin cofactor activity
• Hemorrhage associated with thrombocytosis can be controlled with EACA (Amicar)
• Aspirin is the treatment of choice for erythromelalgia unless ristocetin cofactor activity is reduced (<50 %)
• For platelet count reduction, particularly in patients under age 60, anagrelide or interferon, if tolerated, are preferable to hydroxyurea unless they are contraindicated due to cardiovascular risk factors or unresponsive TIAs are the problem
• It is not necessary to lower the platelet count to normal
Adverse Prognostic Factors

- Anemia (Hgb < 10 gm %)
- Leukocytosis (> 30,000/µL)
- Thrombocytopenia (< 100,000/µL)

Survival with Postpolycythemic Myelofibrosis

The “New” Chicken Little

Reticulin Grade

- SEVERE RISK OF SKY FALLING
- HIGH RISK OF SKY FALLING
- SIGNIFICANT RISK OF SKY FALLING
- GENERAL RISK OF SKY FALLING
- LOW RISK OF SKY FALLING

I

II

III

IV
**Adverse Prognostic Factors**
- Anemia (Hgb <10 gm %)
- Leukocytosis (>30,000/µL)
- Thrombocytopenia (< 100,000/µL)

Blood 2008;111:3383
Complications of Primary Myelofibrosis

• Anemia
  hypoproliferative due to folate or iron deficiency, inflammation, autoimmune hemolysis, hemodilution or impaired stem cell function
• Thrombocytopenia
  Splenic sequestration, impaired stem cell function
• Incapacitating splenomegaly and splenic infarction
• Portal hypertension
• Pulmonary hypertension
• Organ compromise due to extramedullary hematopoiesis

Obstructive uropathy
  Intestinal obstruction
  Ascites, pleural effusions
  Hepatic failure
  Fibrous tumors
  Spinal or cranial compression
  Bone pain due to periostosis or increased vascularity
• Bone marrow failure with pancytopenia
• Acute leukemia
# Prognostic Scoring Systems for PMF

<table>
<thead>
<tr>
<th></th>
<th>Lille (Dupriez 1996)</th>
<th>IPSS (Cervantes 2009)</th>
<th>DIPSS (Passamonti 2010)</th>
<th>DIPSS Plus (Gangat 2011)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Blasts in PB≥1%</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Constitutional Symptoms</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Age &gt;65</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Unfavorable Karyotype</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>PLT&lt;100</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>RBC transfusion Dep</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>
Survival in Primary Myelofibrosis

Four PMF Scoring Systems

Cervantes

Lille

IPSS

DIPSS

Figure 2. Actuarial survival curves of the 4 risk groups of patients according to the new PMF prognostic system.

Figure 3. Kaplan-Meier estimate of survival in primary myelofibrosis according to the DIPSS. Risk categories were according to the score obtained anytime during follow-up. Low risk: score 0; intermediate-1 risk: score 1-2; intermediate-2 risk: score 3-4, and high risk: score 5-6.
Effect of the Number of Deleterious Mutations (EZH2, ASXL1, SRSF2,1DH1/2) on Leukemic Transformation in PMF
Cumulative Incidence of Anemia, Leukocytosis and Thrombocytopenia in PMF by Driver Mutation

Anemia

Thrombocytopenia

Leukocytosis

Blood 124:1062, 2014
Survival in PMF by Driver Mutation

Blood 124:1062, 2014
Survival in PMF According to CALR type 1 and 2 mutations and JAK2 V617F

JAK2/V617F vs type 1/type 1-like, p<0.0001; HR 2.7, 95% CI 1.9-3.7
JAK2/V617F vs type 2/type 2-like, p=0.84; HR 1.1, 95% CI 0.6-1.8
Type 2/type 2-like vs type 1/type 1-like, p=0.003; HR 2.5, 95% CI 1.4-4.5

Blood 124; 2465, 2014
## Factors Affecting the Response to Erythropoietin in PMF

### Table 3. Pretreatment median laboratory values and statistical significance

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment levels</th>
<th>Responders</th>
<th>Non-responders</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median</td>
<td>range</td>
<td>median values</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>70</td>
<td>45–81</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Gender, F/M</td>
<td>9/12</td>
<td></td>
<td>7/5</td>
<td></td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>9</td>
<td>6.7–10.2</td>
<td>9.2</td>
<td></td>
</tr>
<tr>
<td>WBC, × 10⁹/l</td>
<td>4.05</td>
<td>1.2–23.4</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>PLT, × 10⁹/l</td>
<td>107</td>
<td>28–485</td>
<td>142</td>
<td></td>
</tr>
<tr>
<td>β₂-M, μg/l</td>
<td>2,905</td>
<td>1,257–6,370</td>
<td>2,270</td>
<td></td>
</tr>
<tr>
<td>EPO, U/l</td>
<td>123</td>
<td>37–623</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Spleen size, cm</td>
<td>7</td>
<td>2–18</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Transfusions, units/month</td>
<td>1</td>
<td>1–3</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Effect of Low Dose Thalidomide and Prednisone on Anemia and Thrombocytopenia in Myelofibrosis

Figure 1. Effects of THAL-PRED on erythrocyte transfusion requirements. The effects of THAL-PRED on the erythrocyte transfusion requirements are shown for the 10 patients with transfusion-dependent MMM at study onset.

Figure 2. Effects of THAL-PRED on platelet counts. The effects of THAL-PRED on the untransfused platelet counts are shown for the 8 patients with MMM who were thrombocytopenic (baseline platelet count < 100 × 10^9/L) at study onset.

Blood 101:2534, 20003
Results of Nonmyeloablative Marrow Transplantation in PMF

Figure 1. Time to engraftment after RIC transplantation in MMM. Time to recovery of absolute neutrophil counts (ANC > 0.5) (A) and platelets (PLT > 20 K) (B) in 21 patients with MMM following a RIC allogeneic HSC transplantation.

Figure 2. Survival and event-free survival after RIC transplantation in MMM. Estimates of overall survival (OS) (A) and event-free survival (EFS) (B) for patients with myelofibrosis following a RIC allogeneic HSC transplantation.
Survival after BMT for PMF is Influenced by Clinical Risk Score

Blood 125:3347, 2015
Preclinical Summary of Ruxolitinib

- A potent and selective ATP competitive JAK inhibitor

<table>
<thead>
<tr>
<th>Ruxolitinib</th>
<th>JAK1</th>
<th>JAK2</th>
<th>JAK3</th>
<th>Tyk2</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC$_{50}$ (nM)</td>
<td>2.7</td>
<td>4.5</td>
<td>322</td>
<td>19</td>
</tr>
</tbody>
</table>

- 100-fold selectivity against a broad panel of kinases
- Excellent preclinical pharmacokinetic properties
- High oral availability
- Efficacious and well-tolerated in a JAK2$^{V617F}$-driven animal model

Preclinical toxicology:
- Findings restricted to myelosuppression and reduced lymphoid organ cellularity at high doses
Clinical Pharmacology

- Half-life consistent with once or twice daily dosing
- Linear pharmacokinetics over the dose range studied
- No accumulation upon repeated dosing
- Clearance is predominantly via hepatic metabolism
- Ruxolitinib is a substrate for CYP3A4
- No evidence of induction or inhibition of CYP enzymes
  - The probability of drug interactions is low

Ruxolitinib normalizes pSTAT3 levels within 1 month

![Phospho-STAT3 Levels](chart.png)

- 25 mg cohort (n=6)
- Basal
- IL-6

Day 1 | Day 15 | Day 29 | Healthy Donor
Table 2. Adverse Events Observed in 10% or More of Patients Who Received Ruxolitinib.

<table>
<thead>
<tr>
<th>Event</th>
<th>Ruxolitinib (N = 155)</th>
<th>Placebo (N = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>25.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>18.7</td>
<td>0</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>18.7</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>14.8</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>14.8</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>12.9</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>12.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11.6</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11.0</td>
<td>0.6</td>
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<td>Abdominal pain</td>
<td>10.3</td>
<td>2.6</td>
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<tr>
<td>Hematologic abnormalities*</td>
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<td></td>
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<tr>
<td>Anemia</td>
<td>96.1</td>
<td>45.2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>69.7</td>
<td>12.9</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18.7</td>
<td>7.1</td>
</tr>
</tbody>
</table>
Effects of Nonselective JAK2 Inhibitors in PMF
• Majority of ruxolitinib-treated patients maintained a spleen volume reduction

• Majority of crossover patients experienced spleen volume reduction relative to original baseline (median follow-up on ruxolitinib: ~14 months)
  – Lesser degree of reduction likely because these patients experienced a period of spleen growth on placebo before starting ruxolitinib
Effects of Nonselective JAK2 Inhibitors in PMF

Proportion of Patients with ≥50% Improvement in MFSAF Score (%)

- Night Sweats (N=24)
- Itching (N=22)
- Abdominal Pain or Discomfort (N=33)
- Bone or Muscle Pain (N=30)

Change in Weight from Baseline (kg)

- Lowest BMI quartile, 16.2–22.5 (N=25)
- Highest BMI quartile, 27.9–49.7 (N=26)

Change from Baseline (points)

- C-Reactive Protein
- Interleukin-1ra
- MIP-1β
- TNF-α
- Interleukin-6

NEJM 363:110: 1117, 2010
Hemoglobin Levels Over Time By Ruxolitinib Titrated Dose

- Patients titrated to 10 mg BID after nadir hemoglobin showed faster and more complete return of hemoglobin to pretreatment levels

Titrated dose is defined as the average dose patients received between Weeks 8 and 56. Hemoglobin levels within 60 days of transfusion are not included.
• 90/155 (58%) had a 35% reduction at any time point during the study
• 64% maintained a ≥35% reduction for at least 2 years

≥35% reduction: Time from first 35% reduction to <35% reduction and 25% increase from nadir.
≥10% reduction: Time from first 35% reduction to <10% reduction from baseline.
Overall Survival: ITT Population

HR=0.58 (95% CI: 0.36, 0.95); \( P=0.028 \)

No. of deaths: Ruxolitinib=27; Placebo=41

Median follow up: 102 weeks

Age adjusted HR\(^*\)=0.61 (95% CI: 0.37, 0.99); \( P=0.040 \)

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No. at risk

Ruxolitinib 155 154 148 145 136 125 121 113 96 44 6
Placebo 154 148 142 133 117 111 102 95 74 32 7

Note: For this unplanned analysis, \( P \)-values are descriptive and nominally significant.

\(^*\)Age was the only baseline characteristic that differed significantly between treatment groups as reported in Verstovsek S, et al. \textit{N Engl J Med} 2012;366:799-807 (median age: ruxolitinib, 66 years; placebo, 70 years; \( P<0.05 \)).
Reversal of Thrombocytopenia in a PPVPMF Patient on Ruxolitinib 15 mg BID
Management of Primary Myelofibrosis

- Accurate diagnosis is essential (exclude polycythemia vera)
- Staging should include cytogenetic analysis and mutational analysis
- Low risk patients require no therapy unless under age 45, when marrow transplantation should be considered if a matched sibling donor is available
- High risk patients require up to age 75, may benefit from reduced intensity conditioning marrow transplantation
- Symptomatic anemia may respond to corticosteroids, recombinant erythropoietin, folate, danazol or low dose thalidomide
- Splenomegaly may respond to ruxolitinib, low dose thalidomide or hydroxyurea
- Pegylated interferon can reduce myelofibrosis
- Splenic irradiation is only palliative and temporary and associated with severe neutropenia and infection
- Splenectomy is only palliative and should be avoided if possible
Summary

• The chronic MPN, PV, ET and PMF, are distinct disease entities that share in common many clinical features (phenotypic mimicry)
• Since the MPN differ with respect to their natural history and survival, diagnosis must be accurate to ensure that therapy is appropriate
• Polycythemia vera is the most common of the three MPN because it is the ultimate expression of the JAK2 V617F mutation
• The WHO diagnostic guidelines are unacceptable for distinguishing between the three MPN
• All chemotherapeutic agents are leukemogenic in the MPN and should be avoided if at all possible
• JAK2 inhibitors will useful for supportive care but will not eradicate these disorders
• Pegylated interferon or reduced intensity conditioning BMT offer the possibility of complete molecular remission
• Treatment of these three disorders should be tailored to fit their clinical manifestations
• Ruxolitinib is the drug of choice in PMF as supportive therapy