MYELOPROLIFERATIVE NEOPLASM

Classification, Pathogenesis, Diagnosis, and Treatment

Review presented by
Jamal Maatouk
Oncology PGY5

Objectives

- Definition, and history.
- Molecular pathogenesis and updated WHO classification of BCR-ABL-negative MPN.
- Describe in detail the criteria for diagnosis, risk stratification, and management of patients with the classic MPN including PV, ET, and PMF.
- Detail MPL mutant allele and JAK2 V617F, which result in a gain of function mutation due to the constitutive activation of tyrosine kinase dependent cellular signaling pathways, particularly of the JAK-STAT pathway.
- Diagnostic algorithms.

WHAT IS MPN?

- Neoplastic clonal proliferation in pluripotent hematopoietic stem cell.
- Leading to over-production of all cell lines, with usually one line in particular.
- Marrow Fibrosis is a secondary event.
- All MPN share a common variable degrees of BM hypercellularity, Atypical megakaryocytic hyperplasia and clustering, Splenomegaly, Leukocytosis, Thrombocytosis, Clonal cytogenetic abnormalities.

No secondary causes like infections, toxins, autoimmune, non-hematologic malignancy.

- Concept of myeloproliferative disease was first proposed in 1951 by the hematologist William Dameshek.
- The recent WHO classification of Hematologic malignancies, "myeloproliferative diseases" was renamed and given the name of "myeloproliferative neoplasms", reflecting the underlying clonal genetic changes.

Main 4 types of MPN
1. PRV, PV: Erythroid hyperplasia
2. CML: Granulocyte hyperplasia
3. ET: Megakaryocytic hyperplasia
4. MF, MMM, PMF
WHO 2008 revised scheme of the classification of myeloproliferative neoplasms.

**Philadelphia Chromosome positive**
- Chronic myelogenous leukemia (CML)

**Philadelphia Chromosome negative**
- Polycytemia vera (PV)
- Essential thrombocytosis (ET)
- Primary myelofibrosis (PMF)
- Eosinophilic disorders
- Mast cell disorders

Clonal Origination and Evolution in chronic myeloid disorders

2008 WHO classification of chronic myeloid neoplasms

- Myeloproliferative Neoplasms
  - Chronic myelogenous leukemia (CML)
  - Polycythemia vera (PV)
  - Essential thrombocytosis (ET)
  - Primary myelofibrosis (PMF)
  - Eosinophilic disorders
  - Mast cell disorders
Recurrent Molecular Abnormalities Associated with Myeloproliferative Neoplasms

<table>
<thead>
<tr>
<th>Genetic Abnormality</th>
<th>Disease</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>BCR-ABL</td>
<td>Chronic myelogenous leukemia</td>
<td>99%</td>
</tr>
<tr>
<td>JAK2/ABL</td>
<td>Polycythemia vera</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>JAK2/V617F</td>
<td>Essential thrombocythemia</td>
<td>60%</td>
</tr>
<tr>
<td>JAK2/exon 12</td>
<td>Primary myelofibrosis</td>
<td>60%</td>
</tr>
<tr>
<td>JAK2/ABL</td>
<td>MPN, unclassifiable</td>
<td>20%</td>
</tr>
<tr>
<td>JAK2/V617F</td>
<td>Refractory anemia with sideroblasts and thrombocytosis (RARS-T)</td>
<td>50%</td>
</tr>
<tr>
<td>MPL/W515L/K*</td>
<td>Primary myelofibrosis</td>
<td>8%</td>
</tr>
<tr>
<td>MPL/W515L/K*</td>
<td>Essential thrombocythemia</td>
<td>8%</td>
</tr>
</tbody>
</table>

MPN indicates myeloproliferative neoplasm.

Other infrequent mutations, such as W515A or S505N, have been reported.

Calculated on JAK2 V617F-negative patients.

Rationale for using JAK2V617F genotyping in the diagnostic work-up of suspected MPN

Clinical suspicion of an MPN

- JAK2V617F genotyping:
  - Positive
  - Negative

Use additional WHO criteria to distinguish among different categories of MPN.

JAK 2

- In 2005, JAK2 V617F mutation was described.
- 4 studies in a period of 8 weeks describing a unique gain of function mutation in JAK2 in PV, ET, PMF.
- Three confirmed the less frequent occurrence of the same mutation in both atypical MPN and MDS.
- Provided evidence for a common pathogenesis for the Philadelphia Chromosome-negative MPNs.
- JAK2 has an important role in normal hematopoiesis.
- It is a member of the Janus kinase family (JAK1, JAK2, JAK3, and Tyk2), named after the Roman god who has 2 faces, and means ending and beginning, as they contain 2 symmetric kinase domains: the C-terminal JH1 domain, which possesses tyrosine kinase function, whereas the immediately adjacent JH2 domain is enzymatically inactive, and negatively regulates the activity of JH1.
The JAK2 V617F mutation is a frequent genetic event in the three classical Philadelphia chromosome negative chronic myeloproliferative neoplasms: PV, ET & IMF.

These diseases are clonal stem cell disorders arising in an early stem cell progenitor with both lymphoid and myeloid differentiation potential.

The level in the stem cell hierarchy on which the initiating genetic events and the JAK2 V617F mutation occurs is not known.

The Janus kinase 2 mutation, JAK2 V617F, is myeloid neoplasm-specific.

Its presence excludes secondary polycythemia, or thrombocytosis or bone marrow fibrosis from other causes.

Involvement of Janus Kinases in Cytokine Signal Transduction (Panel A) and Structural Map of Janus Kinase 2 (Panel B).
JAK2 exon 12 mutations reported:

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS27.K557*</td>
<td>Idiopathic myelofibrosis, polycythemia vera</td>
</tr>
<tr>
<td>H582Q/K582*</td>
<td>Polycythemia vera</td>
</tr>
<tr>
<td>I536T/K582*</td>
<td>Idiopathic myelofibrosis</td>
</tr>
<tr>
<td>RS401.K582*</td>
<td>Idiopathic myelofibrosis, polycythemia vera</td>
</tr>
<tr>
<td>R554S/E560*</td>
<td>Polycythemia vera</td>
</tr>
<tr>
<td>R554S/E560*</td>
<td>Idiopathic myelofibrosis, polycythemia vera</td>
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<td>R554S/E560*</td>
<td>Polycythemia vera</td>
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<tr>
<td>N542G/E544*</td>
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<tr>
<td>E544K</td>
<td>Idiopathic myelofibrosis</td>
</tr>
<tr>
<td>W536F/E544*</td>
<td>Polycythemia vera</td>
</tr>
<tr>
<td>F577K/E544*</td>
<td>Polycythemia vera</td>
</tr>
</tbody>
</table>

Figure 3. Hypothetical mechanism of slippage mispairing involving the AGA repeat in exon 12 (shown in red) leading to 6 bp deletions (see text for details concerning the mechanisms that can lead from slippage mispairing to the loss of 6 bp fragments in a hematopoietic stem cell)

MPL mutation

- A recurrent molecular abnormality of MPN is represented by somatic mutations at codon 515 of MPL, which involve early myeloid and lymphoid progenitors.

- MPL is named after myeloproliferative leukemia virus oncogene homolog.

- Is the receptor for the cytokine thrombopoietin (Tpo) and is highly expressed in early hematopoietic progenitors and in cells of the megakaryocytic lineage.
POLYCYTHEMIA VERA (PRV)

- A neoplastic Clonal stem cell disorder possessing a JAK-2 mutation.
- Excessive production of all myeloid cell lines, erythroid, myeloid, and megakaryocytic cell lines but predominantly red cells.
- Erythropoietin levels usually very low.

Epidemiology:
- The incidence rate of ~ 2 /100,000.
- Male/female ratio ~ 1.2 to 2:1.
- Median age at diagnosis = 60 years.

When should We suspect PV?
- Hgb level exceeds upper normal limit or high-normal Hgb associated with either a documented increase from baseline or a PV characteristic feature.
- Budd-Chiari syndrome.
- Splenomegaly.
- Persistent leukocytosis, thrombocytosis, or microcytosis.
- Portal vein thrombosis.
- Erythromelalgia.
- Post-bath pruritus.
- Digital ischemia.

PV-Historical

The term polycythemia literally means “many blood cell disease”.

In 1892 Vaquez (Parisian physician) is credited with the initial description of PV.

In 1903 Osler delineated the clinical features of PV and differentiated it from other entities characterized by erythrocytosis.

In 1938 publication of the natural hx of PV by Rosenthal and Bassen.

In 1948, 9 years after the first use of 32P for treating PV, Byron Hall reported the occurrence of acute leukemia following the use of this isotope.

In 1950 hydroxyurea introduced.

In 1954, the natural history of PV was further defined by Wasserman who also studied therapies.

In 1967, the Polycythemia Vera Study Group (PVSG) was organized and identified the optimal approach to the diagnosis and treatment of PV (randomized trial chlorambucil, phlebotomy and 32P).

In 1987 PVSG lost NCI funding.

The French group created for the study of polycythemia vera has had a consensus conference, and the Italian group has developed a low-dose aspirin protocol for treating the disease.

In 2004 ASH meeting > 2000 hematologists debates PV red blood cell mass measurement.
Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid.

**PV-Symptoms**

1. Erythrocytosis leads to hyperviscosity and impaired oxygen delivery causing:
   - Headaches, weakness, fatigue, dizziness, and visual disturbances, night sweats, weight loss
   - Angina pectoris
   - Claudication
2. Hemorrhage: epistaxis, gingival bleeding, ecchymoses, GI bleed
3. Thrombophlebitis
4. Increased histamine release from basophils and mast cells causing pruritis

**PV-Physical findings**

1. Splenomegaly.
2. Hepatomegaly.
3. Hypertension.
4. Facial plethora.
5. Visual disturbances.
6. Fatigue.
7. Dyspnea.
8. Pruritis.

**PV-Diagnostic criteria, prior to Jak 2 Era:**

**Category A:**
1. RBC vol. Males >360ml/kg, females >32ml/kg
2. O2Sat >92% (normal P<50)
3. Splenomegaly

**Category B:**
1. Thrombocytosis (>400,000/)
2. Leucocytosis (12,000/µl)
3. Increased leukocyte alkaline phosphatase
4. Increased vit B12 (900 pg/ml) or unsat. B12 binding capacity (>2200 pg/ml)

(PV is diagnosed when A1+A2+A3 or A1+A2 and any two from category B)

Polycythemia Vera Study Group 75

**Criteria for polycythemia vera (PV)**

Diagnosis requires the presence of both major and one minor criteria or the presence of the first major criterion together with one minor criterion:

**Major criteria**
- Hemoglobin > 17.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume*
- Presence of JAK2 V617F or other functionally similar mutation such as JAK2 exon 12 mutation

**Minor criteria**
- Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
- Serum erythropoietin level below the reference range for normal
- Endogenous erythropoietin colony formation in vitro

*Diagnosis in menopausal women with hematocrits > 0.44 with no other evidence of increased red cell volume or other evidence of increased red cell volume without concomitant symptoms or other signs of PV.

(The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia.)
PV-Diagnostic Algorithm

| JAK2 V617F screen and Epo | V617F (+) | Epo + or high | PV probable
| | V617F (-) | Epo + or high | PV possible
| | V617F (-) | Epo nl or high | PV unlikely

PV probable
- Consider VHL mutation analysis
- Consider EPOR mutation analysis

PV possible
- Consider secondary polycythemia

PV unlikely
- Consider 2,3 DPG deficiency
- Consider high O2 affinity Hgb

PV-Prognosis

- Bleeding
- Thrombosis
- Myelofibrosis
- Leukemia

PV-Treatment

- Phlebotomy to control hematocrit
- low-dose aspirin
- Hydroxyurea
- Avoid iron

Risk stratification for thrombosis.

- **High risk**: age ≥ 60 or previous thrombosis.
- **Low risk**: age <60 and no previous thrombosis and Plt < 1 million.
- **Intermediate risk**: low risk with extreme thrombocytosis (>1 million).
### Essential Thrombocythemia

ET, represents a clonal MPN, with increased megakaryopoiesis with thrombocytosis >450 x 10⁹/L.

<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>Yes**</td>
</tr>
</tbody>
</table>

**Low with extreme thrombocytosis:**
- Yes
- Yes
- No

- After ruling out clinically significant VUS (mutations in co-factor activity > 30%)
- My platelet count between 1500 and 4500 per microliter
- Yes, if platelet transfusions are required
- Yes, if the patient is allergic to aspirin
- Yes, if there is a history of thrombosis (e.g., acute MI, stroke, or PE)
- Yes, if the patient has a history of thrombosis
- Yes, if the patient has a platelet count > 1000 x 10⁹/L
- Yes, if the patient has a platelet count > 1500 x 10⁹/L

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### ET-HISTORICAL

- Historically, essential thrombocythemia (ET) has been called hemorrhagic thrombocythemia/thrombocytosis, primary thrombocythemia, and idiopathic thrombocythemia.

- In 1934, the original term, hemorrhagic thrombocythemia, was described by Epstein and Goedel, beautifully describing the dual clinical manifestations of hemorrhagic and thrombotic in a patient with thrombocythemia, a German paper.

- In a 1951 Blood article, Dameshek speculated that ET belonged in the category of chronic myeloproliferative disorders (CMPDs) along with chronic myelogenous leukemia (CML), polycythemia vera (PV), and chronic idiopathic myelofibrosis (CIMF).

- The definition and diagnostic criteria for ET have changed substantially during the last 30 years.

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### Efficacy and Safety of Low-Dose Aspirin in Polycythemia Vera

Tatjana Landolfi, M.D.
The NEJM 2004

All patients followed for 3 yrs

- Asp 100mg
  - No significant reduction of major thrombosis.
  - No significant increase in bleeding.

Low-dose aspirin can safely prevent thrombotic complications in patients with polycythemia vera who have no contraindications to such treatment.
ET-Symptoms

When to suspect ET?

- Microvascular symptom, Vaso-occlusive events, Cerebral or myocardial infarction
- Transient ischemic attacks
- Seizures, headache, Dizziness, Visual disturbances and deafness
- Hemorrhagic complications, bleeding

ET-Diagnostic Algorithm

ET-Treatment

- Prevention and early intervention in hemorrhagic or vaso-occlusive complications.
- Chemotherapy is the same as in PV (HU, anagrelide, INF alpha, busulfan, bipobroman in Europe, Jak 2 inhibitors).
- Apheresis may be used to reduce platelet counts.
- For symptomatic treatment for pruritis; paroxetine, INF alpha, UVB, Jak2 inhibitors.

PS:
Hydroxyurea as first line Rx at any age
Alfa interferon in hydroxyurea failures or for child-bearing age females
Anagrelide if you can not use the above

Criteria for essential thrombocythemia (ET)

Diagnosis requires meeting all 4 criteria

- Sustained platelet count 450 x 10^10/L
- Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes. No significant increase or left-shift of myeloproliferative elements.
- Not meeting WHO criteria for polycythemia vera, primary myelofibrosis, BCR-ABL positive CML, or myelodysplastic syndrome, or other myeloid disorder.
- Demonstration of JAK2 V617F or other clonal marker, or in the absence of JAK2 V617F, no evidence of reactive thrombocytosis.

ET-Treatment

- Prevention and early intervention in hemorrhagic or vaso-occlusive complications.
- Chemotherapy is the same as in PV (HU, anagrelide, INF alpha, busulfan, bipobroman in Europe, Jak 2 inhibitors).
- Apheresis may be used to reduce platelet counts.
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PS:
Hydroxyurea as first line Rx at any age
Alfa interferon in hydroxyurea failures or for child-bearing age females
Anagrelide if you can not use the above
A total of 322 patients were studied in Mayo clinic series for a period of 13.6 yrs.

- Median survival 18.9 yrs.
- Survival in the first decade of disease was similar to that of the age- and sex-matched control population but became worse beyond the first decade of the disease.
- Older age (>60), thromboses, and leukocytoses predicted decreased survival.
- HU does not alter leukemia risk.
- Jak 2 V617 does not carry a prognostic relevance.

**MYELOFIBROSIS**

**Tear Drop Cells or Tear Drop Poikilocytes**
In 1879, Heuck described the first two cases of myelofibrosis, which he called “leukemia with peculiar blood.”

The phenotypic variability and difficulty in delineating myelofibrosis/myeloid metaplasia from thrombocythemia, polycythemia and leukemia caused considerable confusion, which is illustrated by the fact that since Heuck’s first report more than a dozen different names for myelofibrosis have been used to describe it.

In 1951, William Dameshek talked about relationships between P. vera, idiopathic myelofibrosis, and ET.

He actually proposed that these diseases, as well as CML and erythroleukemia, should be grouped together under the umbrella of myeloproliferative syndromes.

PMF-Pathobiology

1. Marrow fibrosis.
2. Myeloid metaplasia mainly liver and spleen which result from proliferation and emigration of neoplastic and hematopoietic cells, as well as production of cytokines within the marrow microenvironment which leads to reactive proliferation of fibroblasts.
3. The number of circulating hematopoietic progenitors CD34+ is INCREASED (level can be 50 folds higher than in PV and ET).
4. Higher level of circulating CD 34+ cells in IMF are associated with the presence of JAK2 V617F.

Elevated level in IL-1 and TNF alpha are associated with increased production of PDGF, bFGF, angiogenic fact (VEGF) and osteogenic cytokines.
Clinical picture

- Chronic, idiopathic progressive anemia
- Extramedullary hematopoiesis (accumulation of clonal stem cells in the liver, spleen, adrenals, kidney, lymph node, bowel, breast, lungs, mediastinum, mesentery, skin, synovium, thymus and lower urinary tract as well as in body cavities.)
- Splenomegaly is the hallmark
- Bone marrow fibrosis
- Hypercatabolic syndromes (Fatigue, fevers, weight loss, night sweats)
- Evolution to acute leukemia
- Splenic infarct
- Hyperuricemia
- Portal hypertension/ascites

Splenomegaly

Diagnosis: pre JAK-2 era.

- Suggested by peripheral blood smear
  - Normocytic anemia
  - Increased or decreased number of granulocytes and platelets
  - Myelophthisis (Teardrop RBCs, Nucleated RBCs, granulocyte precursors)
- Confirmed by bone marrow biopsy dry tap (Ineffective erythropoiesis, Dysplastic and Hypoplastic megakaryocyte which secrete PDGF, TGF-β, VEGF, bFGF, TNF, increased number of immature granulocytes, Reactive bone marrow fibrosis (polyclonal fibroblasts), Thickening and distortion of the bony trabeculae.
- CML ruled out BCR-ABL rearrangement
Criteria for primary myelofibrosis (PMF)
(The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia)

**Major criteria**
- Presence of megakaryocytic proliferation and style, usually accompanied by either reticulosis or collagen fibrosis, and in the absence of a significant fibrotic lesion, the megakaryocytic changes are accompanied by an increase in bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic cellular phase disease)
- Not meeting WHO criteria for polycythemia vera, BCR-ABL-positive chronic myelogenous leukemia, or other myeloid disorders
- Demonstration of JAK2V617F or other clonal markers, no evidence that bone marrow fibrosis is secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) inflammatory condition

**Minor criteria**
- Increase in serum lactate dehydrogenase level
- Anemia
- Demonstration of megakaryocyte proliferation and atypia, usually accompanied by either reticulin or collagen fibrosis

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

PMF-Treatment

- To alleviate symptoms or modify clinical problems
  - Low dose splenic irradiation if not candidate for sx
  - Splenectomy:
    - To help with severe abd pain
    - Reduce need for transfusion
    - Reduce thrombocytopenia
    - Correct portal hypertension
  - Post splenectomy complication:
    - Rebound thrombocytosis
    - Acute heparin reaction
    - Possible increase risk to AML transformation

PMF-Treatment cont.

- Treatment for anemia, increased WBC or Plts
  - Splenomegaly and extramedullary hematopoiesis:
    - EPO, PIRACE
    - Androgen, Hydroxyurea
    - JAK inhibitors
    - Anagrelide
    - Danazol
    - Thalidomide low dose 50 mg per day
    - Lenalidomide (per kroger 2005 RIC os 84% at 3 yrs)
    - Pomalidomide
    - Iron chelation for transfusion dependant patients
  - Low dose irradiation

- Transplant options: Allogeneic HCT, RIC Transplant
  - Karbaux 2007 ablative regimen, os Int/High risk os 46% and L risk os 80%
Several prognostic score systems for PMF have been proposed.

The most widely used is the "Lille score" reported by Dupriez et al, which features 3 prognostic categories based on hemoglobin level and leukocyte count: median survivals in low, intermediate, and high-risk groups being 93, 26, and 13 months, respectively.

The Mayo Clinic group tried to improve the Lille score by adding thrombocytopenia and monocytosis, but still suboptimal.

Then the scoring system by Cervantes et al, applicable also to younger patients, is based on hemoglobin level and the presence or absence of constitutional symptoms and circulating blasts based on a study of 1054 patients diagnosed with PMF at 7 centers.

Then in March 2009:

International Prognostic Scoring System for PMF

As published in Blood in March 2009:

Based on five independent predictors of inferior survival:

- Age >65 y
- Hemoglobin <10 g/dL
- Leukocyte count >25 x 10^9/L
- Circulating blasts >1%
- Presence of constitutional symptoms

The presence of 0, 1, 2, and ≥3 adverse factors defines low, intermediate-1, intermediate-2, and high risk disease, respectively.

PMF-Prognosis

- Mortality is associated with infection, severe hemorrhage, post splenectomy complications and transformation to acute leukemia.
- Poor prognosis associated with abnormal karyotype: trisomy 8 and del 12p.
- Accelerated phase defined by Kantarjian as Blood or bone marrow blasts > 10%, platelets less than 50 x 10^9/L, and chromosome 17 aberrations, if not treated predict death in less than 12 months (JCO Sep 28, 2009)
- No prognostic value for the JAK 2 mutation.
Acquired Eosinophilia

1-Secondary: infection, parasites, inflammation, neoplasia (HD, NHD, Solid tumor), Drugs.

2-Primary → clonal (cytogenetic, molecular, or bone marrow morphologic evidence of myeloid disorder: AML, ALL, CML, MDS, SM, PDGFR and FGFR1 positive.

→ idiopathic; neither reactive nor clonal → if AEC > 1500/micl for >6 months and presence of organ damage.
12/11/2009

A Tefferi

Systemic Mastocytosis (SM)

Blood eosinophilia
No blood eosinophilia

Mediator Release

symptoms
Urticaria Pigmentosa

Aggressive SM

Topical corticosteroids 0.05% betamethasone
PUVA

Indolent SM

Check for FIP1L1-PDGFRA
Positive Negative

Interferon-α 1-5 MU TIW
Imatinib 100 mg/day

Cladribine

Standard hairy cell leukemia dose

No response

H-2 blockers
Cimetidine 300 mg QID
Ranitidine 150 mg BID

H-1 blockers
Hydroxyzine 25 mg TID
Cyproheptadine 4 mg TID
Chlorpheniramine 4 mg QID
Azelastin 4 mg BID

Inhibitor of mast cell degranulation
Cromolyn sodium 400 mg QID

Anaphylaxis-prone patients

Must wear medical alert bracelets

Practical classification of mast cell disease

1. Cutaneous mastocytosis (skin-only disease)

2. Systemic mastocytosis (SM)

   - Both can manifest mast cell mediator release symptoms

   - Indolent SM

   - Aggressive SM (systemic, bone disease, organomegaly, etc.)

   - FISH for CHIC2 and cytogenetic studies for 5q33 translocations

   - CHIC2+ or 5q33+

   - Imatinib-insensitive eosinophilic disorder

   - Cle, or other myeloid malignancy

   - T-clone positive

   - Chronic therapy

   - Loss of expression of chymase, tryptase, alpha, eotaxin, platelet-activating factor, Lymphotoxin, and others

   - Prednisone for acute therapy

   - FISH for MM and ClqB

Diagnostic Evaluation in Systemic Mastocytosis

Bone marrow biopsy with myeloblast stains

Bone marrow mast cell flow cytometry

Abnormal mast cells — CD117+, CD30+, CD25+

Possible treatments:

- Interferon-α 1-5 MU TIW
- Imatinib 100 mg/day
- Cladribine

- Standard hairy cell leukemia dose
- No response
- H-2 blockers
- Cimetidine 300 mg QID
- Ranitidine 150 mg BID
- H-1 blockers
- Hydroxyzine 25 mg TID
- Cyproheptadine 4 mg TID
- Chlorpheniramine 4 mg QID
- Azelastin 4 mg BID

- Inhibitor of mast cell degranulation
- Cromolyn sodium 400 mg QID

- Anaphylaxis-prone patients
- Must wear medical alert bracelets

Tefferi & Pardanani

Current Hematology Reports

Current Hematology Reports, 2004, 2004
### Innovative Therapies for Classic MPN

<table>
<thead>
<tr>
<th>Drug</th>
<th>Main Targets</th>
<th>In Clinical Trial</th>
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<td>INCB018424</td>
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<td><strong>Non-JAK2 selective inhibitors</strong></td>
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<tr>
<td>CEP-701 (Lestaurtinib)</td>
<td>FLT3</td>
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<td>MK-0457</td>
<td>FLT3, BCR-ABL</td>
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<tr>
<td>Erlotinib</td>
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<tr>
<td>ITF2357</td>
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</tr>
<tr>
<td>Tipifarnib</td>
<td>FT</td>
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</tr>
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MPN indicates myeloproliferative neoplasm; FLT3, FMS-like tyrosine kinase 3; EGFR, epidermal growth factor receptor; FT, farnesyl transferase.

### 51st ASH Annual Meeting, December 5, 2009

Verstovsek presented preliminary findings at the 2008 ASH Annual Meeting that showed that INCB018424 may shrink enlarged spleens and improve disease-related symptoms in patients with myelofibrosis. In the current study analysis, patients with primary myelofibrosis or myelofibrosis occurring after PV or ET (n=153) were enrolled. They were assigned to an optimized dose of 10 mg, 15 mg or 25 mg of INCB018424 BID.

- Efficacy was monitored by MRI measurements of spleen size at 1, 3 & 6 months.
- Exercise capacity measuring a standardized 6-minute walk test at baseline and at 1, 3 & 6 months.
- Dose was started at 10 or 15 mg and optimized to each patient.
- Rapid reduction of spleen volume was noted as early as 1 month and lasted >6 months.
- Improvement was observed for the six-minute walk test.
- There was an association between spleen response and greater improvement in exercise capacity and reduced fatigue.

QUESTIONS?