MYELOPROLIFERATIVE NEOPLASMS

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Objectives

• Discuss an approach to increased cell counts
• Discuss clinical and laboratory diagnosis of myeloproliferative neoplasms
• Overview of treatment options and potential complications of disease and therapy
Figure 12-3 Classical hierarchal map of hematopoietic development

Cantor, A. B. et al. ASH-SAP 2010;2010:331-372
### Myeloproliferative Disorders

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Condition</th>
<th>Activating mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mast cell</td>
<td>Systemic mastocytosis</td>
<td>KITD816V</td>
</tr>
<tr>
<td>Red blood cells</td>
<td>Polycythemia vera</td>
<td>FIP1L1-PDGFRB</td>
</tr>
<tr>
<td>Platelets</td>
<td>Essential thrombocytosis</td>
<td>FIP1L1-PDGFRB</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Chronic eosinophilic leukemia</td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Chronic myeloid leukemia</td>
<td>BCR-ABL</td>
</tr>
<tr>
<td></td>
<td>Chronic myelomonocytic leukemia</td>
<td>TEL-PDGFRB</td>
</tr>
<tr>
<td></td>
<td>Primary myelofibrosis</td>
<td>BCR-PDGFRB</td>
</tr>
<tr>
<td>Monocytes</td>
<td></td>
<td>TEL-JAK2 other fusion TKs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CALR MPL</td>
</tr>
</tbody>
</table>

Source: Nature Reviews | Cancer
## Marrow Production and Peripheral Blood Half-Life

<table>
<thead>
<tr>
<th></th>
<th>Output/day</th>
<th>Blood Count</th>
<th>Lifespan</th>
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<tbody>
<tr>
<td>RBC</td>
<td>$200 \times 10^9$</td>
<td>$\sim 5 \times 10^6/\mu L$</td>
<td>120 days</td>
</tr>
<tr>
<td>WBC</td>
<td>$10 \times 10^9$</td>
<td>$\sim 3 \times 10^3/\mu L$ (neutrophils)</td>
<td>$&lt; 1/2$ day</td>
</tr>
<tr>
<td>Plts</td>
<td>$400 \times 10^9$</td>
<td>$\sim 200 \times 10^3/\mu L$</td>
<td>10 days</td>
</tr>
</tbody>
</table>
Leukocytosis

• A word to discourage from clinical use
  • Be more specific!

• For diagnosing MPNs – focus on Absolute counts, not %

• Specific type of cell will help build your differential
  • Neutrophilia: leukemoid reaction/reactive, CML, myelofibrosis
  • Lymphocytosis: CLL, MBL, pertussis,
  • Monocytosis: CMML, TB/fungal,
  • Eosinophilia: allergy/atopy, parasites, adrenal insufficiency, CEL
  • Basophilia: CML
  • Peripheral Blasts: Acute leukemia, high-grade MDS
Case 1 - Presentation

- 32yo resident presents with sore throat and fever
- Cervical adenopathy is present on exam
- CBC: 35>45%<455k
Case 1 - Differential

- 86% Neutrophils
- 12% Immature Granulocytes
- 2% Lymphocytes

- Rapid strep test is positive
- He improves with a course of antibiotics
Origin of MPN

MF: Dr. Gustav Heuck 1879 Two cases of leukemia with peculiar blood and bone marrow findings, respectively
PV: Dr. Louis Henri Vaquez 1892 On a special form of cyanosis accompanied by excessive and persistent erythrocytosis Dr. Osler coins “Vaquez’s disease” in 1903 chronic cyanosis with polycythemia and enlarged spleen
ET: Drs. Emil Epstein and Alfred Goedel 1934 Hemorrhagic thrombocythemia with a cascular, sclerotic spleen

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Erythroblasts</th>
<th>Granulocytes</th>
<th>Megakaryocytes</th>
<th>Fibroblasts</th>
<th>Potential bone marrow</th>
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<tbody>
<tr>
<td>Chronic Granulocytic Leukemia</td>
<td>±</td>
<td>+</td>
<td>+ to +++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Polycythemia Vera</td>
<td>+++</td>
<td>+</td>
<td>+ to +++</td>
<td>+ to +++</td>
<td>+ to +++</td>
</tr>
<tr>
<td>Idiopathic or Agnogenic Myeloid Metaplasia of Spleen</td>
<td>±</td>
<td>±</td>
<td>+ to +++</td>
<td>+ to +++</td>
<td>+ to +++</td>
</tr>
<tr>
<td>Megakaryocytic Leukemia</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+ to +++</td>
</tr>
<tr>
<td>Erythroleukemia (including d’Ungiulino syndrome)</td>
<td>+++</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>+ to +++</td>
</tr>
</tbody>
</table>

Degrees of Proliferation:
- + slight
- ++ moderate
- +++ marked

Essential Thrombocytosis

Polycythemia vera

Thrombosis
Hemorrhage
Leukemic Transformation

Myelofibrosis

Levine and Gilliland *Blood* 2008;112:2190-2198
Lab Features of PV, ET, and MF

Making a Molecular Diagnosis

Myeloproliferative Neoplasms

- CML
- CEL
- Mastocytosis

Ph positive
- BCR-ABL

Ph negative
- PDGFR
- D816V KIT

MPN-u
- Jak2v617f

CML

PV

ET

Primary MF

Post-PV MF

Post-ET MF

MYELOFIBROSIS

CNL=Chronic neutrophilic leukemia
CEL=Chronic Eosinophilic Leukemia
MF=myelofibrosis
PV=polycthyemia vera
ET=essential thrombocythemia
CML=chronic myeloid leukemia

Making a Molecular Diagnosis

Myeloproliferative Neoplasms

- Ph positive BCR-ABL
  - CML

- Ph negative
  - PDGFR
  - D816V KIT
  - Mastocytosis

Jak2v617f

- CALR, MPL
  - PV
  - ET

- CALR, MPL
  - Primary MF
  - Post-PV MF
  - Post-ET MF

Myelofibrosis

CNL=Chronic neutrophilic leukemia
CEL=Chronic Eosinophilic Leukemia
MF=myelofibrosis
PV=polycthemia vera
ET=essential thrombocythemia
CML=chronic myeloid leukemia


Klampfl NEJM 2013
Jak 2 Testing in MPN

<table>
<thead>
<tr>
<th>Reference</th>
<th>Assay</th>
<th>Source*</th>
<th>PV % (N)</th>
<th>ET % (N)</th>
<th>MMM % (N)</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baxter et al.</td>
<td>AS-PCR</td>
<td>PB &amp; BM</td>
<td>97% (73)</td>
<td>57% (51)</td>
<td>50% (16)</td>
<td>0% (90)</td>
</tr>
<tr>
<td>Levine et al.</td>
<td>PCR</td>
<td>PB</td>
<td>74% (164)</td>
<td>32% (115)</td>
<td>35% (46)</td>
<td>0% (270)</td>
</tr>
<tr>
<td>James et al.</td>
<td>PCR</td>
<td>PB &amp; BM</td>
<td>89% (45)</td>
<td>43% (21)</td>
<td>43% (7)</td>
<td>0% (45)</td>
</tr>
<tr>
<td>Kralovics et al.</td>
<td>PCR</td>
<td>PB</td>
<td>65% (128)</td>
<td>23% (93)</td>
<td>57% (23)</td>
<td>0% (82)</td>
</tr>
<tr>
<td>Zhao et al.</td>
<td>PCR</td>
<td>PB</td>
<td>83% (24)</td>
<td>N/A</td>
<td>N/A</td>
<td>0% (12)</td>
</tr>
<tr>
<td>Teffera et al.</td>
<td>PCR</td>
<td>PB</td>
<td>95% (38)</td>
<td>55% (22)</td>
<td>30% (10)</td>
<td>0% (30)</td>
</tr>
<tr>
<td>Jones et al.</td>
<td>AS-PCR</td>
<td>PB</td>
<td>81% (72)</td>
<td>41% (59)</td>
<td>43% (35)</td>
<td>0% (160)</td>
</tr>
</tbody>
</table>

* purified granulocytes
*T-Lymphocytes, $Buccal mucosal cells, and *hair follicles were negative

Calreticulin as the ‘other mutation’

A Distribution of JAK2, MPL, and CALR Mutations in Philadelphia Chromosome–Negative Myeloproliferative Neoplasms

Polycythemia Vera (N=382)
Nonmutated JAK2, MPL, and CALR
JAK2 mutation
MPL mutation

Essential Thrombocythemia (N=311)
Nonmutated JAK2, MPL, and CALR
CALR mutation
JAK2 mutation
MPL mutation

Primary Myelofibrosis (N=203)
Nonmutated JAK2, MPL, and CALR
CALR mutation
JAK2 mutation
MPL mutation

Klampfl NEJM 2013
PV and ET Diagnostic Criteria

**WHO Criteria¹: PV**

**Major Criteria** (first major + 2 minor or both + 1 minor)
- Hgb > 18.5 g/dL in men, 16.5 g/dL in women or other evidence of RCV*
- Jak2V617F or other mut Jak2 exon 12

**Minor Criteria** (first major + 2 minor or both + 1 minor)
- BM Trilineage proliferation
- Low Epo level
- Endogenous ECF in vitro

**WHO Criteria¹: ET**

**Major Criteria** (all required)
- Plt Count ≥ 450 x 10⁹/L sustained*
- Megakaryocyte proliferation with increased # of enlarged mature megakaryocytes
- Does not meet criteria for other myeloid d/o (PV*, MF†, CML‡, MDS§)
- Clonal marker (Jak2V617F) or no evidence of reactive thrombosis§

* during the w/u

¹ Failure of Fe to to increase Hgb in setting of a low ferritin
† absence of relevant reticulin or collagen fibrosis, leukoerythroblastosis, or abnml meg morphology (n/c ratio, hyperchromatic, bulbous, irregularly folded nuclei, and dense clustering)
‡ absence of BCR-ABL1.
§ absence of erythroid and granulocytic dysplasia
§ the presence of a condition associated with reactive thrombocytosis (Fe def, infection, inflammation, met cancer, connective tissue disease, lymphoproliferative d/o) does not exclude possibility of ET

Case 2 - Presentation

- 65yo woman is referred for ‘abnormal labs’
- Nonsmoker, no OSA, no history of pulmonary disease. She does not live at altitude.
- She reports pruritis but no other symptoms
- O2 saturation 98% RA
- Hb = 19
- WBC 9 Plt 400k

Next Tests?
Case 2 – Diagnostics: Polycythemia Vera

- EPO = 5 (2-18)
- JAK2 V617F mutation positive
- There is no need for a bone marrow with positive JAK2 in PV

- (Potential causes of secondary polycythemia include altitude, lung disease/hypoxia, renal cell carcinoma and hepatocellular carcinoma as well as testosterone/anabolic steroid use or exogenous EPO)
Case 2 – Treatment: Back to the Future

- Goal Hct is <45% (better than <50% in randomized trial by Marchioli et al. *NEJM* 2013 368:22)
  - Phlebotomy
  - Hydroxyurea

- ASA

Patients with PV cannot donate blood, but patients with hemochromatosis can.
CYTO-PV Study: 45% vs 50%

- 365 patients, randomized
- Primary end point
  - death from cardiovascular causes or thrombotic events
- HU or phlebotomy allowed

Marchioli et al. *NEJM* 2013 368:22
ECLAP: ASA vs Placebo in PV

- Efficacy and Safety of Low Dose Aspirin in PV
  - Multicenter European Study
  - 518 patients, randomized
  - Mean follow up 3 years
  - More smokers in ASA arm
  - Other tx as needed
    - Cytoreduction (HU)
    - Phlebotomy
  - No difference in overall mortality
  - NS reduction in major thrombosis
  - Major bleeding not different

Landolfi et al. NEJM 2004. 350:114
Case 3 - Presentation

• 55yo man presents with fatigue, and abnormal labs prior to upcoming hernia surgery.
• He has no active infections. Exam reveals no major findings and his hernia is easily reducible without associated erythema or tenderness.

• CBC: 27>45%<750
• N65%, L25%, M8%, E2%

Next Tests?

Peter Maslak
Case 3 - Diagnostics

- JAK2 V617F mutation negative
- BCR/ABL negative
- CALR positive
- Bone Marrow - increased megakaryocytes, some are increased in size but not abnormal. No increase in fibrosis.

- Diagnosis of Essential Thrombocythemia
HU in High-Risk ET

114 patients randomized
- 52 new diagnosis
- 54 never treated
- 13 previous hydroxyurea
- 15 previous basalahem

Age > 60 or previous thrombosis and plt ≤ 1.5 million

58 patients given no cyto reduction
- ASA and Ticlopidine Continued in both arms
  - 9 patients died
- 20 patients still without cyto reduction

56 patients given hydroxyurea
- 15mg/kg/day
- Plt < 600K
  - 8 patients died
  - 2 lost to follow-up
- 29 patients started hydroxyurea during follow-up
- 46 patients still on treatment with hydroxyurea

Thrombosis-free survival

Hydroxyurea
Controls

p = 0.0001

HU in High-Risk ET

114 patients randomized
52 new diagnosis
34 never treated
13 previous hydroxyurea
15 previous basiliximab

Age > 60
or previous thrombosis
and plt ≤ 1.5 million

58 patients given no cyto reduction
56 patients given hydroxyurea

ASA and Ticlopidine
Continued in both arms
15mg/kg/day
P1t ≤ 600K

9 patients died
20 patients still without cyto reduction
29 patients started hydroxyurea during follow-up
46 patients still on treatment with hydroxyurea

8 patients died
2 lost to follow-up

Thrombosis-free survival

p = 0.0001

years

Who gets treated with ET (and who just phones home)?

<table>
<thead>
<tr>
<th></th>
<th>Age &lt;60yo</th>
<th>Age &gt;60yo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior Thrombosis</td>
<td>NO CYTOREDUCTION</td>
<td>Cytoreduce</td>
</tr>
<tr>
<td>Prior Thrombosis*</td>
<td>Cytoreduce</td>
<td>Cytoreduce</td>
</tr>
</tbody>
</table>

* Includes CVA, TIA, AMI, Arterial thrombus, or VTE

Barbui, JCO. 2011;29: 761.

Barbui, Blood 2012. 120:5128
ET vs. MF vs. Control

Overall Survival (probability)

- Europe
- ET, n=891
- Early/prefibrotic PMF, n=180

HR 1.6 (95% CI 1.05-2.44), p=0.03

Case 4 - Presentation

• 62yo woman presents with LUQ abdominal pain, early satiety and weight loss x 3 months
• Examination reveals splenomegaly 8cm below the costal margin
• Next Test?
# MF Diagnostic Criteria

## WHO Criteria: Primary MF

**Major criteria (all required)**
- Megakaryocyte proliferation and atypia
  - Reticulin or collagen fibrosis
- Does not meet criteria for other myeloid disorders (e.g., PV, CML, MDS)
- Clonal marker (e.g., MPLW515K/L, JAK2V617F) or no evidence for secondary marrow fibrosis

**Minor criteria (must meet 2)**
- Increase in serum LDH
- Palpable splenomegaly
- Leukocyte proliferation
- Anemia

## IWG Criteria: Post-ET MF & Post-PV MF

**Major criteria (all required)**
- Previous diagnosis of ET or PV
- Grade 2-3 bone marrow fibrosis (on 0-3 scale) or Grade 3-4 bone marrow fibrosis (on 0-4 scale)

**Minor criteria (must meet 2)**
- ≥5 cm increase in palpable splenomegaly or new splenomegaly
- Leukoerythroblastosis
- One or more constitutional symptoms
- Increase in serum LDH (Post-ET MF only)
- Anemia with a Hgb ≥2 mg/dL decrease from baseline (Post-ET MF only)
- Anemia or sustained loss of requirement for either cytoreductive treatment or phlebotomy (Post-PV MF only)

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MF Disease Features

- 85% or more of MF patients present with palpable splenomegaly at the time of diagnosis\(^1\)
- 60% to 80% of MF patients report spleen-related symptoms\(^2\)
  - e.g., abdominal pain / discomfort, early satiety
- Other MF symptoms that can be present include\(^3\)
  - Pruritus
  - Night sweats
  - Bone pain

\(^1\)Barosi G. *J Clin Oncol.* 1999;17:2954-2970.
Symptoms in 1179 MPN Patients

COMFORT-I: Spleen Volume Reduction

Jakafi (ruxolitinib) provided significant improvement in spleen volume

Results at 24 weeks

OR 134.4 (18-1004.9) p < 0.0001

≥35% Reduction in Spleen Volume at 24 Weeks (%)

<table>
<thead>
<tr>
<th></th>
<th>Jakafi (n=155)</th>
<th>Placebo (n=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>41.9</td>
<td>0.7</td>
<td></td>
</tr>
</tbody>
</table>

Percent Change From Baseline

COMFORT-I: Symptom Improvement

Significant improvement in MF symptoms (MFSAF v2.0)

- Jakafi (ruxolitinib) provided significant improvement in total MF symptoms
  - Median time to response: <4 weeks
- Total symptom score (TSS) includes
  - Abdominal discomfort
  - Pain under the left ribs
  - Night sweats
  - Bone/muscle pain
  - Early satiety
- Symptom scores ranged from 0 (absent) to 10 (worst imaginable) and were added to create the daily TSS (maximum of 60)

**Results at 24 weeks**

\[ P < 0.0001 \]

- \[ 45.9 \] for Jakafi (n=148)
- \[ 5.3 \] for Placebo (n=152)

Baseline TSS = 18.0 for Jakafi, Baseline TSS = 16.5 for Placebo

Scherber et al. *Blood* 2011;118:401-408
Spleen Size Reduction Is Independent Of JAK Mutation Status Or Disease Subtype

Proportion of Subjects with ≥ 50% Decrease in Palpable Spleen Length

- PMF: N=37
- PPV: N=22
- PET: N=13
- V617F Positive: N=61
- V617F Negative: N=11

Source: Verstovsek et al. ASH 2020: 5758
Overall Survival in COMFORT I

<table>
<thead>
<tr>
<th>Weeks</th>
<th>No. at Risk Ruxolitinib</th>
<th>No. at Risk Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>155</td>
<td>154</td>
</tr>
<tr>
<td>4</td>
<td>155</td>
<td>152</td>
</tr>
<tr>
<td>8</td>
<td>155</td>
<td>151</td>
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<td>12</td>
<td>154</td>
<td>148</td>
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<td>16</td>
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<td>64</td>
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<tr>
<td>68</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>72</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>76</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio, 0.50 (95% CI, 0.25–0.98)
P = 0.04 by log-rank test

56yo man admitted with abdominal pain and leukocytosis

• 4 days of abdominal pain and diarrhea
• Recently discharged from the hospital
• Temp 100.8  HR 110
• Abdomen diffusely tender to palpation
What is the most likely diagnosis?
56yo admitted with abdominal pain and leukocytosis

- 3 months of gradually increasing abdominal pain, L>R
- Temp 100.8  HR 110
- Abdomen TTP in the LUQ, spleen palpable 8cm below the costal margin
What is the most likely diagnosis?
CML clinical features

- ~4500 new US cases per year
- Median age at presentation 53 years
- 60% men
- Disease is clinically divided into three phases
  - Chronic phase
  - Accelerated phase
  - Blast crisis (lymphoid (ALL) or myeloid (AML))
Blast Phase
- >30% blasts
- ~2/3 of patients have myeloid blast crisis
- ~1/3 have lymphoid blast crisis
- Very poor prognosis

Chronic Phase
- Myeloid hyperplasia
- <15% blasts
- Natural history of disease progression, 3-5 years untreated

Accelerated Phase
- >15%, <30% blasts
- Basophilia >20%
- New cytogenetic abnormalities in 50% to 80% of patients
- Plt <100k

Progression of CML
## Clinical Course: Phases of CML

<table>
<thead>
<tr>
<th>Chronic phase</th>
<th>Advanced phases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Accelerated phase</strong></td>
</tr>
<tr>
<td>Median 4–6 years stabilisation</td>
<td>Median duration up to 1 year</td>
</tr>
</tbody>
</table>

*Cooperating mutations*

*loss of p53; trisomy 8; second Ph; PAX5 deletion; others*
CML BCR/ABL1 fusion gene, the result of a genomic rearrangement
Normal Bcr-Abl Signaling*

- The kinase domain activates a substrate protein, e.g., PI3 kinase, by phosphorylation.
- This activated substrate initiates a signaling cascade culminating in cell proliferation and survival.

ADP = adenosine diphosphate; ATP = adenosine triphosphate; P = phosphate.

Mechanism of Activation of Bcr-Abl

- Bcr-Abl
- Substrate
- ATP
- Phosphates
- Tyrosine
Mechanism of Activation of Bcr-Abl

Signal transduction cascade
uncontrolled activity

Genetic Instability

Bcr-Abl
ATP
Substrate
Tyrosine
Phosphates

Proliferation
Survival
Adherence
Mechanism of Action of Imatinib

- Bcr-Abl
- Substrate
- ATP
- Imatinib
Mechanism of Action of Imatinib

Adapted from Goldman JM, Melo JV. *N Engl J Med.* 344:1084-1086
Mechanism of Action of Imatinib

Adapted from Goldman JM, Melo JV. *N Engl J Med*. 344:1084-1086
Imatinib has dramatically improved survival.
Next Generations of TKIs

- Dasatinib – improved responses compared to imatinib (DASISION, Kantarjian NEJM 2010 362(24): 2260)
- Nilotinib – improved responses compared to imatinib (ENESTnd, Saglio NEJM 2010 362(24)2251)
- Ponatinib – effective against T315I mutations
- Bosutinib
Side effects of TKIs

• Common side effects: edema, myalgias (rhabdo), cytopenias, LFTs, CYP450

• Dasatinib – pleural effusions
• Nilotinib – diarrhea, pancreatitis
• Ponatinib- cardiovascular events
• Bosutinib
Can you stop medication?

- In selected patients – yes, but follow very closely
Questions?

"...and you cannot change a thing, as you are completely controlled by your genes."
Treating a Molecular Disease

**PV Results: Hct % (n=34)**

- Normalization of Hct % Achieved in the Absence of Phlebotomy

<table>
<thead>
<tr>
<th></th>
<th>Mean Hct %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (76% with Phlebotomy in Prior 6 months)</td>
<td>46%</td>
</tr>
<tr>
<td>Month 1</td>
<td>43%</td>
</tr>
<tr>
<td>Month 2</td>
<td>39%</td>
</tr>
<tr>
<td>Month 3</td>
<td>37%</td>
</tr>
<tr>
<td>Month 6</td>
<td>39%</td>
</tr>
</tbody>
</table>

- Only 2 subjects required phlebotomy in the first 2 weeks, none since

Ruxolitinib (Jakafi) is a JAK2 inhibitor
Ruxolitinib (JAK2 inhibitor)

**ET Results: Platelets**

- **Rapid and Sustained Reduction in Platelets**
  - Baseline median platelets of 884 decreased to 558 after 6 months

- At baseline, 13 patients (33%) had platelets > 1000 x10^9/L
  - Baseline median platelets of 1443 decreased to 553 after 6 months

**Mean Changes In Platelet Counts**

- **All Patients (n=39)**
  - Baseline: 1052
  - Month 1: 579
  - Month 2: 630
  - Month 3: 681
  - Month 6: 612

- **Patients with Baseline Platelets >1000 x10^9/L (n=13)**
  - Baseline: 1532
  - Month 1: 874
  - Month 2: 734
  - Month 3: 828
  - Month 6: 611
Myeloid Malignancies

Myeloproliferative neoplasms
- enhanced proliferation/survival
- normal differentiation
- high white blood cell count
- may progress to AML

Myelodysplastic syndrome
- impaired differentiation
- low blood cell counts
- may progress to AML

Acute myeloid leukemia (AML)
- enhanced proliferation and survival
- impaired differentiation
- limitless self-renewal
Myeloid Precursors

“Left shift”

Myeloblast  Promyelocyte  Myelocyte  Metamyelocyte  Band Neutrophil

“Left Shift”
Case 5 - Presentation

- 35yo female presents with abdominal pain and jaundice
- She has no history of liver disease, heavy EtOH intake, or thrombosis.
- Exam reveals ascites and RUQ pain, icteric sclerae
• 35yo female presents with abdominal pain and jaundice
• She has no history of liver disease, heavy EtOH intake, or thrombosis. No recent surgery, immobility, trauma, or plane flights.
• Exam reveals ascites and RUQ pain, icteric sclerae

• T Bili = 12
• RUQ ultrasound with doppler reveals portal vein thrombosis.
Mesenteric/portal vein thrombosis without risk factor (cirrhosis):

- JAK2 V617F mutation (~32% of all splanchnic vein thromboses associated with this mutation) (Dentali, Blood 2009, 113:5617)
  - ***about half of these patients will have abnormal blood counts at time of clot
- Flow cytometry to evaluate for PNH (paroxysmal nocturnal hemoglobinuria via CD59, GPI deficient clone) (*rare*)
  - Most of these patients will have intermittent ‘hematuria’/hemolysis
  - May also present with cerebral thromboses
  - May also have cytopenias (aplastic anemia, MDS assoc)

Additional tests to consider