Myeloproliferative Neoplasms

Lymphoma Tumor Board

March 17, 2017
Myelofibrosis (MF)

• Relatively rare bone marrow disorder
• Can be primary or secondary
• Characteristic of Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs)
• Proliferation of an abnormal clone of hematopoietic stem cells results in fibrosis
• Symptoms include:
  • Abdominal fullness – usually caused by splenomegaly or hepatomegaly
  • Bone pain
  • Bruising and easy bleeding – caused by thrombocytopenia
  • Cachexia
  • Fatigue
  • High uric acid levels and gout
  • Pallor and shortness of breath
  • Increased susceptibility to infection
Clinical manifestations of Myelofibrosis

- Anemia
- Symptomatic splenomegaly
- Constitutional symptoms
  - Bone pain
  - Pruritus
- Bleeding
- Infection
- Thrombosis
- Extramedullary hemopoiesis

Francisco Cervantes Blood 2014;124:2635-2642

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Philadelphia Chromosome-Negative Neoplasms

• Three types of Philadelphia chromosome-negative myeloproliferative neoplasms:
  • Essential thrombocythemia (ET)
  • Polycythemia vera (PV)
  • [Primary] Myelofibrosis (MF)
• Most Philadelphia chromosome-negative cases have an activating JAK2 (e.g., V617F) or MPL mutation
• Mutations in CALR (calreticulin) are found in a majority of JAK2 and MPL-negative essential thrombocythemia and myelofibrosis cases
• ET is associated with JAK2 V617F mutation in up to 55% of cases, and with a MPL mutation in up to 5% of cases
  • **Cellular** phase - increased large megakaryocytes with fibrosis and little increase in other bone marrow elements
  • **Fibrotic** phase – collagenous fibrosis with lack of marrow elements
• PV is associated most often with the JAK2 V617F mutation (greater than 95% of cases), whereas the remainder have a JAK2 exon 12 mutation
  • **Cellular phase** - increased megakaryocytes which cluster, reticulin fibrosis, later trichrome fibrosis and increased myeloid and erythroid precursors
  • **Fibrotic phase** - collagenous fibrosis with lack of marrow elements
### Table 1. Philadelphia-negative classical MPNs: clinical, morphological, and molecular features

<table>
<thead>
<tr>
<th>Nosologic entity</th>
<th>Clinical and morphological features</th>
<th>Driver genes</th>
<th>Relationships between genotype, phenotype, and clinical outcome</th>
</tr>
</thead>
</table>
| PV               | Erythrocytosis frequently combined with thrombocytosis and/or leukocytosis (that is, polycythemia) and typically associated with suppressed endogenous erythropoietin production. Bone marrow hypercellularity for age with trilineage growth (that is, panmyelosis) | • JAK2 (V617F) in about 96% of patients  
• JAK2 exon 12 mutations in about 4% of patients (isolated erythrocytosis in most of these patients)  
• Patients with wild-type JAK2 extremely rare, if any | • PV patients are at increased risk of thrombosis  
• PV may progress to myelofibrosis and less commonly to a blast phase similar to AML, sometimes preceded by a myelodysplastic phase |
| ET               | Thrombocytosis. Normocellular bone marrow with proliferation of enlarged megakaryocytes | • JAK2 (V617F) in 60%-65% of patients  
• CALR exon 9 indels in 20%-25% of patients  
• MPL exon 10 mutations* in about 4%-5% of patients  
• Noncanonical MPL mutations* in <1% of patients  
• About 10% of patients do not carry any of the above somatic mutations (the so-called triple-negative cases) | • ET involves increased risk of thrombosis and bleeding, and may progress to more aggressive myeloid neoplasms  
• JAK2 (V617F)-mutant ET involves a high risk of thrombosis, and may progress to PV or myelofibrosis  
• CALR-mutant ET involves lower risk of thrombosis and higher risk of progression to myelofibrosis  
• Triple-negative ET is an indolent disease with low incidence of vascular events |
| PMF              | Pre fibrictic PMF  
• Various abnormalities of peripheral blood  
• Granulocytic and megakaryocytic proliferation in the bone marrow with lack of reticulin fibrosis  
Overt PMF  
• Various abnormalities of peripheral blood. Bone marrow megakaryocytic proliferation with atypia, accompanied by either reticulin and/or collagen fibrosis grades 2/3. Abnormal stem cell trafficking with myeloid metaplasia (extramedullary hematopoiesis in the liver and/or the spleen) | • JAK2 (V617F) in 60%-65% of patients  
• CALR exon 9 indels in 25%-30% of patients  
• MPL exon 10 mutations* in about 4%-5% of patients  
• Noncanonical MPL mutations* in <1% of patients  
• About 5%-10% of patients do not carry any of the above somatic mutations (the so-called triple-negative cases) | • PMF is associated with the greatest symptom burden and the worst prognosis within MPNs, with a variable risk of progression to AML  
• CALR-mutant PMF is associated with longer survival compared with other genotypes  
• JAK2 (V617F)- and MPL-mutant PMF have worse prognosis than CALR-mutant PMF  
• Triple-negative PMF is an aggressive myeloid neoplasm characterized by prominent myelodysplastic features and high risk of leukemic evolution |

*Canonical MPL exon 10 mutations include W515L/K/R, S505N/C, and V501A (transmembrane domain of MPL); noncanonical MPL mutations (outside exon 10) include T119I, S204F/P, E230G, Y252H (extracellular domain) and Y591D/N (intracellular domain).
Pathology of Myelofibrosis

Blasts circulating in the peripheral blood can be found.

Bone marrow biopsy from a patient with primary (also called idiopathic) myelofibrosis (IMF) shows extensive fibrosis with clustered megakaryocytes noted in the center of the specimen. Other hematopoietic elements are not noted.
Representative bone marrow biopsies from patients with MPNs

A. Essential thrombocythemia
B. Polycythemia vera
C. Prefibrotic/early primary myelofibrosis
D. Overt primary myelofibrosis
E. Overt primary myelofibrosis: collagen fibrosis

Elisa Rumi, and Mario Cazzola Blood 2017;129:680-692
Practical Algorithm for Diagnosis of Polycythemia Vera (PV), Essential Thrombocythemia (ET), and Primary Myelofibrosis (PMF)
Megakaryocytes play a central role in MPN pathogenesis

JAK-STAT signaling pathway

- JAK-STAT signaling pathway transmits information to the nucleus resulting in DNA transcription and expression of genes.

- Signaling cascade consists of three main components:
  - Cell surface receptor
  - Janus kinase (JAK)
  - Two Signal Transducer and Activator of Transcription (STAT) proteins

- Disruption of the JAK-STAT functionality can result in immune deficiency syndromes and cancers

- Overactive signaling of the JAK pathway is key to the pathogenesis of myelofibrosis.
JAK2

- Janus kinase 2 (JAK2) – non-receptor tyrosine kinase
- Member of the Janus kinase family
- Implicated in signaling by members of the following families:
  - Type II cytokine receptor family
  - GM-CSF receptor family (IL-3R, IL-5R and GM-CSF-R)
  - GP130 receptor family (IL-6)
- Signaling is activated downstream from the prolactin receptor
- JAK2 lacks the Src homology binding domains (SH2/SH3) & up to 7 JAK homology domains (JH1-JH7)
# Common Somatic Mutations in MPNs

<table>
<thead>
<tr>
<th>Gene function and symbol</th>
<th>Location</th>
<th>Type of mutations</th>
<th>Protein function</th>
<th>Frequency</th>
<th>Consequences</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signaling MPN driver</td>
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<tr>
<td>JAK2</td>
<td>9p24</td>
<td>JAK2V617F</td>
<td>Tyrosine kinase associated with cytokine receptors</td>
<td>95% PV, 50%–60% PMF and ET</td>
<td>Increased RBC, platelet, and granulocyte production</td>
<td>4–7</td>
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<tr>
<td></td>
<td></td>
<td>JAK2 exon 12</td>
<td></td>
<td>3% PV</td>
<td>Increased RBC</td>
<td>17</td>
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<tr>
<td>MPL</td>
<td>1p34</td>
<td>MPLS15L/K/A/R MPLS505N</td>
<td></td>
<td>2%–3% ET</td>
<td>Increased platelet production</td>
<td>19, 22, 23</td>
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<tr>
<td></td>
<td></td>
<td>Other missense mutations</td>
<td></td>
<td>3–5% PMF</td>
<td></td>
<td>25</td>
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<tr>
<td>CALR</td>
<td>19p13</td>
<td>Indel exon 9</td>
<td>Mutant: activator of MPL</td>
<td>20%–25% ET, 25%–30% PMF</td>
<td>Increased platelet production</td>
<td>28, 29</td>
</tr>
<tr>
<td>DNA methylation</td>
<td>Gene</td>
<td>Chromosomal Location</td>
<td>Function</td>
<td>Pathology</td>
<td>Reference</td>
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<tr>
<td>TET2</td>
<td>4q24</td>
<td>Missense, nonsense deletion</td>
<td>α-Ketoglutarate-dependent dioxygenase</td>
<td>Initiation, 10%-20% MPN (ET, PV, and PMF)</td>
<td>70</td>
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<tr>
<td></td>
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<td>Oxidation of 5mC into 5hmC and active 5mC demethylation</td>
<td>Mutations on 2 alleles associated with progression</td>
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<tr>
<td>DNMT3A</td>
<td>2p23</td>
<td>Missense, hotspot</td>
<td>DNA methylase, de novo methylation</td>
<td>Initiation</td>
<td>74</td>
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<tr>
<td>IDH1</td>
<td>2q33.3</td>
<td>Missense, hotspot</td>
<td>Neomorphic enzyme, generation of 2-hydroxyglutarate blocking α-ketoglutarate-dependent enzymes</td>
<td>1%-3% PMF</td>
<td>111</td>
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<tr>
<td></td>
<td></td>
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<td>Initiation, Disease progression</td>
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<tr>
<td>IDH2</td>
<td>15q26.1</td>
<td>Missense, hotspot</td>
<td>Neomorphic enzyme, generation of 2-hydroxyglutarate blocking α-ketoglutarate-dependent enzymes</td>
<td>1%-3% PMF</td>
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<tr>
<td></td>
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<td>Initiation, Disease progression</td>
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<tr>
<td>Histone</td>
<td>EZH2</td>
<td>7q35-36</td>
<td>H3K27 methyltransferase, loss of function</td>
<td>5%-10% PMF</td>
<td>82, 83</td>
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<td>modifications</td>
<td></td>
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<td>Initiation</td>
<td>Disease progression</td>
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<tr>
<td>ASXL1</td>
<td>20q11</td>
<td>Nonsense/indel</td>
<td>Chromatin-binding protein associated with PRC1 and 2</td>
<td>25% PMF</td>
<td>69</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Initiation</td>
<td>Rapid progression</td>
<td></td>
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<tr>
<td>Transcription factors</td>
<td>Chromosome</td>
<td>Mutation Type</td>
<td>Function</td>
<td>Incidence</td>
<td>Clinical Significance</td>
<td>Gene ID</td>
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<tr>
<td>TP53</td>
<td>17p13.1</td>
<td>Missense/indel</td>
<td>Transcription factor regulating cell cycle, DNA repair and apoptosis</td>
<td>&lt;5% (20% of sAML)</td>
<td>Progression to leukemia (mutations on both alleles) complex karyotype</td>
<td>98</td>
</tr>
<tr>
<td>CUX1</td>
<td>7q22</td>
<td>Deletion 7p</td>
<td>Transcription factor regulating TP53 and ATM</td>
<td>&lt;3%</td>
<td>Progression to leukemia</td>
<td>112</td>
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<tr>
<td>IKZF1</td>
<td>7p12.2</td>
<td>Deletion 7p, indel</td>
<td>Master transcription factor in lymphopoiesis</td>
<td>&lt;3%</td>
<td>Progression to leukemia</td>
<td>112</td>
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<tr>
<td>ETV6</td>
<td>12p13</td>
<td>Missense/indel</td>
<td>Transcription factor of the ETs family</td>
<td>&lt;3%</td>
<td>Progression to leukemia</td>
<td>112</td>
</tr>
<tr>
<td>RUNX1</td>
<td>21q22.3</td>
<td>Nonsense/missense/indel</td>
<td>Master transcription factor in hematopoiesis</td>
<td>&lt;3% (10% of sAML)</td>
<td>Progression to leukemia</td>
<td>112</td>
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<tr>
<td>RNA splicing</td>
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<tr>
<td>SRSF2</td>
<td>17q25.1</td>
<td>Missense, hotspot</td>
<td>Serine/arginine–rich pre– RNA splicing factor</td>
<td>&lt;2% ET 10%–15% PMF (association with IDH mutations)</td>
<td>Initiation? Progression</td>
<td>94</td>
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<tr>
<td>SF3B1</td>
<td>2q33.1</td>
<td>Missense</td>
<td>RNA–splicing factor 3b subunit 1, part of U2</td>
<td>&lt;3% ET</td>
<td>Phenotypic change (anemia)</td>
<td>113</td>
</tr>
<tr>
<td>U2AF1</td>
<td>21q22.3</td>
<td>Missense</td>
<td>U2 small nuclear RNA–splicing factor</td>
<td>10%–15% PMF</td>
<td>Phenotypic change (anemia)</td>
<td>94</td>
</tr>
</tbody>
</table>
### Less Common/Rare Somatic Mutations in MPNs

<table>
<thead>
<tr>
<th>Other signaling</th>
<th>Chromosome</th>
<th>Mutation Type</th>
<th>Functional Effect</th>
<th>Frequency</th>
<th>Clinical Impact</th>
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</thead>
<tbody>
<tr>
<td>LNK</td>
<td>12q24</td>
<td>Missense (loss of function) deletion</td>
<td>Negative regulator of JAK2</td>
<td>1% ET, 2% PMF</td>
<td>Synergy with JAK2V617F–Disease progression</td>
</tr>
<tr>
<td>CBL</td>
<td>11q23;3</td>
<td>Missense (loss of function)</td>
<td>Cytokine receptor internalization</td>
<td>4% PMF</td>
<td>Disease progression (progression to AML)</td>
</tr>
<tr>
<td>NRAS</td>
<td>1p13.2</td>
<td>Missense (activation)</td>
<td>ERK/MAPK signaling</td>
<td>Rare PMF</td>
<td>Progression to leukemia (5%–10% in secondary AML)</td>
</tr>
<tr>
<td>NF1</td>
<td>17q11</td>
<td>Missense deletion</td>
<td>ERK/MAPK signaling</td>
<td>Rare PMF</td>
<td>Progression to leukemia (5%–10% in secondary AML)</td>
</tr>
<tr>
<td>FLT3</td>
<td>13q12</td>
<td>FLT3–ITD</td>
<td>Cytokine receptor (FLT3–L)</td>
<td>MPN (&lt;3%)</td>
<td>Progression to leukemia (10%–15% in secondary AML)</td>
</tr>
</tbody>
</table>
Co-occurrence of somatic mutations in MPNs

Table 3.

Co-occurrence of mutations

<table>
<thead>
<tr>
<th></th>
<th>PV JAK2V617F</th>
<th>ET JAK2V617F</th>
<th>ET CALRmut</th>
<th>ET MPLm</th>
<th>PMF JAK2V617F</th>
<th>PMF CALRmut</th>
<th>PMF MPLm</th>
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<tbody>
<tr>
<td>TET2</td>
<td>8.33 (4)</td>
<td>5.26 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>28.95 (11)</td>
<td>2.63 (1)</td>
<td>2.63 (1)</td>
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<tr>
<td>DNMT3A</td>
<td>6.25 (3)</td>
<td>7.02 (4)</td>
<td>0 (0)</td>
<td>3.51 (2)</td>
<td>7.89 (3)</td>
<td>0 (0)</td>
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<tr>
<td>ASXL1</td>
<td>0 (0)</td>
<td>3.51 (2)</td>
<td>0 (0)</td>
<td>1.75 (1)</td>
<td>15.79 (6)</td>
<td>7.89 (3)</td>
<td>0 (0)</td>
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<tr>
<td>IDH1/IDH2</td>
<td>2.08 (1)</td>
<td>1.75 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2.63 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>EZH2</td>
<td>2.08 (1)</td>
<td>0 (0)</td>
<td>1.75 (1)</td>
<td>0 (0)</td>
<td>2.63 (1)</td>
<td>2.63 (1)</td>
<td>0 (0)</td>
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<tr>
<td>SF3B1</td>
<td>4.17 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2.63 (1)</td>
<td>0 (0)</td>
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<tr>
<td>U2AF1</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>7.89 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Results are extracted from Nangalia et al\textsuperscript{29} because it is one of the rare studies in which all types of MPNs are available. Overall, 143 patients: PV, 43; ET, 57; and PMF, 38. Percentages are expressed for each MPN, irrespective of the MPN drive mutation. Thus, percentages are calculated on a very low number of patients due to the heterogeneity of the disorder, explaining differences with other studies, more particularly for the mutations in splicing genes.
Role of cytokine receptors in the oncogenic properties of JAK2 V617F and CALR mutants


©2017 by American Society of Hematology
CALR mutants bind and activate MPL

William Vainchenker, and Robert Kralovics Blood
2017;129:667-679
Genes involved in epigenetic regulation and leukemic transformation


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Presence of myeloproliferative and myelodysplastic features in MPN

A
Signaling mutations
- JAK2
- CALR
- MPL

Proliferation

3 or more mutations
- Epigenetic mutations
  - TET2 / ASXL1
  - EZH2 / DNMT3A
  - IDH1/2
- Splicing mutations
  - SRSF2 / SF3B1
  - U2AF1 / ZRSF2
  - SF1 / PRPF40B

Myelodysplasia

B
Signaling mutations
- JAK2
- CALR
- MPL

Proliferation

2 mutations
- Epigenetic mutations
  - TET2
  - DNMT3A
  - EZH2

Myelodysplasia

C
Signaling mutations
- JAK2
- CALR
- MPL

Proliferation

1 mutation

Myelodysplasia
Circulating CD34^+ cells in patients with MPNs

Elisa Rumi, and Mario Cazzola

Blood 2017;129:680-692

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Treatment of MPNs

• There are currently no curative treatments for MPNs other than allogeneic stem cell transplantation, which involves significant risks.
• For ET and PV, the goal is prevention of thrombohemorrhagic complications.
• For MF, the goal is amelioration of anemia, splenomegaly, and other symptoms.
• Treatment options include:
  • Low-dose aspirin in the setting of PV and ET.
  • Tyrosine kinase inhibitors (imatinib).
  • Ruxolitinib, which is a JAK2 inhibitor and approved for primary myelofibrosis.
• Frequent blood transfusions may be needed.
• In the setting of primary myelofibrosis, lenalidomide and thalidomide may be used.
  • Peripheral neuropathy will be a common side-effect.
• If the patient is diabetic and taking sulfonylurea, this should be stopped periodically to rule out drug-induced thrombocytopenia.
Treatment algorithm for anemia in MF

Epo levels

Inadequate*

- ESA

Response at 3 months?

Yes

- ESA

No

Adequate

- Danazol

Response at 6 months?

No

- Danazol

Yes

- Immunomodulators

* < 125 mU/mL

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Conventional and molecular risk factors for patients with MPNs

<table>
<thead>
<tr>
<th>Essential thrombocythemia</th>
<th>Polycythemia vera</th>
<th>Primary myelofibrosis</th>
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</thead>
<tbody>
<tr>
<td><strong>Thrombosis:</strong></td>
<td><strong>Thrombosis:</strong></td>
<td><strong>Survival &amp; leukemic transformation:</strong></td>
</tr>
<tr>
<td>• previous thrombosis</td>
<td>• previous thrombosis</td>
<td>• age &gt;65 years</td>
</tr>
<tr>
<td>• age ≥ 60 years</td>
<td>• age ≥ 60 years</td>
<td>• presence of constitutional symptoms</td>
</tr>
<tr>
<td>• JAK2 (V617F)</td>
<td></td>
<td>• anemia (Hb &lt;10 g/dL)</td>
</tr>
<tr>
<td><strong>Bleeding:</strong></td>
<td></td>
<td>• leukocytosis (WBC count &gt;25 x 10⁹/L)</td>
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<tr>
<td>• previous major bleeding</td>
<td></td>
<td>• thrombocytopenia (&lt;100 x 10⁹/L)</td>
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<tr>
<td>• high PLT count (≥1500 x 10⁹/L)</td>
<td></td>
<td>• circulating blasts (≥1%)</td>
</tr>
<tr>
<td><strong>Polycythemic transformation:</strong></td>
<td></td>
<td>• degree of bone marrow fibrosis</td>
</tr>
<tr>
<td>• JAK2 (V617F)</td>
<td></td>
<td>• unfavorable karyotype</td>
</tr>
<tr>
<td><strong>Myelofibrotic transformation:</strong></td>
<td></td>
<td>• driver mutation (triple negative vs JAK2/MPL vs CALR mutation)</td>
</tr>
<tr>
<td>• CALR mutation</td>
<td></td>
<td>• co-operating mutations in myeloid genes</td>
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<tr>
<td>• co-operating mutations in myeloid genes</td>
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<td><strong>Leukemic transformation:</strong></td>
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<tr>
<td>• co-operating mutations in myeloid genes</td>
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<td><strong>Survival:</strong></td>
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<td>• previous thrombosis</td>
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<td>• leukocytosis</td>
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<tr>
<td>• co-operating mutations in myeloid genes</td>
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</tbody>
</table>
Priorities for MPN Treatment

**Physicians**
- ET
  - Prevent vascular events
  - Slow or delay condition
  - Healthy blood counts
  - Better QoL
  - Symptom improvement
  - Reduction in spleen size
  - Reduce frequency of phlebotomy

- PV
  - Prevent vascular events
  - Slow or delay condition
  - Healthy blood counts
  - Better QoL
  - Symptom improvement
  - Hematocrit <45%
  - Reduce phlebotomies
  - Reduce spleen size

- MF
  - Prevent vascular events
  - Slow or delay condition
  - Healthy blood counts
  - Better QoL
  - Symptom improvement
  - Anemia treatment
  - Reduce blood transfusion
  - Reduce spleen size

**Patients**
- ET
  - Prevent vascular events
  - Slow or delay condition
  - Healthy blood counts
  - Better QoL
  - Symptom improvement
  - Reduction in spleen size
  - Reduce frequency of phlebotomy

- PV
  - Prevent vascular events
  - Slow or delay condition
  - Healthy blood counts
  - Better QoL
  - Symptom improvement
  - Hematocrit <45%
  - Reduce phlebotomies
  - Reduce spleen size

- MF
  - Prevent vascular events
  - Slow or delay condition
  - Healthy blood counts
  - Better QoL
  - Symptom improvement
  - Anemia treatment
  - Reduce blood transfusion
  - Reduce spleen size
# HSCT options for patients with MF

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Indicated*</th>
<th>Not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATIENT SELECTION</strong></td>
<td></td>
<td></td>
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<tr>
<td>- Patients with intermediate-2 or high-risk disease according to IPSS,</td>
<td>- Patients with intermediate-1-risk disease and age &lt;65 years if they</td>
<td>- Patients with low-risk disease.</td>
</tr>
<tr>
<td>DIPSS or DIPSS-plus, and age &lt;70 years.</td>
<td>present with either refractory, transfusion-dependent anemia, or &gt;2%</td>
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<td></td>
<td>blasts in peripheral blood or adverse cytogenetics.</td>
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<td>- Patients with intermediate 1-risk disease if they are triple negative or</td>
<td>- Patients in blast transformation.</td>
</tr>
<tr>
<td></td>
<td>ASXL1 positive, or both.</td>
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<td>- Patients in blast transformation after achieving a partial or complete</td>
<td></td>
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<td></td>
<td>remission of leukemia with debulking therapy.</td>
<td></td>
</tr>
<tr>
<td><strong>PRETRANSPLANT MANAGEMENT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Iron chelation therapy in severely iron overloaded patients only.</td>
<td>- Ruxolitinib treatment for patients with a symptomatic spleen and/or</td>
<td>- Splenic irradiation</td>
</tr>
<tr>
<td></td>
<td>constitutional symptoms.</td>
<td>- Splenectomy (case-by-case decision)</td>
</tr>
</tbody>
</table>

*, means not a strong recommendation but case-by-case approach.
Kaplan-Meier analysis of survival of PMF patients stratified according to their driver mutation or a clinical-molecular prognostic model that includes IPSS variables and driver mutation.
References


• https://en.wikipedia.org/wiki/Myeloproliferative_neoplasm
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• https://en.wikipedia.org/wiki/Myelofibrosis
• http://www.mpnconnect.com/myelofibrosis.aspx
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