Current Prognostication in Primary Myelofibrosis

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Florence, April 2011
Survival in PMF

No. patients: 1,054
Median Srv (95% CI): 69 (61 - 76)
Deaths: 517 (49 %)

Cervantes et al., Blood 2009
Relative Survival in PMF

Cervantes et al., Blood 2009
Main Prognostic Factors in PMF

- Hb < 10 g/dL
- Constitutional symptoms
- Older age
- Leukocyte counts
- Blood blasts
- Abnormal karyotype
# Dupriez’s Prognostic Score

### Adverse factors
- Hb < 10 g/dL
- WBC < 4 or > 30 x $10^9$/L

<table>
<thead>
<tr>
<th>Prognostic groups</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk: 0 factors</td>
<td>93 months</td>
</tr>
<tr>
<td>Intermediate risk: 1 factor</td>
<td>26 months</td>
</tr>
<tr>
<td>High risk: 2 factors</td>
<td>13 months</td>
</tr>
</tbody>
</table>

Dupriez et al., Blood 1996
Primary Myelofibrosis: Age Distribution (n= 173)

Median: 64 years (17-89)
Survival of PMF Patients ≤ 55 years (n= 121)

Median: 10.6 years

Cervantes et al., Br J Haematol 1998
Survival in PMF

No. patients: 1,054
Median Srv (95% CI): 69 (61 - 76)
Deaths: 517 (49 %)

Cervantes et al., Blood 2009
IPSS: Risk classification of PMF at presentation

Prognostic factors

• Age > 65 years
• Constitutional symptoms
• Hb < 10 g/dL
• Leukocytes > 25 x 10⁹/L
• Blood blasts ≥ 1%

Risk groups

• Low 0
• Intermediate-1 1
• Intermediate-2 2
• High ≥ 3
## PMF- Prognostic groups

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>No. factors</th>
<th>No. cases (%)</th>
<th>Median Srv (95% CI)</th>
<th>No. deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>224 (22%)</td>
<td>135 (117 - 181)</td>
<td>72 (32%)</td>
</tr>
<tr>
<td>Interm. 1</td>
<td>1</td>
<td>229 (29%)</td>
<td>95 (79 - 114)</td>
<td>114 (50%)</td>
</tr>
<tr>
<td>Interm. 2</td>
<td>2</td>
<td>282 (28%)</td>
<td>48 (43 - 59)</td>
<td>161 (71%)</td>
</tr>
<tr>
<td>High</td>
<td>≥ 3</td>
<td>202 (21%)</td>
<td>27 (23 - 31)</td>
<td>147 (73%)</td>
</tr>
</tbody>
</table>

Cervantes *et al.*, Blood 2009
PMF: Relative Survival by Risk Group

Cervantes et al., Blood 2009
Dynamic IPSS (DIPSS) in Overall PMF Patients: Weight of Variables and Risk Groups

Table 3. DIPSS for survival in primary myelofibrosis

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Age, y</td>
<td>≤ 65</td>
</tr>
<tr>
<td>White blood cell count, $\times 10^9$/L</td>
<td>≤ 25</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>≥ 10</td>
</tr>
<tr>
<td>Peripheral blood blast, %</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Constitutional symptoms, Y/N</td>
<td>N</td>
</tr>
</tbody>
</table>

The risk category is obtained adding up the values of each prognostic variable. Risk categories are defined as low: 0; intermediate-1: 1 or 2; intermediate-2: 3 or 4; and high: 5 or 6.

DIPSS indicates Dynamic International Prognostic Scoring System.

Passamonti et al., Blood 2010
Dynamic International Prognostic Scoring System: Time of Appearance of the Risk Factors

Passamonti et al., Blood 2010
Dynamic International Prognostic Scoring System: Survival by risk group (overall series)

Passamonti et al., Blood 2010
**DIPSS in PMF Patients < 65 years: Weight of Variables and Risk Groups**

Table 4. Age-adjusted DIPSS for survival in primary myelofibrosis

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Value 0</th>
<th>Value 1</th>
<th>Value 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count, $\times 10^9/L$</td>
<td>$\leq 25$</td>
<td>$&gt; 25$</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>$\geq 10$</td>
<td>&lt; 10</td>
<td></td>
</tr>
<tr>
<td>Peripheral blood blast, %</td>
<td>&lt; 1</td>
<td>$\geq 1$</td>
<td></td>
</tr>
<tr>
<td>Constitutional symptoms, Y/N</td>
<td>N</td>
<td>Y</td>
<td></td>
</tr>
</tbody>
</table>

The risk category is obtained adding up the values of each prognostic variable. Risk categories are defined as low: 0; intermediate-1: 1 or 2; intermediate-2: 3 or 4; and high: more than 4.

DIPSS indicates Dynamic International Prognostic Scoring System.

Passamonti *et al.*, Blood 2010
Survival by DIPSS PMF risk group (patients < 65 years)

Passamonti et al., Blood 2010
Cytogenetic Abnormalities in PMF

- del 20q
- del 13q
- Trisomy 8
- Trisomy 1q
- Trisomy 9
- Monosomy 7
- t (1;7)
- del 12p
- t (1;6)
IWG-MRT: PMF and Karyotype (n= 409)

• Patients with abnormalities: 30%

• Significant association with survival even after adjustment for prognostic score (p= 0.01)

• The variable “abnormal karyotype” increased the discriminating power of the prognostic score, but only in the intermediate-risk groups.

Cervantes et al., Blood 2009
Karyotype and Prognosis in PMF

Favorable:
- 13q-, 20q-, +9
- Normal diploid

Unfavorable:
- Abnormal 5, 7 or 17
- Complex

Tam et al., Blood 2009
Karyotype and Prognosis in PMF

- **Favorable:**
  13q-, 20q-, +9

- **Unfavorable:**
  Complex, +8

- **Normal diploid**

- **Others**
Karyotype and Prognosis in Intermediate-1 Risk PMF patients

- Favorable + Normal
- Unfavorable + Others

Hussein et al., Blood 2010
Dynamic International Prognostic Scoring System (DIPSS)-Plus for Primary Myelofibrosis

*** Complex karyotype or +8, -5/-5q-, -7/-7q, i(17q), 12p-, inv(3), 11q23 rearr.

Gangat et al., JCO 2011; 29:392-397
DIPSS-Plus for Primary Myelofibrosis

Gangat et al., JCO 2011; 29:392-397
# Summary of Current Prognostic Models for PMF

<table>
<thead>
<tr>
<th>Variable</th>
<th>IPSS</th>
<th>DIPSS</th>
<th>DIPSS-plus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age $&gt;65$ y</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin $&lt;10$ g/dL</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Leukocyte count $&gt;25 \times 10^9$/L</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Circulating blasts $\geq 1%$</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Platelet count $&lt;100 \times 10^9$/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC transfusion need</td>
<td></td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Unfavorable karyotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+8,-7/7q,-i(17q),inv(3),-5/5q,-12p-, 11q23 rearr.</td>
<td>1 point each</td>
<td>1 point each but Hb=2</td>
<td>1 point each</td>
</tr>
</tbody>
</table>

Gangat et al. JCO. 2010; on line Dec 13.
Mutation JAK2 V617F in the MPNs

V617F

Frequency of the JAK2 mutation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV</td>
<td>90-95%</td>
</tr>
<tr>
<td>ET</td>
<td>50-60%</td>
</tr>
<tr>
<td>PMF</td>
<td>50-60%</td>
</tr>
</tbody>
</table>
**Prognostic Value of the JAK2 Mutation in PMF**

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>No. of patients</th>
<th>Prognostic influence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tefferi (2005)</td>
<td>157</td>
<td>No</td>
</tr>
<tr>
<td>Campbell (2006)</td>
<td>152</td>
<td>Yes</td>
</tr>
<tr>
<td>Barosi (2007)</td>
<td>174</td>
<td>Yes *</td>
</tr>
<tr>
<td>Cervantes (2009)</td>
<td>345</td>
<td>No</td>
</tr>
<tr>
<td>Guglielmelli (2009)</td>
<td>186</td>
<td>Yes **</td>
</tr>
</tbody>
</table>

* Higher leukemic transformation rate; ** shorter survival for lower burden
Proposed Algorithm for PMF Treatment

- **Low risk**
  - Wait & see

- **Intermediate-1 risk**
  - Wait & see or Conventional treatment *

- **Intermediate-2 risk**
  - Allo-HSCT or Conventional / Investigational drugs *

- **High risk**
  - Allo-HSCT or Investigational drugs

* Check cytogenetics and transfusion dependence

* Depending on age
Conclusions

• Median survival of PMF patients is higher than 5.5 years but there is a wide heterogeneity.

• Main prognostic factors are age > 65 years, constitutional symptoms, Hb < 10 g/dL, leukocytosis > 25 x10⁹/L, and blood blasts ≥ 1%; certain karyotypic abnormalities, transfusion need and thrombocytopenia also contribute to prognosis.

• Based on the above factors it is possible to identify four risk groups at diagnosis and during the disease evolution.

• These risk groups are of help in treatment-decision making.