One Thousand Patients With Primary Myelofibrosis: The Mayo Clinic Experience

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Abstract

Objective: To share our decades of experience with primary myelofibrosis and underscore the importance of outcomes research studies in designing clinical trials and interpreting their results.

Patients and Methods: One thousand consecutive patients with primary myelofibrosis seen at Mayo Clinic between November 4, 1977, and September 1, 2011, were considered. The International Prognostic Scoring System (IPSS), dynamic IPSS (DIPSS), and DIPSS-plus were applied for risk stratification. Separate analyses were included for patients seen at time of referral (N=1000), at initial diagnosis (N=340), and within or after 1 year of diagnosis (N=660).

Results: To date, 592 deaths and 68 leukemic transformations have been documented. Parameters at initial diagnosis vs time of referral included median age (66 vs 65 years), male sex (61% vs 62%), red cell transfusion need (24% vs 38%), hemoglobin level less than 10 g/dL (38% vs 54%), platelet count less than 100 × 10^9/L (18% vs 26%), leukocyte count more than 25 × 10^9/L (13% vs 16%), marked splenomegaly (21% vs 31%), constitutional symptoms (29% vs 34%), and abnormal karyotype (31% vs 41%). Mutational frequencies were 61% for JAK2V617F, 8% for MPLW515, and 4% for IDH1/2. DIPSS-plus risk distributions at time of referral were 10% low, 15% intermediate-1, 37% intermediate-2, and 37% high. The corresponding median survivals were 17.5, 7.8, 3.6, and 1.8 years vs 20.0, 14.3, 5.3, and 4% for patients younger than 60 years of age. Compared with both DIPSS and IPSS, DIPSS-plus showed better discrimination among risk groups. Five-year leukemic transformation rates were 6% and 21% in low- and high-risk patients, respectively.

Conclusion: The current document should serve as a valuable resource for patients and physicians and provides context for the design and interpretation of clinical trials.

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Myelofibrosis (MF) refers to a myeloproliferative neoplasm (MPN), which is a World Health Organization (WHO) category of myeloid malignancies that also includes polycythemia vera (PV), essential thrombocythemia (ET), and chronic myelogenous leukemia.1 MPF is further subcategorized as primary myelofibrosis (PMF) and post-PV or post-ET MF.2 Luminaries in PMF include Gustav Heuck (1900-1969), who coined the term myeloproliferative disorders in 1951; Philip Fialkow (1934-1996), who led the effort in deciphering the Philadelphia chromosome,9 which was later shown to harbor an oncogenic BCR-ABL1 fusion transcript, which is the disease-causing mutation in chronic myelogenous leukemia.10-14 Accordingly, PMF is currently grouped with PV and ET as BCR-ABL1–negative MPN.15 In addition to the previously mentioned JAK2V617F,7 PMF and the other BCR-ABL1–negative MPNs are characterized by many other somatic mutations, including MPL, TET2, ASXL1, CBL, IDH1, IDH2, IKZF1, LNK, EZH2, DNMT3A, CUX1, and SF3B1 mutations.16-19 None of these mutations are MF-specific, and it is currently believed that these mutations constitute secondary events with poorly defined pathogenetic contribution.16

Primary myelofibrosis is currently diagnosed according to WHO criteria,20 whereas the International Working Group for Myeloproliferative Neoplasms Research and Treatment criteria are used to diagnose post-PV or post-ET MF.2 Patients typically present with anemia, marked splenomegaly, and characteristic laboratory features, including peripheral blood leukoerythroblastosis, dacrocytosis, increased serum lactate dehydrogenase level, excess

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circulating blasts, and bone marrow stromal changes (eg, collagen fibrosis, osteosclerosis, and angiogenesis). Current prognostication in PMF is based on the Dynamic International Prognostic Scoring System (DIPSS)-plus.\textsuperscript{21} Drug therapy in PMF is currently not curative and has not been shown to prolong survival.\textsuperscript{22} Allogeneic stem cell transplant (ASCT) might result in prolonged disease remission in a select group of patients but is associated with a relatively high risk of treatment-related death and morbidity.\textsuperscript{23,24} The constitutive activation of janus kinase–signal transducers and activators of transcription (JAK-STAT) in PMF offered hope for targeted therapy, but currently available JAK inhibitor drugs have yet to meet expectations in terms of hematologic, cytogenetic, or molecular remissions.\textsuperscript{24,25}

This article summarizes our decades of experience with PMF. We considered 1000 consecutive patients who were seen between 1977 and 2011 and in whom clinical and bone marrow pathologic information was available for review. Our objectives were to define (1) presenting clinical and laboratory features for both patients seen at time of diagnosis and those seen at different time points from diagnosis and (2) the natural history of the disease, including overall and leukemia-free survival, in the context of contemporary prognostic scoring systems. This article should serve as a valuable resource for patients and physicians as well as provide context for the design and interpretation of clinical trials.

PATIENTS AND METHODS

The current study was approved by the Mayo Clinic Institutional Review Board. All patients in whom molecular studies were performed provided informed written consent for study sample collection and permission for use in research. Study eligibility criteria included availability of information on bone marrow histology and karyotype at time of referral to Mayo Clinic. On re-review of all 1000 study patients, the availability of cytogenetic information was confirmed in 967 cases (97%). The diagnoses of PMF and leukemic transformation were made according to WHO criteria.\textsuperscript{1} Patients with blast-phase disease at the time of their referral to Mayo Clinic were excluded from the study. MPL and JAK2 mutation analyses were performed according to previously published methods.\textsuperscript{26–29} IDH1 and IDH2 mutations were analyzed by direct sequencing and/or high-resolution melting assay.\textsuperscript{30} Unfavorable karyotype designation\textsuperscript{31} and International Prognostic Scoring System (IPSS),\textsuperscript{32} DIPSS,\textsuperscript{33} and DIPSS-plus\textsuperscript{31} risk categorizations were as previously described. Unfavorable karyotype included complex karyotype or 1 or 2 abnormalities that included +8, \(-77q\), \(-8q\), \(-17q\), inv(3), \(-5/\text{5q}\), \(-12p\), or \(11q23\) rearrangement.\textsuperscript{31}

International Prognostic Scoring System uses 5 risk factors, including age greater than 65 years, hemoglobin level less than 10 g/dL, leukocyte count more than \(25 \times 10^9/L\), circulating blasts of 1% or more, and presence of constitutional symptoms; the presence of 0, 1, 2, and 3 or more risk factors defined low, intermediate-1, intermediate-2, and high risk disease, respectively.\textsuperscript{32} DIPSS uses these same 5 risk factors but assigns 2 points to hemoglobin level less than 10 g/dL and 1 point each to the remaining 4 risk factors; the presence of 0, 1 or 2, 3 or 4, and 5 or 6 points defined low, intermediate-1, intermediate-2, and high risk disease, respectively.\textsuperscript{33} DIPSS plus uses the 5 IPSS risk factors plus 3 more: red cell transfusion need, platelet count less than \(100 \times 10^9/L\), and unfavorable karyotype.\textsuperscript{21} These 8 DIPSS plus risk factors are used to define low (no risk factors), intermediate-1 (1 risk factor), intermediate-2 (2 or 3 risk factors), and high (≥4 risk factors) risk groups.\textsuperscript{34} Leukemic transformation risk was considered high in the presence of unfavorable karyotype or platelet count less than \(100 \times 10^9/L\) or low in the absence of both of these risk factors.\textsuperscript{21}

All statistical analyses considered clinical and laboratory parameters obtained at time of first referral to Mayo Clinic. Separate analyses were included for patients seen at time of initial diagnosis and for those seen within 1 year of diagnosis. Differences in the distribution of continuous variables between categories were analyzed by either the Mann-Whitney (for comparison of 2 groups) or Kruskal-Wallis (for comparison of ≥3 groups) test. Patient groups with nominal variables were compared by the \(\chi^2\) test. Overall survival was calculated from the date of first referral to date of death (uncensored) or last contact (censored). Leukemia-free survival was calculated from the date of first referral to the date of leukemic transformation (uncensored) or death or last contact (censored). Overall and leukemia-free survival curves were prepared by the Kaplan-Meier method and compared by the log-rank test. The Cox proportional hazards regression model was used for multivariate analysis. \(P<.05\) was considered significant. The StatView (SAS Institute, Cary, NC) statistical package was used for all calculations.

RESULTS

A total of 1000 consecutive patients with PMF seen at Mayo Clinic between November 4, 1977, and September 1, 2011, were considered and included 340 patients seen at time of initial diagnosis and 660 patients seen within (n = 274) or beyond (n = 386) 1 year of their diagnosis. Information regarding presenting clinical and laboratory features was available in all 1000 patients for most parameters (Table 1). All patients had information on the 5 variables (see Patients and Methods section) that were required for
risk stratification according to IPSS\(^3\) or DIPSS.\(^3\) DIPSS-plus\(^\text{21}\) and leukemia risk stratification was possible in 967 patients in whom karyotype information was available. Information on JAK2\(^4\), MPL, and IDH mutations was available in 583, 341, and 305 patients, respectively (Table 1).

As expected, there were significant differences in the percentage of patients presenting with transfusion-requiring anemia, hemoglobin level less than 10 g/dL, platelet count less than 100 \(\times 10^9/L\), circulating blasts of 1% or more, constitutional symptoms, and DIPSS-plus risk distribution between patients seen at time of initial diagnosis vs those seen within 1 year of diagnosis vs those seen after 1 year of diagnosis (Table 1). These differences were most apparent between patients seen at time of initial diagnosis (Group A) vs those seen within 1 year of diagnosis (Group B) vs those seen after 1 year of diagnosis (Group C) (Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. evaluable (N=1000)</th>
<th>Patients seen at time of diagnosis (n=340)</th>
<th>Patients seen within 1 y of diagnosis (n=274)</th>
<th>Patients seen more than 1 y after diagnosis (n=386)</th>
<th>P value(^b) for groups A vs B</th>
<th>P value(^b) for groups B vs C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), median (range)</td>
<td>1000</td>
<td>65 (14-92)</td>
<td>66 (14-92)</td>
<td>64 (19-89)</td>
<td>65 (26-90)</td>
<td>.14</td>
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<tr>
<td>Age &gt;65 y, No.</td>
<td>1000</td>
<td>477 (48)</td>
<td>172 (51)</td>
<td>124 (45)</td>
<td>181 (47)</td>
<td>.19</td>
</tr>
<tr>
<td>Males, No.</td>
<td>1000</td>
<td>621 (62)</td>
<td>206 (61)</td>
<td>173 (63)</td>
<td>242 (63)</td>
<td>.52</td>
</tr>
<tr>
<td>Hemoglobin (g/dL), median (range)</td>
<td>1000</td>
<td>10 (5-16.1)</td>
<td>10.8 (5-16.1)</td>
<td>10 (6-15)</td>
<td>10 (5-16)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Leukocytes ((\times 10^9/L)), median (range)</td>
<td>1000</td>
<td>9 (1-236)</td>
<td>10 (1-147)</td>
<td>8 (1-236)</td>
<td>9 (1-179)</td>
<td>.14</td>
</tr>
<tr>
<td>Platelets ((\times 10^9/L)), median (range)</td>
<td>1000</td>
<td>209 (6-2466)</td>
<td>304 (6-2466)</td>
<td>192 (11-1765)</td>
<td>172 (7-1633)</td>
<td>&lt;.001</td>
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<td>Circulating blasts (%), median (range)</td>
<td>1000</td>
<td>1 (0-33)</td>
<td>0 (0-9)</td>
<td>1 (0-33)</td>
<td>1 (0-18)</td>
<td>.009</td>
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<td>DIPSS-plus risk group</td>
<td>967</td>
<td>10</td>
<td>16</td>
<td>10</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Intermediate-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Intermediate-2</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>High</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Constitutional symptoms, No.</td>
<td>1000</td>
<td>336 (34)</td>
<td>99 (29)</td>
<td>105 (38)</td>
<td>132 (34)</td>
<td>.02</td>
</tr>
<tr>
<td>Circulating blasts (\geq 1%), No.</td>
<td>1000</td>
<td>555 (56)</td>
<td>154 (45)</td>
<td>148 (54)</td>
<td>253 (66)</td>
<td>.03</td>
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<tr>
<td>Hemoglobin &lt;10 g/dL, No.</td>
<td>1000</td>
<td>535 (54)</td>
<td>130 (38)</td>
<td>158 (58)</td>
<td>247 (64)</td>
<td>&lt;.001</td>
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<tr>
<td>Transfusion requiring, No.</td>
<td>1000</td>
<td>383 (38)</td>
<td>83 (24)</td>
<td>126 (46)</td>
<td>174 (45)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Leukocytes &gt;25 (\times 10^9/L), No.</td>
<td>1000</td>
<td>159 (16)</td>
<td>43 (13)</td>
<td>38 (14)</td>
<td>78 (20)</td>
<td>.66</td>
</tr>
<tr>
<td>Platelets &lt;100 (\times 10^9/L), No.</td>
<td>1000</td>
<td>256 (26)</td>
<td>61 (18)</td>
<td>76 (28)</td>
<td>119 (31)</td>
<td>.004</td>
</tr>
<tr>
<td>Leukocytes &lt;4 (\times 10^9/L), No.</td>
<td>1000</td>
<td>159 (16)</td>
<td>43 (12)</td>
<td>49 (18)</td>
<td>66 (19)</td>
<td>.04</td>
</tr>
<tr>
<td>JAK2V617F, No.</td>
<td>583</td>
<td>358 (61)</td>
<td>115 (62)</td>
<td>106 (61)</td>
<td>137 (61)</td>
<td>.86</td>
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<td>MPL mutation, No.</td>
<td>341</td>
<td>28 (8)</td>
<td>9 (10)</td>
<td>7 (6)</td>
<td>12 (9)</td>
<td>.31</td>
</tr>
<tr>
<td>IDH mutation, No.</td>
<td>305</td>
<td>12 (4)</td>
<td>4 (5)</td>
<td>6 (6)</td>
<td>2 (2)</td>
<td>.87</td>
</tr>
<tr>
<td>Palpable spleen (\geq 10 cm), No.</td>
<td>1000</td>
<td>307 (31)</td>
<td>70 (21)</td>
<td>61 (22)</td>
<td>176 (46)</td>
<td>.64</td>
</tr>
<tr>
<td>Splenectomy, No.</td>
<td>1000</td>
<td>166 (17)</td>
<td>30 (9)</td>
<td>33 (12)</td>
<td>103 (27)</td>
<td>.19</td>
</tr>
<tr>
<td>Cytogenetic categories</td>
<td>967</td>
<td>568 (59)</td>
<td>218 (69)</td>
<td>169 (63)</td>
<td>181 (47)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td>261 (27)</td>
<td>66 (21)</td>
<td>62 (23)</td>
<td>133 (35)</td>
<td></td>
</tr>
<tr>
<td>Favorable(^c)</td>
<td></td>
<td>134 (18)</td>
<td>33 (10)</td>
<td>36 (13)</td>
<td>69 (18)</td>
<td></td>
</tr>
<tr>
<td>Unfavorable(^c)</td>
<td></td>
<td>34 (3)</td>
<td>9 (3)</td>
<td>13 (5)</td>
<td>12 (3)</td>
<td>.16</td>
</tr>
<tr>
<td>Transplantation, No.</td>
<td>1000</td>
<td>590 (59)</td>
<td>172 (51)</td>
<td>161 (59)</td>
<td>257 (67)</td>
<td>.04</td>
</tr>
<tr>
<td>Deaths, No.</td>
<td>1000</td>
<td>67 (7)</td>
<td>24 (7)</td>
<td>21 (8)</td>
<td>22 (6)</td>
<td>.77</td>
</tr>
</tbody>
</table>

\(^a\) Data are presented as No. (percentage) unless indicated otherwise. DIPSS = Dynamic International Prognostic Scoring System-plus.\(^\text{21}\)

\(^b\) Bold font denotes statistically significant values.

\(^c\) Unfavorable karyotype included complex karyotype or 1 or 2 abnormalities that included +8, −7/7q−, i(17q), inv(3), −5/5q−, 12p−, or 11q23 rearrangement; all other cytogenetic abnormalities were considered favorable.\(^\text{31}\)
agnosis and those seen within 1 year of their diagnosis and much less pronounced between patients seen within 1 year of diagnosis and those seen after 1 year of diagnosis (Table 1).

The independent detrimental effect of the 8 risk factors that are currently used in DIPSS-plus was confirmed in the current series of 967 patients, although multivariate analysis showed only borderline significance for red blood cell transfusion need (Table 2); the latter observation reflects the independent prognostic effect of red blood cell transfusion need and hemoglobin level less than 10 g/dL. Using DIPSS-plus, median overall survival calculated from time of referral (n=967) were 17.5, 7.8, 3.6, and 1.8 years for low, intermediate-1 (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.4-3.2), intermediate-2 (OR, 4.5; 95% CI, 3.1-6.7), and high (OR, 9.9; 95% CI, 6.6-14.7) risk disease, respectively (Figure 1). The corresponding values for patients seen within 1 year of diagnosis (n=584) were largely similar (19.2, 8.1, 4.7, and 1.7 years; P<.001; Supplemental Figure 3, online at http://www.mayoclinicproceedings.org) and, therefore, confirm the value of DIPSS-plus in accurately estimating overall survival from any point during the disease course.

Figures 1 and 2 demonstrate that DIPSS-plus, compared with DIPSS, performed better in discriminating risk groups when overall survival was analyzed from time of referral. The same was true when overall survival was analyzed from within 1 year of initial diagnosis (Supplemental Figures 1, 2, and 3, available at http://www.mayoclinicproceedings.org). For example, for survival calculated from time of referral, the OR (95% CI) for high vs intermediate-2 risk disease was 2.1 (1.8-2.5) using DIPSS-plus (Figure 1) and 1.6 (1.3-2.1) using DIPSS (Figure 2). The corresponding values in the context of survival of patients seen within 1 year of their diagnosis (n=614) were 2.7 (2.0-3.5) for DIPSS-plus, 1.8 (1.3-2.5) for DIPSS, and 2.1 (1.6-2.7) for IPSS (Supplemental Figures 1, 2, and 3, available online at http://www.mayoclinicproceedings.org). Similarly, the distinction between intermediate-2 and intermediate-1 risk disease was more robust with DIPSS-plus (OR, 2.1; 95% CI, 1.5-2.9) or DIPSS (OR, 2.3; 95% CI, 1.8-3.0), as opposed to IPSS (OR, 1.7; 95% CI, 1.2-2.3) (Supplemental Figures 1, 2, and 3, available online at http://www.mayoclinicproceedings.org).

Figure 3 reveals the very good prognosis, in terms of overall survival, of young patients (age <60 years) who are in the DIPSS-plus low (median survival of 20.0 years) or intermediate-1 (median survival of 14.3 years) risk group. Finally, a total of 318 patients were considered at high risk for leukemic transformation because they displayed either an unfavorable karyotype or a platelet count less than 100 x 10^9/L, or both21; their 5-year risk of leukemic transformation was 21% vs 6% in the 649 patients without these risk factors (P<.001; OR, 3.5; 95% CI, 2.1-5.5).

**DISCUSSION**

This report represents the largest single institutional study in PMF (N=1000), and also the largest study of its kind that included cytogenetic information (n=967). The study provides baseline clinical and laboratory information at time of initial diagnosis, as well as at time of referral. The study confirms that PMF is diagnosed relatively late in life (median age, 66 years) and has a male preponderance (3:2). In a previous population-based study, the median age at diagnosis was similar to 67 years.34 At time of referral, only 13% of the patients were younger than 50 years and 31% were younger than 60 years (data not shown). The corresponding figures for patients seen

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**TABLE 2. Univariate and Multivariate P Values and Odds Ratios (95% CI) in 1000 Mayo Clinic Patients With Primary Myelofibrosis for 8 Risk Factors Currently Used in DIPSS-plus**

<table>
<thead>
<tr>
<th>DIPSS-plus risk factor</th>
<th>Univariate P value</th>
<th>Odds ratio (95% CI)</th>
<th>Multivariate P value</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 y</td>
<td>&lt;.001</td>
<td>2.1 (1.7-2.4)</td>
<td>&lt;.001</td>
<td>1.7 (1.5-2.1)</td>
</tr>
<tr>
<td>RBC transfusion need</td>
<td>&lt;.001</td>
<td>2.4 (2.0-2.9)</td>
<td>.06</td>
<td>1.3 (1.0-1.6)</td>
</tr>
<tr>
<td>Hemoglobin &lt;10 g/dL</td>
<td>&lt;.001</td>
<td>2.4 (2.1-2.9)</td>
<td>&lt;.001</td>
<td>1.6 (1.3-2.1)</td>
</tr>
<tr>
<td>Leukocyte count &gt;25 x 10^9/L</td>
<td>&lt;.001</td>
<td>2.1 (1.8-2.6)</td>
<td>&lt;.001</td>
<td>2.0 (1.6-2.4)</td>
</tr>
<tr>
<td>Circulating blasts ≥1%</td>
<td>&lt;.001</td>
<td>1.9 (1.6-2.2)</td>
<td>&lt;.001</td>
<td>1.5 (1.2-1.7)</td>
</tr>
<tr>
<td>Platelet count &lt;100 x 10^9/L</td>
<td>&lt;.001</td>
<td>2.4 (2.0-2.9)</td>
<td>&lt;.001</td>
<td>1.6 (1.3-1.9)</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>&lt;.001</td>
<td>1.7 (1.4-2.0)</td>
<td>.02</td>
<td>1.2 (1.0-1.5)</td>
</tr>
<tr>
<td>Unfavorable karyotypeb</td>
<td>&lt;.001</td>
<td>2.5 (2.0-3.1)</td>
<td>&lt;.001</td>
<td>1.9 (1.5-2.3)</td>
</tr>
</tbody>
</table>

*CI = confidence interval; DIPSS = Dynamic International Prognostic Scoring System-plus21; RBC = red blood cell.

bKaryotype information available in 967 patients.
within 1 year of diagnosis were not significantly different (16% and 34%). Approximately 48% of the patients younger than 60 years displayed either low risk (median survival, 20.0 years) or intermediate-1 risk (median survival, 14.3 years) disease. It is reasonable to conclude that less than 20% of patients with PMF are currently suitable for consideration of treatment with ASCT. In contrast, the latter treatment modality remains indispensable for young patients with high risk (median survival, 1.7 years) or intermediate-2 risk (median survival, 5.3 years) disease because of recent information that did not show a survival advantage in patients treated with novel drugs, including ruxolitinib and pomalidomide.

The current study also provides valuable information regarding the proportion of patients with PMF who present with adverse risk factors and with disease aspects that significantly compromise quality of life. For example, more than half of the patients were symptomatically anemic (ie, hemoglobin <10 g/dL) at time of referral and 38% required red blood cell transfusions, underscoring the dire need for an antianemia drug in PMF. The particular information also points out the limitations of drugs that display anemia as an adverse effect, which is a recurrent issue with certain JAK inhibitors. The study also suggests that about a third of patients present with marked splenomegaly or constitutional symptoms and might, therefore, benefit from JAK inhibitor therapy. However, most of these patients either belong to higher-risk disease categories, which mandate instead consideration for ASCT, or are the same ones who have anemia or thrombocytopenia, which happen to constitute the main adverse effects of such drugs.

One interesting aspect of the current study was the significantly higher prevalence of adverse risk factors in patients seen within 1 year of diagnosis compared with those seen at the time of initial diag-

FIGURE 1. Overall survival data, from time of referral, among 967 Mayo Clinic patients with primary myelofibrosis risk-stratified by the Dynamic International Prognostic Scoring System (DIPSS)-plus.21
nosis, a phenomenon that was much less pronounced when patients seen within 1 year of diagnosis were compared with those seen beyond the first year of diagnosis (Table 1). The particular observation suggests that many patients newly diagnosed with PMF may not have reached phenotypic equilibrium and that more accurate prognostication requires follow-up assessment after a few months. In this regard, the current study illustrates the superiority of DIPSS-plus, as a prognostic tool, over both DIPSS and IPSS, regardless of time of evaluation (ie, at diagnosis or time of referral). This result was not totally unexpected because of the well-established prognostic relevance of karyotype in myeloid malignancies. We have in the past consistently shown the independent prognostic value of cytogenetic abnormalities, as well as thrombocytopenia and red blood cell transfusion need, in PMF. Similarly, there is no doubt that the current prognostic models will be further refined on the basis of new information regarding DIPSS-plus–independent genetic and biological risk factors, some of which also appear to be relevant in the context of myelodysplastic syndromes.

On the basis of observations from the current study, we recommend the use of DIPSS-plus as the principal prognostic tool in PMF, both at time of diagnosis and at any point during the disease course. In this regard, we also encourage deeper examination of cytogenetic details and degree of elevation in circulating blasts and leukocytes in order to identify patients with a very high risk of early death. In the absence of cytogenetic information, we prefer IPSS for prognostication at time of diagnosis and DIPSS for prognostication at time of referral beyond the time of initial diagnosis. Once accurate prognostication has been accomplished, the excellent prognosis associated with low-risk disease (median survival of all patients and up to 20 years for younger patients) mandates a high threshold for intervening with specific therapy. We also do not believe that the risk of ASCT is justified in intermediate-1 risk young patients with PMF because of their relatively good prognosis (median survival estimated at 14 years). In contrast, high-risk patients might be best served by treatment with ASCT. It is reasonable to consider either ASCT or experimental drug therapy in the presence of inter-
mediate-2 risk disease. In this regard, we have yet to be impressed by the overall therapeutic value of any of the currently available JAK inhibitors or other novel drugs used in PMF and encourage patients and physicians to instead consider participating in newer clinical trials.

CONCLUSION

We present results of the largest study ever described in karyotypically annotated PMF. The study provides the full spectrum of clinical and laboratory characteristics of patients with WHO-defined PMF, both at diagnosis and at time of referral to a tertiary center of excellence for MPN. The results indicate that the disease affects primarily older patients (median age at diagnosis, 66 years) and has a slight male preponderance (62% males). At initial diagnosis, approximately 24% of patients display transfusion-requiring anemia, 29%, severe constitutional symptoms; and 21%, marked splenomegaly. However, within 1 year of diagnosis, the corresponding incidences were increased to 46%, 38%, and 22%, respectively, which indicates the need to wait for a few months after diagnosis before establishing a prognostic score for the individual patient. The current study strongly validates the DIPSS-plus prognostic scoring system for PMF and reveals an outstanding prognosis for young patients (age <60 years) with low-risk disease (median survival, 20 years), whereas high-risk or intermediate-2 risk disease was associated with a median survival of less than 5 years, regardless of age. From a practical standpoint, this translates to the prudence of conservative management in low-risk and intermediate-1 risk patients and early consideration of ASCT in higher-risk patients. In this regard, it is of utmost importance to obtain cytogenetic information in every patient with PMF, and this can be accomplished by studying either the bone marrow or peripheral blood. We believe that current prognostication in PMF will improve significantly in the near future due to advances in biotechnology that will allow improved genetic profiling.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org.
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