Allogeneic hematopoietic cell transplantation for patients with myelofibrosis
Dae Young Zang and H. Joachim Deeg

Introduction
Primary myelofibrosis (PMF) [also referred to as myelofibrosis with myeloid metaplasia (MMF) or chronic idiopathic myelofibrosis (CIFM)] is one of the Philadelphia chromosome-negative clonal myeloproliferative disorders (MPDs). PMF is characterized by the proliferation mainly of megakaryocytic and granulocytic elements in the bone marrow, which is associated with deposition of connective tissue (reticulin and collagen) due to a response of marrow fibroblasts to signals derived from the hematopoietic clone. Typical additional features are circulating immature hematopoietic cells and extramedullary hematopoeisis. A similar picture of myelofibrosis may develop in patients originally diagnosed with polycythemia vera or essential thrombocythemia and is termed postpolycythemia vera or postessential thrombocythemia myelofibrosis [1].

Purpose of review
Hematopoietic cell transplantation (HCT) offers potentially curative therapy for patients with myelofibrosis. What is the current status?

Recent findings
Changes in transplant strategies allow offering HCT to patients who, because of age or comorbid conditions, were not considered transplant candidates in the past. The omission of high-dose total body irradiation, adjusting doses of busulfan to achieve defined target levels, using fludarabine instead of cyclophosphamide as an immunosuppressive agent, the addition of melphalan, and the incorporation of antithymocyte globulin all appear to have contributed to better tolerability of new regimens. Reduced-intensity conditioning regimens are associated with a decrease in nonrelapse mortality and allow for successful HCT, even in patients 60–70 years of age. Some 50–75% of patients are cured by HCT. Emerging concepts include new prognostic scoring systems and novel molecular markers such as Janus kinase 2 mutations, which may aid in making treatment decisions and assessing remission status.

Summary
Modifications of transplant-conditioning regimens have reduced transplant-related mortality and allow carrying out successful HCT in increasingly older patients. The selection of patients who should be transplanted, the optimal timing for transplantation, and pretransplant and posttransplant strategies remain challenging problems.

Keywords
allogeneic hematopoietic cell transplantation, myelofibrosis, nonrelapse mortality, relapse
Allogeneic hematopoietic cell transplantation with conventional (myeloablative) conditioning

The extensive marrow fibrosis associated with PMF was initially considered a contraindication for HCT. However, despite earlier concerns that marrow fibrosis may hinder hematopoietic recovery following allogeneic HCT [5,6], multiple reports on small numbers of patients have shown that engraftment is obtained consistently and that extensive fibrosis (and even osteosclerosis) is completely reversible with successful allogeneic HCT [7,8]. Those results were subsequently confirmed in larger series. Guardiola et al. [9] reported in 1999 combined results from several European and American transplant centers. Another report presented by Deeg et al. [10] in 2003 summarized results from the Fred Hutchinson Cancer Research Center in Seattle. In the two cohorts of 55 and 56 PMF patients, the median age at HCT was 42 and 43 years, respectively, treatment-related mortality (TRM) was 27% and 33%, and 5-year survival was 47 and 58%, respectively. The 5-year probability of treatment failure due to relapse or persistent disease after HCT was 36% [28% for patients receiving an unmanipulated human leukocyte antigen (HLA)-matched related transplant] in the report by Guardiola et al. [9]. In the Seattle study [10], the incidence of failure of sustained engraftment, occurring solely in patients receiving transplants from alternative donors, was 10%.

An update of the Seattle data included results in 104 patients (56 related and 45 unrelated allogeneic and 3 syngeneic HCT). Diagnoses included PMF (n = 62), postessential thrombocythemia myelofibrosis (n = 18), postpolycythemia vera myelofibrosis (n = 12), or myelofibrosis with unclassified MPDs (n = 12) [11**]. Patient age was 18–70 (median 49) years, and the source of stem cells was bone marrow in 43 and granulocyte colony stimulating factor mobilized peripheral blood cells in 61 patients. Busulfan or total body irradiation (TBI)-based conventional conditioning regimens were used in 95 patients and a reduced intensity regimen consisting of fludarabine (3 x 30 mg/m²) and 200 cGy of TBI in nine patients. The estimated 7-year survival was 61%, and nonrelapse mortality at 5 years was 34%. In a multivariate analysis, superior survival was observed among patients conditioned with targeted oral busulfan (steady state target levels 800–900 ng/ml) and i.v. cyclophosphamide, 60 mg/kg/day x 2 (tBUCY), among younger patients, patients with a low comorbidity score as described by Sorror et al. [12], and in patients with platelet counts greater than 100 x 10⁹ cells/l at HCT. Data from five important studies are summarized in Table 1 [13–20].

Thus, these results, taken together, show that in patients with myelofibrosis, engraftment can be achieved consistently, and more than 50% of patients survive long term in remission, with follow-up extending currently beyond 15 years. However, results are unsatisfactory particularly in patients more than 60 or 65 years of age, that is, about the median age at the time of diagnosis.

### Table 1 Selected series of allogeneic transplants for myelofibrosis using conventional or reduced-intensity conditioning regimens

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Median age (range), years</th>
<th>Nonrelapse mortality, %</th>
<th>Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional conditioning</td>
<td></td>
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<tr>
<td>Guardiola et al. [9]</td>
<td>55</td>
<td>42 (4–53)</td>
<td>27 at 1 year</td>
<td>47 at 5 years</td>
</tr>
<tr>
<td>Deeg et al. [10]</td>
<td>56</td>
<td>43 (10–66)</td>
<td>20 at 1 year</td>
<td>58 at 3 years</td>
</tr>
<tr>
<td>Daly et al. [13]</td>
<td>25</td>
<td>49 (46–50)</td>
<td>48 at 1 year</td>
<td>41 at 2 years</td>
</tr>
<tr>
<td>Ditkowskii et al. [14]</td>
<td>20</td>
<td>45 (22–57)</td>
<td>45 at 1 year</td>
<td>39 at 3 years</td>
</tr>
<tr>
<td>Kerbauy et al. [11**]</td>
<td>104</td>
<td>49 (18–70)</td>
<td>34 at 5 years</td>
<td>61 at 7 years</td>
</tr>
<tr>
<td>Reduced-intensity conditioning</td>
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<td></td>
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<tr>
<td>Devine et al. [15]</td>
<td>4</td>
<td>56 (48–58)</td>
<td>0 at 1 year</td>
<td>100 at 1 year</td>
</tr>
<tr>
<td>Hessling et al. [16]</td>
<td>3</td>
<td>51 (44–58)</td>
<td>0 at 1 year</td>
<td>100 at 1 year</td>
</tr>
<tr>
<td>Ronzelli et al. [17]</td>
<td>21</td>
<td>54 (27–68)</td>
<td>10 at 1 year</td>
<td>85 at 2.5 years</td>
</tr>
<tr>
<td>Kroger et al. [18]</td>
<td>21</td>
<td>53 (32–63)</td>
<td>16 at 1 year</td>
<td>84 at 3 years</td>
</tr>
<tr>
<td>Merup et al. [19]</td>
<td>10</td>
<td>58</td>
<td>10 at 1 year</td>
<td>90 at 1 year</td>
</tr>
<tr>
<td>Snyder et al. [20]</td>
<td>9</td>
<td>54</td>
<td>40 at 1 year</td>
<td>56 at 1 year</td>
</tr>
</tbody>
</table>

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Allogeneic hematopoietic cell transplantation following reduced-intensity conditioning

The introduction of reduced-intensity conditioning regimens is based on the concept of shifting the emphasis of eradication of tumor cells from high-dose chemo (or radio) therapy to the donor cell-mediated immunological graft-versus-tumor effect. The potential advantages are low regimen-related morbidity and mortality, in general, and the applicability to older patients or patients with clinically significant comorbid conditions, in particular. Evidence for an immunologically mediated graft-versus-myelofibrosis effect comes from reports on patients who relapsed after allogeneic HCT and showed remarkable reduction of bone marrow fibrosis after donor lymphocyte infusion [21,22]. As fibrosis is only a reactive process in response to clonal hematopoietic cells, an antihematopoietic cell effect of donor lymphocytes should lead to the eventual regression of fibrosis. The use of reduced-intensity conditioning regimens in patients with PMF was first reported by Devine et al. [15] and...
Hessling et al. [16]. Those preliminary reports indicated that reduced-intensity conditioning was well tolerated and provided effective therapy. Some important reports on reduced intensity conditioning in patients with myelofibrosis are summarized in Table 1 [9,10,11*,13–20].

In a retrospective registry study, including European and American institutions of the MPDs Consortium, Rondelli et al. [17] reported on 21 patients (including updated results of four patients previously presented by Devine et al. [15]). The median age of the patients was 54 (range 27–68) years. All patients had intermediate or high severity scores according to Dupriez grading, which take into account hemoglobin (Hb) and white blood cell values [23]. No patient had evidence of acute transformation. Various conditioning regimens were used, most containing fludarabine. TRM was 10%, and 2-year overall survival (OS) was 87%. Eighteen patients were alive 12–122 (median 31) months after HCT and 17 were in remission (one after a second transplant); the relapse rate was 14%.

A prospective study of 21 patients, median age of 53 (range 32–63) years, reported remarkably similar data [18]. One patient had accelerated disease with a blast count of 17% at the time of HCT, and two patients had secondary acute myeloid leukemia, but were in complete or partial remission at HCT. The conditioning regimen consisted of busulfan and in-vivo T cell depletion with antithymocyte globulin. TRM was 16% at 1 year. Hematological responses were seen in 100% and complete histopathological remission in 75% of the patients; 25% of the patients showed partial histopathological remission with a continuing decline in the grade of marrow fibrosis. No primary graft failure was observed, and only one secondary graft failure was seen. After a median follow-up of 22 (range 4–59) months, the 3-year estimated overall and disease-free survival was 84%. In this study, five of six patients who were 55 years or older (55, 58, 62, 63, and 64 years, respectively) received transplants from unrelated donors and survived for more than 59, 22, 8, 8, 64 years, respectively, and 6 months, respectively.

A retrospective comparison between two conditioning regimens was performed in a small cohort of 27 patients transplanted between 1982 and 2004 by the Swedish Group for MPDs [19]. Treatment-related mortality was higher (30%) among 17 patients who received cyclophosphamide and TBI (‘high dose’) conditioning compared with 10 patients given ‘reduced intensity’ conditioning with a busulfan and cyclophosphamide regimen ($P = \text{NS}$).

In a prospective trial of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation, 104 patients with PMF and a median age of 55 (range, 32–68) years were included. The risk distribution was as follows: low risk with constitutional symptoms (18%), intermediate risk (58%), and high risk (19%). All, but three patients received peripheral blood stem cells either from related ($n = 31$) or unrelated donors ($n = 69$). Acute graft-versus-host disease (GVHD) (grades II–IV) occurred in 19%, and severe acute GVHD (grades III/IV) in 7%, whereas chronic GVHD was seen in 32% of patients. Nonrelapse mortality at 1 year was 19% [95% confidence interval (CI), 11–27%] and was significantly lower for patients younger than 50 years of age (0 versus 27%; $P = 0.004$) and for patients with low versus intermediate/high-risk disease (0 versus 27%; $P = 0.02$). The 3-year OS and event-free survival was 70% (95% CI, 60–80%) and 55% (95% CI, 42–68%), respectively. Significant factors for superior survival were younger age and low-risk disease, whereas cytogenetic abnormalities, JAK2 mutation status, and donor type (related versus unrelated) had no significant effect [24*].

In another single center study (reported in abstract form), including 39 patients who received a dose-reduced conditioning consisting of thiopeta and cyclophosphamide, favorable factors for improved survival were HLA-identical donor, Karnofsky index of 100%, time from diagnosis to transplantation less than 1 year, and previous splenectomy [25*].

Overall, the most commonly used regimens were busulfan/fludarabine or melphalan/fludarabine based. In comparison to studies with conventional conditioning, the median age of patients in studies using reduced-intensity regimens was more than a decade older. The nonrelapse mortality was less than 20%, and the OS after short follow-up was 55–85% [15–19].

These results suggest that reduced-intensity conditioning regimens, followed by related or unrelated-allogeneic HCT, may be associated with low TRM. It also seems that long-term control of the disease is achieved in a high proportion of patients. Transplantation from unrelated donors is associated with greater TRM, although not so significantly; clearly, however, results need to be confirmed in a larger number of patients. The reversal of disease manifestations or sequelae may not be complete, even in patients without hematologic relapse, as some degree of splenomegaly or marrow fibrosis may persist.

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**Splenectomy in patients with myelofibrosis undergoing allogeneic hematopoietic cell transplantation**

Splenomegaly in PMF is a reflection of an expansion of the underlying malignant clone, and as such, splenectomy may help to debulk the disease and facilitate disease eradication. Moreover, splenomegaly leads to...
sequestration of donor cells after HCT, causing delayed engraftment, if not graft failure. Indeed, some reports have shown faster engraftment in splenectomized patients [9,10]. Li et al. [26] analyzed the impact of pretransplant splenectomy on posttransplant outcome in 26 patients. Posttransplant granulocyte recovery was faster among splenectomized patients, and the need for both red blood cell and platelet transfusions was greater among patients who had their spleens intact. The 3-year probability of disease-free survival was 73% for splenectomized patients and 64% for patients without splenectomy (P > NS). However, this was a retrospective analysis, and splenectomy, for various reasons, generally had occurred by the time the patient was referred to the transplant center.

Thus, the role of splenectomy before allogeneic HCT remains controversial. A compelling reason against routine use of splenectomy is an operative mortality rate of 5–8% [24,27,28]. In clinical practice, splenectomy typically is undertaken in patients who are symptomatic from splenomegaly, patients with refractory hemolytic anemia, or those with complications of portal hypertension [29].

Evaluation for residual disease after allogeneic transplantation

Recently, mutations of JAK2, particularly V617F, have been identified in about 50% of patients with PMF [30,31], about 60% of patients with essential thrombocythemia, and nearly 100% of patients with polycythemia vera [28]. In a longitudinal prospective study by Barosi et al. [32**], the presence of JAK2 mutations, present in 63% of 174 cases, independently predicted progression towards large splenomegaly and leukemic transformation. A confirmation by others, however, is lacking. Methods such as real-time PCR allow for monitoring of treatment responses at the molecular level [33]. The impact of JAK2 mutations and outcome after allogeneic HCT remains to be determined. In one study of 30 patients, the JAK2 mutation status did not appear to influence outcome after allografting [34]. However, JAK2 mutation screening with highly sensitive PCR should prove useful in assessing the level of remission after allografting and should aid in defining complete remission in patients with myelofibrosis, especially after allogeneic HCT. The criteria for complete remission, recently proposed by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT), includes the disappearance of disease-related symptoms, peripheral blood levels of Hb of 110 g/l (11 g/dl) or higher, and platelet counts of 100 x 10^9 cells/l or higher [35]. After allogeneic HCT, the hematologic parameters may be influenced by poor graft function, GVHD, or infections and cannot be used as valid remission parameters. On the contrary, normal blood cell counts and disappearance of disease-related symptoms do not exclude residual disease.

In one study by Kroger et al. [36**] among 21 JAK2 (V617F)-positive patients with myelofibrosis, 78% became PCR-negative after reduced-intensity conditioning and allogeneic HCT. In 15 of 17 patients tested (88%), no JAK2 mutation was detectable after a median follow-up of 20 months. JAK2 negativity was achieved after a median of 89 days following HCT (range, 19–750 days). A significant inverse correlation was seen for JAK2 positivity and donor-cell chimerism (r = -0.91, P < 0.001). Four of five patients who never reached JAK2 negativity during the entire follow-up, nevertheless, fulfilled all criteria for complete remission as proposed by the IWG. In one case, residual JAK2-positive cells were successfully eliminated by donor lymphocyte infusion (DLI). Thus, JAK2 measurement is likely to determine the depths of remission, similar to what has been shown for the BCR/ABL transcript in patients with chronic myeloid leukemia [37]. These results show that allogeneic HCT after dose-reduced conditioning can induce high rates of molecular remission in JAK2-positive patients with myelofibrosis, and quantification of JAK2 (V617F) mutation by real-time PCR allows the detection of minimal residual disease that may guide adoptive immunotherapy.

In another study, Steckel et al. [38] evaluated 25 patients with PMF for the JAK2 mutation prior to allogeneic HCT and monitored them in long-term follow-up of 4–125 (median 15) months after transplant. Results were correlated with the chimerism status. The JAK2 gene mutation was detected in 15 of 25 patients before transplant. Three patients who were again positive for JAK2 after HCT concurrently also had mixed chimerism status. These three patients relapsed with their disease shortly after the JAK2 mutation was detected for the first time after transplantation. These data suggest that JAK2 gene mutation, as determined by real-time PCR, is useful as a minimal residual disease marker after HCT.

After conventional conditioning and allogeneic HCT, about 50% of patients with myelofibrosis are considered cured, and bone marrow fibrosis generally regresses by 6–12 months after HCT [9,10]. Recent data show that similar results are achieved with reduced-intensity conditioning [39**]. In that series of 24 patients with either fibrosis grade II (myelofibrosis-2, n = 13) or grade III (myelofibrosis-3) (n = 11), complete (myelofibrosis-0) or nearly complete (myelofibrosis-1) regression of fibrosis was seen in 59% of patients by day 100, 90% by day 180, and 100% by day 360.

Monitoring of marrow composition by MRI has also been shown to accurately assess the pattern and extent of
myelofibrosis and disease status, correlating with biopsy findings after HCT [40].

**Prognostic scoring systems and the decision on allogeneic hematopoietic cell transplantation**

As allogeneic HCT is increasingly used as a curative treatment option even in older patients, the ever-present morbidity and mortality must be carefully balanced with the patient’s life expectancy without HCT in order to offer optimal management. Several risk scores for myelofibrosis have been developed. The most widely used risk-assessment model is the Lille (or ‘Dupriez’) score [23], which distinguishes low, intermediate, and high risk with median life expectancies of 13 to almost 100 months, depending on Hb levels and white blood cell counts. The Mayo group has recently added a platelet count below 100 × 10^9/l as an additional high risk factor [41].

Another scoring system (Cervantes score) [42] includes Hb (<10 g/dl), circulating blasts, and constitutional symptoms and distinguishes low risk (none to one adverse factor: median survival, 176 months) and high risk (2–3 adverse factors: median survival, 33 months).

The Mayo team has proposed yet another risk-assessment score for patients with PMF [40], adding monocytes at least 1 × 10^9/l to the criteria proposed earlier. With no risk factor, the median survival was 173 months compared with 61 months with one risk factor and 26 months with two or more risk factors [43*,44*].

A peripheral blood blast percentage of at least 3% in addition to a low platelet count may be independent predictors of leukemic transformation in patients with PMF [45]. Vener et al. [46*] reported a prognostic model for OS based on the WHO criteria and marrow fibrosis grading by European consensus in 113 patients with chronic MPDs (98 with PMF and 15 with postpolycythemia vera myelofibrosis) and compared the findings with other prognostic scoring systems. The results showed that the model was significantly associated with OS and, unlike the other prognostic scoring systems, clearly discriminated the OS of intermediate-risk and high-risk patients (fibrosis grade 0 versus III, P = 0.0011; grades I–II versus III, P = 0.0029).

The different prognostic scoring models are listed in Table 2 [23,41,42,43*,44*,45,46*,47], and the scores may be helpful in reaching a decision about allogeneic HCT. However, additional factors such as comorbidities or cytogenetic abnormalities may also be relevant.

**Conclusion**

As PMF progresses, the prognosis worsens. Unfortunately, the success rate with HCT, using conventional

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**Table 2 Prognostic scoring systems for primary myelofibrosis**

<table>
<thead>
<tr>
<th>Prognostic scoring system</th>
<th>Adverse prognostic factors</th>
<th>No. of adverse prognostic factors (risk group)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lille [Dupriez et al. [23], n = 195, all ages (median 65 years)]</td>
<td>Hb &lt; 10 g/dl</td>
<td>0 (low)</td>
<td>93</td>
</tr>
<tr>
<td>Cervantes [Cervantes et al. [42], n = 106, all ages (median 64 years)]</td>
<td>Hb &lt; 10 g/dl</td>
<td>0–1 (low)</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>Constitutional symptomsa</td>
<td>2–3 (high)</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Circulating blasts ≥ 1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervantes [Cervantes et al. [47], n = 116, age ≤ 55 years (median 46 years)]</td>
<td>Hb &lt; 10 g/dl</td>
<td>0–1 (low)</td>
<td>176</td>
</tr>
<tr>
<td></td>
<td>Constitutional symptoms</td>
<td>2–3 (high)</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Circulating blasts ≥ 1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dingli et al. [41], n = 160, age &lt; 60 years (median 52 years)</td>
<td>Hb &lt; 10 g/dl</td>
<td>0 (low)</td>
<td>155</td>
</tr>
<tr>
<td></td>
<td>WBC &lt; 4 or &gt; 30 × 10^9/l</td>
<td>1 (intermediate)</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Platelets &lt; 100 × 10^9 cells/l</td>
<td>≥ 2 (high)</td>
<td>24</td>
</tr>
<tr>
<td>Mayo [Elliot et al. [43*], n = 129, age &lt; 60 years (median 52 years)]</td>
<td>Hb &lt; 10 g/dl</td>
<td>0 (low)</td>
<td>173</td>
</tr>
<tr>
<td></td>
<td>WBC &lt; 4 or &gt; 30 × 10^9/l</td>
<td>1 (intermediate)</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Platelets &lt; 100 × 10^9 cells/l</td>
<td>≥ 2 (high)</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Monocyte ≥ 1 × 10^9/l</td>
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<tr>
<td>Mayo [Tefferi et al. [44*], n = 19, all ages (median 57 years)]</td>
<td>Hb &lt; 10 g/dl</td>
<td>0 (low)</td>
<td>134</td>
</tr>
<tr>
<td></td>
<td>WBC &lt; 4 or &gt; 30 × 10^9/l</td>
<td>1 (intermediate)</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Platelets &lt; 100 × 10^9 cells/l</td>
<td>≥ 2 (high)</td>
<td>29</td>
</tr>
<tr>
<td>Huang et al. [45], n = 311, age &lt; 60 years (median 52 years)</td>
<td>Circulating blasts ≥ 5%</td>
<td>0 (low)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Platelets &lt; 100 × 10^9 cells/l</td>
<td>1 (intermediate)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Monocytes ≥ 1 × 10^9/l</td>
<td>2 (high)</td>
<td>NA</td>
</tr>
<tr>
<td>Vener et al. [46*], n = 113, all ages (median 64 years)</td>
<td>Bone marrow fibrosis grading from 0–III</td>
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<tr>
<td></td>
<td>PMF-0 (low)</td>
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<tr>
<td></td>
<td>PMF-1/2 (intermediate)</td>
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<td></td>
<td>PMF-3 (high)</td>
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</tbody>
</table>

Hb, hemoglobin; NA, not available; NR, not reached; PMF, primary myelofibrosis; WBC, white blood cell count.

*aFever, night sweats, and weight loss.*
or reduced-intensity conditioning, is also inferior with more advanced disease. Clearly, the optimum timing for HCT still remains to be determined. Nevertheless, the various classification systems do provide guidance. Close monitoring of disease evolution, including a decline in platelet counts or Hb or changes in the peripheral white blood cell counts and differential, should alert patient and physician to changes in the disease kinetics that may call for ‘action’ in the form of HCT. The optimum conditioning regimen is likely to depend on patient age and comorbid conditions. Further, the prediction of outcome after HCT may not be the sole element to be taken into account when considering transplantation in PMF patients. As the risk of adverse outcomes is present upfront for patients undergoing HCT, but is delayed for those receiving conventional therapy, risk aversion or risk taking must also be taken into account. To what extent recent insights into the role of activating mutations in the tyrosine kinase JAK2 or mpl-1 in patients with MPD and the development of therapeutic compounds aimed at those mutations will affect treatment decisions remains to be determined.

Acknowledgements
We thank Helen Crawford and Bonnie Larson for help with manuscript preparation.

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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:* of special interest ** of outstanding interest

Additional references related to this topic can also be found in the Current Literature section in this issue (p. 150).


This document summarized the proceedings of the second meeting of IWG-MRT, in which the group discussed and agreed to standardize the nomenclature referring to chronic idiopathic myelofibrosis.


4. Up-to-date overview of classification.


This report showed an excellent long-term survival after allogeneic transplantation and improved survival for patients conditioned with targeted busulfan and cyclophosphamide.


Allogeneic hematopoietic cell transplantation Zang and Deeg 145

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The first paper reporting JAK2 mutation as the first biologic prognostic marker of PMF independent of conventional predictors.


This study added monocytes as a prognostic factor.


An update on prognostic models.


This study showed marrow fibrosis as a major prognostic factor.