Impact of allogeneic stem cell transplantation on survival of patients less than 65 years with primary myelofibrosis.

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Key Points:

- Transplant versus non–transplant approaches were compared in PMF patients grouped by DIPSS status.

- The net benefit of transplant versus non–transplant is marked in higher risk patients.
Abstract

Allogeneic hematopoietic stem cell transplantation (ASCT) is the only curative option for patients with primary myelofibrosis (PMF), but information on the net advantage over conventional therapies is lacking. Using an ad hoc statistical analysis, we determined outcomes in 438 patients younger than 65 years at diagnosis who received ASCT (n=190) or conventional therapies (n=248). Among patients with low risk by Dynamic International Prognostic Scoring System (DIPSS) prognostic model the relative risk of dying after receiving ASCT versus those treated with non-transplant modalities was 5.6 (95% CI: 1.7-19; P=0.0051); for intermediate-1 risk it was 1.6 (95% CI: 0.79-3.2; P=0.19), for intermediate-2, 0.55 (95% CI: 0.36-0.83; P=0.005), and for high risk 0.37 (95% CI: 0.21-0.66; P=0.0007). Thus, patients with intermediate-2 or high risk PMF clearly benefit from ASCT. Patients at low risk should receive non-transplant therapy, while individual counseling is indicated for patients at intermediate-1 risk.

Introduction

Primary myelofibrosis (PMF) is a clonal myeloproliferative neoplasm with a high risk for clonal evolution and mortality. Powerful prognostic tools have been developed that assist clinicians in patient counseling and therapeutic decision-making. The International Prognostic Scoring System (IPSS) is a clinic-based model to assess prognosis at the time of diagnosis;\textsuperscript{1} the dynamic IPSS (DIPSS) was designed to track changes in prognosis related to changes in scoring parameters over time.\textsuperscript{2} The DIPSS defines four risk categories: low, intermediate (int)-1, int-2, and high, which can be assigned on the basis of the instantaneous values of hemoglobin, white blood cell count (WBC), circulating blasts, constitutional symptoms and patient age during the follow-up.

Allogeneic hematopoietic stem cell transplantation (ASCT) is currently the only curative treatment for myelofibrosis (MF);\textsuperscript{3,4} however, because of potential complications, careful patient counseling and accurate selection is mandatory. Conversely, conventional therapies, including cytoreductive agents (hydroxyurea, busulfan, interferon-alpha), erythropoiesis stimulating agents, androgens, immunomodulating drugs, and non-pharmacological options
such as blood transfusions, spleen irradiation, and splenectomy are mainly palliative. In the last decade, major advances have been achieved in the understanding of the molecular basis of MF, in particular the central role of the JAK-STAT pathway. These insights, in turn, have led to the development of molecules with therapeutic anti-JAK2 properties.

One of the critical questions in the management of MF is which patients may benefit from ASCT and when the transplant should be carried out. Since no data from randomized prospective trials are available, we designed a retrospective study including patients who received ASCT (American and European multicenter collection) and patients who did not (independent European multicenter collection) stratified by DIPSS risk.

Patients and Methods

The analysis utilized data from two independent international multicenter databases: one including only patients who received ASCT at referral centers in Europe and in the United States (the transplant cohort), and the other including patients belonging to the DIPSS database, that is an European collection of PMF patients who did not receive any JAK inhibitor at the data cutoff and were censored at the time of ASCT (the non-transplant cohort). In the transplant cohort patients had the parameters composing the DIPSS score collected at the time of transplant, while in the non-transplant cohort parameters were determined according to the DIPSS algorithm, i.e. in a time-dependent way, at diagnosis and longitudinally thereafter with at least 3 visits per year. By merging these two international databases, information on 673 patients with MF was available. Taking into account the commonly used age-threshold for indication of ASCT, we restricted the analysis to patients aged 65 years or younger at diagnosis. We also excluded from the analysis patients with post-polycythemia vera MF and post essential thrombocytemia MF. Thus, 443 patients (188 and 255, respectively, in the two databases) diagnosed with PMF at an age younger than 65 years were included in the analysis. Within the transplant cohort there were no significant differences in outcome between reduced intensity and myeloablative conditioning, nor between HLA-matched unrelated and HLA-matched sibling donor transplants (data not shown), and, hence, data were combined for analysis. Age at diagnosis was higher in the
non-transplant cohort (median 55 vs. 50 years) but was not significantly related to survival in any model and, therefore, was not included in the regressions.

The study was approved by the Institutional Review Board of the University of Hamburg and at all participating centers and conducted in accordance with the principles of the Declaration of Helsinki.

Survival was the focus of comparison; the main criterion of comparability of the two cohorts (transplant vs. non-transplant) was the DIPSS risk status. To define the impact on the natural history of the disease, we considered the date of PMF diagnosis as the starting point of the time scale. Hence, patients of the transplant cohort entered the analysis when receiving ASCT at a specific DIPSS status; they were compared to those of the non-transplant cohort who reached the same DIPSS status at the corresponding time. In the non-transplant cohort the risk category is treated as a time-dependent attribute, i.e. upon progression towards a higher risk category a patient would leave the set of subjects at risk in the former risk category and enter the “at risk” set for the new one. By backdating ASCT data from enrollment to the date of diagnosis, we generated left-truncated data, thereby potentially excluding candidate patients dying before they had the chance of undergoing ASCT. Regressions for left-truncated and right-censored survival data were computed according to the standard Andersen-Gill model. Proportional hazard models were built separately for the four DIPSS categories, considering the cohort as a discrete covariate. The relative risks (RR) between the two cohorts were estimated under the proportional-hazards approximation, and Wald tests were used to report significance. Statistical analyses were performed using R version 3.1.1 and the “survival” package version 2.37.

Results and Discussion

We studied 190 patients who received ASCT, and 248 who received conventional therapies. Available demographics are summarized in Table 1, reporting data at the time of transplant for ASCT cohort and at the time of diagnosis for the non-transplant cohort.
The RR of dying among patients receiving ASCT over those receiving conventional therapies was 5.6 (95% CI: 1.7-19, \(P=0.0051\)) for low risk DIPSS, 1.6 (95% CI: 0.79-3.2, \(P=0.19\)) for int-1 risk, 0.55 (95% CI: 0.36-0.83, \(P=0.005\)) for int-2, and 0.37 (95% CI: 0.21-0.66, \(P=0.0007\)) for high risk DIPSS patients. The 5-year proportions surviving in the transplant and non-transplant cohorts were 69% and 95% for low risk, 52% and 77% for int-1, 50% and 41% for int-2, and 32% and 11% for high risk patients, respectively. Analysis at alternative time points and 95% confidence intervals (CI) are shown in Table 1.

As illustrated in Figure 1, survival differences were pronounced beyond five years from diagnosis for int-2 and high risk patients, and the survival curve for transplanted int-1 risk patients crossed the survival curve for the non-transplant cohort between 15 and 20 years. Hazard ratios were not constant over time, and thus, summarizing the risk in a single “average” RR figure ignores the specifics of the survival trends.

We could not address the potentially confounding factor of selection bias regarding ASCT, nor possible correlations between time of transplant and patient characteristics. Some of the concerns might be addressable in a Markov model, as reported for patients with myelodysplastic syndrome, although that model has other methodological drawbacks.

Despite the curative potential of ASCT, inherent risks of therapy-related complications and mortality, dependent upon disease status and patient-specific risk factors, are of concern in patients with MF. Hence, there is a need to select patients carefully for ASCT in order to obtain the maximum benefit with respect to survival and therapy-related complications. This study gives an indication of ASCT per DIPSS status; conclusions are however restricted to patients with primary and not with secondary myelofibrosis.

The recent implementation of the clinically-based risk scores with mutational profile (\(JAK2/MPL/CALR\)-triple negative or \(ASXL-1\) positive) will be of value in the future for
risk stratification of MF patients and can help in the decision making of patients with intermediate-1 or low risk categories. The recognition of these mutations and the introduction of new treatment modalities such as JAK2 inhibition is changing the MF treatment landscape. Ruxolitinib, the first JAK2 inhibitor approved for clinical practice, has led to early and sustained clinical benefits in patients with int-2 and high-risk MF, including spleen size reduction and improvement of symptom burden in two phase III trials.\textsuperscript{15,16} A survival benefit with ruxolitinib was shown in a long-term update of the COMFORT-I and COMFORT-II studies.\textsuperscript{12,17,18} Since the present analysis did not include ruxolitinib-treated patients, the impact of this drug in comparison to ASCT could not be assessed in this study and results may be different if ruxolitinib patients can be included in subsequent studies.

In conclusion, this study indicates that non ruxolitinib treated PMF patients 65 years of age or younger at diagnosis with intermediate-2 or high risk disease are likely to benefit from ASCT, while for patients with low risk disease non-transplant approaches may be appropriate. Individual counseling is indicated for intermediate-1 risk patients.

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**AUTHORSHIP**

Nicolaus Kröger designed the study, analyzed and interpreted data, and wrote the manuscript.

Francesco Passamonti assisted in study design, analyzed and interpreted data, and edited the manuscript.

Toni Giorgino assisted in study design, performed statistical analysis and edited the manuscript.

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Margherita Maffioli assisted with data interpretation and edited the manuscript.

Arturo Pereira supported statistical interpretation and edited the manuscript.

Dietrich Beelen assisted with data collection and edited the manuscript.

H. Joachim Deeg assisted with study design, data interpretation and co-wrote the manuscript.

**Conflict-of-interest disclosure:**

The authors of this manuscript have no conflicts of interest to disclose as defined by the journal *BLOOD.*
References


**Table 1**  
Patient characteristics and results of patients with primary myelofibrosis receiving allogeneic stem cell transplantation (data at the time of transplant) or non-experimental conventional therapy (data at the time of diagnosis)

<table>
<thead>
<tr>
<th></th>
<th>Allogeneic SCT</th>
<th>Conventional therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>n = 188</td>
<td>n = 255</td>
</tr>
<tr>
<td><strong>Median age at diagnosis</strong></td>
<td>50 years (20-65)</td>
<td>55 years (18-65)</td>
</tr>
<tr>
<td><strong>DIPSS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>low risk</td>
<td>at transplant</td>
<td></td>
</tr>
<tr>
<td>intermediate-1</td>
<td>n = 22</td>
<td>n = 125</td>
</tr>
<tr>
<td>intermediate-2</td>
<td>n = 38</td>
<td>n = 75</td>
</tr>
<tr>
<td>high risk</td>
<td>n = 84</td>
<td>n = 52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n = 3</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>n = 108</td>
<td>n = 154</td>
</tr>
<tr>
<td>female</td>
<td>n = 80</td>
<td>n = 101</td>
</tr>
<tr>
<td><strong>Time from diagnosis to transplant</strong></td>
<td>1.2 year (0.0-22.2)</td>
<td></td>
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<tr>
<td><strong>Conditioning regimen</strong></td>
<td></td>
<td></td>
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<tr>
<td>RIC</td>
<td>n = 91</td>
<td></td>
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<tr>
<td>MAC</td>
<td>n = 97</td>
<td></td>
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<tr>
<td><strong>Donor</strong></td>
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<td></td>
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<tr>
<td>matched unrelated or mismatch related</td>
<td>n = 102</td>
<td></td>
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<tr>
<td>matched related</td>
<td>n = 86</td>
<td></td>
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<tr>
<td><strong>Survival proportion (95% CI)</strong></td>
<td>Year</td>
<td>Year</td>
</tr>
<tr>
<td>low risk</td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>100%</td>
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<td></td>
<td></td>
<td>69% (48-99)</td>
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<td></td>
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<td>60% (38-95)</td>
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<tr>
<td></td>
<td></td>
<td>92% (86-99)</td>
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<tr>
<td>intermediate-1</td>
<td>78% (55-100)</td>
<td></td>
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<tr>
<td></td>
<td>52% (33-83)</td>
<td>41% (24-70)</td>
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<tr>
<td></td>
<td>32% (17-67)</td>
<td>77% (67-88)</td>
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<td></td>
<td></td>
<td>41% (32-54)</td>
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<tr>
<td></td>
<td></td>
<td>11% (5-22)</td>
</tr>
<tr>
<td>intermediate-2</td>
<td>82% (68-98)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50% (37-67)</td>
<td>32% (21-48)</td>
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<td>77% (67-88)</td>
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<td>41% (32-54)</td>
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<td></td>
<td></td>
<td>11% (5-22)</td>
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<tr>
<td>high risk</td>
<td>65% (46-92)</td>
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<tr>
<td></td>
<td>32% (19-56)</td>
<td>27% (15-49)</td>
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<tr>
<td></td>
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<td>67% (30-100)</td>
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<td></td>
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<td>11% (3-44)</td>
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<tr>
<td></td>
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<td>1% (0-10)</td>
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</table>

* These counts refer to PMF patients in each group at diagnosis. The number of patients in each group (risk set) increases or decreases at later times as a consequence of progressions, deaths or loss of follow-up.
Figure 1: Survival probabilities for the four subgroups (DIPSS low, int-1, int-2, high). DIPSS score is taken at SCT (solid, transplant cohort) or at the indicated time (dotted, non-transplant cohort). Time (horizontal axis) elapses from diagnosis.
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