Dynamic of Bone Marrow Fibrosis Regression Predicts Survival after Allogeneic Stem Cell Transplantation for Myelofibrosis

Nicolaus Kröger 1,*, Tatjana Zabelina 1, Haefaa Alchalby 1, Thomas Stübig 1, Christine Wolschke 1, Francis Ayuk 1, Natascha von Hünerbein 1, Hans-Michael Kvasnicka 2, Jürgen Thiele 3, Hans-Heinrich Kreipe 4, Guntram Büsche 3

1 Department of Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
2 Institute of Pathology, University Hospital of Frankfurt, Frankfurt, Germany
3 Institute of Pathology, University of Cologne, Cologne, Germany
4 Institute of Pathology, Hannover Medical School, Hannover, Germany

ABSTRACT

We correlate regression of bone marrow fibrosis (BMF) on day 30 and 100 after dose-reduced allogeneic stem cell transplantation (allo-SCT) in 57 patients with primary or post–essential thrombocytopenia/polycythemia vera myelofibrosis with graft function and survival. The distribution of International Prognostic Scoring System (IPSS) risk score categories was 1 patient with low risk, 5 patients with intermediate-1 risk, 18 patients with intermediate-2 risk, and 33 patients with high risk. Before allo-SCT, 41 patients (72%) were classified as XXX [myelofibrosis (MF)]-3 and 16 (28%) were classified as MF-2 according to the World Health Organization criteria. At postengraftment day +30 (+10 days), 21% of the patients had near-complete or complete regression of BMF (MF-0/-1), and on day +100 (+20 days), 54% were MF-0/-1. The 5-year overall survival rate at day +100 was 96% in patients with MF-0/-1 and 57% for those with MF-2/-3 (P = .04). There was no difference in BMF regression at day +100 between IPSS high-risk and low/intermediate-risk patients. Complete donor cell chimerism at day +100 was seen in 81% of patients with MF-0/-1 and in 31% of those with MF-2/-3. Patients with MF-2/-3 at day +100 were more likely to be transfusion-dependent for either RBCs (P = .014) or platelets (P = .018). Rapid BMF regression after reduced-intensity conditioning allo-SCT resulted in a favorable survival independent of IPSS risk score at transplantation.

© 2014 American Society for Blood and Marrow Transplantation.

INTRODUCTION

Bone marrow fibrosis (BMF) is a hallmark of primary or post–essential thrombocytopenia (ET)/polycythemia vera (PV) myelofibrosis [1]. The fibrogenesis is not completely understood and probably caused by cytokines such as platelet-derived growth factor, β fibroblast–derived growth factor, or transforming growth factor β secreted from clonal megakaryocytes and/or clonal monocyte/histiocyte proliferation [2-4].

Fibrosis grade correlates with other clinical parameters, including hemoglobin, myeloblasts, lactate dehydrogenase, and spleen size [5]. Some studies have found a correlation between grade of fibrosis and survival [5-7]; however, others did not report this correlation [8-11]. BMF is not included in any of the currently used risk classification schemes, including Lille score, Cervantes score, International Prognostic Scoring System (IPSS), Dynamic IPSS, and Dynamic IPSS Plus [12-16]. BMF regression has been reported after allogeneic stem cell transplantation (allo-SCT) [17] and, in some cases, after treatment with IFN-α [18], pomalidomide [19], and, more recently, ruxolitinib [20]; however, the impact of fibrosis resolution—especially the dynamics of resolution—on survival has not been studied to date.

Here we report the impact of dynamic of bone resolution on survival and other graft-specific factors after dose-reduced allo-SCT in a homogenously treated group of patients with advanced primary or post-ET/PV myelofibrosis.

PATIENTS AND METHODS

Between 2002 and 2010, a total of 109 patients underwent allo-SCT for myelofibrosis at the University Medical Center Hamburg-Eppendorf. For inclusion, patients needed to have bone marrow histology investigated by a reference pathologist (M.K., J.T., G.B., or H.K.) before reduced-intensity conditioning allo-SCT and at least on day +30 (+2 weeks) and/or day +100 (+1 month) postengraftment. Fifty-seven patients (median age, 57 years; range, 33-73 years) fulfilled the inclusion criteria. Bone marrow histology was available at both days +30 and +100 in 35 patients, only at day +30 in 13 patients, and only at day +100 in 9 patients. The risk profile was based on IPSS classification [16].

One patient was classified as IPSS low risk; 5, as intermediate-1 risk; 17, intermediate-2 risk, and 34, as high risk. The donor and recipient were related in 11 cases and unrelated in 46 cases, and HLA-mismatched in 38 cases and HLA-mismatched in 19 cases. The conditioning regimen comprised busulfan 10 mg/kg orally or 10 × 0.8 mg/kg i.v. in combination with fludarabine 150 mg/m². Eleven patients received induction therapy with amsacrine, fludarabine, and cytarabine (FLAMA), followed after a 3-day rest by busulfan/fludarabine. All patients received peripheral blood stem cell grafts. Patient characteristics are summarized in Table 1.
BMF was graded according to the European consensus and World Health Organization classification schemes [21]. For this study, only fibrosis regression was evaluated. In cases of residual osteosclerosis but no residual fibrosis, the patient was classified as (MF)-0.

All patients underwent bone marrow investigation before allo-SCT; 48 patients did so again at day $+30$ and 44 at day $+100$. Donor cell chimerism and JAK2V617F mutation were assessed as described previously [22]. Patient care was performed as reported elsewhere [23].

RESULTS

Engraftment and Graft-versus-Host Disease

Three graft failures were observed. All patients received a second donation and successfully engrafted with leukocytes. The median time to leukocyte engraftment ($>1.0 \times 10^{9}$ cells/L) was 13 days (range, 9–26 days), and the median time to platelet engraftment ($>20 \times 10^{9}$ cells/L) was 19 days (range, 9–145 days). Acute graft-versus-host disease (GVHD) grade II-IV occurred in 33% and severe grade III-IV GVHD in 14%. Chronic GVHD was seen in 61% of the patients and classified as mild (19%), moderate (33%), or severe (9%). Eleven patients (19%) died during follow-up, either relapse-related ($n = 4$) or therapy-related ($n = 7$).

Nonrelapse Mortality, Relapse, and Overall Survival

For the entire study population, nonrelapse mortality at 1 year was 11% (range, 3%–19%). The nonrelapse mortality was calculated from day 0 onward; no patient died before day $+30$ after allo-SCT, and only 1 patient died between day $+30$ and day $+100$. The cumulative incidence of relapse at 3 years after allo-SCT was 20% (range, 4%–36%), and the 5-year estimated overall survival was 79% (range, 65%–93%) (Figure 1). Causes of therapy-related death included GVHD ($n = 2$), cardiac failure ($n = 1$), infectious complications ($n = 1$), organ toxicity ($n = 1$), liver cirrhosis ($n = 1$), and secondary graft failure ($n = 1$).

Dynamic of Fibrosis Regression and Survival

At the time of allo-SCT, 72% of the patients were MF-3 and 28% were MF-2. At day $+30$ after allo-SCT, 6% were MF-0 and 15% were MF-1, and at day $+100$, 25% were MF-0 and 29% were MF-1 (Table 2).

<table>
<thead>
<tr>
<th>Table 1 Patient Characteristics ($n = 57$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Age, yr, median (range)</td>
</tr>
<tr>
<td>Males/females, n</td>
</tr>
<tr>
<td>Diagnosis, n</td>
</tr>
<tr>
<td>Primary myelofibrosis</td>
</tr>
<tr>
<td>Post-ET/PV myelofibrosis</td>
</tr>
<tr>
<td>Donor, n</td>
</tr>
<tr>
<td>Related</td>
</tr>
<tr>
<td>Unrelated</td>
</tr>
<tr>
<td>HLA-matched</td>
</tr>
<tr>
<td>HLA-mismatched</td>
</tr>
<tr>
<td>IPSS classification at allo-SCT, n</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Intermediate-1</td>
</tr>
<tr>
<td>Intermediate-2</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Blasts at allo-SCT, % median (range)</td>
</tr>
<tr>
<td>Recipient cytomegalovirus serostatus, n</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Conditioning regimen, n</td>
</tr>
<tr>
<td>Busulfan 10 mg/kg/fludarabine 150 mg/kg</td>
</tr>
<tr>
<td>FLAMSA + busulfan 10 mg/kg/fludarabine 150 mg/kg</td>
</tr>
</tbody>
</table>

Survival of the patients with MF-0/-1 at day $+30$ was 100%, in contrast to 71% (range, 51%–91%) for those with MF-2/-3 ($P = .10$). Patients with fibrosis regression on day $+100$ to MF-0/-1 had an 5-year overall survival of 96% (range, 88%–100%), compared with 57% (21%–93%) in those with persistent MF-2/-3 ($P = .04$) (Figure 1). The improved survival of patients with MF-0/-1 at day $+100$ post-allo-SCT was related to a lower risk of treatment-related mortality (15% versus 4%; $P = .20$) and relapse at 1 year (20% versus 0%; $P = .04$) (Figure 2).

Regarding the fibrosis reduction per level at day $+30$, 28 (59%) had no reduction, 14 (29%) had a 1-grade reduction, 4 (8%) had a 2-grade reduction, and 2 (4%) had a 3-grade reduction. At day $+100$ post-allo-SCT, 9 patients (21%) had no reduction in fibrosis grade, whereas 16 patients (36%) had a 1-grade reduction, 12 patients (27%) had a 2-grade reduction, and 7 patients (16%) had a 3-grade reduction (Table 3). Five-year overall survival was improved for patients with a 2- or 3-grade reduction at day $+100$ in comparison to those with persistent MF-2/-3 (95% [range, 85%–100%] versus 71% [range, 47%–95%]); however, the difference did not reach statistical significance ($P = .19$).

Correlations between Fibrosis Regression and Donor Cell Chimerism, Graft Function, Detection of JAK2V617F Mutation, and IPSS

Comparing the results of fibrosis resolution at day $+100$ with other disease-specific factors revealed no correlation

| Table 2 BMF at allo-SCT and at Day $+30$ and Day $+100$ after allo-SCT |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Time                        | BMF at allo-SCT | BMF at Day $+30$ | BMF at Day $+100$ |
| At allo-SCT ($n = 57$)      | 0               | 3               | 11              |
| Day $+30$ ($n = 48$)        | 3 (6)           | 7 (15)          | 12 (27)         |
| Day $+100$ ($n = 44$)       | 11 (25)         | 13 (29)         | 8 (18)          |
between fibrosis regression and clearance of the JAK2V617F mutation in peripheral blood. In 42% of the JAK2-positive patients with MF-0/-1, JAK2V617F mutation was still detectable in peripheral blood. In contrast, 81% of the patients with MF-0/-1 had complete donor cell chimerism, compared with only 31% of those with MF-2/-3 (Table 4). There was no significant correlation between BMF resolution on day +100 (MF-2/-3) and IPSS category at time of allo-SCT, suggesting that disease status at transplantation had no significant impact on the dynamic of BMF resolution.

At day +100 post—allo-SCT, 53% of the patients were still RBC transfusion-dependent, and 33% were platelet transfusion-dependent. Patients with MF-2/-3 at day +100 were more likely to be still RBC transfusion-dependent (75% versus 35%; P = .014) and platelet transfusion-dependent (50% versus 13%; P = .018). The median hemoglobin concentration, leukocyte count, and platelet count on day +100 were higher in patients with MF-0/-1 compared with patients with MF-2/-3 (hemoglobin, 9.8 g/dL versus 8.7 g/dL [P = .40]; leukocytes, 3.9 × 10⁹/L versus 3.6 × 10⁹/L [P = .90]; platelets, 95 × 10⁹/L versus 55 × 10⁹/L [P = .30]), suggesting better (albeit not significantly so) graft function in those patients with rapid resolution of BMF by day +100 (Table 4). There was no difference in acute GVHD grade II-IV between patients with and those without BMF resolution on day +100 (39% versus 30%; P = .70). Owing to the low number of events within this study, multivariate analysis could not be performed.

DISCUSSION

This study confirms that complete resolution of BMF occurs in patients with primary and post-ET/PV myelofibrosis after allo-SCT, as previously reported by us and others [24,25]. Furthermore, this study shows for the first time that complete or near-complete resolution, defined as MF-0/-1, on day +100 post—allo-SCT is associated with improved survival. Interestingly, the speed of resolution at day +30 or day +100 was not correlated with the IPSS classification at the time of allo-SCT, confirming that reduced-intensity conditioning can induce as rapid resolution of BMF as has been reported for standard myeloablative conditioning [25].

Figure 2. Overall survival according to fibrosis regression on day 30 (A) (based on 48 patient) and day 100 (B) (based on 44 patients) post allografting.

Figure 3. Cumulative incidence of treatment-related mortality (A) and relapse (B) according to BMF regression at day +100 (n = 44).
Furthermore, there was no correlation between complete resolution of BMF on day +100 and disappearance of the JAK2V617F mutant in peripheral blood detected by PCR. Although there was a correlation between donor cell chimerism and fibrosis resolution on day +100, the lack of correlation with JAK2V617F mutant level might be explained by the high sensitivity of the assay used in this study [22]. Furthermore, more rapid resolution of BMF was correlated with improved graft function and significantly fewer RBC and platelet transfusions.

Retrospective studies have shown that grade of BMF correlates with disease status [5], but the prognostic impact remains controversial. Most of those previous studies did not identify fibrosis as independent risk factor, and thus none of the currently used risk scores includes BMF. Even if the number of included patients is too small to allow us to draw a meaningful conclusion, this first study on the dynamics of fibrosis regression and its impact on outcome suggests that a more rapid resolution of BMF is associated with improved graft function, less relapse, and improved long-term outcomes in patients with myelofibrosis who undergo allo-SCT. However, this observation will not affect post-transplantation patient management until methods that accelerate BMF regression become available.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

REFERENCES


Table 3

Reduction of BMF at Day +30 and Day +100 after allo-SCT

<table>
<thead>
<tr>
<th>Time</th>
<th>Level of Reduction, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Day +30 (n = 48)</td>
<td>28 (59)</td>
</tr>
<tr>
<td>Day +100 (n = 44)</td>
<td>9 (21)</td>
</tr>
</tbody>
</table>

Table 4

Correlations between Grade of Fibrosis at Day +100 and JAK2V617F Mutation (Only in JAK2-Positive Patients), Donor Cell Chimerism, Graft Function, Risk Status (IPSS), Treatment-Related Mortality, and Overall Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>MF-0/-1</th>
<th>MF-2/-3</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK2V617F mutation, %</td>
<td>-.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>58</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>42</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>IPSS at treatment, %</td>
<td>.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/intermediate-1/-2</td>
<td>60</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>57</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Transfusion dependency</td>
<td>100</td>
<td>.014</td>
<td></td>
</tr>
<tr>
<td>RBCs</td>
<td>35</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>13</td>
<td>50</td>
<td>.018</td>
</tr>
<tr>
<td>Complete donor cell chimerism, %</td>
<td>81</td>
<td>31</td>
<td>.03</td>
</tr>
<tr>
<td>Median hemoglobin at day +100, g/dL</td>
<td>9.8</td>
<td>8.7</td>
<td>.40</td>
</tr>
<tr>
<td>Median leukocytes at day +100, 10^9/L</td>
<td>3.9</td>
<td>3.6</td>
<td>.90</td>
</tr>
<tr>
<td>Median platelets at day +100, 10^9/L</td>
<td>95</td>
<td>55</td>
<td>.30</td>
</tr>
<tr>
<td>Treatment-related mortality at 1 yr, %</td>
<td>4</td>
<td>15</td>
<td>.20</td>
</tr>
<tr>
<td>Relapse at 1 yr, %</td>
<td>0</td>
<td>20</td>
<td>.04</td>
</tr>
<tr>
<td>Five-yr overall survival, %</td>
<td>96</td>
<td>57</td>
<td>.04</td>
</tr>
</tbody>
</table>