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

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A B S T R A C T

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 thrombocythemia/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 [myclofibrosis (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.

INTRODUCTION

Bone marrow fibrosis (BMF) is a hallmark of primary or post–essential thrombocythemia (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-matched 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/m^2. Eleven patients received induction therapy with amsacrine, fludarabine, and cytarabine (FLAMSA), followed after a 3-day rest by busulfan/fludarabine. All patients received peripheral blood stem cell grafts. Patient characteristics are summarized in Table 1.

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Table 1
Patient Charcteristics (n = 57)

Characteristic	Value
Age, yr, median (range)	59 (9-76)
Males/females, n	32/25
Diagnosis, n	
Primary myelofibrosis	41
Post-ET/PV myelofibrosis	16
Donor, n	
Related	11
Unrelated	46
HLA-matched	38
HLA-mismatched	19
IPSS classification at allo-SCT, n	
Low	1
Intermediate-1	5
Intermediate-2	17
High	34
Blasts at allo-SCT, % median (range)	1 (0-17)
Recipient cytomegalovirus serostatus, n	
Positive	38
Negative	19
Conditioning regimen, n	
Busulfan 10 mg/kg/fludarabine 150 mg/kg	46
FLAMSA + busulfan 10 mg/kg/fludarabine 150 mg/kg	11

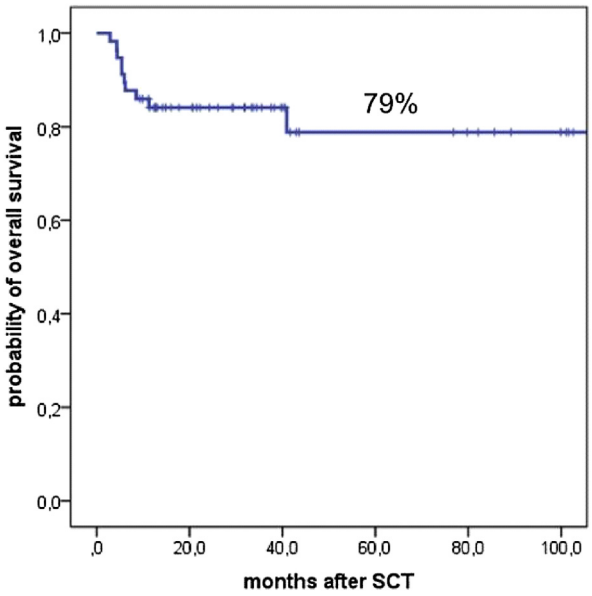

Figure 1. Overall survival after reduced-intensity conditioning for myelofibrosis (n = 57).

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 decribed 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).

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, n (%)			
	MF-0	MF-1	MF-2	MF-3
At allo-SCT (n = 57)	0	0	16 (28)	41 (72)
Day +30 (n = 48)	3 (6)	7 (15)	17 (35)	21 (44)
Day +100 (n = 44)	11 (25)	13 (29)	12 (27)	8 (18)