Allogeneic stem cell transplantation for myelodysplastic syndromes with bone marrow fibrosis

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ABSTRACT

Background

Bone marrow fibrosis in patients with myelodysplastic syndrome is associated with a poor outcome, but whether the outcome after allogeneic stem cell transplantation is related to the degree of bone marrow fibrosis is unknown.

Design and Methods

Patients with myelodysplastic syndrome and known bone marrow histology (n=721) who underwent hematopoietic stem cell transplantation were classified according to the degree of bone marrow fibrosis into those without fibrosis (n=483), those with mild or moderate fibrosis (n=199) and those with severe fibrosis (n=39) and analyzed regarding engraftment, treatment-related mortality, relapse and survival.

Results

The degree of fibrosis was not associated with disease status or abnormal cytogenetics. The cumulative incidence of engraftment achieved at day +30 in non-fibrotic patients was 93% and was significantly lower in those with mild or moderate fibrosis (89%) and severe fibrosis (75%) (P=0.009). Neutrophil engraftment occurred later in patients with mild or moderate fibrosis and severe fibrosis than in patients without fibrosis (median 17 *versus* 20 *versus* 16 days, respectively; P=0.002). The cumulative incidence of relapse at 3 years was significantly higher in patients with severe fibrosis than in those with a lesser degree of fibrosis or no fibrosis (47% *versus* 28% *versus* 27%, respectively; P=0.04), resulting in comparable 3-year disease-free survival rates in patients without fibrosis and in those with mild or moderate fibrosis (42% *versus* 38%, respectively) but a lower disease-free survival rate in those with severe fibrosis (18%; P=0.002). Severe fibrosis remained an independent factor for reduced survival (hazard ratio, 1.9; P=0.006).

Conclusions

Among patients with myelodysplastic syndromes, only severe fibrosis affects survival after hematopoietic stem cell transplantation while patients with mild or moderate fibrosis have an outcome comparable to that of patients without bone marrow fibrosis.

Key words: bone marrow fibrosis, allogeneic stem cell transplantation, myelodysplastic syndromes, engraftment.

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Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic diseases, for which several scoring systems have been developed to predict prognosis. These scoring systems incorporate information on cytogenetics, number of cytopenias and number of blasts (International Prognostic Scoring System, IPSS),[1] or these variables integrated with transfusion dependency (WHO classification-based Prognostic Scoring System, WPSS).[2] Several studies have shown that other factors, such as bone marrow fibrosis, provide additional information associated with poor outcome in MDS patients.[3-7]

Allogeneic stem cell transplantation is now more frequently used as a curative treatment approach for MDS. The introduction of so-called dose-reduced conditioning regimens allows transplantation of patients up to the age of 70 years. The major risk factors for outcome after allogeneic stem cell transplantation for MDS are certain cytogenetic characteristics, number of blasts, status of the disease and age of the patient. Information about the impact of bone marrow fibrosis on outcome after allogeneic stem cell transplantation in patients with MDS is only limited.[8] Here we report on 721 MDS patients with known bone marrow fibrosis status, determined by bone marrow histology, who received an allogeneic stem cell transplant and whose data were reported to the European Group for Blood and Marrow Transplantation (EBMT).

Design and Methods

We collected data from 721 patients with MDS and known bone marrow histology at diagnosis who underwent allogeneic stem cell transplantation between 1978 and 2009. The data were extracted from the EBMT registry of patients with MDS or secondary acute myeloid leukemia (sAML). In this study we included only patients diagnosed with MDS. Patients with primary myelofibrosis or overlap syndrome, i.e. with MDS/myeloproliferative syndrome (MPS) were excluded. Out of these 721 patients, 483 were classified as not having fibrosis, 199 were classified as having mild or moderate fibrosis and 39 as having severe fibrosis. The degree of fibrosis was determined by the hematopathologist at each patient's transplant center. As shown in detail in Table 1 there were no significant differences between the three groups of patients with respect to age, gender, therapy-related MDS/AML, stem cell source, conditioning regimen, donor, disease status, cytogenetics, time from diagnosis to transplant, transplant period and median number of blasts at transplantation. The only difference between the groups was that significantly more patients with mild/moderate fibrosis were positive for cytomegalovirus (P=0.04).

Statistical analysis

The characteristics of the patients were expressed as medians and ranges for continuous variables and frequencies for categorical variables. Categorical data were compared by the χ^2 test, while continuous variables were compared using the Kruskal-Wallis test. Survival curves were either estimated using the Kaplan-Meier method (if no competing risk were involved), and then the significance of the log-rank test was used, or computed in a competing risk framework (to estimate the cumulative incidence of a specific event in the case of competing risks). For multivariate analyses the Cox model was used to estimate hazard ratios and cause-specific hazards but in the case of competing risks, the curve estimates of

Table 1. Patients' characteristics (n=721) according to bone marrow fibrosis.

Known fibrosis (n=721)	None (n=483)	Mild / moderate (n=199)	Severe (n=39)	P value
Male	60 %	57 %	54 %	0.7
Female	40 %	43 %	46 %	
t-MDS / AML	10 %	11 %	15 %	0.6
Stem cell source				
bone marrow	36 %	34 %	35 %	
peripheral blood	62 %	63 %	59 %	
cord blood	1 %	1 %	3 %	0.4
bone marrow + peripheral blood	1 %	1 %	3 %	
missing	–	1 %	–	
Conditioning				
standard	64 %	70 %	77 %	
reduced	36 %	30 %	23 %	0.12
TBI-containing regimen	44 %	44 %	56 %	0.34
HLA-identical sibling	58 %	56 %	59 %	
Syngeneic	0.6 %	2.5 %	0 %	
Matched – other relative	1 %	2 %	0 %	
Matched unrelated	29.4 %	27.5 %	33 %	0.07
Mismatched related	4 %	3 %	3 %	
Mismatched unrelated	7 %	9 %	5 %	
Related	64 %	64 %	62 %	
Unrelated	36 %	36 %	38 %	0.97
Donor sex				
male	61 %	56 %	56 %	
female	39 %	44 %	44 %	0.4
CMV-positive serostatus of recipient	61 %	71 %	64 %	0.04
Disease status at diagnosis (n=721)				
RA/RARS	36 %	39 %	31 %	0.7
RAEB	43 %	43 %	48 %	
RAEB-t	21 %	18 %	21 %	
Disease status at transplant (n = 605)				
RA/RARS	28 %	29 %	22 %	
RAEB	40 %	42.5 %	48 %	
RAEB-t	24 %	23.5 %	26 %	0.8
sAML	8 %	5 %	4 %	
Cytogenetics (n = 706)				
normal	43 %	42 %	29 %	
abnormal	49 %	51 %	58 %	0.40
not done	8 %	7 %	13 %	
Time from diagnosis to SCT				
<6 months	35 %	32 %	31 %	
6–12 months	33 %	33 %	31 %	0.9
>12 months	32 %	35 %	38 %	
IPSS at transplantation (n=294)	n=191	n= 103 (incl. severe fibrosis)		
low	8%	4%		
intermediate 1	39%	39%		0.5
intermediate 2	24%	22%		
high	29%	35%		
Median age of recipient (range)	49 (18–69)	50 (18–67)	47 (23–70)	0.43
Median age of donor (range)	44 (1–74)	44 (11–69)	44 (5–66)	0.70
Median number of blasts in bone marrow (range)	n=149 10% (5–90%)	n=67 12% (5–80%)	n=9 10% (6–70 %)	0.35

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Median interval between diagnosis and SCT: months (range)	7.7 (0.3–259)	8.3 (1.6–92)	8.2 (2.1–122)	0.75
Median follow-up in months (range)	37 (1–262)	35 (1–170)	12 (4–79)	0.71
T-cell depletion (n = 703)				
no	45%	54%	50%	
in vivo	36%	29%	32%	
ex vivo	8%	9%	2%	0.22
in vivo + ex vivo	11%	8%	16%	
Performance status (n = 437)				
good	94%	91%	92%	0.48
poor	6%	9%	8%	
Remission status (n=686)	n=467	n=183	n=36	
complete remission	29%	20%	25%	0.06
no complete remission	71%	80%	75%	

TBI: total body irradiation; CMV: cytomegalovirus; RA: refractory anemia; RARS: refractory anemia with ringed sideroblasts; SCT: stem cell transplantation.

the Cox model were not used since they are inappropriate in such cases. For survival analysis the event was "death from any cause" and the time interval was that from transplantation to the date of this event (uncensored) or the last follow-up date (censored), whichever came first. For disease-free survival the event was defined as "relapse or progression or death from any cause" and the time interval was again from transplantation onwards. For treatment-related mortality the event was defined as "death related to transplantation"; the time interval was again calculated from transplantation until this event (uncensored) or the last follow-up of the patient (censored), which implies that patients who died from other causes were censored at time of death. Engraftment was defined as a leukocyte count of more than 1.0×10^9/L for 3 consecutive days. It was considered that no engraftment had occurred if engraftment was not found at day 30 after transplantation. The cumulative incidence method was used to estimate the incidence of both transplant-related mortality and relapse to account for competing events. The following factors were included in the univariate analysis: sex of the patient, sex of the donor, age, HLA match, disease status, number of blasts, cytogenetics, bone marrow fibrosis at diagnosis, transplant period, donor source and time from diagnosis to transplantation. Factors that had a *P* value of less than 0.1 univariately were included in multivariate Cox regression model (forward elimination) analysis using the hazard ratios estimated in Cox models. Calculations were performed in SPSS version 15 (SPSS, Chicago, IL, USA). The competing risk analyses were done with the ACCorD (V. Gebski, National Health and Medical Research Council, Clinical Trial Center, University of Sydney, Australia).

Results

Treatment-related mortality

The cumulative incidence of treatment-related mortality for the study population at 1 year was 28% (95% CI, 24-32%). There was no difference in treatment-related mortality at 1 year between patients without fibrosis, those with mild/moderate fibrosis and those with severe fibrosis patients (30% and 31% *versus* 26%, respectively; *P*=0.3). Factors that were significantly related with higher treatment-related mortality were HLA-mismatch (HR, 1.65; *P*=0.008), blast content in bone marrow as a continuous variable (HR, 1.01; *P*=0.03), bone marrow as the source of stem cells (HR, 1.34; *P*=0.03). Use of a reduced-intensity conditioning regimen was associated with lower transplant-related mortality (HR 0.64, *P*=0.006). There was also a significant improvement in transplant-related mortality for patients transplanted in more recent years (*P*=0.007) (Table 2). In a multivariate analysis the factors significantly related with higher transplant-related mortality were not being in complete remission (HR, 2.05; *P*<0.001), HLA mismatch (HR, 1.68; *P*=0.007) and standard conditioning (HR, 1.85; *P*=0.001) (Table 3).

Relapse

The cumulative incidence of relapse for the study population at 3 years was 29% (95% CI, 25-33%). Factors significantly related to a higher incidence of relapse were severe bone marrow fibrosis (HR, 2.33; *P*=0.003), abnormal cytogenetics (HR, 1.73; *P*<0.001), donor's age as a continuous variable (HR, 1.01; *P*=0.02), number of blasts at the time of transplantation (HR, 1.02; *P*=0.003), T-cell depletion *in vivo* and *ex vivo* (HR: 1.61, *P*=0.03), and disease status (refractory anemia with excess blasts [RAEB]: HR, 1.61; RAEB in transformation [RAEB-t]: HR, 2.08; sAML: HR, 2.17; *P*=0.006). Furthermore, there was a trend for higher relapse incidence among patients who received reduced-intensity conditioning (HR, 1.29; *P*=0.09) and those for the whom the source of stem cells was peripheral blood (HR, 1.31; *P*=0.08) (Table 2). In a multivariate analysis the following factors remained significant: advanced disease status, defined as RAEB, RAEB-t or sAML (*P*=0.004), abnormal cytogenetics (HR, 1.96; *P*<0.0001) and donor's age (HR, 1.02; *P*=0.02) (Table 3).

Disease-free survival

The 3-year estimated disease-free survival for the study population was 40% (95% CI: 36-44%). In a univariate analysis the following factors were significantly associated with poor disease-free survival: not being in complete remission at the time of transplantation (HR, 1.52; *P*=0.001), high blast percentage at transplantation (HR, 1.02; *P*<0.001), abnormal cytogenetics (HR, 1.44; *P*=0.001) and bone marrow fibrosis (mild/moderate: HR, 1.13; severe: HR, 1.88; *P*=0.003). Furthermore, there was a trend for reduced disease-free survival according to disease stage (RAEB: HR, 1.45; RAEB-t: HR, 1.44; sAML: HR, 1.31; *P*=0.06) and HLA-mismatched transplantation (HR, 1.31; *P*=0.07) (Table 2). In a multivariate analysis, disease stage (*P*=0.004), severe fibrosis (HR, 1.73; *P*=0.02), abnormal cytogenetics (HR, 1.32; *P*=0.02) and not being in complete remission before transplantation (HR, 1.85, *P*<0.001) remained statistically significant (Table 3).

Overall survival

The 3-year estimated overall survival for the study population was 45% (95% CI, 41-49%). Disease stage (RAEB: HR, 1.54; RAEB-t: HR, 1.51; sAML: HR, 1.30; *P*=0.03), not being in complete remission at transplantation (HR, 1.57; *P*=0.001), abnormal cytogenetics (HR, 1.33; *P*=0.01), HLA-mismatch (HR, 1.50; *P*=0.007), blast percentage at transplantation (HR, 1.01; *P*=0.001) and bone marrow fibrosis (mild/moderate: HR, 1.13; severe: HR, 1.94; *P*=0.002) were significant factors in the univariate analysis (Table 2). In a multivariate analysis disease status (*P*=0.005), severe fibrosis (HR, 1.90; *P*=0.006), not being in complete remission at transplantation (HR, 1.88; *P*<0.001) and HLA-mismatch

(HR, 1.48; *P*=0.02) remained independent factors associated with poor survival (Table 3).

Results according to grade of bone marrow fibrosis

The cumulative incidence of engraftment achieved at day +30 in patients without fibrosis was 93% and was significantly lower in those with mild/moderate (89%) or severe (75%) bone marrow fibrosis (*P*=0.009). Furthermore, in those patients who engrafted successfully, the median time to leukocyte engraftment (white cell count > 1×10^9/L) was 16 days in patients with no fibrosis, 17 days in patients with mild/moderate fibrosis and 20

Table 2. Univariate analysis of relapse and therapy-related mortality (TRM), overall survival (OS) and disease-free survival (DFS).

	Relapse HR (95% CI)	*P* value	TRM HR (95% CI)	*P* value	OS HR (95% CI)	*P* value	DFS HR (95% CI)	*P* value
Reduced intensity conditioning	1.29 (0.97–1.73)	0.09	0.64 (0.47–0.88)	0.006	0.82 (0.66–1.03)	0.09	0.91 (0.74–1.13)	0.39
Abnormal cytogenetics	1.73 (1.27–2.34)	< 0.001	–	–	1.33 (1.07–1.65)	0.01	1.44 (1.17–1.77)	0.001
Donor age	1.01 (1.00–1.03)	0.02	–	–	–	–	–	–
Bone marrow fibrosis								
none	1	0.003	1	0.153	1	0.002	1	0.003
mild/moderate	1.002 (0.73–1.39)	0.990	1.25 (0.93–1.67)	0.134	1.21 (0.96–1.51)	0.103	1.13 (0.91–1.40)	0.269
severe	2.33 (1.42–3.82)	0.001	1.51 (0.87–2.63)	0.140	1.94 (1.32–2.86)	0.001	1.88 (1.30–2.72)	0.001
Blasts (in bone marrow)	1.02 (1.07–1.03)	0.003	1.01 (1.00–1.02)	0.03	1.01 (1.01–1.02)	0.001	1.02 (1.01–1.02)	<0.001
Not in complete remission	1.22 (0.88–1.68)	0.23	1.93 (1.35–2.77)	<0.001	1.57 (1.22–2.03)	0.001	1.52 (1.20–1.93)	0.001
Disease								
RA/RARS	1	0.006	1	0.275	1	0.034	1	0.063
RAEB	1.61 (1.05 – 2.48)	0.031	1.34 (0.95 – 1.90)	0.096	1.54 (1.15 – 2.06)	0.003	1.45 (1.10 – 1.90)	0.007
RAEB-t	2.08 (1.34 – 3.24)	0.001	1.03 (0.69 – 1.56)	0.873	1.51 (1.10 – 2.06)	0.010	1.44 (1.07 – 1.93)	0.016
sAML	2.17 (1.17 – 4.01)	0.014	0.79 (0.39 – 1.60)	0.507	1.30 (0.80 – 2.13)	0.287	1.31 (0.83 – 2.07)	0.246
other/unknown	2.21 (1.37 – 3.55)	0.001	1.03 (0.66 – 1.62)	0.892	1.56 (1.11 – 2.20)	0.011	1.48 (1.07 – 2.04)	0.018
HLA mismatch	0.94 (0.58 – 1.53)	0.81	1.65 (1.14 – 2.38)	0.008	1.50 (1.12 – 2.02)	0.007	1.31 (0.98 – 1.75)	0.07
Stem cell source: PB	1.31 (0.97 – 1.77)	0.08	BM: 1.34 (1.02 – 1.76)	0.03	–	–	–	–
SCT in year								
>2001	–	–	1.0	0.007	–	–	–	–
1998–2001			1.20 (0.86 – 1.66)	0.281				
<1998			1.72 (1.23 – 2.40)	0.002				
T-cell depletion								
no	1	0.03	1.0	0.055	–	–	–	–
in vivo	1.43 (1.04 – 1.96)	0.03	0.70 (0.50 – 0.98)	0.040				
ex vivo	0.85 (0.48 – 1.50)	0.57	1.16 (0.74 – 1.82)	0.519				
in vivo + ex vivo	1.61 (1.04 – 2.50)	0.03	1.25 (0.82 – 1.90)	0.309				

RA: refractory anemia; RARS: refractory anemia with ringed sideroblasts; SCT: stem cell transplantation; PB: peripheral blood.

Table 3. Significant factors in multivariate analysis for relapse, transplant-related mortality (TRM), disease-free survival (DFS), and overall survival (OS).

	Relapse (n=543) HR (95 % CI)	*P* value	TRM (n=616) HR (95 % CI)	*P* value	DFS (n=562) HR (95 % CI)	*P* value	OS (n=562) HR (95 % CI)	*P* value
Disease status								
RA/RARS	1	0.004	–	–	1	0.004	1	0.005
RAEB	1.74 (1.05–2.88)	0.033			1.56 (1.15–2.1)	0.004	1.70 (1.23– 2.34)	0.001
RAEB-t	2.26 (1.36–3.77)	0.002			1.97 (1.38–2.8)	0.000	1.97 (1.36– 2.86)	0.000
sAML	2.55 (1.25–5.17)	0.010			1.48 (0.86–2.5)	0.157	1.53 (0.87– 2.69)	0.141
other/unknown	2.66 (1.54–4.58)	0.000			1.60 (1.09–2.32)	0.015	1.60 (1.08– 2.39)	0.021
Abnormal cytogenetics	1.96 (1.41 – 2.72)	<0.0001	–	–	1.32 (1.05 – 1.65)	0.02	–	–
Not CR prior to SCT	–	–	2.05 (1.39 – 3.04)	< 0.001	1.85 (1.37 – 2.50)	< 0.001	1.88 (1.38 – 2.57)	< 0.001
HLA mismatch	–	–	1.68.(1.15 – 2.46)	0.007	–	–	1.48.(1.06 – 2.07)	0.02
Standard conditioning	–	–	1.85 (1.28 – 2.68)	0.001	–	–	–	–
Age of donor	1.02 (1.00 - 1.03)	0.02	–	–	–	–	–	–
Bone marrow fibrosis								
none					1	0.05	1	0.02
mild/moderate					1.05 (0.82 – 1.34)	0.73	1.10 (0.85 – 1.42)	0.487
severe					1.73 (1.11 – 2.69)	0.02	1.90 (1.20 – 3.00)	0.006

RA: refractory anemia; RARS: refractory anemia with ringed sideroblasts; CR: complete remission; SCT: stem cell transplantation.

days in patients with severe fibrosis (P=0.002) (Figure 1). There were no significant differences in acute and chronic graft-*versus*-host disease between the three groups. The incidence of relapse at 3 years was significantly higher in the group with severe fibrosis than in those with mild/moderate or no fibrosis (47% *versus* 27% *versus* 28%, respectively; P=0.04), resulting in a significantly lower disease-free survival at 3 years (18% *versus* 38% *versus* 42%; P=0.002) and, likewise, a significantly lower overall survival at 3 years (21% *versus* 40% *versus* 49%; P=0.002) (Table 4).

Results according to the International Prognostic Scoring System score and fibrosis

To evaluate the impact of fibrosis and the IPSS score, we correlated fibrosis and IPSS score in 294 patients for whom the IPSS score at transplantation was known. The degree of fibrosis was well balanced in patients with all IPSS scores (*data not shown*). The estimated 3-year overall survival rates for patients with intermediate-1-risk MDS with and without fibrosis were 43% and 52%, respectively (P=0.6). The estimated 3-year overall survival rates for patients with intermediate-2-risk MDS with and without bone marrow fibrosis were 42% and 48%, respectively (P=0.6), and those for high-risk patients also did not differ significantly between patients with (22%) and without bone marrow fibrosis (33%, P=0.4).

Discussion

Here we analyzed the impact of bone marrow fibrosis on outcome after allogeneic stem cell transplantation in MDS patients reported to the EBMT registry. We included only patients diagnosed with MDS, while those with primary myelofibrosis or overlap syndrome (MDS/MPS) were excluded from this analysis. The prognostic impact of bone marrow fibrosis in MDS patients has come into focus and several studies have confirmed a negative impact of fibrosis on survival[3-7] with some authors suggesting that MDS with fibrosis could be considered as a distinct entity.[9-11] Although bone marrow fibrosis is not included in the current prognostic risk scores such as the

Table 4. Results of stem cell transplantation in MDS patients without bone marrow fibrosis, with mild or moderate fibrosis and with severe fibrosis.

Fibrosis	None	Mild/ moderate	Severe	*P* value
Cumulative incidence of engraftment at day +30	93 % (91-95)	89 % (85-93)	75 % (61-89)	0.009
Median days to leukocyte engraftment (>1.0×10⁹/L) (range)	16 (1-69)	17 (7-47)	20 (11-34)	0.002
Acute GVHD grade II - IV	31%	35%	31%	0.49
Chronic GVHD n = 450				
none	45 %	35 %	56 %	
limited	26 %	28 %	12 %	0.13
extensive	29 %	37 %	32 %	
1-year therapy-related mortality	26 % (22-30)	30% (24-36)	31% (17-45)	0.34
3-year cumulative incidence of relapse	28 % (24-32)	27 % (21-33)	47 (29-65)	0.04
3-year disease-free survival	42 % (36-48)	38 % (30-46)	18 % (4-32)	0,002
3-year oveall survival	49 % (43-55)	40 % (32-48)	21 % (7-35)	0.002

*GVHD: Graft-*versus*-host disease, in brackets: 95% confidence interval.*

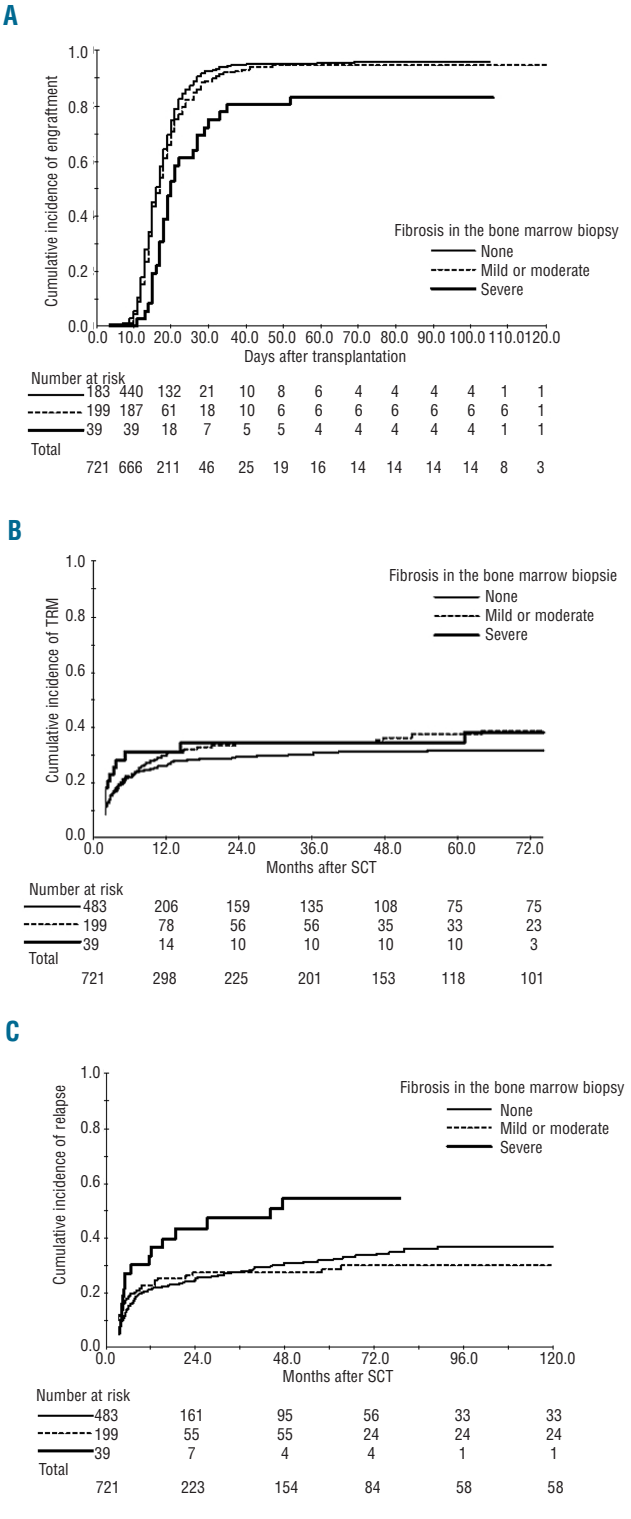

Figure 1. Cumulative incidence of (A) engraftment, (B) treatment-related mortality (TRM), and (C) relapse according bone marrow fibrosis grading.

IPSS1 and WPSS,[2] some investigators recommend more aggressive treatment for patients with bone marrow fibrosis than either the IPSS or WPSS score would dictate.[7] When we analyzed the outcome of patients according to IPSS and whether or not they had bone marrow fibrosis, we found no significant differences in overall survival. Given the low number of patients with severe fibrosis this group of patients could not be analyzed separately regarding IPSS score. The prognostic impact of bone marrow fibrosis in MDS patients who underwent allogeneic stem cell transplantation has not been studied in detail. In one study no differences in overall survival, relapse-free survival and non-relapse mortality were found between patients with or without bone marrow fibrosis. However, when patients with intermediate-2-risk or high-risk MDS were studied separately, the presence of bone marrow fibrosis was associated with a negative impact on outcome.[8]

In our study, based on a large cohort of patients, we found that while patients with mild or moderate bone marrow fibrosis had a similar outcome to those without bone marrow fibrosis after allogeneic stem cell transplantation, patients with severe bone marrow fibrosis had a significantly worse survival. Our results are consistent with reports indicating a lower engraftment rate as well as delayed leukocyte engraftment for patients with increased bone marrow fibrosis,[8,12] although they contrast with those of other investigators who did not find a difference in engraftment for patients with bone marrow fibrosis.[13] In this EBMT study the difficulties in engraftment resulted only in a trend to a higher treatment-related mortality. Notably, bone marrow fibrosis did not influence the incidence of acute or chronic graft-*versus*-host disease. Regarding relapse incidence we observed a significantly higher risk of relapse in the group with severe fibrosis, but only in univariate analysis. In multivariate analysis for relapse and treatment-related mortality, fibrosis was not a significant independent risk factor. However, in a multivariate analysis for disease-free and overall survival severe fibrosis remained a significant independent risk factor.

Some authors interpret bone marrow fibrosis in MDS patients as a more malignant subtype of MDS and found some correlation with multilineage dysplasia or excess of blasts,[6] but in our population of patients mild/moderate and severe bone marrow fibrosis were seen in all categories and disease stages of MDS, and were not associated with other known risk factors such as disease status, abnormal cytogenetics, age or number of blasts.[6,8] The comparable interval between diagnosis and transplantation of about 8 months further suggests that MDS patients with bone marrow fibrosis are not in a more advanced stage. The observed risk factors for relapse such as age, disease status and abnormal cytogenetics, as well as the risk factors for overall survival, such as disease status, not being in complete remission at transplantation and HLA-mismatch, show that this study population was not a selected cohort and represented a common MDS population.

The pathogenesis of fibrosis in MDS patients is unclear. The bone marrow fibrosis may lead to cytopenia and marrow insufficiency. It remains to be determined whether overproduction of cytokines, such as platelet-derived growth factor-α or -β, transforming growth factor-β1 or basic fibroblast growth factor by malignant or inflammatory cells, is involved, as it is in other diseases.[14,15] Also,

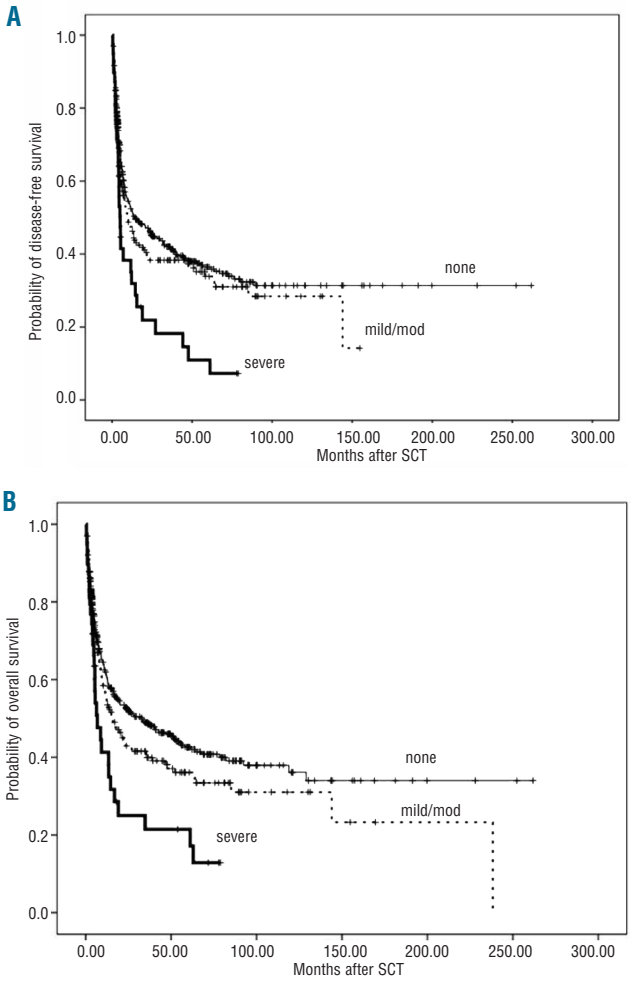

Figure 2. Probability of (A) disease-free survival and (B) overall survival after stem cell transplantation (SCT) according to degree of bone marrow fibrosis.

while MDS with bone marrow fibrosis can share some features with primary myelofibrosis, cytogenetic features and molecular markers differ substantially between the two diseases. Buesche found dyserythropoiesis and greater than 50% micromegakaryocytes with a hypolobulated round nucleus exclusively in MDS patients, while more than 10% giant megakaryocytes were found in 100% of the patients with primary myelofibrosis and in only 6% of the MDS-fibrosis patients. Furthermore, splenomegaly, leukocytosis and thrombocytosis were more common in primary myelofibrosis while thrombocytopenia and anemia were more often seen in MDS-fibrosis patients.[6] In the same trial the investigators observed a correlation between bone marrow fibrosis and multilineage dysplasia, severe thrombocytopenia, a higher probability of clonal karyotype abnormalities and a higher percentage of blasts in peripheral blood and a shorter survival of MDS fibrosis patient. The prognostic significance was independent of the IPSS. In a similar study Della Porta detected moderate to severe bone marrow fibrosis in 17% of the MDS patients and fibrosis was associated with multilineage dysplasia, poor-risk cytogenetic abnormalities and high transfusion requirement. Those patients had a poor outcome irrespectively of the presence of an excess

of blasts.[7] Since our study is a retrospective registry study and no central review was performed to confirm the diagnosis of MDS, it cannot be excluded that some cases were misdiagnosed as MDS and should have been classified as MPS or MDS/MPS overlap syndrome. Unfortunately, data about spleen size or molecular markers such as the *JAK2* mutation are only available for a small minority of the patients, but some indirect facts support the belief that the study population was a MDS population. First, the time from diagnosis to transplantation was only 8 months, which is substantially shorter than that observed in patients with myelofibrosis. Furthermore, the survival of myelofibrosis patients with usually severe fibrosis is reported to be about 50% after allogeneic stem cell transplantation, and substantially better than the observed 18% disease-free survival in patients with severe bone marrow fibrosis in the current study.[16,17]

We conclude that bone marrow fibrosis in MDS patients influences engraftment after allogeneic stem cell transplantation but that only severe bone marrow fibrosis affects survival because of a higher risk of relapse, while MDS patients with mild or moderate bone marrow fibrosis have an outcome comparable to that of MDS patients without bone marrow fibrosis.

Authorship and Disclosures

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References

1. Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89 (6):2097-88.
2. Malcovati L, Della Porta MG, Pascutto C, Invernizzi R, Boni M, Travaglino E, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. J Clin Oncol. 2005; 23(30):7594-603.
3. Lambertenghi-Deliliers G, Annaloro C, Oriani A, Solgio D, Pozzoli E, Polli E. Prognostic relevance of histological findings on bone marrow biopsy in myelodysplastic syndromes. Ann Hematol. 1993; 66(2):85-91.
4. Verhoef GE, De Wolf-Peeters C, Ferrant A, Deprez S, Meeus P, Stuhl M, et al. Myelodysplastic syndromes with bone marrow fibrosis: a myelodysplastic disorder with proliferative features. Ann Haematol. 1991;63(5):235-41.
5. Maschek H, Georgii A, Kaloutsi V, Bandecar K, Kressel MG, Choritz H, et al. Myelofibrosis in primary myelodysplastic syndromes: a retrospective study of 352 patients. Eur J Haematol. 1992;48(4):208-14.
6. Buesche G, Teoman H, Wilczak W, Ganser A, Hecker H, Wilkens L, et al. Marrow fibrosis predicts early fatal marrow failure in patients with myelodysplastic syndromes. Leukemia. 2008;22(2):313-22.
7. Della Porta MG, Malcovati L, Boveri E, Travaglino E, Pietra D, Pascutto C, et al. Clinical relevance of bone marrow fibrosis and CD34-positive cell clusters in primary myelodysplastic syndromes. J Clin Oncol. 2009;27(5):754-62.
8. Scott BL, Storer BE, Greene JE, Hackman RC, Appelbaum FR, Deeg HJ. Marrow fibrosis as a risk factor for posttransplantation outcome in patients with advanced myelodysplastic syndrome or acute myeloid leukemia with multilineage dysplasia. Biol Blood Marrow Transplant. 2007; 13(3):345-54.
9. Lambertenghi-Deliliers G, Orazi A, Luksch Annaloro C, Soligo D. Myelodysplastic syndrome with increased marrow fibrosis: a distinct clinico-pathological entity. Br J Haematol. 1991;78(2):161-6.
10. Marisavljevic D, Rolovic Z, Cemerikic V, Boskovic D, Colovic M. Myelofibrosis in primary myelodysplastic syndromes: clinical and biological significance. Med Oncol. 2004;21(4):325-31.
11. Steensma DP, Hanson CA, Letendre L, Tefferi A. Myelodysplasia with fibrosis: a distinct entity? Leuk Res. 2001;25(10):829-38.
12. Rajantie J, Sale GE, Deeg HJ, Amos D, Appelbaum F, Storb R, et al. Adverse effect of severe marrow fibrosis on haematological recovery after chemoradiotherapy and allogeneic bone marrow transplantation. Blood. 1986;67(6):1693-7.
13. Soll E, Massumoto C, Clift RA, Buckner CD, Appelbaum FR, Storb R, et al. Relevance of marrow fibrosis in bone marrow transplantation: a retrospective analysis of engraftment. Blood. 1995;86(12): 4667-73.
14. Reilly JT, Barnett D, Dolan G, Forrest P, Eastham J, Smith A. Characterization of an acute micromegakaryocytic leukaemia: evidence for the pathogenesis of myelofibrosis. Br J Haematol. 1993;83(1):58-62.
15. Kimura A, Katoh O, Hyodo H, Kuramoto A. Transforming growth factor beta regulates growth as well as collagen and fibronectin synthesis of human marrow fibroblasts. Br J Haematol. 1989;72(4):486-91.