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Prognostic implications and clinical characteristics associated with bone marrow fibrosis in patients with myelofibrosis

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To the editor:

Myelofibrosis (MF) is a heterogeneous, hematopoietic stem cell malignancy characterized by abnormal proliferation of myeloid cells of variable maturity and function [1]. The most common clinical manifestations of the disease are anemia, leukocytosis, leukopenia, thrombocytosis, constitutional symptoms, and marked splenomegaly with extramedullary hematopoiesis [1]. Bone marrow fibrosis (BMF), which results from abnormal deposition of reticulin and collagen fibers in the bone marrow plays a major role in the pathophysiology and clinical manifestation of the disease. Various scoring systems have been developed to evaluate the amount of reticulin and collagen fibers in BMF, the most widely accepted is the 4-grade scoring system (MF 0–3) recommended by the European consensus [2]. The prognostic effect of BMF in MF remains controversial; however, it has been suggested that BMF may affect overall survival (OS) in patients with MF [3–5].

We retrospectively analyzed the medical records of 537 patients who were diagnosed with MF according to World Health Organization criteria [6] and were referred to our institution between February 2005 and December 2009. Project was based on a chart review protocol approved by the Institutional Review Board. Paraffin-embedded trephine bone marrow biopsies obtained from patients at their first presentation to MD Anderson were reviewed. Grades from 0 to 3 were documented, with grade 3 representing the most severe grade of fibrosis [2]. Twenty-five patients were excluded from the final analysis because of incomplete documentation of BMF grading in their reviewed biopsies. The OS rate was

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Authorship Contributions

Contribution: AN designed the research, collected, analyzed and interpreted the data, wrote and approved the manuscript. ZE analyzed and interpreted the data, and wrote and approved the manuscript. JC analyzed and interpreted the data, wrote and approved the manuscript. CB-R analyzed and interpreted the data, wrote and approved the manuscript. HK analyzed and interpreted the data, wrote and approved the manuscript. SV designed the research, analyzed and interpreted the data, wrote and approved the manuscript.

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calculated from the time of first biopsy at MD Anderson to the time of death or last follow-up; the EFS rate was calculated from the time of first biopsy at MD Anderson to time of death, leukemia transformation, or last follow-up. The IPSS and the DIPSS were calculated as described previously [7,8]. Differences among variables were evaluated by the chi-square for categorical variables and by Kruskal-Wallis and Mann-Whitney U tests for continuous variables. A Cox proportional hazard regression module was used to determine the independent predictors of severity of BMF. Time-to-event analyses were performed by the Kaplan-Meier method, and survival curves were compared with the log rank test.

The final analysis included 512 patients (352 patients with primary MF, 88 with post-PV MF, and 72 with post-ET MF). The patient's demographics and disease characteristics are summarized in Table 1. The median time from diagnosis of MF to the first bone marrow biopsy done at MD Anderson was 4 months (range, 0–388 months), and the median follow-up was 16.5 months (range, 0–79 months). Higher grades of BMF were associated with a lower hemoglobin level ($P < 0.001$), lower white blood cell count ($P = 0.03$), and lower platelet count ($P = 0.02$), higher percentage of blasts in peripheral blood ($P = 0.001$), as well as, significantly larger spleen ($P = 0.01$) and liver ($P = 0.04$). In addition, abnormal cytogenetic findings were associated with higher grades of BMF ($P = 0.01$); but, neither the presence of the JAK2 V617F mutation nor the allele burden correlated with the severity of BMF ($P = 0.28$). However, in a multivariate analysis, lower hemoglobin level ($P = 0.003$), higher percentage of blasts in the peripheral blood ($P = 0.015$), and larger spleen ($P = 0.006$) were the only independent prognostic parameters for the severity of BMF. In addition, survival risk assessment of patients using the IPSS and DIPSS scoring systems correlated well with the severity of BMF (Table 1). Vener and colleagues [3] reported the prognostic significance of BMF grading in MF. One hundred thirteen patients were included in their study, 29% had MF-0, 24% MF-1, 23% MF-2, 11% MF-3, and 13% secondary MF. Patients with MF-3 had inferior OS compared to patients with MF-0 ($P = 0.001$), and MF-1+2 groups ($P = 0.003$). In addition, Thiele and colleagues [5] had also reported inferior OS among patients with grades MF-2 or MF-3 compared with those with grades MF-0 or MF-1 (statistical significance was not reported) suggesting that BMF grading may play an important role in the prognosis of patients with MF. Recently, Barosi and colleagues [4] compared the clinical features of prefibrotic myelofibrosis (MF-0) to primary myelofibrosis fibrotic type (MF-1,2, and 3) and found that patients with prefibrotic myelofibrosis are predominantly females with younger age, higher hemoglobin, higher platelet count, lower white blood cell count and smaller spleen. Furthermore, with median follow up of 43 months (range, 1–375 months), the median OS for prefibrotic myelofibrosis patients was not reached and was significantly higher than patients with primary myelofibrosis fibrotic type (16.6 years, $P < 0.001$). In our study, although BMF correlated well with DIPSS and IPSS scoring systems and no patients with MF-0 died or had an event, the rates of OS, EFS, and leukemia transformation free survival were not statistically significant between patients with different BMF grades (Table 1; Figure 1). These differences in our result could be explained by the higher number of patients with MF-3 and the lower number of patients with MF-0 in our patient population resulted from the referral of patients to our institution during their disease course rather than at diagnosis, as well as by the very short follow-up during the study period compared to other studies. Furthermore, it is interesting that significant number

of patients with low/intermediate-1 risk by DIPSS score had high grades of BMF. This suggests that assessments of BMF at diagnosis and during the disease course may be important even in patients with low risk disease. However, given the difficulties of obtaining bone marrow biopsies regularly in clinical practice, regular assessment of BMF grade may not be necessary outside clinical trials and the incorporation of BMF grading in the prognostication systems of MF need to be further evaluated in larger patient population with longer follow up.

In conclusion, severe BMF has significant impact on the clinical manifestation of MF, as it correlates with lower hemoglobin, higher percentage of blasts in the peripheral blood, and larger spleen as well as the IPSS and DIPSS risk assessments. However, the OS, EFS and transformation to acute leukemia were similar in our experience among patients with various degrees of BMF, possibly due to limited number of patients with no or low grade BMF, and short follow up. Further clinical and biological studies and longer follow up are needed to fully understand the significant impact of BMF in patients with MF.

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A **B**

Figure 1. Overall survival, event-free survival, and leukemia-transformation free survival rates by bone marrow fibrosis groups

(A) Kaplan-Meier curves representing overall survival among bone marrow fibrosis groups. (B) Kaplan-Meier curves representing event-free survival among bone marrow fibrosis groups. (C) Kaplan-Meier curves representing leukemia-transformation free survival among bone marrow fibrosis groups.

Table 1

Patient characteristics and outcome by bone marrow fibrosis grades

Patient characteristics	Overall	MF-0	MF-1	MF-2	MF-3	P value
Number (%)	512	7 (1)	44 (9)	170 (33)	291 (57)	
Median age (range) (years)	64 (20–89)	65 (53–81)	65 (31–82)	61 (20–86)	64 (21–89)	0.66
Gender (M/F), No. (%)	310/201 (61/39)	2/5 (29/71)	30/14 (32/68)	103/67 (60/40)	175/116 (60/40)	0.25
Constitutional symptoms ¹ (Y/N) (%)	263/249 (51/49)	3/4 (43/57)	23/21 (52/48)	76/94 (45/55)	147/144 (51/49)	0.61
Transfusion dependency ² (Y/N) (%)	393/119 (77/23)	2/5 (29/71)	6/38 (14/86)	31/139 (18/82)	80/211 (27/73)	0.05
Performance status, No. (%)						
0	177 (34)	4 (57)	17 (39)	67 (39)	89 (31)	
1	285 (56)	3 (43)	24 (55)	91 (54)	167 (57)	0.23
2	50 (10)	0 (0)	3 (6)	12 (7)	35 (12)	
Cytogenetics abnormalities, No. (%)						0.01
Diploid/abnormal	312/179 (61/35)	6/0 (86)	30/14 (68/32)	114/48 (67/28)	162/117 (56/40)	
Not documented	21 (4)	1 (14)	0 (0)	8 (5)	12 (4)	
JAK 2 V617F mutation status, No. (%)						0.47
Positive	186 (68)	2 (1)	15 (8)	68 (37)	101 (54)	
Negative	88 (32)	3 (3)	9 (10)	28 (32)	49 (55)	
Not done	238	2 (1)	20 (8)	74 (32)	141 (59)	
JAK 2 V617F allele burden, No. (%)						0.91
50	76 (41)	1 (1)	6 (8)	30 (40)	39 (51)	
> 50	110 (59)	1 (1)	9 (8)	38 (35)	62 (56)	
Median Hgb, g/dL (range)	10.4 (5.4–18.7)	10.6 (8.1–12.7)	11.1 (7.9–16.4)	11 (6–16.8)	10 (5.4–18.7)	<0.001
Median WBC $\times 10^9$ /L (range)	10.3 (1–361)	11.9 (4.4–30.8)	14.6 (1.3–188)	9.5 (1.4–182)	10.1 (1–361)	0.03
Median platelets $\times 10^3$ /mL (range)	214.5 (9–1969)	313 (121–770)	185 (18–1958)	233 (9–1969)	195 (15–980)	0.02
Median PB BL % (range)	0 (0–16)	0 (0–2)	0 (0–6)	0 (0–16)	1 (0–13)	0.001
Median BM BL % (range)	2 (0–17)	1 (0–2)	1.5 (0–7)	2 (0–15)	2 (0–17)	0.31
Median liver size, cm (range)	0 (0–30)	0 (0–5)	0 (0–12)	0 (0–14)	0 (0–30)	0.04
Median spleen size, cm (range)	9 (0–46)	3 (0–20)	8 (0–25)	5 (0–30)	10 (0–46)	0.01
IPSS, No. (%)						0.005
Low	59 (12)	0 (0)	9 (16)	25 (42)	25 (42)	

Patient characteristics	Overall	MF-0	MF-1	MF-2	MF-3	P value
Intermediate-1	137 (27)	3 (2)	7 (5)	57 (42)	70 (51)	
Intermediate-2	144 (28)	3 (2)	15 (10)	46 (32)	80 (56)	
High	172 (33)	1 (1)	13 (8)	42 (24)	116 (67)	
DIPSS, No. (%)						0.007
Low	59 (12)	0 (0)	9 (16)	25 (42)	25 (42)	
Intermediate-1	215 (42)	5 (2)	18 (8)	81 (38)	111 (52)	
Intermediate-2	195 (38)	1 (1)	13 (7)	58 (29)	123 (63)	
High	43 (8)	1 (2)	4 (10)	6 (14)	32 (74)	
Median OS (months)	Not reached	Not reached	Not reached	47	39	0.82
Median EFS (months)	Not reached	Not reached	Not reached	43.4	37.7	0.41
Leukemia transformation rate, No. (%)	29 (6)	0 (0)	0 (0)	10/170 (6)	19/291 (7)	0.35

Abbreviations: M = male, F = female, Y = yes, N = no, Hgb = hemoglobin, WBC = white blood cell count, PB BL = peripheral blood blasts, BM BL = bone marrow blasts, IPSS = International Prognostic Scoring System, DIPSS = Dynamic International Prognostic Scoring System, OS = overall survival, EFS = event-free survival, MF = myelofibrosis, *Abnormal cytogenetics* was defined in accordance with the International System of Human Cytogenetic Nomenclature (ISCN 2005) [9]. A *constitutional symptom* was defined as the presence of at least 1 of 3 constitutional symptoms (10% weight loss in 6 months, night sweats, and/or unexplained fever of 37.5°C or higher). *Transfusion dependency* was defined as the transfusion of at least 2 units of red blood cells per month over at least a 3-month period.