Prognostic Model to Identify Patients With Myelofibrosis at the Highest Risk of Transformation to Acute Myeloid Leukemia

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Abstract

A fraction of patients with myelofibrosis (MF) will progress to acute myeloid leukemia (AML) but no current tools are available to identify such patients. By multivariate analysis of 649 patients with MF, we have identified several independent prognostic factors for death. Among those factors, the presence of bone marrow blasts >10% and high risk karyotype were identified as independent risk factors for transformation from MF to AML.

Background: Some patients with myelofibrosis (MF) progress to acute myeloid leukemia (AML). Current prognostic tools were not devised to assess risk of AML transformation. **Methods:** Multivariate analysis in 649 patients followed for a median of 19 months (range, 1-180 months). **Results:** We identified age > 60 ($P = .004$; hazard ratio [HR], 1.63), platelets $<100 \times 10^9$/L ($P < .001$; HR, 1.62), bone marrow blast > 10% ($P = .002$; HR, 2.18), high-risk karyotype ($P < .001$; HR, 2.44), transfusion dependency ($P < .001$; HR, 2.64), performance status > 1 ($P = .003$; HR, 1.47), lactate dehydrogenase > 2000 U/L ($P < .001$; HR, 1.62), previous hydroxyurea ($P < .001$; HR, 1.69), and male sex ($P = .005$; HR, 1.41) as independent poor prognostic factors for survival. Using the same baseline variables we identified bone marrow blasts >10% and worst karyotype as independent risk factors for AML transformation. Patients with 1 or both of these risk factors (n = 80; 12%) had a median survival of 10 months and a 1-year AML transformation rate of 13% (2% if none of those factors, $P = .001$). **Conclusion:** We have identified risk factors that predict high risk of transformation from MF to AML.

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Introduction

The median overall survival (OS) of patients with primary or post-polycythemia vera (PV) or postessential thrombocythemia (ET) myelofibrosis (MF) is 5-7 years.[1] However, particular subsets of patients with MF exhibit highly variable survival times that might exceed 15 years in younger patients with no high-risk features.[1] Several prognostic scoring systems have been devised to risk-stratify patients with MF.[1-3] An important cause of death in high-risk MF is transformation to acute myeloid leukemia (AML, ie, myeloproliferative neoplasm [MPN] blast phase), which occurs in 8%-23% of patients with MF in the first 10 years after diagnosis.[4,5] Patients with MF that transform to AML have a dismal outcome,[6] with an OS ranging from 3 to 8 months and a 1-year survival rate of 5%-10%.[4,7]

Though current prognostic models can identify patients with MF with poor prognosis, their ability to predict what patients are at the highest risk of transformation to AML is limited because not all of the risk factors associated with OS in such models independently predict leukemic transformation.[3] This is important because prognostic tools capable of identifying patients at the highest risk of death caused by AML transformation might provide an opportunity to intervene early during the course of the disease with specific therapeutic modalities (eg, allogeneic stem cell transplantation [SCT]). On these grounds, we set out to identify independent risk factors that predict for high risk to transformation to AML in a large cohort of patients diagnosed and followed at our institution.

Patients and Methods

The study was approved by the M.D. Anderson Cancer Center Institutional Review Board. We surveyed a database of 649 pa-

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Table 1 Patient and Disease Characteristics

Parameter	Category	Patients, n (%)	Median (Range)
Age (Years)			62 (20-86)
Hemoglobin (g/dL)			10.4 (1.8-18.7)
Platelets ($\times 10^9$/L)			190 (1-1958)
WBC ($\times 10^9$/L)			9.6 (0.4-361)
% PB Blast			0 (0-17)
% BM Blasts			2 (0-17)
MF Duration (Months)			2.7 (0-353)
LDH (U/L)			1230 (189-1035)
Total Bilirubin (mg/dL)			0.6 (0.1-5.0)
Creatinine (mg/dL)			1.0 (0.4-7.4)
Sex	Female	263 (41)	
Performance Status	0	282 (43)	
	1	314 (48)	
	2	49 (8)	
	3	4 (1)	
Splenomegaly	Yes	380 (59)	
Hepatomegaly	Yes	143 (22)	
Secondary MF	Yes	177 (27)	
Cytogenetics	13q-only	18 (3)	
	20q-only	42 (6)	
	Diploid	367 (57)	
	Insufficient metaphases	17 (3)	
	1 CG Abn	49 (8)	
	2 CG Abn	30 (5)	
	Chromosome 7 Abn	15 (2)	
	Chromosome 17 Abn	7 (1)	
	Complex	34 (5)	
	Complex + 5 Abn	4 (1)	
	Complex + 7 ± 5 Abn	12 (2)	
	Complex + 17 ± 5 or 7	16 (2)	
	Not done	38 (6)	
Previous Therapy	Hydrea	238 (37)	
	Immunomodulatory	108 (17)	
	Alkylating	9 (1)	
	Others	24 (4)	
	None	270 (42)	

Abbreviations: Abn = abnormality; BM = bone marrow; CG = cytogenetic; LDH = lactate dehydrogenase; MF = myelofibrosis; PB = peripheral blood; WBC = white blood cell count.

tients with MF referred to our institution from February 1966 to June 2010, including 177 (27%) with post-PV or post-ET MF (Table 1). The median age was 62 years (range, 20-86 years) and the median bone marrow (BM) blasts was 2% (range, 0%-2%). Splenomegaly was present in 380 patients (59%) and 270 (42%) of them had never received treatment for MF. A complex karyotype was present in 66 patients (10.2%), including 32 (4.9%) with and 34 (5.2%) without deletions of chromosomes 5 and/or 7. AML transformation was established in the presence of ≥ 20% BM and/or peripheral blood (PB) blasts. Survival was analyzed using the Kaplan-Meier method and differences were compared using the log-rank test.

Table 2 Prognostic Scoring System for Overall Survival

Risk Group	Factors, n	Patients, n (%)	Median OS (Months)
Low	0-1	84 (13)	NR
Intermediate-1	2-3	191 (29)	74
Intermediate-2	4-5	208 (32)	29
High	≥ 6	166 (26)	11

Abbreviations: NR = not reached; OS = overall survival.
Independent risk factors for survival included in the scoring system: age ≥ 60 years, baseline platelet count < 100×10^9/L, bone marrow blast > 10%, high-risk karyotype (del17p, −5, −7, and/or complex), transfusion dependency (≥ 2 red cell transfusions), performance status ≥ 1, lactate dehydrogenase > 2000 U/L, previous therapy with hydroxyurea, and male sex.

Results and Discussion

The median follow-up for the whole cohort was 19 months (range, 1-180 months). The yearly rates of AML transformation during the first, second, and third year of follow-up were 3%, 2%, and 3%, respectively. We evaluated an extensive list of baseline patient characteristics by univariate analysis to identify risk factors for OS (Supplementary Table 1), including, among others, previous exposure to alkylating agents, hydroxyurea, immunomodulatory drugs (ie, thalidomide derivatives), MF duration, chromosomal abnormalities, and $JAK2^{V617F}$ mutation (yes vs. no, and as a continuous variable). To determine the relative effect of each variable on survival, a Cox proportional hazard model was constructed entering covariates with a P value ≤ 0.10 in the univariate analysis so as to capture all potential factors independently predicting for survival. The increase in risk was estimated as a hazard ratio (HR). Multivariate analysis identified age ≥ 60 years (P = .004; HR, 1.63; 95% confidence interval [CI], 1.26-2.79), baseline platelet count < 100×10^9/L (P < .001; HR, 1.62; 95% CI, 1.08-3.21), BM blast > 10% (P = .002; HR, 2.18; 95% CI, 1.49-3.01), worst karyotype (del17p, -5, -7, and/or complex; P < .001; HR, 2.44; 95% CI, 1.51-3.17), transfusion dependency (≥ 2 red cell transfusions; P < .001; HR, 2.64; 95% CI, 0.99-2.01), performance status ≥ 1 (P = .003; HR, 1.47; 95% CI, 1.22-2.11), lactate dehydrogenase (LDH) > 2000 U/L (P < .001; HR, 1.62; 95% CI, 0.89-1.33), previous hydroxyurea (P < .001; HR, 1.69; 95% CI, 1.42-2.19), and male sex (P = .005; HR, 1.41; 95% CI, 0.88-1.91) as independent poor prognostic factors for OS. Using the corresponding HRs, a risk model for survival was derived based on weighted scores of 0-1, 2-3, 4-5, and ≥6. The number of patients and median OS for the 4 risk groups were Low, 84 (13%), median OS not reached; Intermediate-1, 191 (29%), median OS 74 months; Intermediate-2, 208 (32%), median OS 29 months; High, 166 (26%), median OS 11 months (Table 2, Figure 1A).

Next, we examined the same baseline variables used in the OS analysis to identify independent risk factors for AML transformation.