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Hemoglobin levels and circulating blasts are two easily evaluable diagnostic parameters highly predictive of leukemic transformation in primary myelofibrosis

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ABSTRACT

To predict leukemic transformation (LT), we evaluated easily detectable diagnostic parameters in 338 patients with primary myelofibrosis (PMF) followed in the Latium region (Italy) between 1981 and 2010. Forty patients (11.8%) progressed to leukemia, with a resulting 10-year leukemia-free survival (LFS) rates of 72%. Hb (<10 g/dL), and circulating blasts (≥1%) were the only two independent prognostic for LT at the multivariate analysis. Two hundred-fifty patients with both the two parameters available were grouped as follows: low risk (none or one factor) = 216 patients; high risk (both factors) = 31 patients. The median LFS times were 269 and 45 months for the low and high-risk groups, respectively ($P < .0001$). The LT predictive power of these two parameters was confirmed in an external series of 270 PMF patients from Tuscany, in whom the median LFS was not reached and 61 months for the low and high risk groups, respectively ($P < .0001$). These results establish anemia and circulating blasts, two easily and universally available parameters, as strong predictors of LT in PMF and may help to improve prognostic stratification of these patients particularly in countries with low resources where more sophisticated molecular testing is unavailable.

1. Introduction

Among the distinct Ph-negative myeloproliferative neoplasms (Ph-neg MPNs), primary myelofibrosis (PMF) is the variety associated with worst prognosis, showing a median survival of one to five years. The most severe complication of PMF is leukemic

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transformation (LT) which is reported to occur in 8–23% of patients at 10 years from diagnosis and that represents one of the major causes of disease related mortality [1–4] Therefore, scoring PMF patients for their risk of LT is clinically relevant, as it will better drive the therapeutic choice including stem cell transplantation.

Several parameters such as leukocytosis, organomegaly, systemic symptoms, anemia, thrombocytopenia, presence of blasts and transfusion dependency assessed at onset or during the course of the disease, have been used to construct static or dynamic prognostic models [5–7]. More recently, karyotypic alterations and molecular lesions in the *JAK2*, *MPL*, *TET2*, *ASXL1*, *CBL*, *IDH*, *IKZF1*, *SRSF2*, *EZH2* and *CARL* genes have been associated with an increased risk of LT [8–11].

However, two types of objective difficulties hamper the possibility to retrieve these data: the difficulty to obtain assessable metaphases in PMF, a condition in which "dry tap" marrow biopsy occurs frequently, and the availability of laboratories equipped to perform the laborious and sophisticated genomic analyses.

Therefore, we retrospectively assessed the LT predictive value of several easily available clinico-biological features in a large series of 338 PMF patients to design a simple predictor model for LT that resulted based on the hemoglobin levels and circulating blasts. This model was validated in an external PMF patient series collected in Tuscany.

2. Materials and methods

2.1. Patients

After the approval from the Institutional Review Board of each participating study center, a common database for Philadelphia-negative MPNs with homogeneous data sheets was created in 2010 to include cases diagnosed and treated in 12 participating hematologic units of the Lazio region in Italy. Three-hundred-thirty-eight PMF patients diagnosed between 1981 and 2010, and evaluable for LT, defined as the occurrence of ≥20% blast cells during follow-up, entered this study. Patients with a PMF following a diagnosis of polycythemia vera (PV) or essential thrombocythemia (ET) were excluded. Four patients with diagnostic Hb levels suggesting a diagnosis of PV were also not included.

Due to the long period of the study, diagnosis of PMF was made according to the criteria accepted at the time the patients were diagnosed.

2.2. Treatment

Therapy was variable and reflected the disease individual characteristics and the therapeutic strategies adopted by single Institutions at the time of PMF diagnosis. They included a "wait and see" approach in asymptomatic patients, single-agent chemotherapy (mainly hydroxyurea, but also pipobroman and melphalan) and interferon-alpha. None of the patients underwent to an allogeneic hematopoietic stem cell transplantation.

2.3. Statistical analysis

The prognostic impact on the occurrence of LT was evaluated considering the following baseline variables: patient sex, age >65 years, presence of constitutional symptoms (weight loss >10% in the year before the diagnosis of PMF or unexplained fever or excessive night sweets persisting for more than one month), hemoglobin (Hb) <10 g/dL, leukocytosis >25 × 10^9/L, platelet (PLT) count less than 100 × 10^9/, presence of circulating blasts in peripheral blood (≥1%), presence of splenomegaly and hepatomegaly (any volume). These variables were present in 79% to 100% of cases. JAK2 mutational status was considered evaluable if assessed within one year from diagnosis and was available in 111 patients (31.5%). Prior treatment with chemotherapy was also considered.

We compared patient groups by the *t*-student's test, Mann–Whitney *U*-test or χ^2 test, when appropriate. Actuarial overall survival (OS) and leukemia-free survival (LFS) curves were calculated by the method of Kaplan and Meir. For the calculation of OS curves patients were censored if they were alive at date of the last follow-up, whereas for the probability of LFS patients were censored if, at date of the last follow-up, they were alive or dead without developing a LT. We used the Cox model to evaluate relationship between variables. Variables with 2-tailed *P*-value <.05 entered into the multivariate analysis. Those factors showing to retain an independent prognostic value were used to construct a simply model to predict LT. Statistical analyses and graphs were generated using SPSS-10 software.

3. Results

The main diagnostic clinic-biological features of the 338 PMF patients are listed in Table 1. The median age of the patients was 66.8 years. Two hundred and thirty-two patients (68.6%) were older than 65 years, whereas 31 patients (9.1%) were younger than 50 years. Of the 111 patients with evaluable JAK2 mutational status, 72 cases (64.7%) presented a JAK2V617F mutation. A karyotype analysis was available in only 159 cases (47.0%). Twelve of these latter patients (3.4%) presented an altered karyotype. At the time of the analysis 142 (42.0%) patients were died. With a median survival time of 89 months, the resulting actuarial OS at 5, 10 and 20 years was 65%, 30% and 22%, respectively.

Among the 338 PMF patients evaluable for the occurrence of LT, 40 patients (11.8%) developed an overt leukemia, resulting in an overall probability of LFS at 5, 10 and 20 years of 86.1%, 72.4% and 66.8%, respectively. The actuarial survival probability of the 40 patients undergoing LT was very dismal, falling to 0 at 48 months, with a median survival of only 2 months.

3.1. Prognosis factors

Table 2 reports the main diagnostic features and the treatment modalities of PMF patients grouped according to the occurrence or not of LT. Compared to patients who did not develop LT, those who progressed to overt leukemia presented at diagnosis a significantly lower Hb level (*P* = .0001) and higher WBC (*P* = .020). In addition, a greater proportion of them had systemic symptoms (*P* = .003), hepatomegaly (*P* = .005), blasts in the peripheral blood (*P* = .005), and had received a chemotherapy-based treatment for their PMF disease (*P* = .006). Hb <10 g/dL (*P* = .0001), presence of circulating blasts (*P* = .0002), systemic symptoms (*P* = .0001), hepatomegaly (*P* = .028) and previous chemotherapy (*P* = .010) were significantly associated with the LFS probability. The cox method indicated that Hb <10 g/dL (*P* = .006) and circulating blasts (*P* = .004) were the only clinical features retaining a significant and independent prognostic value in multivariate analysis.

Based on the Cox model results we used Hb value (<10 g/dL) and presence of circulating blasts (≥1%) as prognostic indicators to design a model predictor of LT. Among the entire series of 338 PMF patients, 250 patients with both the two parameters available could be stratified as follows: 219 cases (87.6%) were scored at low risk (none or one of the two factors), and 31 patients (12.4%) at high risk (both parameters). Among these 250 patients, we observed 30 cases of LT. Twenty-two (10.04%) of these LT occurred among the 219 low risk patients and 8 (25.80%) in the group of the 31 high-risk patients. Fig. 1A illustrates the statistically significant different LFS estimates of the two risk groups. As shown, the median LFS times were 269 and 45 months for the low and high risk groups,

Table 1
The main clinico-biologic features of the 338 PMF patients entered this study and the number of patients evaluable for those parameters.

Features	Evaluable Pts. (%)	Value
Median Age (years) (range)	338 (100.0)	66.8 (30–91)
Gender M/F (%)	338 (100.0)	205/133 (60.6/39.4)
Mean Hb g/dL (range)	329 (97.3)	11.6 (3.5–17)
WBC count 1 × 10^9/L (range)	327 (96.7)	13.1 (1.3–134.0)
PTLs count 1 × 10^9/L (range)	332 (98.2)	424.2 (10.0–2.000)
Symptoms yes/no (%)	292 (86.4)	67/225 (23.1/76.9)
Splenomegaly yes/no (%)	327 (96.7)	276/51 (84.4/15.6)
Hepatomegaly yes/no (%)	330 (97.6)	177/153 (53.7/46.3)
Circulating Blasts ≥1% yes/no (%)	269 (79.6)	71/198 (26.4/73.6)
JAK2V617F[a]	111 (32.8)	72/39 (64.7/35.3)

[a] Tested within one year from diagnosis.