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Myelofibrotic transformation is a well-recognized complication of essential thrombocythemia (ET) and polycythemia vera (PV)(1, 2). However, there is scarce information on life expectancy and prognostic factors of patients developing this complication (1, 3-5). Prognostic models devised for primary myelofibrosis (PMF) are used to drive treatment decisions in patients with post-ET/PV MF, despite the lack of studies validating the prediction accuracy of such stratification models in this setting. Our aim was to evaluate the performance of the most widely used prognostic model in PMF, i.e. the International Prognostic Scoring System (IPSS)(6), in a nationwide series of patients with post-ET/PV MF.

Data from 176 patients diagnosed with post-ET (n=115) or post-PV (n=61) MF in 39 Spanish institutions during January/2000-May/2013 were retrospectively analyzed. Diagnosis was made according to the criteria in use at the time of first observation. Treatment for MF included hydroxycarbamide (n=100) or other cytoreductive therapy (n=25), erythropoiesis-stimulating agents (n=45), JAK inhibitors (n=45), danazol (n=12), immunomodulators (n=12), splenectomy (n=3), splenic irradiation (n=7), and allogeneic transplantation (n=11). Variables taken at MF diagnosis and analyzed for their predictive value on outcomes were sex, previous myeloproliferative neoplasm, splenomegaly, IPSS risk category, each individual factor of the IPSS, thrombocytopenia, *JAK2* status, cytogenetics (7), and whether or not the patient was on cytoreductive therapy at MF diagnosis. Multivariate analysis of factors predicting survival was performed by the Cox regression method. Cumulative incidence of acute myeloid leukemia (AML) or AML-unrelated death was analyzed in the framework of competing risks. Multivariate analyses of factors predicting each of the above competing outcomes were performed by the Fine and Gray method (8). Log-rank

test was used to compare Kaplan-Meier curves. *P*<0.05 was considered statistically significant.

Table 1 shows the patients' characteristics at MF presentation. Median time from original diagnosis to myelofibrosis was 8.6 years for post-ET MF and 9.8 years for post-PV MF. With a median follow-up from post-ET/PV MF diagnosis of 1.8 years, 50 (29%) patients had died, 5 (3%) were lost to follow-up and the remaining were censored alive. Median survival was 8.6 years. Causes of death included progression of MF without AML (n=18), AML (n=11), cardiovascular complications (n=7), transplant-related complications (n=4), infection (n=3), bleeding (n=2), a second malignancy (n=1), or were unknown (n=4).

According to the IPSS, 13% patients were in the low-risk group; 29% in the intermediate-1; 31% in the intermediate-2; and 27% in the high-risk category, and their median survivals were, respectively, not yet reached, 10, 8.5, and 3.1 years. There was no statistically significant difference in survival between the low-risk and the intermediate-1 categories, and between the latter and the intermediate-2, whereas the high-risk group had a significant poorer survival than the intermediate-2 (P=0.008)(Figure 1).

Among factors included in the IPSS, older age, anemia, and circulating blasts retained a univariate association with shorter survival, whereas constitutional symptoms and leukocytosis lacked prognostic value. There was no significant difference in survival between patients with a prior diagnosis of PV or ET. The best predictive model for shorter survival included the following independent variables: age >65 years (Hazard ratio [HR]=3.6; 95% Confidence Interval [CI]:1.8-7.3; P<0.001); Hb <10 g/dL (HR=2.6; 95%CI:1.4-4.6; P=0.002); platelets <100 x 10^9/L (HR=3.5; 95%CI:1.7-7.3;

P=0.001); and being on hydroxycarbamide at MF diagnosis (HR=2.7; 95%CI:1.5-5.9; P=0.002).

Progression to AML occurred in 12 (6.8%) patients over an observation period of 509 patient-years, what accounts for an incidence rate of 2.3 cases per 100 patient-years. Thrombocytopenia <100 x 10^9/L was the only predictor for progression to AML (HR=5.45; 95%CI:1.51-19.6; P=0.01), whereas age >65 years (HR=2.58; 95%CI:1.20-5.55; P=0.01), anemia (HR=2.45; 95%CI:1.22-4.92; P=0.01), and being on hydroxycarbamide at myelofibrotic transformation (HR=1.96; 95%CI:0.98-3.90; P=0.05), were associated with AML-unrelated death.

We presume that the lack of prognostic significance of some variables of the IPSS may be due to the effect of the cytoreductive treatment that many patients were receiving at the time of myelofibrotic transformation for the management of ET or PV. This situation differs from that of PMF patients, in whom the risk factors at disease diagnosis are usually computed without any myelosuppressive treatment. Other factors could have also influenced on our findings. Thus, 39% of patients with constitutional symptoms received JAK inhibitors, whereas this treatment was used in only 19% of those without such symptoms at MF diagnosis. Ruxolitinib has been associated with a reduction in the risk of death compared to conventional therapy (9), which could presumably have blunted the poor prognosis associated with this feature.

In line with our results, in an Italian series (4) of 68 patients with post-PV MF, anemia was the only predictor for survival at disease presentation, whereas age and leukocyte count lacked prognostic significance. In 66 young patients with post-ET/PV MF from the Mayo Clinic (3), anemia was again an independent risk factor for shortened survival, although the strongest adverse factor was the unfavorable

cytogenetics. Neither constitutional symptoms nor the leukocyte count predicted for survival.

By multivariate analysis, two variables not included in the IPSS, namely thrombocytopenia and hydroxycarbamide treatment at myelofibrotic transformation, were shown to correlate with survival. The former has been identified as a poor prognostic factor in PMF (10, 11) and post-PV MF (4). Low platelets are often associated with anemia, making it difficult to qualify thrombocytopenia as an independent prognostic factor, which was the reason why this variable was excluded from the IPSS (6). In our study, thrombocytopenia was an independent predictor for shorter survival probably because it was associated with a higher risk of AML. Such an association has also been reported in PMF (10-13). With regard to the poor prognostic significance of being on hydroxycarbamide at MF diagnosis, we think that some kind of selection bias may be operating here. Indeed, hydroxycarbamide is usually indicated in older patients and in those with more marked myeloproliferative features, what may have contributed to blur the prognostic significance of such features.

In conclusion, the results from the present study indicate that the IPSS fails to accurately discriminate different prognostic groups in post-ET/PV MF. An alternative tool is therefore required for patients' risk stratification to help physicians on therapeutic decision-making.

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Table 1. Demographic and baseline clinical characteristics of patients at diagnosis of post-ET and post-PV MF

Characteristic	All patients (n = 176)	Post-ET MF (n = 115)	Post-PV MF (n= 61)
Age, years*	65 (23 - 88)	64 (23 - 88)	68 (39 - 84)
>65	95 (54%)	55 (48%)	40 (66%)
Sex, male/female	83 / 93	50 / 65	33 / 28
Constitutional symptoms	54 (31%)	33 (29%)	21 (34%)
Palpable splenomegaly	129 (73%)	75 (65%)	54 (86%)
Hb, g/dL*	10.7 (4.5 - 17.7)	10.5 (4.5 - 15.4)	11.1 (7.3 - 17.7)
<10	57 (33%)	42 (37%)	15 (25%)
WBC, x10^9/L*	9.9 (0.3 - 77)	8.7 (0.3 - 77)	10.9 (2.4 - 60)
≥25	23 (14%)	15 (14%)	8 (14%)
Platelets, x10^9/L*	364 (5 - 1564)	427 (5 - 1564)	289 (35 - 1368)
<50	8 (5%)	7 (6%)	1 (2%)
<100	18 (11%)	11 (10%)	7 (12%)
Blood blasts ≥1%	80 (48%)	55 (51%)	25 (42%)
Abnormal karyotype	24/94 (26%)	16/66 (24%)	8/28 (29%)
Unfavorable abnormalities[†]	8%	6%	11%
JAK2 mutation[‡]	80/124 (64%)	37/77 (48%)	43/47 (91%)
IPSS risk group[§]			
Low	22 (13%)	16 (15%)	6 (10%)
Intermediate-1	48 (29%)	28 (26%)	20 (35%)
Intermediate-2	51 (31%)	36 (33%)	15 (26%)
High	45 (27%)	28 (26%)	17 (29%)

Abbreviations: ET, essential thrombocythemia; PV, polycythemia vera; MF, myelofibrosis; IPSS, International Prognostic Scoring System
* Median (range)
[†] +8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3), 11q23 rearrangement or complex karyotype
[‡] These figures represent the *JAK2* V617F mutated cases, since the exon 12 mutations were not studied in most institutions
[§] In 166 evaluable patients

LEGEND FOR THE FIGURE

Fig 1. Survival after diagnosis of post-ET/PV myelofibrosis according to the IPSS risk

category.