Red blood cell transfusion-dependency implies a poor survival in primary myelofibrosis irrespective of IPSS and DIPSS

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ABSTRACT

Risk stratification in primary myelofibrosis is currently based on two international prognostic scoring systems, neither of which takes into consideration red blood cell transfusion-dependency. In 288 consecutive patients with primary myelofibrosis, red blood cell transfusion-dependency at diagnosis affects survival independently of the International Prognostic Scoring System (P<0.001). To evaluate the dynamic impact on survival of red blood cell transfusion-dependency, we performed a Cox's regression analysis with transfusion status as time-dependent covariate in 220 regularly followed patients with primary myelofibrosis. Patients who begin red blood cell transfusions anytime (n=80, 36%) have a significantly worse survival compared to those who continue follow up without transfusions (HR: 7.8, 95%CI: 5.1-11.9; P<0.001). Adjusting for Dynamic International Prognostic Scoring System in a multivariate analysis, red blood cell transfusion-dependency retained an independent prognostic impact on survival. This study suggests that red blood cell transfusion-dependency should be considered to improve risk stratification of primary myelofibrosis during follow up.

Key words: myelofibrosis, leukemia, prognosis, transfusion, *JAK2*, *MPL*.

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Introduction

Primary myelofibrosis (PMF) is a Philadelphia-negative myeloproliferative neoplasm with a heterogeneous clinical presentation including anemia, leukocytosis or leukopenia, thrombocytosis or thrombocytopenia, splenomegaly and constitutional symptoms. At diagnosis, genomic abnormalities include *JAK2* (V617F) mutation in roughly 50-60% of patients[1] and MPL mutations in 5-9%,[2-4] while in blast phase (BP) additional mutations may occur.[5] Survival ranges from four to seven years resulting significantly shortened when compared to that of a healthy population.[6] This reflects the mostly palliative effect of most available treatments. New compounds, called JAK2-inhibitors, are now under investigation with preliminary data showing efficacy in terms of spleen size reduction and relief of constitutional symptoms.[7] Allogeneic hematopoietic stem cell transplantation is the only curative option in PMF patients despite the well known risk of transplant-related mortality.[8]

To support clinical decision making, an international effort led to the formulation of the International Prognostic Scoring System (IPSS) to predict survival at diagnosis.[9] This model, which considers five different parameters (age over 65 years, hemoglobin level lower than 10 g/dL, white blood cell count higher than 25×10^9/L, peripheral blasts equal to or higher than 1% and presence of constitutional symptoms), stratifies patients into four distinct risk categories. IPSS risk factors were later included in a time-dependent model which generated a new prognostic score, the Dynamic International Prognostic Scoring System (DIPSS), which is able to predict survival anytime during follow up.[10]

Almost all scoring systems recognize anemia as a risk factor.[9,11] The DIPSS even showed its enhanced prognostic power when anemia is acquired during follow up. When anemia occurs, PMF patients are mainly treated with prednisone, androgenic steroids and/or erythropoietin, which are ineffective for the majority of patients.[12] Pomalidomide, a second generation IMiD, gave interesting results in terms of improving anemia,[13] which seem to be better than those obtained with thalidomide[14] or lenalidomide.[15]

Investigators from the Mayo Clinic have recently reported that red blood cell (RBC) transfusion-dependency at or within one year of diagnosis may predict shortened survival independently of IPSS category,[16,17] highlighting the impact of severe anemia on survival. Until now, the prognostic role of acquiring RBC transfusion-dependency during follow up has not been clarified.

In this study, we investigated the prognostic impact on sur-

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vival of RBC transfusion-dependency, either present at diagnosis or acquired during follow up, in a cohort of 288 consecutive patients with PMF.

Design and Methods

Study design

The objective of this study was to define whether RBC transfusion-dependency, either present at diagnosis or dynamically acquired during follow up, affects survival of PMF patients. An expert panel consensus conference has recently defined transfusion-dependency as an average transfusion volume of two units of RBC/month.[18] The retrospective design of our study didn't allow the exact number of RBC transfusion per month to be assessed. In general, we considered RBC transfusion-dependency as the onset of regular transfusion requirement to correct anemia (at least one unit per month). This study was approved by the Institutional Ethics Committee of Pavia (Comitato di Bioetica, Fondazione Policlinico San Matteo, Pavia) and the procedures followed were in accordance with the 1975 Declaration of Helsinki, as revised in 2000.

This study was conducted on 288 consecutive patients with PMF diagnosed between 1975 and 2009 at the Department of Hematology Oncology, Fondazione IRCCS Policlinico San Matteo and University of Pavia, Italy. Time-dependent statistical analysis was carried out on 220 patients regularly followed for the whole course of the disease (at least three visits a year). Diagnosis of PMF required the presence of megakaryocyte proliferation and atypia accompanied by increased reticulin and/or collagen in bone marrow, as well as of *JAK2* (V617F) or *MPL* mutations if available and at least two of the following criteria: anemia, splenomegaly, increased lactate dehydrogenase level and leukoerythroblastosis. Diagnosis of BP of PMF was made according to the WHO classification.[19] Patients with post-polycythemia vera and post-essential thrombocythemia myelofibrosis[20] and those with diagnosis of "pre-fibrotic" myelofibrosis[21] were excluded, as well as patients who received erythropoiesis-stimulating agents, thalidomide or any investigative drug to correct anemia. Prognostic stratification for survival was performed at diagnosis by the IPSS[9] and during follow up by the DIPSS.[10] Although these two scores are different, both take into account the following parameters: age over 65 years, hemoglobin level lower than 10 g/dL, white blood cell count greater than 25×10^9/L, peripheral blood blasts equal to or greater than 1%, presence of constitutional symptoms (greater than 10% weight loss in six months, night sweats, unexplained fever over 37.5°C).

Molecular analysis

Of 220 patients with a regular follow up, 112 were assessed for *JAK2* molecular status and 90 for the presence of *MPL* mutations. A quantitative real time polymerase chain reaction based allelic discrimination assay was used to detect the V617F mutation of the *JAK2* gene.[22] High-resolution melting-curve assay and sequencing analyses on circulating granulocytes were performed to assess *MPL* mutational status.[23]

Statistics

Continuous variables are summarized as median and range. Categorical variables are described by count and relative frequency (%) of each category. In the cohort evaluated at diagnosis (n=288), univariate survival analysis was performed with the Kaplan-Meier method and multivariate analysis was carried out by Cox's proportional hazard regression. The acquisition of RBC transfusion-dependency anytime was analyzed as a time-dependent covariate in order to assess its impact on survival in 220 regularly followed patients. Statistical analyses were performed using Microsoft Excel 2000, Statistica 8 (Stat-Soft Inc), Stata SE 11 (StataCorp).

Results and Discussion

This study includes 288 consecutive patients with PMF with a total follow up of 1,347 person-years. Demographic and hematologic characteristics at diagnosis are reported in Table 1, considering patients as a whole and grouped according to transfusion status.

RBC transfusion-dependency was present at diagnosis in 41 (14%) out of 288 patients. When comparing patients receiving RBC transfusions with those who did not, Mann-Whitney U test revealed that the former were older and had an essentially myelodepletive phenotype with lower leukocyte and platelet counts, in keeping with previous data.[17]

During follow up, patients may require RBC transfusions. Within the cohort of 220 regularly followed patients (median follow up 3.1 years, range 0-17.9), RBC transfusion-dependency occurred in 39 (18%). Median time to RBC transfusion-dependency was 2.6 years (range 0.2-17.9).

JAK2 and *MPL* mutational status was available in 112 and in 90 patients, respectively. Within these patients, 68 (61%) of 112 were *JAK2* (V617F)-positive and 5 of 90 (5%) carried *MPL* mutations (all W515L-positive). Fisher's exact test demonstrated that the transfusion status was not associated with the presence of the *JAK2* (V617F) or *MPL* mutations. Concerning *JAK2* (V617F), our results are in keeping with a study focused on RBC transfusion-dependency at diagnosis[17] while they differ from another study reporting that V617F-positive patients were significantly less likely to require RBC transfusions than V617F-nega-

Table 1. Demographic and hematologic characteristics at diagnosis of 288 patients with primary myelofibrosis.

Variables	All patients	Patients transfusion-dependent at diagnosis	Patients non-transfusion dependent at diagnosis	*P* value
N. of patients (%)	288	41 (14%)	247 (86%)	
Median follow up, y (range)	3.2 (0.1-17.9)	1.7 (0.1-7.9)	3.6 (0.1-17.9)	<0.01
Median age, y (range)	61 (24-86)	66 (48-84)	60 (24-86)	<0.01
Age older than 65 (%)	105 (36%)	22 (54%)	83 (34%)	0.01
Male/female ratio	187/101	31/10	156/91	0.08
Median hemoglobin, g/dL (range)	11.0 (3.9-13.5)	7.1 (3.9-9.6)	11.4 (5.5-13.5)	<0.01
Median white blood cell count, $\times10^9$/L (range)	8.8 (1.0-70.6)	3.9 (1.0-29)	9.7 (1.5-70.6)	<0.01
Median platelet count, $\times10^9$/L (range)	255 (15-3279)	152 (15-1000)	300 (20-3279)	<0.01
IPSS*, n (%) (n.evaluated=260)				
Low	77 (30%)	0 (0%)	77 (34%)	
Intermediate-1	68 (26%)	2 (6%)	66 (29%)	<0.01
Intermediate-2	73 (28%)	18 (50%)	55 (25%)	
High	42 (16%)	16 (44%)	26 (12%)	

**IPSS indicates International Prognostic Scoring System.*

tive.[24] This discrepancy could be explained by the design of the studies, patient accrual, time of follow up and weight of the length bias. Regarding *MPL*, a study of 18 *MPL*-positive patients showed that *MPL*-mutant phenotype is associated with a regular RBC transfusion support.[4] It is interesting to note that the proportion of patients RBC transfusion-dependent was 40% (2 of 5) among the MPL-positive group and 15% (13 of 85) among the MPL-negative group. This result, although not achieving statistical significance, favors a higher risk of transfusion need in *MPL*-positive patients.

At the time of the analysis, 141 (49%) of 288 patients had died and the median survival of the whole cohort was 7.1 years (95% CI: 5.3-8.0). Risk assessment in primary myelofibrosis at diagnosis is currently based on IPSS evaluation[9] and we confirmed that IPSS predicts survival (P<0.0001). In addition, we found that RBC transfusion-dependency at diagnosis significantly affects survival (P<0.001), with a median survival of 2.6 years (95% CI: 1.6-4.6) in patients who received RBC transfusions at diagnosis and eight years (95% CI: 6.7-9.6) in those who did not (HR 3.9, 95%CI: 2.5-6.1; P<0.001) (Figure 1). After adjusting for IPSS categories in multivariate Cox's proportional hazard regression, transfusion-dependency retained an independent impact on survival (HR 2.4, 95%CI: 1.5-4.0; P=0.001). These results are in keeping with previous studies[16,17] (*Online Supplementary Table S1*)

In order to assess the dynamic prognostic value of RBC transfusion-dependency on survival, we performed a Cox's regression survival analysis using this parameter as a time-dependent covariate in 220 regularly followed patients. We found that RBC transfusion-dependent patients (n=80) had a significantly worse survival compared to patients who remained transfusion-independent for the whole follow up, with a Hazard Ratio of 7.8 (95%CI: 5.1-11.9; P<0.001). In this dynamic model, patients are followed from diagnosis and contribute to the estimate of survival in the non-transfused category only as long as they remain transfusion-independent. When they eventually develop RBC transfusion need, they shift to the other category. As a consequence, the Kaplan-Meier curves obtained (Figure 2) are both estimated since the time of diagnosis, but each patient contributes to the survival estimates in the transfused group only from the onset of RBC transfusion-dependency. In multivariable analysis with DIPSS categories and transfusion status as time-dependent covariates, RBC transfusion-dependency retained its prognostic impact on survival (HR 3.7; 95%CI: 2.4-5.9; P<0.001).

Taken together, these results underline the fact that RBC transfusion requirement, either present at diagnosis or acquired during follow up, is an essential and independent risk factor for survival in patients with PMF. The critical effect on survival of RBC transfusion-dependency may be explained by a much more aggressive disease with a deeper erythropoietic defect when anemia occurs and, in the mean time, by the worsening of comorbidities due to the anemic state. Causes of death in our cohort were reported in 73 (52%) out of 141 patients and included 24 (33%) blast phase of PMF, 13 (18%) hemorrhagic events, 8 (11%) disease progression, 8 (11%) infections, 6 (8%) cardiac failures, 6 (8%) renal or hepatic failures, 5 (7%) secondary cancers and 3 (4%) thrombotic events. We did not find any significant differences in terms of causes of death according to RBC transfusion status. In this study, we can not draw any conclusion on iron overload in PMF, but it does not seem to affect survival in a series of 185 PMF patients from the Mayo Clinic.[16]

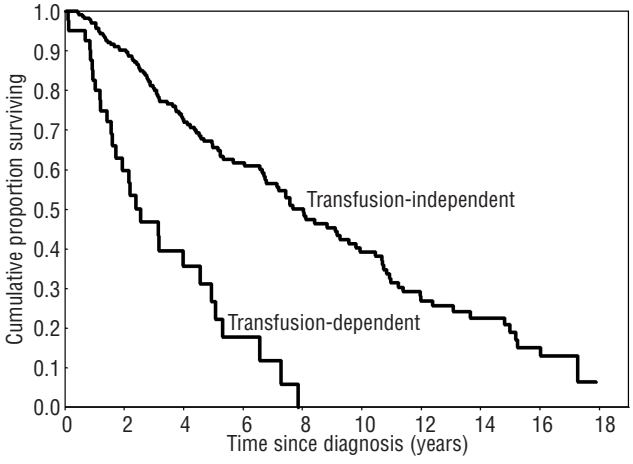

Figure 1. Overall survival according to RBC transfusion-dependency at the time of diagnosis in 288 patients with PMF.

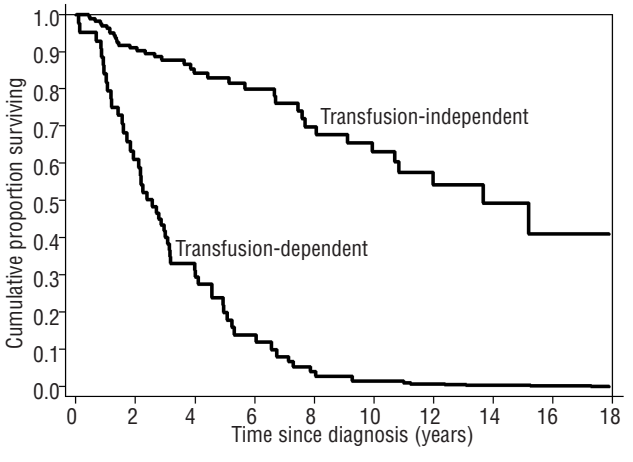

Figure 2. Overall survival according to RBC transfusion-dependency assessed as a time-dependent variable in 220 regularly followed patients with PMF. Observation started from diagnosis of PMF.

This dynamic assessment of the prognostic value of RBC transfusion-dependency on survival could be a useful tool for clinical decision making. New drugs potentially able to correct anemia and affect transfusion-dependency need to be carefully evaluated in order to assess whether they may also improve survival in PMF patients.

Authorship and Disclosures

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