Increased incidence of infection in patients with myelofibrosis and transfusion-associated iron overload in the clinical setting

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Abstract

Transfusion-associated iron overload may lead to increased risk of infection, but its role in myelofibrosis (MF) has been scarcely explored. We evaluated 106 consecutive patients with primary or secondary MF. Up to 38% of patients were transfusion-dependent (TD) with a median of 14 RBC units received. Median observation time was 36 months (range 3–203). Forty-five percent of patients experienced one or more infectious episodes for a total of 69 infectious events, 13 (19%) of which were severe. The 60-month cumulative incidence of infection was $64.1 \pm 6.5\%$. TD patients showed a higher incidence of infection (HR $= 2.13$, $p = 0.019$). Transfusion burden was markedly greater in TD patients with infectious complication (median 24 RBC units vs 15 RBC units; $p = 0.012$). The 60-month overall survival was $40 \pm 5.9\%$. Lower International Prognostic Scoring System (IPSS) risk ($p < 0.0001$) and ruxolitinib ($p = 0.027$) were significantly correlated with higher survival. This real-world study showed increased infections in patients with higher transfusion burden. It may therefore be interesting to further investigate the role of iron chelation in improving infection-free survival in MF patients.

Introduction

Myelofibrosis (MF) is a clonal chronic myeloproliferative neoplasm (MPN) characterized by bone marrow fibrosis, extramedullary hematopoiesis, and progressive cytopenia. Nearly 40% of MF patients show anemia at diagnosis and a further 20% develop it during the course of disease [1]. According to the International Prognostic Scoring System (IPSS), anemia represents an adverse variable [2]. Moreover, 25% of MF transfusion-dependent (TD) patients at time of diagnosis develop transfusion-related iron overload [3]. Excess iron may increase the risk of infection [4]. Some pathogens have the ability to acquire iron, which is essential for their metabolism and growth, from their host. In addition, iron overload induces the production of free iron and oxygen-free radicals or reactive oxygen species (ROS), which impairs immune system response and the natural resistance to infections [4]. Infections are one of the main causes of morbidity and mortality in MF, representing the cause of death in around 10% of cases [5]. The increased risk of infections in MF is probably related to impairment of immune system response, with increased secretion of inflammatory cytokines, and reduced function of T-lymphocytes, monocytes, macrophages, and natural killer cells [6]. In most cases, infections in MF are caused by bacteria and occur in the respiratory and urogenital tract. Risk factors for infection in MF have emerged as high IPSS category risk and splenomegaly [5] and treatment with ruxolitinib, a JAK1/2 inhibitor, is available in MF [7].

Compared to myelodysplastic syndrome (MDS), the impact of hemosiderosis on infection in MF has been scarcely explored [4, 8]. With this aim, we evaluated the role of iron overload and transfusion dependency on the incidence of infections in a single-center cohort of patients with MF.

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Methods

We identified consecutive adult patients diagnosed at our center with primary or secondary MF (post-essential thrombocythemia or polycythemia vera—PET/PPV-MF), between 1998 and 2018. Diagnosis of MF was based on the WHO 2018 classification [9]. Available data concerning demographic, clinical, histological and hematologic information were collected from medical charts. Each patient's IPSS score was also reported. When available, molecular and cytogenetic analyses were reported, in particular regarding JAK2V617F, CALR and MPL mutational profile.

Patients were stratified into two groups: (1) TD patients at the time of the diagnosis or later; (2) non-transfusion-dependent patients. According to the International Working Group-Myelofibrosis Research and Therapy (IWG-MRT) criteria [10], TD is defined as having received ≥ 2 unit of red blood cells (RBC) in the preceding month for an Hb < 8.5 gr/dL that was not associated with clinical bleeding, The total number of RBC units infused was also collected. All infections were recorded and graded according to Common Terminology Criteria for Adverse Events (NCI-CTCAE). Infections with CTCAE grade ≥ 2 were considered severe. The study was conducted in accordance with the Declaration of Helsinki. Categorical variables were compared using the Chi square or Fisher's exact test. Continuous variables were compared using Wilcoxon's rank sum test. The probability of cumulative incidence of infection was estimated after diagnosis. The log-rank test was used to compare two or more groups of stratified patients. Multivariate analysis was performed using the Cox proportional hazards regression model. We evaluated the impact of the following variables on the incidence of infections: primary versus secondary MF, splenomegaly, age > 65 years, ruxolitinib treatment and TD. $P < 0.05$ was considered statistically significant. Data analysis was performed using a standard statistical package (SPSS for Macintosh, Version 21, Chicago, IL).

Results and discussion

A total of 106 MF patients with a median age of 72 years (range 44–89) were retrospectively evaluated. A diagnosis of primary MF was performed in 75 cases (71%), PET-MF in 27 (25%) and PPV-MF in four (4%). Splenomegaly was present in 83 patients (78%) and 30 (28%) reported constitutional symptoms. According to the IPSS, 43 patients (40%) were classified as low or intermediate-1 risk and 63 (60%) as intermediate-2 or high risk. Molecular analysis was performed in 76 patients (72%). Fifty-four of 76 patients (71%) were positive for the JAK2V617F mutation; 10 (13%) for CALR mutation; 4 (5%) for MPL; and 8 (11%) were negative for all tested mutations. Over time, 70 patients (66%) received hydroxyurea, and 23 (22%) ruxolitinib. Overall, 40 patients (38%) were TD with a median of 14 RBC units received during follow-up (range 4–199). The median serum ferritin level in patients with infections was higher in comparison with others (940 vs 772 ng/mL). Three patients treated with ruxolitinib were positive for occult hepatitis B infection; 2 patients underwent prophylaxis with lamivudine and 1 with entecavir.

Median follow-up time was 36 months (range 3–203). At last follow-up, 48 patients (45%) presented one or more infectious episodes. Total infectious events were 69 and 13 of them (19%) were defined as severe (grade 3–4 CTCAE). Anatomical site of the infection was the respiratory tract in 28 cases (41%), gastro-intestinal in 22 (32%),
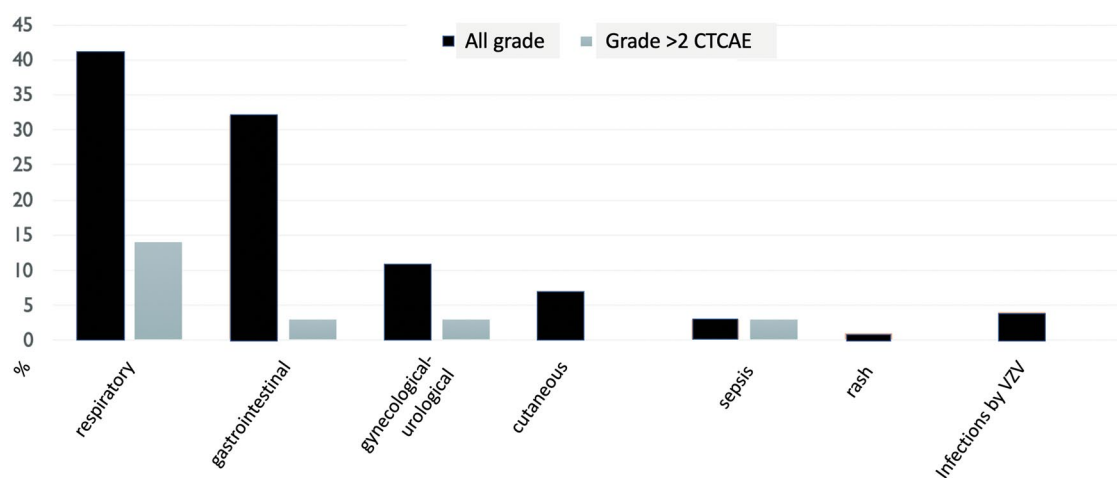

Fig. 1 Incidence on infections according to anatomical site

gynecological–urological in 8 (11%), sepsis in 2 (3%), and unspecified in the remaining cases (Fig. 1). When detected, the etiological agents were bacterial in eight (12%), viral in five (7%) and fungal in four (6%).

The 60-month cumulative incidence of infection from diagnosis of MF was $64.1 \pm 6.5\%$. TD patients showed a higher incidence of infection ($99 \pm 8.8\%$ vs $53.3 \pm 8\%$, $p = 0.007$) (Fig. 2). In multivariate analysis, no association was found between infection incidence and primary vs. secondary MF, splenomegaly, age > 65 years or ruxolitinib treatment; conversely TD patients reported a significant association with infection occurrence ($p = 0.019$; HR = 2.13; 95% C.I. = 1.13–4.01). Among the 40 TD patients, the transfusion burden was significantly higher in those with infectious complication (median 24 RBC units vs. 15 RBC units; $p = 0.012$). The 60-month overall survival was $40 \pm 5.9\%$. Lower IPSS risk ($p < 0.0001$) and ruxolitinib treatment ($p = 0.027$) were significantly associated with higher survival.

In the present real-world study, the incidence of infection in patients with MF and transfusion-associated iron overload was increased. A prophylactic use of anti-fungal or anti-bacteria agent in TD high-risk MF patients could be suggested.

The presence of comorbidities, which may have contributed to infections, was similar both in TD and transfusion-free group.

Transfusion-associated hemosiderosis has an unclear biological and clinical effect in MF and the contribution of iron overload to prognosis is not well known. Clinical outcome and incidence of infections has not yet clearly

Fig. 2 Infection cumulative incidence according to transfusion dependence in 106 patients with myelofibrosis

studied [3]. Increased iron following frequent RBC transfusions and ferritin levels > 1000 ng/ml resulted in adverse prognosis and increased incidence of infections in MDS [11]. Patients with hereditary hemochromatosis and beta-thalassemia major developing iron overload are predisposed to bacterial, fungal, and viral infections, as organisms use iron for metabolism and cell division [12]. Moreover, ROS can affect immune system function, influencing neutrophil, T-cell and macrophage response to infections [4].

Ferritin levels > 500 ng/mL and transfusion dependence predicted inferior survival in patients with MF [13, 14]. In a multicentric study of MF patients, Polverelli et al. found no association between TD and infectious complications and reported that a 5-year cumulative incidence of severe infections mainly bacterial (20%), high/intermediate IPSS, massive splenomegaly and ruxolitinib treatment was associated with a higher cumulative incidence of infections before death [5]. A recent systematic review and meta-analysis suggested that the infection risk may be relevant and that a careful assessment of the risk of infection is necessary before starting ruxolitinib [15]. However, at present there is insufficient evidence to estimate the risk of infection in ruxolitinib-treated MF patients accurately. In our small cohort of 23 MF patients treated with ruxolitinib, we found a higher survival rate and a similar risk of infections compared with other available treatments (Table 1).

Iron chelation treatment has shown potential benefits in MDS [8]. Time to first infection was significantly longer in MDS patients receiving iron chelation therapy suggesting that this procedure may attenuate infection risk [8]. Little is known about the impact of iron chelation in MF. A retrospective analysis of 28 MF patients showed a hematological improvement in 23% of patients treated with deferasirox, with disappearance of transfusion requirement in four cases [16]. A small cohort of 10 TD patients treated with deferoxamine or deferasirox showed improved survival compared to 15 TD patients who did not undergo iron chelation therapy [17]. Notably, three death caused by sepsis were recorded among not-chelated TD patients [17]. In our cohort, only four patients were iron-chelated, one with deferoxamine and three with deferasirox.

This study has some limitations, as it was of a retrospective nature and some patients were enrolled before ruxolitinib became available. Nevertheless, it represents a real-life study of a homogenous and relatively wide single-center cohort of MF patients.

In conclusion, this retrospective single-center real-world study found an increased risk of infections in MF patients with higher transfusion burden. The role of iron chelation in improving infection-free survival in patients with MF and iron overload should be further investigated.
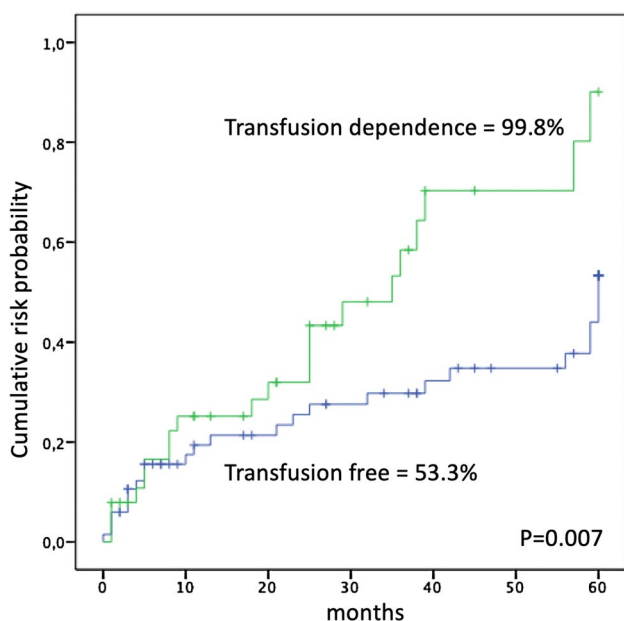
Table 1 Characteristics of 106 patients with myelofibrosis

	Pts with infection	Pts without infection	P
Patients (N, %)	46 (43%)	60 (57%)	
Male (N, %)	30 (65%)	41 (68%)	0.74
Female (N, %)	16 (35%)	19 (32%)	
Median age (years, range)	71 (45–90)	71 (44–88)	0.12
Median age at diagnosis (years, range)	67 (34–88)	66 (38–86)	0.15
Hb, g/dL (median, range)	10.7 (6.3–15.9)	10.5 (6.2–17.5)	0.68
WBC mm^3 (median, range)	9.945 (700–96.260)	9.370 (910–51.770)	0.87
PLT mm^3 (median, range)	315 (23–1.242)	348 (28–1.443)	0.36
B symptoms (N, %)	17 (37%)	13 (22%)	0.08
PMF (N, %)	37 (81%)	38 (64%)	0.11
MF post-ET (N, %)	7 (15%)	20 (33%)	0.06
MF post-PV (N, %)	2 (4%)	2 (3%)	0.78
Splenomegaly (N, %)	40 (87%)	43 (72%)	0.06
Splenomegaly ≥ 10 cm (N, %)	13 (28%)	13 (22%)	0.16
Splenomegaly < 10 cm (N, %)	27 (59%)	30 (50%)	0.37
IPSS int-2/high (N, %)	28 (61%)	35 (58%)	0.79
JAK2V617 + (N, %)	25 (54%)	29 (49%)	0.89
CALR + (N, %)	5 (11%)	5 (8%)	
MPL + (N, %)	2 (4%)	2 (3%)	
TRIPLE negative (N, %)	3 (7%)	5 (8%)	
Unknown (N, %)	11 (24%)	19 (32%)	
Poor risk karyotype (N, %)	3 (7%)	5 (8%)	0.72
Transfusion dependency (N, %)	22 (48%)	18 (30%)	0.01
Ruxolitinib treatment (N, %)	11 (24%)	12 (20%)	0.63
HU treatment (N, %)	28 (61%)	42 (70%)	0.32
Other treatment (N, %)	9 (20%)	8 (13%)	0.39
Iron chelation (N, %)	2 (4%)	2 (3%)	0.79
Ferritin, ng/mL (median, range)	940 (130–12129)	772 (14–3468)	0.08
Comorbidities < 2 (N, %)	41 (89%)	47 (78%)	0.14
Diabetes (N, %)	5 (11%)	8 (13%)	0.71
Autoimmunity (N, %)	4 (9%)	3 (5%)	0.45

PMF primary myelofibrosis, *ET* essential thrombocythemia, *PV* polycythemia vera, *IPSS* International Prognostic Scoring System, *HU* hydroxyurea

Compliance with ethical standards

Conflict of interest The other authors have no conflicts of interest to disclose.

Ethical approval Data on patients were retrospectively collected in accordance with the 1975 guidelines of the Declaration of Helsinki.

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