Myelofibrosis patients in Belgium: disease characteristics

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Objective: To date, only a small number of epidemiological studies on myelofibrosis have been performed. The current study aimed to characterize the myelofibrosis patient population in Belgium according to pre-defined disease parameters (diagnosis, risk categories, hemoglobin <10 g/dl, spleen size, constitutional symptoms, platelet count, myeloblast count), with a view to obtaining a deeper understanding of the proportion of patients that may benefit from the novel myelofibrosis therapeutic strategies.

Methods: A survey was used to collect data on prevalence and disease parameters on all myelofibrosis patients seen at each of 18 participating hematologic centers in 2011. Aggregated data from all centers were used for analysis. Analyses were descriptive and quantitative.

Results: A total of 250 patients with myelofibrosis were captured; of these, 136 (54%) were male and 153 (61%) were over 65 years old. One hundred sixty-five (66%) of myelofibrosis patients had primary myelofibrosis and 85 (34%) had secondary myelofibrosis. One hundred ninety-three myelofibrosis patients (77%) had a palpable spleen. About a third of patients (34%) suffered from constitutional symptoms. Two hundred twenty-two (89%) myelofibrosis patients had platelet count $\geq 50\,000/\mu\text{l}$ and 201 (80%) had platelet count $\geq 100\,000/\mu\text{l}$. Of 250 patients, 85 (34%) had a myeloblast count $\geq 1\%$. Six (2%) patients had undergone a splenectomy. Thirteen (5.2%) patients had undergone radiotherapy for splenomegaly.

Conclusions: The results of this survey provide insight into the characteristics of the Belgian myelofibrosis population. They also suggest that a large proportion of these patients could stand to benefit from the therapies currently under development.

Keywords: Myelofibrosis, Prevalence, Characteristics, Management

Introduction

Primary myelofibrosis (MF), a rare type of myeloproliferative neoplasm (MPN), is a life-threatening hematologic malignancy.¹ The disease can be a primary disorder or secondary to pre-existing polycythemia vera

(PPV–MF) and post-essential thrombocythemia (PET–MF). The disease is characterized by fibrosis of the bone marrow, enlargement of the spleen, progressive cytopenia, leukoerythroblastosis, extramedullary hematopoiesis, constitutional symptoms and functional symptoms as fatigue and itching that can severely diminish the patient's quality of life.^{2,3} The median overall survival for MF patients is 4 to 6 years from time of diagnosis.^{4,5} The major causes of death include

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progressive bone marrow failure, infections and transformation to acute leukemia.⁶

Published data on the incidence and prevalence of MF in Europe are limited.^{5,7–10} Estimates of the annual incidence of MF in Europe range between 0.3 and 0.6 cases per 100 000 persons.^{5,7–9} MF is most commonly diagnosed in patients over the age of 50,^{7,9} and appears to be more frequent in men.^{5,7–9}

Well-established factors predictive of a poor prognosis of MF include age (>65 years), hemoglobin concentration (<10 g/dl), leucocyte count (>25 × 10⁹/l), circulating blasts (>1%) and the presence of one or more constitutional symptoms. Based on these factors, the international prognostic scoring system (IPSS) and the dynamic international prognostic scoring system (DIPSS) stratify MF patients into four groups: Low, Intermediate-1 (Int-1), Intermediate-2 (Int-2) and High risk.^{6,11} The risk scores are fundamental for risk-based management strategies in MF. The IPSS score is valid at diagnosis, while the DIPSS score can be used at any time during the disease.^{6,11} Subsequent to the above risk factors, the 'DIPSS plus' scoring system also takes into account erythrocyte transfusion dependence, thrombocytopenia (<100 × 10⁹/l) and unfavorable karyotype (including +8, -7/7q-, i(17q), inv(3), -5/5q-, 12p-, 11q23 rearrangements and complex karyotypes) as additional risk factors affecting survival.¹²

The only potentially curative approach in MF remains allogeneic hematopoietic stem cell transplantation (AH SCT). This approach tends to be limited to High- or Int-2-risk patients younger than 65 years of age due to a high incidence of morbidity and mortality associated with the procedure.^{13–16} Drug therapy in MF is adjusted to the predominant clinical symptom caused by anemia, splenomegaly (extramedullary hematopoiesis), or constitutional symptoms. Conventional drug therapy includes androgens, corticosteroids, erythropoiesis-stimulating agents (ESAs), danazol, thalidomide, lenalidomide and hydroxyurea.^{1,17,18} Although splenectomy can temporarily reduce spleen-related symptoms, the risks associated with surgery do not qualify it as a routine procedure.¹⁹ Splenic irradiation can be effective for palliating MF-associated splenomegaly, but the effects are transient. It can also increase morbidity and mortality of subsequent splenectomy.²⁰

The discovery and characterization of the JAK2 V617F mutation in 2005^{21–24} in a majority of MF patients deepened the understanding of the pathogenesis of the disease. Subsequent advances in the development of therapies targeting the major symptoms of the disease (splenomegaly, burden of constitutional symptoms)^{25–27} through inhibition of the JAK-STAT pathway offer new strategies in the management of MF patients.^{28–31}

A number of such therapies are now entering clinical phase development.^{25–27} Only one of these to date,

ruxolitinib (a JAK1-JAK2 inhibitor), has published data available on Phase III clinical testing.³² The clinical benefit of ruxolitinib versus placebo and best available therapy for MF was demonstrated in two prospective randomized Phase III clinical trials (COMFORT I&II).^{33,34} The US Food and Drug Administration and European Medicines Agency granted marketing approval for ruxolitinib for the treatment of patients with MF in 2011 and 2012, respectively.³⁴ The US Food and Drug Administration approved ruxolitinib for the treatment of intermediate and high risk MF while European Medicines Agency's approval is for treatment of disease-related splenomegaly or symptoms in adult patients with MF (irrespective of risk score).

The dose limiting toxicities of most JAK inhibitors tested so far include thrombocytopenia and anemia,³¹ potentially limiting the proportion of patients eligible for treatment. CYT387 (mometinib) could be an exception, with recent Phase I/II studies suggesting an improvement in anemia including weaning from transfusion-dependence.³⁶ This finding still needs to be confirmed in the ongoing phase III trial where patients are randomized to mometinib versus ruxolitinib treatment (NCT01969838). The current study was designed to characterize the MF patient population in Belgium according to a number of disease parameters (diagnosis, risk categories, spleen size, constitutional symptoms, platelet count, myeloblast count), in view to obtain a better understanding of the proportion of patients that may benefit from the therapies currently under development. This 'real life' study involved the majority of the hematological centers of Belgium and captured all patients visiting one of the centers during 2011.

Methods

Study design

A scientific survey was designed for investigators to collect data on Belgian MF patients. The scientific survey was developed in collaboration with and endorsed by the MPN subcommittee of the Belgian Hematological Society. Data were collected for MF patients who had visited one of 18 major hematology centers in Belgium at least once during 2011 (see supplementary methods (Supplementary Material) for complete list of collaborating centers).

Microsoft Excel worksheets containing questions on patient details and specific disease-related parameters (gender, age, cell counts, spleen size, and presence of constitutional symptoms) and open questions related to management of their disease were sent to each participating center between January and March 2012. A full list of the parameters/questions included is provided in supplementary methods (Supplementary Material).

Data were entered by the investigator directly into the Microsoft Excel worksheet. Patient data were based on medical records and were collected for the most recent visit at the center, whether this was at time of diagnosis or when already under treatment. For patients being treated with ruxolitinib, data were taken from the last visit prior to starting this treatment.

Anonymization and analysis of data

Once all requested information had been entered into the worksheet, pivot tables automatically consolidated the entered data per site, such that no individual patients could be identified beyond the site. Data were submitted for analysis in aggregated form only. Data from individual sites were then merged. Analyses were descriptive and quantitative. Data were analyzed according to disease sub-type (PMF, PPV-MF or PET-MF), IPSS and DIPSS risk categories and MF-specific characteristics (spleen size, the presence of constitutional symptoms, platelet count and myeloblast count). Both IPSS and DIPSS scoring systems assign points to five predictive risk factors: age (>65 years), hemoglobin concentration (<10 g/dl), leucocyte count ($>25 \times 10^9/l$), circulating blasts ($>1\%$) and the presence of one or more constitutional symptoms.^{6,11} Each risk factor counts for one point, except for anemia (hemoglobin concentration), for which DIPSS assigns two points. The sum of the points correlates with four risk groups: IPSS, Low (0 points), Int-1 (1 point), Int-2 (2 points) and High risk (>2 points); DIPSS, Low (0 points), Int-1 (1–2 points), Int-2 (3–4 points) and High risk (5–6 points).

Results

Demographic characteristics of patients

A total of 250 patients with MF were captured in this survey; of these, 136 (54%) were male and 153 (61%) were over 65 years old. One hundred sixty-five (66%) of MF patients had PMF and 85 (34%) had PET-MF (57 patients, 23%) or PPV-MF (28 patients, 11%).

The distribution of patients according to disease characteristics

The distribution of the number of patients (%) according to IPSS and DIPSS risk categories is shown in Table 1. Ninety per cent of patients were in the Int-1 to High risk categories for both the IPSS

and DIPSS. The IPSS showed a roughly equal distribution between Int-1 (30%), Int-2 (33%) and High risk (27%) categories for MF patients overall. For the DIPSS, about half of the patients (49%) fell into the Int-1 risk category while a considerably smaller proportion of patients (8%) were categorized as High risk; a similar proportion of patients to those in the IPSS were in the Int-2 risk category (34%). As expected, the proportion of patients in the Intermediate and High risk categories was higher for patients older than 65 years than in other patients.

The majority of MF patients (193/250; 77%) had a palpable spleen. In 81 patients (32%), spleen size was ≥ 10 cm below the costal margin. The proportion of patients with a palpable spleen tended to increase with the risk category (up to 82 and 95% in the High risk category for IPSS and DIPSS, respectively) (Fig. 1), as did the proportion of patients with a spleen size ≥ 5 cm (and ≥ 10 cm) (with the exception of Int-1 and Int-2 DIPSS categories, for which there was a similar spleen size distribution).

Most (222/250; 89%) MF patients had a platelet count $\geq 50\,000/\mu l$, 201 (90.5%) of whom had platelet count $\geq 100\,000/\mu l$. Similar proportions of patients with high platelet counts were observed when patients were grouped by age (≤ 65 years or >65 years) (Table 2). The proportion of patients with a low platelet count increased with the risk category (Fig. 2), reflecting the development of thrombocytopenia as the disease progresses. There was no apparent association between spleen size and platelet count (Fig. 3).

About one-third of patients (86/250; 34%) displayed at least one constitutional symptom impacting prognosis [night sweats, fever or weight loss ($>10\%$ of initial body weight)]. Constitutional symptoms were reported for the majority of MF patients in the High risk category (46/67 [69%] for IPSS; 15/19 [79%] for DIPSS). The spleen was palpable for a slightly higher proportion of patients with constitutional symptoms (72/86 [84%]) than with no constitutional symptoms (121/164 [74%]) (Fig. 4). Moreover, spleen size ≥ 5 cm below the costal margin seemed to be associated with the presence of constitutional symptoms (71% of patients with constitutional symptoms vs 42% of patients without constitutional symptoms).

Table 1 The distribution of the number of patients (%) among risk categories according to IPSS and DIPSS risk categories and age classes

Risk category	IPSS			DIPSS		
	Overall N=250	≤ 65 years N=97	>65 years N=153	Overall N=250	≤ 65 years N=97	>65 years N=153
High	67 (27%)	12 (12%)	55 (36%)	19 (8%)	–	19 (13%)
Int-2	82 (33%)	26 (27%)	56 (37%)	84 (34%)	27 (28%)	57 (37%)
Int-1	76 (30%)	34 (35%)	42 (27%)	122 (49%)	45 (46%)	77 (50%)
Low	25 (10%)	25 (26%)	–	25 (10%)	25 (26%)	–

Figure 1 Distribution of patients according to IPSS or DIPSS risk categories and spleen size: (A) number of patients; (B) percentages.

The majority of patients had a myeloblast count $<1\%$ (165/250; 66%). Of these, 73 (44%) had a spleen size ≥ 5 cm below the costal margin and 52 (32%) suffered from constitutional symptoms. Among patients with a myeloblast count $\geq 1\%$ (85/250; 34%), a high proportion (57/85; 67%) had a spleen size ≥ 5 cm below the costal margin and 34 (40%) suffered from constitutional symptoms.

Platelet counts and splenectomy/spleen irradiation in MF

Overall, six (2%) patients (none High risk) had undergone a splenectomy. Of these, four patients had a platelet count $\geq 200\ 000/\mu\text{l}$, one patient had a platelet count between 75 000 and 100 000/ μl , and one patient had a platelet count $<50\ 000/\mu\text{l}$.

Overall, 13 (5%) patients had undergone radiotherapy for splenomegaly. Of these, five patients had a platelet count $\geq 200\ 000/\mu\text{l}$, three patients had a platelet count between 100 000 and 200 000/ μl , three patients had a platelet count between 50 000 and 75 000/ μl , and two patients had a platelet count $<50\ 000/\mu\text{l}$.

Discussion

Here we have presented the results of a recently conducted survey designed to collect quantitative data to describe prevalence and study-specific disease parameters (diagnosis, risk categories, spleen size, cell count, myeloblast count) in Belgian MF patients in 2011.

We aimed to capture the majority of MF patients in Belgium by targeting 18 major hematology centers

in Belgium. There is likely to be a bias for patients in the High and Intermediate risk categories as low-risk patients, with fewer symptoms, may not have been transferred to these centers. We estimate that the 250 patients captured here represent about 60% of the total population of MF patients in Belgium in 2011, considering a PMF prevalence³⁷ of 2.7 per 100 000 (population in 2011: 10.95 million)³⁸ and accounting for the additional patients with secondary MF (34% of the total MF population, according to the present survey). The majority of patients were over 65 years old, with a slightly higher proportion of men, as expected.^{5,7-9}

The various symptoms and characteristics of MF contribute to a diminished quality of life for MF patients. In particular, splenomegaly, reported for over three quarters of the patients here, can be associated with pain, early satiety, bloating and potentially portal hypertension and portal vein thrombosis.²⁰

In order to be considered for transplantation, age and risk category are important selection factors; older patients are less likely to be considered for AHSCT due to the toxicity associated with the procedure. In our survey, 97 out of 250 (39%) MF patients were ≤ 65 years old. Of these, 26 (27%) were Int-2 and 12 (12%) were High risk IPSS. Thus, only 38 (15.2%) of all patients captured in this survey would be considered transplant candidates based on both age and risk category. It should be noted however that age above 65 is not a strict exclusion criterion for AHSCT, as each patient should be

Table 2 Platelet count distribution overall and per age class

Platelet count (μl)	Overall N=250	≤ 65 years N=97	> 65 years N=153
$< 50\ 000$	28 (11%)	11 (11%)	17 (11%)
$\geq 50\ 000 - < 75\ 000$	14 (6%)	3 (3%)	11 (7%)
$\geq 75\ 000 - < 100\ 000$	7 (3%)	3 (3%)	4 (3%)
$\geq 100\ 000 - < 200\ 000$	58 (23%)	20 (21%)	38 (25%)
$\geq 200\ 000$	143 (57%)	60 (62%)	83 (54%)

Figure 2 Distribution of patients (%) according to IPSS or DIPSS risk categories and platelet count.

assessed on an individual base and age is not the only parameter to take into account. Thrombocytopenia is often present in MF patients and it has been added as a negative prognostic factor in the DIPSS Plus scoring system.¹² In our survey, severe thrombocytopenia was not common. A total of 222 (89%) of the patients had platelet counts $\geq 50\,000/\mu\text{L}$. Patients with very low platelet count ($<50\,000/\mu\text{L}$; approximately 11% of patients captured here) are usually not eligible to participate in clinical trials with JAK inhibitors. Thrombocytopenia is a common side effect of JAK inhibitors,³¹ and spontaneous bleeding could have fatal consequences for patients with very low platelets count. However, pacritinib (selective inhibitor for JAK2 and FLT3) was shown to alleviate MF-associated splenomegaly and constitutional symptoms in a Phase II clinical study, where seven out of 34 patients had platelet counts $<50\,000/\mu\text{L}$.³⁹ Different JAK inhibitors under clinical development are selective for different kinases. It remains unclear how the efficacy and side-effects of the JAK inhibitors

can be attributed to the inhibition of individual JAK family members, but it could be envisaged that MF patients may benefit from future rational drug combinations that target multiple signaling pathways.^{25,40}

Ruxolitinib has been tested on Int-2 and High risk MF patients with platelet counts above $100\,000/\mu\text{L}$ and a spleen size over 5 cm in Phase III clinical trials.^{33,34} Data available to date suggest that ruxolitinib may improve survival versus placebo or best available therapy.⁴¹⁻⁴³ The main drug side-effects were thrombocytopenia, anemia and diarrhea. Due to the thrombocytopenic effect, ruxolitinib is not routinely indicated for patients with less than $100\,000$ platelets/ μL . However, ruxolitinib is currently being tested in Phase Ib/II clinical trials in thrombocytopenic MF patients (platelet counts of $50\,000$ – $100\,000/\mu\text{L}$) with positive results (reduction in splenomegaly and constitutional symptoms).⁴⁴

In our survey, out of the total population with spleen size ≥ 5 cm under the costal margin and a platelet count above $50\,000/\mu\text{L}$, almost all patients (97%) were Intermediate to High risk (IPSS and DIPSS). Three quarters IPSS and half DIPSS patients were Int-2 and High risk, respectively. While about one-third of these higher risk patients would be considered eligible for transplantation based on age, the remaining high risk patients could thus potentially benefit from treatment with hydroxyurea or JAK inhibitors.²⁵⁻²⁷ If we applied the inclusion criteria for the Comfort trials^{33,34} to the MF patient population included in the current study, 72/250 (29%) patients would qualify (Int-2 and High risk categories [IPSS], spleen size ≥ 5 cm below the costal margin and a platelet count $\geq 100\,000/\mu\text{L}$). If we expanded this selection to include the Int-1 risk category (IPSS) and all patients Intermediate to High risk (IPSS) with a platelet count $\geq 50\,000/\mu\text{L}$, the proportion of MF patients captured by this survey who could potentially benefit from treatments with JAK inhibitors would be as high as 44% (111/250).

Figure 3 Distribution of patients according to spleen size and platelet count: (A) number of patients; (B) percentages.

Figure 4 Distribution of patients according to IPSS or DIPSS risk categories, spleen size and presence of constitutional symptoms: (A) number of patients; (B) percentages.

The management of anemia, a major symptom of MF and a side-effect of some of the tested JAK inhibitors, can be a challenging aspect of treating patients with MF.^{33,34,45} MF-associated anemia is currently treated with ESAs, prednisone, danazol, thalidomide or lenalidomide.³¹ Pomalidomide, a derivative of thalidomide, was shown to be active in the treatment of anemia in Phase I/II trials,⁴⁶ but in a recently conducted Phase III trial comparing low dose pomalidomide versus placebo in RBC-dependent MF patients, the primary endpoint, RBC-transfusion independence, has not been reached.⁴⁷ Clinical trials are currently underway to test the possible benefits of combining ruxolitinib with anti-anemia drugs (thalidomide, lenalidomide, danazol, or ESAs).⁴⁸ A limitation of the current study is the lack of information on anemia and transfusion-dependency, which lowers our understanding of the potential impact of anemia in the MF patients captured in this survey. Although hemoglobin concentration (<10 g/dl) was used as a predictive risk factor in assessing IPSS and DIPSS risk groups, the pre-defined questions of this survey did not target the distribution of patients according to hemoglobin concentration or transfusion-dependency.

In conclusion, the results of this survey provide important insight into the characteristics of the Belgian MF population, according to specific disease parameters. They also suggest that a large proportion of these patients, particularly in the Intermediate to High risk categories, could benefit from treatment with investigational drugs under development. These new treatments, although they offer promise in the improvement in quality of life of certain MF patients, still do not offer a cure and may not yet be appropriate for all patients.

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