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Title: Disease and treatment characteristics of polycythaemia vera patients in Belgium: results from a scientific survey

Running title: Polycythaemia vera patients in Belgium

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Abstract

Objective: The current survey aimed to gather pre-defined disease parameters and treatment strategies to characterize the polycythaemia vera (PV) patient population in Belgium.

Methods: Cross-sectional data from PV patients, seen at least once between May 2014 and May 2015 at 10 sites in Belgium, were collected in aggregated form and analysed descriptively and quantitatively.

Results: Data from 343 PV patients were collected. Of these, 174 (50.7%) were male and 256 (74.6%) were ≥ 60 years of age. Ninety-two (26.8%) had a prior history of thrombotic events. Considerable proportions of patients had increased haematological parameters (haematocrit $>45\%$ [31.2%], leukocytes $>10 \times 10^9/L$ [33.3%], and platelet $>400 \times 10^9/L$ [38.2%]). Most patients had non-palpable spleen (284, 87.7%) and no phlebotomies during the past 6 months (197, 57.4 %). Low dose aspirin was given as thrombosis prophylaxis in 249 (72.6%) patients, while 232 (67.6%) received hydroxyurea as cytoreductive treatment. Forty-one patients (12.0%) were reported as resistant and/or intolerant to hydroxyurea. Seventeen patients (5.0%) received ruxolitinib in the context of clinical trials.

Conclusion: This survey provides better insight on the characteristics of Belgian PV patients and currently used treatment strategies. It shows that 232 (67.6%) PV patients continue to receive hydroxyurea (HU) despite being potentially HU-resistant.

Keywords: myeloproliferative neoplasm, polycythaemia vera, cytoreductive agents, *JAK2* mutation

Introduction

Polycythaemia vera (PV) is a chronic myeloproliferative disease that results from clonal expansion of haematopoietic progenitors. It is characterised by erythrocytosis, often accompanied by leukocytosis and/or thrombocytosis (1, 2). Systemic symptoms include fatigue, night sweats and pruritus (2-5). Extramedullary haematopoiesis and sequestration can lead to enlargement of the spleen: 36% of PV patients have a palpable spleen (5). The increased risk of thrombotic or haemorrhagic events results in cardiovascular complications (6, 7).

PV patients have an increased risk of disease transformation to myelofibrosis (MF) or to acute myeloid leukaemia (AML) (1, 3). The 10-year risk of transformation to MF or AML is ~10% and ~15% respectively (8, 9, 10).

The most recent World Health Organization (WHO) classification of 2016 defines PV as a chronic BCR-ABL negative myeloproliferative neoplasm (MPN). The 2016 WHO diagnostic criteria for PV require identification of three major criteria or the first two major criteria and a minor criterion (11). Major criteria are (1) increased haemoglobin level (>16.5 g/dL in men or >16.0 g/dL in women), increased haematocrit level (>49 percent in men or >48 percent in

women), or other evidence of increased red cell volume >25% above normal; (2) bone marrow biopsy showing hypercellularity for age with trilineage growth and (3) *JAK2* V617F or *JAK2* exon 12 mutations (present in > 95 percent of PV patients). Subnormal serum erythropoietin level is considered a minor criterion (11).

In the USA, the latest estimation on PV prevalence was 44 to 57 cases per 100000 person-years (py) (12). Incidence estimations of PV vary between 0.7 and 2.8 cases per 100000 py (13-17). No cure for PV is available. Current treatment options aim to prevent the occurrence of thrombotic or haemorrhagic events. These include low-dose aspirin and phlebotomy for low-risk patients and cytoreductive agents for high-risk patients: hydroxyurea (HU) or interferon alfa (IFN- α) as a first-line treatment. Of note, IFN- α is not reimbursed for treatment of PV in many European countries. Unfortunately, these treatments do not significantly improve symptom burden in all PV patients and patients can become resistant or intolerant to HU (18). Furthermore, some evidence shows that PV patients who are resistant to HU have a higher risk of death and transformation to MF or AML (19). Therefore, new therapies to address these unmet needs are in high demand.

Ruxolitinib, a new treatment alternative for patients resistant and/or intolerant to HU, has shown promising results. In the RESPONSE phase III trial, 20.9% of PV patients (with splenomegaly) under ruxolitinib had haematocrit control and spleen size reduction of at least 35% after 32 weeks, versus 0.9% in the control group (receiving best-available therapy (BAT)). 49% of the patients who received ruxolitinib (versus 5% of the patients in the control group) had at least a 50%-reduction of the MPN-SAF total symptom score. The number of reported thrombotic events was lower in the ruxolitinib group (20). After 80 weeks, 89% of

patients maintained the hematological response they obtained at week 32 (21). The RESPONSE-2 study evaluated the efficacy and safety of ruxolitinib versus BAT in HU-resistant or intolerant PV patients with non-palpable spleen: patients treated with ruxolitinib maintained haematocrit control without the need for phlebotomy (22). Ruxolitinib was generally well tolerated by PV patients. The occurrence and severity of adverse events was similar in patients receiving ruxolitinib or best available therapies (20-22). Moreover, long-term follow-up of patients treated with ruxolitinib did not reveal progressively worsening toxicity (21).

The objective of the present scientific survey was to gather pre-defined disease parameters from Belgian patients with PV in order to better understand the disease characteristics, the currently used treatment strategies, and the proportion of patients that may benefit from new promising treatment options.

Methods

A scientific survey was designed to collect data on Belgian PV patients. No treatment was administered as part of this survey.

Participants enrolled in this survey were PV patients who visited one of the 10 participating Belgian sites/hospitals at least once between May 2014 and May 2015. A list of participating sites is provided in **Supplementary Material 1**.

PV data were entered at each study site directly into a Microsoft Excel template, listing anonymously all PV patients seen at least once or being at their last follow-up visit. Patient- (gender, age, blood cell counts, spleen size etc.) and treatment-related parameters (thrombosis prophylaxis, cytoreductive treatment, phlebotomies etc.) were collected. The

full list of parameters/questions included in the survey is provided in **Supplementary Material 2**.

After all information was entered into the worksheet, aggregated data were generated from the individual data, and tables answering each of the survey questions were created via an Excel macro integrated into the tool. No patient identification could be done beyond the site. The tables from all sites were merged into a single aggregated Excel file. Data were submitted for analysis in aggregated form only and after the data from individual sites were merged.

The analysis of the collected information was descriptive and quantitative. No formal statistical analysis plan was set out; neither has any statistical hypothesis been formulated.

Results

Disease characteristics

Data from a total of 343 patients with PV were collected. Of these, 174 (50.7%) were male and 256 (74.6%) were older than 60 years of age. Ninety-two patients (26.8%) had a history of thrombotic event(s). The mean age of the patients enrolled in the survey was 67.3 years and the mean time since PV diagnosis was 7.4 years (**Table 1**).

According to the stratification proposed by Passamonti (10), 65 patients (18.9%) were at low-risk and 278 patients (81.1%) were at high-risk for thrombosis (**Table 1**).

Based on the risk factors for shortened survival proposed by Tefferi and colleagues (5) (advanced age, leukocytosis and history of thrombosis), 47 patients (13.7%) were at low-risk, 65 patients (19.7%) were at intermediate risk and 231 patients (67.6%) were at high-risk for shortened survival (**Table 1**).

The majority of patients (284, 87.7%) had a non-palpable spleen. Thirty-eight (11.7%) patients had a palpable spleen and 2 (0.6%) patients were splenectomised (**Table 1**). Out of the 38 patients with palpable spleen, 26 had a spleen between 1 and 5 cm, 10 between 6 and 10 cm, 1 between 11 and 20 cm, and 1 ≥ 20 cm, below the left costal margin.

A large proportion of PV patients had haematological parameters above normal limits: 106 patients (31.2%) had a haematocrit $>45\%$, 114 (33.3%) a leukocyte count $>10 \times 10^9/L$, and 131 (38.3%) a platelet count $>400 \times 10^9/L$ (**Figure 1**). Among patients with an elevated haematocrit, 51 (15.0%) had haematocrit values ≥ 45 – $<47\%$, 33 (9.7%) ≥ 47 – $<50\%$, and 22 (6.5%) $\geq 50\%$.

Current treatment strategies

The majority of patients (315, 91.8%) received thrombosis prophylaxis, among which 249 (72.6%) received low-dose aspirin and 66 (19.2%) received other thrombosis prophylaxis (with or without low-dose aspirin), including coumarine derivatives, low molecular weight heparin, rivaroxaban, apixaban, dabigatran, clopidogrel or dipyridamole. (**Figure 2**).

Overall, 197 patients (57.4%) did not have any phlebotomy within the last 6 months. Sixty-nine patients (20.1%) had 1 or 2 phlebotomies, 52 (15.2%) had 3 or 4 and 21 (6.1%) 5 or 6 phlebotomies. Four patients had more than 7 phlebotomies, but none had more than 12.

Out of the 65 patients at low-risk for thrombosis, 30 (46.2%) received HU as cytoreductive treatment, and out of the 278 high-risk patients, 202 (72.7%) received HU. Twenty-nine patients (8.5%) were treated with cytoreductive therapy other than HU. Among these, 6 patients (9.2%) at low-risk for thrombosis and 11 patients (4.0%) at high-risk for thrombosis received ruxolitinib in the context of clinical trials (**Figure 3**).

The majority of patients were assessed by the treating physicians as neither intolerant nor resistant to HU (247, 72.2%) and 54 patients (15.8%) were never exposed to HU. A total of 41 patients (12.0%) were assessed by the treating physicians as either HU-resistant, HU-intolerant or both (**Figure 4**). The rates of HU resistance and/or intolerance, as assessed by the treating physicians, tended to be higher in patients with splenomegaly (5/29, 16.1%) than in patients without splenomegaly (30/240, 12.5%). The rates of HU resistance and/or intolerance, as assessed by the treating physicians, were comparable between patients with a prior history of thromboembolic events (13/80, 16.3%) and patients with no such history (28/208, 13.5%). The rate of HU intolerance and resistance as assessed by the treating physicians increased with time since diagnosis: from 6.3% (8/126) for patients diagnosed within the first 4 years after diagnosis to 20.4% (33/162) for patients diagnosed more than 4 years ago (median time since diagnosis was 11-12 years).

According to the European LeukemiaNet (ELN) criteria for HU resistance (23) and based on the haematological parameters of the patients, the rates of HU resistance appeared to be higher than those based on assessment by the treating physicians, as 38.2% of all HU-exposed patients had an increased haematocrit value ($>45\%$; with or without leukocytosis [$>10 \times 10^9$ leukocytes/L] or thrombocytosis [$>400 \times 10^9$ platelets/L]), a combination of leukocytosis and thrombocytosis, or all 3 haematological parameters increased (**Figure 5**). In only 40.4% of patients treated with HU all 3 haematological parameters were within normal limits, whereas 59.6% had one, two, or all haematological parameters increased. Eighty-one patients treated with HU (28.4%) had a haematocrit $>45\%$, 88 (30.9%) a leukocyte count $>10 \times 10^9$ /L, and 97 (34.0%) a platelet count $>400 \times 10^9$ /L.

Discussion

Data from 343 Belgian PV patients were collected by this survey, with an approximatively 1:1 gender ratio, a mean age of 67.3 years, and a mean time since diagnosis of 7.4 years. The age distribution of participants is comparable to those reported in other PV studies (5, 12, 14, 15). A considerable proportion of patients were at high-risk for thrombosis (81.1%), and at high-risk for shortened survival (67.6%). The majority of patients had a non-palpable spleen (87.7%), similar to what was seen in a recent observational study in Spain (~84%) (24). About a quarter of the participating patients (26.8%) had a previous thrombotic event, which is also similar to the 24% proportion reported in the Spanish study (24). The proportion of PV patients receiving thrombosis prophylaxis in this study (91.8%) is also consistent with other studies, where up to 90% of PV patients received this treatment (10, 25-27).

About half of the patients included in our survey (57.4%) did not require any phlebotomy within the last 6 months, while the rest received 1 or more: 1–2 phlebotomies for 69 patients (20.1%), 3–4 phlebotomies for 52 patients (15.2%), and 5–6 phlebotomies for 21 patients (6.1%); 4 patients (1.2%) had more than 7 phlebotomies. Although phlebotomies are a crucial and unique treatment choice in PV patients to obtain a fast decrease of the haematocrit when necessary (often at diagnosis), repeated phlebotomies are not always well tolerated by patients (28).

In our study population, the majority of patients (232/343) received HU as cytoreductive treatment. Although in low-risk patients cytoreductive therapy is only indicated by the ELN treatment guidelines (23) when phlebotomies alone are not sufficiently controlling the disease, a relatively high proportion (30/65, 46.2%) of low-risk patients received HU. This might be due to the disease not being sufficiently controlled by phlebotomies alone, but it

might also reflect a discordance between theoretical guidance and implementation of this guidance in routine clinical practice. A low-dose cytoreductive therapy can also be employed by the treating haematologists solely to reduce the number of phlebotomies in low-risk patients.

Significant proportions of PV patients, independent of whether or not they received cytoreduction, had increased haematological parameters, with a haematocrit value above 45% (31.2%), a leukocyte count above 10×10^9 leukocytes/L (33.3%), and a platelet count above 400×10^9 platelets/L (38.2%). In HU treated patients, 81 patients (28.4%) had a haematocrit >45%, 88 patients (30.9%) had leukocyte counts > 10×10^9 /L, and 97 patients (34%) had platelet counts > 400×10^9 /L. An extensive recent study that provided data for 1080 HU treated patients, reported rates similar to those in our study for haematocrit >45% (34.4%), but higher rates for platelet > 400×10^9 /L (59.4%) and WBC > 10×10^9 /L (58.2%) counts (29).

The large proportion of PV patients with higher than recommended (>45%) haematocrit values in our survey may be explained by insufficient knowledge of existing treatment guidelines or by HU intolerance, limiting its dosage in the absence of adequate alternatives. Another explanation for this observation might be that these patients are less adherent to the prescribed HU regimen than perceived by their physicians.

The majority of patients (72.2%) were assessed by the treating physicians as not intolerant or resistant to HU and 15.8% were never exposed to HU. Twelve percent of the patients were assessed by the investigators as being HU resistant and/or intolerant. Comparing their haematological measurements with the ELN criteria for HU resistance and intolerance (23) suggests that the 12.0% value is an underestimation. The difference between HU resistance/intolerance as assessed by the investigators and HU resistance/intolerance as per

the ELN criteria shows that the strict ELN criteria for HU resistance and intolerance are not often used in the clinical 'real life' practice and are probably not well known.

Limitations of our study include the fact that these parameters were not captured over a period of time, but rather at one time point, and that HU dosage or treatment duration information were not collected, nor could the study distinguish between inadequately treated and truly HU-resistant patients. Such data could have provided more insight regarding the response of Belgian PV patients to HU treatment.

In Phase II and III trials, ruxolitinib, a *JAK1* and *JAK2* inhibitor, showed consistent clinical benefit in PV patients intolerant/resistant to HU (20-22, 30). Based on these findings, ruxolitinib was approved in December 2014 by the U.S. Food and Drug Administration for the treatment of PV patients who have an inadequate response to or are intolerant to HU.

The European Medicine Agency authorised its use, in March 2015, in adult PV patients who are intolerant or resistant to HU (21).

It is clear now that the discovery of *JAK2* mutations has led to a better understanding of PV and that *JAK* inhibitors will improve the symptom burden and life quality of certain PV patients. The results of this survey provide important insight into the disease characteristics and treatment approaches of the Belgian PV population. They also suggest that a large group of PV patients continues to receive HU despite being potentially resistant. Besides the fact that a combination of low dose HU and phlebotomies is often well tolerated by patients, the absence of second line treatment options is probably one of the main reasons why these patients continued to receive HU, as neither ruxolitinib or interferons were reimbursed in Belgium for the treatment of PV patients at the time of data collection.

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Tables and Figures

Table 1. Patient characteristics

Patients characteristics	
Characteristic	Value
Total number of patients, N	343
Mean age, years	67.3
Age ≥60 years, N (%)	256 (74.6%)
Male, N (%)	174 (50.7%)
Mean duration since diagnosis, years	7.4
Previous thrombotic event, N (%)	92 (26.8%)
Patient stratification	
Characteristic	N (%)
Distribution according to risk of thrombotic event ¹⁶	
High-risk of thrombotic event*	278 (81.1%)
Low-risk of thrombotic event**	65 (18.9%)
Distribution according to predictors of overall and leukaemia-free survival ⁵	
High-risk of shortened survival	231 (67.6%)
Intermediate risk of shortened survival	65 (19.7%)
Low-risk of shortened survival	47 (13.7%)

Distribution according to spleen size [§]	
Not-palpable	284 (87.7%)
Palpable	38 (11.7%)
Splenectomised	2 (0.6%)

N (%), number (percentage) of patients in a given category

*High risk: age ≥ 60 years or history of thrombosis

**Low risk: age < 60 years and no history of thrombosis

[§]Data missing for 19 patients





