Symptom Burden and Blood Counts in Patients With Polycythemia Vera in the United States: An Analysis From the REVEAL Study

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Abstract

Approximately half of the patients with polycythemia vera experience substantial symptom burdens. We analyzed data from the ongoing Prospective Observational Study of Patients with Polycythemia Vera in US Clinical Practices (REVEAL) study to evaluate the relationship between blood count control and symptoms. The severity of individual symptoms, except for pruritus and night sweats, was not affected by blood count control. Consequently, regular monitoring of symptom burden should be factored when assessing disease control.

Background: Approximately 50% of patients with polycythemia vera (PV) have PV-related symptoms at diagnosis; these symptoms might develop or worsen with time. Symptoms have been shown to negatively affect quality of life and interfere with daily activities. To our knowledge, an

analysis to evaluate the relationship between blood count control and symptoms has not been published.

Patients and Methods: The Prospective Observational Study of Patients with Polycythemia Vera in US Clinical Practices (REVEAL; NCT02252159) is a multicenter, noninterventional, nonrandomized prospective observational study of patients with PV in the United States. Patients included were required to have a complete blood count result within 30 days before completing the at-enrollment Myeloproliferative Neoplasm Self-Assessment Form Total Symptom Score (MPN-SAF TSS). Symptom severity was compared between those who had blood count control versus those who did not.

Results: At the time of enrollment, 1714 patients (94.5%) were being managed with cytoreductive therapy; 468 patients (25.8%) had complete hematologic remission (CHR), 1614 patients (89.0%) had 1 controlled blood count, and 1122 patients (61.9%) had 2 controlled blood counts. Mean MPN-SAF TSSs were similar across patients in different blood count control groups. Fatigue was the most frequently reported symptom. The severity of individual symptoms, except those of pruritus and night sweats, was not affected by CHR or the number of blood counts that were controlled.

Conclusion: Symptom burden in patients with PV can persist despite control of blood counts, which suggests some discordance between laboratory values and symptom burden. Consequently, regular monitoring of symptom burden should be factored into the assessment of disease control.

Introduction

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) characterized by erythrocytosis, thrombocytosis, leukocytosis, and splenomegaly.[1] There are approximately 148,000 patients with PV in the United States[1]; the prevalence of PV is 44 to 57 cases per 100,000 individuals,[2] and the incidence of PV is 1 to 3 per 100,000 individuals[3]. Patients with PV are at increased risk of medical complications, notably thrombosis, leukemic transformation, and substantial symptom burden.[4–8] Ten years after diagnosis, the risks of transformation to post-PV myelofibrosis (MF) and acute myeloid leukemia (AML) are 10% and 5% to 21%, respectively.[4,9]

Most patients with PV have a mutation in the Janus kinase 2 (*JAK2*) gene. Most patients (95%) carry the *JAK2* V617F mutation, whereas 3% harbor a *JAK2* exon 12 mutation.[10–12] The *JAK2* V617F mutation results in constitutive activation of hematopoietic signal transduction and exaggerated hematopoiesis, leading to PV-associated symptoms, myeloproliferation, and excessive inflammation.[13–15]

Approximately 50% of patients present with PV-related symptoms, including fatigue, headache, visual disturbances, and pruritus, at the time of diagnosis.[5,11,16–20] A subset of patients with PV are asymptomatic at the time of diagnosis and might be diagnosed because of incidental findings from laboratory blood tests.[21–23] Over time, as PV progresses, patients

often experience worsening of symptoms and can also experience new symptoms, such as fatigue, headache, early satiety, and inactivity.[1,8,11,23,24]

The symptom burden associated with PV might negatively affect patient health-related quality of life by interfering with daily activities, family and social life, and work productivity.[8,25] The 10-item Myeloproliferative Neoplasm Self-Assessment Form Total Symptom Score (MPN-SAF TSS) is a valid and clinically relevant tool for assessing MPN symptom burden, including for patients with PV.[5] In the first study of the MPN-SAF TSS, of the 10 symptoms assessed, 8 were reported by more than 50% of patients with PV; this analysis did not include longitudinal evaluation of symptoms.

The durable resolution of PV-related symptoms and peripheral blood count reduction are established primary clinical objectives for the optimal management of PV as outlined by the European Leukemia Net and National Comprehensive Cancer Network (NCCN).[1,26–29] The NCCN MPN guidelines recommend symptom monitoring with the MPN-SAF TSS during the treatment course of patients with MPNs, including PV. To our knowledge, to date, no analysis of the relationship between blood count control and symptom control has been performed.

The ongoing Prospective Observational Study of Patients with Polycythemia Vera in US Clinical Practices (REVEAL) study is an observational study being conducted to describe burden of disease, clinical management, patient-reported outcomes, and health care resource use among patients with PV during an approximate 60-month observation period in the United States. This analysis examines the effect of blood count control on symptom burden measured using the MPN-SAF TSS in these patients.

Patients and Methods

REVEAL (ClinicalTrials.gov, NCT02252159) is an ongoing multicenter, noninterventional, nonrandomized, prospective, observational study of patients with PV in the US community and academic study sites. The data cutoff for the current analyses was May 18, 2017.

Patients

Patients had to be ≥ 18 years old, have a clinical diagnosis of PV, be under the care of a physician, willing and able to provide informed consent, and able to complete patient assessments and questionnaires, either alone or with minimal assistance. Patients with a life expectancy of <6 months, a diagnosis of primary MF, post-PV MF, post essential thrombocythemia MF, secondary AML, or myelodysplastic syndrome were excluded. The study protocol was approved by each investigative site's institutional review board, and written informed consent was obtained from each participant.

Study Design

Patients were enrolled in the study during the course of usual care at each investigative site; patients could be enrolled at any point in their PV disease course. Management of PV was per the discretion of the treating physician; all decisions regarding patient care were made by the treating physician. Patients completed the MPN-SAF TSS survey at the time of

enrollment and at approximately 3-month intervals thereafter. Patients included in the current analysis were required to have a complete blood count result within 30 days before completing the MPN-SAF TSS at enrollment. Only at-enrollment MPN-SAF TSS survey results and near-enrollment blood counts were included in the current analysis.

Data Collection

Symptom severity was quantified using the MPN-SAF TSS. MPN-SAF TSS items included worst fatigue, early satiety, abdominal discomfort, inactivity, problems with concentration, night sweats, itching (pruritus), bone pain, fever, and weight loss. Items were scored on a linear analogue self-assessment scale ranging from 0 (absent) to 10 (worst imaginable).[5] Individual symptom scores >7 were considered "severe," scores of 4 to 6 were considered "moderate," scores of 1 to 3 were considered "mild," and a score of 0 was considered "none."[5] For each patient, the 10 individual symptom scores were added together to calculate a total symptom score (TSS); the maximum score was 100, and the minimum score was 0. Complete hematologic response (CHR) was defined as patients who satisfied all 3 blood count criteria, per the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) Consensus Project, including hematocrit (HCT) <45%, white blood cell count (WBC) $<10 \times 10^9$/L, and platelet count (PLT) 400×10^9/L; these same criteria were used to determine if HCT, WBC, and PLT were controlled.[26,30]

Statistical Analysis

Patient demographic and clinical characteristics were summarized using descriptive statistics. The proportions of patients in each symptom severity group were summarized for patients with and without different blood count control. Significance of the association between MPN-SAF TSS and blood count control was assessed using a regression model adjusting for age, sex, risk category, and disease duration. HCT, WBC, and PLT were the individual laboratory results included in the assessments of blood count control. The degree of blood count control (0, 1, 2, or 3 counts controlled) was also evaluated by determining the number of cell lines (HCT, WBC, PLT) that met the levels specified in the IWG-MRT criteria. A sensitivity analysis was conducted to assess the association between the absolute number of blood counts controlled (0, 1, 2, or 3) and TSS. The interaction between sex and blood count control was used to assess the sex-associated differences in MPN-SAF TSS among blood count control groups, using a regression model controlling for age, risk category, and disease duration. *P* values were not corrected for multiple testing.

Results

A total of 2510 patients were enrolled over an approximate 2-year period (July 2014 to August 2016), with 2307 patients having completed the MPN-SAF TSS at enrollment (Table 1). Of these, 1813 patients (72.2%) had a complete blood count within 30 days before completion of the at-enrollment MPN-SAF TSS and were evaluable. Among evaluable patients, the median age was 67 years (range, 22-95 years), 985 (54.3%) were male, and 1642 (90.6%) were white. The median age at PV diagnosis was 61 years, and the median time from PV diagnosis to enrollment was 4.1 years (range, 0.0-39.2 years). A large

proportion (57.0%) of patients had a PV duration of <5 years, and approximately one-fifth (18.8%) of patients had a PV duration of 10 years.

At the time of enrollment, most patients (n = 1714; 94.5%) were being managed with cytoreductive therapy; 1581 patients (87.2%) were managed with phlebotomy, hydroxyurea, or a combination thereof (Table 1). Patients may have used over-the-counter aspirin as part of treatment regimens[12]; however, because of the method of data collection for this study, its use might not have always been captured.

Approximately one-quarter of evaluable patients (n = 468; 25.8%) had CHR at the time of enrollment; 1614 patients (89.0%) had at least 1 controlled blood count, and 1122 patients (61.9%) had at least 2 controlled blood counts (Table 1).

Mean TSS and Blood Count Control

Mean TSS was calculated and compared in patients grouped according to number of controlled blood counts (uncontrolled counts, 1 controlled count, 2 controlled counts, and CHR). Mean scores were similar among the blood count control groups and differed by 1.5 (Figure 1A). Mean scores were 20.2, 18.7, 18.7, and 19.1 in patients with uncontrolled counts, 1 count controlled, 2 counts controlled, and CHR, respectively (P > .05 for each control group compared with the uncontrolled group). The sensitivity analysis did not show a significant association between TSS and the exact number of blood counts controlled (ie, 1, 2, 3, or no counts controlled; P = .64). Mean scores were also similar among patients regardless of which specific blood counts were controlled, except for WBC (Figure 1B). Scores for patients with WBC control were 10% (20.2 vs. 18.0) lower than scores for patients without WBC control (P = .0036); mean controlled and uncontrolled WBC counts were 6.83×10^9/L and 16.33×10^9/L, respectively. Female patients reported a higher mean TSS than male patients (21.5 vs. 16.6); however, there were no sex-associated differences in mean scores for controlled versus uncontrolled blood counts.

Symptoms and Blood Count Control

The 5 most common patient-reported symptoms were fatigue, early satiety, inactivity, pruritus, and problems with concentration (Figure 2). Fatigue was the most frequently reported symptom, with approximately 80% of patients in each blood count control group experiencing at least mild severity. Additional symptoms experienced by patients at lower frequencies, other than those already mentioned, included night sweats, abdominal discomfort, bone pain, unintentional weight loss, and fever (see Supplemental Figure 1 in the online version). The severity of individual symptoms, except that of pruritus and night sweats, was not affected by CHR or an increasing number of controlled blood counts. A similar proportion of patients who achieved CHR, 2 controlled counts, or 1 controlled count reported severe pruritus (11.0%, 11.3%, and 13.1%, respectively), whereas 17.7% of patients with no controlled counts reported severe pruritus. Furthermore, a similar proportion of patients who achieved CHR, 2, or 1 controlled count reported severe night sweats (11.6%, 9.8%, 9.8%, respectively), whereas 15.1% of patients with no controlled counts reported severe night sweats.

Discussion

In this analysis, mean TSSs were similar in patients with varying degrees of blood count control, with scores differing by 1.5 among categories. Mean TSSs were also similar regardless of which specific blood counts were controlled, with the exception of WBC. Although female patients had higher mean TSSs, in male and female patients, mean TSS did not vary with controlled or uncontrolled blood counts. Among the 10 items included on the MPN-SAF TSS, the most frequently reported symptom was fatigue, which is consistent with results of previous studies.[5,8,31] The next most frequent symptoms were early satiety, inactivity, pruritus, and problems with concentration. Severity was similar among blood count control groups for all symptoms, with the exception of pruritus and night sweats.

The pivotal Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) study showed that patients with a target HCT <45% had significantly lower risks of cardiovascular death and major thrombosis.[6] In a post hoc subanalysis of CYTO-PV, the risk of thrombosis was elevated with increasing WBC counts, reaching statistical significance for WBC $>11 \times 10^9$/L.[32] These results lend support to the importance of controlling HCT and WBC counts, which have been central in the management of patients with PV.

The data presented in this analysis suggest that patients might experience symptom burden irrespective of the degree of blood count control. Mean TSSs were similar across all blood count control groups. With the exception of pruritus and night sweats, patients reported similar symptom burden regardless of blood count control. These data also highlight that symptom burden might not be fully addressed by controlling blood counts. It is notable that a higher percentage of patients reported severe night sweats and pruritus in the context of uncontrolled blood counts (0 blood counts controlled). In MPNs, there is recognition that the Janus kinase cascade plays a central role, not only in myeloproliferation, but also in the signaling of inflammatory cytokines.[33] Furthermore, emerging data demonstrate clear relationships between specific MPN symptoms and specific cytokines. Additional research might well be warranted to determine whether severe night sweats or pruritus, in the context of uncontrolled blood counts, have unique cytokine signatures. With respect to limitations, this analysis was designed to assess the association between symptom control and blood count control at a single time point, a median of 4.1 years into the course of the disease. In this population, the TSS scoring scheme (0-100) has a rather narrow dynamic range with 75% of subjects having scores <32[34]; most of the scores of the patients presented herein (18-20) reflected an "intermediate" symptom burden. Also, the correlations between mean TSS and blood count control might have been affected by patients who had overlapping symptoms from comorbidities.

Conclusion

This analysis suggests that achieving blood count control does not necessarily result in symptom control, with the notable exception that patients with uncontrolled WBC counts experienced higher symptom burden; further analyses might be required to confirm this association. Consequently, physicians should regularly monitor symptom burden in their

patients with PV and not rely exclusively on blood counts as a measurement of disease control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Disclosure

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Clinical Practice Points

- Approximately half of patients with PV experience substantial symptom burden.

- We analyzed data from the ongoing REVEAL study to evaluate the relationship between blood count control and symptoms.

- The severity of individual symptoms, except for pruritus and night sweats, was not affected by blood count control.

- Consequently, regular monitoring of symptom burden should be factored into disease control assessment.
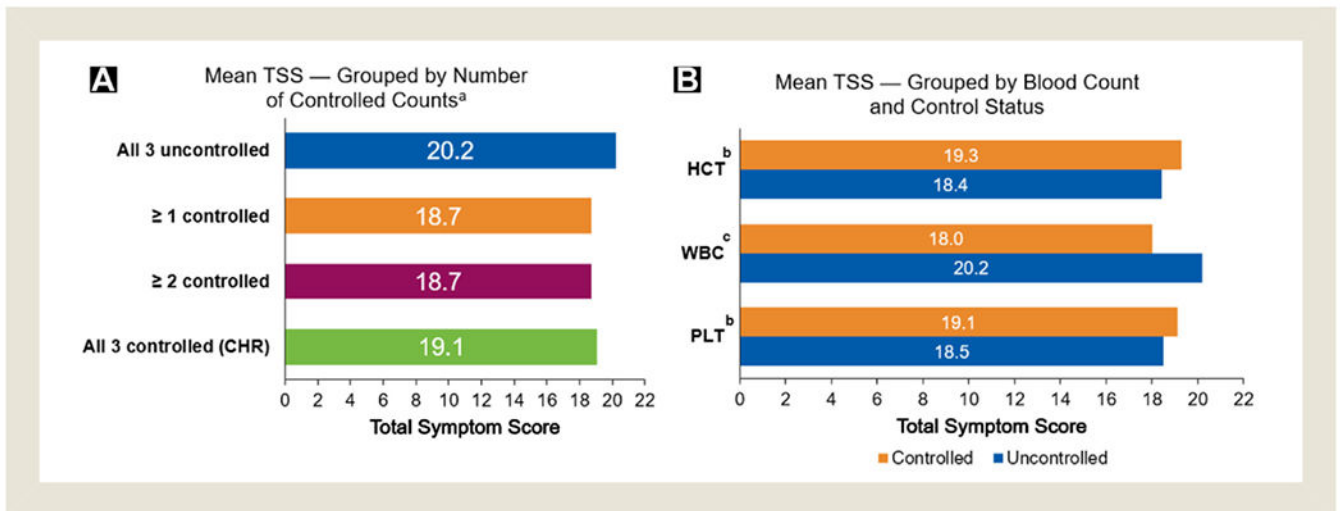
Figure 1. Mean Total Symptom Score (TSS) Among Blood Count Control Groups. (A) Mean TSS Is Listed for Patients According to Blood Count Control Status. (B) Mean TSS Is Listed for Patients According to Blood Count, Noting With or Without Control of the Indicated Blood Count Category. Groups on the Basis of Degree of Blood Count Control (ie, 1, 2, CHR) Are Not Mutually Exclusive

Abbreviations: CHR = complete hematologic remission; HCT = hematocrit; PLT = platelet count; WBC = white blood cell count.

[a] Groups "all 3 controlled," " 1 controlled," and " 2 controlled" are not statistically different from the "all 3 uncontrolled (CHR)" group; $P > .05$. [b] Not statistically different between controlled versus uncontrolled groups; $P > .05$. [c] Statistically significant; $P = .0036$.
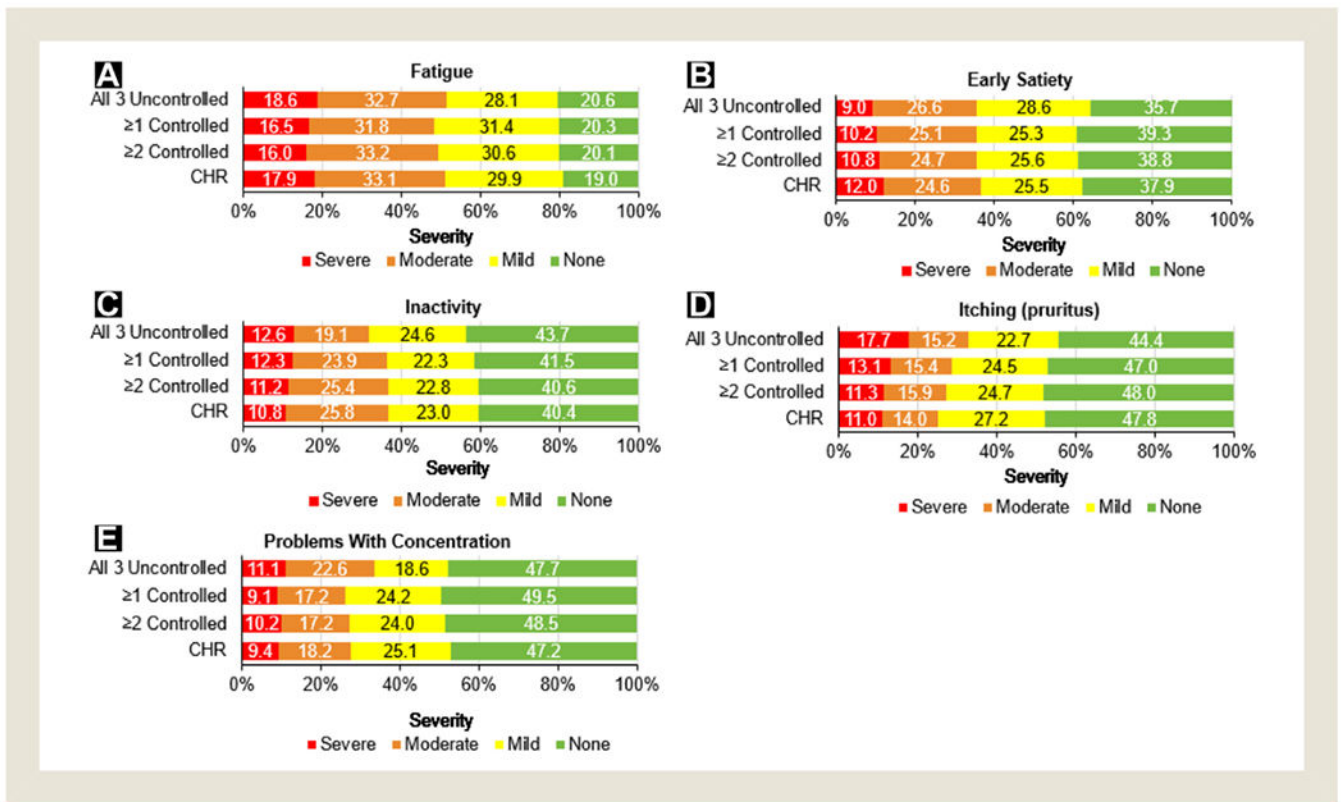
Figure 2. Symptom Severity According to Degree of Blood Count Control. Symptom Severity (Severe, Moderate, Mild, None) Percentages for (A) Fatigue, (B) Early Satiety, (C) Inactivity, (D) Itching (Pruritus), and (E) Problems With Concentration Are Listed for Patients According to Blood Count Control Status. Groups on the Basis of Degree of Blood Count Control (ie, ≥1, ≥2, CHR) Are Not Mutually Exclusive

Abbreviation: CHR = complete hematologic remission.

Table 1

Patient Demographic Characteristics, Disease Management, and Blood Count Control at Time of Enrollment

Variable	Evaluable Patients (n = 1813)
Median Age (Range), Y	67 (22-95)
Sex, n (%)	
Male	985 (54.3)
Female	828 (45.7)
Race, n (%)	
White	1642 (90.6)
African American	93 (5.1)
Asian	21 (1.2)
Other	57 (3.1)
Median Time From PV Diagnosis to Enrollment (Range), Y	4.1 (0.0-39.2)
Median Age at PV Diagnosis (Range), Y	61 (16-93)
Male	60 (18-89)
Female	63 (16-93)
Duration of PV at Enrollment, %	
<1	21.6
1 to <5	35.4
5 to <10	23.5
10 to <15	11.2
15	7.6
Missing	0.7
PV Risk Category, n (%)[a]	
High	1404 (77.4)
Low	409 (22.6)
Disease Management, n (%)[b]	
Watchful waiting only	99 (5.5)
PBT only	640 (35.3)
HU only	447 (24.7)
PBT and HU	494 (27.2)
All other[c]	133 (7.3)
Anagrelide	37 (2.0)
Interferons	15 (0.8)
Ruxolitinib	69 (3.8)
Other	15 (0.8)
Blood Count Control, n (%)	
HCT <45%	934 (51.5)
WBC $<10 \times 10^9$/L	1118 (61.7)

Variable	Evaluable Patients (n = 1813)
PLT 400 × 10^9/L	1152 (63.5)
HCT <45% and WBC <10 × 10^9/L	627 (34.6)
1 Controlled value[d]	1614 (89.0)
2 Controlled values[d]	1122 (61.9)
CHR[d]	468 (25.8)

Abbreviations: CHR = complete hematologic remission; HCT = hematocrit; HU = hydroxyurea; PBT = phlebotomy; PLT = platelet count; PV = polycythemia vera; WBC = white blood cell count.

[a]High risk is age 60 years and/or history of thromboembolism; low risk is age <60 years and no history of thromboembolism.

[b]With or without aspirin use throughout.

[c]Subcategories are not mutually exclusive.

[d]Groups on the basis of degree of blood count control are not mutually exclusive.