Review Article

Contemporary Challenges in Polycythemia Vera Management From the Perspective of Patients and Physicians

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Abstract

Although polycythemia vera (PV) is a chronic and incurable disease, effective management can allow most patients to maintain functional lives with near-normal life expectancy. However, there remain several inter-related factors that contribute to many ongoing challenges associated with the management of PV, which this review aims to explore. First, as a disease hallmarked by constitutive activation of the JAK/STAT pathway, PV is often accompanied by inflammatory symptoms that negatively impact quality of life. Next, patients often require recurrent therapeutic phlebotomies to maintain their hematocrit below the 45% threshold that has been associated with a decreased risk of thrombotic events. The need to closely monitor hematocrit and perform conditional therapeutic phlebotomies ties patients to the healthcare system, thereby limiting their autonomy. Furthermore, many patients describe therapeutic phlebotomies as burdensome and the procedure is often poorly tolerated, further contributing to quality-of-life decline. Phlebotomy needs can be reduced by utilizing cytoreductive therapy; however, standard first-line cytoreductive options (i.e., hydroxyurea and interferon) have not been shown to significantly improve symptom burden. Collectively, current PV management, while reducing thrombotic risk, often has a negative impact on patient quality of life. As researchers continue to advance towards the goal of developing a disease-modifying therapy for patients with PV, pursuit of nearer-term opportunities to shift the current treatment paradigm towards improving symptoms without compromising quality of life is also warranted, for example, by reducing or eliminating the frequent use of phlebotomy.

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Introduction

Polycythemia vera (PV) is one of the 3 main types of myeloproliferative neoplasms, a group of hematopoietic stem cell disorders that also includes primary myelofibrosis and essential thrombocythemia. Erythrocytosis (high concentration of red blood cells) is the hallmark of PV. The current International Consensus Classification diagnostic criteria identify PV by hemoglobin or hematocrit thresholds alongside the presence of a *JAK2* mutation and predefined bone marrow morphology.[1] The incidence of PV across North America, Europe, Asia, and Australia is estimated at 0.67 per 100,000 persons,[2] with frequency being slightly higher in men than in women.[3,4] Most patients with PV are not diagnosed until they reach their 40s and older, with the median age of diagnosis typically in the 60s for both men and women.[5,6] Without appropriate management, hematocrit in patients with PV remains elevated, leading to increased risk of arterial and venous thrombosis as well as cardiovascular death.[7,8] Although PV is a chronic and incurable disease, effective management can allow most patients to maintain relatively normal lives for several years.[5,6] Normal life expectancy is the goal of effective disease management and has become an achievable outcome for some patients managed with current standard of care.[9]

Currently, patients with PV are treated based on risk criteria (Table 1). Major guidelines recommend therapeutic phlebotomy to maintain hematocrit levels below 45%,[10-12] although some recommend different hematocrit thresholds for women versus men for physiologic reasons.[13] For patients who are considered low risk (younger than 60 years of age and with no prior history of thrombosis), phlebotomy is a recommended treatment.[10-12] High-risk patients (aged 60 years and older and/or with any prior history of thrombosis) are additionally treated with cytoreductive therapy, which can include hydroxyurea, ropeginterferon alfa-2b-njft, pegin-

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Table 1 Recommended Treatment Options for PV by Risk Category

Risk Group	Initial Treatment	Subsequent Treatment	Potential Causes for Treatment Change
Low-risk	Manage cardiovascular risk factors Aspirin Phlebotomy	Initiate cytoreductive therapy: • Clinical trial • Hydroxyurea • Peginterferon alfa-2a[a] • Ropeginterferon alfa-2b-njft	New thrombosis or disease-related major bleeding Frequent phlebotomy or intolerant of phlebotomy Splenomegaly Progressive thrombocytosis and/or leukocytosis Disease-related symptoms (e.g., pruritus, night sweats, fatigue)
High-risk	Manage cardiovascular risk factors Aspirin Phlebotomy Cytoreductive therapy • Hydroxyurea • Peginterferon alfa-2a[a] • Ropeginterferon alfa-2b-njft • Ruxolitinib	Ruxolitinib Hydroxyurea Peginterferon alfa-2a[a] Ropeginterferon alfa-2b-njft	Intolerance or resistance to prior cytoreductive treatment New thrombosis or disease-related major bleeding Frequent phlebotomy or intolerant of phlebotomy Splenomegaly Progressive thrombocytosis and/or leukocytosis Disease-related symptoms (e.g., pruritus, night sweats, fatigue)

[a] Peginterferon alfa-2a is an option for younger patients or in pregnant patients in need of cytoreductive therapy.
Source: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms V.1.2024.[11]; NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms V.3.2022.[87]

terferon alfa-2a, or ruxolitinib.[10-12] Treatment switching may be considered under various scenarios, including the development of a thrombotic or disease-related major bleeding event, the need for frequent phlebotomy or intolerance to phlebotomy, splenomegaly, development of progressive thrombocytosis and/or leukocytosis, and disease-related symptoms.[11]

Despite established treatment algorithms for PV, the management of this disease, from timely diagnosis to adherence to appropriate treatment along with real-world treatment success, can be challenging. In some cases, patients with PV do not receive treatment that is consistent with guidelines; for example, 1 analysis of high-risk patients reported that 42% of patients did not receive treatment consistent with guidelines.[14] The current review explores several inter-related factors that contribute to the ongoing challenges associated with the management of PV.

Current Challenges for the Management of PV

Diagnosis and Initial Treatment

Updated diagnostic criteria for PV were published in 2022 as part of the International Consensus Classification of Myeloid Neoplasms and Acute Leukemias collaborative and remain mostly unchanged from the 2016 revision to the World Health Organization diagnostic criteria (Table 2).[1,15] Despite the existence of defined diagnostic criteria, PV can be difficult to recognize and differentiate from other medical complications. Initial disease symptoms are often broad, heterogeneous, and nonspecific, and can include fatigue, night sweating, muscle aches, problems with concentration, and itching,[16,17] although symptoms may take years to develop. Indeed, patients with PV have reported fatigue and headaches as symptoms that they had commonly experienced at least 1 year prior to diagnosis (in 26% and 16% of patients, respectively).[18] Furthermore, current guidelines for primary care do not typically recommend complete blood counts for routine screening so patients who are either asymptomatic or minimally symptomatic would not be identified. Consequently, PV is often an incidental diagnosis following routine blood work conducted for other reasons.[19,20] In many patients, it is the occurrence of a thrombotic event that prompts the follow-up lab tests that eventually lead to a diagnosis of PV.[21] Unsurprisingly, recognition and understanding of PV outside of specialist settings such as academic institutions and other centers of excellence is often limited, and the resulting potential for delays in definitive diagnosis and the start of appropriate therapy may contribute to negative patient outcomes. In one US-based single center analysis of adults with PV, those who had been managed at a specialist center (n = 470) had a 65% lower risk of mortality compared with a broader PV population from a nationwide database (n = 16,492) after controlling for age, sex, race, and year of diagnosis.[9] Furthermore, median overall survival among patients managed at a specialist center was more than double that of the broader population (approximately 27 vs. 13 years). While current guidelines advocate for additional therapy mostly for high-risk patients, the need for new treatment options to manage early stage and/or low-risk PV is also clear as these patients remain at risk for disease progression. Notably, the Low-PV trial evaluating ropeginterferon alfa2b as add-on to standard therapy (aspirin plus phlebotomies) in patients with low-risk PV shows that opportunities to improve standard of care in these clinical settings still exist.[22]

Hematocrit Control

Hematocrit control is a mainstay goal of PV treatment, with maintenance below a 45% threshold cited as a target across nearly all major treatment guidelines.[10-12] Inadequate hematocrit control has been associated with an approximate 60% increased risk of any

Table 2 ICC Diagnostic Criteria for PV

Major Criteria	
1	Hemoglobin >16.5 g/dL(men) Hemoglobin >16.0 g/dL (women) or Hematocrit >49% (men) Hematocrit >48% (women) or Increased red cell mass (>25% above mean normal predicted value)[a]
2	Presence of JAK2 V617F or JAK2 exon 12 mutation[b]
3	Bone marrow biopsy showing age-adjusted hypercellularity with trilineage proliferation (panmyelosis), including prominent erythroid, granulocytic, and increase in pleomorphic, mature megakaryocytes without atypia
Minor Criterion	
1	Subnormal serum erythropoietin level
Requirements for Positive Diagnosis	
All 3 major criteria or The first 2 major criteria plus the minor criterion[c]	

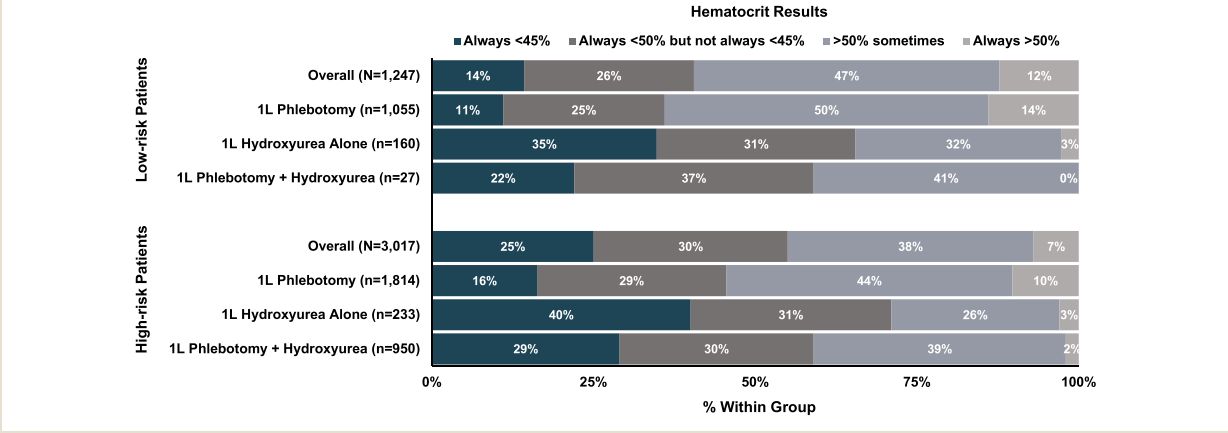
[a] Removal of increased red cell mass as part of the diagnostic criteria for PV is anticipated in the upcoming fifth revision to the WHO diagnostic criteria for PV as determination of increased red cell mass has become uncommon in routine clinical practice.[86]
[b] It is recommended to use highly sensitive assays for JAK2 V617F (sensitivity level <1%). In negative cases, consider searching for noncanonical or atypical JAK2 mutations.
[c] A bone marrow biopsy may not be required in patients with sustained absolute erythrocytosis (hemoglobin concentrations of >18.5 g/dL in men or >16.5 g/dL in women and hematocrit values of >55.5% in men or >49.5% in women) and the presence of a JAK2 V617F or JAK2 exon 12 mutation.
Abbreviations: ICC, International Consensus Classification; JAK2, Janus kinase 2; PV, polycythemia vera; WHO, World Health Organization.
Source: Arber DA, et al. 2022.[1]

thrombotic events.[23] Furthermore, in the Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) clinical trial where patients were treated with phlebotomy, hydroxyurea, or both and randomized to a hematocrit target of either <45% or 45%-50%, patients treated to the higher hematocrit target had nearly a 4-fold increase in risk of death from cardiovascular causes or thrombotic events, and a 2.7-fold increased risk of cardiovascular events, compared with those treated to the standard <45% target.[24] Alternative hematocrit targets have been proposed for female patients due to sex-related variations in plasma volume that equate to higher red cell masses for female patients at equivalent hematocrit levels.[25] Additionally, hematocrit targets may be individualized for patients who achieve symptom control at levels <45% (eg, avoidance of headaches may occur for an individual patient at a hematocrit ≤42%).

It is notable that the CYTO-PV study results occurred despite the investigators reporting that 1 out of every 4 patients in the low hematocrit group did not consistently maintain hematocrit levels <45% throughout the study.[24] With such inconsistent hematocrit levels observed in a controlled trial setting, it is unsurprising that sustained hematocrit control is difficult to achieve in real-world settings. In the prospective observational REVEAL study, over half of patients receiving guideline-recommended hydroxyurea therapy had at least 1 hematocrit result above 45% over 3 months of treatment, and more than one-third had 3 or more above-threshold hematocrit results over the same period.[26] Another study reported that the most recent hematocrit result in approximately one-third of patients with PV who were currently receiving hydroxyurea therapy was above 45%.[27] A separate retrospective analysis of US administrative claims data from patients with PV across multiple treatment lines reported that only 14% of low-risk patients and 25% of high-risk patients consistently maintained hematocrit below 45% over the study observation period (Figure 1).[28] Although the study reported a higher percentage of patients who initiated hydroxyurea with or without phlebotomy in the first-line setting achieved sustained control of hematocrit <45%, it was still well below 50% across the low-risk (22%–35%) and high-risk (29%–40%) groups. A separate study reported that, among patients who had discontinued hydroxyurea and received ruxolitinib as a second-line treatment, ruxolitinib therapy initially increased the proportion of patients with hematocrit levels below 45% from 19% to 63%, but that this had decreased to 52% by the final patient visit.[29]

Although guideline-based therapy can help to effectively manage hematocrit levels for many patients, treatment discontinuation remains a major challenge. Rates of permanent discontinuation for hydroxyurea in studies with multi-year follow-up periods range from 17.5% to 20%,[26,27,30] and many patients with PV interrupt and restart hydroxyurea treatment throughout the course of their disease. Common reasons for hydroxyurea discontinuation or interruption include adverse effects/intolerance, treatment resistance, disease progression, and poor adherence.[26,27,29,30] An analysis of patients who received ruxolitinib after discontinuing hydroxyurea reported that 38.6% discontinued ruxolitinib treatment over a median treatment duration of 31 months.[29] Notably, in the MPN Landmark survey study, 84% of physician respondents reported that their patients "sometimes" or "often" did not wish to comply with the physicians' primary treatment recommendation, but the study authors note the reasons underlying this were unclear.[31] Drivers of poor adherence to treatment are not well-described in the literature, although a study in a mixed cohort of French patients with PV or essential thrombocytopenia suggests forgetfulness and scheduling challenges are primary contributors rather than treatment-related issues.[32] It is possible patients are not adequately

Figure 1 Rates of Sustained Hematocrit Control in PV by Risk Group and First-line Treatment Received. Based on an analysis of US administrative claims data and linked outpatient laboratory data (Symphony Health) from patients who were diagnosed with PV and received treatment between January 1, 2018, and December 31, 2019. Records from January 1, 2011, through December 31, 2019, were queried to identify the initial treatment received for PV. Patients included in the analysis must also have ≥1 year of treatment history for PV as well as ≥1 prescription claim in both 2018 and 2019, ≥1 hospital or medical claim in both 2018 and 2019, and ≥2 hematocrit test results. The analysis included 4264 patients. Reported percentages across patient groups may not add up to 100% due to rounding. Abbreviations: 1L, first-line; PV, polycythemia vera; US, United States. Source: Verstovsek S, et al. 2023.[28]



educated on the importance of periodic monitoring and maintaining hematocrit levels below 45%, leading to reduced adherence to treatment.

Treatment-Associated Challenges

Ongoing Disease Burden Despite Treatment

Although PV has a more favorable prognosis compared with more advanced myeloproliferative neoplasms such as myelofibrosis (MF), the symptoms of PV as well as the impact of current standard-of-care treatment place a substantial burden on patients' quality of life.

Patients with PV often list fatigue as one of the most frequent and debilitating symptoms associated with their disease.[16,18,33] Iron deficiency, a contributing factor to fatigue and other PV-associated symptoms such as cognitive impairment,[34] is often present in patients with PV prior to treatment and can be further exacerbated following multiple phlebotomy procedures.[35,36] Indeed, patients who have undergone phlebotomy and other cytoreductive treatments have frequently reported that the severity of their levels of fatigue and general quality of life became worse with treatment (Table 3).[37-39] For example, in the DALIAH study that randomized patients with myeloproliferative neoplasms to hydroxyurea or interferon therapy, both treatments led to worsening fatigue and overall quality of life scores among patients aged 60 years and older over the first 12–24 months of treatment, although by month 36 only patients treated with hydroxyurea had scores that remained significantly worse than baseline.[40]

Many patients also report experiencing worry and anxiety over their condition.[31,41-43] In particular, disease-related anxiety has been associated with the stress of retaining hematocrit levels below 45% as well as the potential for PV to progress or transform into a more severe malignancy (eg, MF, acute myeloid leukemia).[18,39] Physical symptoms themselves are also associated with the psychological symptoms, particularly depression.[43] Additionally, PV and its management has notable impacts on patients' ability to work, with many patients reporting that they experience some degree of presenteeism or are required to miss work due to disease-associated symptoms or treatment, with some opting for early retirement or a job change due to these impacts.[18,39,44,45]

Impaired quality of life, which is often exacerbated by the effects of disease management, can also be associated with increased use of healthcare resources for patients with PV and other related disorders. For example, patients with PV who indicated having feelings of psychological distress had both more frequent emergency department visits and unplanned hospitalizations compared with patients who did not report distress.[42] Parallels have also been observed in other hematologic disorders. For example, patients with myelofibrosis who were transfusion-dependent had both higher healthcare resource use in the form of hospitalizations, emergency department visits, and outpatient visits compared with matched patients who were not transfusion-dependent,[46] while a systematic review of patients with myelodysplastic syndromes reported that transfusion dependence had a negative impact on patient quality of life.[47] Additional studies in patients with beta-thalassemia and acute myeloid leukemia have similarly reported simultaneously impaired quality of life alongside increased costs and resource use associated with treatment.[48,49]

The consistency of these results across different disease states suggests a goal of treatment would be to extricate patients from the health care system as much as possible, thereby restoring patient freedom and autonomy. Introduction of treatment options to control hematocrit that could be self-administered and/or decrease dependency on phlebotomy, for example, could help reduce the

Table 3 Exacerbation of Fatigue Among Patients With PV Who Were Undergoing Guideline-Recommended Treatment

Study	Population	Key Fatigue Results for Patients With PV
REVEAL[38]	Prospective, observational study of adult patients with PV (N = 400[a])	Patient-reported effects of phlebotomy on fatigue, n (%) Mild: 104 (26.0) Moderate: 78 (19.5) Extreme: 24 (6.0)
MPN Landmark[39]	Survey of patients with PV (n = 223), ET (n = 302), or MF (n = 174) Most patients had received or were currently receiving treatment	Experienced fatigue in past 12 months: 45% MPN-SAF mean fatigue severity score: 6.53 Patients reporting fatigue as the symptom they would most like to have resolved: 84%
MPN-SAF study[37]	Survey of patients with MPNs; this analysis assessed PV only (N = 645)	MPN-10 component scores for worst fatigue Phlebotomy: 5.8 Alternative therapy: 4.4 ($P < .001$)

[a] Population reporting data for the current analysis.
Abbreviations: ET, essential thrombocythemia; MF, myelofibrosis; MPN, myeloproliferative neoplasm; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; MPN-10, 10-item MPN-SAF; PV, polycythemia vera.

need for frequent monitoring and intervention from healthcare providers. Such treatments may yield improvements in quality of life and lower utilization of shared healthcare resources. In many ways, the goal of therapy in PV is to reframe it as a chronic disease rather than as a hematologic malignancy. Yet, such reframing will be challenging if patients continued to be tied to the clinical laboratory and infusion chair.

Phlebotomy-Specific Challenges

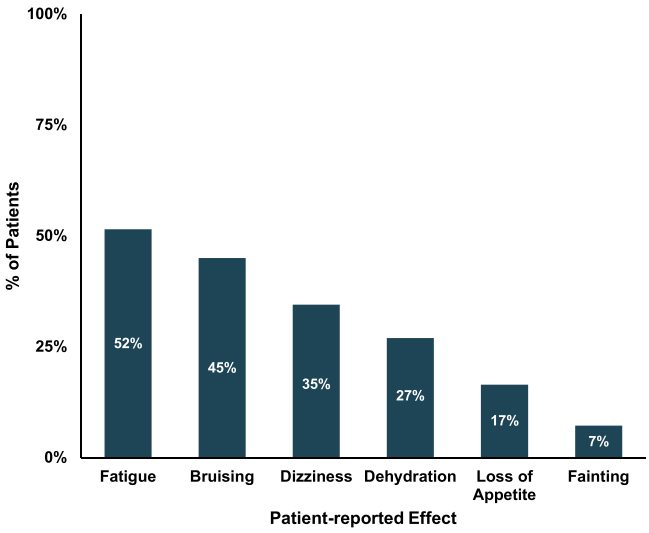
Although therapeutic phlebotomy is part of the current standard of care for PV, frequent use of the procedure to maintain hematocrit below 45% presents a unique set of challenges to patients. Phlebotomy is administered on a reactive basis and is unpredictable by nature. Patients with PV will typically undergo blood panel testing during routine office visits and the need for a phlebotomy procedure will not be known until the test results become available. Patients may therefore experience anxiety in making plans around the time of blood draws and anticipation of results. Furthermore, both patients and their caregivers may experience substantial inconvenience due to the lack of control over their daily schedules and an overall loss of autonomy. For example, among a cohort of 865 patients in the REVEAL study assessed at baseline, patients reported having an average of 2.5 phlebotomies in the 6 months prior to enrollment and that mean total treatment time can be up to 4 hours for each phlebotomy procedure, leading to missed work for those who were employed.[38,50] More than half of patients reported experiencing fatigue within 24 hours after a phlebotomy, with bruising, dizziness, and dehydration being additional commonly-reported effects (Figure 2).[38] Moreover, patients may find it challenging to identify a convenient site to receive a therapeutic phlebotomy. Patients will often need to receive therapeutic phlebotomies in an infusion center or hospital setting as blood donation centers are often unable or unwilling to provide this service. In some cases (eg, when a patient is managed by a specialist who is not located in close proximity), patients may end up settling for consultations with a local physician for the sole purpose of receiving therapeutic phlebotomies or even present to a local emergency room with outpatient labs and request the procedure, where attending staff may be less familiar with standard management of PV.

While phlebotomy is typically well tolerated, rapid fluid shifts can result in adverse events such as hypotension, headaches, fatigue, syncope, weakness, and dizziness.[51] Among patients who experience repeat phlebotomies, poor venous access can become a challenge, and for patients with poor venous access at baseline, phlebotomy may not even be a viable option. These negative effects of phlebotomy have been described in the REVEAL study, where patients who received prior phlebotomy at baseline reported fatigue, bruising, dehydration, and dizziness as their most frequent phlebotomy-associated adverse events.[38] In addition, one in five patients reported phlebotomies to be moderately or extremely bothersome and 16% reported that they were painful or physically uncomfortable. Moreover, most patients with PV experience iron deficiency over the course of their disease, which can be exacerbated with frequent phlebotomies.[35,36] Iron supplementation to alleviate this deficiency is not optimal for patients with PV as it can worsen erythrocytosis and thus increase the need for phlebotomy. Finally, although clinical guidelines note needing frequent phlebotomy or being intolerant of phlebotomy as a potential indication for treatment change,[11] consensus definitions on what is considered frequent or intolerance are unavailable.

Adverse Events Associated With Cytoreductive Therapies

Cytoreductive therapies commonly used to manage PV are associated with several well-known adverse events. For example, the most used initial option for cytoreductive therapy, hydroxyurea, is associated with the development of mouth and skin ulcers, alopecia, and fatigue.[52,53] The association between interferon therapy and several class-specific adverse events is also well-recognized, including: flu-like symptoms; exacerbation of neuropsychiatric, autoimmune, ischemic, and infectious conditions; and pruritus.[52,54] Of note, recently published data from the randomized phase 2 Low-PV trial in patients with low-risk PV suggest lower rates of interferon-associated adverse events are achievable by using lower doses of the most recently approved interferon therapy, ropeginterferon.[55] Although data on the timing and duration of adverse events from clinical trials are limited, the timing and scheduling of interferon doses may affect the onset, severity, and duration of adverse events that are observed in routine clinical practice. Anecdo-

Figure 2 Patient-reported Effects Within 24 Hours After Phlebotomy in PV. Based on an analysis of 400 patients enrolled in the multicenter, non-interventional, non-randomized, observational REVEAL study. Phlebotomy-related burden was assessed with PBQ-21 at enrollment and every 90 days thereafter. PBQ-21 is a 21-item phlebotomy burden questionnaire that assesses patient-reported phlebotomy frequency, practice setting, time required, inconvenience, and phlebotomy-related adverse effects. Abbreviations: PBQ-21, 21-item phlebotomy burden questionnaire; PV, polycythemia vera. Source: Boccia RV, et al. 2015.[38] Reprinted with permission from Boccia RV, Stein B, Mesa RA, et al. Burden of phlebotomy in patients with polycythemia vera in the United States: Baseline data from the REVEAL study. Blood 126(23):5187, 2015. Copyright 2015 The American Society of Hematology.



tally, we have observed improved tolerability of treatment-emergent adverse events such as flu-like symptoms and mood/psychiatric disorders with longer acting ropeginterferon compared with weekly pegylated interferon. Additionally, we have observed lower rates of psychiatric adverse events with ropeginterferon in relation to pegylated interferon. Based on these observations, it is possible that lower doses of ropeginterferon similar to those given in the Low-PV trial may further ameliorate adverse events following use of interferon-based therapy; however, it is still unknown whether this applies to autoimmune adverse events. Ruxolitinib, a standard treatment option for patients with inadequate response to or who are unable to tolerate hydroxyurea, is typically well tolerated but can increase the risk of infections and lead to weight gain and shingles reactivation.[56,57]

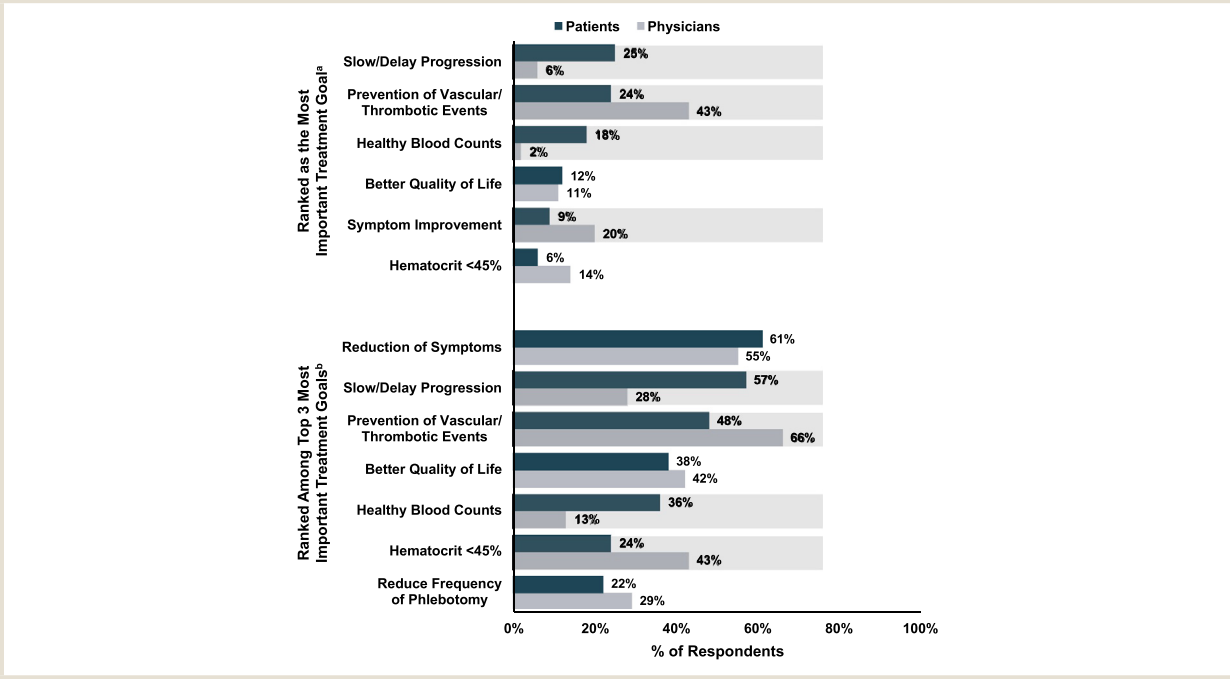
In addition to more acute adverse events, several of the standard cytoreductive therapy options for PV have been associated with increased risk of developing second malignancies. For example, studies have reported approximately 2- to 3-fold increased risk for nonmelanoma skin cancers among patients with myeloproliferative neoplasms (including PV) who received hydroxyurea.[58,59] Similarly, studies in populations of patients with myeloproliferative neoplasms have reported increased risk of any second malignancy and nonmelanoma skin cancers among those who have received ruxolitinib,[58-64] although prior hydroxyurea exposure is often cited as a potential confounding factor.[65] Of note, the risk for nonmelanoma skin cancers can be managed with surveillance and routine surgery on discovery.

Additional Challenges

PV is rare and patients with rare disease often report challenges stemming from lack of awareness, stigma, and misconceptions about their condition. Notably, patients with rare diseases often report frustration from repeatedly having to explain their diagnosis to others, and experience invalidation, disbelief, or lack of understanding and/or recognition of their condition.[66,67] These patients also report accessibility challenges, such as difficulties in social participation and obtaining workplace accommodations.

Understanding how patients and their physicians may differ with respect to their treatment goals and priorities and the implications for PV management is another consideration. For example, patients in the MPN Landmark study reported their most important treatment goals to be slowing or delaying disease progression, reducing symptoms, and preventing thrombotic events, whereas when physicians were asked what they thought patients believed to be the most important treatment goals they focused primarily on preventing thrombotic events and placed lower priority on slowing or delaying disease progression (Figure 3).[31,39] Patients may therefore be more focused on the potential long-term outcomes than their providers realize. Improved communication between patients and providers as well as expanded disease education efforts may reduce some of the disease- and treatment-related anxiety that patients experience and could also help patients further understand the risks and benefits associated with current treatment options. Disease advocacy groups may also play an important role in addressing such challenges as they often interact directly with newly diagnosed patients to provide

Figure 3 Treatment Goals in PV among Patients and Physicians. Based on responses specific to PV from patients and physicians in the international MPN Landmark survey. Responses specific to MF and ET are not shown. Categories shown are those selected by ≥10% PV-specific respondents from either group. Shaded rows represent categories for which the absolute percentage difference between surveyed patients and physicians is ≥10%. [a]For the most important treatment goal, patients and physicians were asked "Other than a cure for diagnosis, what is your most important treatment goal for therapy?" [b]For the top 3 most important treatment goals, patients were asked, "Other than a cure for your condition, what are your 3 most important treatment goals? Please assign rankings (1-3), with 1 being the most important. Physicians were asked, "Other than a cure, what is your most important treatment goal for therapy for each disease? Starting with 1 as the most important, 2 as the second, and 3 as the third, please write 1, 2, and 3 for each disease." Abbreviations: ET, essential thrombocytopenia; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera. Sources: Mesa RA, et al. 2017,[31] Harrison CN, et al. 2017.[39] Reprinted with permission from Mesa RA, Miller CB, Thyne M, et al. Differences in treatment goals and perception of symptom burden between patients with myeloproliferative neoplasms (MPNs) and hematologists/oncologists in the United States: Findings from the MPN Landmark survey. Cancer 123(3):449-458, 2017. Copyright 2017 The Authors. Cancer published by Wiley Periodicals, Inc. on behalf of American Cancer Society.



support, education, and guidance on managing their condition and obtaining necessary care from their respective healthcare systems. These groups can provide guidance to patients on specialists in their area, ongoing clinical trials, and appropriate questions to ask. In an increasingly online ecosystem, patients and community physicians have an unprecedented level of access to disease specialists who work with advocacy groups, medical education companies, and research organizations to review the patient's disease state and emerging treatment considerations.

Notably, the reported differences in patient and physician priorities ties into one of the more evident goals underpinning PV management: reduction in the risk of thrombotic events. This goal is achieved through a procedure (phlebotomy) that requires substantial unpredictable time commitment from the patient, repeated needlesticks, and results in rapid fluid shifts and sustained iron deficiency that can exacerbate existing symptoms such as fatigue. Standard cytoreductive therapies have also been associated with negative impacts on PV symptoms as well as potential longer-term impacts such as the risk of second malignancies. As progress towards the goal of a disease-modifying therapy for PV continues, it remains warranted to pursue nearer-term strategies and interventions to help shift the current treatment paradigm towards improving symptoms with fewer compromises on quality of life, for example, by reducing or eliminating the frequent use of phlebotomy.

Emerging Treatments for PV

Multiple emerging therapies are currently in clinical trials and these therapies have the potential to alleviate some of the challenges that persist with PV management today. This may occur through a reduction in the need for phlebotomies and the ability to lower hematocrit levels without the parallel exacerbation of iron deficiency, which may decrease the burden on patients while still reducing their risk for adverse outcomes.

Some emerging therapies focus on targets that affect iron levels and erythropoiesis. Hepcidin is an iron homeostasis regulatory hormone that binds to ferroportin and results in its endocytosis and

Table 4 Summary of Emerging Treatments and Ongoing Interventional Studies for PV in Phase 2 or Later Clinical Trials

Drug Name(s); Mode of Delivery	Mechanism of Action	Clinical Trial(s); Population	Key Trial Results
Rusfertide (PTG-300) Subcutaneous	Hepcidin mimetic	Phase 2: REVISE (NCT04057040) Patients with phlebotomy-dependent PV (N = 53[a])[72,73]	Primary outcome: response[b] observed in 69.2% of rusfertide-treated patients compared with 18.5% of placebo group ($P = .0003$) 92.3% in rusfertide arm did not receive phlebotomy during 12-week randomization period Open-label treatment with rusfertide (pre-randomization) led to significant improvements from baseline in concentration problems (p=0.0018), itching (p=0.0054), fatigue (p=0.0074), and inactivity (p=0.0005) Most frequent AEs were injection site reactions (erythema 64.3%, pain 41.4%, pruritis 40.0%) Rusfertide controlled hematocrit and reduced erythrocyte count with no clinically significant changes in platelets and leukocytes
		Phase 2: PACIFIC (NCT04767802) Patients with PV and elevated hematocrit (>48%) (N = 20)[74]	Hematocrit was reduced from mean 51% at baseline to <45% within 6 weeks of treatment initiation When treatment was paused: significant ($P < .01$) increases in phlebotomy, hematocrit, and RBC count, and a decrease in serum ferritin Most frequent AEs were transient injection site reactions (59%)
		Phase 3: VERIFY (NCT05210790) Patients with phlebotomy-dependent PV	Trial ongoing
Sapablursen (IONIS-TMPRSS6-LRx) Subcutaneous	TMPRSS6-targeted antisense	Phase 2 (NCT05143957) Patients with phlebotomy-dependent PV	Trial ongoing
SLN124 Subcutaneous	TMPRSS6-targeted siRNA	Phase 1/2 (NCT05499013) Patients with PV	Trial ongoing
Bomedemstat (IMG-7289) Oral	LSD1 inhibitor	Phase 2 (NCT05558696) Patients with PV who have failed at least one standard cytoreductive therapy	Trial ongoing
		Phase 2 (NCT04262141) Patients with ET or PV who have failed at least one standard cytoreductive therapy	Trial ongoing
Givinostat Oral	HDAC inhibitor	Phase 3 (NCT06093672) Patients with JAK2 V617F-positive high-risk PV	Trial ongoing
Ruxolitinib Oral	JAK inhibitor		
Hydroxycarbamide Oral	Ribonucleotide reductase inhibitor	Phase 3: MITHRIDATE (NCT04116502) Patients with high-risk PV	Trial ongoing
Interferon-alpha Subcutaneous	Immune system modulator		

[a] Randomized population during study Weeks 29-41; 70 patients were initially treated with rusfertide in an open-label phase (Weeks 1-16 dose-finding, Weeks 17-28 efficacy evaluation).
[b] Treatment response consisted of: no phlebotomy; completed 12 weeks of treatment; hematocrit control maintained without phlebotomy eligibility (hematocrit ≥45% that was ≥3% higher than Week 29 pre-randomization hematocrit value, or hematocrit >48%, or an increase of ≥5% in hematocrit compared to Week 29 pre-randomization hematocrit value).Abbreviations: AE, adverse event; ET, essential thrombocythemia; HDAC, histone deacetylase; JAK, janus kinase; LSD1, lysine specific demethylase 1; PV, polycythemia vera; RBC, red blood cell, siRNA, short interfering ribonucleic acid; TMPRSS6, transmembrane serine protease 6.

degradation, leading to a decrease in plasma iron concentrations.[68] Elevated hepcidin levels are thought to reduce iron availability and control excessive erythropoiesis. In hepatocytes, the transmembrane serine protease TMPRSS6 negatively regulates the expression of hepcidin.[68,69]

Rusfertide is a potent hepcidin mimetic peptide that is anticipated to decrease dependency on phlebotomy in patients with PV by decreasing erythropoiesis.[70] Rusfertide is currently being evaluated in the phase 3 placebo-controlled VERIFY study.[71] In the phase 2 REVISE study, rusfertide treatment led to a normalization of ferritin levels and a significant reduction in phlebotomy requirements (Table 4).[72-75] Patients also experienced improvements from baseline in PV-associated symptoms, including fatigue/inactivity, itching, and problems with concentration, and the most frequently reported adverse events were injection-site reactions (Table 4).[72,73] In the open-label phase 2 PACIFIC study, patients with high hematocrit at baseline had their levels reduced to below 45% within 6 weeks of treatment (Table 4).[74] Other emerging therapies that

impact hepcidin levels include the TMPRSS6-targeted antisense therapy sapablursen and the TMPRSS6-targeted short interfering RNA therapy SLN124.[69] Both therapies are designed to bind to TMPRSS6 mRNA, causing its degradation, and thus reducing hepcidin suppression. Sapablursen is currently being evaluated in a phase 2 trial,[76] while SLN124 is being evaluated in a phase 1/2 trial in patients with PV.[77]

Bomedemstat is a lysine specific demethylase 1 (LSD1) inhibitor that is currently being evaluated in phase 2 trials that include patients with PV.[78,79] LSD1, a histone demethylating enzyme, has been shown to be overexpressed or dysregulated in various cancer cell types, and several LSD1 inhibitors have been tested or are currently undergoing clinical trials for different cancers.[80] Bomedemstat is being assessed in patients with various myeloid diseases in addition to PV, with early results demonstrating manageable tolerability and some efficacious findings in essential thrombocythemia and MF.[81,82]

Givinostat is a histone-deacetylase (HDAC) inhibitor that is currently being evaluated in a phase 3 clinical trial.[83,84] Inhibition of HDAC leads to the acetylation of the chaperone protein HSP90, which further downregulates JAK2, disrupting its function and reducing proliferation of hematopoietic cells.[84,85] The efficacy and safety of givinostat versus hydroxyurea is currently being assessed in a phase 3 trial of JAK2 V617F-positive high-risk patients with PV.[83]

Conclusion

Patients with PV experience unique and persistent challenges associated with disease management. In particular, the consistent use of phlebotomy procedures for many patients contributes heavily to anxiety, exacerbates symptom burden particularly with respect to fatigue, and may result in a loss of control over everyday activities for both patients and their caregivers. Although cytoreductive therapies are available, these are typically recommended in conjunction with phlebotomy procedures to maintain hematocrit control among high-risk patients and are associated with their own treatment-related burden. While much of the current disease management emphasizes treatments that should improve patient survival, the quality of their lives remains negatively impacted.

Currently, there are no disease-modifying treatment options (ie, a treatment that corrects the JAK2 V617F driver mutation in affected cells) for patients with PV. However, emerging treatments that aim to reduce or eliminate the need for frequent phlebotomy and improve disease-related symptoms may become a critical component in the current standard of care for PV.

CRediT authorship contribution statement

Andrew T. Kuykendall: Writing – review & editing. **Jennifer T. Fine:** Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Marina Kremyanskaya:** Writing – review & editing.

Data Statement

Data and methodology associated with this study will be made available upon written request to the corresponding author.

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Declaration of Financial/Other Relationships

AK has received honorarium and/or consulting fees from Incyte, Protagonist, Kartos, and PharmaEssentia and has received research support from Protagonist Therapeutics, Inc. MK has received honorarium and/or consulting fees from Protagonist Therapeutics, Incyte, Abbvie, and MorphoSys. JF was formerly an employee of Protagonist Therapeutics, Inc. and owns stock in the company.

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