Patient Care in Polycythemia Vera: An Advanced Practice Provider's Perspective

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To gain additional insight into the management of polycythemia vera (PV) by advanced practice providers (APPs), Incyte conducted a survey among community oncology APPs from December 2020 to January 2021. Responses were gathered from 114 APPs, each of whom managed at least 3 patients with PV over the prior 12 months. I was invited to review and offer my perspective on the survey results.

This analysis revealed several key areas where beliefs and clinical practice among the respondents diverged from published clinical data on monitoring and managing patients with PV. These differences point to potential opportunities for APPs to implement strategies to help improve patient care in PV.

Patient Management Considerations in PV

PV is a Philadelphia chromosome–negative myeloproliferative neoplasm that is characterized primarily by erythrocytosis, but may also involve abnormal increases in white blood cell (WBC) and platelet (PLT) production as well as overproduction of inflammatory cytokines.[1,2] The key driver of PV is a *JAK2* mutation (*JAK2*V617F or *JAK2* exon 12 mutation) that leads to an overactive Janus-associated kinase/signal transducer and activator of transcription (JAK/STAT) pathway.[3,4]

This overactive JAK/STAT pathway signaling results in 2 major clinical features of PV: increased hematopoiesis, which can put patients at risk for thrombotic events; and overproduction of proinflammatory cytokines, which may be responsible for several of the burdensome symptoms of PV, including fatigue, itching/pruritus, and day or night sweats.[1,5,6]

Managing these facets of the disease can be challenging for 2 reasons. First, the risk of thrombosis requires regular monitoring of blood counts, and second, symptoms can be vague, so both patients and healthcare providers may not always attribute them to the disease. In addition, because patients with PV often appear less ill and may be perceived as having less imminent needs than patients with myelofibrosis, leukemia, or solid tumors, taking time to consistently perform an in-depth symptom assessment may not be prioritized in a busy practice.

Furthermore, a subset of patients may develop the clinical characteristics of advanced PV, defined as hematocrit (Hct) ≥45% plus either elevated WBC counts >11 × 10^9/L or burdensome disease-related symptoms despite treatment with phlebotomy and the maximum tolerated dose of hydroxyurea (HU).[7-10] The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend that patients be monitored regularly for changes in their disease that would indicate the need for a change of cytoreductive therapy.[11]

Opportunity to Optimally Manage Thrombotic Risk

Let's take a closer look at key clinical data and APP survey responses around 4 topics related to thrombotic risk in PV: controlling Hct, controlling WBC counts, use of cytoreductive therapy, and use of phlebotomy.

Hematocrit

Controlling Hct is one of the key factors in reducing the risk of thrombosis in patients with PV. The Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) study established Hct <45% as the optimal level by showing that patients who were managed to Hct of 45% to 50% experienced a 4-fold increase in the rate of cardiovascular death and major thrombosis compared to patients managed to a target Hct of <45% (hazard ratio [HR], 3.91; 95% confidence interval [CI], 1.45-10.53; $P = 0.007$)[7a] (Figure 1).

However, more than three quarters of the APP survey respondents reported that their maximum acceptable Hct is between 45% and 50% (Figure 2). I believe it is important for APPs to recognize the clinical implications of the <45% Hct threshold. This is the goal for our patients, and my colleagues and I have found that when patients exceed that level, they are at greater risk for a thrombotic event.

White blood cell counts

When asked about the impact of WBC count on thrombotic risk, only 15% of APP survey respondents considered a WBC count >11 × 10^9/L to be "extremely concerning." However, a number of studies have shown the relationship between leukocytosis and adverse outcomes in PV. A multivariable subanalysis of the CYTO-PV study found that the risk of thrombosis was 4 times greater in patients with WBC counts >11 × 10^9/L than in patients whose WBC counts were <7.0 × 10^9/L.[8b] Results from other clinical trials have linked leukocytosis with increased risk of thrombosis.[12,13] In addition, a multivariable time-dependent analysis of patients with PV found that WBC counts ≥11 × 10^9/L independently increased the risk of death 2.1-fold.[14c]

I believe the data from these studies reinforce the importance of monitoring blood counts to detect any trend toward continuing or worsening leukocytosis, as either of these factors should trigger APPs to re-evaluate our management approach for our patients.

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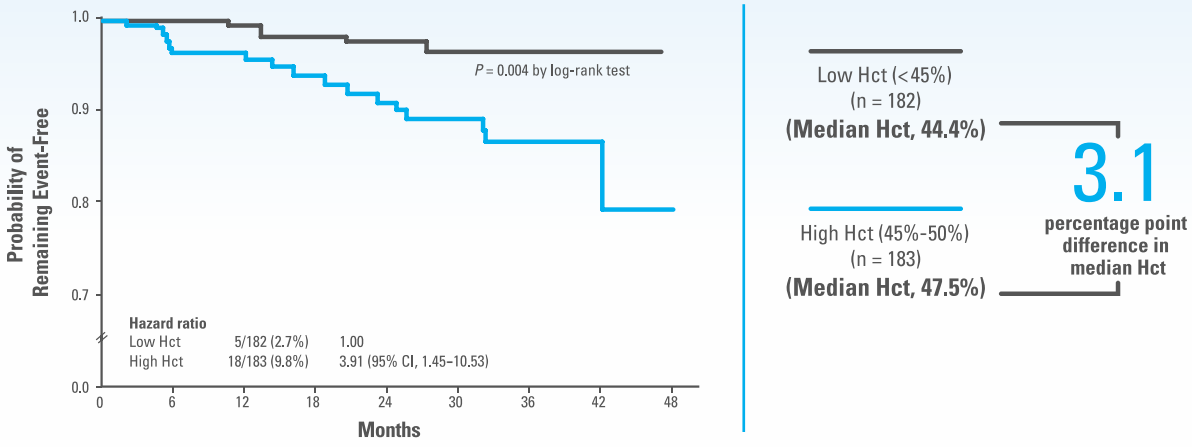
Cytoreductive therapy

HU is the cytoreductive agent most commonly used for high-risk patients with PV. APP survey respondents indicated they believed HU can control elevated Hct and elevated platelet counts "moderately well" (58% and 47%, respectively) in patients with PV. When asked about controlling elevated WBC counts with HU, 61% indicated they believed HU worked "moderately well."

Figure 1. Probability of Remaining Event Free in the CYTO-PV Study (N = 365)[7]



Kaplan-Meier curves for primary composite endpoint.

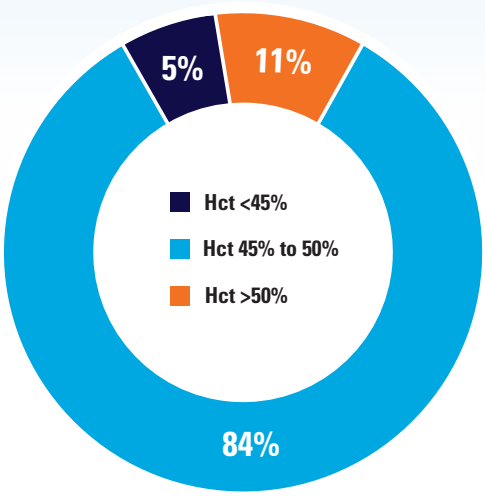
From *N Engl J Med,* Marchioli R, Finazzi G, Specchia G, et al, Cardiovascular events and intensity of treatment in polycythemia vera, Volume No. 368, Page No. 29. Copyright © 2013 Massachusetts Medical Society. Reproduced with permission from Massachusetts Medical Society.

[a] The Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) study included 365 adult patients with PV treated with phlebotomy, HU, or both. Patients were randomized to 1 of 2 groups—either the low-Hct group (n = 182, with more intensive therapy to maintain a target Hct level <45%) or the high-Hct group (n = 183; with less intensive therapy to maintain a target Hct level of 45% to 50%). Baseline characteristics were balanced between the groups. Approximately 50% of patients had received an initial diagnosis of PV within 2 years prior to randomization and 67.1% of patients (n = 245) were at high risk because of age ≥65 years or previous thrombosis. The composite primary endpoint was the time until cardiovascular death or major thrombosis.[7]

[b] In this subanalysis of the CYTO-PV study, there was a trend for increased risk of thrombosis with WBC count >7 × 10^9/L (ie, HR >1), that became statistically significant in patients with WBC counts >11 × 10^9/L [HR, 3.90 (95% CI, 1.24-12.3), $P = 0.02$].[8]

[c] This retrospective, age-adjusted multivariable analysis of 258 patients with PV evaluated the impact of various genetic and clinical features on survival, and found that WBC count ≥11 × 10^9/L independently increased the risk of death 2.1-fold (HR 2.1, 95% CI 1.1-4.0, $P = 0.02$).[14]

Figure 2. APP Survey: Maximum Acceptable Hct Levels When Treating Men With PV (n = 99)



~80% cite a maximum acceptable Hct of 45%-50%

Several studies have shown that blood counts can remain elevated in patients receiving HU. An analysis of the REVEAL study found that, in evaluable patients (n = 1106) who were treated with HU for 3 to 39 months, 57% had at least one Hct value >45% and 45% of patients had at least one WBC count >10 × 10^9/L.[15d]

These data suggest that many patients with PV continue to have elevated blood counts despite treatment with HU.

Phlebotomy

Phlebotomy may be used as an adjunct to cytoreductive therapy for some patients, and 34% of APP survey respondents strongly agreed that frequent phlebotomies are appropriate for patients with persistently elevated Hct. However, phlebotomy may not be effective in controlling Hct in patients who are on cytoreductive therapy. Notably, one analysis of the REVEAL study reported that patients who received phlebotomy while on HU were more likely to have elevated Hct versus those not receiving phlebotomy, regardless of the duration of HU therapy. The study found that 82.9% of patients who received phlebotomies continued to report Hct values >45%.[15]

Additionally, phlebotomy requirement while on HU has been identified as an independent risk factor for thrombosis. In an observational study of patients with PV, a significantly higher rate of thrombosis was found in patients treated with HU plus 3 or more phlebotomies per year compared to HU with 0 to 2 phlebotomies per year (20.5% vs 5.3%, $P < 0.001$).[16e]

These findings further underscore the importance of actively monitoring test results, closely reviewing trends that may indicate progression of PV, and assessing the need for a change in management approach, when appropriate.

Opportunity to Actively Monitor Disease-Related Symptoms

In addition to controlling blood counts, identification and management of symptoms that can impact quality of life are vital aspects of patient care in PV. The overproduction of proinflammatory cytokines seen in PV is responsible for symptoms such as fatigue, pruritus, inactivity, night sweats, bone pain, weight loss, and fever.[6,17] Other symptoms, such as difficulty concentrating, early satiety, and abdominal discomfort, are associated with blood hyperviscosity and splenomegaly, which are hallmarks of PV.[6] A prospective study that assessed symptoms found that 8 of these 10 symptoms occurred to some degree in 50% or more of patients.[9f]

In light of these findings, it is not surprising that symptoms can have a substantial impact on patients' quality of life. In the MPN Landmark survey, which assessed patients' perception of disease burden, 66% of patients with PV reported that their symptoms diminished their quality of life.[18g]

> **In the MPN Landmark survey, 66% of patients with PV reported that their symptoms diminished their quality of life.**

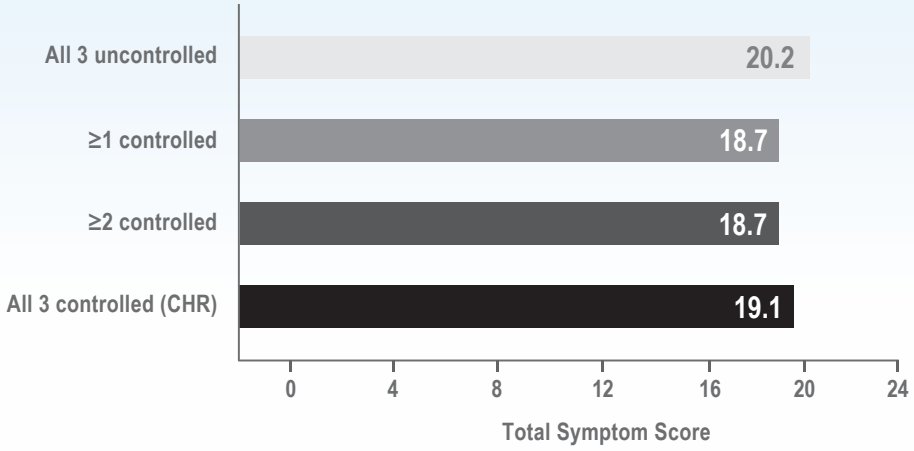
[d] REVEAL was a prospective, observational study of 2510 patients with PV in the United States, sponsored by Incyte. This analysis focused on blood count control in the subset of 1381 patients who had received HU for ≥3 months.[15]

[e] The aim of this observational study, which included 1353 patients, was to assess whether patients with PV treated with HU requiring frequent phlebotomies have the same risk of thrombosis as those managed mainly with HU alone. This cohort included 533 patients treated with HU with available data regarding hematologic values, phlebotomy requirements, and HU dose.[16]

[f] This prospective study included 1433 patients with MPNs (n = 538 with PV) from a variety of practice settings who completed the Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score (MPN-SAF TSS).[9]

[g] The MPN Landmark Survey, funded by Incyte Corporation, was a web-based questionnaire composed of 65 multiple choice questions intended to help evaluate disease burden in the MPN setting. A total of 813 patients in the United States with a previous diagnosis of myelofibrosis (n = 207), PV (n = 380), or essential thrombocythemia (n = 226) completed the survey.[18]

Figure 3. Mean TSS According to Blood Count Control Status (Hct, WBC, PLT)[20]



Total Symptom Score key[19,21]

0-7:	Low symptom burden
8-17:	Intermediate symptom burden
18-31:	**Moderately high symptom burden**
≥32:	High symptom burden

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Association between symptoms and blood counts

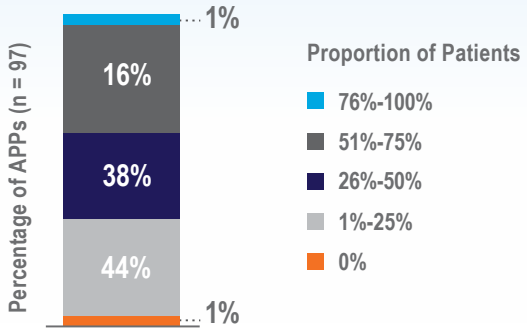
Despite receiving therapy for PV, patients may continue to struggle with burdensome symptoms. A prospective evaluation of patients with PV assessed symptom burden in 3 groups of patients—those who received HU, phlebotomy, or had splenomegaly.[19h] The results showed moderately high symptom burden among those with known HU use (TSS = 29.2), suggesting that symptoms often persist despite use of HU.[19] Further, an analysis of the REVEAL study that examined the relationship between blood counts and symptom burden found that patients experienced moderately high symptom burden despite control of blood counts.[20i] (Figure 3). In addition, the severity of most symptoms was similar whether or not blood counts were controlled.[20]

These data demonstrate the importance of assessing symptoms at baseline and monitoring them regularly. The NCCN Guidelines® note that changes in symptom status could be a sign of disease progression. Therefore, change in symptom status should prompt evaluation.

In considering these data, it is noteworthy that approximately half of APP survey respondents believe that only 25% or fewer of their patients with PV on HU are symptomatic (Figure 4). The fact that APPs perceive the incidence of symptoms to be lower than that seen in these studies suggests that assessment of symptoms can be challenging. There are 2 key reasons for this:

- Many of the symptoms of PV, such as fatigue and headache, can be vague, so patients may attribute them to other causes[22]
- Patients may not be aware of how they are changing their behaviors to accommodate their symptoms

Figure 4. APP Survey: Respondents Who Believe a Certain Proportion of Patients on HU Are Symptomatic



[h] This prospective study of 1334 patients assessed baseline symptoms in subgroups of patients with 1) known HU use (n = 499), 2) known phlebotomy (n = 646), 3) palpable splenomegaly (n = 369), or 4) all 3 features (n = 148). Assessment of MPN symptoms was performed by using the MPN-SAF TSS (MPN-10). All items were evaluated on a 0 (absent) to 10 (worst imaginable) scale. The TSS for each patient was analyzed to place the patient into the quartiles of low symptom burden (TSS, 0 to 7), intermediate symptom burden (TSS, 8 to 17), moderately high symptom burden (TSS, 18 to 31), or high symptom burden (TSS, ≥32).[19]

[i] REVEAL was a prospective, observational study of 2510 patients with PV in the United States, sponsored by Incyte. Of the 2307 patients who completed the MPN-SAF TSS at enrollment, 1813 (72.2%) had a complete blood count within 30 days before completion of the at-enrollment MPN-SAF TSS and were evaluable. 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, HU, or a combination thereof.[20]

Figure 5. Enhance Conversations About Symptoms With Contextual Questions

Fatigue and Inactivity

- Are there activities that you were able to do 3 months ago that you struggle with now?
- How much does your fatigue or inactivity influence your day-to-day activities? Your work around the home? Your time spent with friends or loved ones? The things you do for fun? Your enjoyment of life?

Itching

- Have you noticed changes in your skin, particularly itching?
- When you shower, do you ever feel itchy afterwards? How often?
- Have you found yourself taking shorter/fewer/cooler showers to try to avoid itchiness?

Day or Night Sweats

- Do you experience sweating, particularly at night or in the evenings?
- Does this require you to change your sheets or clothing?
- Does this wake you up or impact your sleep?
- How often did this happen in the past month?

Concentration Problems

- How often have you felt a "brain fog"—memory lapses (such as problems remembering words or dates) or generally having problems concentrating?
- How has this impacted your life? Have you had to change school plans, work, or how you function at home?

Importantly, patients may not report changes in their symptoms to their healthcare team. Because APPs are frequently utilized in all aspects of care for patients with PV, we are well positioned to assess and manage symptoms. A review of systems is often used to evaluate symptoms, but is not tailored for PV-related symptoms and does not allow us to adequately capture changes in symptom frequency, severity, or impact on a patient's quality of life. To help assess these factors, I find it useful to ask contextual questions related to a patient's symptoms, in addition to taking a detailed history, at every visit (Figure 5). Asking specific questions about individual symptoms can encourage patients to express the severity of their symptom burden more openly, based on what they experience in daily life.

I think it is very important to establish a good rapport with my patients so they feel comfortable about sharing more intimate details of life and how symptoms may be impacting them. I like to remind my patients about which symptoms they should watch out for and when to call with questions. I also try to become familiar with a patient's day-to-day activity level and how often they are participating in activities they enjoy, so I can determine whether there has been a decline in these activities. Recording these details in the patient's chart helps me recognize how levels of activity may have changed compared with 6 to 12 months ago.

Another way to get a more thorough assessment of symptoms is for the patient to bring a friend or relative to the appointment. Then, in addition to asking the patient about quality of life and daily activities, I can ask the other person about any changes he or she has noticed.

The Role of the APP in Improving Patient Care

I appreciated the opportunity to review the results of the APP survey, gain insight into how my colleagues manage their patients with PV, and discuss study data we should consider when formulating management strategies for our patients. These data underscore the importance of managing our patients appropriately for their level of thrombotic risk, and of monitoring patients actively to identify those who continue to have elevated blood counts, including Hct ≥45% and either WBC >11 × 10^9/L or new and/or worsening disease-related symptoms despite treatment with a maximum tolerated dose of HU and phlebotomy.

One of the most valuable things we as APPs can do is serve as advocates for our patients. This begins with better understanding PV and the challenges it poses for them. It may also call for spending time with our patients with PV to develop a relationship that allows us to ask the right questions about their symptoms and quality of life, educate them about strategies for managing their disease, and help them receive the support they need.

I encourage you to read more about the clinical studies discussed in this paper and think about ways the management of patients with PV could be optimized at your practice.

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