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Collaborative Care for Patients with Polycythemia Vera

Polycythemia vera (PV) is a chronic, variable disease that may become advanced in some patients. By emphasizing a holistic, collaborative approach, oncology advanced practice providers (APPs) are ideally positioned to establish an evidence-based plan to help patients manage their PV.

In oncology practice, APPs such as physician assistants and nurse practitioners have regular contact with each patient and clinical training that emphasizes an evidence-based approach to disease management.¹ This makes us ideally positioned to coordinate the clinical activities required to effectively care for patients with chronic cancer like PV (see inset). Our role as APPs is especially important given the need to follow up on and track a multitude of laboratory results and other clinical data over the long course of the disease and to share our findings with the extended care team, including oncologists, pharmacists, and nurses. We can also provide the education that patients—and their caregivers—need to become active participants in their care.

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An Evidence-Based Care Plan

Creating an individualized, evidence-based care plan is essential to managing the various aspects of PV and to proactively identify clinical characteristics that may indicate advancing disease. APPs can look to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for MPNs for consensus guidance on the management of patients with PV.² I use these guidelines as the foundation for my approach to risk assessment, monitoring, and treatment for my patients with PV, keeping in mind that each patient is unique and their care plan must reflect their specific personal and clinical circumstances.

Considerations that drive clinical decision-making when managing patients with PV include³:

- An increased risk of thrombosis and/or hemorrhage
- Burdensome disease-related symptoms that impact patient quality of life
- Evidence of disease progression

The following sections outline my approach to patient care. This approach can be customized to suit APPs in a variety of practice settings to address each of these clinical considerations when managing patients with PV.

An Overview of PV

PV is a hematologic cancer estimated to affect approximately 100,000 people in the US, mostly older adults.^{4,5} PV is characterized by erythrocytosis, with a progressive increase over time in erythropoiesis, granulopoiesis, and thrombopoiesis.^{6,7} More than 95% of PV cases are caused by a *JAK2* mutation (*JAK2*V617F or *JAK2* exon 12 mutation), resulting in an overactive Janus-associated kinase/signal transducer and activator of transcription (JAK/STAT) pathway, which is a major factor in the proliferation of these cell lineages.^{8,9}

Considerations that drive clinical decision-making when managing patients with PV are the increased risk of thrombosis and/or hemorrhage, burdensome disease-related symptoms that impact patient quality of life (eg, fatigue, pruritus, and abdominal discomfort), and the possibility of disease progression.^{3,10,11} Current management strategies in PV include a combination of low-dose aspirin, phlebotomy, and other treatments to decrease hematocrit (Hct) to <45%.¹² Management of cardiovascular risk factors—such as diabetes, hypertension, smoking, and dyslipidemia—as well as white blood cell (WBC) counts and platelet levels is also warranted.¹²

In some patients, PV may become advanced despite treatment with the maximum tolerated dose of hydroxyurea and phlebotomy—marked by elevated Hct $\geq 45\%$, plus either elevated WBC count $> 11 \times 10^9/L$ or burdensome symptoms.^{10,13-15} APPs are ideally positioned to promote a holistic, collaborative approach to detect and address subtle or overt changes in their patients' disease status and well-being over the long term.¹⁶

Thrombotic Risk

Thrombosis is a well-known risk associated with PV—a previous thrombosis or age over 60 years alone puts a patient into the high-risk category.^{3,17,18} Thus, it is particularly important at the first patient contact to determine the patient's risk category based on these 2 factors. It is also important to evaluate for the presence of any traditional cardiovascular risk factors, including smoking, dyslipidemia, or comorbidities, such as hypertension or diabetes.¹²

The role of Hct and WBC count

Therapy with phlebotomy, aspirin, and cytoreductive therapy is advocated in patients with PV who have a history of thrombosis or are age 60 years or older to achieve a target Hct <45%.^{14,18,19} This recommendation to maintain Hct <45% in patients with PV was established in the landmark Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) study, a prospective trial of 365 patients with PV that compared the efficacy of conventional treatment (phlebotomy, hydroxyurea, or both) aimed at maintaining the recommended Hct target of less than 45%, as compared with treatment that maintained Hct at a level of 45% to 50%.¹⁴ The findings revealed that patients managed to a Hct <45% had better outcomes, with approximately 4-fold fewer cardiovascular events (cardiovascular death and major thrombosis) compared to patients managed to a Hct between 45% and 50%. A follow-up multivariable subanalysis of CYTO-PV was then conducted to discern the difference between WBC count and Hct control on the risk of thrombosis and it demonstrated that a WBC count >11 x 10⁹/L was associated with an increased risk of thrombosis.¹⁵ Evidence from other large-scale clinical trials has also implicated WBC count in the process of thrombogenesis in PV.²⁰⁻²²

What phlebotomy frequency can tell us

Multiple annual phlebotomies (3 or more)—potentially a sign of inadequate Hct control with hydroxyurea—have also been linked to an increased risk of thrombosis.²³ Knowing how often the patient is receiving phlebotomies is essential to understanding the full clinical picture, as frequent phlebotomies may warrant a change in the management approach.²⁴ Because some patients may go to community blood banks or other facilities for phlebotomy, I always ask my patients about any phlebotomies—or any other relevant clinical events that may have taken place outside our clinic since I last saw them—to ensure that their clinical record is complete.

Conversely, loss of phlebotomy needs or a decrease in the dose of cytoreductive therapy is sufficient to warrant further investigation.²⁵ While lowered blood counts are a desirable outcome in PV, clinicians need to stay vigilant about the possibility of transformation to myelofibrosis (MF). A bone marrow biopsy may be indicated when MF is suspected.⁵

Frequent monitoring is key

Frequently monitoring patients is important to identify changes in blood counts and lab values, and I take the time to ensure all patients understand what counts can tell us about their individual disease status. The NCCN Guidelines® recommend monitoring patients every 3 to 6 months or sooner as clinically indicated.² Weekly follow-ups may be needed for some newly diagnosed patients, after a thrombotic or other significant medical event, or after initiation of therapy such as phlebotomy or hydroxyurea. It cannot be emphasized enough that it is imperative in PV to monitor patients frequently to identify trends and recognize signs of progressive disease. A single data point does not provide enough information to assess this chronic and variable disease process.

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Symptom Burden

It's important for clinicians to appreciate the potential for burdensome disease-related symptoms to persist, worsen, or arise anew in patients with PV. This applies equally to all patients, regardless of risk level, blood count control, or presence of splenomegaly.^{11,26-28} For example, in a prospective study of symptom prevalence among 1334 patients with PV, a moderately high symptom burden was observed among patients despite treatment with hydroxyurea.²⁸ Although the total symptom scores were similar between the 3 arms—patients with known phlebotomy (PV-P), patients with palpable splenomegaly (PV-S), and patients with known hydroxyurea use (PV-HU)—patients in the PV-HU subgroup had the highest symptom scores for microvascular and cytokine-related symptoms (including fatigue, inactivity, concentration problems, night sweats, and bone pain) compared to patients in the other 2 subgroups. The highest symptom burden was seen in patients in the group with splenomegaly who were receiving phlebotomy and taking hydroxyurea (PV-HUPS). The important takeaway is that symptoms related to disease can persist despite hydroxyurea and phlebotomy use.

Probing deeper to evaluate symptoms

In my experience, symptoms are the most challenging aspect of PV for patients. During clinic visits, I start with a subjective assessment—"How are you feeling? Has anything new occurred since I last saw you?" Then I follow up with pointed questions to

obtain a detailed picture of the patient's symptom burden, asking about the specific symptoms known to be associated with PV (**Table 1**). It's helpful to ask about symptoms in the context of how they are experienced in their daily life—for example, asking questions about any changes in sleep or activities (**Table 2**). It's also important to remember that some symptoms, such as fatigue and concentration problems, might be dismissed by the patient as part of the normal process of aging.

Table 1. The 10 Most Clinically Relevant Symptoms Associated with PV¹⁰

- Fatigue
- Concentration problems
- Early satiety
- Itching
- Inactivity
- Night sweats
- Abdominal discomfort
- Bone pain
- Unintentional weight loss
- Fever

Table 2. Example Approaches to Inquiring About PV-Related Symptoms in Your Patients

- Is there anything you were able to do 3 months ago that you struggle to do now?
- Has your ability to perform normal activities throughout your day decreased?
- Do you experience sweating at night that requires you to change your clothing or sheets? How often did this happen in the past month?
- When you shower, do you ever feel itchy afterwards? How often? Are there other times that you get itchy?
- Do you ever get headaches? How often? What helps the headaches go away?
- Since our last visit, was there any event you didn't attend or enjoy as much as you would have liked to because you were too tired?
- Do you have abdominal pain or discomfort after eating? Are you eating less? Have you lost weight? How much in the past 6 months?

Another reason a thorough symptom assessment is critical is that it can serve as a foundational element of the care plan. For example, if aquagenic pruritus is a bothersome symptom for your patient, then being able to enjoy a shower without this distressing symptom may be a meaningful measure of your management approach.

Fortunately, there are excellent validated surveys available, such as the MPN-Symptom Assessment Form (MPN-SAF) and the abbreviated MPN-10, to help guide your symptom assessment and aid in identifying changes over time.^{10,29,30} The questionnaires can be provided to patients to fill out at home or upon checking in at the clinic. This helps empower patients to be their own advocates when meeting with their care team. The forms can also serve as educational tools for other clinicians on the patient's care team.

Incorporating a consistent spleen assessment

Symptoms such as early satiety and abdominal discomfort may be related to splenomegaly, which should be assessed regularly in patients with PV. Palpable splenomegaly is present in approximately one-third of patients with PV.¹⁸ Imaging may be indicated for patients with abdominal pain in the absence of palpable splenomegaly, but APPs can assess spleen size through palpation during routine follow ups. I carry a tape measure for this purpose and find that it is a straightforward and effective means of monitoring spleen status. Having the same individual be responsible for palpation of the spleen can also help standardize the process of data collection.

A Systematic Approach

Identifying and tracking indicators of advancing disease requires a systematic approach. I structure each clinic visit with a subjective assessment based on open-ended questions, and then move on to the

objective aspects of PV. After a thorough review of systems, I discuss the results of the blood test and palpate the spleen. The NCCN Guidelines provide a useful list of clinical aspects of the disease that should be monitored on a regular basis to determine whether cytoreductive therapy should be initiated or changed (Table 3).²

Table 3. Potential Indications for a Change in Cytoreductive Therapy²

- Intolerance or resistance to hydroxyurea^a or interferon
- New thrombosis or disease-related major bleeding
- Thrombocytosis
- Frequent and/or persistent need for phlebotomy, but with poor tolerance of phlebotomy
- Splenomegaly
- Leukocytosis
- Disease-related symptoms

^aResistance and intolerance defined per European LeukemiaNet.

It's also important to consider the information gathered at previous visits, as a single data point does not provide enough information to assess this chronic and heterogeneous disease. Thus, it may be useful to supplement the information in your electronic medical records or patient chart with spreadsheets, checklists, and patient flow sheets to capture historical patient data. By ensuring a comprehensive investigation of the patient's current status as well as any recent changes, APPs are uniquely positioned to assimilate information over time to inform evidence-based clinical decision-making.

A systematic approach is essential to identify and track indicators of advancing disease.

The Human Element

As an APP, I address the physical, emotional, and social aspects of care for my patients. This can include asking broad questions about the patient's lifestyle, comorbidities, and goals. Taking a holistic approach is especially important given the chronic, variable, and potentially progressive nature of PV. We cannot know exactly what the future holds, but patients often appreciate that we can prepare for it with them and their caregivers and share in successes and setbacks along the way. By its very nature PV involves uncertainty, and patients often want to know their status and the risks at each stage as the disease evolves. I make it a priority to educate patients, answer their questions, and help them focus on their life priorities.

Actively involve your patients

Patients and their caregivers are often best suited to identify any change in disease status or burden. By educating them on the common symptoms of PV and helping them identify signs of advanced PV that could lead to thrombotic events, bleeding, and disease transformation, we can empower our patients to be actively involved in their care. I want them to call me when there is a change, or even if there is something that they are uncertain about.

Coordinate with healthcare professionals within your practice

The clinical team caring for patients with PV consists of various healthcare professionals (HCPs) and other staff members who will handle a range

of responsibilities, with the composition of the team potentially differing from one institution to another. Each clinic and HCP will have a distinctive approach that is based on institutional preferences, experience, and patient demographics. What will be consistent between the smallest community clinic and the largest academic center is that a collaborative team effort is required. As APPs, we are well positioned to champion a collaborative team effort with the combination of our clinical expertise and close relationships with patients.

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Coordinate with other specialists

The medical, emotional, and social needs of patients with PV may require a wide variety of specialists, such as endocrinologists to coordinate diabetes care, neurologists to address headaches or follow-up care after a stroke, and social workers to assist patients with community resources help comprise a holistic approach for our patients. The key in any practice is to ensure that the roles of all members of the care team are clearly defined and that expectations are properly set. For example, in my practice, I prefer to take an active role in managing blood pressure because of its relationship to thrombotic risk,³¹ but for diabetes management, I coordinate closely with the patient's endocrinologist.

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Larger centers may have more resources, but smaller teams present in community clinics may have the potential to be even more effective in monitoring all aspects of care in patients with PV because of a deeper understanding of each patient's complete medical history.

Most importantly, all team members are collaborating for the same goal—to help patients with PV live the best life possible. I would encourage anyone uncertain about what is best for their patient with PV to reach out to regional experts, further expanding the team of practitioners collaborating for the good of patients with this chronic, symptomatically burdensome, and potentially progressive disease.

Key Resources

HCPs

- NCCN Guidelines for MPNs www.nccn.org
- Advanced Practitioner Society for Hematology and Oncology (APSHO) www.aphso.org
- American Society of Hematology (ASH) www.hematology.org
- Journal of the Advanced Practitioner in Oncology (JADPRO) www.advancedpractitioner.com

Patients

- MPN Research Foundation (MPNRF) www.mpnresearchfoundation.org
- Voices of MPN www.voicesofmpn.com
- Patient Power www.patientpower.info

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