To better understand the management of polycythemia vera (PV) in the community setting, Incyte conducted a survey among 91 community oncologists across the US from December 2018 to January 2019. These physicians were actively caring for patients with PV, having seen at least 5 patients over the prior 12 months. I was invited to review these data resulting from the survey, provide my thoughts on these practice patterns, and suggest approaches that could potentially improve the management of patients with PV.

Management of PV is challenging for a number of reasons. PV is rare, so most healthcare professionals (HCPs) do not encounter many patients who have the disease. Excessive myeloproliferation puts these patients at risk for thrombotic events, requiring close monitoring of blood counts. Although symptom burden may be substantial, symptoms can be vague, so their association with PV may be overlooked by patients and HCPs alike. Lastly, patients do not always look “sick,” which may result in underappreciation of the seriousness of the disease.

In this paper, we will cover the following topics related to PV:

- Risk Assessment
- Clinical Considerations
- Assessing and Monitoring Thrombotic Risk
- Identifying and Monitoring Symptoms
- What Can We Do to Improve Patient Care?

Risk Assessment

According to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms, patients with PV should be classified at diagnosis as low or high risk for thrombotic events, the most common complications and leading causes of disease-related death in PV. The NCCN Guidelines® define high-risk patients as those aged ≥60 years and/or with a history of previous thrombosis. While respondents in the community oncology survey estimated only 44% of their patients were high risk, 77% of patients enrolled in the REVEAL study—a large prospective observational study of patients during their usual care for PV—were found to be high risk. This suggests that we may have an opportunity to re-examine how we assess risk in everyday practice, so that patients may be managed appropriately.

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Clinical Considerations

The community oncology survey respondents identified reducing risk of thrombotic events and improving symptoms as key goals of treatment; I agree that these are the 2 most important considerations when managing patients with PV. The NCCN Guidelines recommend low-dose aspirin and phlebotomy to maintain hematocrit (Hct) <45% in all patients, with the addition of cytoreductive therapy, most commonly hydroxyurea (HU), in high-risk patients. However, survey respondents reported that 20% of high-risk patients were not receiving cytoreductive therapy.

Because the clinical course of PV is heterogeneous, it is crucial that patients be continually monitored for changes in disease status. This is especially important in the subset of patients whose disease is marked by Hct levels ≥45% plus either white blood cell (WBC) counts >11 x 10⁹/L or disease-related symptoms, despite phlebotomy and the maximum tolerated dose of HU. A useful list of potential indications for a change of cytoreductive therapy in patients with PV can be found in the NCCN Guidelines (Table 1).¹

Ongoing monitoring for these characteristics is an essential part of disease management. The responses in the community oncology survey indicated that practitioners are monitoring patients with PV every 1 to 3 months.

Assessing and Monitoring Thrombotic Risk

Once a management strategy has been implemented for a patient, it is important to be vigilant for the presence of thrombotic risk factors. It is encouraging to see that more than 90% of survey respondents consider the optimal Hct level to be <45%; however approximately 50% of practitioners identified a maximum Hct of 45% to 50% as acceptable (Figure 1). Our goal for our patients should be not just to manage to a Hct level of <45%, but to maintain Hct <45% at all times. Let's review some notable data related to Hct levels.

Table 1. NCCN Guidelines: Potential Indications for Change of Cytoreductive Therapy After Inadequate or Loss of Response¹

- Intolerance or resistance to HU or peginterferon alfa-2a
- 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

¹ Intolerance and resistance defined per European LeukemiaNet (ELN).

I think this is reasonable, because one has to consider the characteristics of each patient to determine the ideal follow-up interval. For example, if I have a patient whose Hct is consistently a percentage point or 2 below 45%, I will see that patient more often to make sure the Hct is not exceeding the important 45% threshold.

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In the community oncology survey, 60% of participants did not select progressive leukocytosis as a top concern in the management of patients with high-risk PV. To illustrate why this should be a concern, I would like to share some of the mounting evidence that links leukocytosis with adverse outcomes. A multivariate subanalysis of the CYTO-PV data found that there was a 4-fold increased risk of major thrombosis among patients with WBC counts >11 × 10^9/L compared to those with WBC counts <7.0 × 10^9/L. These data are consistent with other literature suggesting that leukocytosis may increase the risk of thrombosis in patients with PV. Another multivariable analysis of 258 patients with PV found that WBC count ≥11 × 10^9/L independently increased the risk of death 2.1-fold. The data from these studies support the importance of monitoring patients’ WBC counts closely, especially when elevated above 11 × 10^9/L.

Interestingly, more physicians in the survey reported elevated platelet (PLT) count as a concern in patients whose counts are not controlled with cytoreductive therapy, versus elevated WBC count. When it comes to thrombotic risk, physicians should consider prioritizing controlling WBC count—based on the lack of evidence for the role of the PLT count (studies in essential thrombocythemia actually suggest an inverse correlation between PLT counts and thrombotic risk)—and increasing evidence for the deleterious effects of leukocytosis, as described above.

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1 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.

2 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, hazard ratio [HR] >1), that became statistically significant in patients with WBC counts >11 × 10^9/L (HR, 3.90 [95% confidence interval [CI], 1.24-12.3], P = 0.02).

3 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).
It is important to recognize that blood counts and thrombotic risk are only part of the clinical picture of PV. Identifying symptom prevalence and severity is also a vital aspect of patient management. Common PV symptoms are associated with altered cytokine signaling, blood hyperviscosity, and splenomegaly; they include fatigue, difficulty concentrating, early satiety, itching, inactivity, night sweats, abdominal discomfort, bone pain, unintentional weight loss, and fever. In a prospective assessment of patients with PV, 8 of these 10 symptoms occurred in more than 50% of patients (fever and weight loss were the exceptions). Not surprisingly, symptoms have a major impact on the lives of patients with PV. In the Myeloproliferative Neoplasms (MPN) Landmark Survey, 66% of patients with PV reported that symptoms reduced their quality of life.

The identification of symptoms associated with PV can be challenging for patients and HCPs. Many of these symptoms—fatigue, headache, difficulty concentrating—can be vague, so patients do not always attribute them to their disease. In addition, HCPs may underestimate the impact of their patients’ symptoms, as reflected in the community oncology survey, where 33% of respondents believed most patients with high-risk PV are asymptomatic (Figure 3). This contradicts the findings described above that suggest the majority of patients with PV do, in fact, have symptoms.

Although a major goal of patient management is reducing Hct and WBC counts, several studies illustrate that blood counts can remain elevated in patients who are being treated with HU. The REVEAL study showed that despite receiving HU for ≥3 months, 57% of evaluable patients (n = 1106) had at least one Hct value >45% and 45% had at least one WBC count >10 x 10⁹/L. In addition, 33% of patients continued to receive phlebotomies; 82.9% of these patients requiring phlebotomies continued to report Hct values >45%. These data suggest that many patients with PV continue to have elevated blood counts despite treatment with HU and phlebotomy; this reinforces the importance of regular monitoring for disease progression. In my opinion, one should consider that the longer a patient’s blood counts are uncontrolled, the greater the chances of a thrombotic event.

Figure 3. Community Oncology Survey: Prevalence of Asymptomatic Patients
Survey respondents were asked to specify their level of agreement (scale of 1 to 7) with the following statement: most high-risk PV patients are asymptomatic.

Survey respondents were asked to specify their level of agreement (scale of 1 to 7) with the following statement: most high-risk PV patients are asymptomatic. One-third of survey respondents believe that most patients with high-risk PV do not have symptoms.

Another challenge arises from the fact that current treatments are not always effective in controlling symptoms. In a prospective evaluation of 1334 patients with PV grouped by certain disease features, the subset of patients with known HU use (n = 499) were found to have a moderately high symptom burden, reflected by a Total Symptom Score (TSS) of 29.2 (Figure 4). This suggests that PV symptoms often persist despite interventions such as HU and phlebotomy.

1REVEAL was a prospective, observational study of 2510 patients with PV in the US, sponsored by Incyte. This analysis focused on blood count control in the subset of 1381 patients who had received HU for ≥3 months.  
2This 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).  
3The 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 US with a previous diagnosis of myelofibrosis (n = 207), PV (n = 380), or essential thrombocythemia (n = 226) completed the survey.  
4This 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).
Interestingly, the REVEAL study, which evaluated the relationship between blood counts and symptom burden, showed that patients with PV continued to have a moderately high symptom burden regardless of blood count control. These data indicate that there is a need to be vigilant about evaluating both the onset of new PV-related symptoms and worsening of existing symptoms. It is essential to do this at every visit, since as noted in the NCCN Guidelines, changes in symptom status could be a sign of disease progression.1

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What Can We Do to Improve Patient Care?

The community oncology survey conducted by Incyte provided valuable insights into the management of PV in the community as well as the opportunity to discuss some strategies to improve patient care. First, patients must be placed into the correct risk category and managed accordingly. The frequency at which patients are evaluated should depend on their risk factors and severity of disease. For example, I suggest that patients who require frequent phlebotomies (3 or more per year), have persistent or progressive leukocytosis (especially above 11 × 10^9/L), or who have elevated blood counts despite receiving HU at their maximum tolerated dose be seen more often than every 3 months.

PV is a hematologic malignancy that may not be optimally controlled in a subset of patients despite treatment with a maximum tolerated dose of HU and phlebotomy. One of the most critical things we can do for our patients is proactively identify those who continue to have elevated counts, including Hct ≥45% and either WBC >11 × 10^9/L or burdensome disease-related symptoms despite treatment with a maximum tolerated dose of HU and phlebotomy. I was surprised to see that survey respondents rated frequent/persistent phlebotomy, HU and phlebotomy. I was surprised to see that survey respondents rated frequent/persistent phlebotomy, HU resistance, and progressive leukocytosis as the least concerning signs of disease progression. In my opinion, these should be considered among the most concerning, because they all indicate uncontrolled myeloproliferation that can put patients at risk of thrombosis.

Lastly, I cannot emphasize enough that PV-related symptoms are prevalent and impact your patient’s quality of life. Based on my own experience, if you ask specific, detailed questions about PV-related symptoms—such as fatigue, night sweats, or pruritus, among others—you may find that your patients are experiencing one or more these symptoms to some degree. We must always be vigilant about the course of a patient’s disease so we can tailor treatment strategies that will achieve the best possible outcomes for our patients with PV.

Best Practices for Improving Patient Care in PV

- Assess thrombotic risk category and select a management strategy accordingly
- Monitor blood counts for Hct ≥45% and WBC count >11 × 10^9/L
- Evaluate for PV-related symptoms, such as fatigue, night sweats, and pruritus

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms V1.2020. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed May 21, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their outcomes for our patients with PV.

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