PV-Related Symptoms: A Moving Target for Disease Management

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This article, sponsored by Incyte Corporation, is based on a paid interview with Robyn M. Scherber, MD, MPH, Asst. Prof. of Medicine at the University of Texas Health Science Center at San Antonio, conducted on May 29, 2018.

Symptoms may change over the course of polycythemia vera (PV) and at times may not be reduced by lowering blood cell counts.[1,2] However, consistently monitoring symptoms and therapy may help patients with PV achieve their individual quality of life (QoL) goals.

PV is a myeloproliferative neoplasm (MPN) characterized by abnormal proliferation of mature myeloid cells. It is often highly symptomatic. Proliferation is driven by constitutively active JAK-STAT signaling, primarily due to the presence of the *JAK2*V617F mutation.[3] Patients experience a unique and challenging constellation of troublesome, often debilitating symptoms (~90%), thrombotic events (up to 40%), and transformation to post-PV myelofibrosis (MF; ~10%) or acute myeloid leukemia (AML; ~3%), which are key aspects of PV.[4-7] Our understanding of the disease has evolved to encompass its effects on the entire patient, from blood counts – erythrocytes, leukocytes, and platelets – to a wide range of symptoms and their effect on QoL goals. Given the prevalence of symptoms and the burden they impose on patients, symptom alleviation is a major objective in the evaluation of patients with PV and is frequently included as a clinical trial end point.[8,9]

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Though PV is chronic, symptoms can be dynamic, changing throughout the course of the disease. They can be present or emerge in all patient subgroups, including those who are low-risk or who have well-controlled blood counts and lack splenomegaly.[1,2,6,10] The occurrence of a new event such as thrombosis or diabetes diagnosis may also impact symptoms. Furthermore, treatments themselves can reduce symptoms or side effects from treatment may exacerbate symptoms. Even the way each symptom changes is variable, with many MPN symptoms progressing linearly over time while others tend to stabilize. Fatigue, concentration difficulties, insomnia, sexual concerns, cough, night sweats, pruritus, and QoL all appear to worsen over time, while early satiety, concentration difficulties, insomnia, sexual difficulties, cough, and night sweats all become more prevalent.[11] Abdominal pain/discomfort, inactivity, headaches, dizziness, numbness, sad mood, bone pain, fevers, and weight loss all appear to plateau and remain stable throughout the course of PV.[9] Given their dynamic nature and potential to reveal aspects of the underlying biology, it is essential to monitor symptoms when PV is diagnosed and periodically as the disease is being managed. Any change in medication or related clinical event also warrants administration of a symptom survey in order to interpret how that change has impacted the patient's disease.

Symptom burden is high in MPNs such as PV, MF, or essential thrombocythemia, similar to that seen in AML, non-Hodgkin lymphoma, or metastatic cancer.[9,12] Patients with PV may have the worst impairment of QoL among patients with newly diagnosed MPNs and typically survive for many years.[5,13] Thus they may receive less attention compared with patients with more rapidly progressing neoplasms such as leukemias or lymphomas. This may result in a substantial delay before the higher-risk features of PV are recognized, let alone addressed. As compared with more rapidly progressing cancers, the life of the patient with PV may be longer, but the symptom burden would likewise be extended. The signs of progression in PV can be subtle; symptom monitoring can help with recognizing the transition.[11] It is important

to quickly recognize post-PV MF, assess the patient's risk, and manage them appropriately. At our clinic we often see patients who are referred past the point where the only curative option, stem cell transplantation, is still available. If these patients had been referred earlier, before the development of very advanced disease features such as fibrosis, therapy with curative intent might have been possible.

Tracking Symptoms in PV

Surrogates of disease burden such as risk scores or even blood counts often fail to correlate with symptomatic burden, but validated Patient Reported Outcome (PRO) tools may permit objective and rapid assessment of the symptom burden in PV patients that provide insight into the underlying biology of the disease.[9,14] Early PRO assessments to quantify MPN symptom burden were not specific to myeloproliferative disease, which limited their efficacy. This is why we developed the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) and the more concise MPN-SAF Total Symptom Score (MPN-SAF TSS), commonly known as the MPN-10, to assess the unique spectrum of symptomatology seen in patients with MPNs.[8,12,15] In these surveys, patients score their symptoms on a scale from 0 (absent) to 10 (worst imaginable).

> *The MPN-10 is designed to assess the unique spectrum of symptomatology seen in patients with MPNs.[15]*

Visit mpnconnect.com/mpn-resources.aspx for the MPN-10 form and additional resources

The patient-friendly MPN-10 includes the most representative and pertinent MPN-related symptoms – fatigue, vascular symptoms, constitutional symptoms, and spleen-related symptoms – whereas the MPN-SAF includes 27 questions that more thoroughly address fatigue along with psychiatric symptoms such as depression and the overall QoL for the patient.[8,12,15] The importance of recognizing symptoms in MPNs and the value of surveys to quantify PROs was substantiated by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms incorporating symptom burden assessment as part of routine evaluation of patients with PV in 2017.[16]

When treating patients at our clinic, we provide the MPN-10 to them during the check-in process. This allows physicians to quickly identify any worsening symptoms to focus on during the examination. The MPN-10 opens a discussion between patient and healthcare professional that may add valuable clinical information on how the patient is really doing managing their disease. Patients are also sometimes asked to fill out the survey daily for one week to provide an average that will reduce the impact of any short-term symptom changes that may be unrelated to PV. I document the MPN-10 sum score into the patient's chart and refer back to it at future visits. By providing an objective, quantitative PRO, collecting data through these surveys facilitates management decisions. For example, when the TSS, the sum of all 10 individual scores, reaches 20 or greater or any individual score is more than 5, an update to the management approach might be warranted. Nearly two-thirds of patients experience symptoms that fit these criteria.[17]

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Evaluating Symptom Burden to Assess the Patient's Condition

With the information from the MPN-10, we then thoroughly examine the patients for disease signs such as splenomegaly, requesting confirmation by ultrasound if suspected, and ask probing questions to gain a deeper understanding of symptom burden. Physicians frequently underestimate the symptom burden of their patients with PV. While nearly 90% of patients report symptoms at diagnosis, physicians estimate that only 60% of patients present with symptoms.[18] This is likely due to the nature of symptoms in PV. Extreme fatigue can be clearly identified in the patient's demeanor, but many other subtle or less obvious symptoms are not evident using the "eye test." Bone, abdominal, and muscle complaints are also frequently described as discomfort by my patients, meaning questions specifically about "pain" may lead to answers that understate the symptoms present along with their severity.

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Some of the key symptoms I look for closely during my time with a patient are fatigue, abdominal discomfort, early satiety, headaches, bone pain, pruritus, and depression. Older individuals may not report these symptoms, regarding them as a natural sign of aging, or patients may have grown accustomed to the symptoms as they gradually emerged during the long course of PV. The erroneous acceptance of this new, symptomatic "normal" can be corrected by educating patients about PV. Engaging caregivers at home along with connecting patients to the wider MPN community, both locally and online, are excellent ways to provide patients with education and resources to help them better understand PV and its symptoms. Interacting with others can show patients that their symptoms are common and important to address, but unfortunately, I meet a fair number of patients who are never able to connect with other MPN patients.

A thorough assessment of patient functioning is particularly important given the long natural history of PV. I tell patients with

PV to track their symptoms and explain that these symptoms can change over the course of the disease. I especially want to track their symptoms on therapy. This is because I know that while symptom burden may initially improve with therapy, it may rebound and then worsen with time. A good example of this is a newly diagnosed PV patient who may initially feel better with phlebotomy, but as iron deficiency develops the patient may feel increasingly fatigued with worsened cognitive ability. At our clinic we have noted that serial assessment of symptom burden using PRO tools allows for direct assessment of the patient experience and has been proven in clinical trial settings to be a sensitive clinical indicator of disease progression.[9,15] Recognizing a worsening symptom burden can provide HCPs with a deeper understanding of their patient's disease.

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Incorporating Symptoms Into the Clinical Assessment Routine

Developing a routine can facilitate tracking symptoms in PV. As physicians, even if we do a thorough job when asking PV patients about what symptoms they are experiencing, we may easily miss the severity of the symptoms — especially in patients who have a large number of different symptoms. Reduced QoL can come as a result of both the severity and the multitude of symptoms.[19] In addition, many patients do not recognize common symptoms as MPN-related. For example, in a recent survey 64% of patients with PV did not believe that difficulty sleeping resulted from their disease, and thus would not have mentioned it unless prompted by the MPN-10.[18]

Tracking Symptoms in the Clinic

1. **Recognize symptoms.**
   It is important for physicians to be aware that symptoms may change during the course of PV.
2. **At every visit, administer the MPN-10 and ask patients to report symptoms.**
   Symptoms vary over the course of the disease.
3. **Monitor symptoms over time to identify trends that indicate worsening disease.**
   Our clinic advises obtaining a baseline assessment of symptoms, and monitoring symptom burden over time, and as disease-related events occur.

> *Reduced QoL can result from both the severity and the multitude of symptoms. In addition, many patients do not recognize common symptoms as MPN-related.[18,19]*

Providing individualized care – which encompasses PV disease-related factors, any comorbidities, and the patient's personal health and wellness goals – is the ultimate goal when I treat patients with PV. Particularly for referrals, their treatment history is vital to prevent placing them back on a therapy that is ineffective or to which they are intolerant. Prior thrombotic events and the presence of additional cardiovascular risk factors indicate the need to actively monitor their disease. Alternatively, a retired 75-year-old patient may have different goals than a self-employed 55-year-old patient. The continuum of disease and patient characteristics combined with the chronic nature of PV emphasizes the need to frequently monitor and track therapy, disease signs, and symptoms. Overall, this can be thought of as reading the patient's diary of disease to get a complete picture of the impact of PV on both their underlying biology and their lifestyle goals. Understanding this combination of factors can help guide treatment decisions. Patients with PV can live for many years with a severe symptom burden, and trying to optimize QoL is paramount.

> *The continuum of disease and patient characteristics combined with the chronic nature of PV emphasizes the need to frequently monitor and actively manage disease signs and symptoms.*

Symptoms may change over the course of PV, complicating management for the physician and increasing suffering for the patient. Monitor symptom burden at each visit. Most importantly, use this information to help individual patients achieve their life goals within the confines of this often intractable, chronic cancer.

MPN CONNECT

Access video clips featuring Dr Scherber at ProgressiveSymptomsinPV.com.

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