Leukocytosis and the Threat of Thrombosis in PV

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The classic myeloproliferative neoplasms (MPNs) include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF). These distinct clonal disorders of multipotent hematopoietic progenitor cells have common pathobiologic characteristics.[1] PV is the most prevalent Philadelphia chromosome-negative MPN,[2] with *JAK2*V617F or *JAK2* exon 12 mutations being present in nearly all patients.[1,3] PV is chronic,[4] with variable presentation and progression of the clinical characteristics of disease. Fatal cardiovascular events are a major concern in PV.[1,5] In one study of over 1500 patients with PV, roughly one-fifth of patients had a thrombotic event before or at diagnosis.[5] Cardiovascular events are attributed to both red and white blood cells (WBCs), with either elevated hematocrit (Hct) or WBC counts increasing the risk of thrombosis approximately 4-fold.[6,7] Thromboses in MPNs affect both the arterial and the venous vascular beds and may result in stroke or transient ischemic attacks, myocardial infarction, deep vein thrombosis, and pulmonary embolism.[8] In addition to leukocytosis and erythrocytosis, other features of PV include splenomegaly, bleeding, microcirculatory symptoms, and pruritus. Patients with PV also run the risk of transformation to myelofibrosis (MF) (ie, post-PV MF) or acute myeloid leukemia.[9]

Considering Multiple Cell Types in POLYcythemia Vera

Erythrocytosis has long been considered to be the hallmark of PV. It is less broadly appreciated that an associated increase in circulating leukocytes and/or platelets occurs in over half of patients.[5,10] Leukocytosis is a common marker of aggressive disease biology in MPNs,[11] and is an indicator of advanced disease in PV.[12] Over the past decade, several studies in PV have indicated that leukocytosis is associated with vascular complications and adverse outcomes.[5-7,13-22] These findings firmly place leukocytes alongside red blood cells in terms of their contribution to thrombotic risk in patients with PV. Thrombosis is primarily associated with hyperviscosity from an overproduction of red blood cells, but secondarily to the overabundance of white cells, as described below. Molecular and clinical studies into disease pathology have advanced our understanding of PV to the point that overall myeloproliferation is increasingly recognized as the true target of therapy in PV, rather than single cell lines.[23] That said, the preponderance of available data from clinical studies support erythrocytosis and leukocytosis, but not thrombocytosis, as the key risk factors for thrombosis in PV.

Maintaining strict Hct control is a key therapeutic goal in PV.[24] The Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) study serves as the foundation of our clinical understanding regarding the importance of controlling Hct to a specific target in PV.[6] It demonstrated that patients with a Hct target below 45% had better outcomes, with approximately 4-fold fewer cardiovascular events and cardiovascular-related deaths, than patients with a Hct target

> *Leukocyte burden is more likely a direct causative factor in vascular complications than simply a marker of poor prognosis.*[20]

between 45% and 50%. While clinically invaluable, these definitive findings led many hematologists and oncologists to overlook the complete patient, addressing only the Hct rather than considering the blood cell counts and symptoms in totality. It's also important to be mindful of the other signs and symptoms associated with PV, including splenomegaly, leukocytosis, and symptom burden.[12] Consequently, examining and talking with patients with PV are as essential as assessing the Hct during management of PV.

Identifying Progressive Leukocytosis

While the prospective CYTO-PV trial established that <45% should be the Hct goal for therapy,[6] no prospective trial has been conducted to assess the impact of WBC counts on thrombotic risk in PV. Nevertheless, the evidence from several retrospective analyses strongly suggest an association between leukocytosis and thrombosis in PV, particularly at the time of the thrombotic event.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for MPNs in the United States recognize age and history of thrombosis as the only 2 classical risk factors to guide the decision whether to implement cytoreductive therapy.[25] Along with other disease factors, leukocytosis is currently a factor indicating whether to implement cytoreductive therapy in otherwise low-risk PV patients or to change cytoreductive therapy in high-risk patients. In this setting, progressive leukocytosis is a sign of lack of proper blood cell count control. Given the absence of a prospective study, it is therefore important for experts to

> *Future clinical practice guidelines should expand on the definition of progressive leukocytosis as an indicator of high-risk PV.*

come together and form a consensus in order to educate clinicians about the considerable evidence from retrospective studies, which in our experience has greatly helped our own patients.[26] Clinical practice guidelines should clarify the definition of progressive leukocytosis.[27] Data from retrospective analyses are accumulating, and some community physicians have begun incorporating the management of leukocytosis into their treatment of PV. This is only the beginning for individualized treatment in PV. To standardize clinical practice, it would benefit both clinicians and patients to clearly define progressive leukocytosis and establish a threshold for leukocytosis, similar to what was established for Hct by the CYTO-PV study.

Several retrospective analyses over the past decade examining various stages of disease demonstrated that elevated WBC counts in the range of approximately 10×10^9/L to 15×10^9/L increase the patient's thrombotic risk.[5-7,13-18,20-22] For instance, follow-up analyses of the European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) study that established the importance of low-dose aspirin in treating patients with low-risk PV identified a WBC count threshold of 15×10^9/L while a similar follow-up analysis to the CYTO-PV study found that a cutoff of 11×10^9/L was the level at which the risk of thrombosis became statistically significant.[8,14] Furthermore, a large retrospective study in PV (N = 1545) found that WBC counts >10.5×10^9/L were a predictor of decreased overall survival while WBC counts >15×10^9/L were associated with shorter leukemia-free survival.[5] In our practice, elevated WBCs and/or progressive leukocytosis serve as indications for the initiation of cytoreductive therapy or a change in cytoreductive therapy to effectively manage the patient's thrombotic risk.

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With leukocytosis, it's important to look at the absolute value and to follow the trend in leukocyte counts over time. If the value is increasing over time, cytoreductive therapy should be initiated if it is not already in place. For instance, if the patient's leukocyte count starts at 12×10^9/L and remains there, that is different than going from 12 to 15 to 18 billion cells per liter in a year's time. Frequent monitoring and tracking of the complete blood counts and other aspects of PV, including splenomegaly, symptoms, and history of thrombosis, is thus essential to ensure that advanced disease is detected early and the management strategy updated accordingly.

JAK-STAT Signaling Increases Cellular Counts and Activation

Many MPN-specific factors that promote thrombosis have been identified.[19,22] The evidence now indicates the same JAK2 mutations that drive the overproduction of erythrocytes, leukocytes, and platelets in PV also promote direct activation of leukocytes and platelets. Activated platelets and leukocytes bind to each other and activate endothelial cells, which may contribute to the prothrombotic state.[19,28]

Practice Points for PV Management: Avoiding Autopilot to Provide Individualized Care

Upon identifying the clinical characteristics of advanced disease that may increase the risk of thrombosis, such as leukocytosis and elevated Hct, an adjustment to the management strategy may be warranted. For low-risk patients on low-dose aspirin and phlebotomies, cytoreductive therapy – most commonly hydroxyurea (HU) – may be required. HU can be effective in many patients for several years, but progressive counts or symptoms in a subset of patients may be an indication that those patients have reached an advanced stage of PV and that HU is no longer able to control their disease.[29] Furthermore, others will display intolerance to HU, most commonly in the form of leg ulcers.[30] We don't yet know what aspects of the underlying biology determine whether cytoreductive therapy will control PV. The variable presentation of advanced disease, for example, leukocytosis only in some patients and splenomegaly with burdensome symptoms in others, is poorly understood. Furthermore, the risk factors for thrombosis — elevated Hct, leukocytosis, age, and history of thrombotic events — evolve over time, and though less frequently, thrombotic events do occur in low-risk patients.[29-31] This complexity contributes to the difficulty of managing these patients.

Conventional high-risk PV
Advanced age (>60 years) Previous thrombotic event
Assessing the complete individual
Hct WBCs Platelets Spleen size PV-related symptoms Impact of PV on daily routine Comorbidities

PV, polycythemia vera; Hct, hematocrit; WBC, white blood cell

Because intolerance to or lack of control by cytoreductive therapy may occur soon after the start of treatment or following several years of effective disease management, regular follow-up that closely monitors and tracks the clinical signs of PV is a fundamental aspect of care. Furthermore, it's essential that patients and their healthcare providers assign thrombotic events and symptoms to PV where appropriate.

The key to understanding the pathology of PV is realizing that, ultimately, thrombosis is the most serious problem. Thrombotic complications occur in approximately one-third of patients with PV,[4-6,19,31,32] and cardiovascular-related events represent one of the most common causes of death in PV.[4,5,19,31,32] Reducing this excess mortality requires looking beyond the age or history of thrombosis to new indicators such as leukocytosis. Careful evaluation of the patient throughout the course of disease, rather than considering only Hct control, may help to improve outcomes.

> *"Elevated red or white cell counts may warrant a change in cytoreductive therapy. The difference is that a cutoff for hematocrit has been established at 45%, while the white cells have to be evaluated both as their absolute number as well as their change over time."*

Furthermore, education when dealing with rare cancers such as PV is also important. Whenever possible, educate other healthcare providers such as physician assistants and nurses, as they often oversee the care of patients with PV. Unfortunately, in many settings physicians are more involved with their other patients whose cancer poses a more immediate risk to their survival leading to less thorough examination of patients with PV during their follow-up visits. This reinforces the importance of patient education to enable them to be their own advocates in tracking the efficacy of their disease management strategy.

> *"Many times I see that management of the patient with PV is put on autopilot. And that needs to be changed."*

Finally, the most important factor in the management of PV is to appreciate each patient as an individual, not just an amalgamation of cells. For instance, while risk stratification is valuable for determining an appropriate treatment strategy at diagnosis, monitoring whether the therapy is controlling the disease is essential for optimal management throughout the long course. We encourage healthcare providers to look for additional factors that may help them better assess the individual patient. We talk to the patient, ask about quality of life and symptoms, and examine the patient for splenomegaly, looking at, but also beyond, the total blood cell count before we make treatment decisions. More predictive and prognostic factors are in development, but judicious use of the ones we have available may provide the best possible outcomes for our patients with PV.

MPN CONNECT

Access video clips featuring Dr Verstovsek at ProgressiveLeukocytosis.com.

References:

1. Vainchenker W, Kralovics R. *Blood.* 2017;129(6):667-679.
2. Rumi E, Cazzola M. *Blood.* 2017;129(6):680-692.
3. Verstovsek S. *Hematology Am Soc Hematol Educ Program.* 2009;636-642.
4. Passamonti F, Rumi E, Pungolino E, et al. *Am J Med.* 2004;117(10):755-761.
5. Tefferi A, Rumi E, Finazzi G, et al. *Leukemia.* 2013;27(9):1874-1881.
6. Marchioli R, Finazzi G, Specchia G, et al. *N Engl J Med.* 2013;368(1):22-33.
7. Barbui T, Masciulli A, Marfisi MR, et al. *Blood.* 2015;126(4):560-561.
8. Falanga A, Marchetti M. *Hematology Am Soc Hematol Educ Program.* 2012;2012:571-581.
9. Tefferi A, Vannucchi AM, Barbui T. *Blood Cancer J.* 2018;8(1):3.
10. Parasuraman S, DiBonaventura M, Reith K, Naim A, Concialdi K, Sarlis NJ. *Exp Hematol Oncol.* 2016;5:3.
11. Mangaonkar AA, Hoversten KP, Gangat N. *Expert Rev Hematol.* 2018;11(3):247-252.
12. Vannucchi AM. *Haematologica.* 2017;102(1):18-29.
13. Gangat N, Strand J, Li CY, Wu W, Pardanani A, Tefferi A. *Br J Haematol.* 2007;138(3):354-358.
14. Landolfi R, Di Gennaro L, Barbui T, et al. *Blood.* 2007;109(6):2446-2452.
15. Caramazza D, Caracciolo C, Barone R, et al. *Ann Hematol.* 2009;88(10):967-971.
16. De Stefano VD, Za T, Rossi E, et al. *Am J Hematol.* 2010;85(2):97-100.
17. Barbui T, Masciulli A, Marfisi MR, et al. *Blood.* 2013;122(13):2176-2184.
18. Bonicelli G, Abdulkarim K, Mounier M, et al. *Br J Haematol.* 2013;160(2):251-254.
19. Kroll MH, Michealis LC, Verstovsek S. *Blood Rev.* 2015;29(4):215-221.
20. Lim Y, Lee JO, Kim SH, et al. *Thromb Res.* 2015;135(5):846-851.
21. Cerquozzi S, Barraco D, Lasho TL, et al. *Blood Cancer J.* 2017;7(12):662.
22. Meyer SC, Steinmann E, Lehmann T, et al. *Biomed Res Int.* 2017;2017:9876819.
23. Barosi G, Mesa R, Finazzi G, et al. *Blood.* 2013;121(23):4778-4781.
24. Stein BL, Oh ST, Berenzon D, et al. *J Clin Oncol.* 2015;33(33):3953-3960.
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26. Bose P, Gotlib J, Harrison CN, Verstovsek S. *Clin Lymphoma Myeloma Leuk.* 2018;18(1):1-12.
27. Verstovsek S, Komrokji RS. *Expert Rev Hematol.* 2015;8(1):101-113.
28. Geyer HL, Dueck AC, Scherber RM, Mesa RA. *Mediators Inflamm.* 2015;2015:284706.
29. Nazha A, Khoury JD, Verstovsek S, Daver N. *Crit Rev Oncol Hematol.* 2016;105:112-117.
30. Barosi G, Birgegard G, Finazzi G, et al. *Br J Haematol.* 2010;148(6):961-963.
31. Marchioli R, Finazzi G, Landolfi R, et al. *J Clin Oncol.* 2005;23(10):2224-2232.
32. Parasuraman SV, Shi N, Paranagama DC, Bonafede M. *Manag Care Spec Pharm.* 2018;24(1):47-55.