Putting Knowledge Into Practice:

Self-guided learning in polycythemia vera and myelofibrosis for advanced practice providers

Recognizing and Monitoring Thrombotic Risk in Polycythemia Vera

Incyte

Overview

The Putting Knowledge Into Practice self-guided learning modules have been developed specifically for advanced practice providers (APPs) to help provide education and resources to help manage patients with polycythemia vera (PV) and myelofibrosis (MF).

Recognizing and Monitoring Thrombotic Risk in Polycythemia Vera provides information on recognizing and monitoring thrombotic risk in patients with PV.

Topics include:

- Causes and implications of thrombosis
- Factors that can increase the risk of thrombotic events in patients
- Importance of regular, ongoing monitoring of hematocrit and white blood cell counts

How to Use This Module

This is a self-guided learning module that gives you the flexibility to

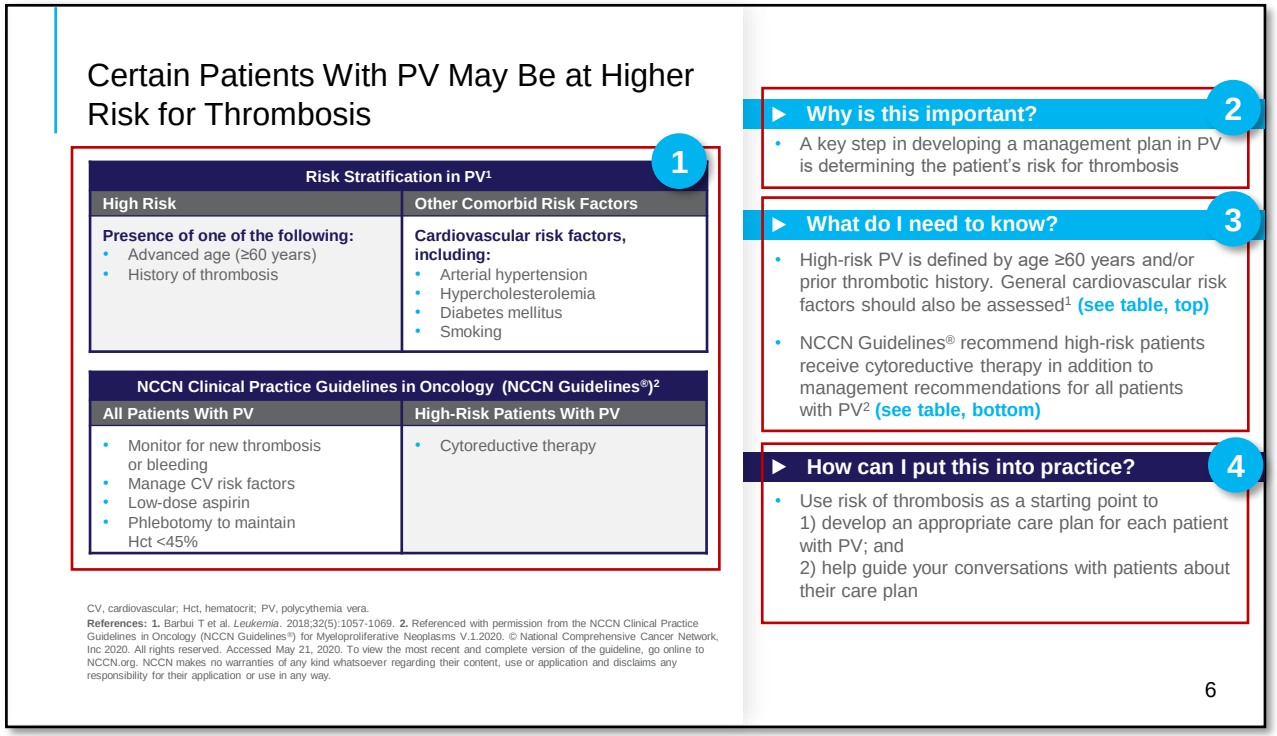
- Proceed through the topic at your own pace
- Return to important points for clarity or reinforcement

Each slide in the module is designed to

- Explain a specific point
- Make the information relevant to your practice

Links to additional resources for APPs can be found at the end of this presentation.

▶ Each slide has 4 sections:



Certain Patients With PV May Be at Higher Risk for Thrombosis

1

Risk Stratification in PV[1]	
High Risk	**Other Comorbid Risk Factors**
Presence of one of the following: • Advanced age (≥60 years) • History of thrombosis	**Cardiovascular risk factors, including:** • Arterial hypertension • Hypercholesterolemia • Diabetes mellitus • Smoking

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[2]	
All Patients With PV	**High-Risk Patients With PV**
• Monitor for new thrombosis or bleeding • Manage CV risk factors • Low-dose aspirin • Phlebotomy to maintain Hct <45%	• Cytoreductive therapy

CV, cardiovascular; Hct, hematocrit; PV, polycythemia vera.

References: 1. Barbui T et al. *Leukemia*. 2018;32(5):1057-1069. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms V.1.2020. © National Comprehensive Cancer Network, Inc 2020. 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 application or use in any way.

2 ▶ Why is this important?

- A key step in developing a management plan in PV is determining the patient's risk for thrombosis

3 ▶ What do I need to know?

- High-risk PV is defined by age ≥60 years and/or prior thrombotic history. General cardiovascular risk factors should also be assessed[1] **(see table, top)**
- NCCN Guidelines® recommend high-risk patients receive cytoreductive therapy in addition to management recommendations for all patients with PV[2] **(see table, bottom)**

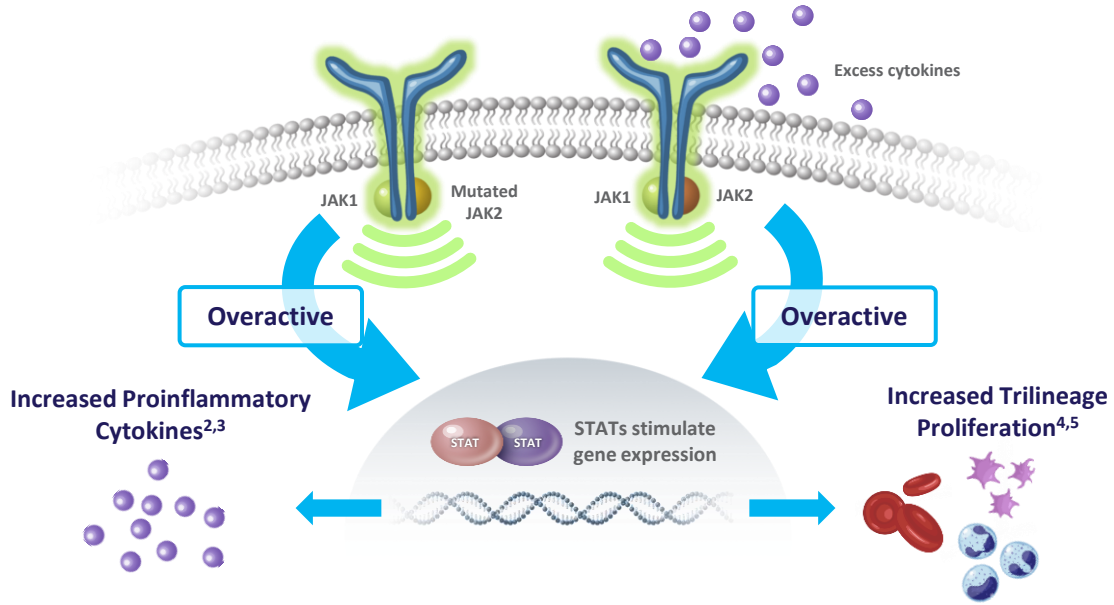
4 ▶ How can I put this into practice?

- Use risk of thrombosis as a starting point to
  1) develop an appropriate care plan for each patient with PV; and
  2) help guide your conversations with patients about their care plan

6

1. Provides key data and contextual information
2. Summarizes the key learning point
3. Expands on the key learning point
4. Reviews ways to implement in practice

Inflammation and Blood Cell Overproliferation Are Features of PV Pathophysiology[1-3]



Inflammation and procoagulation state contribute to THROMBOTIC RISK[5,6]

JAK1 plays an important role in signaling of key proinflammatory cytokines[2]

JAK2 mediates signals for hematopoietic growth factors (eg, EPO, TPO, G-CSF)[2]

EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TPO, thrombopoietin.

References: 1. Quintás-Cardama A et al. *Nature Rev*. 2011;10:127-140. **2.** Quintás-Cardama A et al. *Blood*. 2010;115(15):3109-3117. **3.** Vainchenker W et al. *Blood*. 2017;129(6):667-679. **4.** Arber DA et al. *Blood*. 2016;127(20):2391-2405. **5.** Verstovsek S et al. *Expert Rev Hematol*. 2015;8(1):101-113. **6.** Kroll MH et al. *Blood Rev*. 2015;29(4):215-221.

▶ Why is this important?

- Dysregulated cellular pathway signaling can contribute to the clinical manifestations of PV and thrombotic risk[5]

▶ What do I need to know?

- Overactive JAK/STAT pathway signaling may result in elevated blood cell counts, including hematocrit (erythrocytosis), white blood cells (leukocytosis), and platelets (thrombocytosis)[5,6] **(see figure)**
- This increased blood cell proliferation, along with increased proinflammatory cytokine activity, can contribute to increased risk of thrombosis in some patients[5,6]

▶ How can I put this into practice?

- Educating patients on their disease can help them better understand how PV may put them at risk for morbidities such as myocardial infarction or deep vein thrombosis

Thrombosis Is Associated With Morbidity and Mortality in Patients With PV[1]

Associated Morbidities[1]

Arterial Thrombosis	Venous Thrombosis	Microcirculatory Disturbances
• Myocardial infarction • Unstable angina • Ischemic stroke • Transient ischemic attack • Acute peripheral and visceral thromboembolism	• Deep venous thrombosis (legs and arms) • Pulmonary embolism • Unusual sites of venous thrombosis (visceral vein thrombosis and cerebral sinus and venous thrombosis) • Superficial venous thrombosis	• Erythromelalgia • Seizures • Migraine • Vertigo • Tinnitus • Scintillating scotomas • Amaurosis fugax

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PV, polycythemia vera.

[a] Cause of death was examined in a large, retrospective, international study of 1545 patients with PV; 347 (23%) had died by the time of analysis, of which 164 had a known cause of death.

References: 1. Falanga A et al. *Hematology Am Soc Hematol Educ Program*. 2012;2012:571-581. **2.** Tefferi A et al. *Leukemia*. 2013;27(9):1874-1881. **3.** Passamonti F et al. *Am J Med*. 2004;117(10):755-761. **4**. Parasuraman SV et al. *Manag Care Spec Pharm*. 2018;24(1):47-55. **5.** Kroll MH et al. *Blood Rev*. 2015;29(4):215-221.

▶ Why is this important?

- Thrombotic events represent one of the most common causes of death in PV[2-5]

▶ What do I need to know?

- Patients with PV may be at risk for both arterial and venous thrombotic events. Microcirculatory disturbances also are associated with the disease[1] **(see table)**
- A retrospective, international study of patients with PV found that 20% of patients with a known cause of death (n=164) died due to thrombotic complications[2a]
  - Other causes of death in the study included acute leukemia (22%), second malignancy (22%), heart failure (8%), and non-leukemic progression (7%)[2a]

▶ How can I put this into practice?

- Be sure patients understand the potentially serious morbidities associated with PV to help improve awareness about their disease and encourage communication with their healthcare team

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Risk Stratification in PV[1]	
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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[2]	
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CV, cardiovascular; Hct, hematocrit; PV, polycythemia vera.

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▶ Why is this important?

- A key step in developing a management plan in PV is determining the patient's risk for thrombosis

▶ What do I need to know?

- High-risk PV is defined by age ≥60 years and/or prior thrombotic history. General cardiovascular risk factors should also be assessed[1] **(see table, top)**
- NCCN Guidelines® recommend that high-risk patients receive cytoreductive therapy, in addition to management recommendations for all patients with PV[2] **(see table, bottom)**

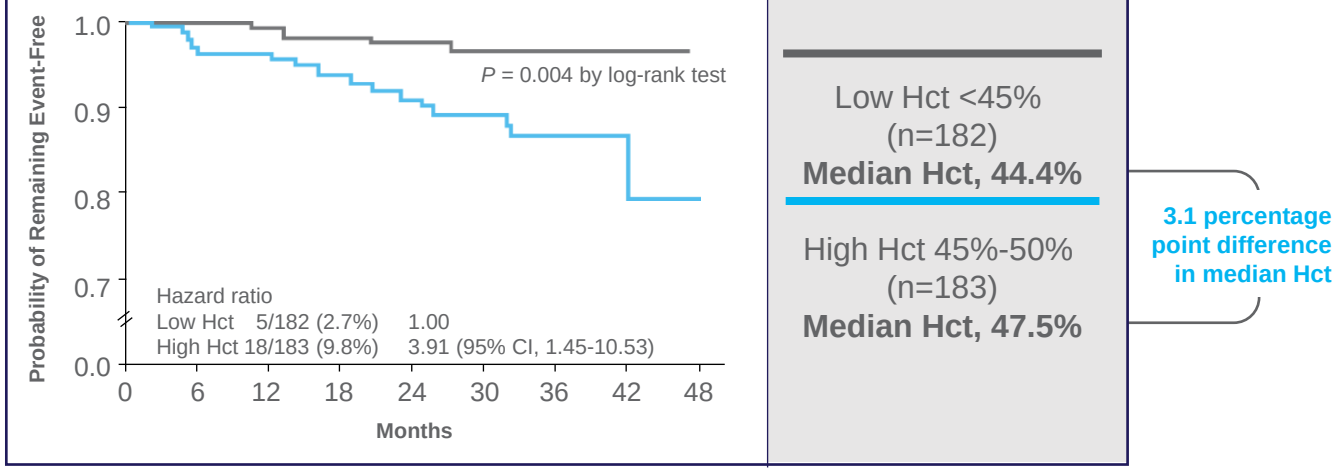
▶ How can I put this into practice?

- Use risk of thrombosis as a starting point to
  1) develop an appropriate care plan for each patient with PV; and
  2) help guide your conversations with patients about their care plan

CYTO-PV Study

Elevated Hct Between 45% and 50% May Contribute to Increased Risk of CV Death and Major Thrombosis

Probability of Remaining Event-Free in the CYTO-PV Study (N = 365)



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.

CI, confidence interval; CV, cardiovascular; CYTO-PV, Cytoreductive Therapy in Polycythemia Vera; Hct, hematocrit; PV, polycythemia vera.

In the Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) study of 365 adult patients with PV treated with phlebotomy, hydroxyurea, or both, patients were randomized to 1 of 2 groups—either the low-hematocrit group (n = 182; with more intensive therapy to maintain a target hematocrit level <45%) or the high-hematocrit group (n = 183; with less intensive therapy to maintain a target hematocrit 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. 67.1% of patients (n = 245) were at high risk because of age ≥65 years or previous thrombosis. The composite primary end point was the time until cardiovascular death or major thrombosis.

Reference: Marchioli R et al. *N Engl J Med.* 2013;368(1):22-33.

▶ Why is this important?

- Hct <45% is an important threshold as even modest elevations above that can increase thrombotic risk in patients with PV

▶ What do I need to know?

- The Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) study found that managing Hct levels between 45% and 50% significantly increased the risk of CV death and major thrombosis compared with Hct levels managed <45% (hazard ratio, 3.91; 95% CI, 1.45 to 10.53; *P* = 0.004) **(see figure)**
- Median Hct was 47.5% in the study cohort managed to Hct 45% to 50%, compared with median Hct 44.4% in the cohort managed to Hct <45%
  - Evidence from the CYTO-PV study showed a 4-fold higher risk of cardiovascular death and major thrombosis when Hct was elevated to between 45% and 50%

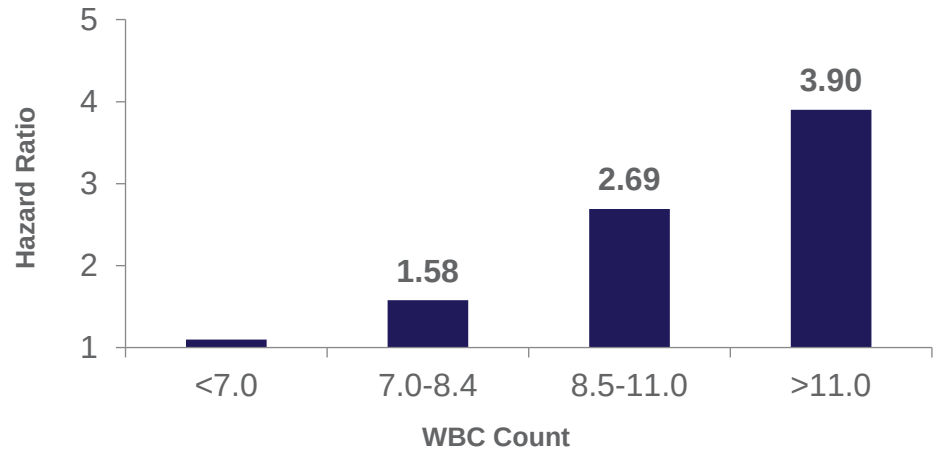
▶ How can I put this into practice?

- Diligent management of Hct to below 45% is a critical component of PV management and can provide context when discussing care plans with patients and why certain interventions are being recommended for them

CYTO-PV Study

Elevated WBC Counts >11 × 10^9/L May Also Increase Thrombotic Risk

Time-Dependent Multivariable Analysis on the Risk of Major Thrombosis in the CYTO-PV study (N = 365)[1a]



Events/Patients (%)	4/100 (4.0)	4/84 (4.8)	8/88 (9.1)	12/93 (12.9)
95% CI		0.39-6.43	0.80-9.05	1.24-12.3
P value		0.52	0.11	0.02

CI, confidence interval; CV, cardiovascular; CYTO-PV, cytoreductive therapy in polycythemia vera; Hct, hematocrit; HR, hazard ratio; PV, polycythemia vera; WBC, white blood cell.

[a] Adjusted for age, gender, CV risk factors, previous thrombosis, and Hct levels.

References: 1. Barbui T et al. *Blood*. 2015;126(4):560-561. **2.** Gangat N et al. *Br J Haematol*. 2007;138(3):354-358. **3.** Landolfi R et al. *Blood*. 2007;109(6):2446-2452.

▶ Why is this important?

- Leukocytosis may contribute to increased risk of thrombosis in patients with PV[2,3]

▶ What do I need to know?

- An additional multivariable time-dependent analysis from the CYTO-PV study found that WBC count >11 × 10^9/L was associated with increased risk of thrombosis (HR, 3.9; 95% CI, 1.24-12.3; *P* = 0.02)[1] **(see figure)**
- In this analysis, 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[1]
- These results are consistent with other literature that suggests leukocytosis may increase the risk of thrombosis[2,3]

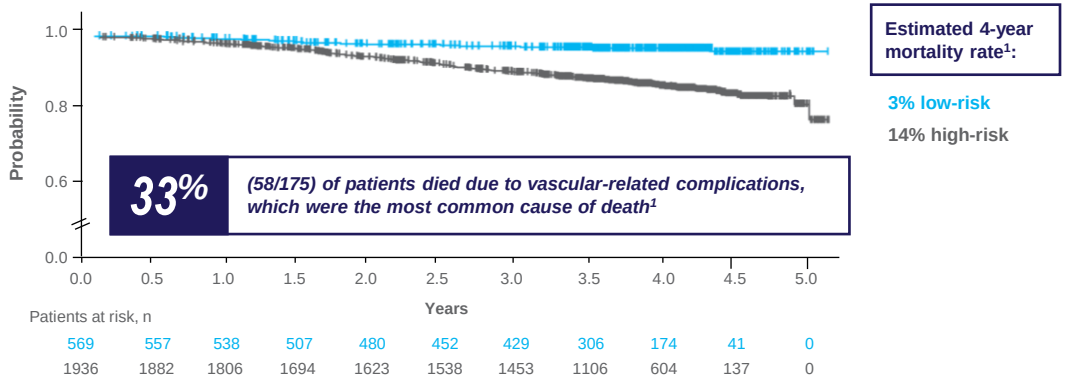
▶ How can I put this into practice?

- Help your patients understand that WBC counts are an important facet of their disease and should be managed to appropriate levels

In the prospective, observational REVEAL study

The Estimated 4-Year Mortality Rate Was 14% in Patients With High-Risk PV[1a]

Overall Survival by Risk Category at Enrollment in the REVEAL Study[1b]



In the 6 months before death[1]:

110/190 of patients had ≥1 **elevated WBC** count >11 x 10^9/L[c]

59/190 of patients had ≥1 **elevated Hct** level >45%

Hct, hematocrit; HU, hydroxyurea; PV, polycythemia vera; WBC, white blood cell.

[a] 77% of patients (1940/2510) were classified as high risk at enrollment based on age ≥60 years and/or history of thrombotic events.[2]

[b] REVEAL was a prospective, observational study of 2510 adult patients with PV in the United States, sponsored by Incyte. Patients were enrolled over an approximate 2-year period (July 2014 to August 2016). This analysis included all enrolled patients and evaluated characteristics of deceased patients, survival by risk, and causes of death over the course of the study. A total of 244 patients died during the study, with 190 having available Hct values and WBC counts in the 6 months before death, and 175 having a known cause of death. Among the 244 patients who died during the study, 82% (n = 200) were categorized as high risk at diagnosis, primarily due to age ≥60 years only (65%; n = 159).[1]

[c] 71% (78/110) of these patients did not experience an infection in the year prior to death.[3]

References: 1. Stein B et al. Presented at: 62nd ASH Annual Meeting and Exposition; December 5-8, 2020. Abstract 484. **2.** Grunwald MR et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(12):788-795. **3.** Data on file. Incyte Corporation. Wilmington, DE.

▶ Why is this important?

- Vascular-related complications are a common cause of mortality among patients with high-risk PV, who may have elevated blood counts in the 6 months before death[1]

▶ What do I need to know?

- In the prospective, observational REVEAL study, 77% of patients (1940/2510) were classified as high risk at enrollment based on age ≥60 years and/or history of thrombotic events[1]
  - 86% of high-risk patients (1660/1940) received HU and/or phlebotomy at enrollment[2]
- The estimated 4-year mortality rate was 14% among high-risk patients, and of patients with known cause of death, 33% (58/175) died to due to vascular-related complications **(see figure)**
  - Some of these patients had elevated WBC counts >11 × 10^9/L (57.9%) or elevated Hct >45% (31.1%) 6 months before death

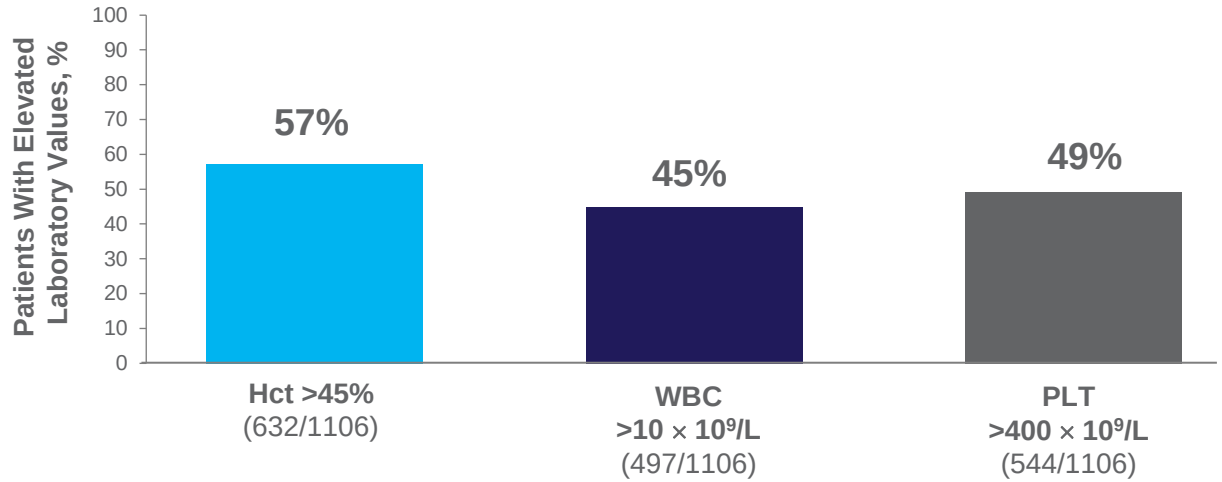
▶ How can I put this into practice?

- Monitoring and managing blood counts is especially important for your patients at higher risk for thrombotic events

In the prospective, observational REVEAL study

Some Patients Continue to Have Elevated Blood Counts Despite Treatment With HU

Elevated Laboratory Values in Patients Who Received HU for ≥3 months in the REVEAL Study[1a]



Reproduced from *Clin Lymphoma Myeloma Leuk*. Vol 20, Issue 4. Grunwald MR et al. Treatment patterns and blood counts in patients with polycythemia vera treated with hydroxyurea in the United States: an analysis from the REVEAL Study. Pages 219-225. Copyright 2020, with permission from Elsevier.

Hct, hematocrit; HU, hydroxyurea; PLT, platelet; PV, polycythemia vera; US, United States; WBC, white blood cell.

[a] REVEAL 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.[1]

References: 1. Grunwald MR et al. *Cl Lymph Myelom Leuk*. 2019;19(9):579-584.e1. **2.** Parasuraman S et al. *Exp Hematol Oncol*. 2016;5:3.

Why is this important?

- Ongoing monitoring of blood counts is critical even in patients with PV receiving standard of care treatments like hydroxyurea and phlebotomy

What do I need to know?

- In the prospective, observational REVEAL study, evaluable patients (n = 1106) who received HU for ≥3 months continued to have elevated Hct and WBC and platelet counts[1a] **(see figure)**
- Additional analysis from the study found that[1]:
  - 33.1% (457/1381) of patients continued to receive phlebotomies after ≥3 months of HU
  - 82.9% of these patients had Hct values >45%

How can I put this into practice?

- Clearly set patient expectations about their treatment:
  - Importance of keeping lab appointments to monitor blood counts
  - Not all therapies are equally effective for all patients
  - Although hydroxyurea is commonly used in PV for managing hematocrit, not all patients may benefit from or be able to tolerate long-term treatment[2]

Key Considerations for Monitoring for Thrombotic Risk in Patients With PV

- Assess patients for **thrombotic risk factors**
- **Manage Hct <45%**
- **Watch for increasing WBC counts,** especially elevated >11 × 10^9/L
- Actively monitor patients on HU for **signs of inadequate response**

Summary

- In polycythemia vera, blood hyperviscosity and increased proinflammatory cytokine activity are caused by overactive JAK/STAT pathway signaling and can contribute to thrombotic risk in some patients
- Thrombosis is associated with significant morbidity and mortality in PV
- All patients with PV should be monitored for thrombotic risk and managed appropriately
  - Cytoreductive therapy is additionally recommended for patients who are considered to be at high risk
- In the CYTO-PV study, managing elevated hematocrit <45% and elevated white blood cell counts <11 × 10^9/L have been shown to reduce the risk of thrombosis and cardiovascular death in patients with PV
- The REVEAL study showed that in some patients with PV, blood cell counts can remain elevated even in patients receiving hydroxyurea and phlebotomy, so it is critical to:
  - Conduct regular blood tests
  - Counsel patients on the importance of keeping their lab appointments and talking openly about possible changes in their disease

JAK/STAT, Janus kinase-signal transducer and activator of transcription; PV, polycythemia vera.

Additional Resources

Click to Explore

Download

[White paper on optimizing the management of PV]

Videos

[Watch a physician talk about thrombotic risk in PV]

[Watch a physician assistant discuss blood count monitoring in advanced PV]

Contact Incyte

[Order a PV blood model]

[Meet with an Oncology Clinical Nurse Educator]