Implementing a Quality Intervention* for Patients With Clinical Characteristics of Advanced Polycythemia Vera

A guide for US healthcare professionals responsible for population-based decision making

Help clinicians identify the subset of patients with clinical characteristics of advanced polycythemia vera (PV)

*The elements of the quality intervention described have not been validated or approved for securing accreditation or reimbursement, nor has the information been supported or endorsed by any entity for these purposes.

Clinical characteristics of advanced PV

PV is a hematologic malignancy that *may become advanced in a subset of patients despite treatment with HU and PBT, resulting in ineffective disease control.*[1-4]

Hct+

Elevated Hct levels ≥45% *plus* one additional factor—despite treatment with HU[5,a] and PBT

[a] After maximum tolerated dose of HU.

Elevated Hct levels[6] **≥45%**

+

Elevated WBC counts[7] >11 × 10^9/L

OR

Burdensome disease-related symptoms[8] (such as fatigue, night sweats, and pruritus)

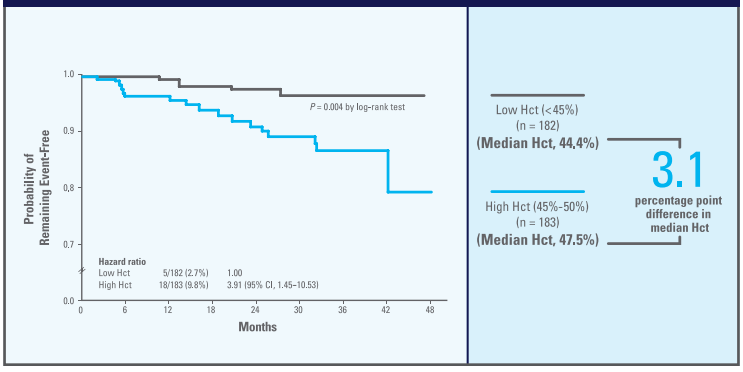
Hct, hematocrit; HU, hydroxyurea; PBT, phlebotomy; PV, polycythemia vera; WBC, white blood cell.

Patients with clinical characteristics of advanced PV are at increased risk of thrombosis

CYTO-PV study

Elevated Hct between 45% and 50%: 4-fold higher rate of cardiovascular death and major thrombosis[6]

Probability of remaining event-free in the CYTO-PV study (N = 365)[6]



Kaplan-Meier curves for primary composite endpoint. From *New Engl J Med*, Marchioli R, Finazzi G, Specchia G, et al; CYTO-PV Collaborative Group, Cardiovascular events and intensity of treatment in polycythemia vera, 368, Page No. Copyright © 2013 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

- Managing Hct levels between 45% and 50% significantly increased the risk of cardiovascular death and major thrombosis compared with an Hct level managed to <45% (HR, 3.91; 95% CI, 1.45-10.53; *P* = 0.007)[6,a]

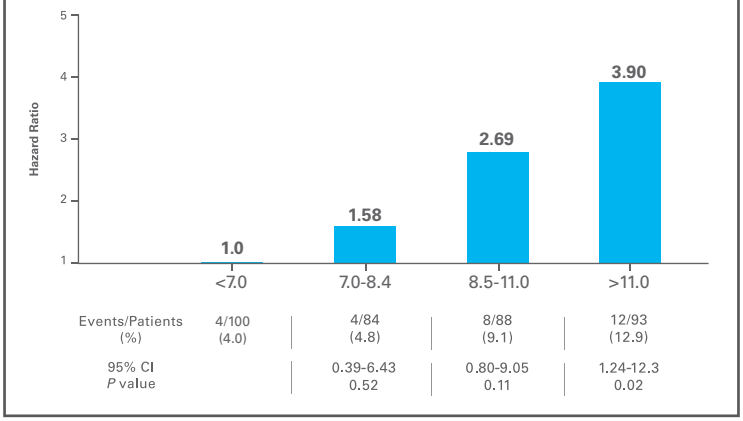
CI, confidence interval; CYTO-PV, Cytoreductive Therapy in Polycythemia Vera; Hct, hematocrit; HR, hazard ratio; HU, hydroxyurea; PBT, phlebotomy.

[a]In the CYTO-PV study of 365 adult patients with PV treated with PBT, 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. 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.[6]

Additional analysis from the CYTO-PV study

Elevated WBC counts >11 × 10^9/L increased the risk of thrombosis[7]

Time-dependent multivariable analysis on the risk of major thrombosis in the CYTO-PV study (N = 365)[7,a]



- In a multivariable time-dependent analysis, WBC counts >11 × 10^9/L were associated with increased risk of thrombosis (HR, 3.9; 95% CI, 1.24-12.3; *P* = 0.02)[7]
- In this analysis, there was a trend for increased risk of thrombosis with WBC count >7 x 10^9/L (ie, HR >1) that became statistically significant in patients with WBC counts >11 x 10^9/L[7]
- These results are consistent with other literature that suggests leukocytosis may increase the risk of thrombosis[9,10]

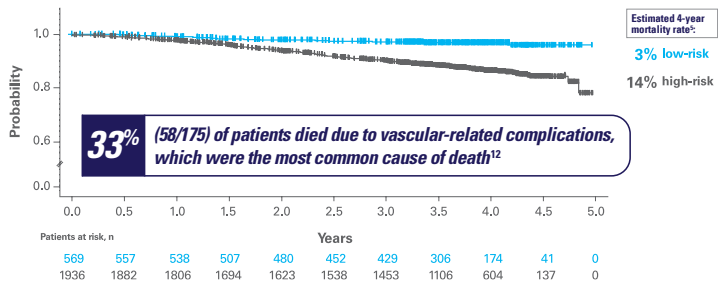
CI, confidence interval; CYTO-PV, Cytoreductive Therapy in Polycythemia Vera; Hct, hematocrit; HR, hazard ratio; WBC, white blood cell.

[a]Adjusted for age, gender, cardiovascular risk factors, previous thrombosis, and Hct levels.[7]

The estimated 4-year mortality rate was 14% in patients with high-risk PV in a prospective, observational study[11,a]

REVEAL study

Overall survival by risk category at enrollment in the REVEAL study[11,a]



In the 6 months before death[11]:

– 58% (110/190) of patients had ≥1 elevated WBC count >11 × 10^9/L[c]

– 31% (59/190) of patients had ≥1 elevated Hct level >45%

- 86% of high-risk patients (1660/1940) received HU and/or PBT at enrollment[12]

ELN, European Leukemia Net; Hct, hematocrit; HU, hydroxyurea; PBT, phlebotomy; 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.[12]

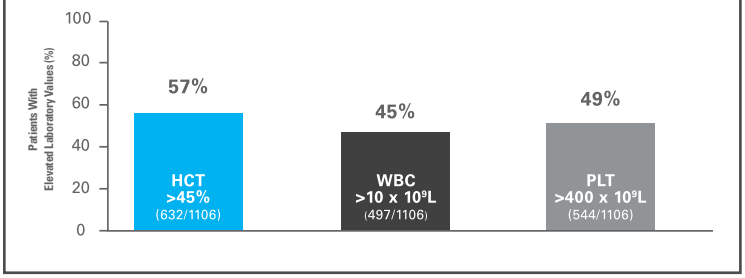
[b]REVEAL was a prospective, observational study of 2510 adult patients with PV in the United States, sponsored by Incyte. Patients were enrolled over an approximate 2-year period (July 2014 to August 2016). This analysis included all enrolled patients and evaluated characteristics of deceased patients, 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 elevated 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).[11]

[c]71% (78/110) of these patients did not experience an infection in the year prior to death.[13]

Some patients with PV continued to have elevated blood counts, despite treatment with HU[14]

REVEAL study

Elevated laboratory values in patients who received HU for ≥3 months in the REVEAL study[14,a]



Analysis included patients with all 3 laboratory values.[14]

Reprinted from Grunwald MR, Kuter DJ, Altomare I, 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. *Clin Lymphoma Myeloma Leuk*. 2020 Apr;20(4):219-225. doi: 10.1016/j.clml.2019.09.601. Copyright 2020, with permission from Elsevier.

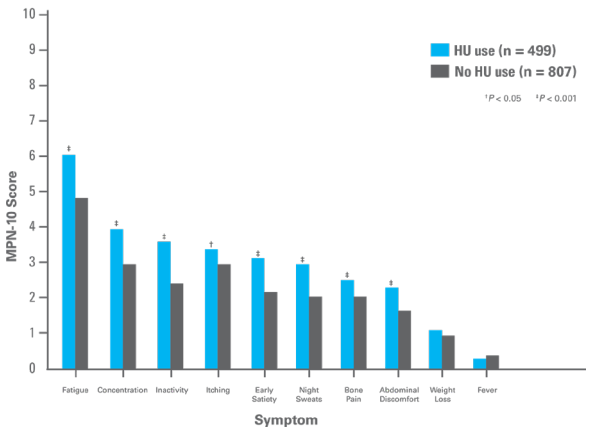
- The median of the maximum Hct value among evaluable patients (n = 1106) who received HU for ≥3 months was 48% for those who reported a value >45% and 42% for those who reported a value ≤45%[15]

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

[a]REVEAL was a prospective, observational study of 2510 patients with PV in the United States, sponsored by Incyte. This analysis focused on blood count control in the subset of 1381 patients who had received HU for ≥3 months.[14]

On average, patients with known HU use had moderately high symptom burden (TSS = 29.2)[16]

MPN-10 mean symptom scores in patients with known HU use[16]



Adapted with permission from Wolters Kluwer Health, Inc.: H Geyer, R Scherber, H Kosiorek, et al, Symptomatic Profiles of Patients With Polycythemia Vera: Implications of Inadequately Controlled Disease, Journal of Clinical Oncology, volume 34, issue 2, pages 151-159, https://ascopubs.org/journal/jco/© 2015 American Society of Clinical Oncology.

PV-related symptoms are prevalent and associated with altered cytokine signaling, blood hyperviscosity, and splenomegaly[8,a]

Cytokine-related:

- 88% Fatigue
- 62% Pruritus
- 61% Inactivity
- 52% Night sweats
- 50% Bone pain
- 31% Weight loss
- 18% Fever

Hyperviscosity-related:

- 65% Concentration problems

Splenomegaly-related:

- 64% Early satiety
- 51% Abdominal discomfort

- A prospective study of 1334 patients with PV, where a subset of patients received HU (n = 499)[16,a]

In the MPN Landmark Survey,[b]

66% of patients with PV reported that their symptoms reduced their quality of life.[17,c]

HU, hydroxyurea; MPN, myeloproliferative neoplasm; MPN-10, MPN Symptom Assessment Form; PBT, phlebotomy; PV, polycythemia vera; TSS, Total Symptom Score.

[a]A prospective study of 1334 patients with PV was conducted to assess baseline symptoms with certain disease features: known HU use (n = 499), known PBT (n = 646), palpable splenomegaly (n = 369), or all 3 features (n = 148), and compared to a control group of patients that lacked the specified feature. Assessment of MPN symptoms was performed by using the MPN-Symptom Assessment Form Total Symptom Score (MPN-SAF TSS; MPN-10). All items were evaluated on a 0 (absent) to 10 (worst imaginable) scale. The MPN-10 TSS has a possible range of 0 to 100 with 100 representing the highest level of symptom severity. 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).[16]

[b]The MPN Landmark Survey, funded by Incyte Corporation, was a web-based questionnaire composed of 65 multiple-choice questions intended to help evaluate the patient disease burden in the MPN disease setting. A total of 813 patients in the United States with a previous diagnosis of MF, PV, or ET completed the survey (MF, n = 207; PV, n = 380; ET, n = 226).[17]

[c]Patients reported whether they strongly agreed, somewhat agreed, somewhat disagreed, or strongly disagreed with the following statement: PV symptoms reduce my quality of life.[17]

[a]This prospective study included a total of 1433 patients with MPNs (n=538 with PV), who were queried on the 10 symptoms from the MPN-SAF TSS/MPN-10. The MPN-SAF TSS is validated for serial tracking of the most pertinent MPN-related symptoms—fatigue, concentration problems, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fever—scored on a scale of 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be), for a total possible score of 100.[8]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms[18]

recommend assessing symptoms (in a provider's office) at baseline and monitoring symptom status (stable, improved, or worsening)

Changes in symptom status could be a sign of disease progression

NCCN, National Comprehensive Cancer Network.

References: 1. Parasuraman S et al. *Exp Hematol Oncol*. 2016;5:3. **2.** Mascarenhas J. *Clin Lymphoma Myeloma Leuk*. 2016;16suppl:S124-S129. **3.** Rumi E, Cazzola M. *Blood*. 2017;129(6):680-692. **4.** Spivak JL et al. *N Engl J Med*. 2014;371(9):808-817. **5.** Barosi G et al. *Br J Haematol*. 2009;148(6):961-963. **6.** Marchioli R et al. N Engl J Med. 2013:368(1):22-33. **7.** Barbui T et al. *Blood*. 2015;126(4):560-561. **8.** Emanuel RM et al. *J Clin Oncol*. 2012;30(33):4098-4103. **9.** Gangat N et al. *Br J Haematol*. 2007;138(3):354-358. **10.** Landolfi R et al. *Blood*. 2007;109(6):2446-2452. **11.** Stein B et al. Presented at: 62nd ASH Annual Meeting and Exposition; December 5-8, 2020. Abstract #484. **12.** Grunwald MR et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(12):788-795. **13.** Data on file. Incyte Corporation. Wilmington, DE. **14.** Grunwald MR et al. *Clin Lymphona Myeloma Leuk*. 2020;20(4):219-225. **15.** Grunwald MR et al. Poster presented at: 59th American Society of Hematology Annual Meeting and Exposition, 2017; Atlanta, GA. **16.** Geyer H et al. *J Clin Oncol*. 2016;34(2):151-159. **17.** Mesa R et al. *BMC Cancer*. 2016;16:167. **18.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms V.1.2020. National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed March 31, 2021. 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.

Actively monitor patients for **Hct+**

Proactively identify the subset of patients with clinical characteristics of advanced PV

Hct+

Elevated Hct levels ≥45% *plus* one additional factor—despite treatment with HU[5,a] and PBT

[a]After maximum tolerated dose of HU.

- In the CYTO-PV study, **elevated Hct** between 45% and 50% was associated with a 4-fold higher rate of cardiovascular death and major thrombosis comparedwith Hct <45%[6]
- In an additional analysis from the same study, **elevated WBC counts** >11 × 10^9/L increased the risk of thrombosis[7]
- Symptom burden in patients with PV is substantial and may not be adequately controlled with HU[16]

CYTO-PV, Cytoreductive Therapy in Polycythemia Vera; Hct, hematocrit; HU, hydroxyurea; PBT, phlebotomy; PV, polycythemia vera; WBC, white blood cell.

Use EHR systems to identify patients with clinical characteristics of advanced PV

1. Select the ***query, report, or list tab*** within your system
2. **Enter ICD-10 Code *D45*** for PV
3. Select drug: ***Hydroxyurea***

Review the list for patients with **Hct+:**

Elevated Hct ≥45%, phlebotomy, *plus* one additional factor:

- **WBC count >11 × 10^9/L,** *or*
- **Burdensome symptoms** (eg, fatigue, night sweats, and pruritus)

- Clinical criteria such as diagnosis, medication, and blood counts can be used proactively to identify the subset of patients with clinical characteristics of advanced PV
- These patients may require a different management approach. Monitor your EHR system regularly, and notify clinicians of patients who have the clinical characteristics of advanced disease

Contact Incyte for information on how to use your EHR system to implement a quality intervention for patients with clinical characteristics of advanced PV

Incyte