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Polycythemia Vera: Aligning Real-World Practices With Current Best Practices

Overview

Ruben A. Mesa, MD, provides practical insights into treating polycythemia vera. In addition to discussing risk stratification, Dr. Mesa uses case scenarios to illustrate how treatment strategies can be selected and modified to meet individual needs.

Content Areas:

- Epidemiology
- Risk-based treatment selection
- Addressing treatment intolerance and resistance
- Current and emerging therapies

Faculty

Ruben A. Mesa, MD
Professor of Medicine
Consultant Hematologist
Chair, Division of Hematology & Medical Oncology
Deputy Director, Mayo Clinic Cancer Center
Mayo Clinic in Arizona
Phoenix, Arizona

Table of Contents

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CE/CME Information

Target Audience

This activity was developed for hematologist-oncologists, hematologists, oncologists, and other health care professionals who have an interest in polycythemia vera.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Explain current best practices in diagnosing polycythemia vera (PV)
- Conduct risk stratification for patients with newly diagnosed PV
- Develop individualized, risk-based management plans for patients with PV
- Incorporate novel management strategies for treatment-refractory PV based on the latest evidence

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INTRODUCTION

Hello, and welcome to this series of videos titled *Polycythemia Vera: Aligning Real-World Practices With Current Best Practices*. Through this series of videos, we will be going through a series of topics that hopefully will be helpful to you as you are diagnosing and managing patients with polycythemia vera (PV). Specifically, we're going to begin with diagnosis and disease burden, and try to drill down further on issues of definitions around PV, the epidemiology of the disease, how we diagnose it currently, and some discussion around the burden these patients face.

Then we'll go into risk stratification and treatment. How do we assess risk for patients with PV? We'll use a case to outline both our treatment goals and how we choose the treatments that we employ. We'll then shift gears and begin working on managing challenges with traditional treatments and discuss a case that will highlight some of the challenges we face when caring for these patients. Finally, we'll look at future directions and envision how the future of care for PV will evolve. We hope you find these videos both instructive and helpful in your practice.

Module 1: Diagnosis and Disease Burden

Let us begin by discussing the diagnosis and disease burden for patients who face PV.

PV is one of the core Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs). This is a disease that I would say is neither common nor rare. It's a disease characterized by a clonal proliferation of hematopoietic stem cells, particularly affecting red blood cells (RBCs), leukocytes, and platelets—in particular of myeloid origin. The MPNs include patients with essential thrombocythemia as well as myelofibrosis—both primary—as well as individuals that have myelofibrosis that evolve from PV or essential thrombocythemia.

Definition

- 1 of 3 rare, Philadelphia-chromosome-negative myeloproliferative neoplasms (MPN) characterized by clonal stem-cell proliferation of red blood cells, white blood cells, and platelets
  – Polycythemia vera (PV)
  – Essential thrombocythemia (ET)
  – Primary myelofibrosis (PMF)

- Increased RBC mass results in hyperviscosity of the blood, increased risk for thrombosis, and a shortened life expectancy

PV can lead to erythrocytosis that can manifest as an increase in RBC mass, as well as risk of thrombosis, hemorrhage, and the potential for decreased life expectancy. The prevalence of PV is approximately 44 to 57 per 100,000 individuals, with a slight predominance of men over women. In the United States this translates to approximately 150,000 patients with PV at any given time. It's a disease that is associated with aging, with a median age of diagnosis typically in the early 60s. However, it's notable that many younger patients have the disease, with a full 20% to 25% being less than age 40 years.

Epidemiology of PV

- US prevalence is ≈44 – 57/100,000 individuals, with men more often affected than women

- Median age of diagnosis is 60 y, but 20%-25% of patients are age <40 y

PV is associated with genetic mutations—in particular, mutations in the Janus kinase 2 *(JAK2)* gene. The association between MPNs and the *JAK2* gene mutation was identified in 2005. The very specific V617F mutation is present in about 90% to 95% of patients with PV. About 1% to 3% of patients may have the *JAK2* exon 12 mutation. Additionally, by complete sequencing, we are now finding other, rare variants of the *JAK2* mutation. Further, individuals may have mutations in other somatic genes. More specifically, they do not have mutations in either calreticulin or the *MPL* gene—these mutations are specifically associated with myelofibrosis or with essential thrombocythemia. But patients with PV may have other mutations, such as mutations in *TET2* and *ASXL1*. Finally, some patients with PV do not have a mutation, but it is a very small minority.
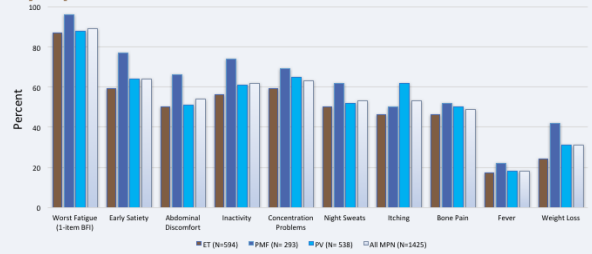
Patients with MPNs can be quite symptomatic, with patients with PV being among the most symptomatic in the group. Symptoms range from difficulties with fatigue to pruritus and difficulties with night sweats. As the disease progresses more toward myelofibrosis, patients may have difficulties such as fever and unanticipated weight loss. Among patients with MPNs, pruritus is the most severe in those with PV.

When should you suspect PV? Typically it's seen in individuals who are being cared for in primary care settings, who have unexplained erythrocytosis, thrombocytosis, and/or leukocytosis. It's notable that if patients have iron deficiency, they may not have overt erythrocytosis to begin with. Another group we need to consider are those with unexplained thrombosis, in particular, in certain vascular distributions. A patient with PV can have a thrombotic event in any vascular distribution, but in particular those who have portal vein thrombosis or sagittal vein thrombosis have a higher likelihood of having PV or another MPN. If patients have pruritus, which is a common feature, we should be even more mindful in the setting of thrombosis.

To quantify these symptoms, our group has helped to develop and validate the MPN System Assessment Form Total Symptom Score (MPN-SAF TSS). This assessment tool has 10 items with scoring from zero to 10 to help to quantify the significant symptom burden these patients face, and track symptoms over time as we treat patients.

Mutations Associated With PV

- Janus kinase 2 gene mutations
  - *JAK2*V617F (90-95%)
  - *JAK2* exon 12
  - Other *JAK2*
- Mutations in other genes

TET2	del20q	FOXP1
ASXL1	Trisomy 9	GAT A2
DNMT3A	CBL	KIF17
EZH2	CUX1	KRAS
NFE2	NF1	MYBL2
IDH1	NRAS	PIAS2
TP53	ARNTL	PRMT5
	EVI1	PTPRT

- No detectable mutation

Lundberg P, et al. *Blood.* 2014;123:2220-2228.

Symptoms Seen in Patients With MPN

Geyer HL, Mesa RA. *J Clin Oncol.* 2014;30:4098-4103.

When to Suspect PV

- Unexplained erythrocytosis, thrombocytosis, leukocytosis

- In particular, unexplained thrombosis affecting the portal vein or sagittal venous sinus – or any unexplained thrombosis with increase in blood counts

- Unexplained significant pruritus with any change in blood counts

MPN-SAF TSS – 10 Items

Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score	
Filling up quickly when you eat (satiety)	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Inactivity	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Problems concentrating compared to before my MPD	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Numbness/tingling (in my hands and feet)	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Night sweats	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Itching (pruritis)	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Bone pain (diffuse, not joint pain or arthritis)	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Fever (> 100° F)	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Unintentional weight loss – previous 6 mo	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)

Emanuel R, et al. *J Clin Oncol.* 2012;30:4098-4103.

How do we diagnose these patients? In 2016, there was a revision to the World Health Organization (WHO) criteria for diagnosing PV. It involves first major criteria, which include a hemoglobin exceeding 16.5 g/dL in men or exceeding 16 g/dL in women. There's a parallel hematocrit (Hct) criterion for increased RBC mass. The second criterion encompasses bone marrow biopsy changes, including hypercellularity, increased erythrocytosis, and no evidence of an alternative myeloid neoplasm. Third is the presence of the *JAK2*V617F or the *JAK2* exon 12 mutation. A minor criterion is subnormal serum erythropoietin (EPO) level. The minor criterion is helpful, in particular, if individuals do not have a *JAK2* mutation. If they have erythrocytosis, changes in the bone marrow, and subnormal EPO, that can be sufficient for diagnosis.

2016 WHO Criteria for PV Diagnosis

	MAJOR CRITERIA				
1	**Hb** > 16.5 g/dL in men > 16.0 g/dL in women	*or*	**Hct** > 49% in men > 48% in women	*or*	**Increased RCM** (> 25% above mean normal predicted value)
2	BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)				
3	Presence of *JAK2*V617F or *JAK2* exon 12 mutation				
	MINOR CRITERION				
	Subnormal serum EPO				

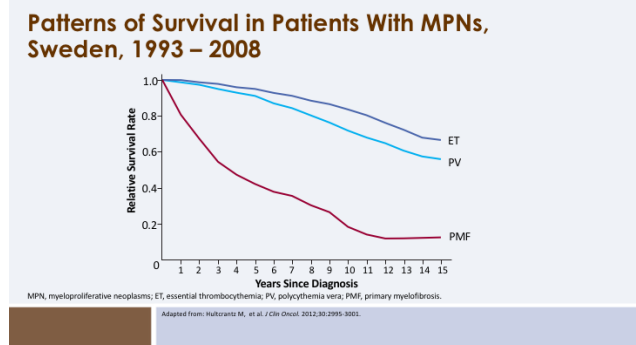Diagnosis of PV requires meeting either all 3 major criteria or the first 2 major criteria and the minor criterion†

†Criterion 2 may not be required in patients with sustained absolute erythrocytosis (Hb levels >18.5 g/dL in men [Hct, 55.5%] or >16.5 g/dL in women [Hct, 49.5%]) if major criterion 3 and the minor criterion are present. However, initial MF (present in ≤ 20% of patients) can be detected only by BM biopsy; if found, this may predict more rapid progression to overt MF (post-PV MF).

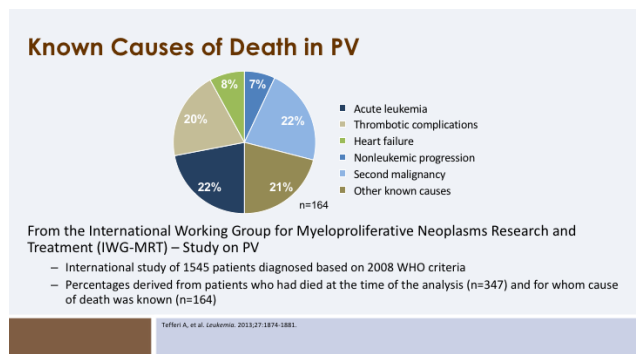Arbor DA, et al. *Blood.* 2016;127:2391-2405.

The disease burden with PV can include risk of vascular events. It can include risk of cytopenias, particularly in the setting of progressive disease or from medical therapy. There's a risk of progression to either myelofibrosis or to acute leukemia. There can be the burden of splenomegaly. There can be the symptoms which I've just discussed. We also need to be mindful of how this disease can aggravate underlying comorbidities.

PV Disease Burden
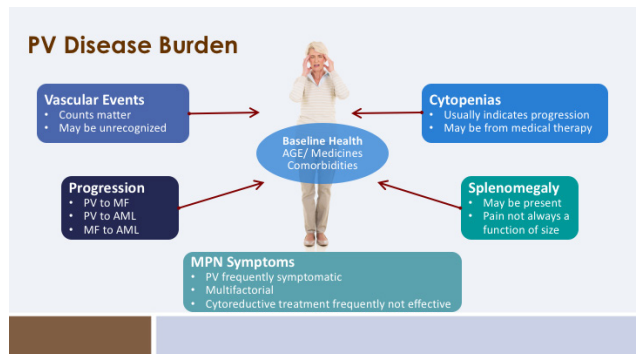
The survival of patients with PV is slightly less than that of age-matched controls. Many individuals, if they do not have progressive disease, will have a normal lifespan. The known causes of death attributable to PV include acute leukemia, thrombotic complications, nonleukemic progression, heart failure, and secondary malignancies.

Patterns of Survival in Patients With MPNs, Sweden, 1993 – 2008

MPN, myeloproliferative neoplasms; ET, essential thrombocythemia; PV, polycythemia vera; PMF, primary myelofibrosis.

Adapted from: Hultcrantz M, et al. *J Clin Oncol.* 2012;30:2995-3001.

I would summarize by saying that PV is one of the 3 MPNs that affects about 150,000 patients in the United States. Most cases do have a detectable change in the *JAK2* gene, although other gene mutations have been found. The diagnosis involves major and/or minor criteria and the presence of proliferative abnormalities as well as the *JAK2* mutations. Patients with PV can experience a range of potentially debilitating symptoms and a shortened lifespan, in particular due to their increased risk of thrombosis and bleeding.
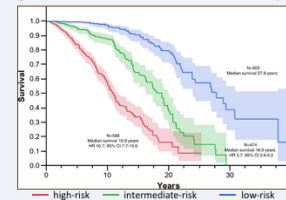
Known Causes of Death in PV

- Acute leukemia
- Thrombotic complications
- Heart failure
- Nonleukemic progression
- Second malignancy
- Other known causes

n=164

From the International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) – Study on PV
- International study of 1545 patients diagnosed based on 2008 WHO criteria
- Percentages derived from patients who had died at the time of the analysis (n=347) and for whom cause of death was known (n=164)

Tefferi A, et al. *Leukemia.* 2013;27:1874-1881.

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Module 2: Risk Stratification and Treatment

Now, let's turn to risk stratification and treatment for patients with PV. First, how do we assess risk? There have been many different analyses over the years; a more recent one is helpful. It helps stratify these patients and identifies in a scoring system the factors contributing to risk, specifically around risk of thrombosis and risk of death. Risk factors included older age, particularly a higher risk if an individual is older than age 67 years vs 57 to 66 years. Next, the presence of leukocytosis with a threshold of greater than 15,000/μL. Finally, the presence of venous thrombosis. Individuals without any of these factors would be low risk. Individuals that have a score of 3 or more are high risk. Individuals at intermediate risk are those somewhere in the middle.

Major Risk Factors That Impact Survival in PV

Risk Group	Adverse Points	Median Survival (y)	HR (95% CI)
High (N=568)	≥3	10.9	10.7 (7.7-15)
Intermediate (N=474)	1 or 2	18.9	3.7 (2.6-5.2)
Low (N=503)	0	27.8	-

Criteria	Adverse Points
Age ≥67 y	5
Age 57-66 y	2
Leukocyte count ≥15x10⁹/L	1
Venous thrombosis	1

- Age, hyperleukocytosis, and thrombosis at diagnosis increase risk of thromboembolism recurrence and dramatically decrease median survival
- Thromboembolism at diagnosis has been shown to be an independent risk factor of relative survival

Tefferi A, et al. *Leukemia*. 2013;27:1874-1881. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License. To view a copy of this license, visit http://creativecommons.org/licenses/by-nc-nd/3.0/

Historically, risk stratification had been based on the presence solely of age over 60 and the presence of a prior thrombotic event. If you had one or both of these factors, you were considered high risk. If you had neither, you were low risk. We also considered other intermediate factors, including cardiovascular risk factors, such as arterial hypertension, smoking, obesity, and diabetes. We'll discuss in a bit how we utilize these risk criteria and risk scores as we determine whether to include cytoreduction in a patient's treatment profile.

Risk Stratification in PV

Risk Factors
Age > 60 years
Previous thrombosis

"Low Risk"*
No risk factors

"High Risk"
≥1 risk factor

*Low-risk patients with extreme thrombocytosis (platelet count >1000 x 10⁹/L) are considered separately.

- Risk stratification in PV (not yet validated prospectively in controlled randomized trials) estimates likelihood of thrombotic events and not survival or leukemic transformation[1]
- "Classic" cardiovascular risk factors (arterial hypertension, cigarette smoking, obesity, diabetes) should be corrected/prevented[2]

1. Tefferi A, et al. *Am J Hematol.* 2013;88:508-516.
2. Reikvam H, et al. *Leukemia.* 2012;26:563-571.

Let's go through a case to help to illustrate some of these principles. The case is a gentleman by the name of Tony. He is 62 years of age, and has been referred by his primary care physician after they found him to have marked erythrocytosis with an elevated Hgb of 21.5 g/dL, a corresponding increase in RBC count and thrombocytosis. He has ongoing symptoms of abdominal discomfort, fatigue, headaches, and visual disturbance, and he has itching that affects both legs. Additional laboratory testing confirms the erythrocytosis

Case 1: Tony K.

- Tony is a 62-year-old male referred by his primary care physician after lab results showing Hb 21.5 g/dL and elevated RBC and platelet counts.
- Tony describes ongoing symptoms of abdominal discomfort, fatigue, headache, and visual disturbance. He has pruritis affecting both legs.
- Further lab testing confirms elevated Hb, erythrocytosis, and thrombocytosis; reveals abnormally low erythropoeitin levels.
- PCR reveals *JAK2*V617F mutation.

What is the first step in treatment for Tony?

and thrombocytosis, and also shows a subnormal serum EPO level. If you'll remember, EPO level is a helpful minor criteria in the WHO diagnostic criteria. Polymerase chain reaction (PCR) reveals that he has the *JAK2*V617F mutation.
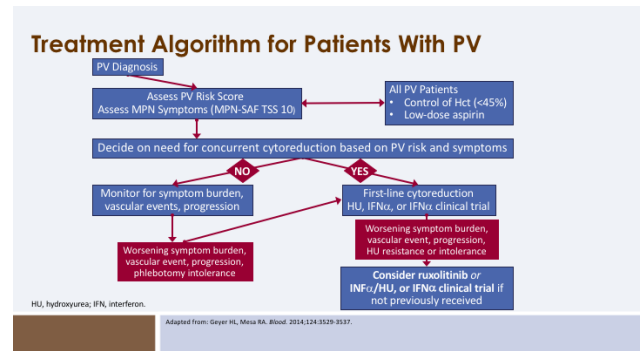
What is the first step in treatment for Tony, now that we have diagnosed PV based on the WHO criteria? Our goals are first to ensure that whatever treatment we use is tolerable. Our goals are to prevent thrombosis and hemorrhage. As surrogate markers, we will try to control erythrocytosis, leukocytosis, and thrombocytosis. We ideally will reduce his disease-related symptoms, such as pruritus. If splenomegaly is present, we'd like to reduce that. In the ideal world, we will delay or prevent progression of the disease.

Here we have a current treatment algorithm for PV. I recommend that we assess the patients' risk, as well as difficulty with their symptoms. With all patients, we begin by targeting an Hct level of less than 45% and we start low-dose aspirin. We then decide on the need for concurrent cytoreduction based on PV risk and symptoms.

This gentleman has both symptoms and he's at higher risk because of his age. Because of that, we look at front-line cytoreduction, which in 2017 includes hydroxyurea (HU), potentially IFN in select individuals, or IFN in a clinical trial. For individuals with worsening symptom burden, vascular events progressive disease, or resistance or intolerance to HU, we'll consider either ruxolitinib or an alternative cytoreductive therapy.

Treatment Algorithm for Patients With PV

HU, hydroxyurea; IFN, interferon.

Adapted from: Geyer HL, Mesa RA. *Blood*. 2014;124:3529-3537.

How did we evolve to these criteria? First, let's look at target hematocrit. The CYTO-PV study, completed in Italy, randomized patients to low and high hematocrit control groups, less than 45% or 45% to 50%, respectively. In this study of more than 300 patients, investigators showed that control of the hematocrit to less than 45% was very important in decreasing risk of thrombosis and bleeding.
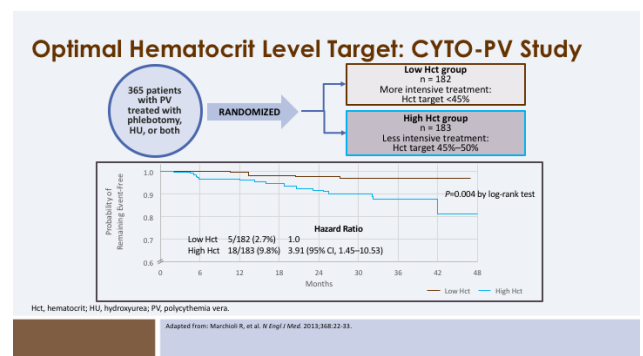
Next, the issue of aspirin. The European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) trial was a randomized study, also done in Italy. The study tested low-dose aspirin (100 mg/day—using the European formulation) vs placebo. The data showed superior control of risk of thrombosis with low-dose aspirin, which has since evolved to be the cornerstone of therapy for all PV patients.

What about HU? It's the most commonly utilized cytoreductive therapy in PV. It can help reduce the risk of thrombosis, hemorrhage, and, in some individuals, it has some impact on pruritus and splenomegaly. Our data regarding HU are fairly limited, as it is an older agent. Our primary data come from the Polycythemia Vera Study Group (PVSG)-08, involving 51 patients. This study showed that HU compared to phlebotomy alone was superior for controlling rates of thrombosis.

Optimal Hematocrit Level Target: CYTO-PV Study

Hct, hematocrit; HU, hydroxyurea; PV, polycythemia vera.

Adapted from: Marchioli R, et al. *N Engl J Med*. 2013;368:22-33.

Aspirin in PV: ECLAP Data

Baseline Platelet Count (per mm³)

Aspirin Group	Placebo Group
388,800 ± 198,900	376,100 ± 193,000

Rates and Relative Risks of Primary Endpoints

Endpoint	Aspirin Group (N=253) no. (%)	Placebo Group (N=265) no. (%)	RR (95% CI)	P value
Death from any cause	9 (3.6)	18 (6.8)	0.54 (0.24 − 1.20)	0.13
Death from CV causes	3 (1.2)	8 (3.0)	0.41 (0.11 − 1.53)	0.18
• Cardiac	2 (0.8)	2 (0.8)	1.07 (0.15 − 7.58)	
• Vascular	1 (0.4)	6 (2.3)	0.18 (0.02 − 1.50)	
Death from non-CV causes	6 (2.4)	10 (3.8)	0.65 (0.24 − 1.79)	0.95
Major cerebral events	3 (1.2)	10 (3.8)	0.32 (0.09 − 1.16)	0.11
Myocardial Infarction	1 (0.4)	2 (0.8)	0.54 (0.09 − 23.7)	0.40
Major venous thrombosis	4 (1.6)	10 (3.8)	0.49 (0.13 − 1.78)	0.08
Major or minor thrombosis	17 (6.7)	41 (15.5)	0.42 (0.24 − 0.74)	0.003
Minor thrombotic complications	10 (4.0)	22 (8.3)	0.47 (0.22 − 0.99)	0.049

ECLAP, European Collaboration on Low-Dose Aspirin in Polycythemia Vera; CV, cardiovascular.

Landolfi R, et al. *N Engl J Med*. 2004; 350:114-124.

Hydroxyurea: Efficacy in Preventing Thrombosis

Polycythemia Vera Study Group (PVSG)-08	
N	51 patients
Follow-up	12 y
Intervention	HU (vs historical controls) Average dose: 500-1000 mg/d
Comparator	Phlebotomy (134 patients from PSVG-01)
Efficacy/toxicity	• Hct control: 80% of patients by 12 weeks • Platelet count control: 88% of patients by 12 wk • Thrombosis rate: — Phlebotomy alone: 32.8% — HU: 9.8% — (P<0.05 compared to placebo)

Donovan PB, et al. *Am J Hematol*. 1984;17:329-334.

HU can have some challenges. It can have toxicities, causing myelosuppression, fever, mucocutaneous symptoms or mouth ulcers, gastrointestinal symptoms or dyspepsia. It can cause a range of cutaneous symptoms, such as rash or hyperpigmentation. It can lead to acute pulmonary reactions. Those are rare. There is some concern, although it is controversial, whether HU may slightly increase the risk of progression to acute leukemia. It is not an option in pregnancy.

To assess response to treatment in individuals with PV, we currently utilize European Leukemia Net (ELN) criteria, which look at improvement in symptoms, blood counts, lack of progressive disease, and even changes in the bone marrow. With these criteria, we can stratify patients into partial and even molecular responses. As part of this, we use improvements in the MPN-SAF TSS, using the different items identified and discussed earlier in the video on diagnosis. This tool can be helpful both at baseline and over time, with monitoring therapy.

I'll conclude this video by saying that risk assessment is the first step in determining the treatment for PV. Conventional, evidence-based treatments include aspirin and phlebotomy in all patients and HU in individuals who are symptomatic or have higher-risk disease. It's important to monitor patients, to determine response to treatment and assess whether any adjustments in treatment are necessary during the longitudinal course of care.

Response Criteria for PV

Full Remission

Durable* resolution of disease-related signs, ≥10-point decrease on the MPN-SAF TSS ...**AND**...

Durable* peripheral blood count remission, ie, Hct <45% without phlebotomies, platelet count ≤400 × 10⁹/L, WBC count <10 × 10⁹/L, absence of leukoerythroblastosis ...**AND**...

No progressive disease; no hemorrhagic or thrombotic events ...**AND**...

BM histological remission (ie, presence of age-adjusted normocellularity and disappearance of trilinear hyperplasia), absence of >grade 1 reticulin fibrosis

Partial Remission

Durable* resolution of disease-related signs, ≥10-point decrease on the MPN-SAF TSS ...**AND**...

Durable* peripheral blood count remission, ie, Hct <45% without phlebotomies, platelet count ≤400 × 10⁹/L, WBC count <10 × 10⁹/L, absence of leukoerythroblastosis ...**AND**...

Without progressive disease, and absence of any hemorrhagic or thrombotic event ...**AND**...

Without bone marrow histological remission (ie, persistence of megakaryocyte hyperplasia)

Molecular Response[†,‡]

Complete Response	Eradication of preexisting abnormality
Partial Response	↓≥50% (applies only to patients with ≥20% mutant allele burden at baseline)

*Durable defined as ≥ 12 weeks; †not required for assignment as complete or partial response; ‡requires molecular assessment of peripheral blood granulocytes.

Barosi G, et al. *Blood*. 2013 Jun 6; 121:4778-4781.

MPN-SAF TSS – 10 Items

Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score	
Filling up quickly when you eat (satiety)	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Inactivity	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Problems concentrating compared to before my MPD	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Numbness/tingling (in my hands and feet)	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Night sweats	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Itching (pruritis)	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Bone pain (diffuse, not joint pain or arthritis)	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Fever (> 100° F)	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)
Unintentional weight loss – previous 6 mo	(Absent) 0–1–2–3–4–5–6–7–8–9–10 (Worst Imaginable)

Emanuel R, et al. *J Clin Oncol*. 2012;30:4098-4103.

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Module 3: Managing Challenges with Traditional Treatments

Now let's shift gears and focus on managing patients with PV who are facing challenges with their traditional treatments. Let's again begin with a case. Margaret is a 63-year-old female who has PV associated with a *JAK2* mutation. She was diagnosed 5 years ago. Two weeks ago she went into the emergency department with angina and was admitted to critical care. As it turns out, she had a myocardial infarction. This was her first known thrombotic event since she was diagnosed. Later, she visits her hematologist, and describes ongoing symptoms of fatigue, headache, and abdominal discomfort; in addition, she is found to have an enlarged spleen.

Case 2: Margaret A.
- Margaret is a 63-year-old female with PV and a *JAK2*V617F mutation diagnosed 5 y previously.
- She presented 2 wk ago in the ED with angina and was admitted to critical care; a mild MI was confirmed. She was discharged 1 wk later.
- *This was the first known thrombotic event since PV diagnosis.*
- She visits her hematologist for follow-up, describing ongoing symptoms of fatigue, headache, and abdominal discomfort; on palpation splenomegaly is present.
- Laboratory values indicate elevated platelet and WBC counts; Hct = 46.2% despite phlebotomy while in the hospital.
- Current/pre-MI medications for PV are HU 1.5 g/d (maximum tolerated dose), low-dose aspirin, and phlebotomy (2–3 times/y).
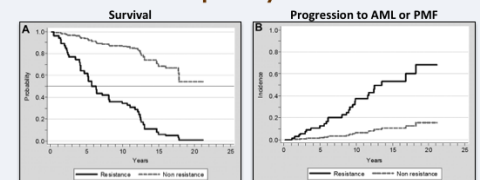
What would you recommend next for Margaret?

Her laboratory values show that she has thrombocytosis and some residual erythrocytosis despite phlebotomies received in the hospital. Before her myocardial infarction, she was taking HU at a dose of 1.5 g/d HU—her maximum tolerated dose. She was on low-dose aspirin and she was still requiring phlebotomies 2 to 3 times a year.

What should we recommend next for Margaret? Margaret has developed resistance to her HU therapy. Using current criteria from the ELN, we can divide patients who are having a suboptimal response to HU into those that face issues of resistance—meaning residual erythrocytosis, leukocytosis, thrombocytosis, splenomegaly, or symptoms—after an adequate trial of HU over more than 3 months at a maximum tolerated dose. Alternatively, patients can be intolerant, having excessive cytopenias, leg ulcers, GI toxicities, fevers, cutaneous manifestations, or recurrent skin cancers. In my practice, I would say that that final one is a common one. I see patients on HU, particularly in my practice in Arizona, who have multiple basal cell carcinomas or actinic keratoses, and it's not a good fit.

Definitions of HU Resistance/Intolerance in PV

RESISTANCE
1. Need for phlebotomy to keep Hct <45%* *OR*
2. Platelets > 400 x 10^9/L & WBC >10 x 10^9/L* *OR*
3. No reduction in massive splenomegaly size by 50%* *OR*
4. Failure to completely relieve spleen symptoms related to splenomegaly*

INTOLERANCE
1. Cytopenias (any)[†]
   - Absolute neutrophil count <1.0 x 10^9/L
   - Platelets <100 x 10^9/L
   - Hemoglobin <100 g/L
   OR
2. Presence of leg ulcers, GI toxicity, fevers, mucocutaneous manifestations, skin cancers, or other unacceptable nonhematologic HU-related toxicities[‡]

*After 3 mo At maximum tolerated dose or ≥2 g/day
[†]At lowest dose to achieve either partial or complete response by European Leukemia Net Criteria.
[‡]At any dose of HU

Barosi G, et al. *Brit J Hematol.* 2009;148:961-963.

A couple of years ago, my group published a paper in the *Journal of Clinical Oncology* showing that individuals who have, quote unquote, "failed" HU can be quite symptomatic, whether they have failed treatment on the basis of a resistance, intolerance, or the presence of splenomegaly. Colleagues in Spain did an analysis that found that patients with PV who met criteria of HU resistance or intolerance had more difficult disease, with a 5.6-fold increased risk of death and a 12-fold increased risk of progression to acute leukemia or primary myelofibrosis. These are not your standard patients. They have much more difficult disease.

Implications of Inadequately Controlled Disease

Survival | Progression to AML or PMF

- N = 261 PV patients; median follow-up = 7.2 y
- Resistance to HU was associated with
  - 5.6-fold increase in risk of death
  - 6.8-fold increase in risk of progression go AML or PMF

AML, acute myeloid leukemia.

Alvarez-Larrán A, et al. *Blood.* 2012;119:1363-1369. With permission of the American Society of Hematology.

In the past, we had limited options for individuals with inadequately controlled PV on HU. We could use IFN, although this treatment can be associated with adverse effects such as flu-like symptoms, fatigue, neuropsychiatric symptoms, or autoimmune disorders. There are other chemotherapy drugs we can use, such as busulfan. However, busulfan can be quite myelosuppressive and is sometimes not well tolerated or toxic to the lungs. We have radioactive phosphorus, which is leukemogenic, and we tend to use this only in very elderly patients. We have anagrelide, which can control thrombocytosis but not erythrocytosis, and really is not a great option.

In this setting, clinical trials were developed to test ruxolitinib in patients with PV. Ruxolitinib is a JAK inhibitor, and it had long been speculated that JAK inhibition would be effective for patients with PV. A phase 2 study demonstrated that it was active and safe in patients that had failed HU. Subsequently, a randomized study of ruxolitinib vs best alternative therapy was conducted with a goal of trying to improve the disease course for patients with PV who had failed HU.

The trial demonstrated that ruxolitinib was superior to best alternative therapy for control of Hct, reduction of splenomegaly, and reduction in PV-related symptoms. There was also a trend toward fewer thrombotic events. At baseline, the trial included a little more than 100 patients in each arm with relatively similar disease features. At the 32-week endpoints, that data showed unequivocally that ruxolitinib was vastly superior for control of the primary endpoint, which included reduction in splenomegaly, (more than 35% reduction in volume), and better control of Hct.

Additionally, the study found that ruxolitinib was superior for improvement in disease-associated symptoms, both symptoms in aggregate and categorized by symptoms associated with elevated cytokines (such as tiredness, pruritus, night sweats), symptoms associated with hyperviscosity (such as headaches, difficulties with concentration, and dizziness), and symptoms associated with the splenomegaly (fullness, abdominal discomfort, etc).


Limited Additional Treatment Options for Uncontrolled PV*

Treatment	Features/ Potential Benefits	Potential Adverse Events
IFN-α*	• Antiproliferative effects on hematopoietic precursor cells • Induces cytogenetic remission • Reduces in JAK2V617F allele burden	• Flu-like symptoms • Fatigue • Neuropsychiatric symptoms • Autoimmune problems
Busulfan*	• Chemotherapeutic agent (DNA alkylator)	• Myelosuppression, interstitial pulmonary fibrosis, cardiac tamponade, hyperpigmentation, rash • Leukemogenic
32P phosphate*	• Radionuclide (not easily obtainable)	• Leukopenia, thrombocytopenia • Leukemogenic
Anagrelide*	• Complex mechanism of action • Reduces high platelet counts not controlled by other treatments	• CV symptoms (peripheral edema, palpitations, headaches) • Diarrhea, abdominal pain

*None of these agents are FDA-approved for treatment of PV.

Griesshammer M, et al. Ann Hematol. 2015;94:901-910.

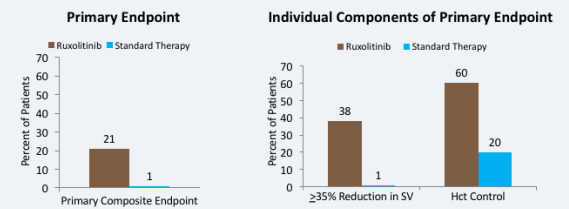**Ruxolitinib (Single Agent) in Polycythemia Vera**
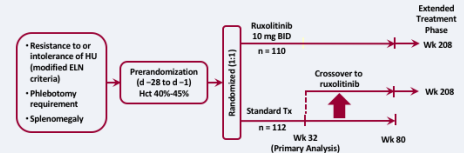
Compared to standard therapy, ruxolitinib (post-HU) in PV provided
• Improved control of Hct
• Improved reduction in splenomegaly
• Improved reduction in PV-related symptoms
• Trend for fewer thrombotic events

Vannucchi AM, et al. N Engl J Med. 2015;372:426-435.
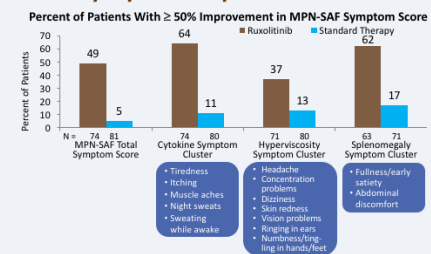

RESPONSE: Endpoints at Wk 32

77% of patients randomized to ruxolitinib met at least 1 component of the primary composite endpoint*

*Primary composite endpoint: Hct control through week 32 and ≥ 35% reduction in SV at week 32. SV, spleen volume.

Vannucchi AM, et al. N Engl J Med. 2015;372:426-435.

RESPONSE: Symptom Improvement at Wk 32

Vannucchi AM, et al. N Engl J Med. 2015;372:426-435.

In addition, responses to ruxolitinib can be durable in terms of impact on reduction in spleen size and in blood counts seen over time. In data now extending to 80 weeks, patients on ruxolitinib had good control of leukocytosis and thrombocytosis.

Over time, as we look at the laboratory values, the rate of grade 3 or 4 thrombocytopenia or anemia was very low with both treatments. This challenge, which can be present more in patients with myelofibrosis, is less of an issue in patients with PV, given the more intrinsic nature of elevated counts in this group.
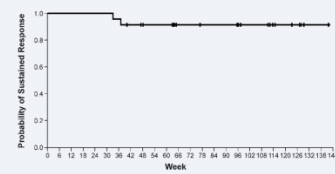
In regard to the rate of thromboembolic events, the trial was not powered to assess this as an endpoint. Regardless, a strong trend toward fewer events was seen among patients treated with ruxolitinib compared to those receiving best available therapy. This may have resulted in part from cytoreduction, but also may reflect improvements in inflammatory cytokines in the blood that may be associated with increased risk of thrombosis.

RESPONSE: Durability of Primary Response With Ruxolitinib*

- Of 25 ruxolitinib-treated patients eligible for assessment of durability of primary response, 20 (80.0%) had a durable primary response at Week 80 (3 of 5 nonresponders were classified as such because of missing assessments)
- Probability of maintaining the primary response in the ruxolitinib arm for ≥80 weeks from time of response was 0.92

*Wk 32 phlebotomy-independent hematocrit control plus ≥35% spleen volume reduction

Verstovsek S, et al. *Haematologica*. 2016;101:821-829.

New or Worsening Hematology Laboratory Values Up to Wk 32

Patients, %	Ruxolitinib (n = 110)		Standard Therapy (n = 111)	
	All Grades	Grades 3 or 4	All Grades	Grades 3 or 4
Hemoglobin (low)	43.6	1.8	30.6	0.0
Platelets (low)	24.5	5.5	18.9	3.6
Neutrophils (low)	1.8	0.9	8.1	0.9

NOTE: No patients discontinued treatment because of anemia or thrombocytopenia

Vannucchi AM, et al. *N Engl J Med*. 2015;372:426-435.

In regard to toxicities observed over time, nonhematologic adverse events occurred at low rates, demonstrating that the drug is quite well tolerated. In regard to longer-term events, the main issues that I advise patients and caution colleagues about when discussing ruxolitinib in PV are, first, to be aware that there seems to be a slightly increased risk of herpes zoster infections; and second, there may be a slightly increased risk of nonmelanomatous skin cancers. These observations are somewhat difficult to differentiate from the patient's prior history, in that all patients were previously exposed to HU and those in the ruxolitinib arm were resistant or intolerant to HU. Thus, there was likely at a much higher rate of risk of skin cancers at baseline.

I'll conclude by saying that patients can become resistant or intolerant to HU, frequently leading to inadequate disease control. These patients have a worse natural history unless we do something different. Until recently, options for such patients were quite limited. But based on the efficacy results from randomized clinical trials, ruxolitinib is now FDA-approved and available for managing patients with PV*. Its use should be based on an assessment of the individual patient's needs and discussion of the risk and benefits, with particular awareness regarding symptom burden, splenomegaly, and the need to control elevated blood counts.

*Ruxolitinib is FDA-approved for treatment of patients with PV who have had an inadequate response to, or are intolerant of, hydroxyurea. It is also FDA-approved for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-PV myelofibrosis and post-essential thrombocythemia myelofibrosis.

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Module 4: Future Directions and Conclusions

Let's now turn to future directions in the care of patients with PV. First, let's begin with information recently presented at the 2016 American Society of Hematology meeting regarding the use of interferon alpha. Over time, it has been of interest to look at this therapy in patients with MPNs. IFN has been used in the past for treatment of diseases including chronic myeloid leukemia, and examined in single-arm studies in patients with PV or essential thrombocythemia. HU has been used based on demonstration of a decrease in thrombotic risk with the strongest data being those for patients with essential thrombocythemia. Concern remains about the long-term safety of HU treatment in patients with PV.

In single-arm studies, the long-acting forms of IFN-alpha—the pegylated forms—have been associated with molecular response as well as control of elevated blood counts. On this basis, 2 randomized phase 3 studies were conducted and the results were recently reported. The first was a trial involving the Myeloproliferative Disorders Research Consortium—led by myself and my colleagues, Drs. John Mascarenhas and Ron Hoffman, both from Mount Sinai. This was a study of high-risk patients with essential thrombocythemia and PV. It examined frontline therapy with HU vs pegylated IFN-alpha 2a. These individuals would then be receiving the therapy with endpoints assessing control of the disease, RBC counts, and rates of vascular events.
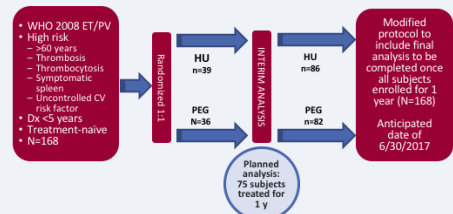
Overall, we found that over a 1-year period, IFN was noninferior to HU and rates of control were similar in both groups of individuals, with overall response rates being 81% for those individuals with pegylated IFN-alpha 2a and 69% for HU.

Next we had looked at molecular response rates in individuals on HU vs those on IFN. This was meant to complement what had been seen in the literature up to this point. There had been reports of IFN having the ability to control molecular allele burden in patients with PV. The data with HU is relatively new. The data demonstrate that both are effective, but there remains the question of whether IFN will be superior over a longer period of time; 12 months may be an inadequate amount of time to assess a difference.

First-Line Treatment of ET/PV With HU vs IFNα: Background

- **Optimal management of "high risk" ET and PV remains unknown**
  - Mascarenhas J, et al. *Haematologica*. 2014;99:945-949.
- **HU therapy associated with reduction in thrombotic risk**
  - Fruchtman SM, et al. *Semin Hematol*. 1997;34:17-23.
  - Harrison CN, et al. *N Engl J Med*. 2005;353:33-45.
- **Concern regarding leukemogenic potential of HU not corroborated by most studies**
  - Harrison CN, et al. *N Engl J Med*. 2005;353:33-45.
  - Finazzi G, et al. *Blood*. 2005;105:2664-70.
  - Tefferi A, et al. *Leukemia*. 2013;7:1874-1881.
- **PEG-IFN-α therapy associated with hematologic overall response rate >75% and complete molecular response of 15% – 20% in phase 2 trials**
  - Quintás-Cardama A, et al. *J Clin Oncol*. 2009;27:5418-5424.
  - Quintás-Cardama A, et al. *Blood*. 2013;122:893-901.
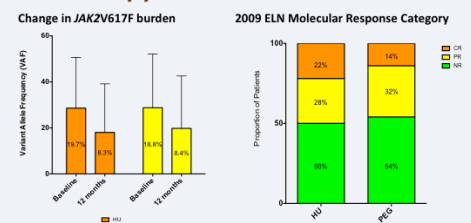 - Kiladjian JJ, et al. *Blood*. 2008;112:3065-3072.

MPD-RC 112 Study Schema

Myeloproliferative Disorders Research Consortium. Available at http://mpdrc.org/readarticle.php?article_id=14.

Overall Response Rates at 12 Mo

	HU			PEG-IFNα			P value
	PHR n (%)	CHR n (%)	ORR n (%)	PHR n (%)	CHR n (%)	ORR n (%)	
Entire cohort (n=75)	14/39 (36)	13/39 (33)	27/39 (69)	19/36 (53)	10/36 (28)	29/36 (81)	0.6*
ET (n=31)	4/16 (25)	7/16 (44)	11/16 (69)	6/15 (40)	6/15 (40)	12/15 (80)	0.8
PV (n=44)	10/23 (44)	6/23 (26)	16/23 (70)	13/21 (62)	4/21 (19)	17/21 (81)	0.6

*CHR comparison based on z-test; did not cross stopping boundary.
PHR, partial hematologic response; CHR, complete hematologic response; ORR, overall response rate.
Mascarenhas J, et al. Proceedings from the 2016 Annual Meeting of the American Society of Hematology. Abstract #479.

Molecular Response by Treatment Arm After 12 Months of Therapy

CR defined as < LOD for NGS assay of 3%
Mascarenhas J, et al. Proceedings from the 2016 Annual Meeting of the American Society of Hematology. Abstract #479.
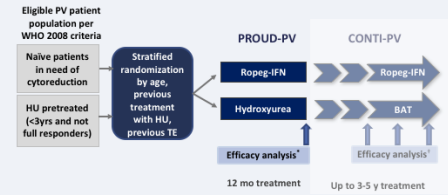
The second study used a different formulation of IFN—ropeginterferon (ropegIFN) alpha 2b. This treatment may well be relevant over time. This is a drug notable for its ability to be given every 2 weeks as well as having primarily one isomer in its formulation. Patients with PV were randomized to ropegIFN or HU. This trial also had a 12-month window, but there is a continuation study that is looking at better molecular response over a longer period of time.

Ropeginterferon Alfa-2b phase 3 Development: PROUD/CONTI-PV

Giaslinger H, et al. Proceedings from the 2016 Annual Meeting of the American Society of Hematology. Abstract #475.

Study data were examined using a noninferiority analysis. Results showed that ropegIFN was noninferior to HU over 1 year in terms of control of blood counts, splenomegaly, etc. Symptoms were not evaluated on this particular study. The authors similarly discussed at the American Society of Hematology meeting that in the ongoing study, called CONTI-PV, there may well be superiority in terms of molecular control in the IFN arm, but more time is needed to be able to make those conclusions.

PROUD-PV: Complete Hematologic Response at 12 Mo

	Ropeg-IFN	HU	Difference % (95% CI)	P-value
Complete hematologic response rate (ITT)	43.1%	45.6%	-2.5 (-14.9 to 9.9)	0.0028*
Responding patients/n	53/123	57/125		
Complete hematologic response rate (PP)	44.3%	46.5%	-2.2 (-15.2 to 10.7)	0.0036
Responding patients/n	50/113	53/114		

→ noninferiority is demonstrated, P = 0.0028

*Noninferiority margin 20.0%.

Giaslinger H, et al. Proceedings from the 2016 Annual Meeting of the American Society of Hematology. Abstract #475.

Both of these phase 3 studies show a robust control of the disease from a hematologic perspective. Both trials show that there is noninferiority of ropegIFN compared to HU. The 2 drugs had different safety profiles, but it is not clear that there is superiority of one drug over the other in terms of toxicity. In the PROUD-PV study, there were secondary malignancies that appeared in the HU cohort compared to the ropegIFN cohort.

Overall, I would conclude these video segments by highlighting a few key observations. The diagnosis of PV is determined by using both major and minor criteria outlined in the WHO 2016 revised classification of myeloid neoplasms and acute leukemia. Management of PV begins with near-universal use of aspirin and control of Hct in all patients. Selective use of cytoreduction continues to be used based on risk; in my practice, I consider cytoreduction in all patients who are not classified as low-risk—defined basically as those with no significant

Conclusions: Management of PV

- Diagnosis of PV is determined using major and minor criteria outlined in the WHO's revised classification of myeloid neoplasms and acute leukemia
- Management begins with near universal use of aspirin and control of Hct
- Front-line cytoreductive therapy is currently based on risk and hydroxyurea (or IFNα in clinical trials)
- Ruxolitinib has been FDA-approved for PV patients with an inadequate response to hydroxyurea
- Ruxolitinib has durable benefits for PV patients, with improved control of erythrocytosis, splenomegaly, PV symptoms, and perhaps risk of vascular events
- Emerging treatments, including novel IFNs, hold promise for safely improving symptoms and survival

cardiovascular risk factors, no significant symptoms, and no other risk factors. Frontline cytoreductive therapy is currently based on risk and primarily is HU, with IFN used in pregnant women and potentially in younger patients, as well as in clinical trials.

Ruxolitinib has been approved for patients with PV who have had an inadequate response to HU. Ruxolitinib has durable benefits for these patients, with improvements seen in erythrocytosis, leukocytosis, thrombocytosis, splenomegaly, and disease-associated symptoms, and likely also reduction in vascular events. There are a few emerging treatments, and studies may further clarify the role of IFNs that show promise for safely improving symptoms and potentially other longer-term outcomes in patients with this difficult disease.

Thank you.

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