Turkish Journal of Medical Sciences

Volume 48 | Number 4 Article 2

1-1-2018

Polycythemia vera: diagnosis, clinical course, and current management

YAHYA BÜYÜKAŞIK

RIDVAN ALİ

MUHLİS CEM AR

MEHMET TURGUT

AKİF SELİM YAVUZ

See next page for additional authors

Polycythemia vera: diagnosis, clinical course, and current management

Authors
YAHYA BÜYÜKAŞIK, RIDVAN ALİ, MUHLİS CEM AR, MEHMET TURGUT, AKİF SELİM YAVUZ, and GÜRAY SAYDAM

TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Review Article

Turk J Med Sci
(2018) 48: 698-710
© TÜBİTAK
doi:10.3906/sag-1806-43

Polycythemia vera: diagnosis, clinical course, and current management

Yahya BÜYÜKAŞIK[1,*], Rıdvan ALİ[2], Cem AR[3], Mehmet TURGUT[4], Selim YAVUZ[5], Güray SAYDAM[6]

[1]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Turkey
[2]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Uludağ University, Bursa, Turkey
[3]Division of Hematology, Department of Internal Medicine, Cerrahpaşa Faculty of Medicine, İstanbul University, İstanbul, Turkey
[4]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey
[5]Division of Hematology, Department of Internal Medicine, İstanbul Faculty of Medicine, İstanbul University, İstanbul, Turkey
[6]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Ege University, İzmir, Turkey

Received: 06.06.2018 • **Accepted/Published Online:** 09.08.2018 • **Final Version:** 16.08.2018

Abstract: Very important developments related to polycythemia vera (PV) have occurred during the last two decades. The discovery of Janus kinase (JAK) 2 mutations has changed both the diagnosis and clinical management of PV. Currently JAK2 molecular testing is essential in the diagnostic work-up and JAK2 mutation positivity is a major diagnostic criterion. The discovery of JAK2 mutations suggested that abnormal JAK-STAT signaling was a pivotal feature in the pathogenesis of Philadelphia-negative myeloproliferative neoplasms. This idea led to the development of JAK inhibitors. Currently ruxolitinib, a JAK1/JAK2 inhibitor, is also approved for PV patients with hydroxyurea resistance or intolerance. International collaborations have made it possible to describe disease characteristics and evolution better. Presently it is possible to quantify the symptomatic burden of the disease and to estimate prognosis. In spite of these developments, management of PV still largely depends on estimation of thromboembolic risk and trying to decrease the risk with or without cytoreductive medications. Different approaches have been proposed by international disease experts for the diagnosis, thromboembolic risk estimation, and drug selection. This paper aims to review clinical aspects of PV and propose a management algorithm. The authors also point to still unresolved questions and unmet needs in diagnosis and management.

Key words: Polycythemia vera, diagnosis, prognosis, treatment

1. Introduction

The reported annual incidence for polycythemia vera (PV), a chronic Philadelphia chromosome (Ph)-negative myeloproliferative neoplasm (MPN), ranges between 0.01/100,000 and 2.61/100,000 with a pooled rate of 0.67/100,000 (1). Median age is 61 years with 10% of patients below age 40 years of age (2). Important developments have occurred in understanding the pathobiology of PV during the last two decades. Discovery of chromosome 9p, exon 14, Janus kinase (JAK) 2 gene-product JAK2 tyrosine kinase V617F mutation in the vast majority (~95%) (3–5) of patients, and JAK2 exon 12 mutations (6) in the majority (3%) (7) of the remaining few cases were the most important developments in PV during the last decades. New alternatives are emerging for treatment of PV. This review aims to examine clinical aspects of PV in detail.

2. Clinical presentation and diagnostic criteria

2.1. Disease presentation

Fatigue, pruritus, epigastric discomfort, early satiety, diaphoresis, weight loss, and vasomotor symptoms such as headache, dizziness, visual disturbances, and erythromelalgia are frequent presenting symptoms (2,8,9). Some patients may also apply due to incidentally found elevated blood cell counts during medical evaluations for other reasons. Splenomegaly, hepatomegaly, plethora, and hypertension are the most frequent presenting physical findings. Arterial and/or venous thromboembolism (TE) was reported in 19% to 34% of Ph-negative MPNs at diagnosis (10), but recently reported figures for PV were somewhat lower (2,11–13). Rates of 16% arterial and 7.4% venous thrombosis before or at diagnosis of PV were reported in the International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) database (2,11). Splanchnic thromboses such as Budd–Chiari syndrome (BCS) and portal vein thrombosis are especially frequent between venous thrombotic events in PV (8,14). The contemporary multicenter IWG-MRT cohort provides valuable information on clinical and laboratory (Table 1) features on presentation (2).

* Correspondence: ybuyukas@hacettepe.edu.tr

2.2. Current diagnostic criteria

The British Committee for Standards in Haematology (BCSH) 2007 (15) and World Health Organization (WHO) 2016 (16) diagnostic criteria are shown in Table 2. Bone marrow biopsy is a major criterion in the WHO 2016 criteria. It is suggested that bone marrow examination could only be omitted in the case of sustained prominently elevated hemoglobin (Hb) and/or hematocrit (Htc) levels (>16.5 g/dL and/or 49.5% in women or >18.5 g/dL and/or 55.5% in men), JAK2 mutation positivity, and a decreased serum erythropoietin (Epo) level (16). Dependence of the diagnosis on bone marrow biopsy in the current WHO criteria has been criticized (17). There are contradictory study results regarding the reproducibility of bone marrow morphological features for diagnosis of PV (17). The BCSH criteria for diagnosis of PV do not require bone marrow investigation (15). These criteria adapt the earlier Polycythemia Vera Study Group (PVSG) criteria for diagnosis of rare JAK2-negative cases.

After the 2016 WHO diagnostic criteria lowered Hb and Htc thresholds to 16.5 g/dL and 49% for diagnosis of PV, there have been concerns that many men with high-normal Hb (16.5–18 g/dL) and/or Htc (49%–54%) levels might be unnecessarily considered for the differential diagnosis of PV and tested for serum Epo level and/or JAK2 mutation. It is obvious that such people should not be considered for testing unless they have associated suspicious findings such as unexplained thrombocytosis, leukocytosis, splenomegaly, splanchnic thrombosis, and iron deficiency.

3. Clinical course and prognosis in PV

Adequately managed PV has a long natural history, but still shorter than the age-matched general population (2) and essential thrombocythemia (ET) patients (18,19). In a recent very large (n = 1545) international study (2), median survival duration was 14.1 years. The cause of death was unknown in over half (53%) of the patients. Acute leukemia (36/347, 10.3%), secondary malignancies (36/347, 10.3%), thrombotic complications (32/347, 9.2%), heart failure (13/347, 3.7%), and nonleukemic progressive disease (12/347, 3.4%) were the leading causes among other patients. Risk factors for survival were defined as older age, leukocytosis, venous thrombosis, and abnormal karyotype. A prognostic model was developed using the first three parameters (Table 3). The cumulative risk of acute leukemia, with death as a competing risk, was calculated as 2.3% at 10 years, 5.5% at 15 years, and 7.9% at 20 years. Progression to myelofibrosis (MF), arterial thrombosis, venous thrombosis, and major hemorrhage were reported as 9%, 12%, 9%, and 4.2% at a median of 6.9 years of follow-up duration.

The clinical course of PV and associated clinical and laboratory findings are summarized in Figure 1. The current WHO diagnostic criteria for post-PV MF were pro-

Table 1. Main laboratory findings at presentation in PV patients diagnosed according to WHO 2008 criteria (adapted from Tefferi et al. (2)).

Laboratory findings	
Hemoglobin (g/dL), median (range)	17.7 (15.1–24.5) in females 18.9 (17.1–26.5) in males
Hematocrit* (%), median (range)	54 (36–76) in females 57 (42–78) in males
Leukocytosis** (>10.5 × 10^9/L) (%)	49%
Thrombocytosis (≥450 × 10^9/L) (%)	53%
Extreme thrombocytosis (≥1000 × 10^9/L) (%)	4%
Elevated lactate dehydrogenase (%)	50%
Leukoerythroblastic smear (%)	6%
V617F/other JAK2 mutation (%)	95%/3%
Serum erythropoietin decreased/normal/elevated (%)	81%/17%/2%
Abnormal karyotype (%)	12%
Endogenous erythroid colony formation (%)	73%

*Red blood cell microcytosis preventing hematocrit elevation is possible at diagnosis due to associated iron deficiency mostly seondary to increased autonomous RBC production.
**Neutrophilia is frequent; basophilia, monocytosis, and eosinophilia are rare.

Table 2. WHO 2016 (16) and BCSH 2007 (15) diagnostic criteria for PV.

<table>
<tr><td>WHO 2016 criteria*</td><td colspan="2">BCSH 2007 criteria**</td></tr>
<tr><td>Major criteria</td><td colspan="2">JAK2-positive PV</td></tr>
<tr><td>1. Increased hemoglobin (>16.5 g/dL in men or >16.0 g/dL in women), hematocrit (>49% in men or >48% in women), or other evidence of increased red cell volume</td><td>A1</td><td>High hematocrit (>52% in men, >48% in women) or raised red cell mass (>25% above predicted)</td></tr>
<tr><td>2. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)</td><td>A2</td><td>JAK2 mutation</td></tr>
<tr><td>3. JAK2 V617F mutation in exon 14 or exon 12 mutations</td><td colspan="2">**Diagnosis requires both criteria to be present</td></tr>
<tr><td>Minor criterion</td><td colspan="2">JAK2-negative PV***</td></tr>
<tr><td>Serum erythropoietin level below the reference range for normal</td><td>A1</td><td>Raised red cell mass (>25% above predicted) or hematocrit >0.60 in men, >0.56 in women</td></tr>
<tr><td rowspan="9">*Diagnosis of polycythemia vera requires meeting either all 3 major criteria or the first 2 major criteria and the minor criterion.

Bone marrow biopsy could be omitted in some circumstances explained in the text. However, biopsy is still recommended on every condition as it may also provide important prognosis-related information: detection of initial myelofibrosis (present in up to 20% of patients), which predicts a more rapid progression to post-PV myelofibrosis, and detection of abnormal karyotype (present in nearly 12% of patients) by marrow cytogenetic analysis.</td><td>A2</td><td>Absence of JAK2 mutation</td></tr>
<tr><td>A3</td><td>No cause of secondary erythrocytosis</td></tr>
<tr><td>A4</td><td>Palpable splenomegaly</td></tr>
<tr><td>A5</td><td>Presence of an acquired genetic abnormality (excluding BCR-ABL) in the hematopoietic cells</td></tr>
<tr><td>B1</td><td>Thrombocytosis (platelet count >450 × 10^9/L)</td></tr>
<tr><td>B2</td><td>Neutrophil leukocytosis (neutrophil count >10 × 10^9/L in nonsmokers; >12.5 × 10^9/L in smokers)</td></tr>
<tr><td>B3</td><td>Radiological evidence of splenomegaly</td></tr>
<tr><td>B4</td><td>Endogenous erythroid colonies or low serum erythropoietin.</td></tr>
<tr><td colspan="2">***Diagnosis requires A1 + A2 + A3 + either another A or two B criteria</td></tr>
</table>

Table 3. Risk factors for contemporary PV survival and transformations to MF and leukemia.

Parameter (reference number)	Risk factor(s)
Survival (2)	Age ≥67 (5 points)
	Age 57–66 (2 points)
	Leukocytes ≥15 × 10^9/L (1 point)
	Venous thrombosis (1 point)
Low-risk (0 points, median survival: 27.8 years), intermediate-risk (1 or 2 points, median survival: 18.9 years), and high-risk (≥3 points, median survival: 10.9 years	
Leukemic transformation (2)	Older age (>61)
	Abnormal karyotype
	Leukocytes ≥15 × 10^9/L
	Exposure to P32, chlorambucil, pipobroman
Progression to MF (21)	Leukocyte count

	Symptoms-signs (details in the text)		Lab findings	Bone marrow
Erythrocytotic phase	INCREASE in EM HEMATOPOIESIS-/ SPLENOMEGALY- AND CYTOPENIA-RELATED SYMPTOMS-SIGNS	DECREASE in HYPERVISCOSITY- AND MICROVASCULAR-RELATED SYMPTOMS-SIGNS	Erythrocytosis leukocytosis thrombocytosis	No or mild increase in reticulin fibers
Inactive phase			Hb-Htc N (no phlebotomy / cytoreductive) LEB and tear-drop RBCs possible Leukocyte and platelet counts variable	May or may not be compatible with myelofibrosis
Spent phase			Anemia LEB Leukocyte and platelet counts variable	Myelofibrosis to osteomyelosclerosis
Acute leukemia	Leukemia-related symptoms-signs Symptoms-signs related to the baseline polycythemia vera phase		Leukemia-specific lab findings possible	Acute myeloblastic leukemia (very rarely ALL)

EM: extramedullary, Hb: hemoglobin, Hct: hematocrit, LEB: leukoerythroblastosis, RBC: red blood cell, ALL: acute lymphoblastic leukemia

Figure 1. Clinical course of PV.

posed by Barosi et al. (20). Transformation to MF obviously shortens survival (21). However, post-PV MF has a better prognosis compared to primary MF (22,23).

Risk factors for transformations to MF and leukemia are also summarized in Table 3. Recently it has been shown that ASXL1, SRSF2, and IDH2 mutations also have a negative impact on leukemia and MF transformation risks and survival independent of clinically derived prognostic models (24). The leukemia cases secondary to PV are nearly always AML (25,26). Post-PV AML has a dismal prognosis (25,27).

3.1. Risk factors for vascular events: what is high-risk PV?

Older age (generally considered as >60 years) and prior thrombosis are the usual risk factors for TE in PV. These factors were first determined to contribute to overall risk of thrombosis in the PVSG01 study cohort (n = 431) (28). Older age and history of thrombosis also emerged as the most important risks for cardiovascular complications in the ECLAP study, a large international study (n = 1638) investigating the role of aspirin in the treatment of relatively low-risk PV (29). In a recent study by Barbui et al. (30) evaluating a large cohort of contemporary PV cases treated according to modern concepts, age ≥65 and previous venous thrombosis were determined as the main risk factors for venous TE. Arterial event history and hypertension were the risk factors for arterial events. Although not formally proved in PV and therefore controversial, some authors consider general cardiovascular risk factors in addition to older age and prior thrombosis as important parameters for TE risk prediction (31). The results of the large contemporary PV study just mentioned (30) are in agreement with this approach. In a recent IWG-MRT study, Barbui et al. investigated the effect of arterial hypertension on TE risk in low-risk PV (n = 604, median age: 49 years, median follow-up duration: 4.9 years) conventionally treated with phlebotomy and aspirin (32). Thrombosis-free survival was significantly lower (34% vs. 66%, P = 0.025) in patients with hypertension. The authors concluded that these data suggest revising the risk stratification of patients with low-risk PV by including further stratification according to the presence of hypertension. Additional supporting data on the importance of cardiovascular risk factors were obtained in ET: some cardiovascular risk factors (active smoking, hypertension, and diabetes mellitus) were found as independent risk factors for thrombosis in the ET IPSET-thrombosis risk model (33).

Some investigators have found that leukocyte count (34–38) and JAK2 V617F allele burden (39) might also be important risk factors for thromboembolic complications in PV, but it is still unclear how to consider these parameters in risk prediction and management.

4. Management of PV

4.1. Aims of management and parameters to be considered

Prevention of thromboembolic complications and relieving symptoms are the current treatment aims in PV. Achieving these aims unambiguously increases quality of life and survival, but current treatments cannot prevent disease transformation to MF or leukemia. An Htc level of <45% is the main target for disease control. Pearson and Wetherley-Mein (40) first showed an association between Htc and thrombotic events. This observation led to the recommended target Htc of <45%. Validity of this recommendation was confirmed in a randomized controlled study within the last decade. The CYTO-PV study (41) showed that PV patients treated with phlebotomy, hydroxyurea (HU), or both with an Htc target of less than 45% had a significantly lower rate of cardiovascular death and major thrombosis than did those with an Htc target of 45% to 50%. In addition to the mentioned Htc level, aiming at normal platelet and leukocyte counts may be preferable in cytoreductive

treatment. This aim has not been determined by means of adequately designed prospective studies, but there have been retrospective data indicating decreased hematologic transformation rate and prolonged survival with normalization of leukocyte counts and decreased thrombohemorrhagic complications with normalization of platelet counts in PV (42). The European LeukemiaNet (ELN) proposed response criteria for treatment of PV first in 2009 (43) and then these criteria were revised in an ELN and IWG-MRT consensus project (44). In these criteria, the definition of peripheral blood count remission includes Hct lower than 45% without phlebotomies, platelet count of $\leq 400 \times 10^9$/L, and leukocyte count of $<10 \times 10^9$/L.

Contemporary management of PV depends on TE risk category. Although risk factors for post-PV MF, secondary AML, and survival have been defined, these factors currently do not affect treatment algorithms. Avoiding unnecessary treatments and follow-up for treatment-related toxicities and emerging vascular risk factors are also important management strategies. Specific guidelines agree on the necessity of cytoreductive treatment in patients at high risk of TE. Additionally, there is no conflict that phlebotomy (aiming at <45% Htc) plus aspirin are enough for PV cases with low TE risk. The management of patients with TE risk factors other than older age and history of TE, importance of some newly proposed thrombosis risk factors such as leukocyte count (34–38,45,46), roles of cytoreductive drugs other than HU (e.g., anagrelide), and leukocyte and platelet count targets are contradictory issues.

4.2. Specific recommendations

Cardiovascular risk factors should be adequately managed in every patient with PV. Htc should be kept below 45% by means of phlebotomy and/or cytoreductive drugs (if indicated) as demonstrated in the randomized CYTO-PV study (41). Low-dose aspirin (100 mg/day) should be prescribed unless there is a specific contraindication. The randomized ECLAP study (29) showed that aspirin as compared with a placebo reduced the risk of combined end point of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes and the risk of combined end point of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes. The incidence of major bleeding episodes was not significantly increased in the aspirin group. Although no randomized studies have been published comparing cytoreduction with only phlebotomy in PV, there is a general consensus on the indications of cytoreductive therapy in PV in various international guidelines (47–49): high TE risk (i.e. older age and/or previous thrombosis), poor compliance to phlebotomy, progressive myeloproliferation (symptomatic splenomegaly, leukocytosis, >1000-1500 $\times 10^9$/L thrombocytosis), and symptoms refractory to (or inadequate for) palliative therapies. Uncontrolled major cardiovascular risk factors (i.e. diabetes mellitus, hypertension, and atherosclerosis) are also considered as indications for cytoreduction by some experts (17). Cytoreductive drug preferences change widely, as summarized below. The authors of this review prefer to use the treatment algorithm summarized in Figure 2.

Standard arterial and venous TE approaches can be applied for acute TE attacks in PV. There is also no problem about antiplatelet drug use for secondary prophylaxis of arterial TE events. However, there are unknowns about the duration of secondary prophylaxis beyond 3–6 months of treatment period of venous TE events as stated in a recent consensus statement (50). Hemorrhages due to treatment (antiplatelet and anticoagulant drugs, thrombocytopenia secondary to HU), disease evolution or complications (thrombocytopenia resulting from disease transformation or splanchnic thrombosis and/or extramedullary hematopoiesis-related portal hypertension/hypersplenism, coagulopathy of liver failure caused by BCS, etc.), acquired von Willebrand syndrome (AVWS), and intrinsic platelet dysfunctions are also possible during the disease course (51). Diagnosis and management of these specific scenarios involve some specific details. AVWS should be suspected in patients with very high platelet counts ($>1000 \times 10^9$/L) and unexplained bleeding. Diagnosis of this condition depends on showing a disproportionately decreased von Willebrand factor activity compared to antigenic concentration of the molecule. Antiplatelet therapy should be withheld in patients with this problem and/or in cases of extreme ($>1000 \times 10^9$/L) thrombocytosis. Rapid platelet reduction (platelet apheresis and cytoreductive treatment) in addition to von Willebrand disease-specific treatments (factor concentrate, desmopressin acetate) is necessary for management of hemorrhages secondary to AVWS. Intrinsic platelet dysfunctions have also been described in MPNs including PV. Hemorrhages induced by intrinsic platelet dysfunction are also an indication for platelet lowering treatment (52).

4.3. HU versus interferon-alpha for cytoreduction

HU has been used in PV for nearly 40 years. It is certainly effective in the normalization of blood counts, splenomegaly, and some disease-related symptoms. Fewer thrombotic events were observed with HU compared to a historical control group (managed only with phlebotomy) in a single-arm study (53). Final results of a randomized French study initiated in 1980 comparing HU and pipobroman were published in 2011 (23). Median survival was 20.3 and 15.4 years in the HU and pipobroman arms, respectively (P = 0.008). Cumulative incidence of AML/myelodysplastic syndrome at 10, 15, and 20 years was 6.6%, 16.5%, and 24% in the HU arm and 13%, 34%, and 52% in the pipobroman arm (P = 0.004). Cumulative MF

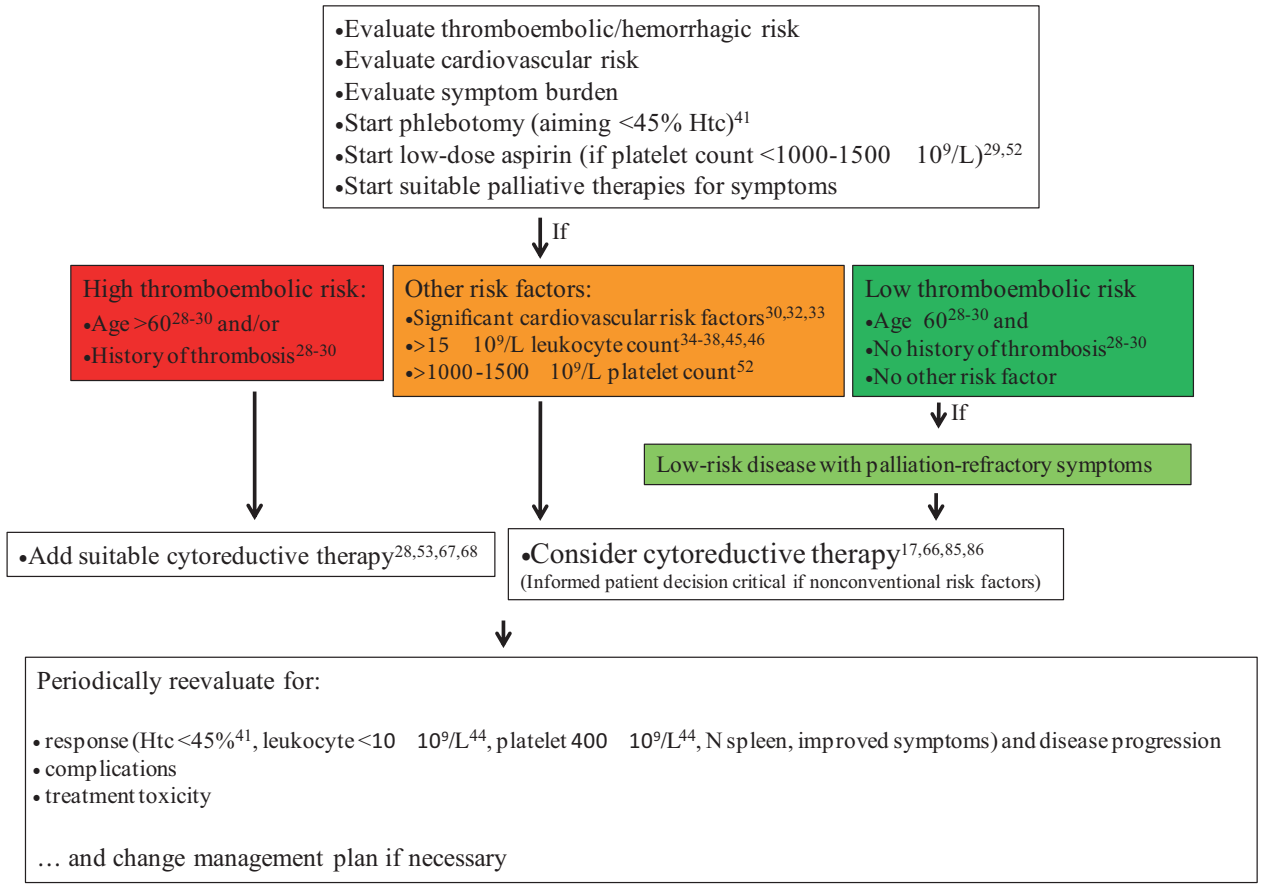

Figure 2. Management of PV based on general experiences and study results (superscripts: reference numbers).

incidence at the same periods according to main treatment received was 15%, 24%, and 32% with HU versus 5%, 10%, and 21% with pipobroman (P = 0.02). Superiority of HU (except MF transformation) supports current treatment algorithms favoring this drug for cytoreduction. Higher than expected leukemia risk with HU as reported in this study was not observed in the prospective ECLAP study cohort (29), in a Sweden population study (54), or in the IWG-MRT cohort (2). These data, extensive experience with this drug, the advantage of oral use, and low treatment cost make HU the preferred drug for cytoreduction in PV (55). However, there are many contradictory small studies related to secondary solid cancer risk in MPN patients who received HU. Additionally, HU-related fertility and teratogenicity issues are important for young patients. Actually, interferon (IFN)-alpha has been more extensively evaluated in phase 2 studies. The clinical responses are favorable (56). It can control erythrocytosis or thrombocytosis in a majority of patients. Reduction in spleen size and relief from pruritus are also frequent. Pegylated IFN-alpha-2a (peg-IFN) can provide high hematologic (up to 82% complete response in phase 2 studies), molecular (up to 28% complete response in phase 2 studies), and histologic responses in PV and ET. The responses are frequently sustained even after stopping treatment. Vascular events are rarely reported during treatment (57–65). However, IFN-alpha is frequently difficult to tolerate due to flu-like symptoms.

In a Chinese open-label, observational, multicenter clinical assessment study, IFN-alpha-2b was associated with deeper molecular responses, lower phlebotomy need, and longer progression-free survival compared to HU (66). Moreover, IFN provided better symptom control for erythromelalgia, distal paresthesias, and headaches. Two recent randomized studies compared peg-IFN and HU in intermediate- or high-risk PV. Interim analysis results of the Myeloproliferative Disorders Research Consortium (MPD-RC) phase III 112 trial comparing frontline Peg-IFN and HU in high-risk PV and ET showed similar hematologic response rates (67). Grade 3 adverse events (depression, pain, dyspnea, injection site reaction) were more frequent with peg-IFN. In the randomized controlled phase III PROUD-PV study comparing ropeginterferon alfa-2b (Ropeg), a novel mono-pegylated IFN, with HU

in chemotherapy-naive or HU-pretreated but not resistant PV patients, Ropeg achieved higher hematologic and molecular response rates (68).

Currently, the BCSH guidelines (47) recommend IFN-alpha for first-line treatment of patients <40 years old in need of cytoreductive treatment. HU was recommended for those aged 40 or above. ELN recommendations (48) propose that either HU or IFN-alpha be the first-line cytoreductive therapy at any age. International experts Tefferi and Barbui recommend HU for first-line treatment in high-risk patients irrespective of age (49).

4.4. Symptom burden and management

Even low-risk PV patients still report significant symptoms limiting quality of life and productivity (69). Symptoms with some variations continue during the disease course (9). Blood count values, myelosuppressive treatment, and disease-specific risk groups may not significantly associate with symptom scores (70,71). The main symptom burden derives from increased cytokines-chronic inflammation (e.g., fever, night sweating), hyperviscosity-microvascular problems (e.g., headache, dizziness, transient visual disturbances), increased cell proliferation (e.g., bone pain, weight loss at diagnosis), and extramedullary hematopoiesis (e.g., splenomegaly and related symptoms). Cytokine symptoms tend to be more frequent at diagnosis and during MF transformation. Hyperviscosity-microvascular symptoms are expected to decrease and extramedullary hematopoiesis and cytopenia-related symptoms to increase toward the spent phase of the disease (Figure 1).

Significant progress has been achieved during the last decade in quantifying the MPN-related symptoms (72–76). Now it is possible to assess this different aspect of PV independently from TE risk evaluation. Adapting the objective symptom assessment (such as the MPN-10 scoring (75)) to routine care of PV patients will probably improve the management of this disease.

Pruritus (73) and a rare problem, erythromelalgia (also associated with ET (77)) are well-defined symptoms that are relatively most specific to PV among hematopoietic neoplasms.

Erythromelalgia is a rare clinical syndrome characterized by burning pain, redness, and objective sensation of increased temperature in the digits (77). Erythromelalgia secondary to PV (and ET) is typically responsive to aspirin. This characteristic supports the idea that erythromelalgia is caused by arterial microcirculation occlusion from intravascular platelet activation and aggregation (78). Cytoreductive treatment of PV may also reduce erythromelalgia symptoms.

Itching has been reported in nearly 60% of PV patients (2,22). It is frequently triggered by water (aquagenic pruritus) and changes in skin temperature (79,80). It occurs most frequently in warmer areas of the skin, such as on the trunk and proximal extensor parts of the extremities. Itching frequency correlates with JAK2 V617F homozygosity (81,82). Mixed results have been reported with antihistamines for treatment of itching in PV (83). Selective serotonin reuptake inhibitors were found as reasonably effective (84). Cytoreductive therapy with HU may provide improvements in some patients. In the RELIEF study (recruiting patients who were well controlled with a stable dose of HU but still reported PV-related symptoms), proportions of patients with ≥50% improvement in itching at week 16 were 32% vs. 54.2% in the HU and ruxolitinib arms, respectively (P = 0.027) (85). Ruxolitinib was reported to improve itching in 95% of phlebotomy-dependent PV patients with splenomegaly in the RESPONSE study (73). Quite effective (nearly 80%) control of pruritus has also been described with IFN-alpha (79,86).

4.5. Definition of resistance/intolerance to HU treatment

The ELN definitions (87) (Table 4) consider three main factors to define resistance/intolerance to HU: uncontrolled myeloproliferation (cytoses, need for phlebotomy, splenomegaly) after 3 months of at least 2 g/day of HU, cytopenia(s) at the lowest dose of HU necessary to achieve a response, or unacceptable nonhematological toxicities. In a PV chart review study undertaken in 5 Spanish centers (261 patients, median follow-up duration: 7.2 years), frequencies of HU resistance and intolerance defined according to these criteria were found as 11% and 13%, respectively (44). In a larger Spanish multicenter study (n = 890) (88), the frequency of HU resistance and/or intolerance was lower (15%), probably due to a shorter (4.6 years) median follow-up duration. Treatment with at least 2 g/day of HU for 3 months as a mandatory requirement for HU resistance is not a common practice among hematologists. This may also be a reason for the different HU resistance prevalence rates reported (88). The associations of inadequately controlled (≥45%) Htc and elevated leukocyte counts with vascular events, leukemic transformation (only for leukocytosis), and decreased survival have been summarized above. More specifically, HU resistance according to the ELN definition has been reported to be related to a higher transformation rate into acute leukemia or MF and a higher mortality risk (42,89). Cytopenia(s) at the lowest dose of HU required to achieve a complete or partial clinicohematological response was especially linked to dismal prognosis (88).

4.6. Second-line treatment

HU or IFN-alpha (whichever was not used in first-line treatment; see Section 4.3), ruxolitinib, and busulfan may be considered as second-line treatment alternatives. Increased leukemia and secondary cancer risk in patients

Table 4. Definition of resistance/intolerance to hydroxyurea in patients with PV (87).

1. Need for phlebotomy to keep hematocrit <45% after 3 months of at least 2 g/day of HU, OR
2. Uncontrolled myeloproliferation, i.e. platelet count >400 × 10^9/L AND leukocyte count >10 × 10^9/L after 3 months of at least 2 g/day of HU, OR
3. Failure to reduce massive* splenomegaly by more than 50% as measured by palpation, OR failure to completely relieve symptoms related to splenomegaly, after 3 months of at least 2 g/day of HU, OR
4. Absolute neutrophil count <1.0 × 10^9/L OR platelet count <100 × 10^9/L OR hemoglobin <10 g/dL at the lowest dose of HU required to achieve a complete or partial clinicohematological response**, OR
5. Presence of leg ulcers or other unacceptable HU-related nonhematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever at any dose of HU.

* Extending by more than 10 cm from the costal margin.
**Complete response was defined as follows: hematocrit <45% without phlebotomy, platelet count ≤400 × 10^9/L, leukocyte count ≤10 × 10^9/L, and no disease-related symptoms. Partial response was defined as follows: hematocrit <45% without phlebotomy, or response in three or more of the other criteria.

who used sequential busulfan and HU has been described (53,90,91). Therefore, busulfan is not a logical second-line alternative probably except for very old patients.

In the MPD-RC 111 study, an international, multicenter, phase 2 trial evaluating ELN response rates to Peg-IFN in patients with high-risk PV and ET who were refractory or intolerant to HU, Peg-IFN achieved 60% overall response rate (22% complete and 38% partial) in PV patients. However, treatment was associated with significant numbers of adverse events limiting tolerability (92).

Effects of ruxolitinib in PV patients have been tested in three randomized studies to date. The RESPONSE trial (74) is an international, randomized, open-label, multicenter phase 3 study. Eligible PV patients had phlebotomy requirements for Htc control and/or a spleen volume of 450 cm^3 or more. They satisfied the criteria of resistance or intolerance to HU according to the modified ELN criteria. Ruxolitinib (10 mg BID) was compared with standard therapy. Patients in the standard therapy arm could cross over to ruxolitinib at week 32 if the primary end point was not met or later in the case of disease progression. The primary end point was both Htc and spleen volume controls through week 32. RESPONSE showed that ruxolitinib was effective in achieving Htc control (60% vs. 19.6%), ≥35% reduction in spleen volume (38.2% vs. 0.9%), and the composite primary end point (20.9% vs. 0.9%, P < 0.001) comprising these two components. Ruxolitinib was also more effective in reducing symptoms (49% vs. 5% at least 50% MPN-SAF-TSS reduction at week 32).

The RESPONSE-2 study (76) is also an international randomized, open-label, phase 3 study assessing ruxolitinib (10 mg BID) versus investigator-selected best available therapy (BAT) in phlebotomy-dependent patients with PV. These patients also had to meet the definition of HU resistance or intolerance according to the modified ELN criteria. In contrast to the RESPONSE trial, this study included patients without splenomegaly. The primary end point was Htc control at week 28. Again, BAT patients could cross over to ruxolitinib from week 28 if therapy was ineffective or for safety-related reasons. Ruxolitinib was superior to BAT at controlling Htc (62% vs. 19%, P < 0.0001) and 81% vs. 40% of patients were phlebotomy-free between baseline and week 28. Ruxolitinib also achieved improvements in all PV-associated symptoms while patients in the BAT arm experienced a worsening of most symptoms (50% vs. 8% complete and 45% vs. 23% ≥50% MPN-SAF-TSS improvement at week 28).

Follow-up durations in the RESPONSE studies were short. It is impossible to make firm conclusions about vascular complications, but patients treated with ruxolitinib in both the RESPONSE and RESPONSE-2 studies had fewer (2 vs. 6 and 2 vs. 9) thromboembolic events compared with the control arm.

RELIEF was a randomized, double-blind, double-dummy, phase 3 trial evaluating cytokine-related symptoms in patients who were hematologically well controlled with a stable dose of HU but still reported symptoms (85). Patients were randomized to ruxolitinib (10 mg BID) or HU (prerandomization dose/schedule). Ruxolitinib was associated with a statistically nonsignificant trend towards improved PV-related symptoms versus HU: the primary endpoint, ≥50% improvement from baseline in MPN-SAF-TSS cytokine symptom cluster (MPN-SAF-TSS-C, the sum of tiredness, itching, muscle aches, night sweats, and sweats while awake) at week 16, was achieved by 43.4% vs. 29.6% of ruxolitinib- and HU-treated patients, respectively (P = 0.139). Proportions of patients with ≥50% improvement in individual symptoms were as follows:

40% vs. 26.4% for fatigue, 54.2% vs. 32% for itching, 38.3 vs. 30.6% for muscle aches, 47.6 vs. 41.7% for night sweats, and 54.8% vs. 34.8% for sweating while awake. Only the difference for itching was statistically significant (54.2% vs. 32%, P = 0.027).

Both ruxolitinib and BAT/HU were associated with few grade 3–4 adverse events in the two RESPONSE trials (74,76) and RELIEF (85).

4.7. Special circumstances

High rates of bleeding or thrombosis have been observed during and after surgeries in PV patients (93,94). It may be safer to perform elective surgeries months after optimal disease control. Significant maternal, fetal, and newborn morbidities have been reported in PV pregnancies (95). Aspirin ± low-molecular-weight heparin ± IFN-alpha has been recommended according to risk estimation (see Griesshammer et al. (95) for details).

5. Unresolved questions and unmet needs

In spite of significant recent developments there are still many questions and unmet needs related to the clinical approach to PV:

1. Discordance even among experienced hematopathologists makes the value of bone marrow biopsy for the diagnosis of PV disputable. It is uncertain if education could lead to sufficient improvement.
2. No current diagnostic criteria are suitable for diagnosis of PV in cases of nonelevated Hb and Htc due to associated iron deficiency and/or hemodilution, etc.
3. How to evaluate treatment response in a patient with masked nonelevated Htc and blood cell counts due to congestive splenomegaly/hypervolemia such as in BCS?
4. Nowadays it is clear that cardiovascular risk factors and leukocytosis impact thromboembolic risk. These cases cannot be considered as low risk. However, these parameters are generally still not considered in the up-to-date treatment guidelines.
5. The value of IFN-alpha in comparison to HU in the first-line treatment of PV is still to be explored.
6. What is the correct sequence of second-line drug choice in a specific patient?
7. Absence of drugs that can change disease course is an unmet need.
8. Treatment of PV patients with a shortened prognostic expectation such as those with HU resistance due to cytopenia(s), post-PV MF, or secondary AML is unsatisfactory.
9. The duration of anticoagulation for secondary prophylaxis of venous TE in PV is arguable.

References

1. Titmarsh GJ, Duncombe AS, McMullin MF, O'Rorke M, Mesa R, De Vocht F, Horan S, Fritschi L, Clarke M, Anderson LA. How common are myeloproliferative neoplasms? A systematic review and meta-analysis. Am J Hematol 2014; 89: 581-587.
2. Tefferi A, Rumi E, Finazzi G, Gisslinger H, Vannucchi AM, Rodeghiero F, Randi ML, Vaidya R, Cazzola M, Rambaldi A et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. Leukemia 2013; 27: 1874-1881.
3. Baxter EJ, Scott LM, Campbell PJ, East C, Fourouclas N, Swanton S, Vassiliou GS, Bench AJ, Boyd EM, Curtin N et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet 2005; 365: 1054-1061.
4. James C, Ugo V, Le Couédic JP, Staerk J, Delhommeau F, Lacout C, Garçon L, Raslova H, Berger R, Bennaceur-Griscelli A et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. Nature 2005; 434: 1144-1148.
5. Kralovics R, Passamonti F, Buser AS, Teo SS, Tiedt R, Passweg JR, Tichelli A, Cazzola M, Skoda RC. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med 2005; 352: 1779-1790.
6. Levine RL, Wadleigh M, Cools J, Ebert BL, Wernig G, Huntly BJ, Boggon TJ, Wlodarska I, Clark JJ, Moore S et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Cancer Cell 2005; 7:387-397.
7. Pardanani A, Lasho TL, Finke C, Hanson CA, Tefferi A. Prevalence and clinicopathologic correlates of JAK2 exon 12 mutations in JAK2V617F-negative polycythemia vera. Leukemia 2007; 21: 1960-1963.
8. Berlin NI. Diagnosis and classification of the polycythemias. Semin Hematol 1975; 12: 339-351.
9. Abelsson J, Andréasson B, Samuelsson J, Hultcrantz M, Ejerblad E, Johansson B, Emanuel R, Mesa R, Johansson P. Patients with polycythemia vera have worst impairment of quality of life among patients with newly diagnosed myeloproliferative neoplasms. Leuk Lymphoma 2013; 54: 2226-2230.
10. Casini A, Fontana P, Lecompte TP. Thrombotic complications of myeloproliferative neoplasms: risk assessment and risk-guided management. J Thromb Haemost 2013; 11: 1215-1227.

11. Barbui T, Vannucchi AM, Carobbio A, Thiele J, Rumi E, Gisslinger H, Rodeghiero F, Randi ML, Rambaldi A, Pieri L et al. Patterns of presentation and thrombosis outcome in patients with polycythemia vera strictly defined by WHO-criteria and stratified by calendar period of diagnosis. Am J Hematol 2015; 90: 434-437.

12. Hultcrantz M, Kristinsson SY, Andersson TM, Landgren O, Eloranta S, Derolf AR, Dickman PW, Björkholm M. Patterns of survival among patients with myeloproliferative neoplasms diagnosed in Sweden from 1973 to 2008: a population-based study. J Clin Oncol 2012; 30: 2995-3001.

13. Hultcrantz M, Björkholm M, Dickman PW, Landgren O, Derolf ÅR, Kristinsson SY, Andersson TML. Risk for arterial and venous thrombosis in patients with myeloproliferative neoplasms: a population-based cohort study. Ann Intern Med 2018; 168: 317-325.

14. Chait Y, Condat B, Cazals-Hatem D, Rufat P, Atmani S, Chaoui D, Guilmin F, Kiladjian JJ, Plessier A, Denninger MH et al. Relevance of the criteria commonly used to diagnose myeloproliferative disorder in patients with splanchnic vein thrombosis. Br J Haematol 2005; 129: 553-560.

15. McMullin MF, Reilly JT, Campbell P, Bareford D, Green AR, Harrison CN, Conneally E; National Cancer Research Institute, Myeloproliferative Disorder Subgroup, Ryan K; British Committee for Standards in Haematology. Amendment to the guideline for diagnosis and investigation of polycythaemia/erythrocytosis. Br J Haematol 2007; 138: 821-822.

16. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016; 127: 2391-2405.

17. McMullin MF, Wilkins BS, Harrison CN. Management of polycythaemia vera: a critical review of current data. Br J Haematol 2016; 172: 337-349.

18. Passamonti F, Thiele J, Girodon F, Rumi E, Carobbio A, Gisslinger H, Kvasnicka HM, Ruggeri M, Randi ML, Gangat N et al. A prognostic model to predict survival in 867 World Health Organization-defined essential thrombocythemia at diagnosis: a study by the International Working Group on Myelofibrosis Research and Treatment. Blood 2012; 120: 1197-1201.

19. Tefferi A, Guglielmelli P, Larson DR, Finke C, Wassie EA, Pieri L, Gangat N, Fjerza R, Belachew AA, Lasho TL et al. Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. Blood 2014; 124: 2507-2513.

20. Barosi G, Mesa RA, Thiele J, Cervantes F, Campbell PJ, Verstovsek S, Dupriez B, Levine RL, Passamonti F, Gotlib J et al. Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. Leukemia 2008; 22: 437-438.

21. Passamonti F, Rumi E, Caramella M, Elena C, Arcaini L, Boveri E, Del Curto C, Pietra D, Vanelli L, Bernasconi P et al. A dynamic prognostic model to predict survival in post-polycythemia vera myelofibrosis. Blood 2008; 111: 3383-3387.

22. Gowin K, Coakley M, Kosiorek H, Mesa R. Discrepancies of applying primary myelofibrosis prognostic scores for patients with post polycythemia vera/essential thrombocytosis myelofibrosis. Haematologica 2016; 101: e405-e406.

23. Passamonti F, Giorgino T, Mora B, Guglielmelli P, Rumi E, Maffioli M, Rambaldi A, Caramella M, Komrokji R, Gotlib J et al. A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. Leukemia 2017; 31: 2726-2731.

24. Tefferi A, Lasho TL, Guglielmelli P, Finke CM, Rotunno G, Elala Y, Pacilli A, Hanson CA, Pancrazzi A, Ketterling RP et al. Targeted deep sequencing in polycythemia vera and essential thrombocythemia. Blood Adv 2016; 1: 21-30.

25. Hidalgo López JE, Carballo-Zarate A, Verstovsek S, Wang SA, Hu S, Li S, Xu J, Zuo W, Tang Z, Yin CC et al. Bone marrow findings in blast phase of polycythemia vera. Ann Hematol 2018; 97: 425-434.

26. Gaweł WB, Helbig G, Boral K, Kyrcz-Krzemień S. Acute lymphoblastic leukemia transformation in polycythemia Vera: a rare phenomenon. Indian J Hematol Blood Transfus 2016; 32 (Suppl. 1): 62-65.

27. Kennedy JA, Atenafu EG, Messner HA, Craddock KJ, Brandwein JM, Lipton JH, Minden MD, Schimmer AD, Schuh AC, Yee KW et al. Treatment outcomes following leukemic transformation in Philadelphia-negative myeloproliferative neoplasms. Blood 2013; 121: 2725-2733.

28. Berk PD, Goldberg JD, Donovan PB, Fruchtman SM, Berlin NI, Wasserman LR. Therapeutic recommendations in polycythemia vera based on Polycythemia Vera Study Group protocols. Semin Hematol 1986; 23: 132-143.

29. Landolfi R, Marchioli R, Kutti J, Gisslinger H, Tognoni G, Patrono C, Barbui T; European Collaboration on Low-Dose Aspirin in Polycythemia Vera Investigators. Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med 2004; 350: 114-124.

30. Barbui T, Carobbio A, Rumi E, Finazzi G, Gisslinger H, Rodeghiero F, Randi ML, Rambaldi A, Gisslinger B, Pieri L et al. In contemporary patients with polycythemia vera, rates of thrombosis and risk factors delineate a new clinical epidemiology. Blood 2014; 124: 3021-3023.

31. Reiter A, Harrison C. How we identify and manage patients with inadequately controlled polycythemia vera. Curr Hematol Malig Rep 2016; 11: 356-367.

32. Barbui T, Vannucchi AM, Carobbio A, Rumi E, Finazzi G, Gisslinger H, Ruggeri M, Randi ML, Cazzola M, Rambaldi A et al. The effect of arterial hypertension on thrombosis in low-risk polycythemia vera. Am J Hematol 2017; 92: E5-E6.

33. Barbui T, Finazzi G, Carobbio A, Thiele J, Passamonti F, Rumi E, Ruggeri M, Rodeghiero F, Randi ML, Bertozzi I et al. Development and validation of an International Prognostic Score of thrombosis in World Health Organization-essential thrombocythemia (IPSET-thrombosis). Blood 2012; 120: 5128-5133

34. Landolfi R, Di Gennaro L, Barbui T, De Stefano V, Finazzi G, Marfisi R, Tognoni G, Marchioli R; European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP). Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. Blood 2007; 109: 2446-2452.

35. De Stefano V, Za T, Rossi E, Vannucchi AM, Ruggeri M, Elli E, Micò C, Tieghi A, Cacciola RR, Santoro C et al. Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments. Haematologica 2008; 93: 372-380.

36. Caramazza D, Caracciolo C, Barone R, Malato A, Saccullo G, Cigna V, Berretta S, Schinocca L, Quintini G, Abbadessa V et al. Correlation between leukocytosis and thrombosis in Philadelphia-negative chronic myeloproliferative neoplasms. Ann Hematol 2009; 88: 967-971.

37. Barbui T, Carobbio A, Rambaldi A, Finazzi G. Perspectives on thrombosis in essential thrombocythemia and polycythemia vera: is leukocytosis a causative factor? Blood 2009; 114: 759-763.

38. De Stefano V, Za T, Rossi E, Vannucchi AM, Ruggeri M, Elli E, Micò C, Tieghi A, Cacciola RR, Santoro C et al. Leukocytosis is a risk factor for recurrent arterial thrombosis in young patients with polycythemia vera and essential thrombocythemia. Am J Hematol 2010; 85: 97-100.

39. Bertozzi I, Bogoni G, Biagetti G, Duner E, Lombardi AM, Fabris F, Randi ML. Thromboses and hemorrhages are common in MPN patients with high JAK2V617F allele burden. Ann Hematol 2017; 96: 1297-1302.

40. Pearson TC, Wetherley-Mein G. Vascular occlusive episodes and venous haematocrit in primary proliferative polycythaemia. Lancet 1978; 2: 1219-1222.

41. Marchioli R, Finazzi G, Specchia G, Cacciola R, Cavazzina R, Cilloni D, De Stefano V, Elli E, Iurlo A, Latagliata R et al. Cardiovascular events and intensity of treatment in polycythemia vera. N Engl J Med 2013; 368:22-33.

42. Alvarez-Larrán A, Pereira A, Cervantes F, Arellano-Rodrigo E, Hernández-Boluda JC, Ferrer-Marín F, Angona A, Gómez M, Muiña B, Guillén H et al. Assessment and prognostic value of the European LeukemiaNet criteria for clinicohematologic response, resistance, and intolerance to hydroxyurea in polycythemia vera. Blood 2012; 119: 1363-1369.

43. Barosi G, Birgegard G, Finazzi G, Griesshammer M, Harrison C, Hasselbalch HC, Kiladjian JJ, Lengfelder E, McMullin MF, Passamonti F et al. Response criteria for essential thrombocythemia and polycythemia vera: result of a European LeukemiaNet consensus conference. Blood 2009; 113: 4829-4833.

44. Barosi G, Mesa R, Finazzi G, Harrison C, Kiladjian JJ, Lengfelder E, McMullin MF, Passamonti F, Vannucchi AM, Besses C et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood 2013; 121: 4778-4781.

45. Gangat N, Wolanskyj AP, Schwager SM, Hanson CA, Tefferi A. Leukocytosis at diagnosis and the risk of subsequent thrombosis in patients with low-risk essential thrombocythemia and polycythemia vera. Cancer 2009; 115: 5740-5745.

46. Passamonti F, Rumi E, Pietra D, Elena C, Boveri E, Arcaini L, Roncoroni E, Astori C, Merli M, Boggi S et al. A prospective study of 338 patients with polycythemia vera: the impact of JAK2 (V617F) allele burden and leukocytosis on fibrotic or leukemic disease transformation and vascular complications. Leukemia 2010; 24: 1574-1579.

47. McMullin MF, Bareford D, Campbell P, Green AR, Harrison C, Hunt B, Oscier D, Polkey MI, Reilly JT, Rosenthal E et al. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. Br J Haematol 2005; 130: 174-195.

48. Barbui T, Barosi G, Birgegard G, Cervantes F, Finazzi G, Griesshammer M, Harrison C, Hasselbalch HC, Hehlmann R, Hoffman R et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol 2011; 29: 761-770.

49. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2017 update on diagnosis, risk-stratification, and management. Am J Hematol 2017; 92: 94-108.

50. Kreher S, Ochsenreither S, Trappe RU, Pabinger I, Bergmann F, Petrides PE, Koschmieder S, Matzdorff A, Tiede A, Griesshammer M et al. Prophylaxis and management of venous thromboembolism in patients with myeloproliferative neoplasms: consensus statement of the Haemostasis Working Party of the German Society of Hematology and Oncology (DGHO), the Austrian Society of Hematology and Oncology (ÖGHO) and Society of Thrombosis and Haemostasis Research (GTH e.V.). Ann Hematol 2014; 93: 1953-1963.

51. Soyer N, Haznedaroğlu İC, Cömert M, Çekdemir D, Yılmaz M, Ünal A, Çağlıyan G, Bilgir O, İlhan O, Özdemirkıran F et al. Multicenter retrospective analysis of Turkish patients with chronic myeloproliferative neoplasms. Turk J Hematol 2017; 34: 27-33.

52. Appelmann I, Kreher S, Parmentier S, Wolf HH, Bisping G, Kirschner M, Bergmann F, Schilling K, Brümmendorf TH, Petrides PE et al. Diagnosis, prevention, and management of bleeding episodes in Philadelphia-negative myeloproliferative neoplasms: recommendations by the Hemostasis Working Party of the German Society of Hematology and Medical Oncology (DGHO) and the Society of Thrombosis and Hemostasis Research (GTH). Ann Hematol 2016; 95: 707-718.

53. Fruchtman SM, Mack K, Kaplan ME, Peterson P, Berk PD, Wasserman LR. From efficacy to safety: a Polycythemia Vera Study group report on hydroxyurea in patients with polycythemia vera. Semin Hematol 1997; 34: 17-23.

54. Björkholm M, Derolf AR, Hultcrantz M, Kristinsson SY, Ekstrand C, Goldin LR, Andreasson B, Birgegård G, Linder O, Malm C et al. Treatment-related risk factors for transformation to acute myeloid leukemia and myelodysplastic syndromes in myeloproliferative neoplasms. J Clin Oncol 2011; 29: 2410-2415.

55. Andıç N, Ünübol M, Yağcı E, Akay OM, Yavaşoğlu İ, Kadıköylü VG, Bolaman AZ. Clinical features of 294 Turkish patients with chronic myeloproliferative neoplasms. Turk J Hematol 2016; 33: 187-195.

56. Kiladjian JJ, Chomienne C, Fenaux P. Interferon-alpha therapy in bcr-abl-negative myeloproliferative neoplasms. Leukemia 2008; 22: 1990-1998.

57. Gilbert HS. Long term treatment of myeloproliferative disease with interferon-alpha-2b: feasibility and efficacy. Cancer 1998; 83: 1205-1213.

58. Foa P, Massaro P, Caldiera S, LaTargia ML, Iurlo A, Clerici C, Fornier M, Bertoni F, Maiolo AT. Long-term therapeutic efficacy and toxicity of recombinant interferon-alpha 2a in polycythaemia vera. Eur J Haematol 1998; 60: 273-277.

59. Silver RT. Long-term effects of the treatment of polycythemia vera with recombinant interferon-alpha. Cancer 2006; 107: 451-458.

60. Kiladjian JJ, Cassinat B, Chevret S, Turlure P, Cambier N, Roussel M, Bellucci S, Grandchamp B, Chomienne C, Fenaux P. Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. Blood 2008; 112: 3065-3072.

61. Turlure P, Cambier N, Roussel M, Bellucci S, Zini JM, Rain JD, Rousselot P, Vainchenker V, Abdelkader A, Ghomari K et al. Complete hematological, molecular and histological remissions without cytoreductive treatment lasting after pegylated-interferon α-2a (peg-IFNα-2a) therapy in polycythemia vera (PV): long term results of a phase 2 trial. Blood 2011; 118: 280a.

62. Quintás-Cardama A, Kantarjian H, Manshouri T, Luthra R, Estrov Z, Pierce S, Richie MA, Borthakur G, Konopleva M, Cortes J et al. Pegylated interferon alfa-2a yields high rates of hematologic and molecular response in patients with advanced essential thrombocythemia and polycythemia vera. J Clin Oncol 2009; 27: 5418-5424.

63. Gowin K, Thapaliya P, Samuelson J, Harrison CN, Radia D, Andreasson B, Mascarenhas J, Rambaldi A, Barbui T, Rea CJ et al. Pegylated interferon alpha-2a in patients with myeloproliferative neoplasms (MPN): international experience in 115 cases. Blood 2011; 118: 2818a.

64. Quintás-Cardama A, Abdel-Wahab O, Manshouri T, Kilpivaara O, Cortes J, Roupie AL, Zhang SJ, Harris D, Estrov Z, Kantarjian H et al. Molecular analysis of patients with polycythemia vera or essential thrombocythemia receiving pegylated interferon α-2a. Blood 2013; 122: 893-901.

65. Stauffer Larsen T, Iversen KF, Hansen E, Mathiasen AB, Marcher C, Frederiksen M, Larsen H, Helleberg I, Riley CH, Bjerrum OW et al. Long term molecular responses in a cohort of Danish patients with essential thrombocythemia, polycythemia vera and myelofibrosis treated with recombinant interferon alpha. Leuk Res 2013; 37: 1041-1045.

66. Huang BT, Zeng QC, Zhao WH, Li BS, Chen RL. Interferon α-2b gains high sustained response therapy for advanced essential thrombocythemia and polycythemia vera with JAK2V617F positive mutation. Leuk Res 2014; 38: 1177-1183.

67. Mascarenhas JO, Prchal JT, Rambaldi A, Mesa RA, Berenzon D, Yacoub A, Harrison CN, McMullin MF, Vannucchi AM, Ewing JC. Interim analysis of the Myeloproliferative Disorders Research Consortium (MPD-RC) 112 global phase III trial of front line pegylated interferon alpha-2a vs. hydroxyurea in high risk polycythemia vera and essential thrombocythemia. Blood 2016; 128: 479a.

68. Gisslinger H, Klade C, Georgiev P, Krochmalczyk D, Gercheva L, Egyed M, Rossiev V, Dulicek P, Illés A, Pylypenko H et al. Ropeginterferon alfa-2b induces high rates of clinical, hematological and molecular responses in polycythemia vera: two-year results from the first prospective randomized controlled trial. Blood 2017; 130: 320a.

69. Mesa RA, Niblack J, Wadleigh M, Verstovsek S, Camoriano J, Barnes S, Tan AD, Atherton PJ, Sloan JA, Tefferi A. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international Internet-based survey of 1179 MPD patients. Cancer 2007; 109: 68-76.

70. Johansson P, Mesa R, Scherber R, Abelsson J, Samuelsson J, Birgegård G, Andréasson B. Association between quality of life and clinical parameters in patients with myeloproliferative neoplasms. Leuk Lymphoma 2012; 53: 441-444.

71. Geyer HL, Scherber RM, Dueck AC, Kiladjian JJ, Xiao Z, Slot S, Zweegman S, Sackmann F, Fuentes AK, Hernández-Maraver D et al. Distinct clustering of symptomatic burden among myeloproliferative neoplasm patients: retrospective assessment in 1470 patients. Blood 2014; 123: 3803-3810.

72. Mesa RA, Schwager S, Radia D, Cheville A, Hussein K, Niblack J, Pardanani AD, Steensma DP, Litzow MR, Rivera CE et al. The Myelofibrosis Symptom Assessment Form (MFSAF): an evidence-based brief inventory to measure quality of life and symptomatic response to treatment in myelofibrosis. Leuk Res 2009; 33: 1199-1203.

73. Scherber R, Dueck AC, Johansson P, Barbui T, Barosi G, Vannucchi AM, Passamonti F, Andreasson B, Ferarri ML, Rambaldi A et al. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): international prospective validation and reliability trial in 402 patients. Blood 2011; 118: 401-408.

74. Vannucchi AM, Kiladjian JJ, Griesshammer M, Masszi T, Durrant S, Passamonti F, Harrison CN, Pane F, Zachee P, Mesa R et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med 2015; 372: 426-435.

75. Emanuel RM, Dueck AC, Geyer HL, Kiladjian JJ, Slot S, Zweegman S, te Boekhorst PA, Commandeur S, Schouten HC, Sackmann F et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol 2012; 30: 4098-4103.

76. Passamonti F, Griesshammer M, Palandri F, Egyed M, Benevolo G, Devos T, Callum J, Vannucchi AM, Sivgin S, Bensasson C et al. Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study. Lancet Oncol 2017; 18: 88-99.

77. Hou JL, Onajin O, Gangat N, Davis MD, Wolanskyj AP. Erythromelalgia in patients with essential thrombocythemia and polycythemia vera. Leuk Lymphoma 2017; 58: 715-717.

78. Michiels JJ, Abels J, Steketee J, van Vliet HH, Vuzevski VD. Erythromelalgia caused by platelet-mediated arteriolar inflammation and thrombosis in thrombocythemia. Ann Intern Med 1985; 102: 466-471.

79. Saini KS, Patnaik MM, Tefferi A. Polycythemia vera-associated pruritus and its management. Eur J Clin Invest 2010; 40: 828-834.

80. Siegel FP, Tauscher J, Petrides PE. Aquagenic pruritus in polycythemia vera: characteristics and influence on quality of life in 441 patients. Am J Hematol 2013; 88: 665-669.

81. Tefferi A, Lasho TL, Schwager SM, Strand JS, Elliott M, Mesa R, Li CY, Wadleigh M, Lee SJ, Gilliland DG. The clinical phenotype of wild-type, heterozygous, and homozygous JAK2V617F in polycythemia vera. Cancer 2006; 106: 631-635.

82. Vannucchi AM, Antonioli E, Guglielmelli P, Rambaldi A, Barosi G, Marchioli R, Marfisi RM, Finazzi G, Guerini V, Fabris F et al. Clinical profile of homozygous JAK2 617V>F mutation in patients with polycythemia vera or essential thrombocythemia. Blood 2007; 110: 840-846.

83. Diehn F, Tefferi A. Pruritus in polycythaemia vera: prevalence, laboratory correlates and management. Br J Haematol 2001; 115: 619-621.

84. Tefferi A, Fonseca R. Selective serotonin reuptake inhibitors are effective in the treatment of polycythemia vera-associated pruritus. Blood 2002; 99: 2627.

85. Mesa R, Vannucchi AM, Yacoub A, Zachee P, Garg M, Lyons R, Koschmieder S, Rinaldi C, Byrne J, Hasan Y et al. The efficacy and safety of continued hydroxycarbamide therapy versus switching to ruxolitinib in patients with polycythaemia vera: a randomized, double-blind, double-dummy, symptom study (RELIEF). Br J Haematol 2017; 176: 76-85.

86. Lengfelder E, Berger U, Hehlmann R. Interferon alpha in the treatment of polycythemia vera. Ann Hematol 2000; 79: 103-109.

87. Barosi G, Birgegard G, Finazzi G, Griesshammer M, Harrison C, Hasselbalch H, Kiladijan JJ, Lengfelder E, Mesa R, McMullin MF et al. A unified definition of clinical resistance and intolerance to hydroxycarbamide in polycythaemia vera and primary myelofibrosis: results of a European LeukemiaNet (ELN) consensus process. Br J Haematol 2010; 148: 961-963.

88. Alvarez-Larrán A, Kerguelen A, Hernández-Boluda JC, Pérez-Encinas M, Ferrer-Marín F, Bárez A, Martínez-López J, Cuevas B, Mata MI, García-Gutiérrez V et al. Frequency and prognostic value of resistance/intolerance to hydroxycarbamide in 890 patients with polycythaemia vera. Br J Haematol 2016; 172: 786-793.

89. Hernández-Boluda JC, Alvarez-Larrán A, Gómez M, Angona A, Amat P, Bellosillo B, Martínez-Avilés L, Navarro B, Teruel A, Martínez-Ruiz F et al. Clinical evaluation of the European LeukaemiaNet criteria for clinicohaematological response and resistance/intolerance to hydroxycarbamide in essential thrombocythaemia. Br J Haematol 2011; 152: 81-88.

90. Finazzi G, Ruggeri M, Rodeghiero F, Barbui T. Second malignancies in patients with essential thrombocythaemia treated with busulphan and hydroxyurea: long-term follow-up of a randomized clinical trial. Br J Haematol 2000; 110: 577-583.

91. Nielsen I, Hasselbalch HC. Acute leukemia and myelodysplasia in patients with a Philadelphia chromosome negative chronic myeloproliferative disorder treated with hydroxyurea alone or with hydroxyurea after busulphan. Am J Hematol 2003; 74: 26-31.

92. Yacoub A, Mascarenhas J, Kosiorek HE, Prchal JT, Berenzon D, Baer MR, Ritchie EK, Silver RT, Kessler CM, Winton EF et al. Single-arm salvage therapy with pegylated interferon alfa-2a for patients with high-risk polycythemia vera or high-risk essential thrombocythemia who are either hydroxyurea-resistant or intolerant: final results of the Myeloproliferative Disorders-Research Consortium (MPD-RC) protocol 111 global phase II trial. Blood 2017; 130: 321a.

93. Wasserman LR, Gilbert HS. Surgery in polycythemia vera. N Engl J Med 1963; 269: 1226-1230.

94. Ruggeri M, Rodeghiero F, Tosetto A, Castaman G, Scognamiglio F, Finazzi G, Delaini F, Micò C, Vannucchi AM, Antonioli E et al. Postsurgery outcomes in patients with polycythemia vera and essential thrombocythemia: a retrospective survey. Blood 2008; 111: 666-671.

95. Griesshammer M, Struve S, Barbui T. Management of Philadelphia negative chronic myeloproliferative disorders in pregnancy. Blood Rev 2008; 22: 235-245.