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ORIGINAL ARTICLE

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Recommendations for the diagnosis and treatment of patients with polycythaemia vera

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Abstract

Objectives: To present the Central European Myeloproliferative Neoplasm Organisation (CEMPO) treatment recommendations for polycythaemia vera (PV).

Methods: During meetings held from 2015 through 2017, CEMPO discussed PV and its treatment and recent data.

Results: PV is associated with increased risks of thrombosis/thrombo-haemorrhagic complications, fibrotic progression and leukaemic transformation. Presence of *Janus kinase (JAK)-2* gene mutations is a diagnostic marker and standard diagnostic

criterion. World Health Organization 2016 diagnostic criteria for PV, focusing on haemoglobin levels and bone marrow morphology, are mandatory. PV therapy aims at managing long-term risks of vascular complications and progression towards transformation to acute myeloid leukaemia and myelodysplastic syndrome. Risk stratification for thrombotic complications guides therapeutic decisions. Low-risk patients are treated first line with low-dose aspirin and phlebotomy. Cytoreduction is considered for low-risk (phlebotomy intolerance, severe/progressive symptoms, cardiovascular risk factors) and high-risk patients. Hydroxyurea is suspected of leukaemogenic potential. IFN-α has demonstrated efficacy in many clinical trials; its pegylated form is best tolerated, enabling less frequent administration than standard interferon. Ropeginterferon alfa-2b has been shown to be more efficacious than hydroxyurea. *JAK*1/*JAK*2 inhibitor ruxolitinib is approved for hydroxyurea resistant/intolerant patients.

Conclusions: Greater understanding of PV is serving as a platform for new therapy development and treatment response predictors.

KEYWORDS

cytoreductive therapy, diagnosis, management, myeloproliferative neoplasms, polycythaemia vera, recommendations

1 | INTRODUCTION

The BCR-ABL-negative myeloproliferative neoplasm (MPN) polycythaemia vera (PV) is a clonal stem cell-derived malignancy, occurring at a reported annual incidence of 0.01-2.61 per 100 000.[1,2] PV presents at a median age of 61 years (10% are below age 40 years), with a similar incidence between genders.[3] PV cases younger than 20 years are reported.[4]

Clinical signs are dominated by myeloproliferation, in terms of erythrocytosis (raised haemoglobin and haematocrit), often with leucocytosis and/or thrombocytosis.[5] Patients with PV may also have splenomegaly and microvascular symptoms such as light-headedness, headaches, palpitations, atypical chest pain, visual disturbances, paraesthesia and erythromelalgia.[1]

PV is associated with an increased risk of thrombosis and thrombo-haemorrhagic complications, and transformation to myelofibrosis or acute myeloid leukaemia (AML).[1,5,6] Thrombosis or splenomegaly is seen in approximately 30% of patients at presentation.[6] Rates of leukaemic transformation at 20 years are estimated at <10%, and rates of fibrotic transformation are slightly higher; in contrast, the risk of thrombosis exceeds 20%.[1] Median survival of patients with PV is estimated at 13.5 years; in patients aged <60 years, median survival was 24 years.[7]

In patients with PV, erythroid progenitor cells have the ability to proliferate in vitro in the absence of erythropoietin, and erythroid and myeloid cells are sensitive to several different growth factors.[8] This hypersensitivity is a result of a mutation in the gene for Janus kinase 2 (*JAK2*^{V617F}) on chromosome *9p24*.[9,10] Janus kinase 2 (*JAK2*) is a nonreceptor tyrosine kinase, which mediates the effects of various hormones and cytokines, including erythropoietin and thrombopoietin, and assists in the proliferation and survival of tumour cells.[11]

The pathophysiology of PV is characterised by upregulation of *JAK*-signal transducer and activator of transcription (*STAT*) target genes, thus constituting activation of the JAK-STAT signalling pathway.[12] It is almost always the result of activating somatic mutations in exon 14 (reported in >95% of *JAK2*^{V617F} PV patients) or in exon 12; the mutation in exon 12 of JAK2 is found in about 3% of all patients with PV.[1,12,13]

As a *JAK2* mutation is likely to occur in practically all adult patients with PV, its presence has been used as a diagnostic marker for the disease and has become a standard criterion for diagnosis in guidelines worldwide.[14–18] However, use of this diagnostic criterion may lead to misdiagnosis in children in whom the occurrence of the *JAK2*^{V617F} mutation was less frequent than in adults and exon 12 *JAK2* mutations were apparently absent.[19]

The Central European Myeloproliferative Neoplasm Organisation (CEMPO) is an international congregation of individuals interested in research in the field of diagnosis and therapy of MPNs in Central Europe. The Organisation was established in 2009, and one of the goals of CEMPO is to develop and publish MPN treatment recommendations based on clinical evidence and recent scientific research.

Presented here are treatment recommendations for the management of PV in Central Europe, which embraces the CEMPO member countries Austria, Croatia, Czech Republic, Germany, Hungary, Poland, Romania, Serbia, Slovak Republic, Slovenia and Ukraine.

The CEMPO group started discussions on PV treatment recommendations at its meeting held on 2 October 2015 in Vienna. An initial draft was modified following further discussions in

TABLE 1 World Health Organization's classification 2016 for polycythaemia vera[20]

Diagnosis of PV requires meeting either all three major criteria or the first two major criteria and the minor criterion[a]	
Major criteria	
1	Haemoglobin >165 g/L in men; haemoglobin >160 g/L in women OR Haematocrit >49% in men; haematocrit >48% in women OR Increased red cell mass: >25% above mean normal predicted value
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)
3	Presence of *JAK2*^{V617F} or *JAK2* exon 12 mutation
Minor criterion	
	Subnormal serum erythropoietin level
Grading of bone marrow fibrosis (myelofibrosis; assess fibre density only in haematopoietic areas)	
MF-0	Scattered linear reticulin with no intersections (crossovers) corresponding to normal bone marrow
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibres mostly consistent with collagen, and/or focal osteosclerosis (an additional trichrome stain is recommended)
MF-3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibres consistent with collagen, usually associated with osteosclerosis (an additional trichrome stain is recommended)

JAK2, Janus kinase 2; MF, myelofibrosis; PV, polycythaemia vera.
[a]A bone marrow biopsy (criterion number 2) may not be required in cases with sustained absolute erythrocytosis: haemoglobin levels >185 g/L in men (haematocrit 55.5%) or >165 g/L in women (haematocrit 49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a bone marrow biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV myelofibrosis).

meetings on 10 June 2016 in Copenhagen and 23-24 February 2017 in Prague. The European LeukemiaNet (ELN) and National Comprehensive Cancer Network (NCCN) provide guidance and strategies for managing patients with PV. The aim of these CEMPO recommendations has been to provide recommendations that can be used in all CEMPO countries. CEMPO wish to acknowledge that the CEMPO recommendations differ in some parts to ELN and NCCN guidelines.

2 | DIAGNOSIS OF POLYCYTHAEMIA VERA

After 8 years since its revision in 2008, further update of the World Health Organization's (WHO) Classification of Tumours of the Haematopoietic and Lymphoid Tissues was considered timely in the light of emerging information and experience from scientific and clinical studies. Specifically, for patients with PV, the possible underdiagnosis using the haemoglobin levels published in 2008 and the role of BM morphology in diagnosis of PV have been addressed in the 2016 revision.[20] The diagnostic consensus is presented in Table 1.

Patients with persistently raised haemoglobin/haematocrit values should be investigated for erythrocytosis. According to the WHO classification 2007/2008 update, the first major diagnostic criterion of erythrocytosis requires one of the following four components: haemoglobin level >185 g/L in men and >165 g/L in women, or red cell mass (RCM) that is >25% above mean normal predicted, or haemoglobin level >170 g/L in men and >150 g/L in women that is associated with a sustained increase of ≥20 g/L from baseline and cannot be attributed to correction of iron deficiency.[21,22] It has been debated that applying these haemoglobin/haematocrit threshold values may result in an underdiagnosis of PV. The 2016 revised criteria for PV have introduced a haemoglobin level of 165 g/L in men and 160 g/L in women or a haematocrit level of 49% in men and 48% in women (Table 1).[20,23,24]

The haemoglobin and haematocrit threshold proposed in the 2016 revised WHO criteria have been lowered mainly for distinguishing *JAK2*-mutant essential thrombocythaemia from the

so-called masked PV, thus avoiding underdiagnosis. This might enable earlier diagnosis, thereby contributing to the prevention of thrombotic events.

As haemoglobin/haematocrit values are expressed with reference to a given volume of whole blood and thus influenced by plasma volume, RCM is considered a more accurate indicator of red cell count.[25] The 2016 guidelines recommend a diagnostic value of >25% above mean normal predicted value (Table 1).[20] RCM has largely been dropped from clinical practice by CEMPO member countries, and haematologists are increasingly using serum erythropoietin (EPO) level, *JAK2* mutations and bone marrow histology as diagnostic tools.

Current diagnostic practice has taken into account the very high mutation frequency of *JAK2* in PV, with the inclusion of *JAK2*^{V617F} (or other functionally similar mutations, eg, *JAK2* exon 12 mutation) as a marker of the disease.[26] The WHO PV diagnostic algorithm considers analysis for mutated *JAK2* as a major criterion (Table 1).[20] However, the presence of *JAK2*^{V617F} alone cannot distinguish PV from essential thrombocythaemia or primary myelofibrosis, which requires a bone marrow examination. *JAK2* mutations may also provide prognostic information in PV whereby a higher *JAK2*^{V617F} allele burden has been associated with increased risk of fibrotic transformation.[27]

Whereas EPO controls red cell production, the increased erythropoiesis in PV is not the result of increased EPO production but reflects the autonomous proliferation of the abnormal clone.[28] A subnormal EPO level is the only minor criterion in the new revision of the WHO classification (Table 1).[20] When PV is clinically suspected, measurements of EPO levels are recommended.[22]

New findings have demonstrated the importance of standardised morphologic criteria for discriminating between the MPNs.[20] Bone marrow morphology provides confirmation of a PV diagnosis, with panmyelosis with prominent erythroid, granulocytic and megakaryocytic proliferation.[29] However, in PV, megakaryopoiesis presents without significant morphological abnormalities but with conspicuous differences in size (pleomorphy).[30] A bone marrow examination rules out *JAK2*-mutated essential thrombocythaemia and can give information regarding the degree of fibrosis, and is promoted to a major criterion for diagnosis in revised diagnostic criteria (Table 1).[20] Bone marrow examination as part of the diagnostic criteria in PV has predictive value in clinical practice. Incidence of mostly minor (grade 1) bone marrow reticulin fibrosis at presentation of WHO-defined PV ranges between 10% and 20% of patients. Patients with PV and such minor increases reticulin fibrosis display a higher prevalence of palpable splenomegaly and are prone to more rapid progression to overt myelofibrosis (post-PV myelofibrosis).[31] Post-PV myelofibrosis represents a natural evolution of PV; the median time to myelofibrosis transformation ranges from 8.5 to 20 years and the cumulating risk increases from 6% to 14% to 26% at 10, 15 and 20 years after the initial diagnosis, respectively.[32] Slight modifications have been made to the grading of reticulin and collagen bone marrow fibres (Table 1).[20] As such, bone marrow morphology is generally routinely investigated in CEMPO countries.

Myeloproliferation and the increased concentrations of the cellular elements of blood in PV frequently lead to splenomegaly, which is present in 75% of patients at the time of diagnosis.[33] Physical examination may reveal a palpable spleen in approximately 40% of cases, and nonpalpable splenomegaly is detected by abdominal ultrasound in the majority of cases.[34,35] Accordingly, spleen size is routinely checked using abdominal ultrasound in member countries of CEMPO.

3 | CHARACTERISTICS OF PATIENTS WITH POLYCYTHAEMIA VERA INITIATING CYTOREDUCTIVE THERAPY

The high risk of thrombosis and disease progression towards myelofibrosis with myeloid metaplasia (the so-called spent phase) constitutes a major reason for cytoreductive therapy in patients with PV. However, exposure to such therapy should be minimal as it can have side effects and increase the risk of AML.[8] Assessment of patients at high risk of thrombosis is therefore paramount. They should assess the benefit of minimising thrombotic events with the risk of drug exposure. The current risk stratification in PV to inform therapeutic decisions is designed to estimate the likelihood of developing thrombotic complications and not necessarily overall survival.

3.1 | Age and history of thrombosis

Thrombosis strongly impacts on morbidity and mortality of patients with PV. It is characterised by arterial and venous thrombosis, and platelet and leucocyte abnormalities, which likely play a role in pathogenesis.[36] Vascular risk is usually assessed on age and past history of thrombosis.[37,38] As such, patients can be stratified as "high risk" (aged >60 years and history of thrombosis, with 1-2 risk factors) or "low risk" (aged <60 years and no history of thrombosis, without risk factors).[39,40]

It is well established that a history of thrombosis and older age (≥60 years) are the most important (ie, high) risk factors for thrombosis in PV, with arterial thrombosis accounting for about three quarters of previous thromboses.[41,42] Patients who are considered to be at low risk are aged <60 years and have no history of thrombosis. The median age at diagnosis in published studies was younger (often 60 years). Multivariate analysis identified age >70 years, white blood cell count >13 × 10^9/L and thromboembolism at diagnosis as independent risk factors.[43]

In the ECLAP study, the incidence of cardiovascular complications was higher in patients either aged ≥65 years or with a history of thrombosis compared with younger subjects with no history of thrombosis.[42] The recommendations of the Czech Collaborative Group for Ph-Myeloproliferative Diseases (CZEMP) in 2011 also recognised age (>65) and previous thrombosis as major risks for thrombosis, which was clearly evidenced in clinical studies.[44,45] Moreover, age and history of thrombosis have been found to be the most important prognostic indicators of cardiovascular events.

The total major thrombosis rate in the ECLAP study was 4.4% patients per year compared to 2.7% in the CYTO-PV study, in which

management of cardiovascular risk factors was more intensive than in the ECLAP study.[46] Therefore, the cardiovascular factors (active smoking, diabetes, hyperlipidaemia and arterial hypertension) had the most relevant prognostic role for the incidence of arterial thrombosis.

The high prevalence of cardiovascular risk factors, such as hypertension (40%) and particularly cigarette smoking (13%), warrants their control in these patients.[42,47] Notably, hypertension is more frequent in PV and probably is associated with increased haematocrit.[46] The independent role of hypertension in the risk of arterial thrombosis suggests a closer evaluation of the relationship between the factors that control blood pressure on the one hand and erythrocytosis on the other is warranted.

Recent guidelines recommend that all patients should be managed aggressively for their risk condition and should be requested to stop smoking.[14] Patients with low-risk PV and arterial hypertension may benefit from the addition of cytoreductive treatment to reduce their risk of thrombosis and its incidence.[48] A more intensive therapy should be explored in prospective studies designed to examine whether the addition of cytoreductive drugs to phlebotomy and aspirin, and ACE inhibitors may reduce the still high incidence of thrombosis.

Controversies still exist regarding definition of the thrombotic risks in Ph-(BCR/ABL1-) myeloproliferative neoplasms.[45] In CEMPO member countries, cytoreductive therapy is generally started in patients at high risk, being aged >65 years or with a previous thrombotic event of any type. However, whereas the proportion of the population aged ≥65 years is increasing in all EU member countries, the diversity of old age is recognised, considering that most people in the 60- to 69-year-old age category are still fit, without cardiovascular risk factors.[49,50] The CEMPO member countries emphasise an individual approach to the middle-to-old age group and therefore allocate two categories, <70 years and ≥70 years within the high-risk group.

Based on consensus of CEMPO members, the use of cytoreductive drugs is indicated in low-risk patients who have cardiovascular risk factors.

The association between *JAK2*^{V617F} mutation and thrombotic complications is also recognised as an independent and predictive factor for thrombosis.[37,51] The *JAK2*^{V617F} mutation is one of the strongest risk factors of thrombosis of any kind (arterial, venous and microcirculatory).[45] However, others have not found a correlation between allele burden and thrombosis.[52]

3.2 | Platelet and leucocyte counts

The relevance of uncontrolled polycythaemia as a risk factor for thrombosis in PV has been well established. Moreover, it is recognised that unless the erythrocyte count is reduced accordingly, neither antiplatelet therapy nor chemotherapy is effective.[8]

Increases in white blood cell (WBC) count can be important in the pathogenesis of thrombosis.[53] Leucocytosis that occurs in most patients with PV is a risk factor for thrombosis in these individuals.[46,54] Patients with PV and a WBC count above 15×10^9/L (vs below 10×10^9/L) had a significant increase in the risk of thrombosis and of inferior survival.[3,38,47] Leucocyte activation occurs and is associated with endothelium and coagulation system activation.[55] Leucocytosis has also been identified as an independent predictor of leukaemic transformation.[3,38]

The role of thrombocytosis in thrombosis in PV is controversial, and no study to date has demonstrated a significant correlation between platelet number or function and thrombosis. Evidence suggests that hypercoagulability and thrombosis may occur without an elevation in platelet count.[8] Along with many retrospective studies that failed to correlate platelet count and thrombosis risk, the Polycythemia Vera Study Group prospective trial also failed to show a correlation between an elevated platelet count and the risk of thrombosis.[8,56] Neither have the platelet function abnormalities occurring in PV been correlated with the development of thrombosis.[8] Moreover, whereas median platelet count prior to the thrombotic event has been shown to be significantly higher than at time points without any ensuing thrombosis (450 vs 400 × 10^9/L), higher platelet counts at diagnosis tended to be connected with fewer thrombotic events.[45] Platelet count at diagnosis is currently not taken as a risk factor of thrombosis.[45]

Platelet-leucocyte aggregates may play a role in thrombosis, particularly in patients with a previous history of thrombosis or microvascular disturbances.[57] High platelet counts and acquired von Willebrand disease (due to a deficiency in von Willebrand multimers caused by their adsorption to platelets) have also been associated with a haemorrhagic diathesis.[8,58] Moreover, poor control of platelet count was found to be strongly associated with progression to myelofibrosis in patients receiving hydroxyurea, suggesting that platelet count may influence transformation to myelofibrosis.[59]

3.3 | Thrombophilia

Hereditary thrombophilic states such as congenital deficiencies of natural anticoagulants (eg, antithrombin, protein C and protein S) and genetic mutations (eg, factor V Leiden and prothrombin G 20210A) are known to play an important function in the pathogenesis of venous thrombosis. A retrospective study has indicated that the prevalence of the factor V Leiden mutation in PV patients is comparable with that observed in the general population. The factor V Leiden mutation has also been identified as a risk factor for venous thromboembolism (VTE) before and at the time of diagnosis and for VTE recurrences.[60] As such, screening for this mutation is a worthy consideration for the identification of PV patients at high risk of VTE recurrences.[60] Although occurrence of a prothrombin mutation has been associated with a moderate risk of VTE only, data indicate that the associated thromboembolic event risk is excessive in PV patients with the mutation compared to PV patients without the mutation.[61] The clinical expression of the factor V Leiden mutation and prothrombin mutation is influenced by the number of variants, whereby heterozygotes have a slightly increased risk for venous thrombosis and homozygotes have a much greater thrombotic risk.[62,63] The

question of whether all patients with PV should be tested for specific thrombophilic factors can only be answered by large prospective clinical trials.

According to CZEMP ET guidelines, the presence of additional thrombophilic states (hereditary and acquired), degree of thrombocythaemia and *JAK2*^{V617F} mutation have been used to define PV patients with high risk for thrombosis.[64]

Due to substantial morbidity, symptom management is one of the primary treatment objectives for patients with PV.[65] Quality of life is significantly worse in these patients compared with controls, with fatigue being the most common symptom, reported by the majority of patients, followed by pruritus, night sweats, bone pain, weight loss and fever.[40] Fatigue and pruritus are not only the most prevalent but also the most troublesome symptoms. Aquagenic pruritus, which is characterised by intense itching, and tingling/burning sensations on contact with water, occurs in two thirds of patients with PV.[66] This debilitating condition is a major factor impacting on daily life, reducing overall health status and causing greater fatigue, pain and dyspnoea. Control of such symptoms with cytoreductive therapy can be difficult but is strongly warranted.

4 | CYTOREDUCTIVE THERAPY IN CLINICAL PRACTICE

Current PV therapy does not cure the disease, or prevent disease transformation to AML or myelofibrosis.[1] Goals of treatment are primarily to prevent thrombo-haemorrhagic complications without increasing the risk of bleeding, to minimise the risk of AML or myelofibrosis or to alleviate microcirculatory symptoms.[1,67]

Generally, low-risk patients are treated first line with low-dose aspirin and phlebotomy.[39] Whereas therapeutic phlebotomy has become the mainstay of treatment, it has limitations. Patients may be intolerant of or have a low acceptance of this therapy, and it may be difficult to gain peripheral vein access.[40,68] Furthermore, high frequency of phlebotomy is necessarily a transient situation as the need for repeated phlebotomy can lead to symptoms of iron deficiency, which include restless legs syndrome[42,69] and anxiety.[43,70]

Cytoreduction is indicated in low-risk patients with poor tolerance to phlebotomy or a high frequency of phlebotomies; patients who still have severe disease-related symptoms (eg, pruritus, weight loss and night sweats) or progressive splenomegaly; patients with erythrocytosis who show excessive erythrocyte proliferation, and therefore inadequate disease control; or patients with progressive leucocytosis and presence of cardiovascular risk factors with emphasis on the presence of arterial hypertension.[32,47,64,71]

First-line treatment recommendations for high-risk patients include the cytoreductives hydroxyurea or interferon-alpha (IFN-α), although IFN-α is not a licensed PV treatment in most CEMPO countries.[46,71] Available for patients who experience hydroxyurea resistance or intolerance, second-line cytoreductive therapies include busulphan, pipobroman or radiophosphorus (^{32}P).[71] More recently, with the discovery of *JAK2* as the underlying molecular basis of PV, targeted therapies (including *JAK* inhibitors) have become a primary theme of PV treatment research. This is of importance because, whereas patients respond well to current treatment options, there remains the increased risk of thrombotic events, clinical intolerance and treatment resistance.[40]

Phlebotomy appears to improve overall and thrombosis-free survival, and as such is currently considered the cornerstone of treatment in PV.[69] In patients with PV, phlebotomy is of greatest benefit in terms of cardiovascular death and major thrombosis to those maintained at a haematocrit target of <45% compared to those at 45%-50%.[72] Phlebotomy is practised in all CEMPO member countries where generally the target haematocrit level is <45%. Frequent and long-term phlebotomies may cause iron deficiency,[42,69] increased symptom burden and lost productivity.[73,74]

Low-dose aspirin is of antithrombotic value and effective in alleviating microvascular symptoms in PV, with some patients benefitting from twice-daily doses.[1,75] However, aspirin should be used with caution in patients with bleeding diathesis, extreme thrombocytosis (ie, platelet count >1000 × 10^9/L) and acquired von Willebrand syndrome.[76,77] Despite its benefits, the risk of bleeding complications with aspirin is recognised across CEMPO member countries.

The antithrombotic benefit of cytoreductive therapy in high-risk patients with PV is well recognised. Hydroxyurea is a widely used first-line cytoreductive agent in PV. However, through its interference with DNA metabolism, it is a cytostatic drug and is therefore considered to be potentially leukaemogenic. Hydroxyurea should be used with caution in young patients (ie, <40 years).[67]

No excess risk of AML and myelodysplastic syndromes was reported in hydroxyurea-treated patients over 2.5 years.[78] However, risk may continuously increase during long-term therapy over the course of decades.[79] In a series of reports, the incidence of AML and MDS is approximately 14% when used alone and markedly increases to about 30% when hydroxyurea is preceded by treatment with busulphan.[80] Moreover, patients can eventually become therapy resistant or intolerant.[40] The criteria for resistance and refractoriness to hydroxyurea have previously been defined by the European LeukemiaNet consensus.[81]

According to a French study, long-term therapy with hydroxyurea increases the risk for AML by 2%, 5% and 10% at 10, 15 and 20 years, respectively. However, no leukaemogenic risk associated with hydroxyurea is reported within a Swedish registry.[82] Larger long-term studies are therefore warranted to ensure the safety and disprove the suspected leukaemogenic potential of hydroxyurea.[79,82,83] More recently, the positive outcomes of IFN-α therapy have promoted IFN-α to the drug of choice in several CEMPO member countries, thus particularly limiting the use of hydroxyurea to older patients.

IFN-α targets *JAK2*^{V617F}-mutated cells, reducing and eventually causing complete disappearance of the mutated allele burden.[84–86] In patients with PV, IFN-α has demonstrated efficacy in many clinical trials, is able to reduce splenomegaly and relieve pruritus and other constitutional symptoms, and lacks leukaemogenic potential.[87,88] Unfortunately, intolerable adverse effects,

including flu-like symptoms, fatigue and neuropsychiatric symptoms, and autoimmune problems, such as thyroiditis, have limited use of IFN-α in PV.[40]

PEGylated interferon, which is better tolerated and enables less frequent administration than standard interferon, has also been associated with high rates of haematological and molecular responses that may prevent evolution to AML or myelofibrosis.[87] Chemical linkage of polyethylene glycol (PEG) to IFN-α to produce PEGylated IFN-α has increased the plasma half-life and improved the toxicity profile of this signalling protein considerably.[89] IFN-α development has since progressed with the introduction of the first mono-PEGylated IFN-α-2b, ropeginterferon alfa-2b. Ropeginterferon offers a longer elimination half-life, thus allowing for administration every 2 weeks, and is associated with a very low adverse event rate.[88] The phase III randomised, controlled clinical trial (PROUD-PV) to compare the efficacy and safety of ropeginterferon alfa-2b with hydroxyurea in patients with PV was designed to assess response rates measured after one year. After 12 months of treatment, patients continued in the CONTI-PV study. PEG-proline-IFN-α-2b treatment led to high response rates on both molecular and clinical levels, with molecular responses generally proceeded by haematological responses.[90] Response or molecular and haematological levels are independent from chromosomal aberrations.[90] Factors such as age and hydroxyurea pretreatment did not significantly influence the outcome to PEG-proline-IFN-α-2b therapy.[88] The final results from the phase III PROUD/CONTI-PV study showed that ropeginterferon alfa-2b was more efficacious than hydroxyurea in the long term. Haematological, clinical and molecular response rates increased between 12 and 24 months of ropeginterferon alfa-2b treatment, whereas rates decreased in the control arm. At month 24 of treatment, the complete haematological response rate was higher in the ropeginterferon alfa-2b arm than in the hydroxyurea/best available therapy arm (70.5% vs 49.3%, respectively; $P = 0.0101$).[91]

Patients with PV who fail hydroxyurea therapy are also effectively managed with busulphan.[1,92] However, busulphan may be used in patients over aged 70 years.[67] There is consensus for use of busulphan in elderly high-risk patients only where other treatment options have not been successful.

Anagrelide is used in PV among CEMPO haematologists to control thrombocytosis in MPN with thrombocythaemia patients who do not respond to or cannot tolerate hydroxyurea or IFN-α. Side effects including palpitations, headache and gastrointestinal disturbances contribute to over half of patients discontinuing after two years of treatment.[93,94] However, the use of anagrelide in PV is limited to situations where extreme thrombocytosis develops into thrombo-haemorrhagic episodes.[95] Anagrelide in combination with aspirin is known to be connected with a higher rate of minor bleeding events compared to history.[45] Bleeding rates can be higher when a bleeding diathesis is worsened by platelet counts of >1000 × 10^9/L.[96]

The *JAK1*/*JAK2* inhibitor ruxolitinib has shown clinical benefit in patients with PV in terms of controlling haematocrit, reducing spleen volume and improving symptoms, and in those patients who are resistant to or intolerant of hydroxyurea or interferon.[40,97,98] Ruxolitinib is also reported to achieve both haematocrit control and a ≥35% reduction in spleen volume compared to patients on best available treatment.[98] Use of ruxolitinib has recently been established in several CEMPO member countries as a second-line therapy in hydroxyurea-refractory patients.

5 | REVISION OF THE TREATMENT ALGORITHM

A revised treatment algorithm in PV is proposed in the light of the limited efficacy of current therapies to prevent thrombosis and emerging clinical data (Figure 1). Regarding cytoreductive therapy, the algorithm has considered minimising thrombotic events and drug exposure:

Low-risk patients.

- First line: low-dose aspirin +phlebotomy
- Second line: IFN-α (eg PEGylated IFN-α)
  - Second-line therapy is indicated in low-risk patients with:
    - Poor tolerance to phlebotomy
      - – High frequency of phlebotomies
      - – Symptoms of iron deficiency (MCH <28)
    - Severe disease-related symptoms (eg, pruritus, fatigue, night sweats)
    - Progressive splenomegaly if there are no signs for progression to overt myelofibrosis (post-PV myelofibrosis)
    - Progressive thrombocytosis
    - Progressive leucocytosis
    - Presence of cardiovascular risk factors (eg, arterial hypertension, diabetes, hyperlipidaemia and active smoking)

High-risk patients.

- Age <70 years without major comorbidities:
  - First line: IFN-α (eg PEGylated IFN-α)
  - Second line: hydroxyurea or *JAK1*/*JAK2* inhibitor
    - Second-line therapy is indicated in high-risk patients aged <70 years with poor tolerance or resistance to first-line therapy
- Age ≥70 years or with major comorbidities:
  - First line: IFN-α (eg, PEGylated IFN-α) or hydroxyurea
  - Second line: *JAK1*/*JAK2* inhibitor
    - Second-line therapy is indicated in high-risk patients aged ≥70 years with poor tolerance or resistance to first-line therapy.

6 | CONCLUSIONS

The progressive character of PV, with transformation to myelofibrosis or AML, and increased risk of thrombosis and

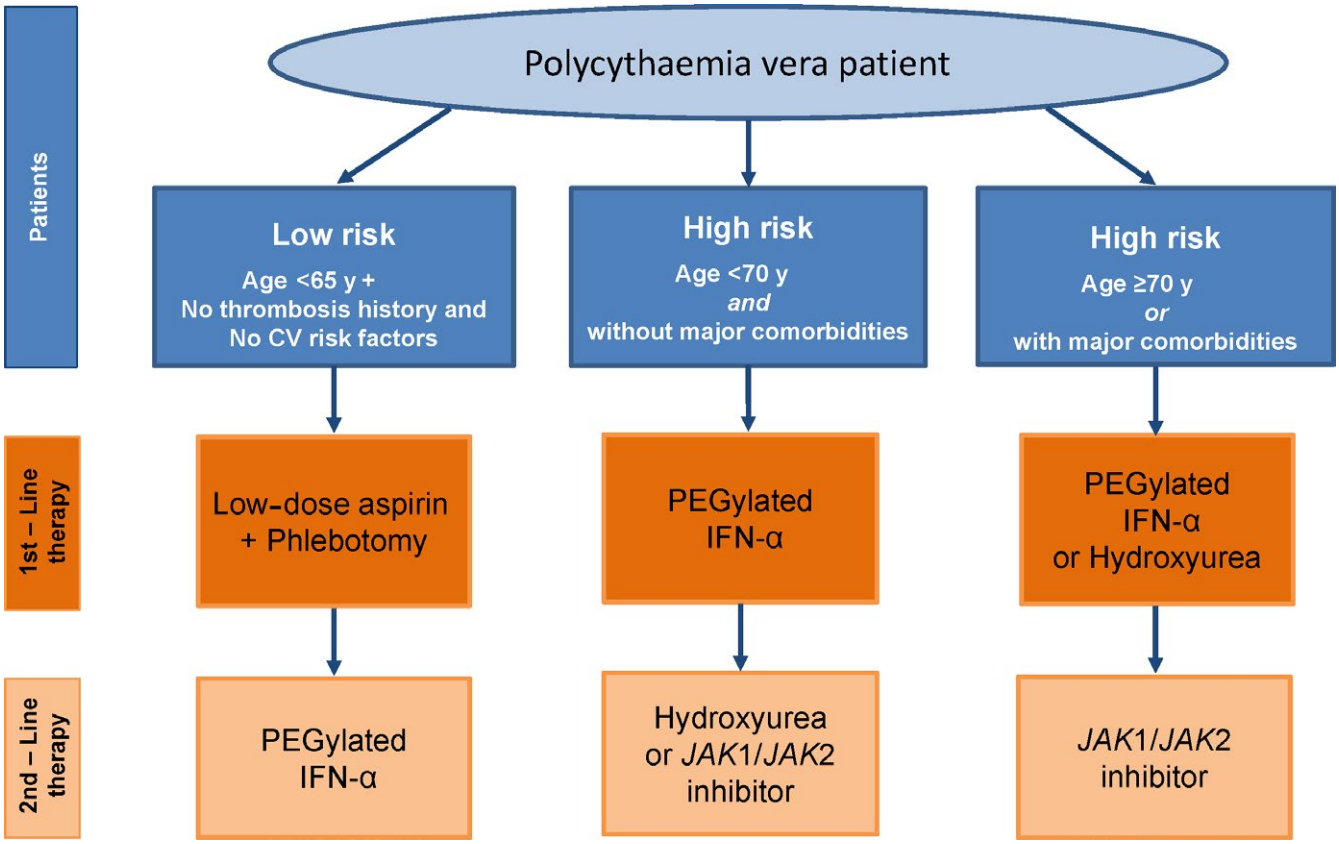

FIGURE 1 Revised treatment recommendations in polycythaemia vera. CV, cardiovascular; IFN-α, interferon-alpha; *JAK*, Janus kinase

thrombo-haemorrhagic complications, warrants its early diagnosis and treatment. The updated WHO classification in 2016 embraces improvements in diagnostic criteria from ongoing extensive study of the morphologic and molecular genetic features correlating with the different MPNs carried out since its publication in 2008. Greater understanding of these features is serving as a platform for development of new therapies, and predictors of prognosis and treatment response. It should be possible to improve the prognosis of PV patients if better treatment strategies are employed. Most recently, PEG-proline-IFN-α-2b has demonstrated benefits over hydroxyurea in terms of safety, tolerability and efficacy in clinical studies and in clinical practice. Introduction of the JAK1/JAK2 inhibitor ruxolitinib also appears to positively impact the management of patients, particularly those with myelofibrosis, extensive splenomegaly and high symptom burden. These CEMPO treatment recommendations for the management of PV have evolved in the light of the limited efficacy of current therapies to prevent thrombosis and emerging clinical data, and thus constitute a significant step forward in the treatment of patients with PV.

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CONFLICT OF INTEREST

AH receives speaker's and consultancy honoraria from AOP Orphan Pharmaceuticals AG and Novartis Pharmaceuticals AG. AH wishes to declare dependence on advice from the medical writer for guidance on preparation and submission of this manuscript. JS has received speaker's and consultancy honoraria from AOP Orphan Pharmaceuticals AG and Novartis Pharmaceuticals AG. MP receives speaker's and consultancy honoraria from AOP Orphan Pharmaceuticals AG and Novartis. MH receives speaker's honoraria from AOP Orphan Pharmaceuticals AG, Roche, Jansen, AbbVie and Novartis Pharmaceuticals AG. RK receives speaker's and consultancy honoraria from AOP Orphan Pharmaceuticals AG and Novartis. ME has received speaker's and consultancy honoraria from AOP Orphan Pharmaceuticals AG and Novartis. MG has received honoraria from Novartis, Shire, AOP Orphan Pharmaceuticals AG, Sanofi, Baxalta and Gilead. MPD receives speaker's and consultancy honoraria from Alexion, AOP Orphan Pharmaceuticals AG, Shire, Novo Nordisk and CSL Behring. SK receives speaker's and consultancy honoraria from Novartis and F. Hoffmann-La Roche and research funding from AOP Orphan Pharmaceuticals AG. PEP

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AUTHOR CONTRIBUTIONS

All authors contributed significantly to the discussions and formulation of these recommendations. AH coordinated the manuscript preparation.

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