VIA MEDICA

GUIDELINES/EXPERT CONSENSUS

Acta Haematologica Polonica 2024
Number 6, Volume 55, pages 231–237
DOI: 10.5603/ahp.102458
ISSN 0001–5814
e-ISSN 2300–7117

Recommendations of Polish Adult Leukemia Group concerning diagnostics and treatment of polycythemia vera

Joanna Góra-Tybor[1], Tomasz Sacha[2], Maria Bieniaszewska[3], Marta Sobas[4], Krzysztof Lewandowski[5], Patryk Sobieralski[3], Olga Chyrko[4], Aleksandra Gołos[1]

[1]Department of Hematology, Medical University of Lodz, Poland
[2]Chair and Clinic of Hematology, Jagiellonian University Medical College, Cracow, Poland
[3]Chair and Clinic of Hematology and Transplantology, Gdańsk Medical University, Poland
[4]Clinic of Hematology, Cell Therapies and Internal Diseases, Jana Mikulicza-Radeckiego University Clinical Hospital, Wrocław, Poland
[5]Clinic of Hematology and Bone Marrow Transplantation, Poznan Medical University, Poland

Abstract

Polycythemia vera (PV) belongs to a group of myeloproliferative neoplasms (MPN). The diagnosis of PV is based on the evaluation of complete blood count, bone marrow trephine biopsy samples, and molecular tests (confirmation of the JAK2 mutation).

The main objectives of PV treatment include preventing thromboembolic complications, alleviating disease symptoms, and lowering the risk of transformation to myelofibrosis, acute myeloid leukemia and myelodysplastic syndrome. Taking into consideration the long-term course of PV, the choice of therapy should be based on an analysis of the risks resulting from the disease as well as from the adverse effects of the medication applied. In patients without risk factors (age <60 years; no history of thrombosis), acetylsalicylic acid (ASA) and phlebotomy are recommended. Cytoreductive treatment is recommended in patients with poor tolerance of phlebotomy and with leukocytosis >20 G/L, symptomatic progressive splenomegaly, significant thrombocytosis, persistent general symptoms of PV, and also in patients with significant cardiovascular risk.

The therapy of choice in these patients is interferon α (IFNα). In a high-risk group of patients, (age ≥60 years and/or a history of thrombosis), treatment with ASA and phlebotomy should be accompanied by cytoreduction: hydroxyurea (HU) or, in the case of HU resistance/ intolerance, ruxolitinib (RUX) or IFNα.

This paper discusses some aspects of the risk evaluation and summarizes the effectiveness of the available therapies, and also presents diagnostic and therapeutic recommendations for PV.

Keywords: polycythemia vera, myeloproliferative neoplasms, diagnosis, treatment

Acta Haematol Pol 2024; x, x: xx–xx

*Address for correspondence: Aleksandra Gołos
Department of Hematology, Medical University of Lodz,
Ciołkowskiego 2, 93–510, Lodz, Polska
e-mail: alexandra_golos@tlen.pl

Received: 10.09.2024 Accepted: 02.10.2024

Introduction

According to the International Consensus Classification (ICC) and to the 2022 classification of the World Health Organization (WHO), polycythemia vera (PV) is included in the group of myeloproliferative neoplasms (MPN), which are neoplasms of the hematopoietic stem cell [1, 2]. On the basis of population studies, the incidence rate of PV is estimated to be c. 1–1.5/100,000 people per year, with median age at onset 61 years, and with comparable incidence in both sexes [3, 4]. In the pathogenesis of the disease, the key role is played by the overactivity of the JAK-STAT (Janus kinase/signal transducers and activators of transcription) signaling pathway and the clonal hyperplasia of cells of bone marrow origin, resulting in the overproduction of blood morphotic elements, most expressed in the erythroid line. The diagnosis of the disease is based on assessment of the peripheral blood, molecular analysis, and histological assessment of a trephine bone marrow sample. The most significant characteristic of PV is polyglobulia. Additionally, approximately half of the patients have thrombocytosis and leukocytosis, and approximately one third have spleen enlargement [5]. The bone marrow abnormalities involve a typical picture of proliferation of all blood hematopoietic lines (panmyelosis) [1, 2]. A mutation in exon 14 of the *JAK2* gene (*JAK2* Val617Phe), discovered in 2005, is responsible for the development of the disease in 97% of patients with PV [6–8]. In other cases, mutations within exon 12 of the *JAK2* gene or non-canonical mutations are found [9–11]. Both at the moment of diagnosis and within the course of the disease, patients may be asymptomatic or present symptoms resulting from increased blood viscosity and from microcirculation disorders. In the majority of PV patients, the course of disease takes many years. It has been proven, however, that patients' predicted lifespan is shorter than in the case of healthy people of the same age, in particular among the younger patient population [12]. The main cause of morbidity and mortality in patients with PV comprises thromboembolic complications, both of venous and arterial types. Moreover, as a result of chronic, increased cell proliferation in the bone marrow and overproduction of proinflammatory cytokines, some of the patients may experience disease progression to post-polycythemia vera myelofibrosis (PPV-MF). Where there is accumulation of secondary cytogenetic and molecular events, inhibition of differentation may occur with the evolution of the disease phenotype to the form resembling acute myeloid leukemia (AML), which is associated with a significantly worse prognosis [5].

Due to the phenotypically diverse patient population and the long-term course of the disease, PV therapy must be conducted based on the analysis of the risk of complications resulting from both the disease itself and the expected prolonged exposure to the therapy used. The objective of the treatment is, first of all, the prevention of thromboembolic complications, alleviation of disease symptoms, and the decrease of the risk of transformation to PPV-MF, AML or myelodysplastic syndrome (MDS).

This article discusses some aspects of the risk evaluation and summarizes the effectiveness of the available therapies, and also presents diagnostic and therapeutic recommendations for PV.

Prognostic factors

Factors affecting risk of progression and survival time

In an international study carried out on 1,545 subjects with PV, the independent risk factors for overall survival (OS) were: leukocytosis >15 G/L, venous thrombosis and defective karyotype [5]. The negative impact of persistent leukocytosis on disease progression was also proven in another recent study [13]. The risk of progression of PV to MF and AML within 10 years is estimated to be 4.9–6% for MF and 2–5% for AML. After 20 years, these risks are estimated to be 26% and below 10% respectively [14]. The risk factors of leukemia transformation comprise: old age, defective karyotype, leukocytosis ≥15 G/L, and exposure to such medications as pipobroman, radioactive phosphorus (P32), chlorambucil, but not hydroxyurea (HU) or busulfan [14]. The risk factors of MF transformation include the allele burden of *JAK2V617F* exceeding 50%, the presence of bone marrow fibrosis at the moment of diagnosing the condition, and persistent leukocytosis [13, 15–17]. Some recent studies have confirmed an adverse effect on OS caused by defective karyotype, leukocytosis, and some mutations not linked with *JAK2*, such as *SRSF2* and *IDH2* [18, 19]. The Mutation-Enhanced International Prognostic Scoring System for Polycythemia Vera (MIPSS-PV) prognoses OS, and the risk of MF or AML transformation, on the basis of demographic, clinical and genetic data [19]. This model was created on the basis of analysis of 404 PV patients, and takes into consideration a negative role of unfavorable spliceosome *SRSF2* mutation, age above 67 years, leukocytosis ≥15 G/L, and a history of a thromboembolic incident [19]. This model is presented in Table I.

Next generation sequencing (NGS) suggests that more than 50% patients with PV have other variants or mutations than those linked with the *JAK2* gene, with the mutations most frequently occurring in the *TET2* (18%), *ASXL1* (15%) and *LNK* (3%) genes [19, 20]. The combined incidence of unfavorable mutations (*SRSF2, IDH2, RUNX1, U2AF1*) was estimated to be c.15%. These mutations were shown to be negative risk factors for OS, leukemia-free survival or progression-free survival to myelofibrosis [19]. Additional prognostic information obtained from NGS or karyotype testing turns out to be very useful, but is not mandatory in routine clinical practice. Additional studies are definitely

Table I. Risk stratification for overall survival (OS) in polycythemia vera on basis of MIPSS-PV model ([19]).

MIPSS-PV	
A history of thrombosis	1 point
WBC ≥15 G/L	1 point
Age >67 years	2 points
SRSF2 mutation	3 points
Risk stratification and interpretation	
Low risk	0–1 point; mOS 24 years
Medium risk	2–3 points; mOS 13.1 years
High risk	≥4 points; mOS 3.2 years

MIPSS-PV — Molecular International Prognostic Scoring System for PV; mOS — median overall survival; WBC — leukocyte count

needed to confirm the reliability of the MIPSS-PV model, and to identify specific cytogenetic aberrations with prognostic significance [21, 22].

Stratification of thrombotic risk

The traditional stratification of thrombotic risk in PV distinguishes between two categories of risk: high (age >60 years or a history of thrombosis) and low (the absence of both risk factors) [23]. The occurrence of arterial or venous thrombosis is the most important risk factor for subsequent vascular events [23]. However, it should be stressed that patients classified as low-risk have a significantly higher rate of thromboembolic complications compared to subjects of the same age without PV. Therefore, it is necessary to revise the definition of high risk in PV [24]. Patients with a mean hematocrit (Hct) value of ≥45% compared to patients with Hct <45% have a significantly higher risk of vascular events and death (hazard ratio [HR] 3.91, 95% CI 1.45-10.53, $p = 0.007$) [25]. Some recent studies have also identified hyperlipidemia and diabetes mellitus as risk factors for arterial events, and leukocytosis >11 G/L and major bleeding at diagnosis (defined as gastrointestinal, internal organ, intra-articular, cerebrovascular, retroperitoneal or any bleeding requiring medical or surgical intervention, hospitalization or leading to death) as risk factors for venous thrombosis [26]. However, a systematic review and meta-analysis of articles involving more than 30,000 patients suggest that leukocytosis above the upper limit of normal plays an important role here in increasing the incidence of arterial but not venous thrombotic incidents [27]. The negative effect of hypertension on arterial thrombosis was demonstrated in another study [28], which listed individual cardiovascular risk factors important in predicting thrombotic events; and also indicated the need to optimize acetylsalicylic acid (ASA) dosage, but the evidence was not strong enough to distinguish the risk of thrombosis in the PV patients from the same risk in the general population [29, 30]. For this reason, the European Society of Cardiology risk classification has been adopted as a reference for assessing baseline vascular risk in PV patients [31, 32]. A calculator for the risk assessment is available at www.heartscore.org [33]. In patients who have already experienced their first thrombotic event, risk factors for recurrence include age >60 years as well as leukocytosis at the time of the first event of arterial thrombosis in patients below 60 [34]. Additional factors that increase the risk of thrombosis include, in addition to leukocytosis, *JAK2V617F* allele burden >50% and the frequency of phlebotomy [15, 27, 30, 34–37].

Diagnostics

The basic abnormalities in peripheral blood counts in which PV is suspected comprise increased Hct and elevated hemoglobin (Hgb) level. According to the 2022 WHO criteria, an Hgb concentration of more than 16.5 g/dL in men and 16.0 g/dL in women or Hct >49% in men and >48% in women is necessary for the diagnosis of PV [1]. More than 50% of patients have an increased platelet count and c.40% of patients have an increased leukocyte count (mainly neutrophils, but basophilia may also occur) [1]. The diagnosis of PV is based on close correlation of clinical, molecular and histological data. The diagnostic criteria developed by the WHO include blood morphology parameters, bone marrow histology, the presence of *JAK2* mutations, and decreased endogenous erythropoietin (Epo) levels [1]. The diagnosis of PV requires the fulfillment of all three major criteria or the first two major criteria plus a minor one [1]. These criteria are listed in Table II. A sample of bone marrow trephine biopsy (included in the WHO criteria as a major criterion) is characterized by the proliferation of all three cell lines — erythroid, granulocytic and megakaryocytic (called panmyelosis), and the presence of atypical megakaryocytes of various sizes with hyper-lobulated nuclei [1].

The diagnostic criteria proposed by the ICC are the same, except for the omission of a bone marrow biopsy in patients with sufficiently high red blood cell parameters, i.e. Hgb >18.5 g/dL or Hct >55.5% (men) and Hgb >16.5 g/dL or Hct > 49.5% (women), the presence of *JAK2* mutation and decreased Epo levels [2]. However, it should be emphasized that only histopathological examination of the bone marrow is able to detect the presence of fibrosis (present in c.20% of PV patients), characteristic of those patients at higher risk of transformation to myelofibrosis [1, 16].

A cytogenetic assessment of bone marrow does not make up part of the diagnostic standard for PV. At the time of diagnosis, uncharacteristic aberrations are found in c. 15% of patients [21]. The most common include trisomy 8, trisomy 9, del (13q), and del (20q). The frequency of karyotype abnormalities increases over time, reaching

Table II. Diagnostic criteria of polycythemia vera according to WHO 2022 [1]

Criteria	
Major	1. Hgb >16.5 g/dL (men); >16.0 g/dL (women) or symptoms indicative of increased red blood cell volume or Hct >49% in men and >48% in women or an increased red blood cell mass (>25%)
	2. Hypercellular bone marrow with signs of erythroid, granulocytic, and megakaryocytic trilineage proliferation
	3. V617F *JAK2* mutation or *JAK2* mutation in exon 12
Minor	1. Serum Epo concentration below normal

Hgb — hemoglobin; Hct — hematocrit; Epo — erythropoietin. For the diagnosis of PV, it is necessary to meet all three major criteria or major criteria 1) and 2) plus the minor one.

80% in patients with a disease existing for more than 10 years [16].

Testing for the detection of *JAK2* mutations makes up a very important element of the diagnosis. In 96% of patients with PV, a *JAK2* gene V617F mutation is found in exon 14. In patients who do not have a V617F mutation, testing for mutations in exon 12 of the *JAK2* gene kinase should be performed [7, 9]. Non-canonical mutations are detected in a very small proportion of patients [10]. Testing for these mutations is not routinely performed, and neither is the determination of the variant allele frequency (VAF) in the *JAK2* gene. In the era of drugs which modify the natural course of the disease and achieve molecular remission (MR), the measurement of VAF is recommended at the diagnosis or at the start of treatment with interferon α (IFNα) or ruxolitinib (RUX) in order to trace the kinetics of changes during therapy [23]. To date, studies of the kinetics of VAF alterations of the *JAK2* gene have been conducted as part of ongoing clinical trials, and there are no clear recommendations about how often they should be performed in routine clinical practice [23]. In patients with PV, NGS testing to detect the presence of additional mutations is not routinely performed. However, it is known that mutations such as *ASXL1, SRSF2, IDH1/2, RUNX1* are present in c.15% of patients, something which is associated with an unfavorable prognosis and increases the risk of transformation to AML and PPV-MF [20, 23]. It is advisable to store the DNA or RNA material for future evaluation, especially in younger patients. NGS testing may also be considered in patients with a clinical picture indicative of PV and with the absence of JAK2 mutations.

Patients with a history of hemorrhagic diathesis should be diagnosed for acquired von Willebrand syndrome (avWS) with a qualitative assessment of von Willebrand factor (vWF) — vWF:RCo or vWF:GPIb [23].

Evaluation of treatment response

Currently, the aim of PV treatment is not only to improve altered peripheral blood parameters (Hgb, Hct, leukocyte and platelet counts), but also to reduce the severity of subjective symptoms associated with disease activity. Depending on the type of therapy undertaken, the methods of assessing the results are diverse, comprising:

- Reduction in Hct and Hgb concentration;
- Restoration of normal leukocyte and platelet counts;
- Reduction in severity of complaints based on MPN-SAF TSS (MPN Symptom —Assessment Form Total Symptom Score) scores;
- Reduction of spleen size;
- Facultative assessment of molecular response during therapy.

Table III sets out the response criteria proposed by European LeukemiaNet and IWG-MRT in 2013 [38, 39]. It should be emphasized that evaluation of samples of bone marrow trephine biopsy is only justified in clinical trials. In practice, this is only performed when there are clinical or laboratory signs suggestive of disease progression.

The assessment of molecular response is not yet used in clinical practice and it does not form the basis for therapeutic decision-making. For the purposes of clinical trials, it has been assumed that a complete molecular response (CMR) should be recognized in the case of complete eradication of the aberration demonstrated previously, whilst a partial molecular response (PMR) should be recognized in the case of a ≥50% reduction in VAF. However, PMR can only be diagnosed in patients with baseline VAF ≥20%.

When HU therapy is used, c.20% of patients develop intolerance or resistance to the medication. The proposed criteria for the diagnosis of this condition are listed in Table IV [31].

Results of studies evaluating efficacy of phlebotomy for treatment of PV

Phlebotomy, makes up a significant part of PV treatment on account of the fast reduction of the Hct value, alleviating the disease symptoms, and also because of its lack of cytotoxic potential [23, 40]. The results of this procedure comprise a secondary absolute iron deficiency condition, whereas the primary goal is the reduction of Hct to <45% in men and <42% in women [41, 42]. According to the CYTO-PV study, maintaining Hct below 45% with phlebotomy or HU significantly reduces the risk of cardiovascular death and major thromboembolic complications [25]. Current

Table III. Revised evaluation criteria of treatment response in patients with polycythemia vera proposed by European LeukemiaNet and IWG-MRT in 2013 [38, 39]

Response evaluation criteria	
A	Resolution of disease-related signs for ≥12 weeks, including hepatosplenomegaly in physical examination, significant improvement of large disease-related symptoms[a]
B	Improvement of peripheral blood parameters for ≥12 weeks, including Hct <45% without need for bloodletting, PLT ≤400 G/L WBC <10 G/L, absence of leukoerythroblastosis in blood
C	Absence of signs of progressive disease or new hemorrhagic of thrombotic complications
D	Bone marrow histological remission including disappearance of megakaryocyte hyperplasia and absence of >grade 1 reticulin fibrosis
Response evaluation	
Complete remission	All criteria are met
Partial remission	A + B + C criteria are met
No remission	Any response which does not meet criteria of partial remission
Progressive disease	Transformation to PPV-MF, MDS or AML[b]

AML — acute myeloid leukemia; Hct — hematocrit; IWG-MRT — International Working Group - Myeloproliferative Neoplasms Research and Treatment; MDS — myelodysplastic syndrome; MPN-SAF TSS — MPN Symptom Assessment Form Total Symptom Score; PLT —platelets; PPV-MF — post polycythemia vera myelofibrosis; WBC — leukocyte count; WHO — World Health Organization
Remarks: [a] Evaluation of disease severity should be performed with use of MPN-SAF TSS. A diagnosis of sustained remission/disease remission is possible in cases of a response persisting at least 12 weeks. Significant improvement in symptom severity is defined as a reduction in disease-related symptom severity ≥10 points assessed with use of MPN-SAF TSS.
[b] Diagnosis of progression to PPV-MF: diagnosis of a specific form of myelodysplastic syndrome or acute myeloid leukemia should be confirmed on basis of criteria proposed by IWG-MRT and WHO 2016.

Table IV. Hydroxyurea intolerance and resistance criteria [31]

Resistance	Intolerance
After 3 months of treatment with a dose of ≥2g/d (or 2.5 g/d in persons >85 kg body mass): need for phlebotomy in order to maintain Hct <45% **OR** PLT >400 G/L **AND**: WBC >10 G/L **OR** Less than 50% reduction in the size of the spleen palpable under left costal margin in palpation examination (refers to initial spleen size ≥10 cm below lest costal margin) **OR** lack of resolution of any symptoms related to splenomegaly **OR** **ELN criteria***	**During treatment with lowest HU dose making it possible to achieve at least a partial clinical response*:** ANC <1,000 G/L **OR** PLT <100 G/L **OR** Hgb <10 g/dL
After 3 months of treatment with any HU dose: PLT >1,000 G/L **OR** microcirculation symptoms **OR** increasing leukocytosis (≥100% increase if baseline WBC <10 G/L **OR** ≥ 50% increase if baseline WBC >10 G/L **OR** persistent leukocytosis >15 G/L	
After one year of HU treatment in a tolerated dose:	**During treatment with any HU dose:**
symptomatic or increasing splenomegaly (by >5 cm under left costal margin (palpation assessment) **OR** need for ≥6 phlebotomies to maintain Hct <45% **OR** increased constitutional symptoms (HU dose ≥1.5 g/d for ≥4 months): MPN-SAF TSS ≥20 points **OR** untreatable persistent skin itching for at least 6 months	Development of one of following symptoms: lower leg ulceration **OR** nonmelanoma skin carcinoma **OR** skin and mucosal symptoms vascular complications: clinically significant bleeding, venous or arterial thrombosis gastrointestinal symptoms pneumonia or fever each HU intolerance other than grade 3 or 4 or prolonged grade 2 HU toxicity according to CTCAE

*Clinical response criteria in polycythemia vera according to ELN. ANC — absolute neutrophil count; CTCAE — Common Terminology Criteria for Adverse Events; ELN — European LeukemiaNet; Hct — hematocrit; Hgb — hemoglobin; HU — hydroxyurea; MPN-SAF TSS — Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; PLT — blood platelets; WBC — leukocytes

recommendations indicate the use of phlebotomy together with ASA especially in the treatment of low-risk PV and in younger patients. In recent years, the role of phlebotomy has been increasingly debated, mainly due to the increased risk of embolic/thrombotic complications compared to other therapies, the suboptimal efficacy in maintaining a stable Hct <45%, and the impact on quality of life.

A retrospective study of a population of 533 patients with PV treated with HU showed that intensive phlebotomy, defined as more than three uptakes per year, was associated with an increased risk of thrombosis [37]. MAJIC PV is another study, suggesting that the average number of flebotomies within the first three years of therapy correlates with a shorter time to first thrombotic incident [43]. The results of this study also suggest that new drugs, such as JAK inhibitors or ropeginterferon alpha 2b (ropegIFNα-2b), may offer a valuable alternative to conventional treatments (including phlebotomy), offering similar efficacy in controlling Hct and potentially reducing the risk of thrombotic complications [43, 44]. Inadequate control of Hct levels and hyperplasia secondary to iron deficiency may turn out to be risk factors for embolic incidents in this patient population [45]. A further problem is the lack of data confirming that phlebotomy can independently maintain stable Hct levels in low-risk PV [46]. Additionally, the PVSG and ECLAP studies have shown that HU cytoreductive therapy is more effective in protecting against thrombosis than phlebotomy alone [47]. It is noteworthy that phlebotomies do not control leukocytosis, which is associated with an increased risk of arterial thrombosis, nor have the potential to reduce VAF *JAK2V617F* and, therefore, they cannot modify the course of the underlying disease, including the rate of thrombotic complications, whilst their risk increases with VAF values >50% [46].

Iron deficiency, which is secondary to phlebotomy, is connected with an excessive production of HIF2-alpha (hypoxia-inducible factor 2 alpha), which stimulates the self-reproduction of hematopoietic stem cells (HSC) and increases the release of CD34+ cells from the bone marrow. These cells, when deposited in the spleen and other tissues, increase extramedullary hematopoiesis [48]. Megakaryocytes taken from iron-deficient individuals show increased expression of the HIF2-alpha protein compared to cells taken from non-iron-deficient individuals [49]. HIF2-alpha stimulates the expression of vascular endothelial growth factor (VEGF), which enhances megakaryocytopoiesis [49].

Improvement of the patients' quality of life constitutes a vital objective of PV therapy [46, 50]. Phlebotomy, by means of reducing the Hct values, may reduce symptoms associated with hyperviscosity, but it cannot reduce the severity of pruritus or decrease splenomegaly. Chronic iron deficiency induced by phlebotomies can cause headaches, insomnia, difficulty in concentrating, dizziness, and restless legs syndrome [51, 52]. Additionally, in children and pregnant women, there is a risk of growth impairment, and there is a risk of delay of intellectual development in children and foetuses. Phlebotomies are commonly used in children, but the target Hct values are not clearly defined; the most commonly recommended Hct values for children are reductions of less than 45% and 48% [53]. In pregnancy, the target for phlebotomy is an Hct value <45% [54].

In conclusion, phlebotomy remains an important tool in the treatment of PV, but its use should be considered and tailored to the individual patient.

Results of studies evaluating efficacy of hydroxyurea

So far, HU has been the standard first line cytoreductive treatment used in order to decrease blood cell numbers in high risk PV patients [55]. HU therapy effectively achieves rapid cytoreduction in this patient group and has a favorable safety profile.

About 90% of patients respond to HU therapy, with 24% achieving a complete response and 66% a partial response, but 25% of the treated group develop resistance or intolerance, so some patients still require periodic phlebotomies to maintain the desired Hct level [47, 56]. Around 25% of patients discontinue therapy, most commonly due to a lack of response or a suboptimal response. Other reasons for discontinuation of HU therapy include drug intolerance or disease progression [57–61]. The factors associated with HU resistance or intolerance comprise low initial Hgb levels, age over 60, and splenomegaly [60]. HU resistance and intolerance are unfavorable prognostic factors in PV, as they increase the risk of disease progression to PPV-MF or AML, although there is no evidence of direct association between HU resistance or intolerance and PV progression to AML [57, 61]. The risk of PV transformation to myelofibrosis 5 and 10 years after the onset of the disease is 3% and 17%, respectively, in patients with HU resistance or intolerance, and 1.5% and 6.7% in other patient groups. Higher rates of transformation after five years are observed in patients who fail to reduce massive splenomegaly (14% vs. 1.6%) and in those who develop cytopenias (10% vs. 1.6%) [61]. Analysis of individual resistance and intolerance criteria has shown that the development of cytopenias during HU treatment correlates with an increased risk of progression to AML (28% vs. 0.8% over five years) [61].

The PSVG study consisted of a comparison of the effect of HU and phlebotomy on the risk of thrombosis [62]. The study compared 51 patients treated with HU in combination with phlebotomy to a group of 134 patients who received phlebotomy only. The analysis made after 378 weeks of therapy showed that the incidence of thrombotic events in patients treated with HU together with phlebotomy (9.8%) was significantly lower than in the control group (32.8%, $p = 0.009$), while the incidence of AML was higher in this

group (5.9% vs. 1.%, p = 0.18), although the difference was not statistically significant. The authors of this study suggested that younger patients who require complementary cytoreductive therapy in addition to phlebotomy should be treated with IFNα due to its lack of leukemogenic and teratogenic effects, and the possibility of achieving cytogenetic remission in some of them [62]. The efficacy of HU compared to phlebotomy was also the subject of the large, multicentre ECLAP trial comprising 1,042 subjects, treated with phlebotomy alone (n = 342) or HU (n = 681) during a follow-up in order to maintain Hct below 45% [56]. The rate of patients with a target Hct below 45% after 12 months was higher in the HU group compared to the patients treated with phlebotomy (52% vs. 31%, p < 0.0001). In high-risk patients (above 60 years or with a history of thrombosis), the rate of fatal and non-fatal cardiovascular events was significantly lower in the HU-treated group (4.8 vs. 8.7/100 patient-years in the HU vs. phlebotomy group), and so was the rate of transformation to myelofibrosis (0.1 vs. 1.5/100 patient-years in the HU vs phlebotomy group) and mortality (0.1 vs. 0.5/100 patient-years in the HU vs. phlebotomy group). The percentage of mortality and cardiovascular events was significantly higher in patients in the phlebotomy group who did not reach the target Hct level of <45% (p = 0.000) compared to the HU-treated patients [56]. Another retrospective, single-centre study involving 470 patients compared the effect of IFNα, HU and phlebotomy alone on myelofibrosis-free survival (MFS) and OS [63]. The mean follow-up period was 10 years (range 0 to 45). Out of 437 patients, 208 belonged to a high-risk group (44%). HU was administered in 189 patients (40%), IFNα in 93 patients (20%), phlebotomy in 133 patients (28%), and other cytoreductive drugs in 55 patients (12%). In low-risk patients, 20-year MFS was 84% for IFNα, 65% for HU, and 55% for phlebotomy, respectively (p <0.001), and 20-year OS was 100%, 85%, and 80%, respectively (p = 0.44). In the high-risk group, 20-year MFS was 89% for IFNα, 41% for HU, and 36% for phlebotomy (p = 0.19), while 20-year OS was 66%, 40%, and 14%, respectively (p = 0.016). Multivariate analysis revealed that a longer duration of IFNα use was associated with a lower risk of developing myelofibrosis (relative risk [HR]: 0.91, p = 0.012) and a lower mortality (HR: 0.94, p = 0.012) [63]. The majority of study results confirm the absence of a leukemogenic effect of HU, but the long-term use of HU is associated with a 20% risk of developing skin cancers other than melanoma [64, 65].

Results of studies evaluating efficacy of interferon alpha

Interferons (IFNs) are cytokines with anti-inflammatory, immunomodulatory and anti-tumour effects. Several subtypes of these molecules function in the healthy human body, but, in this group only IFNα has a therapeutic use in the treatment of myeloproliferative neoplasms [66]. It is characterized by a strong proapoptotic effect, also shown against progenitor cells with the presence of *JAK2* kinase mutations. The forms of recombinant IFNα originally used in MPN therapy were characterized by a short half-life and an unfavourable safety profile, which was the cause of numerous treatment failures [66]. The modification of recombinant interferon by attaching a biocompatible polymer, polyethylene glycol (Peg), to the IFNα molecule allowed the half-life to be extended, thus reducing the frequency of use (to once weekly) and the toxicity [66].

A further structural modification (ropegylation) resulted in an Increase in the half-life of the drug and an increase in the intervals between IFNα administrations to two weeks and a further reduction in toxicity. Peginterferons, while retaining their proapoptotic efficacy, activate the immune system to a lesser extent, leading to a significantly more favourable profile of side effects. The efficacy of modified forms of IFNα in PV therapy has been confirmed in numerous studies. Early phase II and III studies evaluating the safety and efficacy of PegIFNα 2a and 2b included groups with different MPNs, and different criteria were used to assess response. The studies analysing PegIFNα 2a included both patients with newly diagnosed high-risk PV (MPD-RC-112 study) and patients with HU resistance or intolerance (MPD-RC-111 study) [67, 68]. In the population of previously treated patients, the response rate (complete and partial remissions) achieved after 12 months of PegIFNα treatment was 60%. The medication used in the first-line treatment made it possible to achieve a 78% response rate, and this percentage was comparable to that obtained in the hydroxyurea arm. Complete hematological remission (CR) was achieved in 22% and 30% of those treated with HU and those not receiving any treatment prior to PegIFNα, respectively. In subsequent years of follow-up, the percentage of complete remissions in the IFNα-treated patients increased as opposed to the HU-treated group [67, 68].

In recent years, the results of studies conducted exclusively with ropegIFNα-2b have been published. In the PEGINVERA trial, a reduction in toxicity and an improvement in treatment efficacy were reported [69]. Most side effects were mild and transient, while severe symptoms were reported in 19.6% of patients (two depressive episodes, thyroid dysfunction, atrial fibrillation, arthritis, flu-like syndrome, febrile states, and increased transaminase activity). The percentage of CR achieved in the study was 64.3% at 2-year follow-up, while partial hematological remission (PR) was 33%. The time to CR was relatively long at 34 weeks; and the time interval to hematological response was 10 weeks. Once a response was achieved, the drug was administered at a reduced frequency i.e. every four weeks, with no loss of therapeutic effect. Therapy with ropegIFNα-2b resulted in a slow reduction in the mutant allele burden, and a CMR of 28.6% was achieved. The median time to CR was 82 weeks [69].

Subsequent studies (PROUD-PV and CONTINUATION-PV) comparing ropegIFNα-2b to HU confirmed the efficacy and good tolerability of this form of the drug [44, 69]. The study included 257 patients. RopegIFNα-2b was administered subcutaneously every two weeks at an initial dose of 100 µg. After 12 months, the primary endpoint, i.e. CR and normalization of spleen size, was achieved in 21% of patients in the ropegIFNα-2b group and in 28% of the HU-treated patients (p = 0.23). CR without normalization of spleen size was observed in 43% vs. 48%, respectively (p = 0.63). The response rate to ropegIFNα-2b increased over time. The assessment made at 36 months revealed CR in 71% of patients treated with ropegIFNα-2b and in 51% of those receiving HU (p = 0.012). Moreover, CR, reduction in splenomegaly and decrease of the symptoms related to microcirculatory disorders, pruritus and headaches were observed in 53% of patients treated with ropegIFNα-2b and 38% of patients in the HU group (p = 0.044). A progressive reduction in VAF *JAK2*V617F was also observed in the ropegIFNα-2b-treated group. After 36 months of ropegIFNα-2b therapy, VAF decreased from 42.8% to 19.7%, whereas in HU-treated patients the reduction was only transitory and, at 36 months, VAF was not significantly different from the baseline values. Tolerability of ropegIFNα-2b was good. The most common grade 3 and 4 adverse events in the ropegIFNα-2b-treated group were the elevations of GGTP (gammaglutamyltranspeptidase) (6%) and ALT (alanine transaminase) (3%), and in the HU group were leukopenia (5%) and thrombocytopenia (4%). Grade 3 and 4 depression was observed in 2% of patients in each group [44].

The efficacy of ropegIFNα-2b was also evaluated in low-risk PV patients, in whom the drug was compared to flebotomy [70]. The primary objective of the study was to assess the proportion of patients with Hct <45% and without adverse events (thrombotic complications, bleeding, progressive leukocytosis, symptomatic or very high thrombocytosis, symptomatic splenomegaly). The primary objective was achieved in 84% of patients in the ropegIFNα-2b group compared to 60% in the standard arm (p = 0.008). What's more, the patients in the ropegIFNα-2b group required fewer phlebotomies: 43% vs. 57%, had fewer general symptoms assessed according to the MPN Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) (p = 0.033), and had significant reductions in splenomegaly, leukocytosis and platelet count. No differences were observed in the frequency of >3 grade adverse events in the two groups: 6% (ropegIFNα-2b) vs. 8% (phlebotomy) [70].

Results of studies evaluating efficacy of ruxolitinib

The drug registered for the treatment of PV patients manifesting resistance or intolerance to HU is ruxolitinib (RUX). In 2014, Vannucchi et al. [71] published the results of a randomized phase III trial (RESPONSE trial) comparing the efficacy of RUX and best available therapy (BAT) in a group of 222 PV patients with splenomegaly, resistant or intolerant to HU. The study showed significantly better efficacy of RUX compared to BAT with respect to both Hct control and reduction of overall symptoms. The primary study objective of Hct control and spleen size reduction of at least 35% was achieved in 21% of patients in the RUX group, but in only 1% in the BAT group (p <0.001). Hct control was observed in 60% of patients receiving RUX and 20% in the BAT group. CR was achieved by 24% of patients treated with RUX compared to 9% in the BAT group (p = 0.003). Better control of general symptoms was also observed among RUX-treated patients. At week 32 of the study, at least a 50% reduction in MPN-SAF TSS symptom severity was achieved by 49% vs. 5% of patients, respectively. A gradual reduction in VAF *JAK2* was also observed in the RUX group (maximum mean reduction: –34.7% at week 112). The assessment of treatment complications concerned the first 32 weeks of the study, as after this time most patients were switched to the RUX arm. Treatment tolerability was good, yet herpes zoster infections were more frequently observed in patients treated with RUX (6% vs. 0%). On the basis of the results of the RESPONSE trial, RUX was registered for the treatment of PV patients resistant or intolerant to HU [71]. Similar results were observed in the RESPONSE 2 trial, which included patients with PV refractory or intolerant to HU, but without splenomegaly [72]. Hct control was achieved in 62% of patients in the RUX group and 19% in the BAT group (p <0–0.001) [72]. However, it should be noted that in both RESPONSE studies, about one half of the patients in the BAT group received HU [71,72].

The RELIEF study assessed the efficacy of RUX compared to HU in patients who had good Hct control yet with general symptoms [73]. The primary objective of the study was to assess the proportion of patients who experienced at least a 50% reduction in MPN-SAF TSS-assessed symptoms after 16 weeks of treatment. This percentage was higher in the RUX-treated group compared to HU-treated patients (43.4% vs. 29.6%, respectively), yet the difference was not statistically significant, although RUX was significantly more effective in reducing pruritus [73].

The phase II MAJIC-PV study evaluated the efficacy of RUX versus BAT in 180 HU-resistant/intolerant patients [43]. The BAT group was treated with HU (32%), IFNα (15%), and HU together with IFNα (12%). Patients treated with RUX were significantly more likely to achieve CR (43% vs. 26%; p = 0.02), and their response lasted longer (p < 0.001). Event-free survival (EFS), defined as time free from major thrombotic/hemorrhagic episodes and transformation or death, was significantly longer in the patients who achieved CR (p = 0.01) and those treated with RUX (p = 0.03). Patients treated with RUX were more likely to have a >50% reduction in VAF JAK2 (56% of patients after

48 months of follow-up in the RUX group versus 26% of patients after a median follow-up of 36 months in the BAT group, p <0.001). Infections, mostly respiratory and genitourinary infections and *herpes zoster*, were significantly more frequent in the RUX-treated patients (27 vs. 12 grade 3/4 infections, respectively). Skin squamous cell carcinoma was also more common in the RUX group (11 vs. 0, respectively) [43].

Recommendations concerning treatment of patients with PV

Irrespective of the risk group, the treatment goals for patients with PV are unchanged and include [31]:

1) Reduction of risk of thromboembolic complications.
2) Reduction of symptoms resulting from disease.
3) Reduction of risk of disease progression to MF and AML.

In each risk group and at each stage of treatment, efforts should be made to eliminate or minimize cardiovascular risk factors (CVRFs) independent of PV, such as the normalization of body weight, adequate control of blood pressure values, control of lipid metabolism, normalization of serum glucose levels and stopping smoking [74]. The use of hormonal contraceptives is contraindicated, whilst hormone replacement therapy should only be used when the benefits of such treatment outweigh the risk of embolic complications.

In patients with newly diagnosed PV, irrespective of risk group, phlebotomy should be performed to reduce quickly the Hct values. The frequency of phlebotomies should be adjusted to the resolution of subjective symptoms associated with polycythemia or the rate of Hct decline and the planned time period to achieve the desired Hct value, as well as the tolerability of the procedures. After each procedure, the lost blood volume should be replenished with the administration of 0.9% NaCl solution. The frequency of the procedure (every two days or twice a week) as well as the volume of successive phlebotomies (250–400 ml) should be determined individually for each patient depending on comorbidities (especially cardiovascular conditions) and the dynamics of Hct decrease after subsequent procedures [70].

Recommendations concerning treatment of low-risk PV patients

Low-risk patients are a group that requires special care when choosing a therapeutic strategy. According to classical prognostic criteria, they are young patients (<60 years old) who have never had a thromboembolic incident. In this group of patients, in addition to the reduction of the risk of thromboembolic complications and the reduction of symptoms resulting from the disease, the expected long-term course of the disease and, consequently, the significant probability of developing both PPV-MF and AML in the future, should be taken into account.

The CYTO-PV study showed a clear benefit of the strategy of maintaining hematocrit <45%, reducing the rate of thromboembolic complications [25]. In order to reduce red blood cell parameters in patients with low-risk PV, it is advisable to perform phlebotomy first. However, it should be kept in mind that not all patients tolerate phlebotomies well, and a repetition of this procedure may lead to the development of tissue iron deficiency and secondary thrombocythosis resulting in increased microvascular symptoms [75]. The most recent ELN recommendations have identified groups of patients with low-risk PV who may benefit from the inclusion of cytoreductive treatment (see Table V) [31]. The choice of treatment in this group of patients should take into account the expected long-term exposure to the selected drug. Due to the time-dependent skin complications, as well as the lack of effect of HU on the eradication of the *JAK2* mutant clone, the use of this drug is not recommended in patients with low-risk PV. Considering the results of the Low-PV study, which confirmed the safety of ropegIFNα-2b and proved its superiority in hematocrit control over phlebotomy treatment, ropegIFNα-2b is the drug of choice in this patient group [46].

Recommendations concerning treatment of high-risk PV patients

High-risk PV patients require cytoreductive treatment in addition to phlebotomies [31]. The drugs of first choice comprise HU or IFNα. The initial dose of HU is usually 0.5 g twice daily, and then it should be modified to keep Hct below 45%. Approximately 25% of patients experience drug ineffectiveness or intolerance. Adverse effects that HU can cause include cytopenias, mucosal and skin ulcerations, gastrointestinal intolerance, fever, and skin lesions including non-melanoma skin tumors. It is important to emphasize the need to carefully collect medical history and assess the skin condition during and assessthe skin condition during follow-up visitis of patients treated with HU.

Currently, the drug recommended for first-line PV therapy, especially in younger patients, is IFNα [23]. It is believed that its use may lead to bone marrow histology response, a reduction in VAF *JAK2*, and a decrease in the incidence of PV transformation to MF [23]. In 2020, the European Medicine Agency (EMA) approved ropegIFNα-2b for the treatment of patients with PV without significant splenomegaly.

In Poland, ropegIFNα-2b therapy is reimbursed for the following indications: 1) young high-risk patients with indications for cytoreductive therapy; 2) patients intolerant of or refractory to HU therapy; and 3) pregnant women.

It should be noted that the ELN experts claim that patients who are classified as low risk according to the

Table V. Recommendations concerning cytoreductive pharmacotherapy in low-risk PV patients proposed by ELN experts [31]

	Cytoreductive treatment in low-risk PV patients
Recommended	1. Poor tolerance to phlebotomy, defined as recurrent syncope episodes following phlebotomy in spite of preventive measures, or hematophobia, leading to avoidance behaviours or significant difficulties in obtaining venous access (consensus: 100%)
	2. Progressive symptomatic splenomegaly (spleen increase by >5 cm within last year) provided that transformation to myelofibrosis has been ruled out (consensus: 85%)
	3. Persistent leukocytosis (leukocyte count >20 G/L confirmed at 3 months without therapy (consensus: 85%)
To be considered	1. Progressive leukocytosis (increase by at least 100%, with baseline count <10 G/L, or increase by at least 50%, with baseline count >10 G/L) and persistent leukocytosis >15 G/L, confirmed within 3 months (consensus: 80%)
	2. Significant thrombocytosis (>1,500 G/L), bleeding manifestations regardless of platelet count, or both (consensus: 85%)
	3. Suboptimal hematocrit control following phlebotomy, i.e. need to perform at least 6 phlebotomies per year for at least 2 years in maintenance therapy after obtaining hematocrit below 45% in induction therapy (consensus: 80%)
May be considered	1. Severe general symptoms (total symptoms score in MPN-SAF TSS form ≥20 points) or persistent and severe itching (itching score ≥5 points), which do not resolve after phlebotomy, antiplatelet therapy or antihistamine medications (consensus: 93%)
	2. Individualized in cases of patients with significant cardiovascular risk provided that primary prophylaxis was applied (consensus: 85%)

MPN-SAF TSS — Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; PV — polycythemia vera

conventional index, but who are burdened with the factors listed in Table V, should be considered as high-risk patients (requiring the implementation of cytoreductive treatment) [23]. The preferred drug in this group of patients is ropegIFNα-2b. When considering whether to administer ropegIFNα-2b, it is necessary to be aware of potential contraindications to this drug such as end-stage renal failure (glomerular filtration rate [GFR] <15 ml/min/1.73m^2), severe cardiovascular disease (uncontrolled hypertension, congestive heart failure in NYHA [New York Heart Association] class ≥2, severe cardiac arrhythmias, significant coronary stenosis, unstable angina pectoris), the presence of autoimmune disease, and serious psychiatric disorders, especially severe depression with a history of suicidal ideation or attempted suicide. Compensated cirrhosis (Child-Pugh stage A) is not a contraindication for ropegIFNα-2b [76]. During the treatment, regular mood assessment and control of biochemical parameters are required: the levels of aspartate aminotransferase (AST), ALT, GGTP, thyrotropic hormone (TSH), and creatinine. The dose is adjusted individually for each patient starting at the recommended dose of 100 μg (or 50 μg in patients receiving other cytoreductive treatment). The dose should be gradually increased by 50 μg every fortnight (with a concomitant, gradual reduction of other cytoreductive treatment, if applicable) until stabilization of hematological parameters is achieved. The maximum recommended single dose is 500 μg injected every fortnight [76]. In a clinical trial conducted on polycythemia vera, the mean adjustment period for an individual dose of ropegIFNα-2b was 3.7 months of drug administration and for HU was c.2.6 months [76].

In patients with resistance or intolerance to HU (the criteria are listed in Table IV), treatment with a previously unused drug is recommended: RUX or IFNα [23]. When RUX is administered at an initial dose of 10 mg bid, a higher propensity for infectious complications (mainly *herpes zoster*) and skin lesions (non-melanoma skin cancers) must be taken into consideration [43].

In older persons, i.e. >65 years, or patients refractory/intolerant to other therapies, busulfan can be used [23]. However, the use of this drug requires special caution due to its potential irreversible myelotoxic effect. Treatment is initiated at a dose of 2–4 mg/day and should be reduced if the platelet count falls below 150 G/L or the leukocyte count below 5 G/L, while a reduction in platelet count below 100 G/L or leukocyte count below 3 G/L requires discontinuation of the drug. The effects of busulfan may persist for a long period after discontinuation of therapy.

Therapy recommendations for patients with PV are listed in Figure 1.

Antithrombotic prophylaxis and treatment

The most important preventive measure is to maintain Hct values <45% in men and <42% in women. Recent expert recommendations recommend even lower target Hct values

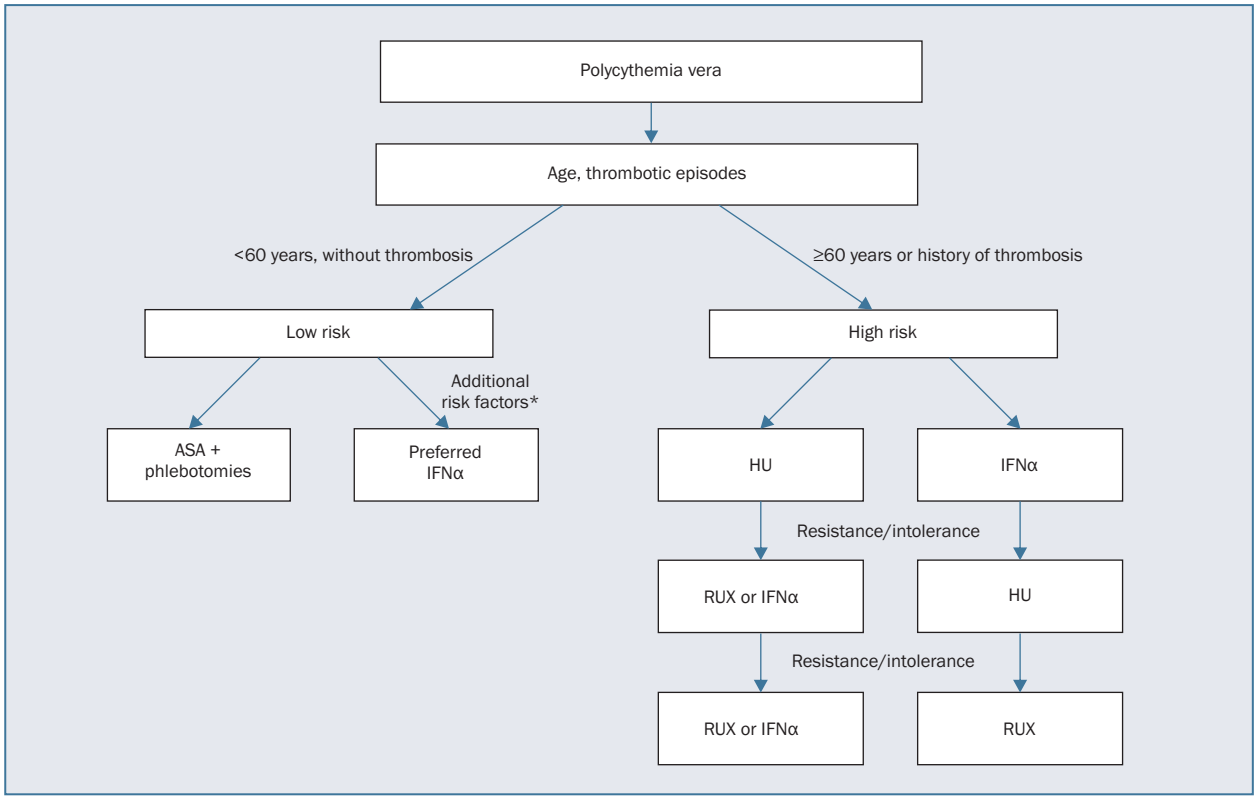

Figure 1. Recommendations for the treatment of polycythemia vera. *As shown in Table V. ASA — acetylsalicylic acid; IFNa — interferon alpha; HU — hydroxyurea; RUX — ruxolitinib

(40–42%) for patients with persistent symptoms of blood hyperviscosity, such as erythromelalgia, transient ocular ischemic episodes, headache, dizziness or amaurosis fugax, despite lowering Hct <45%, if there is a demonstrable benefit of such an option [77].

In low-risk PV patients, the administration of low-dose ASA (40–100 mg) once per day has a documented anticoagulant efficacy [78, 79]. Antiplatelet treatment reduces the incidence of venous thrombosis in patients with a *JAK2* gene mutation present, as well as the incidence of arterial thrombotic episodes in patients with coexisting cardiovascular risk factors [78]. The administration of ASA twice per day should be considered in patients with co-occurring cardiovascular risk factors, leukocytosis or the presence of microvascular symptoms, despite low doses of the drug. ASA should be administered twice per day in high-risk patients after an episode of arterial thrombosis [80]. Cardiovascular risk should be assessed at baseline and once per year with a validated risk assessment scale, e.g. QRISK score or SCORE risk [74, 81]. The details of thromboprophylaxis are presented in Table V.

Treatment of acute thrombotic episodes

The therapy of acute thrombotic complications should follow current guidelines on thrombosis treatment. In cases where the thrombotic complication is the first manifestation of the disease, cytoreductive treatment should be implemented immediately. The management should also include phlebotomy to reduce Hct to <45% [80]. In patients with newly diagnosed PV, as well as in those who develop thrombotic complications during cytoreductive treatment, the therapeutic management should be optimized so that the blood morphotic values remain within the desired range. Thus, in cases of arterial thrombosis, treatment with low doses of ASA should be implemented immediately, together with specialist consultations (e.g. a cardiologist in a case of coronary thrombosis, a neurologist/neurosurgeon in a case of cerebral arterial thrombosis) — it is necessary to follow the current specialist recommendations [81, 82]. In cases of venous thrombosis, it is advisable to start anticoagulation treatment with low-molecular-weight heparins, with a switch to vitamin K antagonist (VKA) treatment according to current guidelines [81, 82].

In patients with an unprovoked episode of venous thrombosis, it is recommended to use long-term anticoagulation with VKA or DOACs (direct oral anticoagulants) for secondary prevention, taking into account the current hemorrhagic risk, including avWS [80]. A similar approach should be applied in cases where visceral venous thrombosis is confirmed and cerebral venous thrombosis is diagnosed [80].

Table VI. Antithrombotic prophylaxis in patients with PV

All patients	
1. Phlebotomies until values adequate to maintain Hct <45% in men and <42% in women are achieved 2. ASA once per day	
Low-risk patients (<60 years, no history of thrombosis)	**High-risk patients (history of thrombosis or age >60)**
ASA twice per day should be considered in following cases: (a) microvascular symptoms despite administration of this drug once per day b) co-existence of cardiovascular risk factors c) leukocytosis	1. Cytoreductive therapy 2. In patients with a history of arterial thrombosis, ASA should be administered twice per day and anticoagulation treatment should be initiated

ASA — acetylsalicylic acid; Hct — hematocrit;

In recent years, DOACs have been increasingly used for thromboprophylaxis. Studies of the efficacy of DOACs carried out in a cancer population indicate that these drugs have significant efficacy and a good safety profile [83]. Unfortunately, there are no randomized trials comparing the activity of DOACs to that of VKAs in MPN patients. However, increasing data indicates similar efficacy in this patient group as well [84–86]. Weronska et al. [84] used DOACs in 48 patients with PV (70.8%) and ET who experienced venous thromboembolism (VTE). Patients were given apixaban (39.6%), rivaroxaban (33.3%) and dabigatran (27.1%). During 30 months of follow-up (range 20.5–41.5), there were four thrombotic episodes (3.3 per 100 patient-years) and one major bleeding episode [84]. Serrao et al. [85] used DOACs in 71 patients with MPN (including 15 with PV) for atrial fibrillation (FA) or VTE. At 12-month follow-up, no patient had thrombotic complications or a major hemorrhagic episode [85]. A multicentre observational study carried out by Barbui et al.[86] included 442 patients with MPN (including 178 with PV). Patients received DOACs (dabigatran, apixaban, rivaroxaban, edoxaban) for AF (n = 203) or a history of VTE (n = 239). After a median follow-up of 1.7 years, there were 10 major thrombotic episodes (2.1 per 100 patient-years) in the AF group and 22 thrombotic complications (4.5 per 100 patient-years), including 17 venous and five arterial ones, among patients with VTE. In the entire group, 26 major bleeding complications were observed (14 in AF patients and 12 in VTE patients), representing 3% and 2.3% per year, respectively. Bleedings most often occurred in the gastrointestinal tract and were mainly observed in patients with MF, more frequently in those treated with dabigatran [86]. The incidence of thrombotic and hemorrhagic complications observed in these studies is similar to that of prophylaxis with VKA, but the retrospective nature of the studies should be emphasized. The decision on the type of thromboprophylaxis should be taken considering thrombotic and hemorrhagic risk factors, renal and hepatic function status, medications taken, and patient preference.

Pregnancy in a patient with PV

Thrombotic complications make up a major cause of morbidity and mortality in patients with MPNs [87]. Since pregnancy is a state of increased thrombotic readiness, the risk of thrombotic complications in pregnant MPNs is higher than in the general population [54, 87, 88]. An analysis of 129 pregnancies in 60 patients with MPNs revealed that 68.2% of pregnancies ended in obstetric success, and the main complications concern the fetus: miscarriages (31.8%) and preterm births (17.8%) [89]. Pregnant women with MPNs are at risk of thrombotic and hemorrhagic complications; however, an analysis conducted by Landtblom et al. [90] between 1973 and 2018 found no statistically significant difference in these complications between patients with and without MPNs.

The treatment of a pregnant woman with MPNs should be carried out in close collaboration between hematologist and obstetrician-gynecologist. The care of a pregnant woman with MPN should begin before conception: the patient (and her partner) should be informed of the risks of pregnancy, and her cardiovascular risk factors and blood count parameters should be assessed. Based of them, the cytoreductive therapy should be modified or planned accordingly (maintenance or introduction of IFNα) [91].

The cytoreductive drug of choice, due to its safety for the proper development of the fetus and the course of pregnancy, is IFNα [92, 93].

However, this therapy is not recommended for all pregnant women with MPN but only for those at high risk, i.e. in whose cases there were:

1) ≥1 miscarriage of unclear etiology <10 weeks' gestation (hbd).
2) ≥1 death of unclear etiology of a morphologically normal fetus ≥10 hbd.
3) ≥1 preterm delivery of a morphologically normal fetus <34 hbd, due to severe pre-eclampsia, eclampsia or placental insufficiency.
4) a history of peripartum hemorrhage requiring transfusion [94].

In addition, the classification of a patient into the high-risk group is determined by the result of a Doppler ultrasound examination of the uterine arteries at 20 hbd. An abnormal test result indicates placental insufficiency (pulsation index >1.4) due to vascular flow disturbances [80, 94–96].

HU and VKA, due to their potential teratogenic effects, should be discontinued at least three months before conception (both in the affected woman and in the partner with MPN). There is no conclusive data on the safety of anagrelide (ANA) in pregnancy, but due to the risk of thrombocytopenia in the fetus, this drug should be discontinued in the affected woman three months before attempting to conceive [80, 94, 95]. However, it should be noted that there have been reports of normal pregnancy outcomes in patients with MPNs who received HU or ANA during the first trimester of pregnancy [97].

Some generally recognized risk factors for complications in pregnant patients with MPN include a history of arterial or venous thrombosis, and also hemorrhage. A high platelet count of more than 1,000 G/L or 1,500 G/L is also considered a risk factor, primarily due to the risk of avWS. The risk of complications is also increased with high leukocytosis, Hct >45% despite phlebotomies, concomitant diseases such as diabetes, hypertension, and older maternal age (>35 years) [80, 94, 95]. At present, the status of directional mutations does not determine the therapy of pregnant women with MPN.

In all pregnant women with MPN, it is recommended to make a blood count check every four weeks until 24 hbd and then every two weeks. Testing for avWS(ristocetin activity) is advisable, especially in patients with PLT count >1,000 G/L. It should be borne in mind that both PLT and Hct counts tend to spontaneously decrease during pregnancy, and iron supplementation is associated with a risk of increased red cell parameters and is therefore not recommended as standard [80, 94–96].

In patients with PV, phlebootmy is additionally recommended in order to maintain Hct <45% or its normal range applicable for the trimester of pregnancy (31–41% in the first trimester, 30–38% in the second trimester, and 28–39% in the third trimester) [80]. Strict monitoring of blood pressure and regular urinanalysis are necessary. If the patient is given low-molecular-weight heparin (LMWH) in a therapeutic dose, it is advisable to determine the anti-X activity every two months [94]. Fetal ultrasound is another important examination in pregnancy to assess normal growth. This assessment should be performed at 32 and 36 hbd [91].

According to the published data, proper management of a pregnant patient with PV based on low doses of ASA and LMWH or INFα alone or in combination with ASA or LMWH, significantly increases the live birth rate from 47.6% to 78.2%. Thus, a low-dose ASA is recommended in every pregnant woman with MPNs provided that there are no contraindications [89,98]. ASA should be administered throughout pregnancy with the exception of the last two weeks before the planned delivery, when a the switch to prophylactic dose of LMWH should be made. The last dose of heparin should be given 12 hours before delivery, another dose c.12 hours after delivery, followed by prophylactic use of LMWH and ASA for six weeks postpartum, in view of the particularly high risk of thrombotic complications characteristic of this period. Prophylaxis with LMWH at the standard prophylactic dose (e.g. enoxaparin 40 mg once a day) should be initiated as soon as possible after pregnancy is confirmed in all women with MPN and a history of venous thrombosis or obstetric failure [80]. In these patients, doubling the dose of LMWH after 16–20 hbd is recommended. In patients with a history of an episode of arterial thrombosis, UK recommendations suggest an intermediate dose of LMWH (e.g. enoxaparin 40 mg bid) [80, 99]. Therapeutic doses of LMWH are administered for thrombotic complications during pregnancy [80, 94–96].

In vitro fertilization (IVF) methods are acceptable, although there are no established standards of therapeutic management in this group of patients. Currently, LMWH is recommended from the start of hormonal therapy up to 12 hbd, with a short interval for oocyte retrieval. IFV is an identified risk factor during pregnancy [91].

In conclusion, all women of childbearing age with MPNs should be informed about possible complications in pregnancy and the need to plan for it. HU and ANA should be discontinued at least three months before pregnancy. A close collaboration between the hematologist and the obstetrician-gynecologist is essential for the correct management of a pregnancy in a patient with MPNs. During pregnancy, it is necessary to check peripheral blood count parameters, fetal ultrasound, and assessment of uterine artery flow at 20 and 24 hbd. In every patient, low-dose ASA should be introduced as soon as possible (preferably before pregnancy) as routine thromboprophylaxis and continued until the end of the postpartum period. The addition of LMWH is recommended if there are additional risk factors for thrombotic complications (thrombotic incident, a history of obstetric failures) and for six weeks postpartum in all women with MPN. Close monitoring of Hct levels <45% (or even <42%) is recommended for PV. Cytoreductive therapy is reserved for women with MPN with a high risk of thrombotic complications, and the drug of choice is IFNα. There are no clear recommendations for IFNα therapy during breastfeeding.

Article information and declarations

Authors' contributions

All authors contributed equally to the article and approved its content.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest

JG-T, TS, MB, MS, KL — Advisory board membership (Novartis, Orphan AOP, GSK), lectures: Novartis, Abbvie, Orphan AOP, Pfizer. AG — lectures: Novartis, Abbvie, Orphan AOP, Pfizer. PS, OCh — no declaration.

Supplementary material

Not applicable.

References

1. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022; 36(7): 1703–1719, doi: 10.1038/s41375-022-01613-1, indexed in Pubmed: 35732831.
2. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022; 140(11): 1200–1228, doi: 10.1182/blood.2022015850, indexed in Pubmed: 35767897.
3. Hultcrantz M, Ravn Landtblom A, Andréasson B, et al. Incidence of myeloproliferative neoplasms - trends by subgroup and age in a population-based study in Sweden. J Intern Med. 2020; 287(4): 448–454, doi: 10.1111/joim.13019, indexed in Pubmed: 31927786.
4. Szuber N, Mudireddy M, Nicolosi M, et al. 3023 Mayo Clinic Patients With Myeloproliferative Neoplasms: Risk-Stratified Comparison of Survival and Outcomes Data Among Disease Subgroups. Mayo Clin Proc. 2019; 94(4): 599–610, doi: 10.1016/j.mayocp.2018.08.022, indexed in Pubmed: 30824279.
5. Tefferi A, Rumi E, Finazzi G, et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. Leukemia. 2013; 27(9): 1874–1881, doi: 10.1038/leu.2013.163, indexed in Pubmed: 23739289.
6. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med. 2005; 352(17): 1779–1790, doi: 10.1056/NEJMoa051113, indexed in Pubmed: 15858187.
7. James C, Ugo V, Le Couédic JP, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. Nature. 2005; 434(7037): 1144–1148, doi: 10.1038/nature03546, indexed in Pubmed: 15793561.
8. Mathur A, Mo JR, Kraus M, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Cancer Cell. 2005; 7(4): 387–397, doi: 10.1016/j.ccr.2005.03.023, indexed in Pubmed: 15837627.
9. Scott LM, Tong W, Levine RL, et al. JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. N Engl J Med. 2007; 356(5): 459–468, doi: 10.1056/NEJMoa065202, indexed in Pubmed: 17267906.
10. Tharakan S, Mascarenhas J, Tremblay D. Understanding triple negative myeloproliferative neoplasms: pathogenesis, clinical features, and management. Leuk Lymphoma. 2024; 65(2): 158–167, doi: 10.1080/10428194.2023.2277674, indexed in Pubmed: 38033130.
11. Sobieralski P, Wasąg B, Leszczyńska A, et al. The molecular profile in patients with polycythemia vera and essential thrombocythemia is dynamic and correlates with disease's phenotype. Front Oncol. 2023; 13: 1224590, doi: 10.3389/fonc.2023.1224590, indexed in Pubmed: 37671053.
12. Szuber N, Vallapureddy RR, Penna D, et al. Myeloproliferative neoplasms in the young: Mayo Clinic experience with 361 patients age 40 years or younger. Am J Hematol. 2018; 93(12): 1474–1484, doi: 10.1002/ajh.25270, indexed in Pubmed: 30157297.
13. Ronner L, Podoltsev N, Gotlib J, et al. Persistent leukocytosis in polycythemia vera is associated with disease evolution but not thrombosis. Blood. 2020; 135(19): 1696–1703, doi: 10.1182/blood.2019003347, indexed in Pubmed: 32107559.
14. Cerquozzi S, Tefferi A. Blast transformation and fibrotic progression in polycythemia vera and essential thrombocythemia: a literature review of incidence and risk factors. Blood Cancer J. 2015; 5(11): e366, doi: 10.1038/bcj.2015.95, indexed in Pubmed: 26565403.
15. Passamonti F, Rumi E, Pietra D, 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(9): 1574–1579, doi: 10.1038/leu.2010.148, indexed in Pubmed: 20631743.
16. Barraco D, Cerquozzi S, Hanson CA, et al. Prognostic impact of bone marrow fibrosis in polycythemia vera: validation of the IWG-MRT study and additional observations. Blood Cancer J. 2017; 7(3): e538, doi: 10.1038/bcj.2017.17, indexed in Pubmed: 28282034.
17. Barbui T, Thiele J, Passamonti F, et al. Initial bone marrow reticulin fibrosis in polycythemia vera exerts an impact on clinical outcome. Blood. 2012; 119(10): 2239–2241, doi: 10.1182/blood-2011-11-393819, indexed in Pubmed: 22246040.
18. Tefferi A, Vannucchi AM. Genetic Risk Assessment in Myeloproliferative Neoplasms. Mayo Clin Proc. 2017; 92(8): 1283–1290, doi: 10.1016/j.mayocp.2017.06.002, indexed in Pubmed: 28778261.
19. Tefferi A, Guglielmelli P, Lasho TL, et al. Mutation-enhanced international prognostic systems for essential thrombocythaemia and polycythaemia vera. Br J Haematol. 2020; 189(2): 291–302, doi: 10.1111/bjh.16380, indexed in Pubmed: 31945802.
20. Tefferi A, Lasho TL, Guglielmelli P, et al. Targeted deep sequencing in polycythemia vera and essential thrombocythemia. Blood Adv. 2016; 1(1): 21–30, doi: 10.1182/bloodadvances.2016000216, indexed in Pubmed: 29296692.
21. Barraco D, Cerquozzi S, Hanson CA, et al. Cytogenetic findings in WHO-defined polycythaemia vera and their prognostic relevance. Br J Haematol. 2018; 182(3): 437–440, doi: 10.1111/bjh.14798, indexed in Pubmed: 28695995.
22. Tang G, Hidalgo Lopez JE, Wang SaA, et al. Characteristics and clinical significance of cytogenetic abnormalities in polycythemia vera. Haematologica. 2017; 102(9): 1511–1518, doi: 10.3324/haematol.2017.165795, indexed in Pubmed: 28473622.
23. Tefferi A, Barbui T. Polycythemia vera: 2024 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023; 98(9): 1465–1487, doi: 10.1002/ajh.27002, indexed in Pubmed: 37357958.
24. Barbui T, Carobbio A, Rumi E, et al. In contemporary patients with polycythemia vera, rates of thrombosis and risk factors delineate a new clinical epidemiology. Blood. 2014; 124(19): 3021–3023, doi: 10.1182/blood-2014-07-591610, indexed in Pubmed: 25377561.

25. Marchioli R, Finazzi G, Specchia G, et al. The CYTO-PV: A Large-Scale Trial Testing the Intensity of CYTOreductive Therapy to Prevent Cardiovascular Events in Patients with Polycythemia Vera. Thrombosis. 2011; 2011: 794240, doi: 10.1155/2011/794240, indexed in Pubmed: 22084668.
26. Cerquozzi S, Barraco D, Lasho T, et al. Risk factors for arterial versus venous thrombosis in polycythemia vera: a single center experience in 587 patients. Blood Cancer J. 2017; 7(12): 662, doi: 10.1038/s41408-017-0035-6, indexed in Pubmed: 29282357.
27. Carobbio A, Ferrari A, Masciulli A, et al. Leukocytosis and thrombosis in essential thrombocythemia and polycythemia vera: a systematic review and meta-analysis. Blood Adv. 2019; 3(11): 1729–1737, doi: 10.1182/bloodadvances.2019000211, indexed in Pubmed: 31175128.
28. Barbui T, Vannucchi AM, Carobbio A, et al. The effect of arterial hypertension on thrombosis in low-risk polycythemia vera. Am J Hematol. 2017; 92(1): E5–E6, doi: 10.1002/ajh.24583, indexed in Pubmed: 27737508.
29. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2017 update on diagnosis, risk-stratification, and management. Am J Hematol. 2017; 92(1): 94–108, doi: 10.1002/ajh.24607, indexed in Pubmed: 27991718.
30. Landolfi R, Marchioli R, Kutti J, et al. 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(2): 114–124, doi: 10.1056/NEJMoa035572, indexed in Pubmed: 14711910.
31. Marchetti M, Vannucchi AM, Griesshammer M, et al. Appropriate management of polycythaemia vera with cytoreductive drug therapy: European LeukemiaNet 2021 recommendations. Lancet Haematol. 2022; 9(4): e301–e311, doi: 10.1016/S2352-3026(22)00046-1, indexed in Pubmed: 35358444.
32. Lyon AR, Dent S, Stanway S, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. Eur J Heart Fail. 2020; 22(11): 1945–1960, doi: 10.1002/ejhf.1920, indexed in Pubmed: 32463967.
33. European Assotiation of Preventive Cardiology E. Heart Score; Calculate the 10-year risk of fatal and non-fatal cardiovascular disease events of your patients 2021 [cited 2024 Aug 15]. Available from:. https://www.heartscore.org/en_GB.
34. De Stefano V, Za T, Rossi E, et al. GIMEMA Chronic Myeloproliferative Neoplasms Working Party. Leukocytosis is a risk factor for recurrent arterial thrombosis in young patients with polycythemia vera and essential thrombocythemia. Am J Hematol. 2010; 85(2): 97–100, doi: 10.1002/ajh.21593, indexed in Pubmed: 20052743.
35. Barbui T, Masciulli A, Marfisi MR, et al. White blood cell counts and thrombosis in polycythemia vera: a subanalysis of the CYTO-PV study. Blood. 2015; 126(4): 560–561, doi: 10.1182/blood-2015-04-638593, indexed in Pubmed: 26206947.
36. Barbui T, Carobbio A, Ghirardi A, et al. No correlation of intensity of phlebotomy regimen with risk of thrombosis in polycythemia vera: evidence from European Collaboration on Low-Dose Aspirin in Polycythemia Vera and Cytoreductive Therapy in Polycythemia Vera clinical trials. Haematologica. 2017; 102(6): e219–e221, doi: 10.3324/haematol.2017.165126, indexed in Pubmed: 28255021.
37. Alvarez-Larrán A, Pérez-Encinas M, Ferrer-Marín F, et al. Grupo Español de Neoplasias Mieloproliferativas Filadelfia Negativas. Risk of thrombosis according to need of phlebotomies in patients with polycythemia vera treated with hydroxyurea. Haematologica. 2017; 102(1): 103–109, doi: 10.3324/haematol.2016.152769, indexed in Pubmed: 27686377.
38. Barosi G, Mesa R, Finazzi G, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood. 2013; 121(23): 4778–4781, doi: 10.1182/blood-2013-01-478891, indexed in Pubmed: 23591792.
39. Kim SY, Bae SH, Bang SM, et al. The 2020 revision of the guidelines for the management of myeloproliferative neoplasms. Korean J Intern Med. 2021; 36(1): 45–62, doi: 10.3904/kjim.2020.319, indexed in Pubmed: 33147902.
40. Barbui T, Barosi G, Birgegard G, et al. European LeukemiaNet. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol. 2011; 29(6): 761–770, doi: 10.1200/JCO.2010.31.8436, indexed in Pubmed: 21205761.
41. Tefferi A, Spivak JL. Polycythemia vera: scientific advances and current practice. Semin Hematol. 2005; 42(4): 206–220, doi: 10.1053/j.seminhematol.2005.08.003, indexed in Pubmed: 16210034.
42. Landolfi R, Di Gennaro L. Prevention of thrombosis in polycythemia vera and essential thrombocythemia. Haematologica. 2008; 93(3): 331–335, doi: 10.3324/haematol.12604, indexed in Pubmed: 18310537.
43. Harrison CN, Nangalia J, Boucher R, et al. Ruxolitinib Versus Best Available Therapy for Polycythemia Vera Intolerant or Resistant to Hydroxycarbamide in a Randomized Trial. J Clin Oncol. 2023; 41(19): 3534–3544, doi: 10.1200/JCO.22.01935, indexed in Pubmed: 37126762.
44. Gisslinger H, Klade C, Georgiev P, et al. PROUD-PV Study Group. Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. Lancet Haematol. 2020; 7(3): e196–e208, doi: 10.1016/S2352-3026(19)30236-4, indexed in Pubmed: 32014125.
45. Jimenez K, Leitner F, Leitner A, et al. Iron deficiency-induced thrombocytosis increases thrombotic tendency in rats. Haematologica. 2021; 106(3): 782–794, doi: 10.3324/haematol.2019.245092, indexed in Pubmed: 32079699.
46. Barbui T, Vannucchi AM, De Stefano V, et al. Ropeginterferon alfa-2b versus phlebotomy in low-risk patients with polycythaemia vera (Low-PV study): a multicentre, randomised phase 2 trial. Lancet Haematol. 2021; 8(3): e175–e184, doi: 10.1016/S2352-3026(20)30373-2, indexed in Pubmed: 33476571.
47. Fruchtman SM, Mack K, Kaplan ME, et al. From efficacy to safety: a Polycythemia Vera Study group report on hydroxyurea in patients with polycythemia vera. Semin Hematol. 1997 Jan. ; 34(1): 17–23.
48. Andréasson B, Swolin B, Kutti J. Increase of CD34 positive cells in polycythaemia vera. Eur J Haematol. 1997; 59(3): 171–176, doi: 10.1111/j.1600-0609.1997.tb00971.x, indexed in Pubmed: 9310125.
49. Jimenez K, Khare V, Evstatiev R, et al. Increased expression of HIF2α during iron deficiency-associated megakaryocytic differentiation. J Thromb Haemost. 2015; 13(6): 1113–1127, doi: 10.1111/jth.12884, indexed in Pubmed: 25715026.
50. Crodel CC, Jentsch-Ullrich K, Reiser M, et al. Cytoreductive treatment in real life: a chart review analysis on 1440 patients with polycythemia vera. J Cancer Res Clin Oncol. 2022; 148(10): 2693–2705, doi: 10.1007/s00432-021-03855-5, indexed in Pubmed: 34807311.

51. Scherber RM, Geyer HL, Dueck AC, et al. The potential role of hematocrit control on symptom burden among polycythemia vera patients: Insights from the CYTO-PV and MPN-SAF patient cohorts. Leuk Lymphoma. 2017; 58(6): 1481–1487, doi: 10.1080/10428194.2016.1246733, indexed in Pubmed: 27830999.
52. Tobiasson M, Alyass B, Söderlund S, et al. High prevalence of restless legs syndrome among patients with polycytemia vera treated with venesectio. Med Oncol. 2010; 27(1): 105–107, doi: 10.1007/s12032-009-9180-5, indexed in Pubmed: 19225914.
53. Kucine N. Myeloproliferative Neoplasms in Children, Adolescents, and Young Adults. Curr Hematol Malig Rep. 2020; 15(2): 141–148, doi: 10.1007/s11899-020-00571-8, indexed in Pubmed: 32172359.
54. Gangat N, Tefferi A. Myeloproliferative neoplasms and pregnancy: Overview and practice recommendations. Am J Hematol. 2021; 96(3): 354–366, doi: 10.1002/ajh.26067, indexed in Pubmed: 33296529.
55. Lebowa W, Ignatowicz A, Ząber J, et al. Current status of hydroxyurea in treatment of polycythemia vera. Acta Haematologica Polonica. 2024; 55(3): 145–150, doi: 10.5603/ahp.99436.
56. Barbui T, Vannucchi AM, Finazzi G, et al. A reappraisal of the benefit-risk profile of hydroxyurea in polycythemia vera: A propensity-matched study. Am J Hematol. 2017; 92(11): 1131–1136, doi: 10.1002/ajh.24851, indexed in Pubmed: 28699191.
57. Demuynck T, Verhoef G, Delforge M, et al. Polycythemia vera and hydroxyurea resistance/intolerance: a monocentric retrospective analysis. Ann Hematol. 2019; 98(6): 1421–1426, doi: 10.1007/s00277-019-03654-6, indexed in Pubmed: 30919072.
58. Parasuraman S, DiBonaventura M, Reith K, et al. Patterns of hydroxyurea use and clinical outcomes among patients with polycythemia vera in real-world clinical practice: a chart review. Exp Hematol Oncol. 2015; 5: 3, doi: 10.1186/s40164-016-0031-8, indexed in Pubmed: 26839736.
59. Barosi G, Birgegard G, Finazzi G, 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(6): 961–963, doi: 10.1111/j.1365-2141.2009.08019.x, indexed in Pubmed: 19930182.
60. Chiaranairungrot K, Kaewpreechawat K, Sajai C, et al. Prevalence and clinical outcomes of polycythemia vera and essential thrombocythemia with hydroxyurea resistance or intolerance. Hematology. 2022; 27(1): 813–819, doi: 10.1080/16078454.2022.2105582, indexed in Pubmed: 35894859.
61. Alvarez-Larrán A, Kerguelen A, Hernández-Boluda JC, et al. Grupo Español de Enfermedades Mieloproliferativas Filadelfia Negativas (GEMFIN). Frequency and prognostic value of resistance/intolerance to hydroxycarbamide in 890 patients with polycythaemia vera. Br J Haematol. 2016; 172(5): 786–793, doi: 10.1111/bjh.13886, indexed in Pubmed: 26898196.
62. Dingli D, Tefferi A. Hydroxyurea: The drug of choice for polycythemia vera and essential thrombocythemia. Curr Hematol Malig Rep. 2006; 1(2): 69–74, doi: 10.1007/s11899-006-0025-4, indexed in Pubmed: 20425334.
63. Abu-Zeinah G, Krichevsky S, Cruz T, et al. Interferon-alpha for treating polycythemia vera yields improved myelofibrosis-free and overall survival. Leukemia. 2021; 35(9): 2592–2601, doi: 10.1038/s41375-021-01183-8, indexed in Pubmed: 33654206.
64. Wang R, Shallis RM, Stempel JM, et al. Second malignancies among older patients with classical myeloproliferative neoplasms treated with hydroxyurea. Blood Adv. 2023; 7(5): 734–743, doi: 10.1182/bloodadvances.2022008259, indexed in Pubmed: 35917456.
65. Hansen IO, Sørensen AL, Hasselbalch HC. Second malignancies in hydroxyurea and interferon-treated Philadelphia-negative myeloproliferative neoplasms. Eur J Haematol. 2017; 98(1): 75–84, doi: 10.1111/ejh.12787, indexed in Pubmed: 27471124.
66. Kiladjian JJ, Mesa RA, Hoffman R. The renaissance of interferon therapy for the treatment of myeloid malignancies. Blood. 2011; 117(18): 4706–4715, doi: 10.1182/blood-2010-08-258772, indexed in Pubmed: 21389325.
67. Mascarenhas J, Kosiorek HE, Prchal JT, et al. A randomized phase 3 trial of interferon-α vs hydroxyurea in polycythemia vera and essential thrombocythemia. Blood. 2022; 139(19): 2931–2941, doi: 10.1182/blood.2021012743, indexed in Pubmed: 35007321.
68. Vachhani P, Mascarenhas J, Bose P, et al. Myeloproliferative Neoplasms Research Consortium (MPN-RC) 111 and 112 trial teams. A prospective evaluation of pegylated interferon alfa-2a therapy in patients with polycythemia vera and essential thrombocythemia with a prior splanchnic vein thrombosis. Leukemia. 2019; 33(12): 2974–2978, doi: 10.1038/s41375-019-0524-7, indexed in Pubmed: 31363161.
69. Gisslinger H, Zagrijtschuk O, Buxhofer-Ausch V, et al. Ropeginterferon alfa-2b, a novel IFNα-2b, induces high response rates with low toxicity in patients with polycythemia vera. Blood. 2015; 126(15): 1762–1769, doi: 10.1182/blood-2015-04-637280, indexed in Pubmed: 26261238.
70. Barbui T, Vannucchi AM, De Stefano V, et al. Ropeginterferon versus Standard Therapy for Low-Risk Patients with Polycythemia Vera. NEJM Evid. 2023; 2(6): EVIDoa2200335, doi: 10.1056/EVIDoa2200335, indexed in Pubmed: 38320126.
71. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med. 2015; 372(5): 426–435, doi: 10.1056/NEJMoa1409002, indexed in Pubmed: 25629741.
72. Passamonti F, Griesshammer M, Palandri F, 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(1): 88–99, doi: 10.1016/S1470-2045(16)30558-7, indexed in Pubmed: 27916398.
73. Mesa R, Vannucchi AM, Yacoub A, 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(1): 76–85, doi: 10.1111/bjh.14382, indexed in Pubmed: 27858987.
74. Cardiovascular risk collaboration of ESC swg. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021 Jul 1. ; 42(25): 2439–2454.
75. Heidel FH, Al-Ali HK, Hirt C, et al. Working Party Myeloproliferative Neoplasms of the East German Study Group Hematology/Oncology (OSHO). Questions arising on phlebotomy in polycythemia vera: prophylactic measures to reduce thromboembolic events require patient-focused decisions. Leukemia. 2018; 32(9): 2085–2087, doi: 10.1038/s41375-018-0214-x, indexed in Pubmed: 30042412.
76. European Medicine Agency E. Besremi prescribing information 2021 [cited 2024 Aug 22]. Available from: . https://www.ema.europa.eu/en/documents/product-information/besremi-epar-product-information_en.pdf.
77. Barbui T, Passamonti F, Accorsi P, et al. Evidence- and consensus-based recommendations for phlebotomy in polycythemia vera. Leukemia. 2018; 32(9): 2077–2081, doi: 10.1038/s41375-018-0199-5, indexed in Pubmed: 29955128.

78. Alvarez-Larrán A, Cervantes F, Pereira A, et al. Observation versus antiplatelet therapy as primary prophylaxis for thrombosis in low-risk essential thrombocythemia. Blood. 2010; 116(8): 1205–10; quiz 1387, doi: 10.1182/blood-2010-01-263319, indexed in Pubmed: 20508163.
79. Falanga A, Marchetti M, Schieppati F. Prevention and Management of Thrombosis in BCR/ABL-Negative Myeloproliferative Neoplasms. Hamostaseologie. 2021; 41(1): 48–57, doi: 10.1055/a-1334-3259, indexed in Pubmed: 33588455.
80. McMullin MFF, Mead AJ, Ali S, et al. British Society for Haematology Guideline. A guideline for the management of specific situations in polycythaemia vera and secondary erythrocytosis: A British Society for Haematology Guideline. Br J Haematol. 2019; 184(2): 161–175, doi: 10.1111/bjh.15647, indexed in Pubmed: 30426472.
81. Duerden M, O'Flynn N, Qureshi N. Cardiovascular risk assessment and lipid modification: NICE guideline. British Journal of General Practice. 2015; 65(636): 378–380, doi: 10.3399/bjgp15x685933.
82. NICE) NIfHaCE. National Institute for Health and Care Excellence: Clinical Guidelines Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. London: National Institute for Health and Care Excellence. (NICE): 2023.
83. Schieppati F, Falanga A. Evidence-Based Minireview: Are DOACs an alternative to vitamin K antagonists for treatment of venous thromboembolism in patients with MPN? Hematology Am Soc Hematol Educ Program. 2021; 2021(1): 448–452, doi: 10.1182/hematology.2021000318, indexed in Pubmed: 34889434.
84. Weronska A, Papuga-Szela E, Broniatowska E, et al. Nonvitamin K Antagonist Oral Anticoagulant in Patients With Venous Thromboembolism and Polycythemia Vera or Essential Thrombocythemia: A Cohort Study. J Cardiovasc Pharmacol. 2021; 78(5): e743–e748, doi: 10.1097/FJC.0000000000001112, indexed in Pubmed: 34321399.
85. Serrao A, Breccia M, Napolitano M, et al. A multicenter real-life study on anticoagulant treatment with direct oral anticoagulants in patients with Ph-negative myeloproliferative neoplasms. Am J Hematol. 2020; 95(12): E329–E332, doi: 10.1002/ajh.25990, indexed in Pubmed: 32886820.
86. Barbui T, De Stefano V, Carobbio A, et al. Direct oral anticoagulants for myeloproliferative neoplasms: results from an international study on 442 patients. Leukemia. 2021; 35(10): 2989–2993, doi: 10.1038/s41375-021-01279-1, indexed in Pubmed: 34012132.
87. Barbui T, Finazzi G, Falanga A. Myeloproliferative neoplasms and thrombosis. Blood. 2013; 122(13): 2176–2184, doi: 10.1182/blood-2013-03-460154, indexed in Pubmed: 23823316.
88. Tefferi A, Vannucchi AM, Barbui T. Essential thrombocythemia: 2024 update on diagnosis, risk stratification, and management. Am J Hematol. 2024; 99(4): 697–718, doi: 10.1002/ajh.27216, indexed in Pubmed: 38269572.
89. Wille K, Brouka M, Bernhardt J, et al. Outcome of 129 Pregnancies in Polycythemia Vera Patients: A Report of the European LeukemiaNET. Hemasphere. 2023; 7(5): e882, doi: 10.1097/HS9.0000000000000882, indexed in Pubmed: 37153877.
90. Landtblom AR, Andersson TML, Johansson ALV, et al. Pregnancy and childbirth outcomes in women with myeloproliferative neoplasms-a nationwide population-based study of 342 pregnancies in Sweden. Leukemia. 2022; 36(10): 2461–2467, doi: 10.1038/s41375-022-01688-w, indexed in Pubmed: 36071101.
91. Robinson S, Ragheb M, Harrison C. How I treat myeloproliferative neoplasms in pregnancy. Blood. 2024; 143(9): 777–785, doi: 10.1182/blood.2023020729, indexed in Pubmed: 38145575.
92. Yazdani Brojeni P, Matok I, Garcia Bournissen F, et al. A systematic review of the fetal safety of interferon alpha. Reprod Toxicol. 2012; 33(3): 265–268, doi: 10.1016/j.reprotox.2011.11.003, indexed in Pubmed: 22200624.
93. Beauverd Y, Radia D, Cargo C, et al. Pegylated interferon alpha-2a for essential thrombocythemia during pregnancy: outcome and safety. A case series. Haematologica. 2016; 101(5): e182–e184, doi: 10.3324/haematol.2015.139691, indexed in Pubmed: 26819057.
94. Griesshammer M, Sadjadian P, Wille K. Contemporary management of patients with BCR-ABL1-negative myeloproliferative neoplasms during pregnancy. Expert Rev Hematol. 2018; 11(9): 697–706, doi: 10.1080/17474086.2018.1506325, indexed in Pubmed: 30084669.
95. Vannucchi AM, Barbui T, Cervantes F, et al. ESMO Guidelines Committee. Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015; 26 Suppl 5: v85–v99, doi: 10.1093/annonc/mdv203, indexed in Pubmed: 26242182.
96. Mesa RA, Jamieson C, Bhatia R, et al. NCCN Guidelines Insights: Myeloproliferative Neoplasms, Version 2.2018. J Natl Compr Canc Netw. 2017; 15(10): 1193–1207, doi: 10.6004/jnccn.2017.0157, indexed in Pubmed: 28982745.
97. Sobas M, Kiladjian JJ, Beauverd Y, et al. Real-world study of children and young adults with myeloproliferative neoplasms: identifying risks and unmet needs. Blood Adv. 2022; 6(17): 5171–5183, doi: 10.1182/bloodadvances.2022007201, indexed in Pubmed: 35802458.
98. Griesshammer M, Struve S, Harrison CM. Essential thrombocythemia/polycythemia vera and pregnancy: the need for an observational study in Europe. Semin Thromb Hemost. 2006; 32(4 Pt 2): 422–429, doi: 10.1055/s-2006-942763, indexed in Pubmed: 16810618.
99. Harrison C. Pregnancy and its management in the Philadelphia negative myeloproliferative diseases. Br J Haematol. 2005; 129(3): 293–306, doi: 10.1111/j.1365-2141.2005.05400.x, indexed in Pubmed: 15842653.