Polycythaemia Vera (PV)

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases
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Compliance rules:

- Guideline
- Conflict of interests

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1 Summary

Polycythaemia Vera is a clonal myeloproliferative neoplasm characterized by erythrocytosis frequently accompanied by leukocytosis, and/or thrombocytosis (so-called panmyelosis in the bone marrow). In almost all cases (about 98%), a mutation in the JAK2 tyrosine kinase gene is detectable. The natural course of the disease includes different stages. An initial prolonged polycythemic phase with increasing splenomegaly and a later so-called 'spent phase' or phase of postpolycythemic myelofibrosis with reduced proliferation of blood cells are characteristic. The natural course of the disease includes the possible transformation into acute leukemia.

The survival prognosis is favorable. The most frequent complications are arterial and venous thromboses. Risk factors for thrombosis are older age and previous thrombosis. Main goal of therapy is the primary and secondary prevention of thromboembolic complications. The recommended therapy for all patients is the combination of phlebotomy with low-dose acetylsalicylic acid to inhibit platelet aggregation. During the course of the disease, the majority of patients require cytoreductive therapy to control the increased myeloproliferation. Quantification of the JAK2 V617F allele burden allows to assess the response to therapy.

2 Basics

2.1 Definition and basic information

Polycythaemia Vera (PV) is a clonal myeloproliferative neoplasia (MPN) characterized by erythrocytosis and frequently accompanied by leukocytosis and/or thrombocytosis, and an increased risk of thromboembolic (arterial and venous) and hemorrhagic complications. Mutations in the JAK2 gene (JAK2 V617F or JAK2 exon12) are strongly associated with PV [1, 2].

2.2 Epidemiology

PV is a rare disease. According to a recent analysis of SEER data, the overall incidence (95% CI) was 1.57 (1.55-1.60) per 100 000 person-years. The median age at diagnosis was 65 years. PV is slightly more common in men than in women [3]. PV is not inherited, according to current knowledge. However, predisposing genetic constellations for the occurrence of MPN (including PV) are known (detailed reviews in [4, 5]).

- Characteristic compositions of known genes (alleles) present in a subset of the population that increase the risk of sporadic MPN (e.g., a particular genetically defined JAK2 genotype (haplotype) associated with a higher risk of JAK2 V617F mutation occurrence).
- Rare differentially penetrant risk alleles or mutant genes that may promote familial clustering of MPN (approximately 5% of MPNs) (Chapter 3).
• Extremely rare germline mutations, e.g., in the *JAK2* gene, *MPL* gene, *EPO* receptor gene, or *EPO* gene (families with hereditary MPN-like disease) (Table 6).

### 2.3 Pathogenesis

*BCR-ABL*-negative MPNs are acquired clonal diseases of the hematopoietic stem cell. PV, essential thrombocythemia (ET) and primary myelofibrosis (PMF) represent the three classic forms of Philadelphia chromosome- and *BCR::ABL1*-negative entities of MPN. According to the natural course, the diseases persist for life.

The etiology of PV is unclear. In about 98% of patients with the clinical signs of PV, a somatic mutation in the *JAK2* tyrosine kinase gene can be detected (Table 1). In healthy individuals, JAK tyrosine kinases regulate the proliferation of hematopoietic cells representing "transmitters" between cytokine-binding receptors on the cell surface and signaling molecules in the cell (JAK/STAT signaling pathway). The *JAK2* mutation activates the kinase in a ligand-independent manner, followed by uncontrolled (clonal) proliferation of hematopoietic cells [6]. Further evidence indicates that *JAK2* mutation induces functional changes in hematopoietic stem cells and bone marrow niche cells, which promotes clonal cell expansion as well as the development of thrombosis and inflammatory processes, and affects iron metabolism and other metabolic pathways [7]. Based on experimental data, JAK2 and other driver mutations may probably occur already in childhood (possibly even in utero) and the latency to clinical manifestation of MPN can be up to several decades [8]. The amount of mutant alleles has an impact on symptoms, course and prognosis [7].

*JAK2* mutations are not specific for PV. They are also present in approximately 50% of patients with ET or PMF and rarely in other myeloid neoplasms. In approximately 2% of patients with the clinical presentation of PV, none of the conventional mutations in the *JAK2* gene can be detected using standard methods. In some cases, atypical (noncanonical) *JAK2* mutations can be detected using modern sequencing technologies such as next generation sequencing, whole genome sequencing (NGS, WGS), and others [2, 9]. In contrast to ET and PMF, PV does not harbor mutations in the calreticulin (*CALR*) or thrombopoietin receptor (*MPL*) genes.

In addition to the *JAK2* mutation, other somatic gene mutations may be present in PV, ET and PMF. These are so-called 'non-driver' mutations (e.g. in the genes *TET2*, *ASXL1*, *EZH2*, *DNMT3A*, *IDH1/IDH2*, *SRSF2*, *TP53* and others). These mutations are not MPN-specific, as they may also be associated with other hematologic neoplasms. The frequency of these mutations increases with age. A higher number of 'non-driver' mutations correlates with an individually less favorable disease course [10].

**Table 1: JAK2 mutations in polycythemia vera (driver mutations)**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Localization</th>
<th>Mutation</th>
<th>Frequency for PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK2</td>
<td>exon 14</td>
<td>V617F</td>
<td>95%</td>
</tr>
<tr>
<td>JAK2</td>
<td>exon 12</td>
<td>different</td>
<td>approx. 3%</td>
</tr>
<tr>
<td>JAK2</td>
<td>exon 12 to 15</td>
<td>different</td>
<td>individual cases</td>
</tr>
</tbody>
</table>

### 3 Prevention and early detection

No recommendations are available regarding prevention and early detection of MPN, including PV.

More recently, the number of germline mutations discovered in hematologic neoplasms has expanded significantly due to the availability of modern gene sequencing methods. Although the majority of myeloid neoplasms associated with germline predisposition [1, 2] described in
4 Clinical presentation

4.1 Symptoms

In the early stage of the disease, main symptoms are hypertension, due to increased blood viscosity, reddened facial skin, livid skin and mucous membranes, itching, head pressure and headache. The etiology of thromboembolic complications is complex. In addition to hematocrit elevation and the frequently increased leukocyte and platelet count, other thrombogenic and inflammatory mechanisms contribute to the development of thromboses, which may additionally cause activation of the vascular endothelium, coagulation system, and of leukocytes and platelets [12]. Other possible vascular risk factors may increase the risk of thromboembolic complications.

The spectrum of clinical symptoms is diverse and often changes during the course of the disease. Microvascular disturbances often lead to characteristic clinical symptoms (e.g., visual disturbances, paresthesias, erythromelalgia, headache, impaired concentration). In the larger vessels, cardiac and cerebral arterial vascular occlusions and peripheral venous thrombosis predominate. Less common, but not uncommon for PV and other MPNs, are abdominal venous thrombosis and thrombosis in the venous cerebral sinus [13, 14] (Section 5.2.1.3). The risk of thrombosis increases in older age and if thromboembolism has already occurred. Severe bleeding is rare. Bleeding may be promoted by a high platelet count causing acquired von Willebrand syndrome. Clinical symptoms that can considerably impair quality of life include fatigue and pruritus (often severe) in up to 70% of cases, mainly triggered by contact with water, sweating or friction (“aquagenic pruritus”). This may precede the diagnosis of PV by several years [15].

4.2 Disease progression

The natural history of PV includes various stages.

- **Chronic (polycythemic) phase:**
  The chronic phase, usually lasting for years, is characterized by the clinical features of increased myeloproliferation, which often involves all three rows of cells (erythropoiesis, megakaryopoiesis, granulopoiesis) and is accompanied by increasing splenomegaly. The proliferation of erythropoiesis is in the foreground and determines the clinical picture. Most frequent and potentially threatening complications are arterial or venous thromboembolism in up to 40% of patients. In untreated PV, they represent the most frequent cause of death in a historical publication, accounting for more than 60% of deaths [16]. Life-threatening bleeding is rare.

- **Late phase:**
  The main problem of the late phase is the transition into a so-called 'spent' phase (decrease in erythrocytosis, increase in splenomegaly, associated with fibrosis of the bone marrow), which may be followed by transformation into (secondary) post-PV myelofibrosis (MF) and/or acute leukemia. The overall rate of post-PV MF is approximately 15% after a median observation period of 10 years, and 50% after 20 years. Direct transi-
tion to acute leukemia is rare (approximately 4%), while approximately 20% of patients with post-PV MF transform to AML [17].

5 Diagnosis

5.1 Diagnostic criteria

5.1.1 Diagnostic criteria of PV

The diagnosis of PV is based on the 2022 WHO/ICC criteria (Table 2).

Table 2: Diagnostic criteria of PV*

<table>
<thead>
<tr>
<th>Major criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1 Hb &gt;16.5 g/dl men (M)/ &gt;16.0 g/dl women (F) or hematocrit &gt;49% M/ &gt;48% F 1,2</td>
</tr>
<tr>
<td>A2 Increased trilineage myeloproliferation with pleomorphic megakaryopoiesis in bone marrow biopsy.</td>
</tr>
<tr>
<td>A3 Presence of detection of a mutation in the JAK2 gene (JAK2 V617F or exon 12 mutation).3</td>
</tr>
<tr>
<td>Minor criterion</td>
</tr>
<tr>
<td>B1 Subnormal erythropoietin level</td>
</tr>
</tbody>
</table>

The diagnosis of PV requires either all three major criteria or the first two major criteria plus the minor criterion.

Legend:

*1, 2
1 In cases with persistent erythrocytosis (males: hemoglobin >18.5 g/dl or hematocrit >55.5%, females: Hemoglobin >16.5 g/dl or hematocrit >49.5%), bone marrow biopsy may not be required if a JAK2 mutation (major criterion 3) is detected and erythropoietin levels (minor criterion) are decreased.
2 Relatively widely used, an elevated hematocrit >45% is uniformly used in men and women.
3 It is recommended to use highly sensitive assays for JAK2 V617F (‘sensitivity level’ <1%); in negative cases, non-canonical or atypical JAK2 mutations in exons 12 to 15 should be considered [2].

The determination of red cell mass with 51 Cr-labeled red cells allows the differentiation between true polycythaemia and pseudopolyglobulina. This method is not intended for routine clinical use.

5.1.2 Diagnostic criteria for post-PV myelofibrosis

Definition of post-PV-MF is described in the WHO/ICC classification (Table 3) [24]. Specifics of post-PV-MF are discussed in the Onkopedia guideline Primary Myelofibrosis (German Guideline).
Table 3: Diagnostic criteria for post-PV myelofibrosis [1, 2]

<table>
<thead>
<tr>
<th>Required criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1) Documentation of the previous diagnosis of PV according to WHO criteria.</td>
</tr>
<tr>
<td>• 2.) Bone marrow fibrosis Grade 2 to 3 (on a scale of 0 to 3),</td>
</tr>
<tr>
<td>Grade 3 to 4 (on a scale 0 to 4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional criteria (two required)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1.) Anemia¹ or phlebotomy therapy no longer required (without cytoreductive therapy) or cytoreductive therapy no longer required to reduce erythrocytosis.</td>
</tr>
<tr>
<td>• 2.) Leukoerythroblastosis</td>
</tr>
<tr>
<td>• 3) Increasing splenomegaly, (defined either as an increase of palpable splenomegaly &gt;5 cm from baseline (distance from the left costal margin) or the development of a newly palpable splenomegaly).</td>
</tr>
<tr>
<td>• 4.) Development of any 2 or all 3 of the following constitutional symptoms:</td>
</tr>
<tr>
<td>&gt;10% weight loss in 6 months, night sweats, etiologically unexplained fever</td>
</tr>
<tr>
<td>(&gt;37.5 degrees Celsius, measured rectally).</td>
</tr>
</tbody>
</table>

Legend:
1 below the reference values for age, sex, and adjustment to the corresponding altitude above sea level.

5.2 Diagnostics

5.2.1 Initial diagnosis

The first important measure is to distinguish reliably between PV and reactive (secondary) erythrocytosis. In this context, a targeted general internal history (Chapter 5.2.1.1) and blood count follow up over a preceding period (as long as available) are usually indicative. If the clinical and laboratory findings clearly point in the direction of a secondary erythrocytosis, the corresponding underlying disease has to be diagnosed and treated internally. The recommended diagnostic algorithm for erythrocytosis is shown in Figure 1.

Figure 1: Algorithm for the diagnostic procedure

5.2.1.1 General diagnostics

Evaluation of history with regard to PV:
Characteristic symptoms and signs: Head pressure, dizziness, arterial or venous thromboembolism (current or history), microvascular disturbances (esp. visual disturbances, paresthesias, erythromelalgia, migraine-like headaches, impaired concentration), pruritus (predominantly aquagen), bleeding, evidence of risk factors for vascular complications (nicotine use, known hypertension, diabetes mellitus, hypercholesterolemia), evidence of cardiac or pulmonary disease or malignant tumors, consider possibility of uncontrolled testosterone use or doping, also consider erythropoietin (EPO)-secreting renal tumors.

Physical examination:
Spleen and liver size, evidence of microcirculatory disturbances, evidence of cardio-pulmonary disease, skin inspection.

Laboratory (mandatory):
Blood count including differential blood count, ESR or CRP, LDH, ferritin, uric acid, EPO.

Other recommended examinations:
- Quick, PTT, AST, ALT, γGT, alkaline phosphatase, bilirubin
- Arterial blood gas analysis
- Sonography of the abdomen
- If necessary, sonography with vascular imaging by duplex sonography (depending on the problem)
- X-ray examination of the thorax
- ECG, echocardiogram, pulmonary function test, stress ECG if necessary.
- Thrombophilia screening in case of previous thrombosis
- Cholesterol (LDL and HDL), triglycerides, glucose (HbA1c), (to assess non-MPN-related vascular risk factors).

5.2.1.2 Special hematological diagnostics

If PV is suspected (erythrocytosis, concomitant leukocytosis and/or thrombocytosis and/or splenomegaly, left shift and/or single erythroblasts in the blood smear) or even another MPN, special hematological diagnostics are required.

- Molecular genetics:
  Determination of JAK2 V617F mutation (from peripheral blood). If negative, screening for JAK2 exon 12 mutations.
  Using modern essays with a sensitivity level of below 1%, it is possible to quantify the JAK2 V617F allele burden to assess the possible progression (Section 5.4) [18].
  Screen for other driver mutations (CALR and MPL mutations) only if there is no mutation in the JAK2 gene. BCR::ABL1 fusion gene only if all of the above markers are negative or if CML is suspected as a secondary disease; if necessary, tryptase determination and screening for KIT mutations (see German Onkopedia guidelines Eosinophilia and Mastocytosis).
  'Non-driver' mutations (e.g., TET2, ASXL1, EZH2, DNMT3A, IDH1/IDH2, SRSF2, TP53,
and others) and evidence of abnormal cytogenetics are paid increasing attention in individual decision-making because of their potential prognostic significance, especially in progressive disease or transformation. However, they are presently not part of the routine diagnostic program.

Screening for atypical JAK2 and 'non-driver' mutations by NGS or WGS may be helpful in diagnostically unclear cases.

- **Cytogenetics**: conventional cytogenetics (bone marrow or peripheral blood) is not mandatory for diagnosis. In case of transformation to myelofibrosis or acute leukemia, it is part of the diagnosis.

- **Bone marrow**: aspiration cytology and bone marrow histology with iron and fiber staining (if possible, coassessment in a reference center) (Table 2). Examples of microscopic diagnostics are available at eLearning Curriculum Hematology (eLCH), https://ehaematology.com/.

- **In case of unexplained erythrocytosis after performing the preceding diagnostics**: if necessary, investigations to detect or exclude rare congenital and rare reactive causes of erythrocytosis (Table 6).

- **In case of venous thrombosis in unusual locations** (chapter 5.2.1.3): Molecular screening for mutations in the JAK2 gene (if necessary also for atypical mutations); if negative, screening for other driver mutations and (diagnostic diagnosis) also PNH screening (paroxysmal nocturnal hemoglobinuria) and thrombophilia screening recommended.

- **In case of positive family history**, human genetic counseling (see chapter 2.2 and 3).

### 5.2.1.3 Vascular complications in unusual locations

In cases of venous thrombosis in unusual locations, an underlying MPN (including PV) has always be excluded as an obligatory part of the diagnostic measures, and screening for a JAK2 mutation or one of the other driver mutations should be performed.

Abdominal thrombosis (portal vein, splenic vein, hepatic veins (Budd-Chiari syndrome), mesenteric and renal veins) can be the initial manifestation of MPN even with normal blood values. Especially in cases of hepatic vein or portal vein thrombosis, laboratory findings are often not conclusive because the clinical picture of MPN and laboratory parameters (blood count) may be overlaid secondarily by the sequela of vascular disease (portal hypertension with ascites, liver cirrhosis, hemorrhage, splenomegaly) (Table 4). Therefore, the underlying MPN is often not primarily recognized [13, 14]. In patients with visceral thrombosis without evidence of a clonal marker, exclusion or confirmation of MPN can be difficult [13]. Cerebral vein thrombosis (especially sinus vein thrombosis) represents another vascular complication with a much lower prevalence of an underlying MPN. Again, the detection of a clonal marker may initially be the only evidence of MPN.
Table 4: Reliability of diagnostic markers in PV pat. with Budd-Chiari syndrome or portal vein/splenic vein thrombosis [13].

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of JAK2 V617F mutation or other clonal marker.</td>
<td>not diagnostic in MPN without clonal marker (triple negative)</td>
</tr>
<tr>
<td>Increased erythrocyte cell mass</td>
<td>determination by means of $^{51}$Cr-labeled erythrocytes not generally available, not a routine method</td>
</tr>
<tr>
<td>Panmyelosis of the bone marrow</td>
<td>may be difficult to distinguish from KM changes in splenomegaly (hypersplenia)</td>
</tr>
<tr>
<td>Increased cell counts in peripheral blood</td>
<td>unreliable, as not always available</td>
</tr>
<tr>
<td>Decreased serum EPO level</td>
<td>can be normal in some cases</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>limited diagnostic value (splenomegaly may be due to portal hypertension)</td>
</tr>
</tbody>
</table>

5.3 Classification

The diagnosis of PV is made according to the current WHO/ICC classification 2022 (chapter 5.1.1). The criteria for the diagnosis of post-PV myelofibrosis have also been established in the WHO/ICC classification. (Chapter 5.1.2) [1, 2]. Subdivision into subgroups is not present in PV.

5.4 Prognostic factors

Life expectancy in completely untreated PV is massively limited due to vascular complications (median survival ca.1½ years; historical report) [16]. With good control of the disease, the median survival probability was about 19 years in a retrospective analysis of 1545 PV patients [17].

Prognostic scoring systems:

In recent publications, retrospective analyses have been used to present various prognostic scores for survival, some of which include molecular markers (MIPPS-PV score) [19]. However, with considerable divergence of these survival scores and still ‘preclinical’ inclusion of molecular markers, risk stratification for treatment decisions continues to be based on thrombosis risk. Here, a distinction is defined between a **high and a low risk of thrombosis** (Table 5). Confirmed risk factors for thromboembolism and main stratification parameters are older age (≥60 years, although biological age is also taken into account in clinical practice) and previous arterial or venous thrombosis. According to a more recent risk classification, younger patients without thrombosis are assigned to an intermediate risk group in the presence of cardiovascular risk factors or leukocytosis (not yet validated) [20].

JAK2 allele burden:

Increasingly, the level of JAK2 variant allele frequency (VAF) at diagnosis and during follow-up is also considered a relevant prognostic parameter [7]. Recent results of prospective studies and indirect evidence from retrospective evaluations show a correlation of the degree of allele burden reduction with treatment response and long-term prognosis. Lower allele burden correlated with lower rates of venous thrombosis and of transformation to myelofibrosis or AML [21, 22, 23]. Also, more favorable results in event-free and progression-free survival (EFS, PFS) were shown in part with favorable impact on overall survival [23]. It should be emphasized that JAK2 allele burden is not yet a validated and generally accepted parameter for therapy stratification. However, its determination may be helpful in making decisions in individual cases. Despite complete regression of mutant JAK2 alleles under therapy, other mutations (e.g., TET2) may persist [24].
Table 5: PV risk stratification

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Age &lt; 60 years, no thromboembolism (in the overall course).</td>
</tr>
<tr>
<td>High risk</td>
<td>Age ≥ 60 years and/or thromboembolism (in the overall course).</td>
</tr>
</tbody>
</table>

5.5 Differential diagnosis

Table 6 presents an overview of the main differential diagnoses of PV.

PV has to be distinguished from other MPNs with increased red cell counts and from reactive erythrocytoses. The stringent application of the WHO/ICC criteria 2022 allows assignment to the different entities of MPN. In some borderline cases that cannot be clearly assigned to PV, ET, or the hyperproliferative stage of PMF based on clinical and laboratory findings, a definitive diagnosis can only be made by bone marrow histology or on the basis of the longer clinical course [1, 2].

Cases of PV with pure erythrocytosis (characteristic of mutations in exon 12 of the JAK2 gene) are particularly noteworthy with regard to their need for differentiation from secondary erythrocytoses [25]. Congenital (sporadic or familial) forms of primary erythrocytosis are extremely rare (Chapter 3 and Table 6).

Table 6: Differential diagnosis of PV

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myeloproliferative neoplasms</strong></td>
<td></td>
</tr>
<tr>
<td>Essential thrombocythemia</td>
<td>Increased levels of hemoglobin and hematocrit and/or decreased levels of EPO may be present, especially in JAK2 V617F-positive forms.</td>
</tr>
<tr>
<td>Primary myelofibrosis</td>
<td>In the early hyperproliferative stage, proliferation of all three rows of cells including erythrocytosis may be present; moderate marrow fibrosis is also possible in PV, which may complicate differentiation</td>
</tr>
<tr>
<td><strong>Reactive erythrocytoses</strong></td>
<td></td>
</tr>
<tr>
<td>Erythrocytosis due to decrease in plasma volume</td>
<td>Pseudopolyglobulia with increase in erythrocyte count in stress or severe exsiccosis</td>
</tr>
<tr>
<td>Erythrocytosis caused by severe nicotine abuse</td>
<td>triggered by an increased level of carbon monoxide hemoglobin</td>
</tr>
<tr>
<td>Acquired secondary erythrocytosis</td>
<td>as a result of arterial hypoxia in chronic heart and lung diseases, in sleep apnea syndrome or in tumor diseases with paraneoplastic EPO production and in drug-induced polyglobulia (e.g. testosterone), condition after kidney transplantation, doping</td>
</tr>
<tr>
<td><strong>Rare congenital causes of erythrocytosis [26]</strong></td>
<td></td>
</tr>
<tr>
<td>- Erythropoietin receptor mutations leading to increased EPO sensitivity of erythroid progenitors.</td>
<td></td>
</tr>
<tr>
<td>- VHL mutation with impaired EPO gene regulation (Chuvash polycythemia).</td>
<td></td>
</tr>
<tr>
<td>- Germline mutations in additional genes, e.g. EGLN1 (PHD2)-EPAS1 (HIF2A) mutations and others.</td>
<td></td>
</tr>
<tr>
<td>- Rare cases of germline mutations in the JAK2 gene.</td>
<td></td>
</tr>
<tr>
<td>- Hemoglobinopathy with increased oxygen affinity (e.g., alpha- or beta-globin gene variants) or 2,3-DPG deficiency (e.g., 2,3-DPG mutase deficiency).</td>
<td></td>
</tr>
<tr>
<td>- Disorders of hemoglobin formation with normal O2 affinity of hemoglobin (heterozygous beta-thalassemia, alpha-thalassemia minor, mild iron deficiency anemias; hemoglobin concentration, hematocrit, and mean red cell volume are decreased in this case.</td>
<td></td>
</tr>
</tbody>
</table>
6 Therapy

6.1 Therapy structure

The course of PV usually extends over years. It is characterized by different disease stages, which requires adaptations of therapy to the respective clinical situation (Table 7). In the primary (chronic) phase, the main aim of therapy is to prevent arterial or venous thrombosis. The therapy is stratified according to whether there is a low or high risk of thromboembolic complications (Table 5). Good control of symptoms is usually associated with improvement in quality of life. Prevention of disease progression and avoidance of transformation (post-PV-MF or leukemia/MDS) is particularly desirable in the long-term course. Here, different effects and influences of the therapeutic agents used in the chronic phase are emerging. No cures are achieved (by definition) by the available drug therapy options [20]. However, it should be emphasized that stable long-term remissions under IFN-alpha were described as early as in the 1990s, which has again become the focus of interest in the recent past [27].

Table 7: Main therapeutic targets in PV

| • Reduction of the risk for thromboembolism |
| • Control of clinical symptoms |
| • Prevention or delay of late complications (myelofibrosis and acute leukemia/MDS). |

Initial therapy for all risk groups consists of rapidly lowering the hematocrit to a level below 45% by phlebotomy and initiating therapy with low-dose acetylsalicylic acid (ASA). The usual dose is 100 mg/day [20, 28, 29].

For cytoreductive first-line therapy, hydroxyurea (hydroxycarbamide) or pegylated interferon alpha (Peg-IFN-alpha) are available (Figure 2). A proven benefit in terms of reduction of thromboembolic complications by cytoreductive therapy is only available for the high-risk group. For the low-risk group, ELN recommendations have recently been issued under which circumstances cytoreductive therapy is recommended (chapter 6.1.1.1) [20, 30].

The tyrosine kinase inhibitor (TKI) ruxolitinib is approved for second-line or multi-line therapy. Alternatives depending on the choice of first-line therapy are hydroxyurea or peg-IFN-alpha [20, 30].

A treatment algorithm is shown in Figure 2.
Primary therapy for low-risk PV

Primarily, therapy consists of phlebotomy and ASA. The goal is to keep the hematocrit value stable below 45%. In low-risk PV, phlebotomy/ASA is usual without addition of cytoreductive therapy, since a benefit of cytoreductive therapy at low thromboembolism rates is not expected [20].

A recently published ELN consensus gives recommendations under which circumstances cytoreductive therapy (preferably with IFN-alpha) are considered to be indicated in low-risk PV, even if the criteria of high-risk constellation are not formally fulfilled (Chapters 6.1.1.1 and 6.1.1.2) [30]. This consensus opinion is widely shared but also controversial.

Parameters for initiation of cytoreductive therapy in low-risk PV

Cytoreductive therapy is recommended in [30]:

- Poor tolerance or limited feasibility of phlebotomy,
- Increase in spleen size (greater than 5 cm over the past year) or symptomatic splenomegaly,
- Persistent leukocytosis (>20 000/µl) confirmed after 3 months.

Cytoreductive therapy should be considered in [30]:

Legend:
ASA: acetylsalicylic acid, IFN: interferon.
1 Phlebotomy for hematocrit adjustment below 45%.
2 IFN alpha (approved for PV without symptomatic splenomegaly: ropeginterferon alfa-2b),
3 Approval of ruxolitinib in patients who are intolerant of or resistant to hydroxyurea,
4 Detailed recommendations for initiation of cytoreductive therapy in Section 6.1.1.1.
• Increase in leukocyte count (at least 100% increase in leukocyte count at baseline <10 000/µl and at least 50% increase at baseline >10 000/µl); persistent leukocytosis >15 000/µl confirmed after 3 months),
• Platelet count >1 500 000/µl; PV-related bleeding independent of platelet count,
• inadequate hematocrit control under phlebotomies in the maintenance phase to keep the hematocrit below 45% (6 or more phlebotomies per year for at least 2 years),
• severe or distressing disease-related symptoms,
• relevant cardiovascular risks.

6.1.1.2 Therapy choice in low-risk PV

• For untreated patients with indication for cytoreductive therapy, Peg-IFN-alpha and hydroxyurea are available. Peg-IFN-alpha should be preferred if patients qualify for this therapy. This is especially true for patients under 60 years of age (Chapter 2) [30].

6.1.2 Primary therapy for high-risk PV

Previous thromboembolism and older age (over 60 years, taking into account biological age) are established risk factors for the occurrence of vascular complications. These parameters (high-risk PV) represent an established indication for the initiation of cytoreductive therapy at diagnosis in addition to phlebotomy/ASA therapy [20]. Therapeutic agents available include hydroxyurea or IFN-alpha (Chapter 2). Current data (Chapter 6.2.4.2) suggest that IFN should preferably be used at least in younger patients (under 60 years of age), but also in older patients if they qualify. The additional phlebotomies that may be necessary in the course of treatment to keep the hematocrit below 45% will depend on the individual blood values.

6.1.3 Second-line or multi-line therapy

Possible second-line therapies include the tyrosine kinase inhibitor (TKI) ruxolitinib and, depending on the first-line therapy, hydroxyurea or Peg-IFN-alpha. Ruxolitinib is approved for second-line therapy. The agent was highly effective in controlling myeloproliferation (blood counts and splenomegaly) and clinical symptoms. Anagrelide or busulfan are available as alternative therapies for special situations (Chapter 6.2.4.4).

In case of insufficient efficacy (resistance) to the primary therapy or intolerance, an alternative therapy should be administered (Figure 2). If hydroxyurea was given as first line therapy, a change in therapy is recommended if there is an inadequate response under a minimum dose of 1.5 g/day for at least 4 months (based on a consensus) [30], rather than at least 2.0 g/day for three months as in the past [31].

Switching cytoreductive therapy when efficacy is inadequate should be considered in: [30]

• Increase in leukocyte count (at least 100% increase in leukocyte count at baseline <10 000/µl and at least 50% increase at baseline >10 000/µl); persistent leukocytosis (>15 000/µl, confirmed after 3 months),
• Platelet count >1 000 000/µl, microvascular disturbances for a period longer than 3 months,
• Inadequate hematocrit control under phlebotomies in the maintenance phase to keep the hematocrit below 45% (6 or more phlebotomies per year),
- Symptomatic or progressive splenomegaly with increase in spleen size by 5 cm in one year,
- Severe or distressing disease-related symptoms (e.g. persistent pruritus, etc.),
- Occurrence of thrombosis or bleeding.

6.2 Treatment modalities

6.2.1 General measures

Weight normalization, regular exercise, avoidance of desiccation and prolonged sitting especially during travel (compression stockings if necessary, low-dose heparin prophylaxis if necessary), reduction of vascular risk factors and effective treatment and prevention of cardiovascular disease, abstention from nicotine.

6.2.2 Phlebotomy

Phlebotomy is the fastest and easiest measure to lower hematocrit and eliminate hyperviscosity. In newly diagnosed PV, isovolemic phlebotomies of 500 ml (possibly of 300 ml at the beginning) are recommended once or twice a week, depending on individual tolerance, until the hematocrit is adjusted below 45% (regardless of gender). As proven by a randomized study (CYTO-PV study), a significant reduction of the thromboembolism rate could be achieved by a stringent adjustment of the hematocrit value below 45% and a control of the leukocyte count. This was also associated with a reduction in cardiovascular mortality and mortality caused by other major thromboembolic events [29]. The frequency of phlebotomy required during the course has to be adjusted to the individual hematocrit values. Occasional phlebotomies may be required in addition to cyto-reductive therapy to maintain hematocrit within the desired range if a change in cyto-reductive therapy does not appear possible or warranted. Erythrocytapheresis represents as an alternative to phlebotomy. However, this procedure is only possible at special centers equipped for this purpose.

The iron deficiency that occurs during phlebotomy therapy is a "desirable" side effect and shall not be substituted. Only in exceptional cases with symptomatic iron deficiency, oral iron can be given cautiously under close laboratory controls. Increasing iron deficiency is often the cause of a secondary platelet increase.

Recent studies suggest that freedom from phlebotomy is possible with the application of a new drug therapy interfering with iron metabolism. Rusfertide (PTG-300) is a subcutaneously injectable mimic of hepcidin, which is a key regulator controlling the absorption, distribution and storage of iron in the body. Rusfertide and other hepcidin mimetics under clinical investigation redistribute iron in the body and reduce the availability of iron for red cell formation in the bone marrow. Based on Phase II studies, the compound was able to eliminate phlebotomy in PV combined with improvement in PV-associated symptoms. Rusfertide is currently being evaluated in a randomized phase III trial compared to placebo and is not yet approved (NCT05210790) [32].

6.2.3 Antiplatelet agents

Low-dose acetylsalicylic acid (low dose aspirin, ASA) at a dosage of 100 mg/day, is indicated for primary prophylaxis of thrombosis in patients without contraindications to the drug (history of ulcers, previous bleeding complications, and others), regardless of whether concomitant
cytoreductive therapy is used. Peripheral and cerebral microvascular disturbances are a symptom-related indication for ASA [28].

With a platelet count above 1 million/µl, ASA should be administered only after lowering of the platelet count (desirably below 600 000/µl) due to the increased risk of bleeding, as the frequently observed loss of high molecular weight von Willebrand factor multimers (associated with high platelet counts) may lead to an increased bleeding tendency. ASA is not indicated below a value of 30% of vWF activity.

There is positive experience with the use of other antiplatelet agents (e.g., ADP antagonists such as clopidrogel), but there a no confirmed data.

### 6.2.4 Cytoreductive therapy

#### 6.2.4.1 Hydroxyurea

**Hydroxyurea** is administered orally at a starting dose of 15-20 mg/kg body weight/day. Individual adjustment to blood values is required. As a leukemogenic potential of hydroxyurea is not excluded, the drug should be used with caution in young patients. Special attention is necessary to the possible occurrence of skin toxicity, especially skin tumors [20].

Within the framework of the ELN consensus recommendations, new criteria were set for therapy changes. In this context, the recommendations for the evaluation of resistance and intolerance to hydroxyurea were also updated basing on the basis of the previous version [30, 31].

Regarding **resistance** to hydroxyurea, criteria for therapy change in case of insufficient efficacy of drugs are shown in chapter 6.1.3. A withdrawal of hydroxyurea should be considered if there is insufficient efficacy on ≥1.5 g/day hydroxurea for at least 4 months [30] (see also chapter 6.1.3).

**Intolerance should be assumed regardless of dosage, at [30]:**

- Non-hematologic toxicity grade 3 to 4,
- Hematologic toxicity at the lowest dose of hydroxyurea (Hb <10 mg/dl, platelet count <100 000/µl, neutrophil count <1 000/µl),
- Incidence of non-melanotic skin cancer,
- Occurrence of thrombosis or bleeding.

#### 6.2.4.2 Interferon alpha

Pegylated IFN-alpha (ropeginterferon alfa-2b) is approved for the primary therapy of PV without age limit. IFN-alpha is not teratogenic. Pegylated interferon-alpha is significantly better tolerable in terms of the side effect and efficacy spectrum than conventional interferon-alpha, which is practically no longer used. The conventional form of pegylated IFN (off label) is administered once a week (IFN alfa-2a, average dosage 90 µg per week): The dosage as well as the application intervals have to be adjusted individually during the course. Pegylated IFN-alpha is administered subcutaneously.

A new pegylated form (ropeginterferon alfa-2b (Ro-Peg-IFN), approved for PV patients without symptomatic splenomegaly) with longer persistence of action allows application at 14-day intervals. Further dilating of intervals is possible if response is good. The results of the randomized pivotal trial in untreated or hydroxyurea-pretreated high-risk patients (‘follow up’ over 6 years) showed significant advantages in favor of Ro-Peg-IFN over hydroxyurea or best available
therapy (rate of complete hematologic remission, reduction of allele burden, achievement of MRD (measurable residual disease)-negative and prolongation of EFS) [33, 34, 35].

In a randomized phase II trial in low-risk PV (Low-PV Study) (n=127), Ro-Peg-IFN (100 μg every 14 days) was compared with standard therapy phlebotomy plus low-dose ASA. Results of the interim analysis at 12 months showed that hematocrit was more stably maintained below 45% with IFN (significant benefit of IFN therapy (p=0.0075) with respect to the combined endpoint for treatment response: "stable maintenance of hematocrit below 45% and no disease progression"), [36]. Subsequent analysis at 24 months (based on the selection of pat. who had responded to therapy in both arms at the 12-month analysis) showed a benefit in terms of treatment response to Ro-Peg-IFN in 82.7% vs. 59.4% of pat. in the phlebotomy arm (p=0.02), respectively. Overall, of the 64 pat. randomized to the IFN arm, 46 pat. were still on Ro-Peg-IFN (71.8%) after 24 months. Despite the occurrence of adverse events (55% with IFN-alpha vs 6% with standard therapy; grade 3-4 adverse events in 9% vs 8%), the regression of PV-related symptoms resulted in overall positive effects of Ro-Peg-IFN on quality of life [37].

In another retrospective non-randomized study, the results of IFN long-term therapy in 93 patients with PV (median ‘follow up' 10 years, ‘range' 0 to 45) were evaluated. The data showed a clear advantage of IFN in comparison with conventional therapy (phlebotomy, hydroxyurea) regarding the reduction of myelofibrosis rate (significant in the ‘low risk' group: p=0.0011) and long-term survival (significant in the ‘high risk' group: p=0.016). A longer treatment duration with IFN proved to be beneficial with respect to both outcomes [38].

Further observations (published only in abstract form to date) revealed that interruption of IFN therapy was possible in MPN and that a greater reduction in JAK2 allele burden before discontinuation of IFN therapy had a beneficial effect on remission duration [39].

**In summary,** IFN-alpha is considered to have the potential to sustainably and positively influence the natural course of PV and to completely prevent progression and late sequelae of PV. For younger patients, but also in older age (if suitable), the substance is considered as the treatment of choice [20, 30]. However, it should be emphasized that this therapy is associated with a considerable potential of side effects reducing the tolerability over the long-term. It would therefore be desirable to have parameters that would allow early assessment of the influence of IFN therapy on the individual long-term course.

### 6.2.4.3 Ruxolitinib

Ruxolitinib (JAK1/JAK2 inhibitor) is approved for PV therapy in cases of intolerance or resistance to hydroxyurea (second-line or later lines). The initial dose, to be adjusted over time, is 2x10 mg/day. Ruxolitinib results in control of increased myeloproliferation, particularly hematocrit and splenomegaly with overall good tolerability. Other beneficial effects include regression of fatigue and pruritus and other PV-associated symptoms with significant improvement in quality of life. The effect occurs in the majority of patients within the first 4 weeks. Five-year follow-up of the two RESPONSE trials showed persistent hematocrit control in 22% of patients (RESPONSE 2) and a 55% probability of maintaining complete hematologic response (RESPONSE) [40, 41].

In a randomized Phase II study in patients with resistance/intolerance to hydroxyurea (MAJIC study), ruxolitinib was compared to BAT (best available therapy). There was better control of hematologic parameters and symptoms. Of particular note, molecular response was associated with significantly better prognosis (EFS, PFS, OS) [23]. (Details on VAF regression included in [23]).
Attention should be paid to the possible occurrence of skin tumors and infections (especially herpes zoster) under ruxolitinib [40, 41]. Therefore, zoster vaccination is recommended by some authors at the start of ruxolitinib therapy. The combination of ruxolitinib with IFN-alpha is being investigated with regard to efficacy and safety in studies (NCT02742324).

6.2.4.4 Cytoreductive therapies with limited indication in PV.

Because of its leukemogenic potential, busulfan should only be used as an alternative therapy in PV of advanced age when no other therapeutic options are available. Recent literature indicates that the leukemogenic effect of busulfan is considered to be low and that a good decrease in JAK2 V617F allele burden can be achieved with the substance in addition to control of blood levels [42].

The administration of radiophosphorus is associated with an increased risk of leukemia and is therefore not recommended. The use of chlorambucil is considered obsolete due to the significantly increased incidence of acute leukemias.

Anagrelide (1 to 2 mg/day) is exclusively reducing the platelet production. The drug is therefore not suitable as monotherapy for PV. Anagrelide may be combined (off-label) with other drugs (e.g., hydroxyurea or IFN-alpha) in cases of severely elevated platelet counts, if satisfactory platelet count reduction is not possible with monotherapy alone. Anagrelide in combination with ASA may lead to an increased risk of bleeding [43].

6.2.4.5 Splenic irradiation and splenectomy

Splenic irradiation in low, fractionated doses and splenectomy (high risk of morbidity and mortality) are only indicated in individual cases with splenomegaly-related problems. This predominantly concerns patients with transition to myelofibrosis. Both therapeutic measures should only be considered under very strict indications [44].

6.2.5 Allogeneic bone marrow or peripheral blood stem cell transplantation

Due to the favorable prognosis of PV, the indication for allogeneic peripheral blood stem cell or bone marrow transplantation is given, if at all, only in very rare individual cases (especially in young patients) with a particularly complicated course. The indication must be considered extremely carefully.

6.3 Special situations

6.3.1 Rethrombosis prophylaxis

Previous thrombosis is a risk factor for rethrombosis. Retrospective studies showed a reduction in the rate of rethrombosis in the arterial and venous system when continuous prophylaxis with vitamin K antagonists was performed. Recently published retrospective analyses suggest that direct oral anticoagulants (DOAK; factor Xa and thrombin inhibitors) are at least comparably effective, possibly even more effective, compared with oral anticoagulation with vitamin K antagonists [45, 46, 47]. However, data in this regard are still limited. A summary of further details on diagnosis, prevention and therapy of thrombosis and bleeding complications in MPN can be found in the recommendations of the Working Group Hemostaseology of the DGHO [48, 49].
6.3.2 Late complications (post-PV myelofibrosis, MDS/acute leukemia).

In post-PV MF (see Table 3 for diagnostic criteria), the indication for allogeneic transplantation is usually made according to the recommendations for primary myelofibrosis (Primary Myelofibrosis Guideline (in German only)).

Allogeneic transplantation is indicated in cases of transition to acute (mostly myeloid) leukemia. Since the duration of remission after anthracycline/Ara-C-based chemotherapy alone is usually short, such therapy is primarily suitable if subsequent transplantation is possible. Palliative approaches can slow down progression and induce complete remissions in a limited percentage of patients (e.g., demethylating agents possibly in combination with venetoclax) [50, 51]. Overall, the prognosis of patients with transformation to acute leukemia remains very poor.

6.3.3 Surgical interventions

It is particularly important to have good control of blood counts (hematocrit and platelet count) prior to surgery. In some cases, cytoreductive therapy may be useful to improve blood cell levels around the time of surgery. There is an increased risk of surgery if blood counts are poorly controlled. If possible, ASA should be withdrawn one week before the planned surgery and replaced perioperatively with low-molecular-weight heparin. The individual risks of interrupting ASA therapy should be considered and weighed in an interdisciplinary manner.

6.3.4 Desire for children and pregnancy

PV per se is not a contraindication to pregnancy. However, it is always a high-risk pregnancy that should be well planned if possible. It requires close interdisciplinary monitoring by obstetricians and hematologists and adapted PV-specific therapeutic measures. In analogy to ET, an increased rate of early and late abortions is to be expected. Furthermore, the risk for the mother is increased. However, an indication for interruptio for medical reasons is only given in exceptional cases.

Recommendations for therapy of MPN (including PV) during pregnancy are based on case collections. Should cytoreduction be necessary in case of high risk of thrombosis during pregnancy, only IFN is an option due to the teratogenicity of other drugs. Data suggest a positive impact of IFN on the rate of successful pregnancies. In 78 pregnancies of patients with ET or PV with different risk profiles, the rate of live births under IFN was 94%. The limited published case series of pregnant patients treated with pegylated IFN showed no evidence of adverse effects of the pegylated dosage form [52, 53].

Specifically for PV, a case collection of 129 pregnancies in 69 patients revealed an overall live birth rate of 68.2%. With PV-specific therapy (ASA, low-molecular-weight heparin, IFN-alpha each as monotherapy or in various combinations), the live birth rate was 78.2% in pregnant women who had delivered before or at the time of diagnosis of PV, compared with only 47.8% in cases without PV-specific therapy. Thus, low-dose ASA, preferably in combination with low-molecular-weight heparin and, if necessary, in combination with IFN-alpha, is recommended during the duration of pregnancy, regardless of whether cytoreductive therapy is performed. Peripartum, ASA should be paused and only heparin should be continued, e.g., from the 34th week of pregnancy until 6 weeks postpartum [54].

6.3.5 Vaccinations

The general vaccination recommendations of the STIKO should be followed.
In addition to the usual booster vaccinations against conventional pathogens, special reference should be made to the vaccinations against pneumococci and herpes zoster recommended for older age groups (60 years and older), as well as annual vaccinations against influenza (RKi vaccination calendar-2023) [55]. An extension to younger patients with MPN should be considered depending on the individual situation.

In SARS-CoV-2 (COVID-19) infection, older age, comorbidity (e.g., chronic previous cardiac and pulmonary diseases and hematologic neoplasms) are risk factors for a severe clinical course. Thus, a significant proportion of PV patients fall into the risk group for a complicated course of infection. For this reason, a protective vaccination against COVID-19 is generally recommended for patients with MPN and an annual booster vaccination is urgently recommended for patients over 60 years of age (if necessary, also for younger patients) (see also German Onkopedia guideline Coronavirus infection (COVID-19) in patients with blood and cancer diseases and recommendations of the STIKO: RKI - Vaccinations A - Z - STIKO recommendation for COVID-19 vaccination) [56].

7 Rehabilitation

If the course of PV is complicated, the usual rules for initiating rehabilitation procedures in tumor diseases/leukemias apply.

8 Follow-up

Clinical examination and blood count: intervals depend on the form of therapy and the therapy phase as well as the individual course of the disease. In the initial phase of therapy and in the case of therapy changes, at short notice; once a stable phase has been reached, usually once a month to every three months. Occasionally, there are long phases without required phlebotomies with possible extension of the control intervals.

Microscopic analysis of the blood count (peripheral blood smear): by left shift, detection of erythroblasts and/or erythroocyte teardrop forms or leukemic blasts, evidence of transition to post-PV-MF or MDS/leukemia can be detected. Confirmation is obtained by bone marrow aspiration. Follow-up bone marrow histology examinations are not routinely indicated, but should be performed when there are signs of disease progression (e.g., increasing splenomegaly or blood count changes) to detect transition to myelofibrosis or acute leukemia and, if possible, when changing therapy.

A sonographic check of the spleen once a year is a useful.

Quantitative progression monitoring of mutant JAK2 alleles (VAF) allows to assess treatment response at the molecular level when using IFN-alpha or ruxolitinib. In progressive disease, testing for additional somatic mutations and cytogenetics is useful to assess individual prognosis.

9 References


the Haemostasis Working Party of the German Society of Hematology and Oncology (DGHO), the Austrian Society of Hematology and Oncology (ÖGHO) and Society of Thrombosis and Haemostasis Research (GTH e.V.). Ann Hematol 93:1953-1963, 2014. DOI:10.1007/s00277-014-2224


55. RKI Vaccination Calendar 2023

56. RKI - Vaccinations A - Z - STIKO recommendation on COVID-19 vaccination

10 Active studies / registers

<table>
<thead>
<tr>
<th>Study</th>
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<tr>
<td>Ruxo-BEAT</td>
<td>Feasibility, safety, and efficacy of ruxolitinib versus best-available therapy in patients with high-risk PV (or high-risk ET).</td>
<td>Prof. Dr. Steffen Koschmieder E-mail: <a href="mailto:skoschmieder@ukaachen.de">skoschmieder@ukaachen.de</a> Phone: 0241-8080981/-800</td>
<td>NCT02577926</td>
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**German MPN Registry and Biomaterial Bank for BCR::ABL1-negative myeloid neoplasms** (NCT03125707).

Homepage:

http://www.cto-im3.de/gsgmpn/

Inclusion criteria: Patients with BCR::ABL1-negative myeloid neoplasia according to WHO/ICC classification or IWG-MRI criteria, age ≥18 years; no upper age limit, Signed informed consent.

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14 Links

A video on how to perform bone marrow aspiration was created by the Elisabethinen Hospital in Linz for training and for pat. (https://www.youtube.com/watch?v=3RgGmErO50g).

www.mpd-netzwerk.de/
https://www.cto-im3.de/gsgmpn/

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16 Disclosure of Potential Conflicts of Interest
according to the rules of the responsible Medical Societies.