Management of polycythemia vera: Recommendations from the BHS MPN subcommittee anno 2021

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SUMMARY

Polycythemia vera (PV) is classified by the World Health Organization (WHO) under the BCR-ABL-negative myeloproliferative neoplasms (MPNs) and is characterised by clonal proliferation of myeloid cells, which leads primarily to an increased red blood cell mass. Bone marrow morphology remains the cornerstone of diagnosis. Patients can present with thrombosis, microcirculatory symptoms, haemorrhage, splenomegaly, pruritus and other symptoms that reduce their quality of life and they are at risk of transformation to secondary myelofibrosis (MF) or acute myeloid leukaemia (AML). The main goal of therapy in PV is to minimise the thrombotic risk. To achieve this goal PV patients are being treated with low-dose aspirin and phlebotomies to reach a target haematocrit below 45%. In addition, high-risk patients are being treated with cytoreductive agents. Over the last years, new insights in the pathophysiology, diagnosis and prognosis of polycythemia vera were acquired and novel therapeutic options are available. In this paper we give an update on PV and provide diagnostic and therapeutic recommendations, taking into account the Belgian situation.

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INTRODUCTION

Polycythemia Vera (PV) is a myeloproliferative neoplasm (MPN) characterised by the constitutive activation of haematopoiesis with overproduction of fully functional mature red blood cells. Complications such as thrombosis, haemorrhage, transformation to myelofibrosis (MF) or acute myeloid leukaemia (AML) can arise.

PV is a chronic disease and the current treatments mainly aim at preventing thrombotic complications while preserving a decent quality of life but do not affect the natural history of the disease in regard to myelofibrosis-free or leukaemia-free survival. The only curative option remains allogeneic stem cell transplantation, which is exclusively restricted to fit patients with progressive disease (evolution to myelofibrosis or AML).

Herein, we provide a practical review on how to manage PV patients, based on the most recent European LeukemiaNet (ELN) guidelines.[1] Our recommendations are adapted to the local situation in Belgium in 2021.

PHYSIOPATHOLOGY OF PV

PV is currently classified by the World Health Organization (WHO) under the major category of BCR-ABL-negative MPN. PV constitutes a stem cell-derived clonal

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TABLE 1. WHO 2016 diagnostic criteria of polycythemia vera.

Major criteria	
1	Haemoglobin > 16.5 g/dL in men or > 16.0 g/dL in women **OR** haematocrit > 49% in men or > 48% in women **OR** increased red cell mass (more than 25% above mean normal predicted value; this examination is now rarely performed in Belgium)
2	BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size) (***)
3	Presence of JAK2V617F or JAK2 exon 12 mutation
Minor criterion	
Subnormal serum erythropoietin level	
Diagnosis of PV requires all 3 major criteria, or the first 2 major criteria and the minor criterion	

(***) Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: haemoglobin levels. 18.5 g/dL in men (haematocrit, 55.5%) or 16.5 g/dL in women (haematocrit, 49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF).[7]

myeloproliferation, characterised by the "driver" mutation in the JAK2 gene. The most frequent MPN-associated JAK2 mutation is the exon 14 JAK2 V617F mutation, which is responsible for 95% of those seen in PV. The remainder of JAK2 mutations are insertions or deletions in exon 12. Patients with exon 12 PV have a slightly different profile than patients with JAK2 V617F PV: at diagnosis their age is significantly younger with a predominant erythrocytosis without leucocytosis or thrombocytosis. Otherwise, the clinical course in terms of thrombotic complications and myelofibrosis evolution is the same.[2,3]

JAK2 V617F and exon 12 mutations are directly responsible for JAK2 constitutive activation, a tyrosine kinase associated with the erythropoietin-receptor (EPO-R), the thrombopoietin-receptor (MPL) and the G-CSF receptor. Activated JAK2 subsequently induces the constitutive stimulation of STAT, PI3K and MAPK pathways, eventually leading to clonal haematopoietic stem cell proliferation, erythrocytosis, thrombocytosis and neutrophilia.[4]

The role of mutated JAK2 in the genesis of thrombotic events seems rather complex.[5] Mutated JAK2 may play a direct role by activating leukocytes and platelets that subsequently bind to endothelial cells provoking endothelial injury, endothelial expression of tissue factor and endothelial release of procoagulant microparticles and procoagulant factors such as von Willebrand factor (vWF).

Indirectly, JAK2 mutation participates to thrombogenesis by enhancing red cell mass. In these high shear conditions, platelets are pushed closer to the vessel wall and are then forced to bind to collagen and vWF, thus initiating thrombus formation. These conditions also promote platelet-leucocyte interactions that further amplify platelet aggregation and coagulation activation.

The JAK2 mutations do not explain the entire heterogeneity of PV. The development of new techniques such as next generation sequencing (NGS) allowed the identification of several other acquired mutations in PV and their prognostic contribution will be discussed further below.[6]

DIAGNOSIS AND WHO DEFINITION OF PV

The hallmark of PV, and the basis for its diagnosis, is an increased red cell mass, evident as an elevated haemoglobin (Hb) and/or haematocrit (Hct). The 2016 WHO diagnostic criteria are listed in *Table 1*.[7] Diagnosis of PV requires meeting all three major criteria or the first two major criteria and the minor criterion. Compared to the previous WHO criteria (2008), the haemoglobin/haematocrit levels are lower because under-diagnosis of PV was seen.[8] In comparison to the criteria of 2008 a bone marrow puncture should be performed at diagnosis as, first, bone marrow morphology is a major diagnostic criterion for PV and, second, initial myelofibrosis should be excluded

TABLE 2. MPN symptom assessment form total symptom score (MPN-SAF TSS) or MPN-10 score.

Symptom	1 to 10 (0 if absent) ranking 1 is most favourable and 10 least favourable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours*	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes how, during the past week how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last six months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
The MPN-SAF TSS has been described for the first time by Emmanuel RM, Dueck AC, Geyer HL, et al. J Clin Oncol 2012; 30: 4098-4103.[17]	

as this finding at diagnosis predicts faster progression to post-PV myelofibrosis (PPV-MF) with a need for closer follow up.

The following tests should be initially performed: full blood count with differentiation of white blood cells (WBC), CRP, LDH, ferritin, prothrombin time, liver tests and uric acid. To exclude secondary forms of polycythemia, the EPO-level should be measured. Increased EPO-levels can be caused by EPO-producing tumours, renal artery stenosis, chronic hypoxemia in *e.g.* lung or heart disease or due to high altitudes and cause erythrocytosis.

Molecular testing (JAK2 V617F or JAK2 exon 12 mutation) can be performed on peripheral blood samples: Other mutations can be detected by NGS and will be discussed in the chapter 'prognosis in PV'.

PV: SIGNS AND SYMPTOMS

The median age at diagnosis is approximately 60 years, with around 10% of patients below the age of 40.[9] There is a slight male predominance. Patients are often asymptomatic with polycythemia regularly being an incidental finding on a routine blood test. Frequently there is a trilinear myeloproliferation, with leucocytosis and/or thrombocytosis in about 50% of patients.[9] Furthermore, bone marrow hyperactivity is demonstrated by elevated levels of lactate dehydrogenase (ca. 50% of patients) and uric acid.

Signs and symptoms of PV comprise mainly of thrombotic events, microvascular disturbances, haemorrhage, organomegaly with early satiety, pruritus, facial plethora and fatigue.

Thrombotic events before or at diagnosis are seen in approximately 25% of patients, with roughly two thirds being of arterial origin and the remaining third of venous origin.[9,10] After diagnosis there remains a thrombotic risk, with circa 20% of patients experiencing an event in the course of their disease.

Apart from major thrombotic events, patients can experience microvascular circulatory disturbances, seen in

TABLE 3. Management of PV according to risk profiles.

	Low risk PV pts *(age ≤ 60 years AND no history of thrombosis)*	High risk PV pts *(age > 60 years OR history of thrombosis)*
ASA (once daily) (75-100mg)	**Yes** *(unless otherwise contra-indicated)* If platelets > 1.000.000/µl exclude acquired Von Willebrand Disease.	**Yes** *(unless otherwise contra-indicated)* If platelets > 1.000.000/µl exclude acquired Von Willebrand Disease.
Phlebotomy to maintain haematocrit < 45%	**Yes** *Avoid iron supplements*	**Yes**, if still necessary to control haematocrit despite use of cytoreductive therapy *Avoid iron supplements*
Management cardiovascular risk factors	**Yes**	**Yes**
Cytoreductive therapy	No unless in case of: * uncontrolled PV symptoms * progressive leukocytosis (>15.000/µL) * thrombocytosis (>1.500.000/µl) * symptomatic/progressive splenomegaly * intolerance for phlebotomies First line: hydroxyurea	**Yes** First line: hydroxyurea (HU) If HU refractory or intolerant: * ruxolitinib * interferons [1] * busulfan if patient > 75 years [1] *Not reimbursed in Belgium*
Twice daily ASA	Consider if: *leukocytosis (>15.000/µL) *cardiovascular risk factors (especially if arterial hypertension) *inadequate control of microvascular symptoms with once daily ASA.	Consider if history of arterial thrombosis
Based on reference 54		

approximately one third of patients at presentation.[9] Erythromelalgia is the most known example of these microvascular complications, with burning pain in hands or feet, accompanied by erythema, pallor or cyanosis.[11] Other microvascular symptoms are headaches, lightheadedness and visual disturbances.[12] These problems are mostly related to a high platelet count, yet are aggravated by increased Hct and blood hyperviscosity.[11,13] Improvement of these symptoms is often seen with low-dose aspirin.

Besides thrombotic events, major haemorrhage (mostly gastro-intestinal bleeding) can be seen as presenting symptom, occurring in 2-8% of patients, especially in patients with a very high platelet count as they can experience acquired von Willebrand's disease.[9,11,14]

Another debilitating symptom of PV is pruritus, seen in 31-69% of patients.[15] This is often triggered by contact with water at any temperature, thus called aquagenic pruritus. The underlying pathophysiology is incompletely understood. Mast cells, histamine and induction of cytokine hypersensitivity, through the JAK2 V617F allele, have been implicated in this phenomenon.[15]

Clinical examination in PV patients reveals splenomegaly in about one third of the patients.[9] In a small number of patients also hepatomegaly can be found. This organomegaly can cause early satiety and abdominal discomfort. Facial plethora can be seen, as can excoriation lesions of the skin suggestive of pruritus.

Fatigue is an important and often underestimated symptom

in PV patients. Furthermore, symptoms such as concentration problems, night sweats, weight loss and fever are reported. Yet, the latter three are less frequent in PV than in myelofibrosis.[16] These symptoms are often underreported by patients, but add quite a lot to the burden of disease and diminish the quality of life. To have a better view on the symptomatic burden and the effect of treatment, a short questionnaire (MPN-SAF TSS or MPN-10 score) has been developed and proves useful in clinical practice (*Table 2*).[17]

PROGNOSIS AND PROGNOSTIC SCORES IN PV

RISK FACTORS FOR THROMBOSIS

Risk scores assess the risk for thrombosis rather than transformation to AML (or blast phase disease; MPN-BP) or post-polycythemia vera myelofibrosis (PPV-MF).

Traditionally, the main risk factors for thrombosis in PV have been defined as age above 60 years and/or history of previous thrombosis. **Low-risk PV patients** do not have any of these two risk factors. Nevertheless, low risk patients still have a higher risk of thrombosis compared to the general population. The patients who have at least one of these risk factors are considered as **high-risk PV patients** (*Table 3*).

More recent studies have shown that the thrombotic risk rises with leukocytosis: the ELN management guidelines advices to keep leukocytes lower than 15 x 10^9/L.[1] The score developed by the International Working Group for Myeloproliferative Neoplasm Research and Treatment (IWG-MRT) focuses on survival: adverse points are assigned to age ≥ 67 years (five points), age 57-66 years (two points), leukocyte count ≥ 15 x 10^9/L (one point) and venous thrombosis (one point): the score distinguishes a low risk (zero points), intermediate-risk (one or two points) and high-risk group (≥3 points) with a median survival of 27, 18 and 10 years, respectively.[9]

RISK FACTORS FOR SURVIVAL AND TRANSFORMATION

Twenty-eight JAK2 V617F positive PV patients were studied by targeted NGS of eighteen genes and 1.6 mutations per patient were detected on average. Patients who had evidence of progression at three years were more likely to have additional mutations at diagnosis. Patients with disease progression were also more likely to have additional mutations with an allele burden greater than 20% at diagnosis. Finally, disease progression at three years was associated with an allele burden increase of at least one mutation.[18]

One hundred thirty three PV patients were studied by targeted NGS of 27 genes. In 53% of patients one or more sequence variants/mutations other than JAK2/CALR/MPL were detected (most frequently TET2 and ASXL1). ASXL1, SRSF2 and IDH2 were identified as negative prognostic epigenetic mutations in PV patients, both shortening myelofibrosis- and leukaemia-free survival.[6] In another study by the same group, the spliceosome mutation (SRSF2) was confirmed to adversely affect overall survival in PV, hence the creation of the Mutation-enhanced International Prognostic Systems Score (MIPSS-PV).[19] In the MIPSS-PV genetic information (SRSF2 mutation, abnormal karyotype) is combined with clinically relevant risk factors (age > 67 years, thrombosis history, leukocyte count ≥ 11 x 10^9/l) in order to predict overall survival.[19] This score however is not used in daily clinical practice yet because up till now it has no therapeutical implications and because NGS testing is not reimbursed in PV.

BM fibrosis (≥ grade 1) has been significantly associated with shorter myelofibrosis-free survival (MFFS) but not with leukaemia-free or thrombosis-free survival. Other risk factors for progression to PPV-MF include leukocytosis ≥ 15 × 10^9/L, presence of palpable splenomegaly, older age and JAK2 V617F allele burden > 50%.[20,21] Risk factors for leukaemic transformation are older age, leukocytosis ≥ 15 × 10^9/L and abnormal karyotype.[9]

The cumulative incidence of post-PV AML is 2.3% at ten years and 5.5% at fifteen years and the reported incidence of PPV-MF ranges between 5-6% at ten years and 6-14% at fifteen years.[9,22]

Current treatments have not led to better leukaemia-free or myelofibrosis-free survival in PV patients. However it is important to avoid certain treatments because of their leukaemogenic potential, for instance chlorambucil, radioactive phosphate (^{32}P) and pipobroman (discussed further below).

MANAGEMENT OF POLYCYTHEMIA VERA PATIENTS

GOALS OF TREATMENT IN PV AND RISK-BASED MANAGEMENT

The major aim of therapy in PV is the prevention of thrombosis. In addition, reducing the symptom burden to improve quality of life is essential. Many clinical trials have been performed regarding the management of PV and the most important trials are listed in *Table 4*.

The management of **low-risk PV patients** consists of antiplatelet therapy and phlebotomies to reach a target Hct below 45%.[23] The management of **high-risk PV patients** consists of antiplatelet therapy, phlebotomies and cytoreductive

TABLE 4. Clinical trials regarding the management of PV.	
Thrombosis and haematocrit [79]	Haematocrit above 45% as main risk factor for thrombosis in PV
PVSG-01 trial [80]	Use of phlebotomy and leukaemogenic risk of 32P and chlorambucil in PV patients
PVSG-08 trial [26]	Efficacy of hydroxyurea in PV
ECLAP trial [25]	Low dose aspirin as safe prevention of cardiovascular events in PV
Cyto-PV trial [23]	Optimal haematocrit is less than 45% in PV patients: randomised prospective trial
FPSG long-term trial [81]	Pipobroman is leukaemogenic in PV patients
Interferon studies [43-46]	Impact of interferon on molecular remission in PV
RESPONSE trial [33]	Effect of ruxolitinib in hydroxyurea intolerant or resistant PV patients with splenomegaly
RESPONSE-2 trial [34]	Effect of ruxolitinib in hydroxyurea intolerant or resistant PV patients without splenomegaly

List of important clinical trials concerning the management in PV: the name and reference of the trial at the left and the main outcome at the right.

treatment to reach a target Hct below 45%. An overview is given in *Table 3*.

ANTIPLATELET THERAPY

An early Polycythemia Vera Study Group (PVSG) study with high dose aspirin (3x 300 mg daily) in combination with dipyridamole (3x 75 mg daily) led to significant bleeding problems while maintaining a high risk of thrombosis and discouraged the further use of high dose aspirin in PV patients.[24] Later on, the European Collaboration on Low Dose Aspirin in PV (ECLAP) trial showed that aspirin 100 mg a day in PV patients led to a reduced risk of fatal and non-fatal arterial and venous thrombotic events without a significant increase in major bleeding episodes. The investigators concluded that low dose aspirin can be safely used and should be given to all PV patients.[25]

PHLEBOTOMY

An elevated haematocrit leads to increased blood viscosity and confers a higher thrombosis risk. In a normal-sized adult a phlebotomy with removal of 500 ml of blood lowers the Hct on average with 3%. From the CYTO-PV trial we know it is of the utmost importance to bring and keep the Hct below 45%: in this prospective randomised study in 365 V617F JAK2 positive PV patients, patients were randomised into either a more intensive treatment group with a target haematocrit less than 45% or a less intensive treatment group with a target Hct between 45 and 50%.[23] Treatment consisted of phlebotomy, hydroxyurea (HU) or both. After a median follow up of 31 months there was a significantly higher rate of cardiovascular death and major thrombosis in the second group (2.7% vs. 9.8%). Similar results were found in men and women. Notably, the authors of the CYTO-PV trial did not address whether lower haematocrit thresholds would be even better, so the optimal Hct for PV patients is not exactly known even at this time point. Some authors advocate a lower target Hct for female patients (below 42%). So far however, the question of gender difference in Hct target remains unanswered and cannot be formally recommended. The current recommendations are thus to bring and keep the haematocrit below 45%, both in women and in men with PV.

Phlebotomies exert their effect by creating an iron deficiency state. It is therefore important not to give these patients iron supplements.

CYTOREDUCTIVE TREATMENT

An overview of the advantages and disadvantages of the different cytoreductive treatments is given in *Table 5*.

FIRST LINE TREATMENT

In earlier times chlorambucil, radioactive phosphate (^{32}P) and pipobroman have been used as myelosuppressive therapy in PV patients but this at the cost of a high risk of secondary malignancies and myelofibrosis. Therefore nowadays their use is abandoned and can only be accepted

TABLE 5. Advantages and disadvantages of different cytoreductive agents in PV.

	Advantages	Disadvantages
Hydroxyurea (HU)	- efficiency - ease of administration - long-term safety data well known - rather favourable toxicity profile - low cost	- some concerns on teratogenicity - although no higher leukaemia risk has been found in different studies, there are still concerns to use in young pts (< 45y) (studies available are non-controlled studies).
Interferon (IFN) and Pegylated interferon alfa (PEG-IFNα)	- efficiency - not teratogenic - possible molecular remission - not leukaemogenic	- Although molecular remission possible, disease-modifying ability still not proven. - Side effects (though less with mono-pegylated IFN) Long-term tolerability? - Expensive
Busulfan	- efficiency, - proven durable response - low cost	- Less favourable toxicity profile than HU: possible long lasting cytopenias/ marrow aplasia - Risk of pulmonary fibrosis - Teratogenicity
Ruxolitinib	- very efficient on pruritus and constitutional symptoms; improving quality of life - reduces splenomegaly - efficient haematocrit control	- Expensive - higher incidence of infections like *e.g.* herpes zoster - withdrawal syndrome when stopping - to be considered as teratogenic - effects on the very long term are still unknown

Based on reference 54

in highly exceptional cases, for instance a very old patient (at least > 75 year old) who has no other therapeutic alternative. Nowadays hydroxyurea is the first-line cytoreductive agent in high-risk PV.

HYDROXYUREA (HU)

Hydroxyurea is an inhibitor of ribonucleotide reductase and interferes with DNA repair. This strategy is largely based on evidence of its efficacy in preventing thrombosis in trials of essential thrombocythemia (ET) patients and on the results of the PVSG-08–study. This study showed that HU-treatment was associated with a lower incidence of thrombosis compared to previous PVSG-trials (9% in the first two years for HU compared to 23% for phlebotomy-only and 16% for the ^{32}P–treated patients) and this without a significant rise in acute leukaemia incidence.[26]

The advised starting dose of hydroxurea is 500 à 1000 mg daily followed by regular controls of blood values during the first weeks of treatment.

SECONDARY MALIGNANCIES AND THE USE OF HU

The possible leukaemogenic potential of HU has been a matter of concern. Older data in PV patients have not been able to show that single-agent HU is leukaemogenic.[27,28] Neither do the most recent data that come from an international study which comprised 1,545 PV patients: with a mean follow up of 6.9 years this study could not find a significant association between single agent HU use and leukaemic transformation.[9]

SPECIFIC POINTS OF ATTENTION WITH HU

• Cutaneous toxicity: cutaneous ulcers, typically in the malleolar region, occur more frequently in patients taking HU for a long time (*i.e.* more than five years). They can occur spontaneously or in the setting of venous insufficiency, after trauma or surgery. Ulcers are a reason to stop HU and switch to another therapy. Subsequently, the use

TABLE 6. Definition of hydroxyurea resistance and intolerance.

HU RESISTANCE (according to the ELN consensus)[30]	When after taking HU ≥ 2 gram a day for at least 3 months **OR** a maximum tolerated dose 1. phlebotomy is still needed to keep Hct < 45% **OR** 2. platelet count still exceeds 400 x 10*9/L and WBC count still exceeds 10x10*9 /L **OR** 3. there is no reduction of splenomegaly by >50% as measured by palpation or symptoms related to splenomegaly are not completely relieved.
HU INTOLERANCE (according to the ELN consensus)[30]	1. haematologic toxicity: - anaemia (Hb < 10g/dL) or - neutropenia (ANC < 1x 10*9 /L) or - thrombocytopenia (< 100 x 10*9 /L) at the lowest dose of HU needed to achieve a complete or partial clinico-hematologic response. 2. non – haematologic toxicity: e.g. development of leg ulcers, other significant mucocutaneous manifestations, pyrexia, gastrointestinal symptoms, pneumonitis at any dose of HU.

HU: hydroxyurea, ELN: European LeukemiaNet.

of HU has to be avoided in patients already known to have leg ulcers. Wound healing after trauma or surgery will be affected by HU and may be reason to withdraw treatment with HU or to reduce the dose, until the wound has healed.[29] Long-term use of HU is associated with skin cancer, both squamous cell and basal cell carcinomas, mostly at sun exposed areas. Patients have to know they have to avoid unprotected sun exposure and a dermatological check up every six to twelve months is advised.

• Hypersensitivity: drug fever has been reported, with a typically onset within six weeks of treatment initiation. It resolves with discontinuation and usually recurs within 24 hours after re-challenge.[29]

SECOND LINE TREATMENT AND BEYOND

Some patients develop serious side effects to HU (*e.g.* development of significant cytopenias, mucocutaneous ulcers, diarrhoea, pyrexia, peripheral neuropathy, lung toxicity) and can obviously not continue this agent. In addition, about 10% of patients develop HU-resistance; this means that they need a dose of 2 gram HU or more a day (or a maximum tolerated dose) to achieve the treatment goals that the haematocrit cannot be maintained below 45% without causing severe cytopenias or that they do not achieve adequate symptom control (*Table 6*).[30,31]

HU-resistance is an adverse prognostic factor. These patients have a significantly higher mortality risk and a higher risk of transformation of their disease. In a recent study addressing the genomic complexity of PV patients developing resistance to HU, resistant patients were more frequently located in the high-risk molecular group than the non-resistant patients.[32] This high-risk molecular group contains the patients with spliceosome/chromatin gene mutations, who have a higher risk of transformation to MF and the patients with *TP53* mutations, who have a high probability of AML in the first five years of therapy.[32] HU-intolerant and -resistant patients (+/- 15 à 20% of HU-treated PV patients) are thus in need of other therapies.[31]

JAK-INHIBITOR THERAPY: RUXOLITINIB

Ruxolitinib is an oral JAK1/2 inhibitor and is approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for HU-intolerant and –resistant PV patients based on the results of the randomised phase III RESPONSE trial. In this trial, it was demonstrated that in HU-resistant and -intolerant PV patients, ruxolitinib was able to improve haematocrit control, reduce splenomegaly and improve symptom burden of PV patients in comparison to best available therapy.[33] The RESPONSE-2 trial, in addition, showed that ruxolitinib was also effective and safe as a second line therapy in PV patients without splenomegaly.[34] Efficacy and safety data at five-year follow-up are now available: the probability of maintaining overall clinico-haematological responses was 67%. With the availability of ruxolitinib a lot of HU-resistant patients will meet their treatment goals

TABLE 7. Dosing of ruxolitinib in PV patients.

Normal starting dose:	RUX 10 mg twice daily po
Dose adjustments while on treatment: – Hb < 12g/dl or – platelets < 100.000/µll	Consider dosage adjustment to 5 mg twice daily to avoid dose interruptions later
– Hb < 10g/dl	Reduce dose to 5 mg twice daily or, if already receiving 5 mg twice daily, reduce to 5 mg once daily
– Hb < 8g/dL or – Platelets < 50.000/µll or – ANC < 500/µl	Interrupt dosing, when blood counts rise above these cut-offs: restart with 5 mg twice daily.
If treatment goals are not met and blood counts allow to (not sooner than after 4 weeks of treatment):	Increase dose by max 5 mg twice daily, maximum every 2 weeks, up to a maximum dose of 25 mg twice daily.
Starting dose if renal impairment: – creatinine clearance < 30ml/min – ESRD in haemodialysis	 5 mg twice daily 10 mg once daily given after dialysis and only on days of dialysis.
Starting dose if liver impairment: Child-Pugh scores A, B and C	 5 mg twice daily Control blood counts every 1 or 2 weeks in the first 6 weeks after starting.

ANC: absolute neutrophil count, ESRD: end stage renal disease.

and will have a better quality of life but since there is no evidence that ruxolitinib alters the natural history of PV (*i.e.*, leukemic transformation, myelofibrosis) HU-resistance remains an adverse prognostic factor.

Anaemia was the most common adverse event in patients receiving ruxolitinib though most anaemia events were mild to moderate in severity. Non-haematological adverse events were generally lower with long-term ruxolitinib treatment than with best available therapy. Thromboembolic events were lower in the ruxolitinib group than the best available therapy group.[35]

In Belgium ruxolitinib is reimbursed for adult patients with PV who are either HU-intolerant or HU-resistant. For patients with PV the recommended starting dose of ruxolitinib is 10 mg twice daily. The dose should then be titrated based on efficacy and safety. If necessary, the dose can gradually be increased up to a maximum of 25 mg, twice daily. If the haemoglobin level drops below 10 g/dl or platelets drop below 50,000/µL, dose reductions are recommended. If the haemoglobin level drops below 8 g/dl, ruxolitinib should be temporary interrupted. For patients with liver or renal impairment a lower starting dose is recommended (*Table 7*).

Patients under ruxolitinib have a moderate increased infection risk. Urinary tract and herpes infections are more frequent.[34] Every patient should be informed about the symptoms of herpes zoster and be advised to seek medical attention as soon as the first symptoms develop. Prophylaxis can be considered on an individual basis. As reactivation of hepatitis B virus infection has been described under ruxolitinib, the viral load in patients with chronic hepatitis B infection should be monitored and treated according to local guidelines.[36] Exclude tuberculosis infection (TBC) before starting ruxolitinib if there is any clinical suspicion or exclude latent TBC according to local guidelines if there are some risk factors. A list of case reports or series concerning infections under ruxolitinib has recently been published.[37]

Treatment with ruxolitinib is associated with an increase in the lipid parameters and weight gain, therefore monitor and treat appropriately. There might be a higher risk of non-melanoma skin cancer with this treatment but so far

no causal relationship has been shown. These patients have also been treated with HU and some had a history of non-melanoma skin cancer or precancerous skin lesions.[33] Finally, there have been concerns about an increased risk for B-cell lymphoma in patients taking JAK inhibitors. In 2018, a Viennese group published a study showing that treatment with JAK inhibitors is associated with an increased risk for aggressive B-cell lymphoma.[38] In 2019 however, *Pemmaraju et al.* found no significant increase in lymphoma rates in their patient data base of 2,583 MPN patients.[39] When taking a closer look to the patients in the Viennese study there are factors suggesting that these patients had B-cell clones before starting JAK inhibition and that these progressed to high-grade lymphoma during treatment.[40] With this information an Italian group looked at their database consisting of 3,069 patients and found that the rate of lymphoproliferative disorders among their MPN patients was low (24/3,069 0.78%) but higher than expected in the general population.[41] It was however not associated with a previous exposure to ruxolitinib. None of the patients developing a lymphoid neoplasm showed B-cell clonality on peripheral blood before ruxolitinib treatment.[41] In the absence of B cell clones, ruxolitinib treatment thus may be considered relatively safe and can be initiated with monitoring.

BUSULFAN

Although there are data that busulfan, when given in monotherapy, has not been found to be leukaemogenic, there are concerns about leukaemogenicity of the drug.[9] For this reason we advise to use this agent only in PV patients of 75 years or older without any other cytoreductive alternative. To prevent long-lasting and profound cytopenias it is better to start with lower doses and frequently monitor the patients: *e.g.* starting doses of 2 or 4 mg daily, with weekly blood evaluations during the first weeks, and further adapting the dose in function of tolerance and blood values. Interrupt treatment if platelets drop below 150,000/µL or white cells drop below 3,000/µL. Do not forget that the myelosuppressive effect of busulfan can be long lasting, so it is important to taper or stop this drug on time.

INTERFERON

Interferon-alfa (IFN-α) is an efficient treatment. About 80% of interferon-treated patients obtained haematocrit control, decrease of thrombocytosis and pruritus, a lower thrombo-haemorrhagic risk and a reduction in spleen size. But up to 35% stopped their treatment because of side effects (fever, malaise, nausea, vomiting, depression).[42] Pegylated interferon α-2a (PEG-IFN) is given subcutaneously (sc) once a week. PEG-IFN induces more complete haematological and molecular responses than IFN-α, has a better toxicity profile but is more expensive.[43] Recent data demonstrate that PEG-IFN induces 22% CR and 38% PR (ORR 60%) in high-risk PV patients, either refractory or intolerant to HU.[44] Ropeginterferon-α2b (Besremi®), administered every two weeks sc and once monthly during long-term maintenance treatment, is a novel monopegylated form.[45] Besremi® is EMA-approved for PV treatment but is not available yet in Belgium. In patients with early PV, ropeginterferon α-2b (ropeg) is effective in inducing haematological responses. At twelve months of treatment, ropeg was non-inferior to hydroxyurea regarding haematological response, however response to ropeg continued to increase over time with improved responses compared with HU at 36 months. Molecular responses are seen under ropeg and the overall tolerability of the drug is good.[46]

Interferon is the only safe cytoreductive treatment for pregnant PV patients (discussed further below). Interferons are prescribed in many countries for the treatment of PV but in Belgium interferon is unfortunately not reimbursed in this indication.

Trials with histone deacetylase (HDAC)-inhibitors (*e.g.* givinostat) and HDM2-antagonists (*e.g.* idasanutlin) are running.[47] Recently a promising combination of ruxolitinib and interferon in MPN patients has been reported.[48]

MANAGEMENT OF CARDIOVASCULAR RISK FACTORS IN PV PATIENTS

The incidence of cardiovascular events is increased in PV. A careful baseline assessment of cardiovascular risk factors is essential with stringent ensuing management. Positive health-promoting behavior, including lifestyle modification (healthy diet, smoking cessation, regular exercise, weight control) should be strongly advised. The available literature does not advocate specific treatment targets for PV patients however treatment targets are based on the most recent guidelines for the general population issued by the European Society of Cardiology (*Table 8*).[49,50]

Barbui et al. showed that among the cardiovascular risk factors arterial hypertension in particular is correlated with a significantly higher incidence of arterial thrombosis.[50] In PV patients the angiotensine converting enzyme-inhibitors (ACE-I) are of particular interest in the treatment of arterial hypertension as there is evidence that the renin-angiotensin system is overexpressed in the bone marrow of PV patients.[52] In addition it is known that starting treatment with ACE-I can lead to a reduction in haemoglobin levels.[53]

TABLE 8. Goals and treatment targets for conventional cardiovascular risk factors.	
Smoking	No exposure to tobacco in any form
Diet	Diet low in saturated fat, with focus on wholegrain products, vegetables, fruit and fish; dietary sodium restriction (< 5g salt/day); moderation of alcohol consumption.
Physical activity	At least 150 minutes a week of moderate aerobic physical activity (30 minutes for 5 days/week) or 75 minutes a week of vigorous aerobic physical activity (15 minutes for 5 days/week) or a combination thereof.
Body weight	BMI 20-25 kg/m^2. Waist circumference < 94 cm (men) or < 80 cm (women).
Blood pressure	The first objective of treatment should be to lower BP to < 140/90 mmHg in all patients, and provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 or lower in most patients. In patients <65 years receiving BP-lowering drugs, it is recommended that SBP should be lowered to a BP range of 120-129 mmHg in most patients (less evidence available in low-moderate risk patients). In older patients (aged ≥ 65 years) receiving BP-lowering drugs, it is recommended that SBP should be targeted to a BP range of 130-139 mmHg.
Lipids LDL is the primary target HDL Triglycerides	 Low risk < 116 mg/dL Moderate risk <100 mg/dL. High risk <70 mg/dl or a reduction of at least 50% reduction from baseline Very high-risk <55 mg/dL or a reduction of at least 50% from baseline No target, but >40 mg/dL in men and > 45 mg/dL in women indicate lower risk. No target, but < 150 mg/dL indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c < 7% (< 53 mmol/mol)
Interpretation note: risk stratification is based on the SCORE charts (for an electronic version: *www.heartscore.org*), estimating an individual's 10 year risk of fatal cardiovascular disease (Conroy et al. European Heart Journal 2003; 24: 987-1003), presence of chronic kidney disease, presence of diabetes with our without target organ damage and presence of documented cardiovascular disease.	

Up to now, no significant correlation has been shown between thrombocytosis and increased risk of thrombosis.[54] But blood platelets above 1 x 10^6/µl need to be avoided (see chapter 'prevention and management of bleeding').

RELIEVE OF SYMPTOM BURDEN IN PV PATIENTS

PRURITUS

About 40-50 % of patients with PV have to deal with pruritus, often aquagenic. Sometimes this is the first symptom of the disease. It is difficult to treat and interfere with the quality of life in almost half of the patients. Low dose aspirin can alleviate pruritus in some patients. For the others, the classical cytoreductive agents often fail to offer relief. Ruxolitinib though is more likely to be effective. For aquagenic pruritus using a lower water temperature and drying the skin by dabbing instead of rubbing can help. Sometimes selective serotonin reuptake inhibitors (SSRI), *e.g.* paroxetine 20 mg daily or fluoxetine 10 mg daily, are used in daily practice without data from randomised trials. Other possible treatments are antihistamines, IFNα, narrow-band ultraviolet B phototherapy, photochemotherapy with psoralen and ultraviolet A light (PUVA) or mTOR inhibitors.[54]

TABLE 9. Definition of high-risk pregnant PV patients according to different guidelines.

ESMO Guidelines 2015 [68] Nordic Guidelines 2017 [70] ELN Guidelines 2011 [71]	NCCN Guidelines 2017 [69]
Previous venous or arterial thrombosis in mother	Previous microcirculatory disturbances or presence of two or more hereditary thrombophilic factors
Previous haemorrhage (AND attributed to MPN, as mentioned in ESMO guidelines [68])	
Previous pregnancy complications that may have been caused by MPN as defined by: – recurrent unexplained first trimester loss – otherwise unexplained IUGR – otherwise unexplained IUFD or stillbirth – (severe) preeclampsia necessitating preterm delivery – features of placental insufficiency	
Additional criterion in ESMO guideline: abnormal uterine artery doppler at 20 weeks = risk factor developing during pregnancy[68]	
	Age > 35 years

IUGR: intra-uterine growth retardation, IUFD: intra-uterine foetal death.

ERYTHROMELALGIA

In most cases low dose aspirin (max 100 mg/day) is sufficient. If not, one can consider giving aspirin twice daily. In case the platelets are above 400,000/µl, starting cytoreductive therapy to bring the platelet count to normal, can offer relief.

GOUT / HYPERURICEMIA

Allopurinol could be considered in PV patients with high urate or a history of gout.

NON-PHARMACOLOGICAL INTERVENTIONS

Many PV patients also have to cope with fatigue and the psychological burden this disease brings along. For these problems non-pharmacological interventions such as psychological support, yoga, mindfulness and participating in patient organisations can be useful.[55,56]

TREATMENT OF THROMBOSIS

A general recommendation is to treat thrombosis in PV patients as in patients without a myeloproliferative neoplasia but, importantly, combine with myelosuppressive therapy if not already done. There are not many available data to give more precise instructions. There is evidence from observational studies that oral anticoagulants as well as aspirin can prevent recurrent venous thrombosis (VTE) in PV and thus can be used for secondary VTE prophylaxis.[54] Concerning the duration of therapy: secondary prevention with therapeutic anticoagulation beyond 3 to 6 months after the event can only be recommended after careful weighing of benefits against potential risks.[57] For patients with a splanchnic vein thrombosis however, lifelong therapeutic anticoagulation is recommended as well as for patients with recurrent VTE or life-threatening VTE.[57,58] The combination of aspirin and anticoagulation, especially vitamin K antagonists (VKA), should be avoided if possible, because of the increased bleeding risk, except of course when there is a clear indication to combine as *e.g.* after cardiac stenting.[57] After termination of anticoagulation for VTE, effective cytoreduction and aspirin are indicated.

PREVENTION AND MANAGEMENT OF BLEEDING

Major bleedings are reported in 9-15% of PV patients, especially in older patients.[59,60] They are observed more frequently than in ET. A severe haemorrhage is defined as any bleeding with a drop in haemoglobin of at least 2 g/dl, requirement for blood transfusions or central nervous system bleeding. Upper gastrointestinal bleeding is the most common bleeding in PV patients.[55] There are multiple

reasons to explain the increased risk of haemorrhage in PV patients: platelet dysfunction, therapy-induced haemorrhage (antiplatelet agents and anticoagulation) and acquired von Willebrand syndrome (AvWS).[61,62]

Cytoreductive treatment and disease control improve the platelet function in PV patients and are important to reduce haemorrhages. In case of bleeding, tranexamic acid should be administered unless contraindicated. Only when life threatening bleeding related to platelet dysfunction occurs, platelet transfusions are indicated, in addition to treating the underlying disease.

The use of aspirin or other anti-aggregation agents has to be evaluated and questioned regularly, in function of a correct balance between the thrombotic risk assessment and bleeding risk calculation in the PV patient. When there is a need for anticoagulation (*e.g.* after a prior thrombosis or for atrial fibrillation), both LMWH and VKA can be prescribed and should be closely monitored in PV patients. Evidence-based recommendations about the use of NOACs do not yet exist. More data are awaited. Recently *Ianotto et al.* reported the impact of NOACs in PV and ET patients: the incidence of major bleeding (12%) was not increased compared to a case-control group (under low dose aspirin) and there were no additional safety concerns.[63]

PV patients with thrombocytes higher than 1 x 10^6/µl are at risk for AvWS. If ristocetin cofactor activity is lower than 30%, antiplatelet therapy should be withheld, if justifiable, unless avWs resolves due to therapy. Cytoreductive treatment should be started to keep the thrombocytes under 1 x 10^6/µl. In case of acute severe bleeding, desmopressin and tranexamic acid should be administered unless contraindicated. Platelet transfusions, vWF-containing concentrates, and/or rFVIIa (off-label use) should be reserved for severe or life threatening bleeding episodes.

SPECIFIC SITUATIONS

PV AND PREGNANCY

BACKGROUND

Only 10% of female patients with PV are younger than 40 and 23% are younger than 50. Pregnancy in PV patients is therefore a much rarer event than in ET patients.[9,64] Consequently data on the natural history of pregnancy in PV patients is very limited. A non-published systematic review of the literature on the issue of PV in pregnancy identified six relevant papers in English since 2005.[65] Two of these papers describe incidence and natural outcome, four are management guidelines.[66-71] Consistent with the pathophysiology of the disease, the main complications of polycythemia vera during pregnancy in these limited series are related to thromboembolism.[72] This includes small vessel thrombosis, pre-eclampsia and placental loss. Maternal bleeding complications, possibly related to treatment rather than the underlying disease, seem to be more prevalent than in healthy individuals. Intra-uterine growth retardation (IUGR) is reported.

ISSUES IN PREGNANT PV PATIENTS

- **Diagnosis of PV before conception:** the incidence of JAK2 V617F mutation in women with repeated pregnancy loss is less than 1%.[73] Although this is not supported by published evidence, patients with repeated pregnancy loss and patients with a history of unexplained thromboembolism could be considered for JAK2 V617F testing besides the usual screening for thrombophilia. An increase in haematocrit above the upper limits of normal during pregnancy is unusual and should raise the suspicion of PV.
- **Management of a PV patient willing to become pregnant:** optimal control of PV and primary prevention of cardiovascular disease as mentioned before in this paper is imperative. Counselling on pregnancy and maternal risk by a haematologist and an obstetrician with experience in high-risk pregnancies should be provided.[74]
- **Risk stratification:** all published guidelines suggest a different approach for low-risk and high-risk patients. The definition of low- and high-risk is based on expert opinion and differs between guidelines.[68-71] The same risk classification is applied for all MPN-subtypes during pregnancy (*Table 9*).
- **Management:** management is mainly based on expert opinion and various risk-based guidelines have been published by collaborative groups. The management is mainly directed at the prevention of thrombotic complications, balancing this against the risk of bleeding.
- *Management of low risk (pregnancy) patients:*
  - Timely discussion of the wish to become pregnant. Ideally, hydroxyurea or ruxolitinib should be stopped two to three months before. However, data from sickle cell patients suggest that the risk of teratogenic effect of hydroxyurea may be overestimated.[75,76]
  - Pre-conception meeting with obstetrician.
  - Low dose aspirin throughout pregnancy. LMWH from delivery up to six weeks postpartum. Replacement of aspirin by LMWH already starting two weeks before the estimated delivery date should be considered and discussed with the obstetrician.
  - Add phlebotomy to keep Hct under 45%. Counsel obstetricians and midwives not to routinely administer iron supplements.

- Foetal monitoring at 20 and 24 weeks with uterine artery doppler. Switch aspirin to LMWH when pulsatile index increases or IUGR is suspected.[77]
- Awareness of attending obstetrician, anaesthesiologist (concerning epidural anaesthesia) and midwives for increased bleeding risk at delivery and in the postpartum days. Advised interruption of LMWH: if prophylactic LMWH, twelve hours before labour; if therapeutic LMWH, 24 hours before labour.

- *Management of high risk patients: in addition to the management of low risk patients:*
  - LMWH throughout pregnancy. Evaluate individual bleeding risk and consider association of aspirin until two weeks before expected labour.
  - If cytoreduction is necessary (Hct > 45% despite frequent phlebotomies; thrombocytes > 1,000 x 10^9/L): interferon or pegylated interferon are the drugs of choice.[42] These drugs are not reimbursed in Belgium for the indication of PV.
  - Increase rate of foetal growth monitoring by a dedicated obstetrician.
  - Consider increase of anti-coagulation intensity when IUGR is detected.

PV PATIENTS AND SURGERY

There is an increased operative risk in polycythemia vera patients. Retrospective studies show this is associated to an increased incidence of both thrombotic complications and bleeding episodes. Data from a retrospective study show that the incidence in a mixed PV and ET-population is about 7% for both postoperative vascular occlusion (primarily deep vein thrombosis in PV) and major bleeding.[78] Guidance for the perioperative management of PV patients is based on expert opinion, in the absence of published guidelines. The approach to the individual patient must take into account the individual risk for thrombosis and bleeding. It is generally recommended to, whenever possible, delay surgery until there is a stable control of disease activity as described above: Hct levels strictly below 45%, leucocyte count below 15 x 10^9/L.

For minor surgery, not requiring interruption of aspirin, no additional measures are needed. For major surgery, prophylaxis with low molecular weight heparin (or a novel anticoagulant agent in orthopaedic surgery) is considered mandatory. Whether to continue aspirin prophylaxis in this setting should be an individualised decision, weighing the benefits of prophylaxis for arterial thrombosis against bleeding risk.

It is the responsibility of the haematologist to draw attention of surgeons and anaesthesiologists involved in perioperative and immediate postoperative care on the specificity of the situation. These health care professionals should be aware that despite adequate prophylaxis, patients with PV have an increased perioperative thrombotic risk compared to healthy patients or patients with other cancers receiving the same thromboprophylaxis. They should also be aware that thromboprophylaxis (although necessary for thrombosis prevention), paradoxically induces an increased perioperative bleeding risk in these patients.

DISCUSSION AND CONCLUSIONS

Over the last years, new insights in the pathophysiology, diagnosis and prognosis of polycythemia vera were acquired and novel therapeutic options are now available. These recommendations give an update of PV, taking into account the Belgian situation.

The first goal of PV management remains the reduction of thromboembolic events, as they are the main cause of mortality and morbidity. Although PV is considered to be a less aggressive pathology in the spectrum of haematological diseases, the overall survival is lower compared to the general population. Low dose aspirin should be given to all PV patients unless they have a contra-indication (*e.g.* bleeding tendency, allergy). For patients with a low risk of thrombosis, phlebotomies are necessary to keep the haematocrit below 45%. Iron supplements should be avoided. For high-risk PV patients (> 60 years old and/or previous thrombosis) cytoreductive therapy is indicated. Hydroxyurea remains the first-line cytoreductive treatment in PV. Cytoreductive therapy should also be taken into consideration for PV patients with leukocytosis or many cardiovascular risk factors.

More attention has been drawn to the quality of life of PV patients over the last years. Since May 2017, ruxolitinib is reimbursed in Belgium as second-line therapy in PV, for hydroxyurea resistant or intolerant PV patients. This has been a big step forward as there was no efficient second-line therapy and also because ruxolitinib strongly improves debilitating and sometimes unbearable symptoms (*e.g.* pruritus, night sweats, splenomegaly). We continue to deplore the non-reimbursement of interferon for PV patients in our country, especially for younger PV patients. Complete molecular remissions have been described in PV patients on interferon. To date, it remains unclear whether lowering the mutant JAK2 burden in PV patients will also translate into a better survival.

One of the most frustrating symptoms in PV, both for patients and doctors, is fatigue. PV patients do not look sick but often complain of tiredness. Consequently, they frequently feel misunderstood by their environment (family,

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Polycythemia Vera is characterised by elevated blood cell counts and the presence of a JAK 2 mutation.**
2. **Clinical manifestations are mainly thrombosis, bleeding, microcirculatory symptoms, splenomegaly, pruritus, fatigue and there is a risk of leukemic or fibrotic transformation over time.**
3. **The main goal of therapy in PV is to minimise the thrombotic risk with low-dose aspirin and phlebotomies (target haematocrit below 45%). In addition, high risk PV patients (age > 60 years or thrombosis history) are being treated with cytoreductive treatment. A curative treatment does not exist at this time.**
4. **Hydroxyurea is the first-line cytoreductive agent in PV. Ruxolitinib is the second-line treatment in case of hydroxurea resistance or intolerance. In Belgium, interferons are not reimbursed for the indication of PV.**

friends, and colleagues) and occasionally isolated. Through publications and MPN patient groups, there is now a better awareness of fatigue and the consequences on daily life activities for PV patients, even though there is still room for improvement.[54,55]

Indeed, to conclude, in PV there are still challenges remaining. The biggest one being the development of strategies that can cure or lower the risk of transformation to MF or AML, giving our PV patients better perspectives.

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