

Optimising the Use of Ruxolitinib in Inadequately Controlled Polycythaemia Vera

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Polycythaemia vera (PV) is an uncommon chronic myeloproliferative neoplasm characterised by increased red-cell mass. The condition is currently managed by phlebotomy and/or palliative cytoreductive therapy, most commonly using hydroxyurea (HU). However, around 25% of patients have an inadequate response and/or unacceptable adverse effects; furthermore, patients with resistance to HU appear to have shorter survival than other patients with PV. Recently, a second-line treatment has become available. Ruxolitinib, an oral inhibitor of the Janus kinase (JAK) 1 and JAK 2 tyrosine kinases, has recently received regulatory approval for the treatment of patients with PV who are resistant to or intolerant of HU. This treatment offers the potential to significantly reduce phlebotomy requirements and improve the symptom burden. However, in order to determine which patients will benefit most from ruxolitinib, it is necessary to identify those who are inadequate responders to HU, a definition that is not currently consensual in the literature. Five patient groups, for whom ruxolitinib may be a beneficial second-line treatment option, have been proposed. These comprise patients who are at high risk and retain a high symptom burden after HU, require frequent phlebotomy, have an elevated leukocyte count, are intolerant to HU or interferon, or have palpable splenomegaly.

Keywords

Myeloproliferative neoplasm, polycythaemia vera, ruxolitinib

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Polycythaemia vera (PV) is a chronic myeloproliferative neoplasm characterised by unregulated proliferation of red blood cells, and sometimes leukocytes and platelets in the absence of a recognisable physiological stimulus.^{1–4} Increased red blood cell mass leads to hyperviscosity of the blood and increased risk of thrombosis. In addition, patients may have a high symptom burden that includes intractable pruritus, fatigue and altered quality of life (QoL).^{5,6} If inadequately controlled, the condition can lead to serious complications including increased risk of cardiovascular events, together with the development of splenomegaly as the disease progresses.¹ The disease progresses slowly and is associated with a reduced life expectancy;³ the median survival of PV patients is 14.1 years,⁷ and is lower in patients who are resistant or intolerant to hydroxyurea (HU), as well as patients at high risk of thrombosis. In addition, PV may transform into acute myelogenous leukaemia (AML) in up to 15% of patients every 10 years^{7,9} or myelofibrosis (MF) in up to 10% of patients every 10 years.^{10–12}

PV is an uncommon but not so rare condition: its annual incidence is approximately 2.8 per 100,000 population of men and approximately 1.3 per 100,000 population of women. The prevalence of PV is approximately 22 cases per 100,000 people.³ The median age at presentation is in the sixth decade but one third of patients with PV are under 50 years of age.¹³

Despite advances in the treatment of PV, the symptom burden is often underestimated by physicians and is poorly managed, resulting in impaired QoL,¹⁴ restricted participation in social events and physical activity.⁵ Most therapies in PV appropriately aim to reduce thrombotic risk, which is the first cause of mortality and morbidity in the short term, but do not address PV symptoms. Recently, the Janus kinase (JAK) inhibitor ruxolitinib was approved for patients with PV who are intolerant to or resistant of HU, the most widely used first-line therapy for high-risk patients with PV. However, ruxolitinib is not commonly used in clinical practice¹⁵ and there is a need to identify patients who will derive the most benefit from this therapy and to define inadequately controlled PV. This article aims to examine what constitutes inadequate control in PV and explores current treatment strategies.

Current strategies for the management of polycythaemia vera

The primary aim of present PV therapy is not to eliminate disease, but to reduce the incidence of thrombotic events while minimising the risk of haematological transformation to AML or MF.¹⁶ Patients with PV are therefore treated according to their risk for thrombosis: patients aged <60 years and with no history of thrombosis are considered low risk while those age >60 years and/or with history of thrombosis are high risk (see *Table 1*).^{17–19} Some centres will also treat according

Table 1: Current treatment approaches to polycythaemia vera

Risk category	Treatment
Low-risk without extreme thrombocytosis (age <60 years and no thrombosis history)	Low-dose aspirin + phlebotomy
Low-risk with extreme thrombocytosis (platelets >1,000 x 10 ⁹ /L)	Low-dose aspirin provided ristocetin cofactor activity >30% + phlebotomy
High-risk (age ≥60 years and/or presence of thrombosis history)	Low-dose aspirin + phlebotomy + hydroxyurea
High-risk disease that is refractory or intolerant to hydroxyurea	Low-dose aspirin + phlebotomy + Interferon-α (age <65 years) or Busulfan (age ≥65 years)

Adapted from Terrefi, 2015.¹⁹

to symptoms when they have an impact on patient's life, i.e. itching, splenomegaly, fatigue etc. Low-risk patients are currently managed by phlebotomy and low-dose aspirin.¹⁹ Phlebotomy has been associated with increased survival in PV though with an increased thrombotic risk during the first three years of treatment.²⁰ However, phlebotomy has little impact on PV symptoms,²¹ and has recently been associated with an elevated risk of thrombosis.²² Among possible symptomatic treatments, paroxetine has been associated with relief of PV-associated pruritus, one of the most common symptoms of PV.²³

For high-risk patients, the currently proposed management includes cytoreductive therapy, most commonly using HU.¹⁶ The multicentre Cytoreductive therapy in Polycythemia Vera (CYTO-PV) trial established the threshold of 45% of haematocrit as the target of therapy in PV, achieved either with phlebotomy or cytoreductive drug. This study randomised 365 patients with PV to high-intensity treatment aimed at maintaining a low target haematocrit of <45% or to low intensity treatment with a higher target haematocrit of 45–50%. At a median follow-up of 31 weeks, the primary endpoint (death from cardiovascular causes or major thrombotic events) was reported in 2.7% in the low haematocrit group and 9.8% of the high haematocrit group (hazard ratio in the high haematocrit group, 3.91; 95% confidence interval [CI], 1.45 to 10.53; $p=0.007$).²⁴ In addition, an analysis of data from the CYTO-PV study and the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) study⁵ found that symptom burden was more severe in patients with haematocrits >45%. However, strict maintenance of a haematocrit below 45% was also associated with loss of concentration, insomnia, weight loss, night sweats, pruritus and significantly higher levels of fatigue, most likely a result of iron deficiency.²⁵

In addition to controversy regarding the treatment goals of cytoreductive therapy, concerns persist around the use of HU. Although recent retrospective studies or registry data have not found a link between HU use and leukaemic transformation,^{7,26} some study findings suggest that long-term HU treatment increases the risk of transformation to AML, leading to unease among both patients and haematologists.^{12,27–32} In addition, around 20 to 25% of patients have an inadequate response to HU or have unacceptable side effects at the doses required for haematocrit control.^{33,34} Dose titration of HU up to 2 g per day to achieve complete response is acknowledged under current recommendations¹⁶ and can improve the therapeutic response, but few patients can tolerate this dosage in clinical practice. Toxicities associated with HU include leukopenia, thrombocytopenia, painful leg ulcers, skin cancers, extensive dermatitis and fever.³⁵

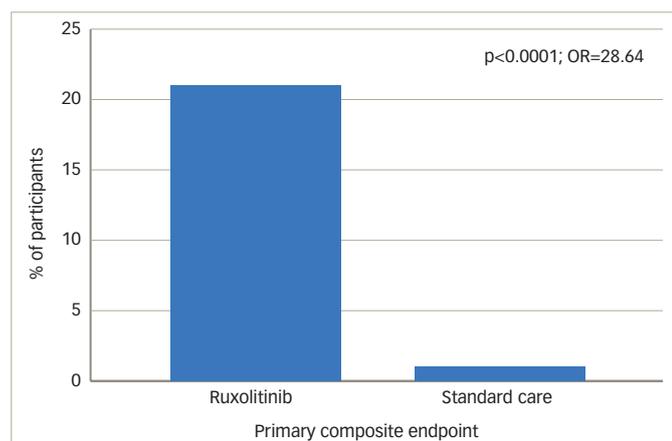
Resistance to HU was shown to be associated with disease transformation and reduced survival: compared with other patients with PV, patients with resistance to HU have a 5.6-fold increase in the risk of death.³⁴ However, therapeutic options for PV patients with resistance or intolerance to HU are limited, given that no drugs had approval in this particular setting, except pipobroman in few countries (France and Italy). As a result, many patients continue to receive HU despite an inadequate response or significant adverse effects. Clinical trials on the optimum treatment to improve survival of PV are difficult to perform because of the prolonged survival of patients with PV (typically one to two decades), necessitating an extended follow-up period in order to fully assess the benefits and risks associated with a therapeutic intervention. In addition, the rarity of the condition limits access to sufficient numbers of patients at individual treatment centres.²⁸

The use of interferon alpha (IFN-α) in the treatment of PV was first proposed in 1993.³⁶ IFN-α inhibits the growth of the abnormal clone in patients with myeloproliferative disorders, has a direct inhibiting effect on bone marrow fibroblast progenitor cells, and antagonises the action of platelet-derived growth factor, transforming growth factor-β, and other cytokines that may be involved in the development of MF.^{32,37} It can achieve molecular responses and is recommended by European LeukemiaNet (ELN) as possible first-line therapy for PV.¹⁶

Despite its proven clinical efficacy, the use of IFN-α has been limited by toxicity, and prolonged evaluation of IFN-α in PV is difficult due to high discontinuation rates.^{29,30} Lower doses of IFN have reduced the toxicity while maintaining efficacy.³⁸ Reduced administration frequency has also been associated with improved tolerability.³⁹ In addition, sustained-release preparations such as pegylated IFN-α 2a (Pegasys®, Genentech, California, US) and ropeg IFN-α 2b have been associated with excellent clinical activity and high rates of molecular response, in patients with PV.^{40–44} However, while pegylated forms are better tolerated than standard IFN-α, toxicity remains a problem: in an analysis of the long-term (median 42 months) use of peg-IFN-α in 103 patients with high-risk essential thrombocythemia, discontinuation was reported in 47% of patients. Of these, 59% discontinued due to toxicity.⁴⁵ In addition, IFN is less convenient to administer (by subcutaneous injection) than an orally available drug. The use of peg-IFN-α allows a weekly or twice-monthly (with ropeg IFN-α 2b) injection regimen, which is preferred by patients and can also be adjusted for a flexible dosing schedule, for example, when a patient is on holiday. In addition, since peg-IFN-α is not a cytotoxic therapy, patients typically have a more positive emotional response to treatment.

Although the ELN guidelines recommend using either HU or IFN (off label) as first-line therapy of high-risk PV,¹⁶ other experts proposed some limitations in the use of this drug. For example, Passamonti recommends peg-IFN-α in high-risk females with childbearing potential (but avoiding peg-IFN-α while pregnant); high-risk young patients who refuse HU because of the fear of evolution to leukaemia; and as second-line therapy after HU intolerance or resistance in high-risk young people.⁴⁶ However, others consider peg-IFN-α safe in pregnancy, highlighting the need for larger clinical studies of peg-IFN-α in PV. To date, efficacy and safety data on IFN is restricted to small cohort studies. Two randomised controlled studies are ongoing^{47,48} but no data are currently available. The treatment is not approved for PV and is not available for this indication in many European countries.

The only possible curative treatment for PV is allogeneic stem cell transplantation, and this can be effective in patients whose disease has

Figure 1: The RESPONSE trial – primary endpoint achieved by patients in the ruxolitinib versus standard care

OR = odds ratio; RESPONSE = Randomized Study of Efficacy and Safety in Polycythemia Vera with JAK Inhibitor INCB018424 versus Best Supportive Care. Adapted from Vannucchi et al., 2015.⁵³

undergone transformation to AML or MF. However, it does not represent a viable treatment option for the vast majority of patients in the chronic phase of the disease, due to the risk of complication.⁴⁹⁻⁵¹ In addition, most patients with PV are of advanced age and have comorbidities, further increasing the risk of transplant-related mortality.

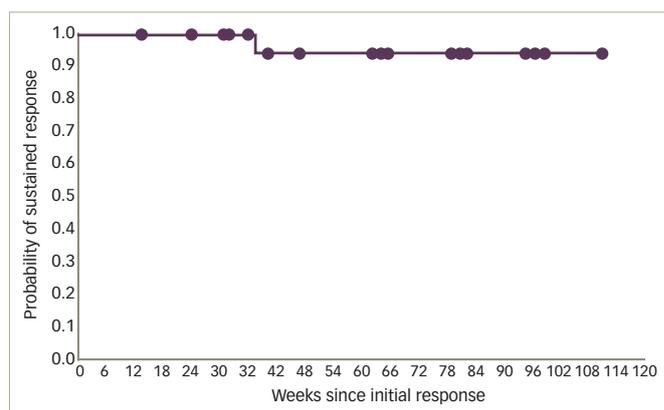
The ELN recommends IFN- α as second-line therapy of PV in patients intolerant or resistant to HU. Conversely, HU is recommended as the second-line therapy for patients who are intolerant or refractory to first-line therapy with IFN- α .¹⁶ The efficacy of IFN as second-line therapy in patients with PV who had an inadequate response to HU is unknown. In a recent clinical study, a subset of 13 HU intolerant or resistant patients received IFN: three achieved a complete haematologic response, four had haematocrit control, and none had a reduction of 35% or more in spleen size.^{52,53}

Pipobroman⁵⁴ and radioactive phosphorus (³²P)⁵⁵ are effective second-line options for patients with a short life expectancy, but they have been associated with a significant rate of transformation to acute leukaemia or myelodysplastic syndrome, so their use should be avoided in younger patients.^{7,12,26} Busulfan (Myleran®, GlaxoSmithKline, Brentford, UK) can be very effective in elderly patients,⁵⁶ especially if the patient has concerns regarding medication; a maintenance dose (5–10-day course of 4 mg/day) may be administered weekly. The drug is well tolerated,⁵⁷ and can also be given as a pulse dose for 5–10 days when the platelet count rises over desired range. In some cases it may only require an average of four pulses a year. While some studies suggest that busulfan is associated with a significant rate of leukaemic transformations,^{26,56} a large (n=1,545) study found no such association.⁷ However, busulfan is clearly mutagenic and carcinogenic, as reported in the summary of product characteristics of this drug.

Other novel therapies, including histone deacetylase inhibitors⁵⁸⁻⁶⁰ and heat-shock protein-90 inhibitors,⁶¹ are currently being investigated in PV.

Ruxolitinib, a new second-line therapy for the treatment of polycythaemia vera

Ruxolitinib (Jakavi®, Novartis Oncology, known as Jakafi® and marketed by Incyte Corporation in the US) is an inhibitor of JAK1 and JAK2, which are non-receptor tyrosine kinases, approved for several years for the treatment of MF.⁶² Approximately 96% of PV patients have a mutation of

Figure 2: Duration of primary response of ruxolitinib in the RESPONSE trial

RESPONSE = Randomized Study of Efficacy and Safety in Polycythemia Vera with JAK Inhibitor INCB018424 versus Best Supportive Care. Adapted from Vannucchi et al., 2015.⁵²

the JAK2 gene (JAKV617F),^{63,64} which is involved in intracellular signalling of cytokine receptors, including the receptor of erythropoietin. This mutation causes constitutive activation of the kinase and hyperactivity of the JAK-STAT pathway, resulting in uncontrolled growth of blood cells. Ruxolitinib is administered orally at a starting dose of 10 mg twice daily in PV.⁶⁵

In a phase II study, ruxolitinib was associated with rapid and sustained improvements in PV symptoms.⁶⁵ Following these findings, the Randomized Study of Efficacy and Safety in Polycythemia Vera with JAK Inhibitor INCB018424 versus Best Supportive Care (RESPONSE) trial was initiated.⁵² This phase III study randomised patients (n=222, with splenomegaly and needed phlebotomy for adequate haematocrit control) to ruxolitinib (n=110) or best available therapy (n=112). At week 32, patients were given the option to cross over to ruxolitinib if the primary end point was not met or could switch later in the case of disease progression. Among patients assigned to standard care, 96 (85.7%) crossed over to ruxolitinib at or after week 32. At week 32, the proportion of patients who achieved the primary composite end point (haematocrit control and a reduction of 35% or more in spleen volume from baseline) was significantly higher among patients in the ruxolitinib group than in the standard-therapy group (20.9% versus 0.9%, $p < 0.001$; see Figure 1), with 77% of patients meeting at least one component of the composite endpoint. A complete haematologic remission occurred in 24% of patients in the ruxolitinib group versus 9% of those in the standard-therapy group ($p = 0.003$). In addition, a reduction of at least 50% in the in the MPN-SAF at week 32 was reported in 49% of the ruxolitinib group versus 5% of those receiving standard care.⁵²

Ruxolitinib was generally well tolerated: grade 3 or 4 anaemia occurred in 2% of patients taking ruxolitinib versus 0% receiving standard care, grade 3 or 4 thrombocytopenia occurred in 5% versus 4%, and grade 1–3 Herpes zoster infection in 6% versus 0%. Four patients in the ruxolitinib group and two patients in the standard-therapy group had newly diagnosed non-melanoma skin cancer (basal-cell or squamous-cell carcinoma); all but one patient (in the standard-therapy group) had a history of non-melanoma skin cancer or precancerous skin lesions. Only one thrombotic event was observed in patients receiving ruxolitinib versus six events in the standard care group. Although not powered to determine the significance of this endpoint, this was an interesting finding that should be explored in further studies. At the study end, MF developed in three patients receiving ruxolitinib, and one patient had received a diagnosis of AML. In the standard

Table 2: European LeukemiaNet definition of response in patients with polycythaemia vera

Response category	Criteria (all must be present)
Complete response	Durable* resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement† Durable* peripheral blood count remission, defined as Ht lower than 45% without phlebotomies; platelet count $\leq 400 \times 10^9/L$, WBC count $< 10 \times 10^9/L$ Without progressive disease, and absence of any haemorrhagic or thrombotic event Bone marrow histological remission defined as the presence of age-adjusted normocellularity and disappearance of trilinear hyperplasia, and absence of >grade 1 reticulin fibrosis
Partial response	Durable* resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement† Durable* peripheral blood count remission, defined as Ht lower than 45% without phlebotomies; platelet count $\leq 400 \times 10^9/L$, WBC count $< 10 \times 10^9/L$ Without progressive disease, and absence of any haemorrhagic or thrombotic event Without bone marrow histological remission defined as persistence of trilinear hyperplasia
No response	Any response that does not satisfy partial response
Progressive disease	Transformation into post-PV MF, myelodysplastic syndrome or acute leukaemia

MF = myelofibrosis; PV = polycythaemia vera; WBC = white blood cell. *Lasting at least 12 weeks; †Large symptom improvement (≥ 10 -point decrease) in Myeloproliferative Neoplasm Symptom Assessment form total symptom score. Adapted from Baroso et al., 2013.⁸⁸

therapy group, MF developed in one patient assigned to standard therapy. These rates of transformation were consistent with those expected in a high-risk population of patients with PV.⁵²

As a result of these data, ruxolitinib received approval from the European Medicines Agency⁶⁶ and the US Food and Drug Administration⁶⁷ for PV patients who have an inadequate response to, or cannot tolerate HU. Follow-up data indicate that ruxolitinib responses are durable and the treatment is well tolerated, with 83% of patients still receiving treatment at a median 111 weeks.⁶⁸ Since not all patients present with splenomegaly, ruxolitinib is also being investigated in the RESPONSE 2 study, which includes PV patients with a non-palpable spleen.⁶⁹ Recently released data showed that ruxolitinib achieved haematocrit control in 62% of patients compared with 19% receiving best available therapy ($p < 0.0001$).⁶⁹ In addition, the ongoing Randomized Switch Study from Hydroxyurea to Ruxolitinib for RELIEF of Polycythemia Vera Symptoms (RELIEF) study is investigating the effect of a switch from HU to ruxolitinib for the relief of PV symptoms.⁷⁰

Several other JAK inhibitors have been evaluated in clinical trials for PV, including momelotinib,⁷¹ pacritinib⁷² and fedratinib.⁷³ However, the development of fedratinib has been discontinued, and the programme of pacritinib is currently on hold, waiting for more detailed safety results of phase III studies.

Definition of patients with inadequately controlled polycythaemia vera

A recent prospective study ($n=1,334$), including a mixture of patients with current and prior therapy use, found the presence of prior HU use, the need for phlebotomy or palpable splenomegaly was associated with

an unacceptably high symptom burden, regardless of PV risk category. Patients with all three features had the highest symptom burden.⁷⁴ The authors suggested that patients with PV who had any of these three features might benefit from ruxolitinib treatment.

Response to PV therapy is currently defined according to ELN criteria (see Table 2). We propose that the definition of inadequate response to first-line therapies could be further refined to incorporate five patient types who do not have an adequate response to HU and may benefit from ruxolitinib treatment.

Patients with a high symptom burden after taking hydroxyurea

Symptom burden can remain high despite treatment with HU. In a 2007 internet survey of 405 patients with PV who were receiving standard treatments, symptoms included: fatigue (85%), pruritus (65%), night sweats (49%), bone pain (43%), fevers (13%), undesired weight loss (10%) and spleen pain (4%). All of these had a significant negative impact on patients' overall QoL and ability to work.⁶ A study of patients with myeloproliferative neoplasms ($n=1,470$) found that distinct clustering of symptom burden exists within PV with significant heterogeneity of symptoms and with significant symptom burdens among all risk categories. The MPN-SAF total symptom score (MPN-SAF TSS; MPN-10) is a well-validated instrument for the evaluation of the symptom burden that should be used to better identify patients in need of therapy.

Patients who require frequent phlebotomy

In the RESPONSE study, phlebotomy dependence was defined as two or more phlebotomies within 24 weeks prior to screening and at least one within 16 weeks before screening.⁵² While therapeutic phlebotomy has become the mainstay of treatment, it has limitations. Patients may be intolerant or have a low acceptance, and it may be difficult to gain peripheral vein access.⁷⁵ In addition, phlebotomy can cause physical and psychological distress if venous access is difficult, and not all patients can tolerate venesections – many feel quite unwell afterwards or require intravenous fluid replacement.

Phlebotomy has been associated with complications, including reactive thrombocytosis during the first three months of treatment.²⁰ Venesections may also be inconvenient in terms of taking time out of work, the need for hospital visits as well as the potential for bruising and scarring from frequent phlebotomy. Furthermore, the need for repeated phlebotomy can lead to iron deficiency, symptoms of which include restless leg syndrome⁷⁶ and anxiety,⁷⁷ and can further induce an increase in platelet counts. Repeated phlebotomies under HU therapy have also been associated with an increased risk of thrombosis.²²

Patients with elevated leukocyte count

Leukocyte activation has been associated with activation of endothelial cells and pro-coagulant responses at sites of vascular injury,⁷⁸ as well as being associated with thrombosis and major haemorrhage in other myeloproliferative neoplasms.⁷⁹ In addition, leucocytosis is associated with decreased overall survival in PV.⁷ In the CYTO-PV study, the platelet count was not significantly different between treatment arms, but the leukocyte (WBC) count was significantly higher in the high-haematocrit group.²⁴ These data highlight the importance of leukocyte count in identifying inadequate response in PV. A sub-analysis of the CYTO-PV study showed that the risk of thrombosis was increased at WBC count $> 7 \times 10^9/L$, which became statistically significant when the WBC count exceeded $11 \times 10^9/L$, and suggested that this should be taken into

account when evaluating response to therapy in PV.⁸⁰ Elevated platelet counts may also be an indicator of inadequately controlled PV.

Intolerance to hydroxyurea or interferon

Clinical data suggest that up to 20% of patients develop toxicities to HU, including painful leg ulcers, skin cancers, extensive dermatitis, hyperpigmentation, alopecia, fever and significant fatigue,^{35,81,82} which may necessitate dose reduction or drug discontinuation. A recent study of 890 patients with PV identified resistance/intolerance to HC was recorded in 15.4% of patients. This consisted of: need for phlebotomies (3.3%), uncontrolled myeloproliferation (1.6%), failure to reduce massive splenomegaly (0.8%), development of cytopenia at the lowest dose of HC to achieve a response (1.7%) and extra-haematological toxicity (9%). Cytopenia was also associated with a risk of transformation to MF and acute leukaemia.⁸³ IFN treatment, currently mostly using pegylated forms, has well-defined contra-indications and is associated with toxicities including exacerbation of autoimmune disorders, depression, neuropathy, hyperthyroidism, heart and ocular disease, leading to permanent discontinuation in about 25% of patients.^{40–44,84}

Symptomatic splenomegaly

Another burdensome symptom is symptomatic splenomegaly. Palpable splenomegaly has been reported in up to 40% of patients with PV^{85,87} and can lead to severe splenomegaly, with symptoms including early satiety, bloating, pain, portal hypertension, weight loss and exacerbation of cytopenias.⁴ Severe splenomegaly at diagnosis is also associated with decreased survival in PV.⁸⁵ Real-world data on the use of ruxolitinib in patients with lower-risk MF suggest that ruxolitinib is well tolerated and is associated with marked reduction in splenomegaly.⁸⁶

Summary and concluding remarks

Despite advances in treatment, the symptom burden of patients with PV remains high and is often underestimated by physicians focusing on vascular events. The traditional stratification of patients as ‘high-risk’ and ‘low-risk’ has limitations, and in order to optimise outcomes, it is necessary to redefine inadequate response to treatment. Certain groups of patients with PV may be considered inadequate responders to HU. These include high-risk patients who retain a high symptom burden after HU, require frequent phlebotomy, have an elevated leukocyte count, are intolerant to HU or IFN- α , or have symptomatic splenomegaly. For patients with these factors, ruxolitinib may be a beneficial second-line treatment option, and such expanded indications for the use of ruxolitinib could reduce the symptom burden and improve the QoL of many PV patients.

The most important safety concern of younger patients with PV is the potential for transformation into AML or MF. Evidence to date suggests that ruxolitinib is not associated with these risks, but there is a need for further data, including larger clinical trials and real-world data, to assess the long-term risk. The availability of ruxolitinib has raised the hypothesis that disease elimination may be possible in future by combining a JAK inhibitor and a low dose of IFN; a recent case report shows a rapid decline in the JAK2V617F allele burden following combination therapy, an impressive finding that warrants further investigation.⁸⁷ In conclusion, the development of ruxolitinib represents a major breakthrough for patients with PV as it has the potential to reduce disease burden and substantially improve QoL in many patients with inadequately controlled PV for whom effective treatment opportunities have been limited. □

- Tefferi A, Vardiman JW. Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms. *Leukemia*, 2008;22:14–22.
- Spivak JL. Polycythemia vera: myths, mechanisms, and management. *Blood*, 2002;100:4272–90.
- Leukemia and Lymphoma Society. Polycythemia Vera Facts, FS13, revised April 2015. Available at: www.lls.org/sites/default/files/file_assets/FS13_PolycythemiaVera_FactSheet_final5.1.15.pdf (accessed 4 December 2015).
- Cassinat B, Laguillier C, Gardin C, et al., Classification of myeloproliferative disorders in the JAK2 era: is there a role for red cell mass? *Leukemia*, 2008;22:452–3.
- Scherber R, Dueck AC, Johansson P, et al., The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): international prospective validation and reliability trial in 402 patients. *Blood*, 2011;118:401–8.
- Mesa RA, Niblack J, Wadleigh M, et al., The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international Internet-based survey of 1179 MPD patients. *Cancer*, 2007;109:68–76.
- Tefferi A, Rumi E, Finazzi G, et al., Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. *Leukemia*, 2013;27:1874–81.
- Hernandez-Boluda JC, Alvarez-Larran A, Gomez M, et al., Clinical evaluation of the European LeukemiaNet criteria for clinicohaematological response and resistance/intolerance to hydroxycarbamide in essential thrombocythaemia. *Br J Haematol*, 2011;152:81–8.
- Finazzi G, Caruso V, Marchioli R, et al., Acute leukemia in polycythemia vera: an analysis of 1638 patients enrolled in a prospective observational study. *Blood*, 2005;105:2664–70.
- Passamonti F, Rumi E, Pungolino E, et al., Life expectancy and prognostic factors for survival in patients with polycythemia vera and essential thrombocythaemia. *Am J Med*, 2004;117:755–61.
- Barosi G, Mesa RA, Thiele J, et al., Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythaemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. *Leukemia*, 2008;22:437–8.
- Kiladjian JJ, Chevret S, Dosquet C, et al., Treatment of polycythemia vera with hydroxyurea and pipobroman: final results of a randomized trial initiated in 1980. *J Clin Oncol*, 2011;29:3907–13.
- Passamonti F, Malabarba L, Orlandi E, et al., Polycythemia vera in young patients: a study on the long-term risk of thrombosis, myelofibrosis and leukemia. *Haematologica*, 2003;88:13–8.
- Abelsson J, Andreasson B, Samuelsson J, et al., Patients with polycythemia vera have worst impairment of quality of life among patients with newly diagnosed myeloproliferative neoplasms. *Leuk Lymphoma*, 2013;54:2226–30.
- Tefferi A, Barbui T. Essential Thrombocythemia and Polycythemia Vera: Focus on Clinical Practice. *Mayo Clin Proc*, 2015;90:1283–93.
- Barbui T, Barosi G, Birgegard G, et al., Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol*, 2011;29:761–70.
- Finazzi G, Barbui T. Evidence and expertise in the management of polycythemia vera and essential thrombocythemia. *Leukemia*, 2008;22:1494–502.
- Vannucchi AM, Barbui T, Cervantes F, et al., Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 2015;26 Suppl 5:v85–99.
- Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2015 update on diagnosis, risk-stratification and management. *Am J Hematol*, 2015;90:162–73.
- Berk PD, Goldberg JD, Donovan PB, et al., Therapeutic recommendations in polycythemia vera based on Polycythemia Vera Study Group protocols. *Semin Hematol*, 1986;23:132–43.
- Landolfi R, Marchioli R, Kutti J, et al., Efficacy and safety of low-dose aspirin in polycythemia vera. *N Engl J Med*, 2004;350:114–24.
- Alvarez-Larrán A, Pérez-Encinas M, Ferrer-Marín F. Risk of thrombosis according to need of phlebotomies in patients with polycythemia vera treated with hydroxyurea. *Haematologica*, 2016.152769 [Epub ahead of print].
- Tefferi A, Fonseca R. Selective serotonin reuptake inhibitors are effective in the treatment of polycythemia vera-associated pruritus. *Blood*, 2002;99:2627.
- Marchioli R, Finazzi G, Specchia G, et al., Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med*, 2013;368:22–33.
- Emanuel R, Marchioli R, Dueck A, et al., Impact of hematocrit on symptom burden among polycythemia vera patients. European Hematology Association Annual Meeting Abstracts. p 276. (EHA18ABSSUB-4343), 2013.
- Bjorkholm M, Derolf AR, Hultcrantz M, et al., Treatment-related risk factors for transformation to acute myeloid leukemia and myelodysplastic syndromes in myeloproliferative neoplasms. *J Clin Oncol*, 2011;29:2410–5.
- Fruchtman SM, Mack K, Kaplan ME, et al., From efficacy to safety: a Polycythemia Vera Study group report on hydroxyurea in patients with polycythemia vera. *Semin Hematol*, 1997;34:17–23.
- Mascarenhas J, Mesa R, Prchal J, et al., Optimal therapy for polycythemia vera and essential thrombocythemia can only be determined by the completion of randomized clinical trials. *Haematologica*, 2014;99:945–9.
- Weinfeld A, Swolin B, Westin J. Acute leukaemia after hydroxyurea therapy in polycythemia vera and allied disorders: prospective study of efficacy and leukaemogenicity with therapeutic implications. *Eur J Haematol*, 1994;52:134–9.
- Tatarsky I, Sharon R. Management of polycythemia vera with hydroxyurea. *Semin Hematol*, 1997;34:24–8.
- Kiladjian JJ, Rain JD, Bernard JF, et al., Long-term incidence of hematological evolution in three French prospective studies of hydroxyurea and pipobroman in polycythemia vera and essential thrombocythemia. *Semin Thromb Hemost*, 2006;32:417–21.
- Kiladjian JJ, Giraudier S, Cassinat B. Interferon-alpha for the therapy of myeloproliferative neoplasms: targeting the malignant clone. *Leukemia*, 2016;30:776–81.
- Barosi G, Birgegard G, Finazzi G, et al., A unified definition of clinical resistance and intolerance to hydroxycarbamide in polycythemia vera and primary myelofibrosis: results of a European LeukemiaNet (ELN) consensus process. *Br J Haematol*, 2010;148:961–3.
- Alvarez-Larran A, Pereira A, Cervantes F, et al., Assessment and prognostic value of the European LeukemiaNet criteria for clinicohaematological response, resistance, and intolerance to hydroxyurea in polycythemia vera. *Blood*, 2012;119:1363–9.
- Antonelli E, Guglielmelli P, Pieri L, et al., Hydroxyurea-related toxicity in 3,411 patients with Ph⁻negative MPN. *Am J Hematol*, 2012;87:552–4.
- Silver RT. Interferon-alpha 2b: a new treatment for polycythemia vera. *Ann Intern Med*, 1993;119:1091–2.
- Kiladjian JJ, Mesa RA, Hoffman R. The renaissance of interferon therapy for the treatment of myeloid malignancies. *Blood*, 2011;117:4706–15.
- Silver RT, Kiladjian JJ, Hasselbalch HC. Interferon and the treatment of polycythemia vera, essential thrombocythemia and myelofibrosis. *Expert Rev Hematol*, 2013;6:49–58.
- Gisslinger H, Buxhofer-Ausch V, Thaler J, et al., Switch from Every Two Weeks to Every Four Weeks Administration Schedule of AOP2014, an Innovative Pegylated Interferon Alpha, in Polycythemia Vera Patients Allows Maintaining of Efficacy with Improved Toxicity Profile in Phase I/II Study Presented at the 56th ASH Annual Meeting and Exposition, December 6–9, 2014, San Francisco, CA, abstract 3177, 2014.
- Gisslinger H, Zagrijtschuk O, Buxhofer-Ausch V, et al., Ropeninterferon alfa-2b, a novel IFNalpha-2b, induces high response rates with low toxicity in patients with polycythemia vera. *Blood*, 2015;126:1762–9.
- Quintas-Cardama A, Kantarjian H, Manshouri T, et al., Pegylated interferon alfa-2a yields high rates of hematologic and molecular response in patients with advanced essential thrombocythemia and polycythemia vera. *J Clin Oncol*, 2009;27:5418–24.
- Kiladjian JJ, Cassinat B, Chevret S, et al., Pegylated interferon- α -2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. *Blood*, 2008;112:3065–72.
- Quintas-Cardama A, Abdel-Wahab O, Manshouri T, et al., Molecular analysis of patients with polycythemia vera or

- essential thrombocythemia receiving pegylated interferon alpha-2a, *Blood*, 2013;122:893-901.
44. Lu M, Zhang W, Li Y, et al., Interferon- α targets JAK2V617F-positive hematopoietic progenitor cells and acts through the p38 MAPK pathway, *Exp Hematol*, 2010;38:472-80.
 45. Roy L, Ianotto JC, Guilhot J, et al., Long Term Efficacy and Tolerance of Pegylated Interferon Alpha Therapy for Patients with High Risk Essential Thrombocythemia: An Observational Study of the French Intergroup of Myeloproliferative Disorders (FIM) Presented at the 56th ASH Annual Meeting and Exposition, December 6-9, 2014, San Francisco, CA; Abstract 1845, 2014.
 46. Passamonti F, How I treat polycythemia vera, *Blood*, 2012;120:275-84.
 47. Clinicaltrials.gov, Randomized Trial of Pegylated Interferon Alfa-2a Versus Hydroxyurea in Polycythemia Vera (PV) and Essential Thrombocythemia (ET). Available at: <https://clinicaltrials.gov/ct2/show/NCT01259856>; Accessed 4 December 2015.
 48. NCT01949805, Pegylated Interferon Alpha-2b Versus Hydroxyurea in Polycythemia Vera (PROUD-PV). Available at: <https://clinicaltrials.gov/ct2/show/NCT01949805> Accessed 27 June 2016.
 49. Kerbauy DM, Gooley TA, Sale GE, et al., Hematopoietic cell transplantation as curative therapy for idiopathic myelofibrosis, advanced polycythemia vera, and essential thrombocythemia, *Biol Blood Marrow Transplant*, 2007;13:355-65.
 50. Ballen KK, Woolfrey AE, Zhu X, et al., Allogeneic hematopoietic cell transplantation for advanced polycythemia vera and essential thrombocythemia, *Biol Blood Marrow Transplant*, 2012;18:1446-54.
 51. Lussana F, Rambaldi A, Finazzi MC, et al., Allogeneic hematopoietic stem cell transplantation in patients with polycythemia vera or essential thrombocythemia transformed to myelofibrosis or acute myeloid leukemia: a report from the MPN Subcommittee of the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation, *Haematologica*, 2014;99:916-21.
 52. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al., Ruxolitinib versus standard therapy for the treatment of polycythemia vera, *N Engl J Med*, 2015;372:426-35.
 53. Vannucchi AM, Ruxolitinib versus standard therapy for the treatment of polycythemia vera, *N Engl J Med*, 2015;372:1670-1.
 54. Kiladjian JJ, Gardin C, Renoux M, et al., Long-term outcomes of polycythemia vera patients treated with pipobroman as initial therapy, *Hematol J*, 2003;4:198-207.
 55. Berlin NI, Treatment of the myeloproliferative disorders with 32P, *Eur J Haematol*, 2000;65:1-7.
 56. Alvarez-Larran A, Martinez-Aviles L, Hernandez-Boluda JC, et al., Busulfan in patients with polycythemia vera or essential thrombocythemia refractory or intolerant to hydroxyurea, *Ann Hematol*, 2014;93:2037-43.
 57. Vannucchi AM, How I treat polycythemia vera, *Blood*, 2014;124:3212-20.
 58. Rambaldi A, Dellacasa CM, Finazzi G, et al., A pilot study of the Histone-Deacetylase inhibitor Givinostat in patients with JAK2V617F positive chronic myeloproliferative neoplasms, *Br J Haematol*, 2010;150:446-55.
 59. Finazzi G, Vannucchi AM, Martinelli V, et al., A phase II study of Givinostat in combination with hydroxycarbamide in patients with polycythemia vera unresponsive to hydroxycarbamide monotherapy, *Br J Haematol*, 2013;161:688-94.
 60. Andersen CL, McMullin MF, Ejerblad E, et al., A phase II study of vorinostat (MK-0683) in patients with polycythemia vera and essential thrombocythemia, *Br J Haematol*, 2013;162:498-508.
 61. Kucine N, Marubayashi S, Bhagwat N, et al., Tumor-specific HSP90 inhibition as a therapeutic approach in JAK-mutant acute lymphoblastic leukemias, *Blood*, 2015;126:2479-83.
 62. Harrison C, Kiladjian JJ, Al-Ali HK, et al., JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis, *N Engl J Med*, 2012;366:787-98.
 63. Passamonti F, Maffioli M, Caramazza D, et al., Myeloproliferative neoplasms: from JAK2 mutations discovery to JAK2 inhibitor therapies, *Oncotarget*, 2011;2:485-90.
 64. Rampal R, Al-Shahrour F, Abdel-Wahab O, et al., Integrated genomic analysis illustrates the central role of JAK-STAT pathway activation in myeloproliferative neoplasm pathogenesis, *Blood*, 2014;123:e123-33.
 65. Verstovsek S, Passamonti F, Rambaldi A, et al., A phase 2 study of ruxolitinib, an oral JAK1 and JAK2 inhibitor, in patients with advanced polycythemia vera who are refractory or intolerant to hydroxyurea, *Cancer*, 2014;120:513-20.
 66. EMA, Jakavi. Available at: www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002464/human_med_001568.jsp&mid=WC0b01ac058001d124; (accessed 3 December 2015).
 67. FDA, FDA News Release: FDA approves Jakafi to treat patients with a chronic type of bone marrow disease, December 4, 2014. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm425677.htm (accessed 4 December 2015).
 68. Verstovsek S, Vannucchi AM, Griesshammer M, et al., Ruxolitinib in polycythemia vera: Follow-up from the RESPONSE trial., *J Clin Oncol*, 2015;33 (suppl); abstr 7087.
 69. Passamonti F, Griesshammer M, Palandri F, et al., Ruxolitinib proves superior to best available therapy in patients with polycythemia vera (PV) and a nonpalpable spleen: Results from the Phase IIIb RESPONSE-2 Study. Abstract #S112. 21st Congress of the European Hematology Association (EHA), Copenhagen, Denmark, 2016.
 70. Mesa R., Vannucchi AM, Yacoub A, et al., The efficacy and safety of continued hydroxyurea therapy versus switching to ruxolitinib in patients with polycythemia vera: A randomized, double-blind, double-dummy, symptom study (RELIEF). Presented at the American Society of Hematology Annual Meeting, December 6-9, 2014, San Francisco, CA. Abstract no 3168.
 71. NCT02124746, Long-term Safety and Efficacy of Momelotinib in Subjects With Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, Post-essential Thrombocythemia Myelofibrosis, Polycythemia Vera or Essential Thrombocythemia. Available at: <https://clinicaltrials.gov/ct2/show/NCT02124746> (accessed 2 February 2016).
 72. Komrokji R, Wadleigh M, Seymour J, et al., Results of a phase 2 study of pacritinib (SB1518), a novel oral JAK2 inhibitor, in patients with primary, post-polycythemia vera, and post-essential thrombocythemia myelofibrosis, *ASH Annual Meeting Abstracts* 118: 282, 2011.
 73. Pardanani A, Harrison C, Cortes JE, et al., Safety and Efficacy of Fedratinib in Patients With Primary or Secondary Myelofibrosis: A Randomized Clinical Trial, *JAMA Oncol*, 2015;1:643-51.
 74. Geyer H, Scherber R, Kosiorek H, et al., Symptomatic Profiles of Patients With Polycythemia Vera: Implications of Inadequately Controlled Disease, *J Clin Oncol*, 2016;34:151-9.
 75. Assi TB, Baz E, Current applications of therapeutic phlebotomy, *Blood Transfus*, 2014;12 Suppl 1:s75-83.
 76. Tobianson M, Alyass B, Soderlund S, et al., High prevalence of restless legs syndrome among patients with polycythemia vera treated with venesection, *Med Oncol*, 2010;27:105-7.
 77. Kim J, Wessling-Resnick M, Iron and mechanisms of emotional behavior, *J Nutr Biochem*, 2014;25:1101-7.
 78. Falanga A, Marchetti M, Evangelista V, et al., Polymorphonuclear leukocyte activation and hemostasis in patients with essential thrombocythemia and polycythemia vera, *Blood*, 2000;96:4261-6.
 79. Campbell PJ, MacLean C, Beer PA, et al., Correlation of blood counts with vascular complications in essential thrombocythemia: analysis of the prospective PT1 cohort, *Blood*, 2012;120:1409-11.
 80. Barbui T, Masciulli A, Marfisi MR, et al., White blood cell counts and thrombosis in polycythemia vera: a subanalysis of the CYTO-PV study, *Blood*, 2015;126:560-1.
 81. Harrison CN, Campbell PJ, Buck G, et al., Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia, *N Engl J Med*, 2005;353:33-45.
 82. Gisslinger H, Gotic M, Holowiecki J, et al., Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHDRET Study, a randomized controlled trial, *Blood*, 2013;121:1720-8.
 83. Alvarez-Larran A, Kerguelen A, Hernandez-Boluda JC, et al., Frequency and prognostic value of resistance/intolerance to hydroxycarbamide in 890 patients with polycythemia vera, *Br J Haematol*, 2016;172:786-93.
 84. Kiladjian JJ, Chomienne C, Fenaux P, Interferon- α therapy in bcr-abl-negative myeloproliferative neoplasms, *Leukemia*, 2008;22:1990-8.
 85. Abdulkarim K, Ridell B, Johansson P, et al., The impact of peripheral blood values and bone marrow findings on prognosis for patients with essential thrombocythemia and polycythemia vera, *Eur J Haematol*, 2011;86:148-55.
 86. Davis KL, Cote I, Kaye JA, et al., Real-World Assessment of Clinical Outcomes in Patients with Lower-Risk Myelofibrosis Receiving Treatment with Ruxolitinib, *Adv Hematol*, 2015;2015:848473.
 87. Bjorn ME, de Stricker K, Kjaer L, et al., Combination therapy with interferon and JAK1-2 inhibitor is feasible: Proof of concept with rapid reduction in JAK2V617F-allele burden in polycythemia vera, *Leuk Res Rep*, 2014;3:73-5.
 88. Barosi G, Mesa R, Finazzi G, et al., Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project, *Blood*, 2013;121:4778-81.