Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2015 June ; 15(0): S27–S33. doi:10.1016/j.clml.2015.02.013.

New therapeutic approaches in PV

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Abstract

Polycythemia vera (PV) is one of the three Philadelphia-negative myeloproliferative neoplasms. Clinically, PV is an indolent disease but its course can be complicated by arterial and venous vascular accidents, evolution to myelofibrosis or leukemic transformation. Treatment of PV is, therefore, aimed at preventing such acute complications. The cornerstone of therapy of low-risk patients remains strict control of cardiovascular risk factors, the use of phlebotomy and low dose aspirin. Higher risk patients should also receive cytoreductive treatments. Hydroxyurea and interferon- α represent standard first-line options for newly diagnosed high-risk PV patients. Recommendations for patients who fail these therapies are less clearly defined. The discovery of a mutation in the Janus kinase 2 gene (V617F) in almost all cases of PV has prompted the development of molecularly targeted agents for the treatment of these patients. In this review we will discuss key clinical aspects, the current therapeutic armamentarium and data on the use of novel agents in patients with PV.

Keywords

polycythemia vera; hydroxyurea; interferon; *JAK2*; ruxolitinib

Introduction

Polycythemia vera (PV) is one of three Philadelphia-negative myeloproliferative neoplasms (MPNs) which also include essential thrombocythemia (ET) and primary myelofibrosis (PMF). These disorders arise from the clonal proliferation of an aberrant hematopoietic stem cell and are characterized by distinct clinical phenotypes.¹ The clinical course of PV is indolent but can be complicated by thrombotic events and evolution into myelofibrosis and/or acute leukemia.² The treatment of PV is currently focused on decreasing thrombotic risk associated with the disease and preventing acute complications. Almost a decade ago a mutation in the Janus kinase (*JAK*)2 gene (V617F) was found to be present in about 95% of patients with PV and over half of those with ET and PMF.^{3,4} The *JAK2*V617F mutation and the rare *JAK2* exon 12 mutations play a central role in the pathogenesis of PV.⁵ Its discovery

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L.F. and **K.J.N.** have no conflict of interest to declare.

has opened new avenues of research and led to the development of targeted therapies, such as ruxolitinib, a JAK inhibitor presently approved as therapy for patients with MF.^{6,7} In this review we will discuss key clinical aspects as well as current and novel therapeutic approaches to PV.

Epidemiology

PV can occur at any age, but its incidence peaks in the 5th to 7th decade of life. PV is more common in men than in women.⁸ The natural history of PV is variable, although the majority of reports suggest a shorter survival of PV patients compared to the general population.⁹⁻¹¹ In general, studies of the incidence and prevalence of MPNs, including PV, are hampered by the very indolent behavior of the disease. Many patients remain asymptomatic for long periods of time and thus do not seek medical attention, resulting in an underestimation of the true annual incidence of these disorders.

In recent literature-based reports, multiple studies of the incidence and prevalence of PV were collectively analyzed. The annual incidence rate of PV was 0.01-2.80 per 100,000 with a pooled incidence rate of 0.84 per 100,000 (95% CI: 0.70–1.01). European studies showed an incidence rate of 1.05 per 100,000 (95% CI: 1.03–1.07) compared to 0.94 per 100,000 (95% CI: 0.92–0.96) in North America. Crude annual incidence rates did not significantly differ between males (0.87 per 100,000, 95% CI: 0.58–1.30) and females (0.73 per 100,000, 95% CI: 0.46–1.15). An analysis of eight studies revealed a prevalence of PV ranging from 0.49 to 46.88 per 100,000.^{12,13}

Such an indolent clinical course, along with the requirement for indefinite therapy (most patients with PV need some form of therapy) translates into an ever expanding population of patients with PV in need of treatment.

Clinical burden

Although PV can remain clinically silent, associated symptoms are reported as debilitating by nearly 40% of patients. Clinical manifestations of the disease include constitutional symptoms (fatigue, pruritus, and night sweats), microvascular symptoms (headache, lightheadedness, acral paresthesias, erythromelalgia, atypical chest pain and pruritus),¹⁴ and macrovascular complications (thrombosis, stroke or heart attacks).¹⁵ Symptom assessment tools, such as the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)¹⁶ or the abbreviated version, the MPN-SAF Total Symptom Score (MPN-SAF TSS)¹⁷ have been developed to better and more meaningfully define patients' symptoms and their response to therapy.

Arterial or venous thrombotic complications are observed in up to 39% of PV patients,¹⁸ with arterial thrombosis observed more frequently than venous thrombosis. Venous thromboembolism (VTE) in patients with MPNs may happen at unusual sites, such as the splanchnic and cerebral venous systems. The most common sites of splanchnic VTE are hepatic, mesenteric, portal and multi segmental.¹⁹ The incidence of VTE in patients with MPN and the incidence of MPN in patients found to have splanchnic VTE vary substantially in retrospective case series.¹⁹ Splanchnic VTE, but not VTE at other sites, is more common

in patients with the *JAK2V617F* mutation, although a causal relationship between the mutation and splanchnic VTE has not been established.²⁰ Other risk factors include age (older for all VTE, younger for splanchnic VTE),²¹ female gender (especially with concomitant use of oral contraceptive pills),²² and splenomegaly/splenectomy.²³ Due to a high recurrence rate, splanchnic VTE in patients with MPN is treated with long-term anticoagulation therapy. In cases of extreme thrombocytosis, patients may be at risk for developing acquired von Willebrand factor deficiency, which may result in spontaneous hemorrhage or worsen bleeding in patients treated with aspirin therapy.²⁴

Fifteen to 20% of PV patients go on to develop a spent phase of the disease, resembling primary myelofibrosis (PMF). Moreover, in approximately 5% - 10% of patients PV acquires a more accelerated pace. This acceleration manifests as a leukemic phase clinically resembling acute myeloid leukemia (AML) and may or may not be preceded by a MF phase.²⁵ Transformation is believed to occur as a result of genetic instability, leading to the acquisition of additional mutations. The *JAK2V617F* or *JAK2* exon 12 mutations are not found at a higher frequency in transformed MPN (in fact AML clones often do not have *JAK2* mutation). Mutations in other genes, including *TET2*, *ASXL1*, *EZH2* and *DNMT3*, are found in patients with PV at frequencies between 5 and 15%, but none of these have been shown to have transforming potential in patients with PV.²⁶ The use of agents such as phosphorus (P)-32, pipobroman or melphalan has been associated with leukemic transformation (see below). Hydroxyurea (HU) is not considered leukemogenic in patients with MPN based on the available data. Treatment of transformed MPN is challenging. Responses are typically short-lasting and with no clear impact on the natural course of the disease. Allogeneic stem cell transplant remains the only chance of cure for these patients. However, only a minority of patients are candidate for this procedure.²⁶

Risk stratification: who should we treat?

Since PV is usually associated with a long indolent clinical course, initiation of therapy is aimed at preventing disease complications, namely thrombosis, evolution to MF and transformation into AML. Two factors have been consistently shown to independently predict the risk of thrombosis: age over 60 and prior thrombotic event.²⁷ High hematocrit²⁸ and leukocytosis,²⁹ but not thrombocytosis, have also been associated with the development of thrombotic complications. Several prognostic models have been proposed for PV patients. In a recent study, independent predictors of arterial thrombosis included leukoerythroblastosis, hypertension, and prior arterial thrombosis. Abnormal karyotype and prior venous thrombosis were predictors of venous thrombosis.³⁰ *JAK2V617F* mutations or *JAK2* exon 12 mutations are not associated with the development of thrombosis or evolution into AML in patients with PV.³¹

First-line therapy

Phlebotomy and aspirin

Thrombosis, hemorrhage, and systemic hypertension are known to be induced by hyperviscosity associated with the increased red cell mass characteristic of PV.³² Therefore, current recommendations for PV patients at low risk for thrombosis (age <60 years, no

history of thrombosis or major hemorrhage) include tight control of cardiovascular risk factors, low-dose aspirin, and phlebotomy to reduce hematocrit below 45%.³³

Patients at higher risk of thrombosis and related complications (age older than 60 years and/or history of thrombosis) should be considered for cytoreductive therapy in addition to the above treatments. Cytoreduction may also be considered for patients with low-risk disease who cannot tolerate phlebotomy, have severe disease-related symptoms or progressive splenomegaly, or have platelet counts $>1500 \times 10^9/L$ (thus, increased risk of bleeding)³⁰ or progressive leukocytosis.²⁹ Historically, the use of aspirin had been controversial, due to a significant incidence of gastrointestinal bleeding when aspirin was employed at high doses (ie, 900 mg daily).³⁴ It was later shown that much lower aspirin doses achieved a similar reduction in the risk of thrombosis³⁵ with improved tolerance³⁶. Results from the multicenter European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) study showed that the use of 100 mg aspirin daily in PV patients with no other indication and no contraindication to aspirin reduced the risk of fatal and non-fatal arterial and venous thrombotic events (relative risk, 0.40; 95% CI, 0.18-0.91; $P = 0.03$) without a significant increase in major bleeding episodes.³⁷

Early studies suggested that the incidence of thrombosis in PV was directly correlated to the hematocrit level when it was $>45\%$.²⁸ Moreover, suboptimal cerebral flow was demonstrated in patients with hematocrit levels between 46% and 52%.³⁸ In fact, a high incidence of thrombosis was observed in the prospective Polycythemia Vera Study Group 1 (PVSG-1) trial, which used a target hematocrit of 52% for the phlebotomy treatment arm.³⁹ These seminal observations led to the adoption of a target hematocrit level below 45% in subsequent studies and in routine clinical practice, despite the lack of data from prospective randomized studies addressing the value of different hematocrit thresholds in the management of PV.

More recently, the issue of the optimal hematocrit level necessary to prevent cardiovascular events in patients with PV has been addressed in a randomized controlled study, the Cytoreductive Therapy in Polycythemia Vera (CYTO PV) trial.⁴⁰ Three-hundred and sixty-five patients with PV who were treated with phlebotomy and/or HU were randomized to either a more intense therapy to maintain the hematocrit below 45% or a more flexible approach with hematocrit goals of 45% - 50%. The incidence of cardiovascular-related deaths or major thrombotic events was 2.7% in the low-hematocrit arm versus 9.8% in the higher hematocrit group (HR 3.91, $P 0.007$). Differences in the rate of disease progression or adverse events were not significant within the study follow-up time.

Hydroxyurea

Currently, first-line cytoreductive treatment choices for patients with high-risk PV include HU or interferon (IFN)- α (see below).³³ HU is a potent ribonucleotide reductase inhibitor which interferes with DNA repair in ultraviolet-irradiated human cells. When used alone, HU does not appear to be associated with an increased incidence of leukemic transformation. However, the ELN recommends caution in treating younger patients with HU.³³ Long-term use of HU is associated with the insurgence of resistance. This phenomenon occurs in about 10% of patients over time. The definition of resistance is

inevitably tied to a definition of a response. For clinical trial purposes, response criteria in PV were initially published by the ELN in 2009.⁴¹ Complete response was defined as hematocrit <45% without phlebotomy, platelet count $400 \times 10^9/L$, WBC count $10 \times 10^9/L$, normal spleen size on imaging, and absence of disease-related symptoms. Partial response was defined as no complete response but achievement of a hematocrit <45% without phlebotomy or 3 or more of the other criteria. In an effort to validate the clinical significance of such criteria, 261 PV patients treated with HU were followed for a median of 7.2 years. Achieving complete or partial response did not translate into improved survival or decreased thrombosis or bleeding.⁴²

Therefore, in 2013 the ELN convened to release revised recommendations for response evaluation.⁴³ Defining elements of a CR include (1) resolution of disease signs and improvement in symptoms (10-point decrease in the MPN-SAF TSS) for at least 12 weeks; (2) normalization of peripheral blood counts (WBC $10 \times 10^9/L$, platelet count $400 \times 10^9/L$, and hematocrit <45% without phlebotomy) for at least 12 weeks; (3) absence of vascular events and disease progression; and (4) disappearance of bone marrow histological abnormalities. For the definition of PR, the first three criteria must be met in the absence of bone marrow histological remission. Molecular complete remission, defined as clearance of the *JAK2V617F*-positive clone, was not included as a category in the recommendations. Based on these criteria, one can reappraise the efficacy of HU. About 10% of patients with PV show resistance or intolerance to HU, as defined by the 2009 ELN criteria. These patients showed a higher risk of death from any cause death (HR 5.6; $P < .001$), as well as higher risk of progression to AML (HR 6.8; $P < .001$).⁴²

Interferon- α

IFN α is a pleiotropic agent endowed with antiangiogenic, antiproliferative, proapoptotic, immunomodulatory and differentiating properties. As such, it has been employed in the treatment of several solid tumors, including Kaposi sarcoma, renal cell carcinoma, melanoma, and bladder cancer, as well as hematologic malignancies, such as chronic myeloid leukemia (CML) and MPNs.⁴⁴

IFN- α binds to a surface receptor which signals through the Janus kinase (JAK)-Signal Transducers and Activators of Transcription (STAT) pathway, causing G1 arrest, G2 and S prolongation,⁴⁵ and down-regulation of multiple cyclins and cyclin-dependent kinases.⁴⁶ Moreover, IFN- α can directly induce caspase 8-mediated apoptosis.⁴⁷ IFN- α bolsters the host immune response by inducing the activation of T cells, monocytes, NK cells and macrophages.⁴⁸ Lastly, IFN- α inhibits *JAK2V617F*-mutated CD34+ hematopoietic progenitors, likely through activation of the p38 MAPK pathway.⁴⁹

Clinical experience with IFN- α in MPNs began in the mid-1980s with a series of small studies conducted on ET and PV patients. The drug proved effective in normalizing thrombocytosis, erythrocytosis, leukocytosis, splenomegaly and constitutional symptoms.⁵⁰⁻⁵³ Pooled analyses of these and other trials showed response rates of 42 - 100% and discontinuation rates of 0 - 42% in patients with PV.^{54,55} However, these studies used multiple forms of IFN and heterogeneous definitions of response.

The considerably high rate of discontinuation seen in early studies, mostly due to flu-like symptoms, fatigue, and neuropsychiatric adverse effects, discouraged further investigation of IFN α in MPN, despite impressive clinical efficacy in patients with PV. However, further research led to the introduction of a new formulation of the drug with the addition of a polyethylene glycol (PEG) moiety to the native IFN α molecule. PEG-IFN α presents several advantages over the “naked” form: it has a longer half-life and greater stability (requiring less frequent administrations), is less immunogenic, and potentially better tolerated.⁵⁶ The two commercially available PEG-IFN- α formulations are PEG-IFN α -2a (PEGASY, Hoffman-La Roche) and PEG IFN α -2b (PEGINTRON, Schering-Plough).

In a phase II study of patients with PV, PEG-IFN α -2a was administered at a starting dose of 90 ug weekly and escalated as tolerated. At a median follow up of 31.4 months this therapy yielded a 100% hematologic response rate in 37 evaluable patients, 94.6% of which were complete responses. The discontinuation rate was 24.3%. The majority of patients experienced adverse events, all grade 1-2. No thrombotic or hemorrhagic events were recorded. Among 29 patients with available follow-up samples, the V617F allele burden decreased over time in 89% of cases and became undetectable in 7 of them, even after treatment discontinuation.⁵⁷ The long-term follow-up (6.4 years) of this study confirmed sustained complete hematologic response in 28 of 34 (82%) of patients. Sustained molecular responses were confirmed in 83% of patients. Of note, 10 of the 13 patients who discontinued therapy and received no additional treatment, maintained a hematologic remission.⁵⁸ Quintas-Cardama et al. conducted a separate phase II study of PEG-IFN α -2a in 40 patients with PV and 39 patients with ET, all with advanced disease. The initial dose of 450 ug weekly was not well-tolerated; thus, the majority of patients were de-escalated to 270 (19), 180 (26) or 90 (28) ug weekly as their final titrated dose. After a median follow up of 21 months, 80% of patients with PV achieved a hematologic response and 70% a complete response. At the lower doses, the drug was well tolerated. The vast majority of patients experienced grade 1-2 adverse events, the only grade 3 toxicity being neutropenia. Among 35 patients with PV for whom sequential measurements of the V617F allele burden were available 54% had a molecular response, and the mutation became undetectable in 14%. The V617F mutant allele burden continued to decrease over time.⁵⁹ In a follow-up analysis of the same trial, including 43 patients with PV and 40 with ET, after a median follow-up of 42 months, *JAK2*V617F was undetectable in 18% of patients with PV. Patients failing to achieve a molecular response had a higher frequency of mutations in other genes, such as *TET2*, *ASXL1*, *EZH2*, *DNMT3A*, or *IDH1/2* and were more likely to acquire additional mutations during therapy. Patients with concomitant *JAK2*V617F and *TET2* mutations at baseline were less likely to achieve a molecular response.⁶⁰ In a more recent analysis, 118 MPN patients received treatment with PEG-IFN α -2a at various centers in the US and Europe at a median dose of 90 ug weekly. Among the 55 patients with PV, the hematologic response rate was 87% and a complete response was observed in 54% of cases. The discontinuation rate was 17%. Among all 118 patients, adverse events were mostly grade 1-2, with only 4 patients experiencing grade 3 complications.⁶¹

PEG-IFN α -2b was initially tested in patients with ET and showed considerable activity and reasonable tolerability.⁶² This agent was subsequently investigated in patients with PV in 2

phase II studies. In the first one, 21 PV patients and 21 ET patients were treated at a dose of 0.5-1 ug/kg per week for up to 24 months. Assessment of quality of life (QoL) was also included among the study outcomes. Sixty-nine percent of patients achieved a complete response (i.e., platelets $<400 \times 10^9/L$ in symptomatic patients or $<600 \times 10^9/L$ in asymptomatic patients). No thromboembolic or hemorrhagic complications were observed. Seven of the 9 phlebotomy-dependent PV patients experienced reduction or elimination of the need for phlebotomy during treatment. Nineteen patients completed the full 2 years of therapy. Side effects were the cause of discontinuation in 16 of 23 patients. QoL measurements revealed clinically significant impairments in several aspects of functioning at 6 months, with a return to baseline at 2 years.⁶³

In a second study 38 patients with MPN, including 4 patients with PV, were treated with PEG-IFN α -2b at a dose of 2-3 ug/kg per week. All 4 patients with PV responded, 2 with a complete response (defined as hemoglobin <15 g/dL in the absence of phlebotomy and disappearance of splenomegaly) and 2 with a partial response (defined as a 50% reduction in the number of phlebotomies required and 50% reduction in splenomegaly). Two of the four patients eventually discontinued therapy due to side effects. Overall, grade 3-4 toxicities included fatigue, myelosuppression, and musculoskeletal pain.⁶⁴

A new, longer acting formulation of PEG-IFN- α (peg-proline-IFN α -2b, AOP2014), has recently undergone phase I/II testing. Thirty-four patients with PV were treated at a dose of 50 to 450 ug every 2 weeks (mean dose, 287 ug) for a median of 41 weeks. Of 28 evaluable patients at 28 weeks, 71% had achieved an overall response and 33% a complete response. After 1 year, 10/11 (91%) evaluable patients achieved a response (46% complete response). After 68 weeks, 3 of 7 evaluable patients had a partial molecular response, and one patient had an undetectable transcript. Twenty-seven (79%) patients experienced drug-related adverse events, of which 9 (26%) were serious. Five (15%) patients discontinued the study drug. Based on the results of this preliminary experience, a phase III study of AOP2014 versus HU is under way.⁶⁵

Second-line therapy

For patients who fail first-line cytoreductive therapy (HU and/or interferon), existing treatment options include alkylating agents, (e.g., busulfan, chlorambucil, or pipobroman) and P-32. However, a body of evidence shows that these agents are associated with an increased incidence of leukemic transformation in patients with PV.⁶⁶⁻⁶⁸ In an analysis of 1,638 patients included in the ECLAP project, independent predictors of the development of AML/MDS included, among others, treatment with pipobroman, busulfan or P-32, but not HU, phlebotomy or IFN.⁶⁶ In line with these findings, a population-based analysis from Sweden showed the risk of developing AML/MDS was not significantly increased in patients receiving HU, regardless of the dose, whereas patients treated with P-32 and alkylating agents had a 4.6-fold and 3.4-fold increased risk of AML/MDS, respectively. Similarly, patients receiving two or more cytoreductive therapies had a 2.9-fold increased risk of transformation.⁶⁷ Kiladjian et al. recently reported the final results of a randomized study of HU versus pipobroman in patients with PV younger than 65 years after a median follow-up time of 16.3 years. Median survival was significantly longer in patients treated

with HU compared to those receiving pipobroman (20.3 vs 15.4 years, $P = .008$), mainly owing to a cumulative incidence of AML/MDS that was doubled in the latter group ($P = .004$).⁶⁹ Taken together, these data indicate that alkylating agents or pipobroman should be reserved as a second-line treatment option for elderly patients (over the age of 80 years) or those for whom the risk of thrombosis outweighs that of transformation.³³

Novel agents

JAK inhibitors

Ruxolitinib (Jakafi, Incyte), an inhibitor of JAK1 and JAK2, is approved by the US Food and Drug Administration for the treatment of MF.⁶ Ruxolitinib was tested in a phase II study in patients with PV who were refractory to treatment with HU or for whom HU was contraindicated. A total of 34 patients received the drug at 10 or 25 mg twice daily or 50 mg once daily. At a median follow up of 35.4 months, 8 patients (24%) had discontinued therapy, 2 of which were due to adverse events. Most patients had a resolution of disease-related symptoms: 97% of patients responded by week 24 and 59% achieved a complete response, mostly within the first 12 months. Three quarters of the responders maintained their response at 144 weeks. One patient required phlebotomy during the study period. Five patients experienced grade 3 anemia and/or thrombocytopenia and 12 patients grade 3 non-hematologic adverse events. The JAK2V617F allele burden was reduced by a median of 8%, 14% and 22% at 48, 96, and 144 weeks, respectively.⁷⁰ Two separate phase 3 trials of ruxolitinib have been initiated in patients with PV. The results of the first study, RESPONSE, have been recently published. In the RESPONSE study 222 patients with PV resistant to or intolerant of HU were randomized to receive either ruxolitinib or best available therapy. The composite primary endpoint was the proportion of patients who achieved both hematocrit control through week 32 (60% vs. 20% in patients treated with ruxolitinib vs. standard therapy, respectively) and 35% reduction in spleen volume at week 32 (38% vs. 1%, respectively). This was achieved by 21% of patients receiving ruxolitinib vs. 1% of those treated with standard therapy. Forty-nine percent and 5% of patients, respectively, experienced 50% improvement in MPN-SAF total symptom score. During the first 32 weeks, grade 3/4 hematologic toxicity was infrequent and similar in the two treatment arms. Herpes zoster was reported in 6.4% of ruxolitinib-treated and 0% of standard therapy patients, respectively (all episodes grade 1/2). Thromboembolic events occurred in 1 patient on ruxolitinib and 6 patients on standard therapy.⁷¹ Results of the second study, RELIEF (switch study from HU to ruxolitinib) are awaited.

HDAC inhibitors

Histone-deacetylases (HDACs) are enzymes involved in the remodeling of chromatin that have a key role in the epigenetic regulation of gene expression. HDAC inhibitors (HDACi) can reverse aberrant epigenetic changes associated with cancer. Up-regulation of several HDACs has been found in patients with MPN, suggesting that HDAC inhibitors may be effective.⁷²

Givinostat is an HDACi with *in vitro* and *in vivo* anti-cancer activity.⁷³⁻⁷⁵ Givinostat inhibits the growth of JAK2V617F cell lines as well as primary hematopoietic cells from patients

with PV and ET.⁷⁶ In a phase IIA study, 12 patients with PV and 1 with ET received givinostat orally at a starting dose of 50 mg twice daily for 24 weeks. Among 13 PV/ET patients, 1 complete response and 6 partial responses were documented. Two patients discontinued prematurely and 4 patients had no response. Pruritus disappeared in most patients and 75% had a reduction in splenomegaly. A trend towards reduction of the *JAK2V617F* allele burden was also observed.⁷⁷ In a subsequent multicenter phase II study, 44 patients with PV not responsive to maximal doses of HU, were treated with givinostat (50 or 100 mg/d) in addition to HU. Over half the patients had a partial response or better by ELN criteria, and pruritus was controlled in two thirds of patients. Eighteen percent of patients discontinued the study drug. Grade 3 adverse events were reported in 4.5% of patients.⁷⁸

Vorinostat, another HDACi, has also shown preclinical activity in *JAK2V617F* knock-in mice.⁷⁹ In a phase II study of 63 patients, including 44 patients with PV, vorinostat given at a dose of 400 mg once daily yielded a response rate of 35% (based on an intention to treat analysis). Symptom control was achieved in all patients and splenomegaly was reduced in half of the cases. Two thirds of patients had a decrease in the *JAK2V617F* allele burden, with a median reduction of 5.6%. The discontinuation rate was 52%, mostly due to adverse events.⁸⁰

Conclusions

PV is an MPN characterized by a very indolent clinical course, but burdened by a variety of clinical symptoms as well as thrombosis, bleeding and transformation to MF or AML. Therapy is aimed at preventing these complications. Low-dose aspirin and phlebotomy represent the cornerstone of treatment for newly diagnosed low-risk PV patients. Higher-risk individuals (i.e., age >60 years and/or prior thrombosis) require the addition of cytoreductive therapy. HU is currently the standard of care for cytoreduction in this patient population. IFN- α is also recommended as first-line therapy for PV patients. About 10% of patients develop resistance and intolerance to HU and have poor outcomes. Data on second-line treatments mostly come from retrospective studies with limited numbers of patients and relatively short follow-up, especially considering the indolent clinical course of PV. Moreover, response criteria have been recently revised and need to be prospectively validated. PEG-IFN α -2a is arguably the most effective second-line therapy and a promising first-line agent at a final titrated dose of 45 or 90 ug/week. Busulfan, pipobroman, or P-32 can be effective but are burdened with leukemogenic potential. The presence of the *JAK2* mutations that activate the JAK-STAT pathway in PV prompted the use of targeted therapies for these patients. The JAK inhibitor ruxolitinib may represent an auspicious therapeutic option for patients with PV who are resistant or intolerant to HU.

Acknowledgments

S.V. received research support for conduct of clinical studies by Incyte Corporation, Astrazeneca, Lilly Oncology, Roche, Geron, NS Pharma, Bristol Myers Squibb, Celgene, Infinity Pharmaceuticals, Gilead, Seattle Genetics, Promedior, Cell Therapeutics, Inc., Galena BioPharma, Pfizer.

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