Novel Therapeutic Approaches in Polycythemia Vera

Charles Elliott Foucar, MD, and Brady Lee Stein, MD, MHS

Abstract: Polycythemia vera (PV) is the most common Philadelphia chromosome–negative myeloproliferative neoplasm. Whereas low-risk patients are treated with aspirin and phlebotomy, high-risk patients receive cytoreductive therapy, which most commonly consists of hydroxyurea in the United States. Concerns about the long-term safety of hydroxyurea, as well as a desire for more efficacious and targeted therapy, have led to the development of novel therapies for high-risk patients with PV. Pegylated interferon (IFN) has shown promise in phase 2 studies of PV, and preliminary data from ongoing phase 3 studies suggest noninferiority as a frontline therapy. Efficient count control, tolerability, and even molecular responses as a salvage therapy have been demonstrated. Ropeginterferon-α-2b, a monopegylated IFN with a longer half-life and less frequent dose interval compared with recombinant or pegylated IFN, is an impressive agent in development. Ruxolitinib has a proven role as second-line therapy for PV, but an ongoing trial combining ruxolitinib and IFN as salvage therapy is under way. Early-phase clinical trials have also suggested that MDM2 inhibitors such as idasanutlin and histone deacetylase inhibitors should continue in their development. If these novel agents are able to modify the natural history of PV, the treatment paradigm in newly diagnosed patients will evolve from risk-adapted or reactive treatment toward early interventions.

Introduction

Polycythemia vera (PV) is the most common Philadelphia chromosome–negative myeloproliferative neoplasm (MPN), with an estimated prevalence of approximately 50 per 100,000 people in the United States. By comparison, the prevalence of the other common MPNs is approximately 47 per 100,000 for essential thrombocytosis (ET) and 5 per 100,000 for myelofibrosis (MF). The vast majority of patients with PV have a mutation in the Janus kinase 2 (JAK2) nonreceptor tyrosine kinase, the most common being JAK2 V617F. Constitutive phosphorylation of JAK2 results in cellular
proliferation in the absence of external growth factors, and thereby leads to clonal proliferation of hematopoietic cells. According to updated guidelines, the diagnosis of PV requires the presence of either 3 major criteria or 2 major criteria plus 1 minor criterion (Table 1).

The potential complications of PV include an increased risk for arterial or venous thrombosis and hemorrhage, as well as the possibility of myelofibrotic and/or leukemic transformation (Table 2). In addition to reducing the risk of these events, the goals of PV therapy include alleviating the PV symptom burden, which has been well-characterized in the last decade. Therapy at present is risk-adapted, with low-risk patients (age <60 years, without prior thrombosis) traditionally receiving low-dose aspirin (81-100 mg per day) and phlebotomy to maintain hematocrit below 45%. Patients are considered for cytoreductive therapy if they develop symptoms such as intolerable fatigue or pruritus, progressive or symptomatic splenomegaly, new thrombosis, or disease-related major bleeding.

High-risk patients, in contrast, receive cytoreductive therapy up-front, in addition to low-dose aspirin. The most commonly used cytoreductive therapy in the United States is hydroxyurea (HU), with guidelines recommending consideration of interferon (IFN) as first-line therapy in younger or pregnant patients. Concern about the safety of long-term HU therapy, and importantly, the desire for more targeted, efficacious therapy, have fueled the development and clinical investigation of novel therapies. At present, the most promising frontline therapies are new formulations of long-acting interferons, and the most promising novel salvage therapies include MDM2 inhibitors, histone deacetylase inhibitors, JAK1/2 inhibitors, and potentially, a combination of IFN and JAK1/2 inhibitors (Table 3). Overall, it appears that the paradigm of HU as the best first-line option for cytoreductive therapy in high-risk patients with PV may soon evolve. Many new second-line therapies for PV patients are on the horizon, and are reviewed herein.

**Table 1. World Health Organization Diagnostic Criteria for Polycythemia Vera**

<table>
<thead>
<tr>
<th>Polycythemia Vera</th>
<th>Diagnosis requires 3 major criteria or 2 major criteria + 1 minor criterion</th>
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<tbody>
<tr>
<td><strong>Major Criteria</strong></td>
<td>One of the following:</td>
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<tr>
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<td>- Hgb &gt;16.5 g/dl in men, &gt;16 g/dl in women</td>
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<td>- Hct &gt;49% in men, &gt;48% in women</td>
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<td></td>
<td>- Increased red cell mass</td>
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<td></td>
<td>Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis), including prominent erythroid granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)</td>
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<td></td>
<td>Presence of JAK2 V617F or JAK2 exon 12 mutation</td>
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<tr>
<td><strong>Minor Criterion</strong></td>
<td>Subnormal serum EPO level</td>
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EPO, erythropoietin; Hgb, hemoglobin; Hct, hematocrit; WHO, World Health Organization.

* Changed from 2008 WHO criteria, in which Hgb is >18.5 g/dl in men and >16.5 g/dl in women.
* Now considered a major criterion, unless WHO 2008 Hgb criteria are met, along with JAK2 mutation and subnormal EPO.
* Endogenous erythroid colony formation was removed as a criterion for diagnosis.


Recombinant IFN-α has been a therapeutic option in patients with PV for decades, but frequent parenteral administration and poor short-term and long-term tolerability due to side effects tempered enthusiasm for widespread use as a cytoreductive therapy. However, pegylated formulations of IFN (peg-IFN) that are better tolerated and require less frequent dosing are challenging this practice pattern.

Renewed interest in peg-IFN as a potential first-line therapy in patients with PV stems from the PVN1 trial (Efficacy and Safety of Pegylated Interferon Alfa in Polycythemia Vera). This multicenter prospective trial followed 37 patients with PV who either were previously untreated or had undergone phlebotomy or cytoreductive therapy for less than 2 years. They were treated with a median dose of 90 μg weekly of peg-IFN-α-2a. After 12 months of treatment, 94.6% of patients achieved a complete hematologic response (CHR) and 5.4% achieved a partial response. Long-term follow-up at a median of 77.3 months showed that 82% of patients had a CHR, 12% had a partial hematologic response (PHR), and 6% had disease relapse. The molecular response to peg-IFN-α-2a was also measured in 29 patients who had an initial median JAK2 V617F allele burden of 45%. The median JAK2 V617F allele burden in these patients decreased to 3% at 36 months and then increased to 10% at 72 months. At 24 months, 34% of patients had a reduction of the JAK2 V617F clone to 1% or less and 24% of patients had no detectable JAK2 V617F mutation. By 72 months, 28% of patients did not have a detectable JAK2 V617F mutation. In terms of treatment toxicity, 89% of patients reported adverse events during the first 12 months of the study. After...
Table 2. Risk Factors for Thrombosis, Disease Progression, and Reduced Overall Survival in Patients With Polycythemia Vera

<table>
<thead>
<tr>
<th>Risk Factors for Thrombosis&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Risk Factors for Disease Progression&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Risk Factors for Reduced Survival&lt;sup&gt;ab&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Advanced age&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Age ≥60 y</td>
<td>Age (≥67 y at highest risk, 57-66 y at moderate risk)</td>
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<tr>
<td>Prior history of thrombosis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Longer disease duration</td>
<td>Leukocytosis ≥15 × 10⁹/L</td>
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<tr>
<td>Leukocytosis/erythrocytosis</td>
<td>Leukocytosis at diagnosis (&gt;15 × 10⁹/L)</td>
<td>Venous thrombosis</td>
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<tr>
<td>Mutational profile (increased JAK2 % may increase risk; impact on non-JAK2 somatic mutations such as TET2 is unclear with regard to thrombosis risk)</td>
<td>Marrow fibrosis at diagnosis&lt;sup&gt;35,37&lt;/sup&gt;</td>
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<tr>
<td>Inflammation (eg, hs-CRP)</td>
<td>JAK2 allele burden &gt;50%</td>
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<tr>
<td>CV risk (hypertension, diabetes, hyperlipidemia, and smoking)</td>
<td>ASXL1, SRSF2, and/or IDH2 mutation&lt;sup&gt;ab&lt;/sup&gt;</td>
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<tr>
<td>Sex (younger women are at higher risk for venous thrombosis)</td>
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<td></td>
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<tr>
<td>Leukocyte, endothelial, and platelet activation</td>
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<td></td>
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<tr>
<td>Increased neutrophil extracellular trap formation&lt;sup&gt;40&lt;/sup&gt;</td>
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CV, cardiovascular; hs-CRP, high-sensitivity C-reactive protein; y, year(s).
<sup>a</sup>Factors currently used in risk stratification of PV patients.
<sup>b</sup>May independently influence acute myeloid leukemia and overall survival.

In terms of treatment toxicity, no grade 4 adverse events occurred in patients receiving either treatment. However, grade 3 adverse events occurred in 14% of patients receiving HU and 44% of patients receiving peg-IFN-α-2a. This interim analysis suggests that there is no difference in treatment efficacy between HU and peg-IFN-α-2a, although the latter had a higher rate of treatment toxicity. However, the rates of CHR in the peg-IFN arm of this trial are lower than those observed in the PVN1 trial described above. Whereas HU can offer responses in the short-term, the impact of long-acting IFNs depends on time, and it is anticipated that results may differ with longer follow-up time and analysis of the full cohort.
age and treatment response. Lastly, 1 patient with PV experienced a transformation to myelofibrosis during the trial period.13 Regarding treatment tolerability, grade 3 adverse events occurred in 38% of patients (both ET and PV patients included) and five grade 4 adverse events occurred, including acute myeloid leukemia, depression, hyperuricemia, and neutropenia in 2 patients.13 This trial shows that peg-IFN is an effective salvage therapy in patients who are either resistant to or intolerant of HU, even if they are older.

**Ropeginterferon-alfa-2b**

Ropeginterferon-α-2b is a novel IFN with a longer half-life compared with recombinant or pegylated IFN, which allows administration every 2 weeks (or monthly during long-term maintenance). This agent is currently undergoing clinical testing.14-16 Ropeginterferon α-2b was first investigated in both newly diagnosed and previously treated PV patients. A phase 1 dose-escalation study of 25 patients was performed that determined the maximum tolerated dose (540 µg of ropeginterferon α-2b every 2 weeks) using a 3+3 dose-escalation protocol. For the second phase of the trial, 26 additional patients were enrolled, for a total of 51 patients. These patients were followed prospectively while receiving a mean dose of 263 µg of ropeginterferon α-2b every 2 weeks.14 Dosing was based on efficacy and long-term tolerability. After 10 weeks of treatment, 26% of patients had a CHR and 49% had a PHR. These rates of hematologic response appeared relatively constant for up to 146 weeks of follow-up, with the best response rates occurring after a median of 82 weeks.
when 47% of patients had a CHR. However, it should be noted that the number of patients analyzed dropped considerably as the length of follow-up increased, with data from only 9 patients being available at 146 weeks. Molecular response was also measured, and the median JAK2 V617F allele burden decreased from 41% at enrollment to 25% after 50 weeks of follow-up. Twenty percent of patients discontinued therapy owing to treatment toxicity, and 88% of patients experienced adverse events.

These results led to the PROUD-PV study (Pegylated Interferon Alpha-2b Versus Hydroxyurea in Polycythemia Vera), a multicenter randomized controlled trial comparing ropeginterferon α-2b with HU in patients who either were treatment-naive or had prior treatment with HU and were neither intolerant of the agent nor complete hematologic responders, with a maximum cumulative treatment of 3 years. The trial enrolled 254 patients with PV. The primary endpoint was noninferiority of CHR at 12 months, and a secondary endpoint was the rate of molecular response (MR). Based on the intention-to-treat analysis, CHR was achieved by 43.1% of patients randomly assigned to ropeginterferon α-2b and 45.6% of patients assigned to HU, meeting the criteria for noninferiority. Molecular analysis of 13 patients, 5 of whom received ropeginterferon and 8 of whom received HU, provided information regarding MR. The median JAK2 V617F allele burden decreased from 39.4% to 13.8% in patients treated with ropeginterferon and decreased from 46.5% to 33.2% in those who received HU.

After 12 months, patients from the PROUD-PV study were rolled over into the CONTI-PV study (AOP2014 vs. BAT in Patients With Polycythemia Vera Who Previously Participated in the PROUD-PV Study). Ninety-five patients continued to receive ropeginterferon and 76 patients continued to receive HU or best available therapy (BAT) at the investigators’ discretion. An interim analysis that included 24 months of follow-up was presented at the 2017 American Society of Hematology annual meeting. A total of 88 patients taking ropeginterferon and 73 patients taking HU/BAT completed 24 months of therapy, with a comparable dropout rate between the groups of 8.4% and 6.6%, respectively. The rate of CHR was significantly higher in patients receiving ropeginterferon (70.5%) than in those receiving HU/BAT (49.3%). The composite endpoint of CHR and symptom improvement occurred in 49.5% of patients receiving ropeginterferon compared with 36.6% for those receiving HU/BAT, but this was not a statistically significant difference. Further, a partial MR occurred in 69.6% of patients receiving ropeginterferon and 28.6% of those receiving HU/BAT. Lastly, a comparable number of patients (70.1% for ropeginterferon and 77.2% for HU/BAT) experienced treatment-related adverse events. A formal symptom assessment tool, such as MPN-SAF, was not used in this study. Although this trial is ongoing, this interim analysis suggests that ropeginterferon α-2b may prove to be a more efficacious and safe treatment for PV compared with HU.

**Histone Deacetylase Inhibition**

Histone deacetylase (HDAC) inhibition is another mechanism under investigation. Givinostat is one such therapy that was initially piloted in two phase 2 trials that included patients with PV who were HU-resistant or intolerant. In these studies, givinostat was generally well-tolerated and possibly clinically beneficial. Patients were allowed to continue givinostat as part of a long-term open-label study if they had tolerated treatment and achieved clinical benefit. Forty-five patients with PV were treated for a median of 4 years, with the most common dose being 100 mg/day. CHR and PHR were observed in 11% and 89% of patients, respectively, and 56% of patients had a normal spleen size by palpation or imaging at the end of the study. Only one serious adverse drug reaction (ADR) was reported, and a total of two grade 3 ADRs were reported.

More recently, a phase 1b/2 study was conducted to assess the maximum tolerated dose of givinostat and to assess its efficacy in PV patients. The study enrolled JAK2 V617F–positive patients with active or uncontrolled disease, as defined by the following criteria: hematocrit of at least 45%, platelet count of greater than 400 × 10^9/L, and white blood cell count of greater than 10 × 10^9/L. In the first part of the trial, the maximum tolerated daily dose was found to be 200 mg. Thirty-six patients were then treated at a starting dose of 200 mg per day for phase 2. After 3 months of therapy, the combined CHR and PHR rate was 86% in 30 evaluable patients, which increased to 90% at 6 months. It was noted that there was a net improvement on the MPN-SAF symptom score and a decrease in the median JAK2 V617F allele burden. Givinostat was well-tolerated, with only one serious grade 3 ADR reported and no grade 4 ADRs. These studies suggest that givinostat may be a well-tolerated and efficacious treatment for PV patients in the future, with durable hematologic responses over years of therapy.

**MDM2 Inhibition**

Another novel mechanism being studied in patients with PV is MDM2 inhibition. MDM2, a negative regulator of p53, has been found to be overexpressed in JAK2 V617F–positive MPN hematopoietic progenitor cells harboring...
wild-type TP53. Preclinical data showed that blocking the p53-MDM2 interaction in CD34+ PV and PMF cells increased the rate of apoptosis.22

A phase 1 dose-escalation trial of idasanutlin (IDA), an oral MDM2 inhibitor, in patients with JAK2 V617F-positive PV or ET was performed to test the safety of IDA.23 Thirteen patients were enrolled who were resistant to or intolerant of hydroxyurea and/or IFN therapy and had not received prior JAK2 inhibitor therapy. Patients received either 100 mg or 150 mg daily for 5 consecutive days, which was repeated in 28-day cycles. Patients were eligible to continue receiving IDA in combination with peg-IFN-α at 45 µg weekly if they did not attain at least a partial response by cycle 6. Patients received a median of 33 weeks of therapy, and no hematologic treatment-emergent adverse events were recorded during the study. After 28 weeks, the overall response rate was 78%, and 70% of patients achieved an improvement of at least 50% in total symptom score (TSS) from baseline. The JAK2 V617F allele burden decreased from 45% to 13% after 36 weeks of treatment.24 One patient received combination therapy with peg-IFN and achieved freedom from phlebotomy, normalization of palpable spleen, reduction of leukocyte count, reduction in PV-related symptoms, and a 20% reduction in JAK2 V617F allele burden by cycle 8.25 Although further clinical testing is needed, this study suggests that IDA may prove to be an efficacious second-line therapy for patients who are resistant to or intolerant of HU and IFN therapy.

**JAK Inhibition**

The discovery that mutations in JAK2 were integral to MPN disease pathogenesis has led to the development of targeted inhibitors of JAK2. The development and US Food and Drug Administration (FDA) approval of ruxolitinib (Jakafi, Incyte), a JAK1/2 inhibitor, for patients with MF has been reviewed elsewhere.26 The drug’s efficacy and safety in patients with MF led to its clinical investigation in PV. Initially, a phase 2 study showed that ruxolitinib was tolerated and exhibited durable responses for up to 48 weeks.27 These promising results led to the RESPONSE trial (Study of Efficacy and Safety in Polycythemia Vera Subjects Who Are Resistant to or Intolerant of Hydroxyurea; JAK Inhibitor INC424 Tablets Versus Best Available Care), an ongoing, open-label, phase 3 trial comparing the efficacy and safety of ruxolitinib vs BAT in patients with PV who are resistant to or intolerant of HU.28 Eligible patients had splenomegaly and required phlebotomy to control hematocrit. Patients were randomly assigned to receive either 10 mg of ruxolitinib twice a day or BAT. The primary endpoint was a composite endpoint of achieving both hematocrit control without phlebotomy through week 32 and a reduction in spleen volume of at least 35% according to imaging at week 32. The primary endpoint was achieved in 21% of patients receiving ruxolitinib and 1% of those randomly assigned to BAT, which was statistically significant. In addition, patients receiving ruxolitinib had better hematocrit control (60% vs 20%) and a higher rate of at least 35% reduction in spleen volume (38% vs 1%). A CHR was observed in 24% of patients receiving ruxolitinib compared with 9% receiving BAT.29 Both ruxolitinib and BAT had a low rate of grade 3 or 4 nonhematologic adverse events. Herpes zoster infections occurred in 6.4% of those receiving ruxolitinib vs none of those in the group receiving BAT. Other infections, nonmelanoma skin cancers, weight gain, and cholesterol changes were additional adverse events attributed to ruxolitinib. Lastly, at 32 weeks, thromboembolic events occurred in 1 patient receiving ruxolitinib and 6 patients receiving BAT.26

Four-year follow-up from this study was recently published and showed that 76% of the primary responders to ruxolitinib had maintained their response.27 In addition, 70% of patients who achieved CHR maintained this response. Ruxolitinib continued to be well-tolerated, and 37% of the patients who were originally randomly assigned to the ruxolitinib arm were still receiving therapy.27 Lastly, it should be noted that an interim report showed that the majority of patients who did not achieve hematocrit control at the initial 32-week point did so with prolonged ruxolitinib treatment. In addition, many patients also experienced a delayed spleen response and had a reduction in spleen volume after 32 weeks with continued therapy.28 Ruxolitinib was also studied as second-line therapy in patients without splenomegaly who were resistant to or intolerant of HU in the RESPONSE-2 trial (Ruxolitinib Efficacy and Safety in Patients With HU Resistant or Intolerant Polycythemia Vera vs Best Available Therapy).29 This was a randomized, open-label, phase 3b trial in which patients were randomly assigned to 10 mg of ruxolitinib twice a day or BAT. The primary endpoint was patients receiving hematocrit control at week 28.29 When data from 149 patients were analyzed, hematocrit control was achieved in 62% of patients receiving ruxolitinib vs 19% of those receiving BAT. The rates of serious adverse events were low, and similar between the 2 groups.29 These findings were also affirmed in a study enrolling patients with PV who were resistant to or intolerant of HU, had no treatment options, and were not eligible for another clinical trial in PV.30 After 24 weeks of treatment with ruxolitinib, 69% of patients with PV in this study achieved hematocrit control.30

Recently, the results of a randomized phase 2 trial comparing ruxolitinib with BAT in a “real-world” setting for patients with PV who met modified European...
and Myelofibrosis).33 Thirty-two patients with PV were presented. 31 The primary outcome was CHR LeukemiaNet criteria for HU intolerance/resistance were presented.31 The primary outcome was CHR within 1 year, and patients randomly assigned to the ruxolitinib arm received 5 to 10 mg twice daily. A total of 190 patients were recruited, and CHR was achieved in 49.5% of the patients who received ruxolitinib vs 27% of those who received BAT. This was a statistically significant difference. In addition, patients receiving ruxolitinib had better symptom control, attained hematologic responses faster, and had, on average, a longer duration of overall response. The number of thrombotic events and hemorrhagic events recorded in the 2 treatment groups were almost identical. There was no difference in overall survival, but the authors suggested a trend toward transformation-free survival.31 Adverse events attributed to ruxolitinib included grade 3 anemia (6.5%) and infections (grades 3 and 4: 8.6% and 2.2%, respectively).

PV-related symptom control of HU vs ruxolitinib was also studied in the RELIEF trial (Randomized Switch Study From Hydroxyurea to Ruxolitinib for RELIEF of Polycythemia Vera Symptoms).32 This was a randomized, double-blind, double-placebo, phase 3b trial that reported PV-related symptoms on a stable dose of HU. A total of 110 patients were enrolled, with a primary endpoint of at least 50% improvement from baseline in MPN-SAF TSS at week 16. This endpoint was achieved by 43.4% of patients receiving ruxolitinib compared with 29.6% receiving HU; however, the difference was not statistically significant. Both treatments were well-tolerated, with primarily grade 1 or 2 adverse events reported in both treatment arms.32 The above trials provide strong evidence for ruxolitinib as a second-line agent in patients with PV who are resistant to or intolerant of HU, regardless of the presence of splenomegaly.

Combination Therapy With Interferon and Ruxolitinib

Ruxolitinib is also currently being studied in combination with peg-IFN in patients with MPNs in the COMBI study (Safety and Efficacy of Combination Therapy of Interferon-α-2a and Ruxolitinib in Polycythemia Vera and Myelofibrosis).33 Thirty-two patients with PV were enrolled, most of whom were intolerant of IFN previously. The primary endpoint was the rate of CR or PR at 12 and 24 months. Evidence of active disease was required. Patients were treated with peg-IFN-α-2a at 45 µg per week or peg-IFNα2b at 35 µg per week, plus ruxolitinib at 20 mg twice daily. Nine percent of patients with PV obtained a PR, and 44% experienced a CHR. The JAK2 V617F allele burden decreased from a median of 47% to 23.5% by 12 months. Eighty-one percent of patients with PV remained on treatment by month 12. Twenty percent of patients had to discontinue therapy owing to adverse events. Hematologic toxicity was most common, and included grade 1 or 2 anemia in 56% of patients, grade 1 or 2 leukopenia in 50% of patients, and grade 1 or 2 thrombocytopenia in 28% of patients. The toxicity was in part attributed to a higher dose of ruxolitinib than is typically used in PV.33 The study investigators wrote that they envision further development of this combination, but at lower doses.

Conclusion

Many therapies are currently under development for high-risk patients with PV. Peg-IFN has proven efficacy in the treatment of patients with PV. Preliminary results from ongoing head-to-head trials suggest that IFN therapy is noninferior to HU as a frontline therapy for PV. Emerging data also suggest efficacy in a salvage setting. Although trials are still ongoing, ropeginterferon α-2b, with its longer half-life compared with standard IFNs and resultant less frequent dose interval, is a highly promising IFN that is in development. Ruxolitinib has an established role as a second-line therapy for patients with PV who are resistant to or intolerant of HU. Though only a small number of patients have been studied and longer follow-up time is needed, a combination of ruxolitinib and IFN is intriguing. Early-phase clinical trials have shown a signal for potential efficacy with MDM2 inhibitors. Finally, HDAC inhibitors promise as salvage therapy, but their role is still investigational and remains to be defined. Provided that continued clinical investigation is able to confirm the efficacy of the novel PV therapies discussed here, the treatment paradigm can finally shift away from nonselective, restrictive/reactive treatments toward early targeted interventions in newly diagnosed patients, with an aim to modify the natural history of this chronic myeloid neoplasm.

Disclosures

Dr Foucar has no relevant disclosures. Dr Stein has served as a consultant for Incyte Corporation.

References


