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Therapeutic options for patients with polycythemia vera and essential thrombocythemia refractory/resistant to hydroxyurea

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Abstract

Hydroxyurea (HU) has traditionally been the first-line treatment for patients with PV or ET at high-risk for vascular complications. However, approximately 20-25% of patients develop resistance or intolerance to HU and must be treated with second-line therapies. Resistance is associated with disease transformation and reduced survival. However, given the dearth of large-scale controlled clinical trials in this patient population, there is no clear consensus on how to best treat patients who develop resistance or intolerance to HU. Herein, we review current literature on treatment options for patients with HU-refractory/resistant PV or ET and provide recommendations for treating these patients.

Keywords

polycythemia vera; essential thrombocythemia; hydroxyurea

Introduction

Polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) represent the classic Philadelphia-negative myeloproliferative neoplasms (MPNs). All three disorders arise from proliferation of an aberrant hematopoietic stem cell clone, leading to thrombotic complications and potential for transformation to acute leukemia. However, the three disorders develop distinct phenotypes. PV and ET typically present with elevated hematocrit and platelets, respectively, while PMF presents with myelopoiesis and bone-marrow fibrosis [1,2]. Both PV and ET have the potential to progress to a fibrotic state resembling PMF (post-PV and post-ET MF), myelodysplastic syndrome (MDS), or acute myeloid leukemia (AML). The JAK2^{V617F} mutation, which results in constitutive activation of the JAK-STAT (Janus kinase-signal transducer and activator of transcription) pathway, is present in about 95% of patients with PV and 60% of patients with ET and PMF, and the JAK2^{V617F} allele burden is hypothesized to partially contribute to the distinct phenotypes of these diseases [3,4]. Although PV and ET are more benign conditions than PMF—patients

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have near normal life expectancy [5]—they are estimated to be about 10 times more prevalent than PMF [6].

The main complications of PV and ET are vascular disease (thrombosis and bleeding), reduced quality of life, and transformation to MF or AML. Thus, the goal of treatment is to prevent thrombotic and hemorrhagic complications, control systemic symptoms, and minimize the risk of transformation to MF and AML [7]. Hydroxyurea (HU) has traditionally been the first-line treatment for patients with PV or ET at high risk for vascular complications. However, up to 24% patients with PV or ET develop resistance or intolerance to HU and must be treated with second-line therapies [8,9]. In this article, we review the current treatment options for patients with high-risk PV or ET who are resistant or refractory to HU.

Diagnosis and management of polycythemia vera and essential thrombocythemia

Patients with PV or ET should be diagnosed according to the 2008 World Health Organization (WHO) criteria, which are based on assessment of both clinical features and laboratory values [1,2]. Risk stratification identifies patients most at risk of thrombosis and related complications who should be considered for cytoreductive treatment in addition to low dose aspirin (and phlebotomy for patients with PV). Patients older than 60 years or those with a history of thrombosis are regarded as being at high risk for vascular complications [10]. Currently, HU is the first-line treatment recommendation for high-risk patients with ET, while HU or interferon α [IFN- α] are considered as first-line choices for patients with high-risk PV. Cytoreductive therapy should also be considered for patients with low-risk disease who cannot tolerate phlebotomy (for patients with PV), have severe disease-related symptoms or progressive splenomegaly, or those with platelet counts above $1500 \times 10^9/L$ or progressive leukocytosis. Second-line cytoreductive therapy choices for patients with ET and PV who experience resistance or intolerance to HU include IFN- α , busulfan, pipobroman, or P-32, and for those with ET also anagrelide (2).

Revised criteria for response assessment in polycythemia vera and essential thrombocythemia

The widely adopted European Leukemia Network (ELN) response criteria from 2009 [7,11] were recently shown not to predict clinically relevant endpoints. For example, patients defined by these criteria as having achieved a complete clinicohematologic response (CR) do not have a lower incidence of thrombosis or improved survival [8,9,12,13]. This led to the development of revised response criteria for PV and ET, which were recently published by the ELN and International Working Group-Myeloproliferative Neoplasms Research and Treatment [14]. The 2009 ELN criteria defined CR as white blood cell count (WBC) $< 10 \times 10^9/L$, platelet count $< 400 \times 10^9/L$, normal spleen size on imaging, and absence of disease-related symptoms; for PV, hematocrit $< 45\%$ without phlebotomy is an additional criterion. The new recommendations, which were designed to be used as response criteria in clinical trials, now include more specific evaluation of symptomatic improvement and histological bone marrow changes, along with required durability of response. Four response categories were defined for evaluation of CR and partial response (PR). CR requires 1) resolution of disease signs and improvement in symptoms (10-point decrease in the MPN-Symptoms

Assessment Form Total Symptom Score) for at least 12 weeks; 2) normalization of peripheral blood counts (as defined above) for at least 12 weeks; 3) absence of vascular events and disease progression; and 4) disappearance of bone marrow histological abnormalities. PR includes the first 3 criteria, but does not require the remission of bone-marrow histological abnormalities. Although some therapies have been shown to reduce JAK2 V617F allele burden, molecular remission was not included in the revised response definition, given, for example, that nearly half of patients with ET lack the JAK2^{V617F} mutation, and remission of the JAK2^{V617F} clone has not been definitely shown to correlate with eradication of the disease. Whether these new response criteria, which are reflective of consensus expert opinion, better define clinically relevant endpoints for studying the effects of new drugs will need to be determined in future studies.

Criteria for resistance/intolerance to hydroxyurea

Approximately 10% of patients with PV or ET treated with HU will show resistance, while some experience unacceptable side effects (intolerance) [8,9,11,15]. Recognizing intolerance or resistance to HU is important for making appropriate decisions about when to offer patients a second-line therapy. In addition, unified criteria for defining intolerance or resistance to HU are important for identifying patients who may be eligible for clinical trials testing new therapies, and to allow for comparison of clinical studies that use resistance/intolerance as inclusion criteria. For this reason, specific criteria have been established by experts in the field, to identify HU intolerance/resistance in ET and PV [15,16]. For patients with PV on a daily dose of at least 2 g HU for at least 3 months, resistance/intolerance is defined when a patient experiences at least one of the following: a need for phlebotomy to keep hematocrit < 45%; platelet count > 400 × 10⁹/L and WBC > 10 × 10⁹/L; < 50% reduction in splenomegaly or no improvement in symptoms related to splenomegaly; absolute neutrophil count < 1.0 × 10⁹/L, platelet count < 100 × 10⁹/L, or hemoglobin < 10 g/dL at the lowest dose of HU necessary to achieve CR or PR; or presence of unacceptable HU-related non-hematologic toxicities [16]. For patients with ET, intolerance and resistance to HU is defined as one of the following criteria: platelet count < 600 × 10⁹/L after a daily dose of at least 2 g HU for at least 3 months; platelet count < 400 × 10⁹/L and WBC < 2.5 × 10⁹/L at any dose of HU; platelet count < 400 × 10⁹/L and hemoglobin < 10 g/dl at any dose of HU; or presence of unacceptable HU-related non-hematologic toxicities, including fever [15].

Two retrospective studies evaluated the ELN-defined response and resistance/intolerance criteria in patients with PV [8] and ET [9] to assess the value of using the criteria in a clinical setting to make decisions about when to use second-line therapeutic options. In the PV study, 261 patients received HU for a median of 4.4 years. Only 24% of patients achieved a CR, and 10% did not have any response after a median 4.6 months on therapy. Thirty (11.5%) patients were resistant to HU, as defined by ELN criteria, and 33 (12.6%) met criteria for intolerance. Resistance was associated with a higher risk of death (hazard ratio [HR] 5.6, $p < 0.001$) and transformation to AML or MF (HR 6.8, $p < 0.001$), but intolerance did not have any prognostic significance. Median survival after developing resistance to HU was 1.2 years.

In the ET study, 166 patients treated with HU for a median of 4.5 years were evaluated [9]. After a median 3.3 months on treatment, 134 (81%) patients had achieved a CR. Thirty-three (20%) patients met at least one ELN-defined criterion for resistance or intolerance. Patients with HU resistance, but not those with intolerance, had an increased risk of death from any cause (HR 10.4, $p < 0.001$) and a higher incidence of MF (47% patients with resistance to HU vs 2.5% without resistance). Thus, in both PV and ET, HU resistance appears to lead to an increased risk of death and transformation to MF, highlighting the importance of second-line therapeutic options for these patients.

Pegylated interferon- α

IFN- α has been shown to have antiproliferative effects on hematopoietic precursor cells, induce cytogenetic remissions, and reduce *JAK2*^{V617F} allele burden in MPNs [17]. However, intolerable side effects [18], including flu-like symptoms, fatigue, and neuropsychiatric symptoms, and the need for frequent administration have limited its use in PV and ET. Approximately 25-40% of patients with PV and 20-50% of patients with ET treated with IFN- α in clinical trials discontinued treatment within 1-2 years due to side effects [19].

More recently, newer pegylated formulations of IFN- α (PEG-IFN), which are better tolerated and allow for less frequent administration [20], have renewed interest in IFN- α as a therapeutic option for patients with PV and ET. The covalent attachment of polyethylene glycol (PEG) to IFN- α changes its pharmacokinetic and pharmacodynamic characteristics, leading to possible differences in the timing and frequency of side effects and allowing for weekly administration [21-23]. For patients refractory or resistant to HU, PEG-IFN represents an effective second-line treatment option. In addition to having a more favorable toxicity profile than native IFN- α , PEG-IFN yields high rates of hematologic and molecular responses, which may prevent evolution to MF, MDS, and AML. However, some caution is necessary, as similar to its native formulation, it is contraindicated in patients with thyroid and psychiatric disorders [18]. Also, compared with HU, data on its prevention of thromboembolic events is limited. Below we discuss clinical development in PV and ET of the two PEG-IFN formulations that are commercially available: PEG-IFN- α -2a (PEGASYS; Hoffman-La Roche) [24] and PEG-IFN- α -2b (PegIntron, Schering-Plough) [25].

Clinical experience with PEG-IFN- α -2a

PEG-IFN- α -2a is generated by the covalent attachment of a 40-kDa branched PEG molecule to a lysine residue in IFN- α -2a. The first study of PEG-IFN- α -2a in MPNs was a phase II study enrolling patients with PV [26]. Patients initially received 90 μ g weekly subcutaneously, followed by dose escalations to 135 μ g/week and 180 μ g/week as tolerated. At 12 months, all 37 evaluable patients had a hematologic response, with 94.6% CRs. After a median follow-up of 31.4 months, 35 patients remained in CR. Adverse events (AEs) were common (89% of patients), but all were grade 1 or 2 except for one grade 3 skin toxicity. During the first month on treatment, 65% of patients experienced grade 1 or 2 adverse events, most commonly musculoskeletal pain, skin toxicity, and asthenia. Over the entire study period, nine (24.3%) patients discontinued treatment due to toxicities. No vascular events were recorded. For 29 patients with *JAK2*^{V617F} testing available, 26 (90%) had reductions in their allele burden. The median allele burden decreased progressively from

45% before treatment to 22.5% at 12 months and 3% at 36 months. Seven (24%) patients achieved a complete molecular response (CMR, defined as undetectable *JAK2*^{V617F}), which was maintained even after discontinuation of treatment (in 5 patients).

Similar results were seen in another phase II study enrolling patients with PV (*n*=40) and ET (*n*=39) [27]. The first three patients were treated subcutaneously with 450 µg/week; however, due to poor tolerance the dose was decreased stepwise based on tolerance. Most patients received 270 µg/week (*n*=19), 180 µg/week (*n*=26) or 90 µg/week (*n*=28). After a median follow-up of 21 months, an overall hematologic response was observed in 80% of patients with PV (70% CR) and 81% of patients with ET (76% CR). Although 96% of patients experienced some toxicity, most AEs were grade 1 or 2. The most common grade 3 or 4 toxicity was neutropenia (8% PV, 34% ET). Notably, none of the patients who started on therapy at 90 µg/week experienced any grade 4 toxicity and only 2 patients experienced grade 3 neutropenia. There were no thrombohemorrhagic events reported and one patient progressed to MF while on treatment. Of patients evaluable for *JAK2*^{V617F} allele burden (35 with PV and 16 with ET), 54% with PV and 38% with ET had a molecular response (defined as > 19% reduction in allele burden). In addition, five (14%) patients with PV and one (6%) with ET achieved a CMR. In a long-term follow-up analysis, after a median time of 42 months, 76% of patients with PV and 77% of those with ET had achieved a CR [28]. None of the patients had progression to AML, but two progressed to MF. The median allele burden was reduced from 64% at baseline to 19% after 24 months and 8% at 60 months, with 18% of patients with PV and 17% of patients with ET achieving a CMR.

More recently, a retrospective study evaluating patients with PV (*n*=55), ET (*n*=46), and MF (*n*=17) treated with PEG-IFN-α-2a at several clinical sites in Europe and the US reported similar results [29]. After a median 17 months on treatment (median dose 90 µg/week), 30 (54%) patients with PV and 29 (63%) with ET achieved a CR. Only 4 patients (3%) experienced a grade 3 AE. The most common grade 1 or 2 hematologic AEs were thrombocytopenia (8%), anemia (6%), and leukopenia (6%), and fatigue (20%) was the most common non-hematologic toxicity.

Clinical experience with PEG-IFN-α-2b

PEG-IFN-α-2b (PegIntron) is formed by the covalent attachment of a 12 kDa PEG molecule to histidine 34 on IFN-α-2b. PEG-IFN-α-2b was initially tested in ET and more recently in PV. In a pilot study of 11 patients with ET, patients were treated with 1.5-4.5 µg/kg per week subcutaneously for a median duration of 9 months. After 4 months on therapy all patients had achieved a CR (defined as platelets < 400 × 10⁹/L, with no thrombohemorrhagic events for > 1 month) [30]. Eight patients (73%) experienced grade 2 or 3 flu-like symptoms, which were controlled with acetaminophen and resolved spontaneously in five of eight patients, and two patients discontinued therapy due to flu-like symptoms/fatigue (one patient) and anxiety depression (one patient). No thrombohemorrhagic events were reported. In a phase II study of 36 patients with high-risk ET, 39% achieved a CR (defined as platelet count < 450 × 10⁹/L for 1 month) after 3 months on treatment, and 67% were in CR after 12 months of treatment [31]. Seventy-eight percent of patients experienced flu-like symptoms during the first 6 months on therapy, a frequency that decreased to 36% of those still on

therapy after 12 months. Other common side effects included grade 1 or 2 skin dryness (37% of patients), hair loss (18% of patients) and mild depression (15% of patients). After a median follow-up of 23 months, 13 (36%) patients had discontinued therapy, 10 (28%) due to grade 1 to 2 treatment-related side effects, mostly flu-like symptoms. One patient who had achieved a partial response on a dose of 100 µg/week, had a cerebral stroke after 23 months on treatment.

PEG-IFN-α-2b was also tested in patients with PV in two studies. In a phase II study enrolling 21 patients with PV and 21 patients with ET, after 6 months on treatment (0.5-1.0 µg/kg per week), 29 (69%) patients achieved a CR (defined as platelets < 400 × 10⁹/L in symptomatic patients and < 600 × 10⁹/L in asymptomatic patients) and no thromboembolic or bleeding events occurred [32]. The most common grade 3 adverse events were fatigue (15% of patients), flu-like symptoms (10% of patients), and headache (5% of patients). Sixteen patients discontinued therapy due to side effects, mainly fatigue (six patients) and muscle pain (three patients). After 24 months, 19 (45%) patients maintained a CR (12 with PV and seven with ET).

In another phase II study, 13 patients with ET and four with PV were treated with PEG-IFN-α-2b (2 or 3 µg/kg per week) for a median of 27 months [33]. For patients with ET, CR was defined as platelet count < 440 × 10⁹/L and PR as a 50% reduction in platelet count. For patients with PV, CR was defined as hemoglobin < 15 g/dL without phlebotomy and disappearance of splenomegaly, and PR as a 50% reduction in the number of phlebotomies required and 50% reduction in splenomegaly. Seven (54%) patients with ET had a CR and two (15%) a PR. Five patients stopped therapy due to side effects and one patient had disease progression. All four patients with PV responded: two with a CR and two with a PR. However, two of them discontinued treatment after 24 and 38 months because of toxicity. The most common grade 3 and 4 toxicities were fatigue, musculoskeletal pain and weakness, and thrombocytopenia. No thrombohemorrhagic events were reported.

Recently, a phase III study with a new formulation of PEG-IFN (peg-proline-IFN-alpha-2b, AOP2014) was initiated. This next generation long-acting form of the drug has a distinct pharmacokinetic and pharmacodynamic profile, which allows for subcutaneous dosing every two weeks. In a phase I/II study, 34 patients with PV were treated for a median of 41 weeks with between 50 and 450 µg every 2 weeks (mean dose, 287 µg) [34]. Of 28 evaluable patients at 28 weeks, 71% had achieved an overall response (33% CR). After one year, 10/11 (91%) evaluable patients had an overall response (46% CR). After 68 weeks, three of seven evaluable patients had a partial molecular response, and one patient had a CMR by 36 weeks. Twenty-seven (79%) patients experienced drug-related AEs. Nine patients (26%) developed serious AEs, four of which were thought to be therapy related. Five (15%) patients had to discontinue the study (three due to AEs). Although this was a small study, the results warranted further investigation of AOP2014 in a phase III study.

Anagrelide as a second-line treatment for essential thrombocythemia

Anagrelide is recommended by the ELN as a second-line treatment for patients with high-risk ET. Anagrelide blocks megakaryocyte differentiation and proliferation and inhibits cyclic AMP phosphodiesterase activity [7]. A large open-label randomized study, (UK-PT1)

compared anagrelide to HU in 809 patients, who were followed for a median of 39 months [35]. Anagrelide plus aspirin was associated with increased rates of arterial thrombosis, serious hemorrhage, and transformation to MF. Furthermore, patients were less likely to complete treatment due to higher rates of side effects, which were mainly cardiovascular. On the other hand, patients treated with anagrelide had a significantly lower incidence of venous thromboembolism.

More recently, two studies reported updated data on the clinical use of anagrelide [36,37]. The ANAHDRET study, a randomized non-inferiority study, compared anagrelide with HU in 259 patients with high-risk ET. Non-inferiority of anagrelide was evaluated on the basis of platelet and leukocyte counts, hemoglobin levels, and ET-related events [37]. There was no significant difference in the incidence of major and minor arterial or venous bleeding and thrombotic events. During the 36-month follow-up, no case of transformation to MF or acute leukemia was reported. The authors suggested that the differences between results from their study and those reported in the UK-PT1 study could be due in part to the patient populations studied: ANAHDRET enrolled patients with previously untreated disease, while the UK-PT1 trial included patients previously treated with HU. In addition, 2008 WHO criteria were used for diagnosis in ANAHDRET, while the UK-PT1 trial used Polycythemia Vera Study Group (PVSG) criteria, which could result in different hematologic phenotypes at presentation and differences in thrombotic risk between the two study populations. However, the UK-PT1 trial enrolled significantly more patients than the ANAHDRET study (809 vs 259), and given differences in patient population and duration of follow-up between the studies, direct comparison of the outcomes is difficult.

Another long-term study followed 21 patients with ET who had been treated with anagrelide for 7 years. Because the prospective study was initiated in 1998, bone marrow trephines were re-examined and WHO 2008 diagnostic criteria were used to reclassify the diagnoses after 7 years of follow-up. Twenty-one of the 40 initial samples were confirmed as “true ET” according to the WHO criteria; 17 were reclassified as PMF, and two as MPN, unclassified. During the follow-up period, none of the patients with “true ET” had transformation to MF, AML, or MDS while on anagrelide [36].

Two small retrospective studies suggest that for patients with ET or PV that have intolerance to HU, a combination of low-dose HU and anagrelide can be effective in controlling thrombocytosis with fewer hematologic toxicities [38,39]. In both studies, the lower-dose combination therapy was better tolerated and better able to control thrombocytosis than HU monotherapy at higher doses. Hemoglobin levels and WBC counts were also increased on combination therapy, likely due to the reduction in the HU dose.

JAK2 inhibitors

The discovery of the *JAK2*^{V617F} mutation in MPNs led to the development of JAK2 inhibitors, which have demonstrated remarkable activity in patients with PMF and post-PV/post-ET MF [40,41]. Ruxolitinib is the first (and so far only) JAK inhibitor to be approved by the US Food and Drug Administration to treat MF. Ruxolitinib is currently being studied in patients with PV (*n*=34) and ET (*n*=39) who are refractory to or intolerant of HU [42-44]. In the phase II study, patients were treated with a starting dose of 10 mg (for PV) or 25 mg

(for ET) twice daily, with dose adjustments allowed as necessary. After a median follow-up time of 15 months, 97% of patients with PV had their hematocrit reduced to < 45% without the need for phlebotomy. For patients with palpable splenomegaly, 59% had at least a 50% reduction in palpable spleen length. Most patients had reduction or resolution of symptoms, including pruritus, night sweats and bone pain. The most common AEs were anemia and thrombocytopenia (mostly grade 1) and could be managed with dose reductions. In a long-term follow-up 74% of patients with a response at 24 weeks, maintained their response at week 144, and the median duration of response had not been reached. In the ET cohort, 49% of patients had a normalization of platelet counts and 82% achieved platelet counts < $600 \times 10^9/L$. Marked reductions in bone pain, pruritis, and night sweats were also achieved in patients with ET. Overall, ruxolitinib therapy was well tolerated and provided durable clinical benefits. In a step towards FDA approval of ruxolitinib in PV, an open-label, randomized phase III trial comparing ruxolitinib to best available care in patients with PV who are resistant to or intolerant of HU (RESPONSE trial) is underway.

Histone deacetylase inhibitors

Another class of novel targeted agents being tested in patients with PV and ET that are resistant to HU are histone deacetylase (HDAC) inhibitors. Givinostat, an HDAC inhibitor with specificity for JAK2^{V617F}-mutated cells was tested in a pilot phase II study in patients with HU-resistant/intolerant JAK2^{V617F}-positive PV ($n=12$) and ET ($n=1$) [45]. Givinostat given orally (50 mg BID) was well-tolerated, with no grade 4 toxicities reported. Low-grade (grade 2) gastrointestinal toxicities, including diarrhea (62% of patients; only one grade 3 event), nausea (10%) and gastric pain (7%), were most common. Other toxicities occurring in more than one patient included anemia (21% of patients), low-grade thrombocytopenia (10%), and low-grade fatigue (17%). Ten patients had their doses reduced and 15 patients had at least one dose interruption due to adverse events that included diarrhea, gastric pain, increased liver enzymes, fatigue, thrombocytopenia, and anemia. Seventy-five percent of patients had a reduction in splenomegaly and 54% had a clinical response after 12 weeks on treatment. Results of a more recent phase II study of givinostat in combination with HU shows that the combination has modest activity (50% overall response rate) in patients with PV who did not respond to the (MTD) of HU [46]. The combination was well-tolerated, with only two grade 3 adverse events reported (nausea and anemia). Grade 2 thrombocytopenia (25% of patients) and diarrhea (23%) were the most common toxicities. Another HDAC inhibitor, vorinostat was tested in a phase 2 multicenter trial enrolling patients with PV ($n=44$) and ET ($n=19$). Most patients who completed 24 weeks of treatment (24/33; 72%) had a response; however, 44% of patients discontinued treatment before the end of the treatment period due to adverse events (25% of which were serious adverse events), including deep vein thrombosis, diarrhea, headache, progression to AML, palpitations, neuropathy, fatigue, and renal impairment. The authors suggest that a strategy combining lower, potentially less toxic doses of HDAC inhibitors with other therapies, such as HU or JAK inhibitors, could be tested in patients with treatment-refractory PV or ET.

Pipobroman, busulphan and radioactive phosphorus

Pipobroman, busulphan and radioactive phosphorus are recommended by the ELN as second-line agents for patients after failure of primary therapy with either HU or IFN- α [7].

However, due to the potential leukemogenicity of these agents, low rate of progression of PV and ET to malignant neoplasms, and relatively long life expectancy for patients with PV and ET, these agents should be reserved for elderly patients (> 80 years) or those with advanced disease, where the risk of thrombosis outweighs the risk of AML/MDS. For example, in a Swedish population study, the use of two or more lines of cytoreductive therapy (commonly HU followed by alkylating agents) was associated with a 2.9-fold increase in transformation rate [47].

Conclusion

Resistance and intolerance to HU can develop in about 20-25% of treated patients with PV or ET, and resistance is associated with disease transformation and reduced survival. Most data on the use of alternative therapies in this patient group comes from retrospective analyses or clinical studies originating from a single or few academic centers, with a relatively small number of patients and short follow-up time. In addition, these studies have used different treatment response criteria that have not been prospectively validated (as they are consensus opinion of the experts in the field). The key question is, therefore, how does one choose the least toxic therapy for patients refractory/resistant to HU? In the authors' opinion, for patients refractory/resistant to HU, the best second-line treatment option among commercially available medications is PEG-IFN- α -2a. A starting dose of 45 or 90 μ g/week given subcutaneously has been reported to be better tolerated than short acting IFN- α and results in high response rates, particularly in patients with PV. For patients with ET, anagrelide is also a good second-line treatment option, and recent data suggest it may be equally as effective as HU. The authors reserve the use of busulphan or radioactive phosphorus for exceptional cases, due to the proven potential of these agents to increase the risk of transformation to acute leukemia. Much emphasis is therefore put on the development of new agents for these patients: among investigational agents, the JAK inhibitors may represent a valuable therapeutic option for patients with HU-resistant/refractory ET and PV, and results from the phase III study are eagerly awaited.

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