Polycythemia Vera: From New, Modified Diagnostic Criteria to New Therapeutic Approaches

Margherita Maffioli, MD, Barbara Mora, MD, and Francesco Passamonti, MD

Drs Maffioli and Mora are hematologists in the hematology department at ASST Sette Laghi - Ospedale di Circolo in Varese, Italy. Dr Passamonti is a professor of hematology in the department of medicine and surgery at the University of Insubria and head of the hematology department at the ASST Sette Laghi - Ospedale di Circolo in Varese, Italy.

Corresponding author:
Francesco Passamonti, MD
Dipartimento di Medicina e Chirurgia
University of Insubria
Via Guicciardini 9
Varese 21100
Italy
Tel: (39) 0332 393 648
E-mail: francesco.passamonti@uninsubria.it

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Abstract: Polycythemia vera (PV) is a Philadelphia chromosome–negative chronic myeloproliferative neoplasm that is associated with a Janus kinase 2 (*JAK2*) mutation in most cases. The most recent update to the World Health Organization diagnostic criteria for PV was published in 2016. These were the modifications with the greatest effect: (1) lowering the hemoglobin threshold, allowing a diagnosis of PV at 16.5 g/dL in males and at 16.0 g/dL in females and (2) introducing a hematocrit cutoff (49% in males and 48% in females). Patients with PV who are older than 60 years or have had a previous thrombotic event are considered at high risk for thrombosis. Leukocytosis and a high allele burden are additional risk factors for thrombosis and myelofibrosis, respectively. After disease has progressed to post–polycythemia vera myelofibrosis (PPV-MF), survival must be assessed according to the recently developed Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM). This model is based on age at diagnosis, a hemoglobin level below 11 g/dL, a platelet count lower than 150×10^9/L, a percentage of circulating blasts of 3% or higher, a *CALR*-unmutated genotype, and the presence of constitutional symptoms. Therapy is based on phlebotomy to maintain the hematocrit below 45% and (if not contraindicated) aspirin. When a cytoreductive drug is necessary, hydroxyurea or interferon can be used as first-line therapy, although the demonstration of an advantage of interferon over hydroxyurea is still pending. In patients whose disease fails to respond to hydroxyurea, ruxolitinib is a safe and effective choice.

Introduction

Polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) constitute the so-called classic Philadelphia chromosome–negative chronic myeloproliferative neoplasms (MPNs).[1-4] PV is characterized by erythrocytosis and, in approximately 40% of patients, some degree of leukocytosis and thrombocytosis. Splenomegaly occurs in 30% of cases and is rarely massive.[5-8] The estimated incidence of PV is 0.4 to 2.8×10^5 per year in Europe and 0.8 to 1.3×10^5 per year in United States, and the reported

Table 1. World Health Organization Criteria for the Diagnosis of Polycythemia Vera

A diagnosis of polycythemia vera requires that either all 3 major criteria, or the first 2 major criteria plus the minor criterion, be met.	
Major criteria	
Criterion No. 1 (clinical)	
Hemoglobin	>16.5 g/dL in men, >16.0 g/dL in women, or
Hematocrit	>49% in men, >48% in women, or
Red cell mass	25% increase above mean normal predicted value
Criterion No. 2 (morphologic)	
Bone marrow morphology[a]	Hypercellularity for age with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
Criterion No. 3 (genetic)	
JAK2 V617F mutation or *JAK2* exon 12 mutation	Present Present
Minor criterion	
Serum erythropoietin level	Subnormal

JAK2, Janus kinase 2.

[a] Major criterion No. 2 (bone marrow morphology) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels >18.5 g/dL in men (hematocrit, 55.5%) or >16.5 g/dL in women (hematocrit, 49.5%) if major criterion No. 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can be detected only with a bone marrow biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post–polycythemia vera myelofibrosis).

median age of patients at diagnosis ranges from 65 to 74 years.[9,10] The natural history of PV is characterized by an increased risk for thromboembolic complications and a predisposition to the development of post–polycythemia vera myelofibrosis (PPV-MF), myelodysplastic syndrome (MDS), or acute myeloid leukemia (AML).[11-14]

Polycythemia Vera: Diagnostic Criteria

The updated World Health Organization (WHO) diagnostic criteria for PV, published in 2016 and reported in Table 1, introduce several significant changes with respect to previous criteria.[1,2]

The modifications with the greatest effect are probably lowering of the hemoglobin threshold used to diagnose PV (to 16.5 g/dL in males and to 16.0 g/dL in females) and introduction of a hematocrit cutoff (49% in males and 48% in females). These modifications derive from retrospective studies recognizing the existence of patients with a Janus kinase 2 (*JAK2*) V617F–mutated MPN, which most often is diagnosed as ET but has PV-consistent bone marrow features, hemoglobin levels below 18.5 g/dL in males and 16.5 g/dL in females, an increased risk for thrombotic complications during follow-up, and a worse disease evolution.[15-21] Such patients are defined as having "masked" or "prodromic" PV.[20]

The current WHO diagnostic criteria place these patients in the PV category, and rightfully so. However, the new hemoglobin and hematocrit cutoffs may lead to a significant excess in diagnostic examinations if they are used to define whom to screen for potential PV, especially males. A retrospective analysis of 248,839 patients with presumptively normal complete blood cell count results showed that 6.48% of the males had hemoglobin levels above 16.5 g/dL or hematocrit levels above 49%, whereas 0.28% of the females had hemoglobin levels above 16.0 g/dL or hematocrit levels above 48%.[22] In patients with borderline hemoglobin levels, it is therefore important to assess carefully for possible causes of secondary polycythemia and perform a diagnostic workup for PV in the presence of clinical features (eg, pruritus, splenomegaly, previous thrombosis) and/or laboratory features (eg, leukocytosis, thrombocytosis) associated with MPN.

A recent commentary, however, warned about the risk of missing a PV diagnosis if the presence of additional MPN-associated clinical and/or laboratory features is deemed mandatory before the clinician can proceed with diagnostic screening. It should be noted that the patients included in this analysis had a WHO-defined diagnosis of PV and were not individuals undergoing diagnostic screening. Furthermore, the analysis showed that using a hemoglobin cutoff of 17 g/dL in males resulted in 14% of PV diagnoses being missed; however, when males with lower hemoglobin values (≥16.5-17 g/dL) who had

a platelet value of at least 440 × 10^9/L were included, only 3% of diagnoses were missed.[23] Notwithstanding these considerations, the focus should clearly remain on diagnosing PV correctly according to the current WHO classification because doing so has significant prognostic and therapeutic implications.

A second important modification introduced by the 2016 WHO criteria is the upgrade of histopathologic features to major diagnostic criteria. Bone marrow morphology in PV is characterized by age-adjusted hypercellularity and panmyelosis. Approximately 20% of patients with PV have grade 1 bone marrow reticulin fibrosis at diagnosis, which does not necessarily imply a diagnosis of myelofibrosis but is associated with a higher risk for myelofibrosis evolution.[24] A recent retrospective study that included 262 patients with PV whose disease was diagnosed according to the 2016 WHO criteria confirmed the association between bone marrow reticulin fibrosis of at least grade 1 at diagnosis (present in this study in as many as 48% of patients) and subsequent fibrotic progression.[25] It should be noted that the presenting clinical and laboratory features did not differ significantly between patients with and without bone marrow fibrosis. The prognostic information derived from a bone marrow biopsy performed at diagnosis may translate in a more careful follow-up strategy and may be an additional reason to undertake such an analysis beyond strictly adherence to the WHO diagnostic criteria, especially in younger male patients with hemoglobin values above 18.5 g/dL or female patients with hemoglobin values above 16.5 g/dL.

The third major diagnostic criterion is the mutational characterization. *JAK2* mutations, which result in JAK-STAT pathway activation, are present in the vast majority of patients (the V617F mutation is present in 95% to 97% of patients,[26,27] and exon 12 mutations are present in most of the remaining patients).[28,29]

The new diagnostic criteria allow a diagnosis of *JAK2*-unmutated PV, which is exceedingly rare. Few cases of *CBL* or *LNK* mutations have been described, and diagnostic testing for these mutations is not widely available.[30] For patients without evident causes of secondary polycythemia and without a *JAK2* mutation, careful follow-up is recommended.

A reduced serum erythropoietin (EPO) level is the only minor diagnostic criterion that has been retained in the 2016 WHO criteria. However, a significant proportion of patients with PV—ranging from 7% to approximately 40%—seem to have normal serum EPO values, pointing to a low negative predictive value for this test.[31]

Prognosis of Patients With Polycythemia Vera

The *ECLAP (*European Collaboration on Low-Dose Aspirin in Polycythemia Vera) trial was the first randomized study to assess prospectively the efficacy of low-dose aspirin in reducing thrombotic events in patients with PV.[32] The results of this pivotal trial led to the use of prophylactic low-dose aspirin in all patients with PV and no contraindications. Furthermore, the ECLAP study showed that the incidence of thrombosis in patients younger than 65 years without prior thrombosis was 2.5% persons per year, the incidence in those older than 65 years or with prior thrombosis was 5.0% persons per year, and the incidence in patients older than 65 years with prior thrombosis was 10.9% persons per year. Accordingly, patients older than 60 years or with a previous thrombotic event are considered to be at high risk for thrombosis (the presence of either factor defines high-risk patients, whereas the absence of these risk factors defines low-risk patients), and therapeutic choices are often made solely on this basis.[33] However, a growing amount of data show that an elevated leukocyte count,[34,35] the presence of cardiovascular risk factors,[36] a high (>50%) *JAK2* V617F allele burden,[8] and the presence of bone marrow fibrosis[24] may affect the likelihood of thrombosis, progression, and survival.

A multicenter, retrospective, observational study conducted in a cohort of 1545 patients with PV (diagnosed according to the 2008 WHO criteria) focused on the evaluation of survival patterns.[37] In multivariable analysis, survival was negatively affected by older age, leukocytosis, venous thrombosis, and abnormal karyotype; a prognostic model that included the first 3 factors (with older age bearing significant weight) identified risk groups with median survival times of 10.9 to 27.8 years (hazard ratio [HR], 10.7; 95% CI, 7.7-15.0).

A recent study that included 271 patients with PV (diagnosed according to the 2008 WHO criteria) reported a 20% incidence of abnormal karyotype with sole del(20q); double abnormalities and complex karyotype negatively affected survival.[38]

Post–Polycythemia Vera Myelofibrosis: Diagnosis, Genetics, and Prognosis

PPV-MF is currently diagnosed according to the 2008 International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) Criteria (Table 2),[39] with histopathology clearly playing a prominent role. Because the therapeutic needs and available strategies in PV and PPV-MF differ significantly, bone marrow biopsy is mandatory when disease evolution is suspected.

Patients with PPV-MF or post–essential thrombocythemia myelofibrosis (PET-MF) are often included in interventional studies along with those who have PMF.

Table 2. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) Criteria for the Diagnosis of Secondary Myelofibrosis

A diagnosis of post–polycythemia vera myelofibrosis requires that the 2 major criteria and at least 2 minor criteria be met.	
Major criteria	
Criterion No. 1	
Documentation of a previous diagnosis of polycythemia vera (WHO criteria)	Met
Criterion No. 2	
Bone marrow morphology	Reticulin fibrosis grade 2/3 (on scale of 0-3), or reticulin fibrosis grade 3/4 (on scale of 0-4)
Minor criteria	
Anemia[a] or sustained loss of requirement for phlebotomy or cytoreduction	Present
Leukoerythroblastosis	Present
Spleen size	Increasing splenomegaly, defined as either an increase in palpable splenomegaly of ≥5 cm (from left costal margin) or the appearance of newly palpable splenomegaly
Constitutional symptoms[b]	Development of ≥1 of 3

WHO, World Health Organization.

[a] Defined as a hemoglobin value <12 g/dL for men and <13.5 g/dL for women.

[b] Defined as weight loss of ≥10% in 6 months, night sweats, and unexplained fever (temperature >37.5°C).

However, clinical, molecular, and prognostic information specific to patients with PPV-MF or PET-MF (together referred to as secondary myelofibrosis [SMF]) has been lacking for some time, in contrast to the growing body of knowledge regarding PMF. The need for further information about SMF led to the development of the MYSEC (Myelofibrosis Secondary to PV and ET) project, an international effort generated in 2014 to collect retrospective data on SMF. In an initial analysis of 685 molecularly annotated SMF cases, all patients with PPV-MF carried the *JAK2* V617F mutation, and the driver mutation distribution in PET-MF appeared similar to that in PMF, although a direct comparison was clearly not feasible.[40] Furthermore, the analysis disclosed that survival varied significantly according to genotype, with patients who had *CALR*-mutated PET-MF living longer than those who had *JAK2*-mutated PPV-MF or PET-MF. PPV-MF and PET-MF appear to have a higher mutational load (*JAK2* V617F–mutated and *CALR*-mutated allele burden) compared with PV and ET, suggesting a role for the accumulation of mutated alleles in the progression to SMF.[41-43] With regard to additional, nondriver mutations, 25% of patients with SMF have been found to harbor a mutation in *ASXL1*, *EZH2*, *SRSF2*, *IDH1*, or *IDH2*.[44] Only mutations in *SRSF2* appear to correlate with reduced survival, which is different from what occurs in PMF. Further molecular insight is clearly warranted in SMF, especially when one considers the differences that are emerging with respect to PMF.

The prognostic assessment of patients with PPV-MF has in recent years relied on tools that were originally developed in patients with PMF, such as the International Prognostic Scoring System (IPSS),[45] the Dynamic IPSS (DIPSS),[46] and DIPSS Plus.[47] Retrospective studies have shown, however, that such tools may not be ideal to analyze prognosis in PPV-MF and PET-MF.[48-50] The MYSEC project has provided an ideal framework to develop a prognostic system specifically tailored for PPV-MF and PET-MF, named the MYSEC Prognostic Model (MYSEC-PM). A cohort of 685 patients with SMF (333 with PET-MF and 352 with PPV-MF) and a known phenotype driver mutational status were analyzed.[51] Median survival in patients with SMF was 9.3 years (95% CI, 8-not reached). Cox regression models and least absolute shrinkage and selection operator were employed to select the following subset of significant covariates: hemoglobin level below 11 g/dL, platelet count below 150 × 10^9/L, at least 3% circulating blasts, *CALR*-unmutated genotype, and the presence of constitutional symptoms. Age at diagnosis was also found to be an important predictor of survival according to multivariate models and was retained as a continuous covariate. Each discrete variable was assigned a risk point (obtained by rounding the risk coefficients): 2 points for hemoglobin

level below 11 g/dL, at least 3% circulating blasts, and *CALR*-unmutated genotype; 1 point for platelet count below 150 × 10^9/L and for the presence of constitutional symptoms. Age-related risk, calculated on the points scale, accounted for approximately 0.15 points per year of age. The sum of risk points and age-related risk was mapped into 4 risk categories with different median overall survivals: *low risk* (score <11), median survival not reached; *intermediate 1 risk* (score ≥11 and <14), median survival of 9.3 years (95% CI, 8.1-not reached); *intermediate 2 risk* (score ≥14 and <16), median survival of 4.4 years (95% CI: 3.2-7.9); and *high risk* (score ≥16), median survival of 2 years (95% CI, 1.7-3.9). A nomogram to facilitate the use of the model has been developed. The large set of patients with SMF included in the MYSEC project made it possible to develop a model with superior discriminatory power with respect to the IPSS in this specific subset of myelofibrosis.

Treatment of Polycythemia Vera

To date, patients with PV have been treated with the aim of reducing the risk for vascular complications. The aforementioned ECLAP study provided high-quality data that supported the use of low-dose aspirin in all patients who do not have clear contraindications.[32] Furthermore, it aided the identification of low-risk patients (ie, those <60 years and without a history of thrombosis) and high-risk patients (ie, those not considered low risk). Low-risk patients are commonly treated with phlebotomy and antiplatelet therapy, whereas high-risk patients receive cytoreductive treatment in addition to low-dose aspirin (depending on the type and date of the previous thrombotic event, oral anticoagulation may be indicated instead of low-dose aspirin).[33]

The ideal target hematocrit for either phlebotomy or cytoreduction has long been unclear, resulting in different approaches that largely depend on the clinician's inclination. Some clinicians will aim for more stringent hematocrit control—for example, below 45%—whereas others who are satisfied with a more "relaxed" approach will seek hematocrit values between 45% and 50%, or even below 52%. The CYTO-PV (Cytoreductive Therapy in PV) randomized trial has demonstrated a reduction in fatal and nonfatal thrombotic events in the group of patients treated to maintain hematocrit levels below 45%.[52] This is therefore the treatment goal in all patients with PV. However, additional risk factors for thrombosis, such as leukocytosis and cardiovascular risk factors, need to be considered in the treatment algorithm of patients with PV. A progressive increase in the leukocyte count is considered a criterion to initiate cytoreductive treatment, and actionable cardiovascular risk factors should be managed to ameliorate the patient's risk profile.[33,53,54] Thrombocytosis (platelet count >1000 × 10^9/L) constitutes a risk factor. In the event of thrombocytosis, it is therefore advisable to consider the use of low-dose aspirin with caution. Extreme thrombocytosis (platelet count >1500 × 10^9/L), although rare in PV, is regarded as an indication for cytoreductive treatment. Symptomatic splenomegaly or disease-related symptoms may be an indication to start cytoreduction.[9,55,56]

The objective of reducing the risk for evolution to myelofibrosis, MDS, and/or AML remains elusive, although certain therapeutic agents are thought to have some disease-modifying effect.

For cytoreduction, hydroxyurea, an oral antimetabolite that prevents DNA synthesis by inhibiting the enzyme ribonucleoside reductase, is the most commonly used first-line agent. Hydroxyurea is generally well tolerated and only rarely associated with the development of significant side effects, such as leg ulcers and gastrointestinal toxicity (eg, nausea, diarrhea). However, it is necessary to warn patients about possible skin and nail changes and to recommend strict dermatologic surveillance in the case of new skin lesions. No definitive association has been demonstrated between the use of hydroxyurea (as a single agent, not as part of a sequence of cytotoxic drugs) and the development of AML.[57] Furthermore, a large population-based study has shown that 25% of people with post-MPN AML were never exposed to cytoreductive treatment, that hydroxyurea at any dose was not associated with an increased risk for AML, and that only an increasing cumulative dose of alkylators is associated with AML.[58]

The European LeukemiaNet recommendations[33] and the subsequent European Society for Medical Oncology guidelines[9] suggest interferon alfa as a first-line alternative to hydroxyurea, although interferon alfa is not approved for the treatment of PV in any of its various presentations. Interferon alfa induces a high rate of hematologic responses and can significantly reduce the *JAK2* V617F allele burden.[59] Even though an elevated allele burden is associated with more aggressive disease features, such as leukocytosis, splenomegaly, and increased risk for thrombosis, and even though a *JAK2* V617F allele burden above 50% is associated with an increased risk for myelofibrosis evolution,[8] it is still unclear whether and to what extent reduction of the mutational load translates into a clinical benefit.

First-Line Therapy: Hydroxyurea or Interferon?

Two prospective trials in the first-line setting were presented at the 2016 meeting of the American Society of Hematology.[60,61]

PROUD-PV (A Randomized Controlled Phase 3 Trial Comparing Ropeginterferon Alfa-2b to Hydroxyurea in Polycythemia Vera Patients) is a randomized,

controlled, parallel-group multicenter phase 3 study that is being conducted in patients with PV (diagnosed according to the 2008 WHO classification) who either are treatment-naive or have been pretreated with hydroxyurea for less than 3 years. Patients are randomly assigned to receive ropeginterferon alfa-2b or hydroxyurea. The study was designed as a noninferiority trial, with complete hematologic remission at 12 months being the primary endpoint. Of the 257 patients randomized, 62% were treatment-naive. Both treatments have been well tolerated, with a dropout rate of 15%. Overall, 45% of patients have had a hematologic response, without significant differences noted between the 2 treatments.

The MPD-RC (Myeloproliferative Disorders Research Consortium) 112 Global Phase III Trial is comparing pegylated interferon alfa-2a with hydroxyurea in PV and ET. The PV group includes patients with newly diagnosed PV (<5 years) and treatment-naive patients at high risk for thrombosis (age >60 years, history of thrombosis, extreme thrombocytosis, symptomatic splenomegaly, and/or uncontrolled cardiovascular risk factors). Complete hematologic remission after 12 months is the primary endpoint. A total of 168 patients have been enrolled, without significant differences in clinical presentation noted between the 2 groups. Complete hematologic remission, partial hematologic remission, and overall response have been observed in 33%, 36%, and 69% of the hydroxyurea-treated patients and in 28%, 53%, and 81% of the patients treated with pegylated interferon, without statistically significant differences. Among 38 patients, phlebotomy was performed in none of those treated with hydroxyurea vs 20% of those treated with pegylated interferon (P=.02). No differences in terms of MPN Symptom Assessment Form Total Symptom Score have been reported (>50% reduction in total symptom score in 32%-35% of patients). Concerning toxicity, grade 3 adverse events have occurred in 14% of the hydroxyurea-treated patients and in 44% of the patients treated with pegylated interferon.

Overall, when the 12-month results of these 2 prospective studies are taken into account, hydroxyurea remains the first-line treatment of choice in high-risk patients with PV, arguably with some exceptions, such as women of childbearing potential at high risk and young patients at high risk who refuse hydroxyurea because of the fear that it may favor leukemic evolution. However, the ongoing phase 3 studies will provide further results with longer follow-up.

Second-Line Therapy

The European LeukemiaNet recommendations list hydroxyurea or interferon as second-line cytoreductive therapy for patients who received interferon or hydroxyurea first, respectively. The efficacy of pegylated interferon in PV has been demonstrated retrospectively.[59,62,63] These analyses reported a reduction of the *JAK2* V617F load from baseline value in 48% of patients. Overall hematologic response was excellent (95%), although 24% of patients discontinued pegylated interferon because of toxicity. Similar results were obtained in 40 patients treated after a median time of approximately 5 years from PV diagnosis.[62,63] The overall hematologic response rate was 80%, and abrogation of the V617F clone occurred in 14% of cases. However, it must be said that the (albeit preliminary) results of the PROUD-PV and MPD-RC 112 trials, reported in the previous section, have lowered the expectations for interferons.

On the other hand, the concept of second-line therapy in PV is not so clear. Criteria for hydroxyurea intolerance and resistance for clinical trials (not for clinical practice) have been proposed thanks to an international effort.[64] Recently, a Spanish study provided the size of this condition: overall, the criteria for hydroxyurea intolerance or resistance were found in 15% of 890 patients with PV. In detail, a need for phlebotomy was reported in 3.3%, uncontrolled myeloproliferation in 1.6%, failure to reduce massive splenomegaly in 0.8%, cytopenia at the lowest hydroxyurea dose to achieve response in 1.7%, and extra-hematologic toxicity in 9%. Concerning the predictive role of these criteria, cytopenia affected survival, progression to myelofibrosis, and AML, and splenomegaly increased the occurrence of myelofibrosis.

Two prospective, randomized studies, RESPONSE (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) and RESPONSE-2 (Ruxolitinib Efficacy and Safety in Patients With HU Resistant or Intolerant Polycythemia Vera vs Best Available Therapy), have reported data in the last 2 years.[65,66] RESPONSE included 222 patients with hydroxyurea intolerance/resistance, need of phlebotomy, and splenomegaly, and RESPONSE-2 included 173 patients with the same entry criteria except for splenomegaly. Patients were randomly assigned to receive ruxolitinib (Jakafi, Incyte) or best available therapy. Initial standard therapy included hydroxyurea (59% in RESPONSE, 49% in RESPONSE-2); interferon (12% in RESPONSE, 13% in RESPONSE-2); or no medication (15% in RESPONSE, 28% in RESPONSE-2). The primary composite endpoint included hematocrit control (phlebotomy independence from week 8 to week 32, with ≤1 phlebotomy after randomization) in the absence of phlebotomy and 35% reduction in spleen volume at week 32 (the latter absent in RESPONSE-2).

In RESPONSE, the primary endpoint was achieved in 21% of patients treated with ruxolitinib and 1% of

those in the standard therapy group. Hematocrit was controlled in 60% of patients receiving ruxolitinib and 20% of those receiving standard therapy. A reduction in spleen volume of at least 35% occurred in 38% of the patients treated with ruxolitinib and 1% of those who received standard therapy. A complete hematologic remission was achieved in 24% of the patients in the ruxolitinib group and 9% of those in the standard therapy group. A 50% reduction in the total symptom score was obtained in 49% of the ruxolitinib patients vs 5% of the standard therapy patients.

In RESPONSE-2, hematocrit control was achieved in 62% of the ruxolitinib-treated patients and 19% of those receiving best available therapy. The most frequent hematologic adverse events of any grade were anemia (14% with ruxolitinib vs 3% with best available therapy) and thrombocytopenia (3% with ruxolitinib vs 8% with best available therapy). No cases of grade 3/4 anemia or thrombocytopenia occurred in the patients treated with ruxolitinib.

In the 80-week follow-up analysis of RESPONSE, the rate of all thrombotic events (any grade) was 1.8 × 100 patient-years of exposure to ruxolitinib and 8.2 × 100 patient-years of exposure to standard care.[67]

Taken together, results from the RESPONSE and RESPONSE-2 trials indicate that ruxolitinib is the standard of care for second-line therapy in a patient population previously treated with hydroxyurea. Data derived from the RESPONSE study showed that patients receiving ruxolitinib (from randomization or after crossover) had consistent reductions in *JAK2* V617F allele burden (up to 40%) throughout the study.[68] The relationship between changes in allele burden and clinical outcomes in patients with PV, however, remains unclear.

Conclusions

The management of PV has changed since the discovery of the *JAK2* mutation. Basically, doctors must consider the revised WHO diagnostic criteria in light of the new cutoffs for hemoglobin level and hematocrit. First-line therapies are hydroxyurea and possibly interferon (although the advantage of interferon over hydroxyurea is still to be demonstrated). In patients whose disease fails to respond to hydroxyurea, ruxolitinib is a safe choice.

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