Polycythemia Vera: Contemporary Updates in Diagnosis, Prognosis, and Treatment

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Abstract

Polycythemia vera (PV) is a myeloproliferative neoplasm characterized primarily by erythrocytosis and complicated by thrombosis, myelofibrosis, leukemic transformation, and increased mortality. PV also carries with it a significant symptom burden regardless of risk classification. The discovery of the *JAK2* V617F mutation in 2005 has triggered a new era of scientific discovery, impacted diagnostic capabilities, and led to new developments in treatment. In this review, we address updates in molecular pathogenesis, including impact from non-*JAK2* mutations on prognosis. Changes to the diagnostic criteria are reviewed, along with updates in treatment options. Finally, management of special situations that may arise in patients with PV, such as surgery and pregnancy, are discussed.

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Introduction

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) characterized by excess production of erythrocytes, and often leukocytes and platelets, with significant symptom burden and increased risk for thrombosis, myelofibrosis (MF), and leukemic transformation. PV has an interesting history that has been previously reviewed.[1] Important milestones include the first descriptions by Louis Henri Vaquez in 1892 and, subsequently, by William Osler, who described 4 additional cases in a series published in 1903.[1] In 1951, William Dameshek recognized that PV shared a number of overlapping clinical and laboratory features with other "myeloproliferative disorders" (MPDs), a term he coined to classify PV, along with essential thrombocythemia (ET) and MF, which are now considered the classical MPNs. He also speculated that the MPDs shared a common pathogenesis and represented "variable manifestations of proliferative activity of the bone marrow cells." He alluded to the presence of a "myelostimulatory factor;" this would be discovered about 55 years following his landmark perspective.[2] Regarding therapy, early studies suggested potential harm when using certain cytoreductive therapies, including radioactive phosphorus, a treatment thought to increase the incidence of acute myeloid leukemia (AML).[3] Concerns about the safety and efficacy of PV therapies were among the major incentives that led to the creation of the Polycythemia Vera Study Group (PVSG). In addition to establishing diagnostic criteria, the PVSG completed several trials of major importance to the field. In 2005, with the discovery of the *JAK2* mutation, PV entered a new era.

Here, we review important contemporary updates in the epidemiology of PV, changes in diagnostic criteria and prognostic assessment, contemporary insights into disease pathogenesis, and updates from ongoing important clinical trials.

Epidemiology

The contemporary epidemiology of PV has been recently described, centered on a population-based study, using Surveillance, Epidemiology, and End Results program data from 2001 to 2012.[4] Including MPN and MPN/myelodysplastic (MDS) overlap syndromes, PV was the most commonly identified myeloid neoplasm in this group, with an incidence of 10.9 per 1 million persons. Although described in all age ranges, the median age at presentation was 65 years, and a male predominance was noted.[4] In another study using data from large United States health plans, the prevalence of PV was found to be 44 to 57 per 100,000 persons.[5] Currently underway is a large, real-world, prospective observational study of 2000 patients with PV that will describe contemporary demographics.[6]

Molecular Pathogenesis

The molecular basis of PV and the other MPNs was unknown until 2005, when the discovery of the *JAK2* V617F mutation was made. This mutation leads to constitutive tyrosine kinase phosphorylation that promotes cytokine hypersensitivity and induces erythrocytosis.[7] The erythroid progenitor cells that carry this acquired mutation are able to grow both in the presence and absence of erythropoietin, whereas wild-type progenitors are unable to grow without erythropoietin.[8] This causal relationship was evidenced by the development of erythrocytosis in mice 4 weeks after transplantation of bone marrow cells infected with retrovirus containing mutant *JAK2*, but not with wild-type *JAK2* or an empty vector.[7] This mutation has since been found to be present in most patients with PV and is located on exon 14 for 96% of patients and on exon 12 for 3% of patients with the mutation.[9] In a comparison of

patients with ET with and without the *JAK2* mutation, it was found that those with the mutation had increased hemoglobin, increased neutrophil count, more venous thrombosis (VT), and a higher rate of conversion to PV.[10] Some use this evidence as a hypothesis that PV and *JAK2*-positive ET exist on a continuum rather than as distinct disease processes.[10] Approximately 30% of patients with PV experience loss of heterozygosity on chromosome 9p for the V617F mutation as a result of mitotic recombination. Homozygosity appears to modify the disease phenotype and clinical consequences.[11]

Some patients with PV may be genetically predisposed to developing *JAK2*-positive clonal hematopoiesis. A recent study performed genome-wide association analysis and confirmed a previously recognized association with a predisposition haplotype (46/1).[12] These predisposition alleles are associated with the following genes: *TERT*, associated with myeloproliferation; *SH2B3*, which interferes with *JAK-STAT* activation; *ATM*, which is involved in DNA repair along with *CHEK2*; *PINT*, which is regulated by p53; and *GFI1B*, required for erythropoiesis and megakaryopoiesis.[12] Individuals with these genes may be genetically predisposed to acquiring the *JAK2* mutation and, subsequently, an MPN.

Other non-*JAK2* mutations that may alter phenotype have been identified in patients with PV. Compared with MF, the average number of mutations in PV (and ET) is lower, which is consistent with MF being a more advanced stage of disease.[13] One such mutation is *TET2*, which is present in approximately 10% of patients with the *JAK2* mutation, as identified by genotyping hematopoietic colonies or through next-generation sequencing. Twenty-four patients of the 246 screened had both mutations, of which 11 had PV and the remaining had either ET or MF. The order by which *JAK2* and *TET2* mutations are acquired may affect phenotype. The *JAK2*-first patients presented at a younger age, were more likely to present with PV, were more likely to have a thrombotic event, and had a better in vitro response to ruxolitinib.[14] Additionally, a recent study identified additional non-*JAK2* mutations in patients with PV that may have prognostic value. In a study of 216 patients, 133 of whom had PV, a myeloid panel of 27 genes identified 3 particular genes, *ASXL1*, *SRSF2*, and *IDH2*, that were associated with worse overall survival and greater frequency of progression to MF.[15] In a study of 19 patients, gene expression in circulating CD34-positive cells was evaluated and demonstrated specific differences in gene regulation based on gender; women with PV had fewer deregulated genes, but more molecular pathways activated compared with men. Further, there was a difference in gene expression patterns between those with indolent and aggressive disease courses.[16]

Diagnostic Criteria and Challenges

The World Health Organization (WHO) criteria for PV were updated in 2016 with some notable changes (**Table**). The hemoglobin threshold, which was previously greater than 18.5 g/dl in men and greater than 16.5 g/dl in women, is now 16.5 g/dl and 16 g/dl, respectively.[17] This change may be based on a prior recognition of a "masked PV" phenotype, a recognition that came from a study suggesting that patients with PV features, especially those with consistent bone marrow morphology, despite having hemoglobin values below the prior diagnostic threshold, had worse overall survival.[18] In a practical sense, this lower hemoglobin threshold allows for better differentiation between PV and *JAK2*-positive ET.[19] This is an important distinction since the cornerstone of PV management and thrombosis risk reduction includes phlebotomy; those misclassified as having ET may miss out on this opportunity. Along these lines, patients with masked PV had higher rates of thrombosis compared with those with PV diagnosed based on the 2008 WHO criteria; these higher thrombosis rates were thought to be secondary to delays in treatment based on underrecognition of masked PV.[20]

Updated diagnostic criteria include the bone marrow findings as a major criterion for diagnosis, unless the hemoglobin is greater than 18.5 g/dl.[17] Some patients with PV are found to have bone marrow fibrosis at diagnosis; if diagnostic criteria for PV are met, this diagnosis remains, rather than being changed to a diagnosis of MF, although this presentation influences prognosis. In a review of 260 patients with PV, those with grade 1 or higher bone marrow fibrosis at the time of diagnosis were more likely to have progression to MF, although there was not an effect on overall survival or leukemic transformation.[21]

Another diagnostic challenge involves patients with abdominal VT, such as hepatic or portal VT. As has been well described, a significant proportion of these patients have *JAK2* mutations, even in the absence of other MPN features, such as erythrocytosis, which may be masked by hypersplenism, hemodilution, and bleeding. Although these patients with occult MPN do not meet diagnostic criteria for PV at the time of thrombosis, in many cases, an overt MPN, most commonly PV, presents after a period of latency.[22] These patients are commonly young women who are presenting with their first manifestation of MPN/PV.[23]

Prognosis/Risk Factors for Complications

The most well known complications associated with PV include its thrombotic tendency, a long-term possibility of evolution to MF or AML, and compromised longevity (**Figure**). It has also become clear that regardless of risk, patients with PV have a symptomatic burden that impacts quality of life.[24]

Thrombosis

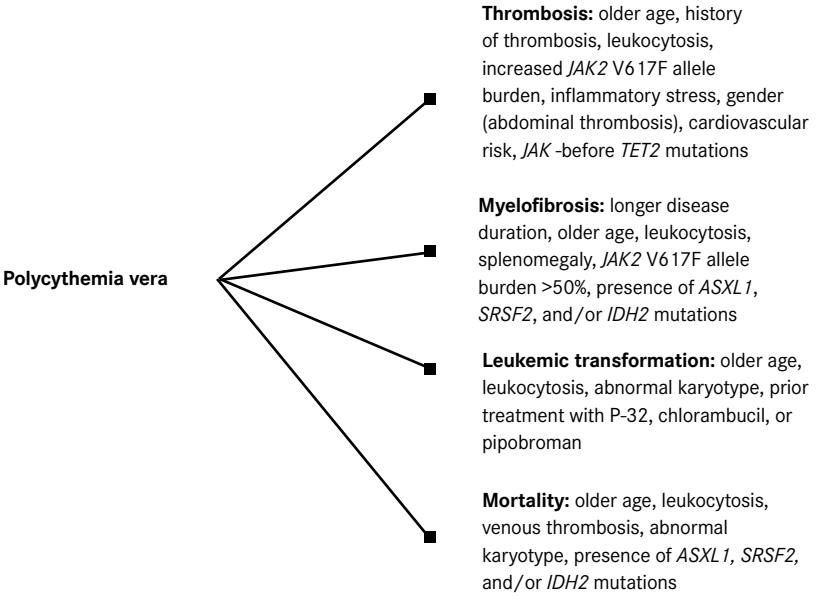
The risk of thrombosis ascertained from the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) data from 2004 was 4.4% of patients per year.[25] The more recent Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) study placed the risk of thrombosis at 2.7% of patients per year; this lower rate may be reflective of more aggressive treatment.[26] Traditionally, thrombosis risk assessment has been based on age and thrombosis

TABLE. World Health Organization Criteria for Polycythemia Vera

2008 Criteria	2016 Criteria
Major Criteria	
1. a) men: hgb >18.5; women: hgb >16.5; OR b) hgb or hct >99% reference range; OR c) men: hgb >17; women: hgb >15, if ≥2 from baseline and not due to correction of iron deficiency; OR d) red cell mass >25% baseline 2. Presence of *JAK2* V617F	1. Men: hgb >16.5 g/dL or hct >49%; women: hgb >16 g/dL or hct >48% 2. Presence of *JAK2* V617F or *JAK2* exon 12 mutation 3. Bone marrow biopsy with hypercellularity for age with trilineage growth
Minor Criteria	
1. Subnormal serum EPO level 2. Bone marrow biopsy with trilineage growth 3. Endogenous erythroid colony growth	1. Subnormal serum EPO level
Diagnostic Requirements	
Both major criteria and 1 minor criterion, or first major criterion and 2 minor criteria	All 3 major criteria, or first 2 major criteria and the minor criterion

EPO indicates erythropoietin; hct, hematocrit; hgb, hemoglobin. Adapted from Arber et al.[17]

FIGURE. Complications of Polycythemia Vera and Their Associated Risk Factors



history. Notably, subanalysis of the CYTO-PV data identified leukocytosis as an additional risk factor for thrombosis.[27] Additionally, an increased *JAK2* V617F allele burden has been considered as a potential risk factor.[28] Other contributing/emerging mechanisms for thrombosis may include inflammatory stress, activation of the endothelium and platelets, and activated protein C resistance.[29]

While advanced age is an accepted risk factor for thrombosis, some younger patients have a unique predisposition to thrombosis. For example, in 1 study of younger patients with PV (age <45 years at diagnosis) compared with patients diagnosed after age 65 years, the overall thrombosis rates were statistically similar (27% vs 31%), but younger patients, especially women, were much more likely to have VT involving abdominal veins. Further, these younger patients may experience a thrombotic event despite having lower leukocyte counts and *JAK2* allelic burdens compared with those diagnosed at a typical age.[23]

The associations among cardiovascular risk factors and vascular consequences in PV are becoming better appreciated. In a retrospective review of 604 patients, 75 patients (12%) experienced a thrombotic event within a median follow-up period of 4.9 years. A statistically significant association between hypertension and arterial thrombosis was found in this patient population that was otherwise deemed to have low risk for thrombosis.[30] Of the cardiovascular risk factors, hypertension is more common in patients with PV, particularly those with higher hematocrit. In a prospective study of 3620 men who were followed between the years 1998 and 2009, every 1% increase in hematocrit was associated with a 7% increase in incidence of hypertension. This may be in part due to the effect of increased viscosity on resistance and the load that it subsequently places on the arterial system.[31] If an antihypertensive agent is required in a PV patient, angiotensin- converting enzyme (ACE) inhibitors may be beneficial; they are also utilized after kidney transplants to reduce erythrocytosis.[30] A review of the ECLAP database demonstrated that patients on ACE inhibitors required chemotherapy less frequently than those on different classes of antihypertensives; however, there were not significant differences in hematocrit or in thrombosis-free survival.[32] This interesting question requires further study.

Myelofibrosis, Leukemia, and Survival

A long-term consequence of PV is evolution to post PV MF, which has a prevalence of approximately 5% at 10 years and 6% to 14%

at 15 years.[33] The diagnosis requires bone marrow fibrosis at least greater than grade 2 on a 3-point scale, and at least 2 of the following: anemia or no longer requiring treatment to maintain a hematocrit goal; a leukoerythroblastic peripheral smear; splenomegaly; or at least 1 constitutional symptom.[34] In addition to disease duration, risk factors for progression to MF include older age, leukocytosis, splenomegaly, marrow fibrosis at diagnosis, and *JAK2* allele burden greater than 50%. Allele burden does not portend a worse prognosis regarding survival or leukemic transformation.[35]

The rate of leukemic transformation at 20 years is less than 10%.[19] Younger patients (aged <45 years) transform to leukemia at a median of 19 years while older patients (aged >60 years) transform at a median of 7 years. Transformation to AML has a very poor prognosis.[36] Transformation typically occurs through an MF phase, but can occur directly from a PV phase of the illness. Risk factors for transformation include leukocytosis, advanced age, and abnormal karyotype. An additional risk factor is prior use of agents such as radioactive phosphorus (32P), chlorambucil, or pipobroman. Of note, single-agent use of hydroxyurea (HU) or busulfan has a controversial association with leukemic transformation.[37]

In a study of 826 patients with PV at Mayo Clinic, survival was 14 years for those older than 60 years and 24 years for those under 60 years.[38] Risk factors for mortality and leukemic transformation in another recent study of 1545 patients with PV included older age, leukocytosis, thrombosis, and abnormal karyotype.[37]

Impact on Quality of Life

It is also important to recognize that even in the absence of thrombosis, MF, or leukemic transformation, patients with PV can have a high symptom burden, independent of risk. Among 519 patients with PV, patients were clustered based on results of the Myeloproliferative Neoplasm Symptoms Assessment Form (MPN-SAF), a questionnaire that allows patients to rank symptoms and quality of life on a 10-point scale. No correlation was found between the total score collected from the form and risk category: In other words, even patients traditionally characterized as low risk could have significant symptoms.[24] Symptoms that negatively impacted quality of life, with their associated prevalence based on survey data of 402 patients, included fatigue (97%), insomnia (58%), pruritus (40%), sexual dysfunction (51%), abdominal discomfort (45%), early satiety (62%), difficulty with concentration (58%), and sad mood (57%), among others.[39] Another study further evaluated the symptomatic profile of patients with PV, and noted that the symptom burden was increased in those with splenomegaly, phlebotomy needs, and history of past or current HU use.[40] Of note, in a recent survey of 813 patients with MPN and 457 hematologist/oncologist responders, discordance was noted between patients and physicians regarding evaluation of symptoms. Many patients reported being asked questions about general well-being rather than about specific symptoms, and they reported that they didn't realize particular symptoms were associated with their underlying disease. Physicians underestimated the symptom burden of patients with MPN at the time of diagnosis.[41] This study highlights the importance of recognizing and educating patients about the symptom burden associated with PV.

Treatment

Cornerstones of Therapy

Phlebotomy has been a cornerstone of therapy for PV since the 1900s. In a more recent randomized study of adults with PV treated with a target hematocrit of either less than 45% or 45% to 50%, the primary endpoint, which included thrombosis or cardiovascular deaths, was less prevalent in the group that maintained a hematocrit <45%.[26] Thus, all patients with PV should utilize phlebotomy to maintain a hematocrit target of less than 45%.

Aspirin is another cornerstone of therapy. ECLAP evaluated the safety and efficacy of daily low-dose aspirin in a prospective study of 518 patients and favored once-daily dosing of low-dose aspirin for decreasing risk of thrombosis without a risk for significant bleeding.[25] Microvascular disturbances involving platelet-rich arteriolar microthrombi can cause many symptoms, including lightheadedness, ocular/neurologic disturbances, tinnitus, chest discomfort, and erythromelalgia,[42] but aspirin can help alleviate these symptoms. Since patients with MPNs and thrombocytosis may have more rapid turnover of platelets and an incomplete response to aspirin, patients who do not respond to once-daily dosing may benefit from twice-daily dosing, although this is clinically unproven and use would be extrapolated from a preclinical study with ET patients.[43] Patients with platelet quantities greater than 1000×10^9 should be screened for ristocetin cofactor activity, which, if reduced, may compromise tolerability of aspirin and increase bleeding risk.[44]

Cytoreductive Therapies

Traditional indications for cytoreduction include age over 60 years and thrombosis history. Either variable has historically suggested a higher risk for vascular complications. Consideration for cytoreduction can also be given with the presence of progressive leukocytosis, symptomatic or extreme thrombocytosis, symptomatic splenomegaly or other uncontrolled symptoms, or intolerance of phlebotomy.[45] When cytoreduction is indicated, hydroxyurea (HU) has been considered frontline by most practicing hematologists.[46] Use of HU as a first-line agent was established by the PVSG, although high-quality data in PV are actually scarce. In the study, there was a lower incidence of thrombosis with use of HU compared with a historical cohort treated with phlebotomy alone, and the incidence of AML was lower compared with treatment with both chlorambucil and radioactive phosphorus.[1]

Second-line therapy is often considered in the presence of HU intolerance or resistance. In a study of 890 patients treated with HU, 15% of patients developed resistance/intolerance to HU. Resistance was defined as requiring phlebotomy to maintain the hematocrit goal; uncontrolled thrombocytosis and leukocytosis; failure to reduce massive splenomegaly by 50%; or related symptoms, despite

a sufficient dose and duration of therapy. A key aspect of intolerance included cytopenia(s) incurred with the lowest dose required to achieve a response. While previous HU resistance was thought to be associated with worse survival,[47] the results of 1 study indicated that it was specifically the presence of intolerance due to cytopenias that is associated with worse prognosis regarding leukemic transformation, progression to MF, and mortality.[48] Therefore, patients with this form of HU intolerance not only need a transition in treatment, but a reevaluation of their disease status.

While it is clear that patients with HU intolerance or resistance need to transition therapies, patients often continue treatment with HU despite having ongoing phlebotomy needs. The implications of an ongoing phlebotomy requirement despite HU therapy are under evaluation. A study found that patients treated with HU who required 3 or more phlebotomies per year had a higher risk for thrombosis compared with those who required 0 to 2 phlebotomies per year (20.5% vs 5.3% at 3 years; P <.0001).[49]

JAK2 Inhibition

In the RESPONSE study, ruxolitinib was evaluated as a second-line treatment after treatment failure with HU in a cohort of 222 patients; the endpoints were hematocrit control and reduction in spleen volume by at least 35%. In the ruxolitinib arm, 60% of patients had a reduction in hematocrit (vs 20% in the group receiving best available therapy [BAT], which was most commonly HU); 38% of patients had spleen volume reduction (vs 1% in BAT); and 49% of patients had better symptom control (vs 5% in BAT). After 32 weeks of treatment, patients originally in the BAT arm were able to crossover to ruxolitinib, which limits ability to make long-term comparisons between the groups. A subsequent report with follow-up at 80 weeks demonstrated durable responses regarding maintenance of hematocrit control and spleen volume reduction.[50] Although not a prespecified endpoint, there was suggestion of lower thrombosis rates, which were 1.8 per 100 patient-years of exposure in those treated with ruxolitinib, 4.1 in ruxolitinib after cross over, and 8.2 in BAT. Additionally, the rate of MF progression in the ruxolitinib arm was 1.3 per 100 patient-years (2 after crossover, 1.4 in BAT), and the rate of leukemic transformation in that arm was 0.4 (0.7 after crossover, 0 in BAT). Notable adverse events (AEs) that were more common in the ruxolitinib arm compared with BAT included herpes zoster and nonmelanoma skin cancer.

Subsequently, the RESPONSE-2 study evaluated ruxolitinib as a second-line treatment option in 173 patients with HU intolerance and resistance, but without splenomegaly. The primary endpoint was hematocrit control at week 28, which was met by 62% of patients in the ruxolitinib arm compared with 19% in the BAT arm (P <.0001). The most common AEs included anemia (14% ruxolitinib vs 3% BAT), hypertension (7% vs 4%), and pruritus (0% vs 3%).[51]

Interferons

Interferons are also considered first-line or second-line therapy for PV, although used less frequently in practice. Renewed interest in use of pegylated-inteferon (peg-IFN) has come from phase II studies in newly diagnosed and previously treated patients with PV showing high rates of complete hematological response (CHR) and impressive rates of molecular responses.[52,53] Recently, peg-IFN was compared in a randomized study with HU. In this study, presented at the 2016 American Society of Hematology Annual Meeting, 168 patients with high-risk PV who were newly diagnosed (<5 years) were randomized to peg-IFN or HU with a primary endpoint of CHR.[54] Interim results of 75 patients after 12 months did not show a significant difference in the primary endpoint between the 2 treatment groups. CHR was seen in 33% of patients treated with HU and 28% of patients treated with peg-IFN. Normalization of spleen size was seen in 2 of 7 patients treated with HU and 5 of 7 patients treated with peg-IFN. Grade 3 hematologic and nonhematologic AEs occurred in 5 of 36 patients treated with HU and 16 of 36 patients treated with peg-IFN.[54] Of the 75 patients enrolled, 66 completed questionnaires (MPN-SAF) to characterize symptoms and quality of life. The mean MPN-SAF was higher with HU compared with peg-IFN for the first 6 months; however, after 6 months patients treated with peg-IFN had worse total symptom scores, and the patients who achieved CHR reported a worse symptom burden compared with those who did not.

Novel interferons have also been developed, and 1 such form is ropeginterferon alpha-2b, which has a longer elimination half-life and can be dosed every 2 weeks.[55] A trial of 51 patients began as a phase I study that demonstrated no dose-limiting toxicities. Subsequently, additional patients were enrolled during the phase II portion; results indicated that after 12 months of therapy, an overall hematologic response was observed in 82% of patients, with 29% experiencing a CHR. There was no association between treatment dose and hematologic response. A molecular response was observed in 33% of patients at 12 months, with 12% having a complete molecular response. Of note, patients who experienced a hematologic response were more likely to have a molecular response. Of the 51 patients, 13 discontinued at various points in the study—the earliest at week 10 and the latest at week 50. Four patients discontinued due to administrative/consent reasons, 1 patient discontinued due to lack of efficacy, and the remaining 9 experienced AEs, such as fatigue, deterioration of general well-being, depression, elevated thyroid antibodies, rheumatoid arthritis, and elevated antinuclear antibodies associated with hyperkeratosis.[55] This agent is also being compared with HU in a randomized study of 257 patients. Twelve-month data from this phase III noninferiority trial were presented at the 2016 American Society of Hematology Annual Meeting, and preliminary data also suggested noninferiority between the ropeginterferon alpha-2b and HU groups.[56]

Busulfan

Busulfan is an older agent, but one that can be considered as a second-line cytoreductive therapy for older adults with HU intolerance or resistance. A recent retrospective study of 36 patients (15 with PV,

21 with ET) with HU intolerance/resistance reported an 83% CHR durable at 1 year (87%).[57] Partial MR was achieved in 3 of 9 patients; there were 8 (30%) discontinuations, an 11% thrombosis rate at 2 years, and 3 transformations to MDS or AML.

Additional Indications for Therapy

As mentioned, patients with PV can experience a considerable symptom burden, even in the absence of objective measures of disease severity. Lower-risk patients with a considerable symptomatic burden despite phlebotomy and aspirin may require additional therapies. One specific symptom that can negatively impact quality of life is pruritus, which can be severe and is often exacerbated by hot showers. Although the exact mechanism behind aquagenic pruritus is yet to be determined, many have hypothesized that it is related to histamine release from mast cell degranulation. Nonetheless, treatment with antihistamines has unreliable results.[58] Treatments that have helped some patients with pruritus include paroxetine,[59] JAK2 inhibitors,[60] and narrow band ultraviolet B phototherapy.[19,61]

Special Situations

Hematologists also manage special situations, including pregnancy and surgery. Most information regarding management of MPN associated pregnancies pertains to ET, given a second peak incidence in women of childbearing age. In a recent prospective study of MPN pregnancies, among 58 patients, only 5 had PV.[62] Including patients with ET and MF in this cohort, the miscarriage rate was 1.7%; 9% had pre-eclampsia or hemorrhage, and no thrombotic events were reported, although a significant number of patients were on aspirin, venous thromboembolism (VTE) prophylaxis, and/or cytoreduction.

There are consensus recommendations that advise on the hematocrit target (<45%), the use of aspirin, and VTE prophylaxis (typically postpartum or possibly antepartum in those who are at high risk or have had prior thrombosis).[45] Consensus from European medical societies provide similar recommendations, and guidance from the National Comprehensive Cancer Network (NCCN) is anticipated.[63,64] For patients requiring cytoreduction prior to pregnancy due to high risk, interferons are an option. Recombinant interferons have been utilized, as there have been limited data available regarding use of peg-IFN in PV pregnancies. A recent observational series has been published, describing use of peg-IFN, but this included only 10 patients with ET.[65] The authors suggested that this option was safe and effective in this small series.

Another special situation includes management of the patient with PV around the time of surgery. A retrospective analysis included 105 patients with PV (as well as 150 patients with ET) who underwent 156 minor and 155 major surgeries.[66] Most patients were on cytoreduction and/or phlebotomy and had excellent hematocrit control, with a mean under 43%. Despite these measures and additional VTE prophylaxis, however, vascular occlusion still occurred in 7.7% of the cohort. In patients with PV, there was an increased hazard for VT (hazard ratio, 7.3). Guidelines are available, and guidance from the NCCN regarding perioperative management of PV is anticipated.[63,64]

Conclusion

The last decade of PV research has featured an abundance of discovery. Important recent developments include an updated description of the epidemiology of PV, with additional information to come from a large, natural history study of PV, which includes more than 2000 patients from academic and community medical centers.[6] The molecular pathogenesis continues to be characterized, and diagnostic criteria allow for recognition of more subtle presentations of PV. There has been increasing awareness of risk factors for thrombosis beyond traditional ones such as advanced age and thrombosis history. Use of next-generation sequencing may help identify patients at higher risk for MF transformation. Further, the impact of PV on quality of life has been elucidated. Given that PV is a rare disease, it is expected that treatment practices are heterogeneous.[46] However, the development of guidelines by the NCCN will provide a framework for decision making. This will be increasingly important as new therapies for PV are developed and the role and sequence of current therapies is better defined. In this regard, large-scale, randomized studies comparing peg-IFN with HU are underway. With ruxolitinib, PV finally has a specifically approved therapy. This agent is currently used for those with an inadequate response to HU. Given the efficiency and durability of hematocrit control, spleen volume reduction, and symptom management with *JAK2* inhibitors, these therapies may eventually have a frontline role, though studies do not yet support this practice and this is not recommended.

Room exists for improved therapies and novel strategies. One could involve a combination of peg-IFN and ruxolitinib, which was presented at the 2015 American Society of Hematology Annual Meeting.[67] The rationale for this combination is to utilize the anti-inflammatory properties of ruxolitinib to improve the efficacy of peg-IFN, which is thought to be limited in the setting of inflammation.[67] Another combination involves the use of an MDM2 inhibitor and peg-IFN.[68] MDM2 negatively regulates p53, which is more frequently mutated in MPN patients who experience leukemic transformation.[69] Preclinical data demonstrated that *JAK2* V617F upregulates La antigen, which increases translation of MDM2, thus decreasing apoptosis via p53. Peg-IFN was selected because it upregulates p53 and decreases *JAK2* V617 hematopoietic progenitor cells. Additionally, using peg-IFN in conjunction with an MDM2 inhibitor may decrease the duration of treatment required by peg-IFN, which may limit AEs.[70]

Hopefully, the progress of PV research will continue to be as rapid in the next decade as it has been in the preceding one. If it is, we may be able to offer our patients therapies that are proven to modify the natural history of this myeloid neoplasm.

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