Primary Myelofibrosis: Update on Definition, Pathogenesis, and Treatment

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Key Words
chronic myelogenous leukemia (CML), extramedullary hematopoiesis (EMH), essential thrombocythemia (ET), Janus kinase 2 (JAK2), myeloproliferative neoplasm (MPN), polycythemia vera (PV), primary myelofibrosis (PMF)

Abstract
Primary myelofibrosis (PMF) is a clonal stem cell disorder that manifests clinically as anemia, splenomegaly due to extramedullary hematopoiesis, leukoerythroblastic, and constitutional symptoms, which are the clinical hallmarks of PMF. Within the past three years it has been determined that a single, recurrent, somatic mutation in the gene encoding the cytoplasmic tyrosine kinase Janus kinase 2 (JAK2) occurs in the majority of patients with PMF, and more recently, activating mutations in the gene encoding the thrombopoietin receptor MPL have also been identified in a subset of PMF patients. These discoveries have yielded important insights into the pathogenesis of PMF and have brought about the first opportunity for rationally targeted therapy for this disorder. Here we present an updated review of the pathogenesis, definition, and treatment of PMF in light of the discovery of JAK2 and MPL mutations, as well as other recent work in the myeloproliferative neoplasm field.
INTRODUCTION

Primary myelofibrosis (PMF) is a clonal stem cell disorder characterized by chronic myeloproliferation, atypical megakaryocytic hyperplasia, and bone marrow fibrosis. The disorder manifests clinically as anemia, splenomegaly due to extramedullary hematopoiesis (EMH), leukoerythroblastosis, and constitutional symptoms. Based on the seminal editorial by Dameshek in 1951 (1), PMF is classified as one of the prototypic myeloproliferative neoplasms (MPNs), along with polycythemia vera (PV) and essential thrombocytosis (ET). In 2005, several groups reported that the majority of patients with these three disorders acquire an activating somatic mutation in the gene encoding the cytoplasmic tyrosine kinase Janus kinase 2 (JAK2) (2–5), or in the gene encoding the thrombopoietin receptor MPL (6). The study of mutations in JAK2 and MPL has yielded insights into the pathogenesis of PMF as well as opening the possibility of rational, targeted therapy for patients with PMF.

DEFINITION AND DIAGNOSTIC CRITERIA

PMF was first described in 1879 (7); since that time, approximately one dozen terms have been used synonymously in the literature to describe this disorder, including agnogenic myeloid metaplasia, myeloid metaplasia with myelofibrosis, and chronic idiopathic myelofibrosis. In order to standardize the nomenclature, the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) proposed in 2007 that the term primary myelofibrosis (PMF) should be used (8) for patients who present with myelofibrosis without an antecedent diagnosis of PV or ET. In contrast, patients who develop a clinical picture consistent with myelofibrosis in the setting of pre-existing PV or ET are diagnosed with “post-PV myelofibrosis” and “post-ET myelofibrosis,” respectively (8).

The concept of MPNs was first described in 1951 (1). At that time, chronic myelogenous leukemia (CML), PV, ET, PMF, and erythroleukemia (Di Gugliemo’s syndrome) were the members of this group, collectively known as the chronic myeloproliferative diseases. The 2008 World Health Organization (WHO) treatise on the classification of hematopoietic tumors has replaced the term chronic myeloproliferative disease with the term myeloproliferative neoplasm (MPN) (9). The MPN category includes CML, PV, ET, PMF, chronic eosinophilic leukemia without mutation in the fibroblast growth factor receptor 1 or platelet-derived growth factor receptor A/B, hypereosinophilic syndrome, and mast cell disease. The revised WHO criteria for MPNs utilize knowledge of the molecular pathogenesis of CML and the BCR-ABL fusion gene–negative MPNs (PV, ET, PMF) in the revised classification criteria for PMF. There is no standard definition for the diagnosis of PMF, but consensus criteria have been created by the Italian Society of Hematology and the WHO. The 2007 WHO revised diagnostic criteria for PMF, listed in Table 1 (9), describe the key histologic and diagnostic laboratory features that should allow clinicians to differentiate PMF from related disorders, including the other MPNs, myelodysplastic syndrome, acute myelofibrosis, and secondary causes of myelofibrosis.

Given that megakaryocytic hyperplasia, thrombocytosis, and even bone marrow fibrosis can be observed in CML, molecular or cytogenetic testing for the Philadelphia chromosome is advised to exclude a diagnosis of CML. A diagnosis of myelodysplastic syndrome with concomitant marrow fibrosis, as opposed to PMF, is suggested by the finding of dyserythropoiesis (dysplastic bone marrow hyperplasia associated with variable peripheral blood cytopenias) (9) (Figure 1). Also, certain cytogenetic findings, when present, such as abnormalities involving chromosome 5 or 7, may help to differentiate myelodysplastic syndrome with narrow fibrosis from PMF (10, 11). Acute myelofibrosis is a syndrome that is classified as a variant of acute megakaryocytic leukemia (the M7 subtype of the French-American-British classification) and is occasionally confused...
Table 1  Proposed revised WHO criteria for primary myelofibrosis (PMF). Diagnosis requires meeting all 3 major criteria and 2 minor criteria

<table>
<thead>
<tr>
<th>Major criteria</th>
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<td>Presence of megakaryocyte proliferation and atypia, usually accompanied by reticulin and/or collagen fibrosis, or, in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (i.e., prefibrotic cellular phase disease)</td>
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<tr>
<td>Not meeting WHO criteria for polycythemia vera, chronic myelogenous leukemia, myelodyplastic syndrome, or other myeloid neoplasm</td>
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<tr>
<td>Demonstration of JAK2V617F or other clonal marker (MPLW515L/K), or, in the absence of a clonal marker, no evidence of bone marrow fibrosis due to underlying inflammatory or other neoplastic diseases</td>
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<table>
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<th>Minor criteria</th>
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<tr>
<td>Leukoerythroblastosis</td>
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<td>Increase in serum lactate dehydrogenase level</td>
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<tr>
<td>Anemia</td>
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<td>Palpable splenomegaly</td>
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aSmall to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering.

bRequires the failure of iron-replacement therapy to increase hemoglobin levels to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels. Red cell mass measurement is not required.

cRequires the absence of BCR-ABL.

dRequires the absence of dyserythropoiesis and dysgranulopoiesis.

fSecondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia, or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies. It should be noted that patients with conditions associated with reactive myelofibrosis are not immune to primary myelofibrosis and the diagnosis should be considered in such cases if other criteria are met.

degree of abnormality could be borderline or marked.

with PMF. Both conditions are characterized by bone marrow fibrosis, cytopenias, and a leukoerythroblastic smear. However, patients with acute megakaryocytic leukemia almost never have splenomegaly (a common finding in PMF, described below), frequently have acute bone marrow failure, and commonly have an excess of megakaryoblasts in their bone marrow and peripheral blood (12).

Bone marrow fibrosis can be observed in several other hematologic disorders, including hairy cell leukemia, lymphoma, and multiple myeloma; however, each of these conditions is characterized by a constellation of clinical, pathologic, and molecular findings not characteristic of PMF. In addition, many nonhematologic disorders can be associated with bone marrow fibrosis, including solid tumor metastases to bone marrow, autoimmune disorders (systemic lupus erythematosus, scleroderma, mixed connective tissue disorder, polymyositis), and secondary hyperparathyroidism associated with vitamin D deficiency. In most cases, it is possible to distinguish between these disorders and PMF, although in rare cases the presence of the JAK2V617F or MPLW515L/K mutation can be used to demonstrate the presence of a clonal MPN and to exclude the possibility of reactive fibrosis.

In contrast, excluding a diagnosis of post-PV/ET myelofibrosis can be challenging. Given that almost all patients with PV are JAK2V617F-positive (13, 14), the absence of an activating mutation in JAK2 is helpful in excluding the diagnosis of post-PV myelofibrosis but does not rule out the possibility of post-ET myelofibrosis. Although it can be difficult to distinguish between post-PV/ET myelofibrosis and PMF, existing clinical and laboratory studies do not suggest any prognostic or therapeutic differences between post-PV/ET myelofibrosis and PMF, and most clinical trials include patients with both. Moreover, although we clinically distinguish between post-PV/ET myelofibrosis and PMF, there is little evidence to suggest these are biologically distinct entities, and it remains possible that some, or even all, patients with PMF have an antecedent...
Peripheral blood

Bone marrow

Spleen

Reticulin

Figure 1

Histology of the peripheral blood, bone marrow, and spleen of a patient with primary myelofibrosis. Peripheral blood smear reveals nucleated and tear-drop-shaped red blood cells as well as immature white blood cells. This smear is described as a “leukoerythroblastosis smear.” Bone marrow histology reveals atypical megakaryocyte hyperplasia. This same atypical megakaryocytic hyperplasia is seen just outside of a lymph nodule within the spleen as evidence of extramedullary hematopoiesis. Reticulin staining of the same marrow reveals moderate marrow fibrosis.

proliferative MPN that did not manifest clinically.

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

The largest population-based epidemiologic study of MPN was recently published and found that the incidence of PMF in the United States is ~0.21 per 100,000 population. This figure was based on data culled from the North American Association of Cancer Registries and the Surveillance, Epidemiology, and End Results Program during 2001–2004 (15). Overall, MPNs were found to be more common in men than in women, but a sex association has never been reported in PMF specifically (15–17). The median age of diagnosis in most series is ~67 years (15–17).

The most common presenting symptoms of PMF are fatigue and symptoms related to splenomegaly (16, 17). The latter include abdominal fullness, early satiety, and left upper quadrant pain. Acute left upper quadrant pain may be evidence of the development of spontaneous splenic infarction. Splenomegaly in PMF is due to extramedullary hematopoiesis (EMH). The list of other regions that can be affected by EMH includes the liver (resulting in hepatomegaly and portal hypertension), lymph nodes (resulting in lymphadenopathy), serosal surfaces (causing ascites or pleural effusions), and epidural spaces (causing nerve or cord compression) (18). In addition to vertebral column involvement from EMH, musculoskeletal complaints from osteosclerosis, hypertrophic osteoarthritis, and periostitis may be reported in patients with PMF (16, 18). Symptoms due to the hypercatabolic state of PMF are also common and include fever, night sweats, and weight loss. Constitutional symptoms are often severe and necessitate PMF-directed therapy in a significant proportion of patients with PMF (19).

The most common laboratory abnormality in PMF is anemia, and ~50% of PMF patients present with Hb < 10 gm/dl (16, 20, 21). In contrast, platelet and white blood cell counts in PMF vary widely at presentation, and patients can present with elevated or decreased platelet/white blood counts. In one series, 13% of PMF patients were noted to have extreme thrombocytosis (platelet count > 500,000/mm³) and 37% were found to have thrombocytopenia (platelet count < 150,000/mm³) (16). As for white blood count, 7%–8% of patients present with leukopenia (WBC < 4 × 10⁹/dl) and 9%–11% present with leukocytosis (WBC > 30 × 10⁹/dl) (16, 21a).

PMF is characterized by specific morphologic and histologic features, which are important in establishing a diagnosis. The peripheral blood smear of PMF has a characteristic pattern, with nucleated red blood cells, granulocyte precursors, and tear-drop-shaped erythrocytes (dacrocyes) (Figure 1). This pattern has been designated leukoerythroblastosis, and although it is observed in other diseases that cause bone marrow replacement (termed myelophthisis), it is an important feature of PMF. As
described above, reticulin or collagen stains can be used to demonstrate bone marrow fibrosis in most patients with PMF. Although the bone marrow is usually extensively fibrotic, a variant of PMF, known as prefibrotic cellular PMF, which is not associated with marrow fibrosis, has been described (22, 23). This variant of PMF is commonly diagnosed by excluding the other conditions described in Table 1 and by observing histologic features of PMF including megakaryocytic dysplasia (22, 23). Although many investigators believe that prefibrotic cellular PMF is a clinical entity distinct from other MPNs, such as ET, clinicopathologic analysis of the large cohort of ET patients enrolled in the prospective Primary Thrombocythaemia 1 trial did not discern clinical, laboratory, pathologic, molecular, or prognostic differences between patients diagnosed with ET and those with prefibrotic PMF (24). These data suggest that there is likely a prefibrotic phase that can be identified in some patients who subsequently develop PMF with marrow fibrosis; however, whether this is a distinct clinicopathologic and biologic entity from the other prefibrotic MPNs requires further evaluation.

The principal causes of death in PMF are similar to those of other MPNs and include infection, leukemic transformation, and thrombohemorrhagic events. Transformation to acute leukemia in PMF is associated with a dismal outcome and has been estimated to occur in 3.9%–20% of patients (16, 17). The largest single series of PMF patients to date studied with respect to leukemic transformation identified 91 patients who transformed out of a total of 2333 consecutive patients with PMF (3.9%) (25). Leukemic transformation occurs most commonly within the first 10 years of diagnosis. It is important to note that a diagnosis of leukemic transformation can be difficult, given the abnormal blood counts, morphologic abnormalities, and extensive marrow fibrosis seen in all patients with PMF. In such cases, the diagnosis depends on bone marrow histology demonstrating an increase in blasts ≥20% or biopsy of extramedullary leukemic deposits. From a clinical perspective, it is advised that all patients with a marked change in clinical (new infections, marked change in spleen size) or laboratory (new cytopenias or increase in peripheral blasts) parameters undergo repeat bone marrow testing to assess for leukemic transformation. One interesting biologic finding relevant to leukemic transformation is that a subset of patients with a JAK2V617F-positive MPN transform to a JAK2V617F-negative acute myelogenous leukemia (26, 27), suggesting JAK2V617F may be dispensable for leukemic transformation.

PATHOGENESIS
PMF, along with the other MPNs, is a clonal disorder of multipotent hematopoietic progenitors, arising in the hematopoietic stem cell compartment. This fact was established in the late 1970s by studies of X chromosome inactivation in women who had a polymorphic variant of the gene for glucose-6-phosphate dehydrogenase as well as PV, ET, PMF, or CML (28, 29). Moreover, cytogenetic studies have identified clonal cytogenetic abnormalities in a subset of PMF patients, most commonly 20q– and 13q– (10, 11), and these abnormalities can be seen in multiple lineages (30), consistent with the likely stem cell origin of these disorders.

A major advance in our understanding of the underlying etiology of PMF occurred in 2005, when four groups independently identified a single recurrent mutation that resulted in the activation of JAK2 signaling in most patients with PV, ET, and PMF (2–5). JAK2 is a member of the Janus family of cytoplasmic nonreceptor tyrosine kinases, which also includes JAK1, JAK3, and TYK2. The mutation in JAK2, which is recurrent in MPN, is a guanine-to-thymine mutation resulting in a substitution of valine to phenylalanine at codon 617 within the pseudokinase domain (JH2) of JAK2 (JAK2V617F).

In vitro studies have shown that the JAK2V617F protein has constitutive kinase activity (2–5), and in vivo studies have shown that expression of JAK2V617F in murine
bone marrow results in a fully penetrant myeloproliferative disorder notable for polycythemia, myelofibrosis, and extramedullary hematopoeisis, but not thrombocytosis (31, 32). These studies demonstrate that JAK2V167F is an oncogene and that acquisition of this allele contributes to the pathogenesis of these disorders. Although the V617F substitution results in JAK2 activation, the mechanism by which this single amino acid change alters JAK2 activity has not been fully delineated. On the basis of structural modeling and deletion studies, it is believed that the JH2 domain serves an autoinhibitory role in mediating JAK2 activity, as deletion of JAK2 JH2 leads to increased JAK2 activity (33, 34). Thus, it is likely that the V617F mutation results in a loss of autoinhibition and constitutive JAK2 activity.

Sensitive, allele-specific assays have determined that JAK2V617F is present in 90%–95% of patients with PV, 50%–70% of patients with ET, and 40%–50% of patients with PMF (35). These data suggest that acquisition of the JAK2V617F allele is central to the pathogenesis of JAK2V617F-negative MPNs. Many alternative alleles have been investigated to identify a genetic basis for disease in JAK2V617F-negative ET and PMF patients, particularly in the JAK-STAT signaling pathway. This search led to the identification of somatic mutations at codon 515 at the transmembrane-juxtamembrane junction of the thrombopoietin receptor gene MPL in JAK2V617F-negative PMF and ET (6, 36). Three different substitutions at codon 515, to leucine (W515L), lysine (W515K), or alanine (W515A), have been identified, and more recently three patients with somatic MPLS505N mutations have been identified (24); this allele had previously been seen in patients with inherited thrombocytosis (37). MPL mutations occur in 8.5% of JAK2V617F-negative ET patients (24) and ~10% of JAK2V617F-negative PMF patients (6, 36, 38). MPLW515-positive PMF patients present with more severe anemia than JAK2V617F-positive patients, and in some studies endogenous megakaryocyte colonies, but not endogenous erythroid colony formation, can be grown from MPLW515-positive patient cells (24). These data suggest there are differences between JAK2V617F and MPLW515 mutations that modulate clinical phenotype. Experimental data are consistent with this hypothesis. Although both JAK2V617F and MPLW515L transform hematopoietic cells to cytokine-independent growth, expression of MPLW515L in murine bone marrow causes a distinct phenotype notable for thrombocytosis, leukocytosis, and myelofibrosis, but not polycythemia.

The discovery of MPL mutations has provided insight into the pathogenesis of PMF. However, a significant proportion of patients with PMF are JAK2/MPL-negative, and the underlying cause for clonal hematopoiesis in these patients is yet to be discovered. Based on existing genetic data, we predict that additional oncogenic alleles in the JAK-STAT pathway will be identified in these patients, and that additional genomic and functional studies will provide further insight into the pathogenesis of JAK2/MPL-positive and -negative PMF.

Although the discovery of activating mutations in JAK2 and MPL has greatly improved our understanding of the pathogenesis of MPNs, a number of questions remain unanswered. First, the exact mechanism by which mutations in JAK2 and MPL result in constitutive activation of these proteins is not clear. Resolution of the crystal structure of critical domains in these proteins may help to demonstrate the exact mechanism of constitutive activation. Another unanswered question is how the same activating mutation in JAK2 results in the varying clinical phenotypes of PV, ET, and PMF. It is hypothesized that the identity of the cytokine receptors present during myeloid and erythroid differentiation may influence the clinical phenotype (39). JAK2 interacts with a number of cytokine receptors, including the receptors of erythropoietin, thrombopoietin, granulocyte-macrophage colony stimulating factor, and interleukin-3. These receptors are expressed at
different times and levels during hematopoietic differentiation, and differences in interaction between these receptors and JAK2V617F may yield different MPNs. Moreover, it is likely that additional inherited and acquired alleles contribute to the pathogenesis of JAK2V617F-positive MPN and contribute to the determination of MPN phenotype in individual patients (40).

Moreover, additional insight is needed to delineate aspects of constitutive signaling along the JAK-STAT pathway in the different MPNs and how different MPN disease alleles differentially signal in a physiologic context. It is currently not known whether there is a difference in the role and recruitment of downstream signaling cascades based on the type of MPN mutant allele (JAK2V617F, JAK2 exon 12 mutation, MPLW515L/K). It is also likely that JAK2 gene dosage influences clinical phenotype, particularly given that a significant proportion of PV and PMF patients are homozygous for JAK2V617F, whereas JAK2V617F-positive ET patients are almost always heterozygous for this allele, suggesting differences in JAK2 signaling in the different disorders (5). It is postulated that the role and recruitment of downstream signaling scaffolds and regulation of signaling may vary based on the type of JAK2 or MPL allele, and on allele gene dosage, but this has not been studied in sufficient detail (Figure 2) (35).

Although genetic and signaling studies are of utmost importance in improving our understanding of the molecular basis of PMF, even less is known about the etiology of clinically significant aspects of PMF pathogenesis and progression, including bone marrow fibrosis, extramedullary hematopoiesis, and bone marrow failure. As mentioned earlier, marrow fibrosis is a histologic hallmark of PMF and contributes to many of the clinical signs and symptoms of the disease (Figure 1). It is believed that the clonal hematopoietic stem cell disorder leads to secondary proliferation of polyclonal, normal fibroblasts and excessive deposition of collagen by fibroblasts (41). The prevailing hypothesis is that fibroblasts are specifically stimulated by clonally expanded megakaryocytes through secretion of transforming growth factor-beta (TGFβ) (42). Animals exposed to excessive concentrations of thrombopoietin are found to have elevated levels of TGFβ as well as megakaryocyte hyperplasia, splenomegaly, EMH, bone marrow fibrosis, and increased circulating hematopoietic progenitor cells (HPCs) (43, 44), suggesting that thrombopoietin activation of the JAK-STAT signaling cascade can cause myelofibrosis through a TGFβ-mediated mechanism. However, genetic and functional experiments to test this postulated mechanism are needed; it is hoped the recent development of models of JAK2V617F- and MPLW515L-mediated MPN will allow direct investigation of the relationship between JAK-STAT signaling and marrow fibrosis. In addition, little is known about the etiology of extramedullary hematopoiesis in these disorders, and the relationship of this clinical phenomenon to JAK2 activation.

![Diagram of JAK-STAT signaling](image-url)
Patients with PV, ET, and most notably PMF have been noted to have increased numbers of circulating CD34+ HPCs. The median number of CD34+ HPCs in PMF patients was found to be 400 times that of healthy subjects in one series (46). Whether this mobilization of HPCs is a direct result of increased stem and progenitor cell proliferation, a change in the interaction between PMF stem/progenitor cells and their bone marrow niche, or a change in the adhesion or trafficking of PMF stem/progenitor cells is not known. Moreover, whether an increase in circulating progenitors is required for the development of EMH is not known. Additional studies are needed to investigate the biologic basis of these important clinical features of PMF.

PROGNOSIS

Median survival in PMF has been estimated to be between 3.5 and 5 years (16, 21, 45), which is much worse than for the other classic MPNs. However, there is a wide range in the survival of PMF. The most important prognostic factors in PMF are anemia, leukocytosis, leukopenia, advanced age, and the presence of hypercatabolic symptoms. A number of prognostic scoring systems have been developed; the simplest, the Dupriez system, depends only on (a) anemia (Hb < 10 g/dl) and (b) white blood cell count (WBC < 4000/µL or > 30,000/µL). Patients with none (low risk), one (intermediate risk), and two (high risk) of these features have a median survival of 93, 26, and 13 months, respectively. These data are helpful in guiding management of PMF (see below). In particular, as mentioned above, leukemic transformation in PMF is associated with a poor prognosis. In a series of 91 patients from the Mayo Clinic, the median survival was 2.6 months (range 0 to 24 months) (25). Twenty-four of these patients were treated with acute myelogenous leukemia–like induction therapy; no patients achieved a complete remission despite a 33% treatment-related mortality rate.

TREATMENT

The only potentially curative therapy for PMF currently is allogeneic stem cell transplantation (ASCT). Initial reports of ASCT in PMF patients raised concerns about delayed engraftment; however, time for engraftment has not been shown to be problematic in PMF (47). The largest barrier to ASCT in PMF is the fact that the majority of patients with PMF are >60 years old. In the largest series of PMF patients treated with myeloablative ASCT, recipient age significantly impacted survival, with a five-year survival of 14% for patients ≥45 years old compared with 62% for those <45 years old (48). The toxicity associated with myeloablative ASCT in PMF has prompted the use of nonmyeloablative (or reduced-intensity conditioning) allogeneic transplants in this clinical setting. In the most recent and largest series of PMF patients treated with nonmyeloablative ASCT, 104 patients with a median age of 55 were treated with a reduced-intensity busulfan/fludarabine conditioning regimen followed by ASCT (49). One-year mortality was 19%, and 32% of patients experienced chronic graft-versus-host disease. At three years the overall survival was 70%, and the cumulative incidence of relapse at three years was 29%.

Currently, it is reasonable to recommend full myeloablative ASCT for patients with PMF below 45 years of age and for those with high-risk PMF who can tolerate full myeloablative conditioning (high-risk is defined by the presence of two factors in the prognostic scoring system mentioned above) (19). All other patients <65–70 years of age should be considered for a nonmyeloablative transplant or drug therapy, particularly in light of the recent development of JAK2-targeted therapy.

Drug therapy in PMF is indicated by the presence of symptoms due to anemia, splenomegaly, or EMH, or constitutional symptoms. Conventional agents utilized include androgens, prednisone, erythropoiesis-stimulating agents, danazol, hydroxyurea, lenalidomide, and thalidomide; given that none of these agents have been shown to influence
the natural history of disease, the choice of
drug therapy is influenced by the patient's
signs of disease. For instance, hydroxyurea
is commonly employed to treat leukocytosis,
thrombocytosis, and splenomegaly in PMF.
In a series of 59 patients with PV, ET, or
PMF and thrombocytosis, hydroxyurea
decreased platelet count to <500,000/uL in 6 of
10 patients with PMF (50). The angiogenesis
inhibitors thalidomide and lenalidomide have
been used to treat splenomegaly, cytopenias,
and constitutional symptoms in PMF. In com-
bination with prednisone, these drugs have an
overall response rate of 20%–30% in most se-
ries as measured by improvement in anemia, de-
creased red cell transfusions, increased platelet
count, and a 50% decrease in spleen size (20,
51). However, tolerability of thalidomide and
lenalidomide has been a major limitation in
their use in PMF. In one series of 63 PMF pa-
tients treated with thalidomide, the cumulative
dropout rate due to adverse events was 51% af-
ter six months of therapy, and the median max-
imal tolerated dose was 100 mg per day. Side ef-
effects included drowsiness, constipation, fatigue,
paresthesias, and neutropenia (20). Gentler
treatments for symptomatic anemia in PMF in-
clude androgens combined with prednisone and
the use of erythropoiesis-stimulating agents.
The erythropoiesis-stimulating agents, as well
as the drug danazol, have been utilized to in-
crease hemoglobin in PMF. However, a recent
report from a retrospective case series at the
Mayo Clinic suggests that these drugs increase
the risk of leukemic transformation in PMF
patients (52).

Splenectomy is occasionally performed in
patients with PMF in hopes of treating symp-
toms due to splenomegaly. Unfortunately, this
is a high-risk procedure with a 9% procedure-
related mortality, and severe hepatomegaly and
thrombocytosis occur in the postsurgical pe-
riod in ~25% of patients (53). Splenic irra-
diation can be employed as an alternative to
splenectomy but relieves symptoms for only
~3–6 months (54). Irradiation of other sites of
EMH has been reported in PMF. Irradiation
to spinal, paraspinal, and peritoneal implants
has been reported to have some success at re-
lieving symptoms with minimal sequelae (18).
However, low-dose irradiation of the liver is
myelosuppressive and only transiently relieves
hepatomegaly (55).

Recognition of abnormal JAK-STAT sig-
naling in the pathogenesis of PMF has gen-
erated great excitement about the possibil-
ity of molecularly targeted therapy. JAK2
inhibitors can be classified as JAK2-selective
(class I) or non-JAK2-selective (class II) drugs
(56). The class I drugs include four oral
JAK2-selective ATP mimetics: TG101209,
TG101348, INCB01824, and XL019. Class
II drugs include the aurora kinase inhibitors
MK0457 and AT9283, the FLT3 inhibitor
CEP701, and the histone deacetylase inhibitor
ITF2357.

Phase I trials with class I and II JAK2 in-
hibitors have been initiated in PMF and post-
PV/ET myelofibrosis. ICNB018424 is an orally
bioavailable JAK1/JAK2 inhibitor that entered
early-phase clinical trials in the second half of
2007 (57). PMF and post-PV/ET myelofibro-
sis patients treated with ICNB018424 have ex-
perienced marked reductions in splenomegaly
and improvements in constitutional symptoms
and body weight. There have been only mod-
est reductions in JAK2V617F allele burden
or bone marrow fibrosis after 3–6 months
of therapy. In addition, patients given es-
calating ICNB018424 doses developed re-
versible thrombocytopenia; it is not known
if this is a JAK2 effect. These results sug-
gest ICNB018424 is of benefit in patients
with PMF and post-PV/ET myelofibrosis, but
many important questions remain regarding
the role of JAK2-specific agents, particularly
as to whether they will reduce disease burden,
reverse bone marrow fibrosis, and improve
cytopenias. The ongoing clinical development of
JAK2-specific inhibitors will provide critical in-
sight into whether JAK2 is a bona fide therapeu-
tic target in these disorders.

In vitro data demonstrate suppres-
sion of hematopoietic colony growth by
JAK2-selective inhibitors regardless of JAK2 mutational status (58). This suggests JAK2 inhibitors should be used to treat PMF patients with \( MPL \) mutations or without \( JAK2/MPL \) mutations to determine if JAK-STAT signaling is universal to the pathogenesis of PMF. More importantly, recent studies have shown the myeloid leukemic blasts in patients with \( JAK2V617F \)-mutant MPNs are often \( JAK2V617F \)-negative (27). This suggests that leukemic blasts derive from a pre-JAK2 progenitor cell and that JAK2 inhibitor therapy may increase the risk of leukemic transformation.

**CONCLUSION**

Although PMF may have a variety of clinical presentations and may be seen in a wide age range, the vast majority of patients present over the age of 60 with anemia and symptoms related to EMH. Because of the age at presentation, most patients have been eligible only for drug therapy with palliative intent. Therefore, most PMF patients are excellent candidates for phase I/II trials of JAK2 inhibitors and for other novel therapies. It is an exciting time for translational investigation in PMF, as there is a great need for an improved understanding of its pathogenesis and the role of novel therapies in its treatment.

**SUMMARY POINTS**

1. PMF is a clonal stem cell disorder characterized by ineffective erythropoiesis and dysplastic megakaryocytic hyperplasia, usually accompanied by reactive marrow fibrosis and extramedullary hematopoiesis in the spleen.
2. In a significant proportion of PMF patients, \( JAK2V617F \) or \( MPL \) mutation contributes to PMF pathogenesis.
3. The only curative treatment in PMF is autologous stem cell transplant. Because of the average age of PMF patients, most are treated with a variety of drugs with palliative intent.
4. Clinical trials of JAK2-selective inhibitors are under way. JAK2-selective inhibitors have the potential for great impact on treatment of PMF with minimal adverse effects, but data are scarce at this time.

**FUTURE ISSUES**

1. Discovery of a mutation that precedes \( JAK2V617F \) in myelopoiesis.
2. Elucidation of differences in signaling interaction between the various MPN mutant alleles.
3. Explanation and prognostic relevance of differences in \( JAK2V617F \) gene dosages in PV, ET, and PMF.
4. More clinical data on the efficacy and adverse effects of JAK2-selective and -nonselective inhibitors in PMF.
5. Discovery of an underlying genetic abnormality in PMF without mutations in \( JAK2 \) or \( MPL \).
DISCLOSURE STATEMENT
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LITERATURE CITED


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Contents

Transcatheter Valve Repair and Replacement
   Susheel Kodali and Allan Schwartz ........................................... 1

Role of Endothelin Receptor Antagonists in the Treatment
   of Pulmonary Arterial Hypertension
   Steven H. Abman ................................................................. 13

Oral Iron Chelators
   Maria Domenica Cappellini and Paolo Pattoneri .......................... 25

The Treatment of Hyperhomocysteinemia
   Bradley A. Maron and Joseph Loscalzo ..................................... 39

Stroke Rehabilitation: Strategies to Enhance Motor Recovery
   Michael W. O'Dell, Chi-Chang David Lin, and Victoria Harrison ...... 55

Cardiomyopathic and Channelopathic Causes of Sudden Unexplained
   Death in Infants and Children
   David J. Tester and Michael J. Ackerman .................................. 69

Bisphosphonate-Related Osteonecrosis of the Jaw: Diagnosis,
   Prevention, and Management
   Salvatore L. Ruggiero and Bhoomi Mehta .................................. 85

IL-23 and Autoimmunity: New Insights into the Pathogenesis
   of Inflammatory Bowel Disease
   Clara Abraham and Judy H. Cho ............................................ 97

Necrotizing Enterocolitis
   Marion C.W. Henry and R. Lawrence Moss ................................. 111

Cancer Screening: The Clash of Science and Intuition
   Barnett S. Kramer and Jennifer Miller Croswell .......................... 125

Biomarkers for Prostate Cancer
   Danil V. Makarov, Stacy Loeb, Robert H. Getzenberg, and Alan W. Partin ........... 139

Management of Breast Cancer in the Genome Era
   Phuong Khanh H. Morrow and Gabriel N. Hortobagyi ...................... 153
MicroRNAs in Cancer
Ramiro Garzon, George A. Calin, and Carlo M. Croce ........................................... 167

Erythropoietin in Cancer Patients
John A. Glaspy .......................................................... 181

Thrombopoietin and Thrombopoietin Mimetics in the Treatment of Thrombocytopenia
David J. Kater .................................................................... 193

Evolving Treatment of Advanced Colon Cancer
Neil H. Segal and Leonard B. Saltz .................................................. 207

Barrett’s Esophagus and Esophageal Adenocarcinoma
Robert S. Bresalier ................................................................ 221

Primary Myelofibrosis: Update on Definition, Pathogenesis, and Treatment
Omar I. Abdel-Wabab and Ross L. Levine ....................................... 233

Nicotine Dependence: Biology, Behavior, and Treatment
Riju Ray, Robert A. Schnoll, and Caryn Lerman ................................ 247

Food Allergy: Recent Advances in Pathophysiology and Treatment
Scott H. Sicherer and Hugh A. Sampson ......................................... 261

Immunomodulation of Allergic Disease
David H. Broide .................................................................... 279

Hypereosinophilic Syndrome: Current Approach to Diagnosis and Treatment
Amy Klion ........................................................................ 293

Extensively Drug-Resistant Tuberculosis: A New Face to an Old Pathogen
Sheela Shenoi and Gerald Friedland .............................................. 307

Polycystic Kidney Disease
Peter C. Harris and Vicente E. Torres ........................................... 321

The Kidney and Ear: Emerging Parallel Functions
Elena Torban and Paul Goodyer .................................................. 339

The Expanded Biology of Serotonin
Miles Berger, John A. Gray, and Bryan L. Roth ............................... 355

Advances in Autism
Daniel H. Geschwind .......................................................... 367

Chronic Consciousness Disorders
James L. Bernat ............................................................. 381
Goals of Inpatient Treatment for Psychiatric Disorders  
Steven S. Sharfstein ................................................................. 393

Understanding and Reducing Variation in Surgical Mortality  
John D. Birkmeyer and Justin B. Dimick ..................................... 405

MRI-Guided Focused Ultrasound Surgery  
Ferenc A. Jolesz ................................................................. 417

Genetic Testing in Clinical Practice  
Steven W. J. Lamberts and André G. Uitterlinden ............................. 431

The HapMap and Genome-Wide Association Studies in Diagnosis and Therapy  
Teri A. Manolio and Francis S. Collins ........................................ 443

Prospects for Life Span Extension  
Felipe Sierra, Evan Hadley, Richard Suzman, and Richard Hodes ......... 457

Emerging Concepts in the Immunopathogenesis of AIDS  
Daniel C. Douek, Mario Roederer, and Richard A. Koup ................... 471

Lessons Learned from the Natural Hosts of HIV-Related Viruses  
Mirko Paiardini, Ivona Pandrea, Cristian Apetrei, and Guido Silvestri ........ 485

Indexes

Cumulative Index of Contributing Authors, Volumes 56–60 .................. 497
Cumulative Index of Chapter Titles, Volumes 56–60 .......................... 501

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