Chapter 2
Primary Myelofibrosis

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2.1 Introduction

Myelofibrosis (MF) in the context of a myeloproliferative disorder is a clinicopathologically defined entity characterized by anemia, marked splenomegaly, constitutional symptoms, leukoerythroblastosis (i.e., the presence of immature granulocytes and nucleated red blood cells), dacryocytosis (i.e., presence of teardrop-shaped red blood cells), and a bone marrow that displays dysplastic megakaryocyte hyperplasia, granulocyte proliferation, and reticulin and/or collagen fibrosis (1). Disease presentation could be either *de novo* (primary MF; PMF) or preceded by either polycythemia vera (post-PV MF) or essential thrombocythemia (post-ET MF). PMF is also known by many other names (Table 2.1), including chronic idiopathic myelofibrosis (CIMF), the term used by the World Health Organization (WHO) system for classification of myeloid neoplasms (2). However, the use of the term "PMF" was recently endorsed by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) (3).

2.2 Historical Perspective and Disease Classification

The first description of PMF is credited to Heuck (1879) (4). He described two cases, which he referred to at the time as "splenic-medullary leukemia" and "pure splenic leukemia" (4). The term "osteosclerosis," which refers to the new bone formation that often accompanies bone marrow fibrosis in PMF, was first introduced by Assman in 1907 (5). Post-PV MF was recognized as early as 1935 by Hirsch-. (6). Similarly, the typical histological characteristics of the disease, including hepatosplenic extramedullary hematopoiesis (1908) (7, 8), bone marrow fibrosis (8), and leukoerythroblastosis (1939) (9), were all recognized in the first half of the 20th century. PMF was referred to as agnogenic myeloid metaplasia of the spleen (AMM), a term first used in 1940 (10) and later endorsed by Dameshek in 1951 (11).

Dameshek classified PMF as a myeloproliferative disorder (MPD), along with chronic myeloid leukemia (CML), ET, and PV (11). In 1960, Nowell and

S.M. Ansell (ed.), *Rare Hematological Malignancies.*

Table 2.1 Terms used to refer to primary myelofibrosis

Agnogenic myeloid metaplasia
Atypical myeloid leukemia
Atypical myelosis
Aleukemic myelosis with osteosclerosis
Chronic idiopathic myelofibrosis
Chronic nonleukemic myelosis
Chronic erythroblastosis
Chronic megakaryocytic leukemia
Chronic megakaryocytic-granulocytic myelosis
Heuck–Assman disease
Idiopathic myelofibrosis
Idiopathic myeloid metaplasia
Leukoerythroblastic anemia
Leukanemia
Megakaryocytic myelosis with osteosclerosis
Megakaryocytic splenomegaly
Myelosis
Myelofibrosis with myeloid metaplasia
Myeloid metaplasia with myelofibrosis
Megakaryocytic myelosis
Myelosclerosis
Osteosclerotic pseudoleukemia
Osteomyeloreticulosis
Osteomyelosclerosis
Osteosclerotic anemia
Osteomyelofibrosis
Primary myelofibrosis

Hungerford described the Philadelphia chromosome in CML (12),which was later shown to harbor first the t(9;22)(q32;q13) (13) and subsequently the *BCR-ABL* disease-causing mutation (14). Accordingly, modern classification systems list PMF, PV, and ET as *BCR-ABL*-negative classic MPDs (15). In 1978, G6PD-based clonality studies established PMF as a stem-cell-derived clonal myeloproliferation (16). In 2005, a novel gain-of-function (GOF) mutation involving the JAK2 tyrosine kinase (*JAK2*V617F) was described in approximately 50% of PMF patients but also in the majority of those with PV as well as ET (17). In 2006, another GOF mutation involving MPL (*MPL*W515L/K) was described in approximately 5% of patients with PMF (18).

In 1967, an International Polycythemia Vera Study Group (PVSG) was created under the auspices of the National Cancer Institute and the group provided, for the first time, formal criteria for the diagnosis of each one of the *BCR-ABL*-negative classic MPDs, including PMF (19). Subsequently, a WHO-sponsored committee on the classification of hematological malignancies revised the PVSG

diagnostic criteria for PMF and reorganized the overall classification system for myeloid neoplasms (2). The WHO system considers two broad categories of myeloid malignancies: acute myeloid leukemia (AML) and chronic myeloid disorders (CMDs) (20). AML is defined by the presence of 20% or more "blasts" in either the bone marrow or blood and/or certain recurring cytogenetic abnormalities including t(8;21)(q22;q22), t(15;17)(q22;q12), inv(16)(p13;q22), and t(16;16)(p13;q22) (20). Table 2.2 presents the current WHO classification scheme for CMD. Most recently, a semimolecular classification system has been proposed (Table 2.3) (21).

2.3 Epidemiology

The prevalence of PMF is similar in men and women (M:F = 1.6:1) and overall reported incidence figures range from 0.4 to 1.5/100,000 (22–26). A higher incidence has been suggested in persons of Jewish ancestry (27). Median age at diagnosis is estimated between 55 and 60 years and approximately 2%, 10%, and 30% of patients are diagnosed before age 30, 40, and 50 years, respectively (28). In one study of 323 patients, 9 (2.8%; 6 females) were age 30 years or younger (range: 17–30). The clinical course in these nine young patients was more indolent compared to that seen in older adults and more like that seen in children, where disease occurrence is very rare (29, 30). In general, there is little evidence that links PMF to environmental toxins. However, the possibility of some association with exposure to benzene, other industrial solvents, thorotrast injections, and radiation accidents has been suggested in the past (31–35).

Table 2.2 The World health Organization classification system for chronic myeloid disorders

Major categories	Subcategories
1. Myelodysplastic syndrome (MDS)	
2. Myeloproliferative disorder (MPD)	i. Chronic myeloid leukemia (CML)
	ii. Polycythemia vera
	iii. Essential thrombocythemia
	iv. Primary myelofibrosis
	v. Chronic neutrophilic leukemia
	vi. Chronic eosinophilic leukemia
	viii. Hypereosinophilic syndrome
	ix. Unclassified MPD
3. MDS/MPD	i. Chronic myelomonocytic leukemia
	ii. Juvenile myelomonocytic leukemia
	iii. Atypical CML
4. Systemic mastocytosis (SM)	

Table 2.3 A semimolecular classification of chronic myeloid disorders

Main categories	Clinicopathologic subcategories	Molecular subcategories
I. Myelodysplastic syndrome	*According to WHO classification system*	
II. Classic myeloproliferative disorders	**1. Chronic myeloid leukemia**	*100% BCR-ABL(+)*
	2. Polycythemia vera	*~100% JAK2V617F(+)*
	3. Essential thrombocythemia	*~50% JAK2V617F(+)*
		~1% MPLW515L/K(+)
	4. Primary Myelofibrosis	*~50% JAK2V617F(+)*
		~5% MPLW515L/K(+)
III. Atypical myeloproliferative disorders	**1. Chronic myelomonocytic leukemia**	*~3% JAK2V617F(+)*
	2. Juvenile myelomonocytic leukemia	*~30% PTPN11 mutation(+)*
		~15% NF1 mutation(+)
		~15% RAS mutation(+)
	3. Chronic neutrophilic leukemia	*~20% JAK2V617F(+)*
	4. Chronic eosinophilic leukemia/eosinophilic MPD	**A. *PDGFRA*-rearranged**
		B. *PDGFRB*-rearranged
		C. *FGFR1*-rearranged
		D. Molecularly undefined
	5. Hypereosinophilic syndrome	
	6. Chronic basophilic leukemia	
	7. Systemic mastocytosis	***A. KIT*D816V(+)**
		B. Other *KIT* mutation
		C. *FIP1L1-PDGFRA*(+)
		D. Molecularly undefined
	8. Unclassified MPD	*~20% JAK2V617F(+)*
	i. Mixed/overlap MDS/MPD	
	ii. CML-like but *BCR-ABL*(−)	

2.4 Pathogenesis

The central pathogenetic process in PMF is stem-cell-derived clonal myeloproliferation (16, 36). Unlike the case with CML and *BCR-ABL*, the primary oncogenic event in PMF has not been characterized. However, activating mutations of the JAK2 tyrosine kinase (*JAK2*V617F) and thrombopoietin receptor (*MPL*W515L/K) have recently been reported in approximately 50% and 5% of patients, respectively (17, 18). *JAK2*V617F is an exon 14 *JAK2* mutation at nucleotide position 1849 representing a G to T somatic point mutation. The mutation results in the substitution of valine to phenylalanine at

codon 617. *MPL*W515L mutation represents a G to T transition at nucleotide 1544, resulting in a tryptophan to leucine substitution at codon 515 of the transmembrane region of the MPL receptor (18). *JAK2*V617F has also been described in ET at a similar mutational frequency and in PV, where almost all patients carry the mutation (17, 37–39). Similarly, *MPL*W515L/K also occurs in approximately 1% of ET patients (40). Both mutations induce an MPD phenotype in mice, the former a PV-like disease (17, 41, 42) and the latter a PMF-like disease (43). Regardless, about half of the patients with PMF do not display either mutation and the precise pathogenetic role of these mutations, when they are present, remains to be clarified.

The bone marrow stromal reaction in PMF, including reticulin/collagen fibrosis, osteosclerosis, and angiogenesis is currently believed to be reactive in nature and cytokine mediated. In mice, for example, PMF-associated bone marrow stromal changes have been induced by either systemic overexpression of thrombopoietin (TPO^{high} mice) or by megakaryocyte lineage restricted underexpression of the transcription factor GATA-1 ($GATA\text{-}1^{low}$ mice). In both instances, the megakaryocytes display abnormal distribution of P-selectin that is believed to promote a pathologic interaction between megakaryocytes and neutrophils (emperipolesis), resulting in the release of both fibrogenic and

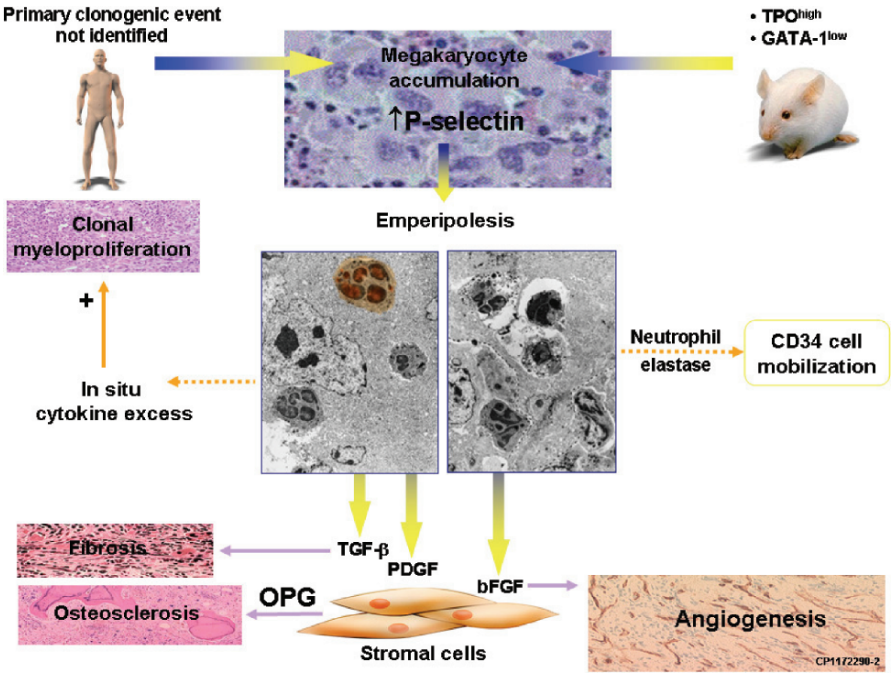

Figure 2.1 Pathogenesis of primary myelofibrosis. TPO, thrombopoietin; TGF, transforming growth factor; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor; OPG, osteoprotegerin. (From Ref. 51; published with permission)

angiogenic cytokines, including transforming growth factor-β1 (TGF-β), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), tissue inhibitors of matrix metalloproteinases, and neutrophil-derived elastase and other proteases (44, 45). Among the latter, megakaryocyte-derived TGF-β1 might be the most important in the pathogenesis of the stromal reaction in PMF (46–48). Peripheral blood expansion of both CD34-positive myeloid progenitors and endothelial cells provide additional evidence for aberrant bone microenvironment in PMF (49, 50). Figure 2.1 summarizes the current speculation regarding the mechanisms of stromal reaction in PMF (51, 52).

2.5 Clinical Features and Diagnosis

Most, but not all, patients with PMF are symptomatic at diagnosis. The typical presentation includes anemia, marked splenomegaly, and profound constitu tional symptoms, including fatigue and night sweats. Other manifestations, either at diagnosis or during the course of the disease, include left upper quadrant discomfort, including recurrent pain from splenic infarcts (may be referred to the left shoulder), early satiety and change in bowel habits, pruritus, easy bruising, peripheral edema, lymphadenopathy, ascites, bleeding, and thrombosis (53–55). The spleen is palpably enlarged in approximately 80% of patients at diagnosis (marked splenomegaly in half of the cases) and the liver in 50% (56). Organomegaly in PMF is secondary to extramedullary hematopoeisis (EMH) that might also involve other organs: lymph nodes (lymphadenopathy), pleura (effusion), peritoneum (ascites), lung (interstitial process), and the paraspinal and epidural spaces (spinal cord and nerve root compression) (57–60).

The peripheral blood smear in PMF often shows leukoerythroblastosis (presence of nucleated red blood cells and immature granulocytes) and teardrop-shaped red blood cells (Figure 2.2). Anemia is present at diagnosis in the majority of the patients and approximately 20% might be red blood cell transfusion-dependent at presentation (59, 61–63). Other laboratory abnormalities at diagnosis include leukocytosis (41–49% incidence), leukopenia (7–22%), thrombocytosis (13–31%), thrombocytopenia (21–37%), presence of circulating blasts (33–53%), increased serum levels of lactate dehydrogenase (LDH; 83%), and low cholesterol levels (32%) (59, 60, 62, 63).

Bone marrow examination reveals both “cellular phase” and “overtly fibrotic” stages of the disease (Figure 2.3) (64). In cellular-phase disease, reticulin fibrosis, might be absent (i.e., prefibrotic stage). Therefore, the most helpful diagnostic feature in the bone marrow is the presence of dense megakaryocyte clusters with atypical megakaryocyte morphology (cloudlike nuclear morphology) that is accompanied by increased granulocyte proliferation and reduced erythropoiesis (64). Additional histological features of advanced disease include osteosclerosis, dilated sinuses, and intrasinusoidal hematopoiesis (Figure 2.4).

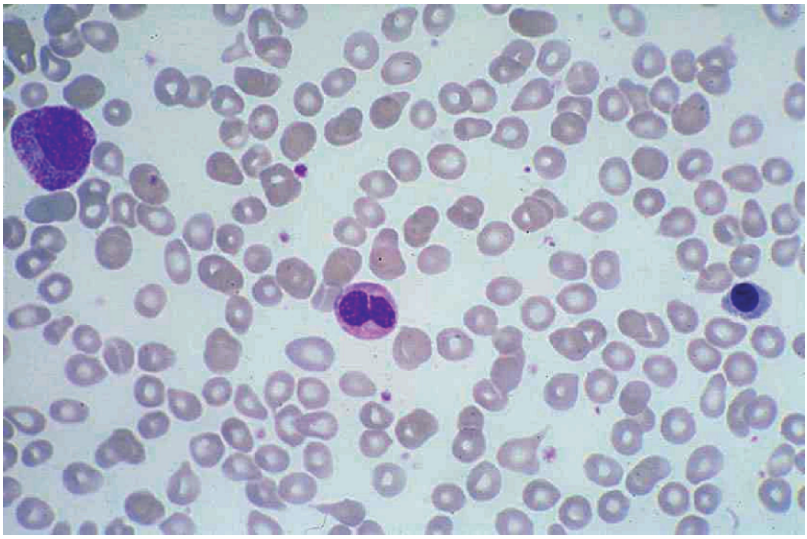

Figure 2.2 Peripheral blood smear in primary myelofibrosis showing myelophthisis; presence of nucleated red blood cells, immature granulocytes, and dacryocytes

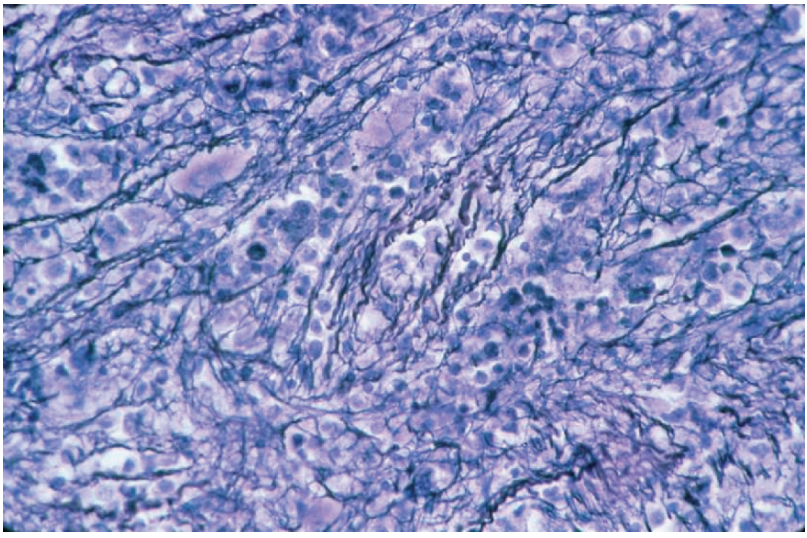

Figure 2.3 Reticulin fibrosis in primary myelofibrosis

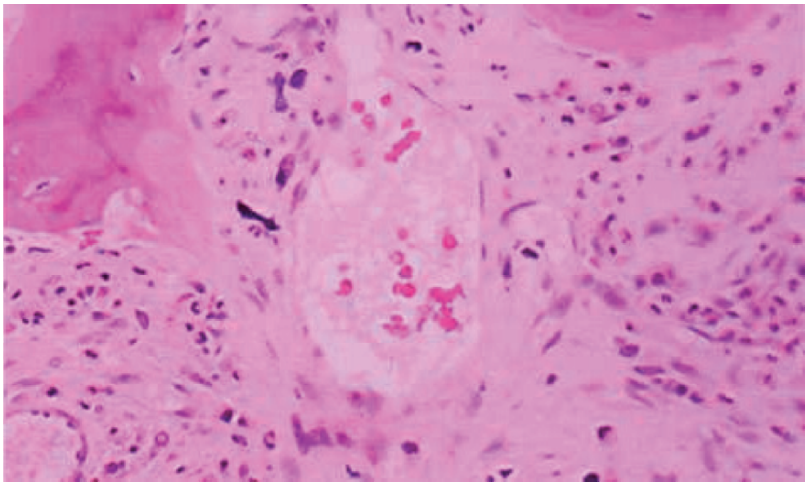

Figure 2.4 Osteosclerosis and intrasinusoidal hematopoiesis in primary myelofibrosis

2.6 Differential Diagnosis

Neither leukoerythroblastosis nor bone marrow fibrosis is specific to PMF. Bone marrow fibrosis might accompany a number of hematologic and nonhematologic conditions, as listed in Table 2.4. In most situations, mutation screening for *BCR-ABL* (to exclude the diagnostic possibility of CML) and *JAK2*V617F (to exclude the possibility of bone marrow fibrosis associated with nonmalignant condition, lymphoid disorder, or metastatic cancer) is highly recommended. It should be noted, however, that *JAK2*V617F cannot distinguish PMF from other myeloid disorders such as MDS, ET, PV, or atypical MPD. Therefore, accurate diagnosis requires careful morphological evaluation of the bone marrow.

Primary MF is typically characterized by the presence of morphologically abnormal megakaryocytes (bulbous and hyperchromatic nuclei) in dense clusters. MDS is characterized by the presence of erythroid and/or granulocytic dysplasia. As mentioned earlier, reticulin fibrosis can be absent in cellular-phase PMF and it is thus possible to confuse cellular-phase PMF with ET. Unlike ET, however, bone marrow in PMF is markedly hypercellular with both granulocytic and megakaryocytic proliferation in PMF as opposed to often normocellular bone marrow with only megakaryocytic hyperplasia in ET (65). Other distinguishing features between cellular-phase PMF and ET include the presence of myelophthisis and/or increased LDH in the former but not the latter.

Acute myelofibrosis, considered a variant of AML, can sometimes be confused with PMF. In general, patients with acute myelofibrosis usually present with severe constitutional symptoms, pancytopenia, mild or no splenomegaly, and circulating blasts. Both immunohistochemistry and cytogenetic studies are helpful in

Table 2.4 Causes of bone marrow fibrosis

Hematologic disorders		
Myeloid disorders	Lymphoid disorders	Nonhematologic disorders
• Primary myelofibrosis (1)	• Hairy cell leukemia (122)	• Metastatic cancer (126)
• Chronic myeloid leukemia (112)	• Hodgkin's lymphoma (123)	• Autoimmune myelofibrosis (127)
• Myelodysplastic syndrome (113)	• Non-Hodgkin's lymphoma (124)	• Systemic lupus erythematosus (128)
• Chronic myelomonocytic leukemia (114)		• Kala-Azar (leishmaniasis) (129)
	• Multiple myeloma (125)	• Tuberculosis (130)
• Chronic eosinophilic leukemia (115)		• Paget's disease (131)
• Systemic mastocytosis (116)		• HIV infection (132)
• Acute megakaryocytic leukemia (117)		• Vitamin D-deficient rickets (133)
• Other acute myeloid leukemias (118)		• Renal osteodystrophy (134)
• Acute lymphocytic leukemia (119)		• Hyperparathyroidism (135)
• Acute myelofibrosis (120)		• Gray platelet
• Malignant histiocytosis (121)		• Familial infantile myelofibrosis (137)
		• Idiopathic pulmonary hypertension (138)

distinguishing PMF from both acute myelofibrosis and MDS with fibrosis. For example, CD34 and CD61 immunoperoxidase staining provides a better estimate of the marrow blast and megakaryocyte content, respectively. Similarly, although cytogenetic abnormalities that occur in approximately half of the patients with PMF are mostly not specific to the disease [e.g., del(20)(q11;q13), del(13)(q12;q22), trisomy 8, trisomy 9, del(12)(p11;p13), monosomy or long arm deletions involving chromosome 7, and partial trisomy 1q] (66). the presence of either del(13)(q12;q22) or der(6)t(1;6)(q21–23;p21–23) is strongly suggestive of PMF diagnosis (67).

2.7 Clinical Course and Prognosis

Primary MF displays a progressive course in the majority of cases, and disease complications include cachexia, peripheral edema, severe fatigue, excessive night sweats, low-grade fever, symptomatic portal hypertension, variceal bleeding, ascites, debilitating diffuse and/or extremity bone pain, and "idiopathic" pulmonary hypertension (68). Causes of death includes development of blast-phase PMF,

which occurs in approximately 10% of patients during the first decade of their disease (60, 63, 69, 70), infections (26–29%), bleeding (11–22%), heart failure (7–15%), liver failure (3–8%), solid tumor (3%), respiratory failure (3%), and portal hypertension (6%) (63, 69).

Survival in PMF is estimated by the use of one of several prognostic scoring systems (PSSs) that rely on the presence or absence of well-established adverse prognostic features (Table 2.5) (62, 63, 69, 71). Among the latter, the Mayo Clinic PSS has been reported to be superior, compared to other PSSs, in delineating both low-risk and intermediate-risk disease categories. According to the Mayo PSS (Table 2.5), median survival for low-risk young patients (age < 60 years) approaches 15 years compared to approximately 5 years in intermediate-risk patients and less than 3 years in high-risk patients. Additional risk factors for inferior survival, in addition to those listed in Table 2.5, include circulating immature granulocytes of ≥ 10% (59), circulating blast count of ≥ 3% (69), advanced age (61, 69, 72), male sex (69), and cytogenetic abnormalities other than 13q- or 20q- (66, 73, 74).

2.8 Management

Unfortunately, current therapy for PMF is inadequate and often palliative at best. Among the several treatment modalities that are currently employed, allogeneic stem cell transplantation (ASCT) is the only one with a potential for prolonging survival. However, ASCT is associated with substantial mortality and morbidity and is currently utilized in a select group of patients with high-risk disease. Drug therapy in PMF is used to alleviate symptomatic cytopenias, organomegaly, or marked thrombocytosis and/or leukocytosis. Other treatment modalities are also palliative and include involved field radiation, splenectomy, and blood component transfusions. Therefore, in the asymptomatic patient with low-risk PMF, it is currently reasonable to defer therapy (i.e., watchful waiting), regardless of age. In the presence of symptoms, either conventional or experimental drug therapy is advised in older patients as well as in younger low-risk patients. The risk associated with ASCT might be justified in young patients with high-risk disease and in some with intermediate-risk disease (Table 2.6). The choice between myeloablative versus reduced intensity conditioning (RIC) ASCT is made taking age and the presence of other comorbid conditions into consideration (Table 2.6).

2.8.1 Drug Therapy

The primary reason for using drug therapy in PMF is the presence of either anemia or splenomegaly that is symptomatic. Drug options for the former include subcutaneous (SC) erythropoietin (Epo) or oral drugs, including androgen preparations, corticosteroids, danazol, thalidomide, and lenalidomide. The starting dose for SC

Table 2.5 Prognostic models in primary myelofibrosis

Prognostic scoring system	Risk category	Score sum	Median survival (months)	Score for Hgb < 10 g/dL	Score for WBC < 4 or > 30 × 10^9/L	Score for Plt < 100 × 10^9/L	Score for AMC ≥ 1 × 10^9/L	Score for symptoms*	Score for circulating blasts ≥ 1%
Elliott et al. (139) (n = 129) (ages < 60 years; median: 52) (Mayo prognostic model)	Low	0	173	1	1	1	1	N/A	N/A
	Intermediate	1	61						
	High	≥2	26						
Dingli et al. (71) (n = 160) (ages < 60 years; median: 52)	Low	0	155	1	1	1	N/A	N/A	N/A
	Intermediate	1	69						
	High	≥2	24						
Cervantes et al. (140) (n = 116) (ages ≤ 55 years; median: 46)	Low	0 or 1	176	1	N/A	N/A	N/A	1	1
	High	≥2	33						
Cervantes et al.63 (n = 106) (all ages; median: 64 years)	Low	0 or 1	99	1	N/A	N/A	N/A	1	1
	High	≥2	21						
Dupriez et al.62 (n = 195) (all ages; median: 65 years)	Low	0	93	1	1	N/A	N/A	N/A	N/A
	Intermediate	1	26						
	High	2	13						

Hgb, hemoglobin; WBC, white blood cell count; Plt, platelet count; AMC, absolute monocyte count.

Table 2.6 Suggested treatment algorithm in primary myelofibrosis

Risk stratification	Age <45 years	Age 45–60 years	Age >60 years
Low risk (no risk factors)[a]	Watchful waiting or Experimental drug therapy	Watchful waiting or Experimental drug therapy	Watchful waiting or Experimental drug therapy
Intermediate risk (one risk factor)	Experimental drug therapy or RIC ASCT	Experimental drug therapy	Experimental drug therapy
High risk (≥2 risk factors)	Myeloablative ASCT	RIC ASCT	Experimental drug therapy

RIC, reduced-intensity conditioning; ASCT, allogeneic stem cell transplant.

[a]According to Mayo prognostic scoring system; hemoglobin <10 g/dL, platelet count < 100×10^9/L, monocyte count ≥ 1×10^9/L, leukocyte count > 30×10^9/L or < 4×10^9.

Epo injection is 40,000 units weekly and such therapy is most appropriate in the presence of an endogenous serum Epo level below 100 U/L, where an approximately 50% response rate is expected (75). Some patients under Epo therapy experience further enlargement of their spleen. Several androgen preparations, including testosterone enanthate (400–600 mg IM weekly) and oral fluoxymesterone (10 mg TID) have been shown to improve anemia in a third of treated patients (76). The response rate from androgen therapy is improved by the concomitant use of corticosteroids (e.g., prednisone 30 mg/day) and compromised by the presence of cytogenetic abnormalities (76, 77). Danazol (600 mg/day) is a synthetically modified testosterone and produces response rates in PMF that is similar to that seen with other androgen preparations (78).

Thalidomide and lenalidomide have recently been shown to have therapeutic activity in PMF (79, 80). The mechanism of action for both drugs is not clearly understood but believed to be related to their anticytokine and immunomodulatory properties. The anticytokine treatment approach in PMF is based on both circumstantial evidence from affected patients and experimental myelofibrosis in mice. Thalidomide displays both antiangiogenic (81) and anti-tumor necrosis factor (TNF)-α (82) activity. There are currently two classes of thalidomide analogs: the selective cytokine inhibitory drugs (SelCIDs) and the immunomodulatory drugs (ImiDs) (83). Like thalidomide, both drug classes have anti-TNF-α, antiangiogenic, and anti-inflammatory activity (84). The activity of SelCIDs is mostly tied to phosphodiesterase 4 inhibition. The ImiDs, including CC-5013 (lenalidomide™) and CC-4047 (actimid™), do not inhibit phosphodiesterase 4 and have a broader cytokine inhibitory activity [inhibit TNF-α, interleukin (IL)-1β, IL-6, and IL-12]. In addition, they costimulate T-cells with upregulation of IL-2 and interferon (IFN)-γ production by T helper-1 cells and IL-5 and IL-10 production by T helper-2 cells (85). Lenalidomide (CC-5013) is the lead compound among the ImiDs and its ex vivo antiangiogenic as well as anti-TNF property is estimated to be at least 50-fold higher than that of thalidomide (83, 84). In PMF, thalidomide works best

at low doses (50 mg/day) and in combination with corticosteroids (prednisone 15–30 mg/day) (86) and lenalidomide in the presence of del(5)(q31) (80). Single-agent therapy in unselected patients with either thalidomide or lenalidomide produces 15% and 20% response rates in anemia, respectively. The addition of corticosteroids doubles the response rate with thalidomide and the presence of del(5)(q31) is associated with complete hematologic remission in the majority of patients treated with lenalidomide. In addition, both drugs have been shown to improve thrombocytopenia (approximately 50% response rates) and splenomegaly (approximately 30% response rate) (79, 80).

The drug of choice for symptomatic splenomegaly in PMF is hydroxyurea (starting dose 500 mg TID). The drug is also used for controlling symptomatic thrombocytosis and/or leukocytosis. Hydroxyurea-refractory cases are sometimes managed by the use of alternative myelosuppressive agents, including intravenous cladribine (5 mg/m^2/day in a 2-h infusion for 5 consecutive days to be repeated monthly for four to six cycles) (87), oral melphalan (2.5 mg three times a week) (88), and oral busulfan (2–6 mg/day with close monitoring of blood counts) (89, 90). In contrast, interferon-α therapy is poorly tolerated and has limited efficacy in the treatment of PMF (91–96).

It is expected that all clinicians disclose the side effects of the above-mentioned drugs before prescribing them. In addition, one must always look out for the presence of contraindications to the use of these drugs. For example, androgen use requires monitoring of serum prostate-specific antigen in men, liver function tests in both men and women, and underscoring the possibility of masculinizing side effects in women. Similarly, the use of thalidomide requires strict supervision and any possibility of pregnancy during its use must be prevented. Other side effects of thalidomide include somnolence, constipation, rash, and neuropathy. Lenalidomide is myelosuppressive and can result in neutropenic fever and sepsis. Therefore, one has to follow CBC closely and intervene with myeloid growth factors if the absolute neutrophil count drops to below 1×10^9/L. Other notable side effects of drugs used in PMF include mucocutaneous ulcers and skin/nail pigmentations associated with hydroxyurea use and the usual complications of corticosteroid use.

2.8.2 Splenectomy

Splenectomy is a strictly palliative treatment modality in PMF and does not alter the natural history of the disease. The procedure is associated with approximately 10% mortality and a higher incidence of morbidity that includes thrombosis, bleeding, postsplenectomy enlargement of the liver, and exacerbation of thrombocytosis/leukocytosis. Current indications for splenectomy in PMF include complications of portal hypertension, including ascites and variceal bleeding, drug-refractory symptomatic splenomegaly, or very frequent red blood cell transfusions (97). Severe thrombocytopenia in PMF is a marker of impending leukemic transformation and overall outcome in its presence might not be favorably affected with splenectomy.

In preparation for splenectomy, prophylactic therapy with hydroxyurea is advised in patients with leukocyte count of $>5 \times 10^9$/L and/or platelet count $>150 \times 10^9$/L in order to prevent postsplenectomy thrombocytosis and/or leukocytosis that might facilitate thrombotic complications (97). In addition, there is some evidence that suggests an increased incidence of bleeding in patients displaying laboratory evidence of DIC (i.e., presence of markedly increased d-dimer). Anecdotal evidence supports the use of low-dose prednisone (20 mg/day) in preparation for surgery. In addition, short-term (4–8 weeks) systemic anticoagulation, once hemostasis is secured after surgery, might reduce the risk of postoperative thrombotic complications.

2.8.3 Radiation Therapy

Involved field radiotherapy provides transient (median response duration of 3–6 months) relief of mechanical discomfort from hepatosplenomegaly (98, 99). However, such therapy is often complicated by protracted pancytopenia and drug therapy is instead preferred. In contrast, irradiation therapy is very useful in patients with nonhepatosplenic EMH; most frequent sites include vertebral column, lungs, pleura, and peritoneum. When symptomatic, nonhepatosplenic EMH is effectively treated with low-dose radiation therapy (0.1–1 Gy in 5–10 fractions) (58). Sometimes, occult pulmonary EMH presents with "idiopathic" pulmonary hypertension and a technetium 99m sulfur colloid scintigraphy is recommended if such an occurrence is suspected and treatment with single-fraction (0.1 Gy) whole-lung irradiation has been shown to be effective (68, 100).

2.8.4 Allogeneic Stem Cell Transplant

An increasing amount of information is being gathered regarding the use of ASCT in PMF, in the context of both myeloablative (101–104) and RIC (105, 106) transplant. Early engraftment rate is acceptable in both instances regardless of whether a related or matched unrelated donor is used. The experience so far with myeloablative ASCT is encouraging in very young patients (age <45 years), but posttransplant long-term survival in older patients is less than 20% (103, 104). Furthermore, the majority of survivors after ASCT experience reduced quality of life because of chronic graft versus host disease (GVHD) (101). A recent multivariable analysis involving 320 patients with PMF registered to an international transplant database identified young age, HLA-matched sibling transplant, excellent performance status, absence of circulating blasts, and more recent transplant date as independent indicators of favorable transplant outcome (107). To date, the advantage of RIC transplant over myeloablative ASCT has not been examined in a controlled setting, although single-cohort studies suggest better outcome in terms of both 1-year mortality (0–33%) and morbidity (0–50% rate of acute GVHD) (108).

2.9 Conclusions

Over the last two decades, many drugs have been investigated for their therapeutic value in PMF. Negative studies have included drugs such as IFN-α, anagrelide, suramin, pirfenidone, imatinib mesylate, farnesyl transferase inhibitors such as R115777, and certain VEGF receptor inhibitors, including PTK-787 and SU5416 (109). In contrast, promising results were obtained with cladribine (87), etanercept (110), thalidomide (111), and lenalidomide (80). Despite such progress, treatment in PMF remains suboptimal in terms of both survival and quality of life. At present, it is reasonable to consider all high-risk patients for either ASCT (if transplant-eligible) or experimental drug therapy. It is equally reasonable to undertake a "watchful waiting" approach in low-risk patients. Management in intermediate-risk patients should be individualized and is often dictated by age, performance status, and patient preference. In all patients, the presence of del(5)(q31–32) warrants a therapeutic trial with lenalidomide. The recent discovery of PMF-associated activating mutations involving *JAK2* and *MPL* has raised the prospect of small molecule drug therapy that targets JAK2.

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